Osteoporotic Fractures

Osteoporotic Fractures: Relation to Mortality, Medication Use, and Rheumatoid Arthritis

Shahab Abtahi

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Shahab Abtahi

Supervisors

Prof Dr Frank de Vries
Prof Dr Annelies Boonen

Co-supervisors

Dr Johanna H M Driessen
Dr Andrea M Burden (from the Swiss Federal Institute of Technology Zurich [ETH Zürich], Switzerland)

Assessment Committee

Prof Dr Martijn Poeze (Chair)
Dr Sandrine P G Bours
Prof Dr Olaf H Klungel (from the Utrecht University, Utrecht)
Prof Dr Willem Lems (from the Amsterdam UMC, Amsterdam)
Prof Dr Matty P Weijenberg

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CHAPTER 1

General Introduction

a. Osteoporosis and osteoporotic fractures

Osteoporosis is a chronic disease characterised by loss of bone mass and microarchitectural deterioration of the bones, culminating in bone fragility and ultimately an increased risk of fractures, named osteoporotic (OP) fractures.[1,2] It is estimated that around 22% of women and 7% of men aged 50 years and above were afflicted with osteoporosis in Europe in 2010.[3] There are two main variants of the disease by aetiology. Primary osteoporosis occurs predominantly along with the natural ageing process or due to hormonal changes, as observed in elderly individuals and postmenopausal women. Secondary osteoporosis occurs due to another medical condition or medication use, such as inflammatory rheumatic diseases including rheumatoid arthritis (RA), endocrine abnormalities (thyroid disorders, hyperparathyroidism, hypogonadism, hypopituitarism, or type I diabetes mellitus), inflammatory bowel disease, exposure to glucocorticoids (GCs), prolonged immobility (e.g. due to spinal cord injury, Parkinson's disease, stroke, or muscular dystrophy), and organ transplantation.[4] According to the definition by the World Health Organisation (WHO), diagnosis of osteoporosis is based on the bone mineral density (BMD) measurement by dual-energy X-ray absorptiometry (DXA).[5] A BMD T-score of 2.5 standard deviations (SDs) below the mean BMD of the young adults from the reference population defines osteoporosis, while a BMD T-score between -1 and -2.5 SDs compared with the reference mean shows osteopenia, and a BMD T-score above -1 SD denotes normality.

The main manifestation of osteoporosis are OP fractures. Various definitions exist for OP fractures in the literature, however most identify these as fractures occurring from a low-energy trauma, such as falling from a standing position.[6-8] The WHO/FRAX definition considers hip, clinically symptomatic vertebral, humerus, and forearm (radius/ulna) as major OP fractures (MOFs).[9,10] But still, other anatomical sites such as pelvis, ribs, distal femur, clavicle, scapula, sternum, tibia and fibula are considered as an OP fracture site.[6] Vertebral fracture is the most common OP fracture, where one in every five men or women aged 50+ years is affected by at least one vertebral fracture.[11] The diagnosis of a vertebral fracture is based on vertebral deformity on radiographs or clinical features. Two thirds of vertebral fractures remain to be asymptomatic and might only be accidentally found on chest radiographs for other reasons.[12] Hip fracture is the 2nd most common OP fracture, with observed increasing rates in older age and also with postmenopausal status in women. In 2010, the lifetime probability of hip fracture from the age of 50 years in Europe (the weighted average of the five largest European countries and Sweden) was

estimated to be 15% among women and 5% in men.[8] It is the most severe among OP fractures with substantial need for hospitalisation and treatment, and high morbidity, mortality and substantial societal costs.[13] Forearm fracture is the other common OP fracture, associated with much less morbidity and mortality, compared with hip and vertebral fractures. The term 'advanced severe osteoporosis' has been proposed, when there is a hip fracture or at least two other non-hip fractures in addition to the BMD T-score ≤-2.5 SDs.[14]

b. Secular trends in osteoporotic fractures

The absolute number of hip fractures is generally increasing due to the worldwide increase in life expectancies and ageing trajectory. In the UK, the incidence rate (IR) of hip fracture between 2008 and 2012 was 33.5 per 10,000 person years (PYs) among women aged 50+ years and 13.4 per 10,000 PYs among men aged 50+.[15] However, the trend in age-standardised IRs is different across the globe. Most reports from North European and North American countries (i.e., those with the highest IRs of hip fracture) indicate rising trends until the 1980s/1990s and then a decrease in the subsequent two decades.[16-19] In contrast, increasing trends in age-standardised IRs of hip fracture have been observed in the Asian countries over a similar time period, highlighting a contrast in the reported trends between the West and the East.[20-23] There are fewer reports on the secular trend in OP fractures other than hip. These studies from the UK and the US reported a mostly increasing trend in humerus and vertebral fractures and a decline in other fracture sites.[15,24]

Considering the impending ageing trajectory and the increase in absolute number of OP fractures, the burden of these fractures on patients and healthcare systems will become more critical in the near future. The associated costs of OP fractures in Europe, including the costs of acute treatment of fracture, the costs of pharmacologic prevention and long-term care, was estimated to be €37.4 billion in 2010, where more than half was caused by hip fracture alone.[3,25] These costs are expected to double by 2050.[26] The changing trends of OP fractures in various countries and the huge expected economic burden accompanied with OP fractures in the near future led the International Osteoporosis Foundation (IOF) working group on Fracture Epidemiology to ask for updates on secular trends in IRs of OP fractures.[16] As there were few reports globally on the secular trend in all OP fractures, and no report in a North European country, we investigated, as part of

this thesis, the IRs of hip and other MOFs among adults aged 50+ years in Denmark between 1995 and 2010.

c. Mortality after fracture and the role of bisphosphonates

High mortality is a devastating outcome of an OP fracture. More than one third of men and more than one fifth of women suffering a hip fracture will die within one year.[19] This 1-year all-cause mortality after hip fracture is 3.5-fold higher in males and 2.4-fold higher in females compared with controls without a fracture.[27] Of those patients who sustained an OP fracture, around 51% of men and 39% of women will die within five years.[28] A significant contributor to this high mortality is a subsequent fracture and mortality after that.[28,29]

Anti-osteoporotic treatment such as bisphosphonates (BPs) can prevent a subsequent fracture in patients with osteoporosis.[30] There is conflicting evidence from randomised controlled trials (RCTs) that BPs can reduce mortality after hip fracture.[31-33] Observational studies have also found contrasting results regarding the effect of BPs on mortality risk after fracture, although their findings might be flawed due to methodological limitations.[34-36] There is no established biological mechanism for BPs to reduce mortality aside from secondary fracture prevention. However, some evidence points to anti-atherosclerotic effects of BPs, such as reducing arterial wall calcification or decreasing lipid profiles.[37-40] This pile of evidence brought scepticism for any beneficial effect of BPs on mortality risk after fracture. Therefore, we examined the association between oral BP use and all-cause mortality after OP fractures in a large nationwide cohort study.

d. Oral glucocorticoids, risk factor for osteoporotic fractures

Oral GCs are one of the oldest and most important anti-inflammatory medications that are widely used for a constellation of chronic inflammatory conditions including rheumatic, respiratory, dermatologic, neurologic, and gastrointestinal diseases. Epidemiologic studies showed that the prevalence of oral GC use at any time point was about 1% in the general population of the UK and the US.[41,42] But besides their potent anti-inflammatory effects, oral GCs incur considerable side effects to the patient. Osteoporosis and OP fractures are amongst the best-established side effects.[43-45] The reason behind this GC-induced higher fracture rate is apoptosis of osteoblasts and osteocytes and reduced bone formation, elevated bone resorption and hence lowered BMD, and some microarchitectural changes in bone quality.[44,46]

Previous studies have shown that the OP fracture risk associated with oral GC use is dose-dependent.[44,47,48] The existing evidence signifies a potential role for both daily dose and cumulative dose of oral GCs in raising the OP fracture risk, but with more emphasis on daily dose.[44,47,48] However, taking oral GCs for short periods, even in high daily doses, would not substantially increase the fracture risk when the cumulative use is less than 1 g prednisolone equivalent dose (PED).[47] Many patients with chronic inflammatory conditions use oral GCs intermittently in short periods, or sometimes for a longer time, due to the repeated relapses of the underlying disease. There is already limited data on the OP fracture risk associated with various exposure patterns of oral GCs. Thus, we sought to examine the association between daily dose and cumulative exposure to oral GCs and OP fracture risk by using a large national registry.

e. Rheumatoid arthritis and its pharmacotherapy, risk factors for osteoporotic fractures

RA is a chronic autoimmune inflammatory musculoskeletal disease with an unknown aetiology. It affects around 0.5-1.0% of adult population in developed countries and is more prevalent among elderly individuals and women.[49] The hallmark of RA is the presence of synovitis, which in a subgroup of patients can result in joint damage of mainly the small joints of hands and feet.[50] Patients experience pain, morning stiffness, and limited range of motion in the affected joints. In addition, extra-articular manifestations such as rheumatoid nodules can be detected in clinical examination. In the majority of patients, laboratory tests reveal presence of serum rheumatoid factor (RF), anticitrullinated protein antibody (ACPA), and elevated levels of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). In more advanced cases, bone and cartilage erosions are observed in imaging. These manifestations drive the clinical diagnosis of RA but are also part of the RA classification criteria available for research purposes.[51]

The treatment for RA should start as early as possible to prevent further damage and to avoid complications and comorbidities. Analgesics and non-steroidal anti-inflammatory drugs (NSAIDs) are prescribed to control the pain and stiffness in patients. The European Alliance of Associations for Rheumatology (EULAR) recommends starting a conventional synthetic disease-modifying antirheumatic drug (csDMARD, such as methotrexate, leflunomide, sulfasalazine, or hydroxychloroquine) as first-line therapy, in combination with short-term GCs (or low-dose GC therapy, i.e., ≤7.5 mg PED/day).[52] In case of an

absence of clinical improvement at 3- and 6-months targets, change to other csDMARDs or adding a biological DMARD (bDMARD) or a targeted synthetic DMARD (tsDMARD, i.e., Janus kinase inhibitors, such as tofacitinib, baricitinib, and filgotinib) should be considered. The bDMARDs recommended for RA include tumour necrosis factor (TNF) inhibitors (i.e., adalimumab, infliximab, certolizumab, etanercept, and golimumab), costimulation inhibitors (such as abatacept), interleukin (IL)-6 blockers (tocilizumab, sarilumab, clazakizumab or sirukumab), and anti-B-cell agent rituximab. Despite the growing number of new medications, a considerable number of patients do not achieve optimal disease control, which is partly due to adverse effects of the medications.[53]

The inflammatory process of RA can contribute to comorbidities such as osteoporosis, in addition to cardiovascular disease, depression, and disability (especially in severe cases or with under-treatment).[54,55] Previous studies showed that patients with RA have a 1.5-fold increased risk of OP fractures compared with controls without a history of RA, which was more prominent in the hip/femur and spine (significant adjusted relative risks 2.0 and 2.4, respectively).[56] The increased fracture risk in RA is also dependent on the duration of RA disease, persistent disease activity, and the pharmacotherapy that RA patients receive, particularly GCs.

Using GCs in RA is advised to be short-term and preferably in lower doses to minimise the risk of adverse effects.[52] There is evidence from RCTs that low-dose GC therapy in RA could even have protective effects on bone: taking 7.5 mg prednisolone once daily had reduced BMD loss in hand or hip compared to placebo.[57,58] Plausible biological explanations might not only be the regulation of the adverse impact of RA-related systemic inflammation on bone metabolism, but also the beneficial effect of increased physical performance due to the improved functional status of patient. Based on this reasoning, low-dose GC therapy may also bring about beneficial effects on OP fractures. To date, there are few observational studies that examined the association between low-dose GC therapy (≤7.5 mg PED/day) and OP fracture risk in RA patients.[59-61] Most of these studies have found higher fracture rates with low-dose GC use compared with non-use. These findings are in contrast to the aforementioned RCTs on BMD and might be spurious due to methodological limitations. Thus, we aimed to investigate the use of low-dose oral GCs on OP fracture risk among patients with RA, in a large cohort study that considers various thresholds of low-dose oral GC use and different OP fracture sites.

Apart from GCs, other medications frequently prescribed for patients with RA might also be associated with OP fractures. Proton pump inhibitors (PPIs) are routinely co-prescribed with various NSAIDs to counterbalance their gastrointestinal side effects.

There is evidence from observational studies that PPIs might increase hip and vertebral fracture risk.[62-65] This increased fracture risk by PPIs was attributed to induced hypochlorhydria by PPIs and reduced calcium absorption, or to unmeasured bias or confounding according to other authors.[66,67] To the best of our knowledge, the association between concomitant use of oral GCs and PPIs and risk of fracture was never studied among patients with RA, and only once in the general population but yet with no definite conclusions.[67] Furthermore, with the increasing life expectancies and ageing populations, use of PPIs could become more ubiquitous, as it is commonly used among elderly patients. So, we investigated the association between concomitant use of oral GCs and PPIs and the risk of OP fractures among patients with RA with a well-designed cohort study.

A more recently developed class of drugs for RA treatment, the bDMARDs, have been postulated by the literature to be related to fragility fractures as they are potent suppressors of disease activity. Certain types of inflammatory cytokines in RA have important roles in activation and maturation of osteoclasts and finally bone resorption, including macrophage colony-stimulating factor, TNF-α, IL-1, IL-6, and IL-17.[68] They are ultimately responsible for an increase in the ratio of receptor activator of nuclear factor-κB ligand to osteoprotegerin (RANKL/OPG ratio), which directly results in bone loss. Previous clinical trials reported inconsistent results for a protective effect on bone health in RA patients by maintaining BMD in hands, hip or vertebrae after using infliximab or adalimumab (TNF-α inhibitors).[69-72] But, the studies on the association between various bDMARDs and fracture risk in RA or similar chronic arthropathies failed to show such a beneficial role for bDMARDs.[73-76] Lack of RCTs due to ethical considerations, paucity of observational studies, and the contrasting results of the existing literature have led the IOF working group on Chronic Inflammation and Bone Structure to affirm the unmet need for additional and high quality data on the association between bDMARDs and OP fracture risk in RA.[68] Therefore, we aimed to investigate the effect of bDMARDs on OP fracture risk compared with no treatment with biologicals in patients with RA in a nationwide cohort study.

f. Pharmacoepidemiology, applications and limitations

Pharmacoepidemiology is an interdisciplinary field to study the effectiveness and side effects of medications in real-world settings.[77] It brings together various fields such as pharmacology, clinical and medical knowledge of diseases, epidemiology, and statistical

methods to design and conduct studies, and then to interpret the results. Pharmacoepidemiological studies and methodologies are used for post-authorisation drug evaluations. This ideally allows to have enough time for some of the longer-term or rarer adverse effects (or sometimes beneficial effects) of drugs to develop in real patients, for whom the drug was originally intended. This is in contrast with pre-authorisation RCTs that have stringent inclusion and exclusion criteria without enough generalisability to the real-world populations. In this thesis, we tried to address the previously mentioned knowledge gaps in the literature by means of the pharmacoepidemiological methodologies. It is also very advantageous to use observational pharmacoepidemiological studies for studying a debilitating and uncommon outcome such as OP fracture. One can name various reasons that make it practically impossible to conduct RCTs to study OP fractures, such as ethical considerations, generalisability issues, high costs, and a necessity for a long follow-up time and a large sample size.

To answer the study objectives in this thesis, a couple of validated and robust electronic healthcare databases (EHDs) were used, and some established or state-of-the-art study designs were employed. For three studies, data were used from the British Clinical Practice Research Datalink, CPRD GOLD. This is one of the world's largest primary care databases, which covered 11.3 million patients from 674 practices in the UK in 2013.[78] The other three studies were based on data from the Danish National Patient Registry (DNPR, with information on all hospitalisation and outpatient records), and the DANBIO (a specific register for certain inflammatory rheumatic diseases such as RA in Denmark), both with comprehensive nationwide coverage and quality research data.[79,80] For the study on trends of OP fractures, a series of cross-sectional analyses was used. A case-control design was utilised to investigate the oral GCs-fracture association in the general population of Denmark. For the other studies, we made use of a retrospective cohort design.

Pharmacoepidemiological studies as a form of observational research investigate the real-world evidence, and in theory cannot randomise patients to various treatment arms, as in RCTs that are considered gold standard for studying the causal effects of interventions. To mimic the randomisation performed in RCTs, one needs proper and sometimes complicated study designs and methodologies, which in turn can end up in important limitations.[81] It is key to be aware of these limitations when designing the study and to find ways to avoid or minimise them. An in-depth methodological evaluation of the studies conducted in this thesis is provided in **Chapter 8**, as the general discussion

of this thesis. There, we explain different sorts of confounding and bias that we might have encountered in our studies, the strategies to minimise or avoid them, and any remaining impact on the final results.

g. Objectives of this thesis

The overall objective of this thesis was to study the OP fractures and their relation to mortality, medication use and RA. There are two sub-objectives in this thesis, each represented with a corresponding section: 1) investigating various attributes of OP fractures in the general population, including a recent secular trend, the mortality after fracture in association with oral BP use, and the association between various exposure patterns of oral GCs and OP fracture risk; 2) evaluating the role of medications (low-dose oral GCs, concomitant oral GCs and PPIs, and bDMARDs) in OP fracture risk among patients with RA.

h. Outline of chapters

This thesis contains two sections and eight chapters. **Section 1** addresses the 1st sub-objective of this thesis regarding the various attributes of OP fractures in the general population. Under this section, **Chapter 2** describes recent secular trends in OP fractures in Denmark, and in **Chapter 3** the association between oral BP use and mortality risk after an OP fracture has been studied using the CPRD. Still, **Chapter 4** addresses the role of various exposure patterns of oral GC use in OP fracture risk in the general population of Denmark. **Section 2** answers the 2nd sub-objective of this thesis, entailing three chapters representing three cohort studies conducted among patients with RA, which investigate the association between various medication use and OP fracture risk. In **Chapter 5**, we studied the effect of low-dose oral GC therapy on OP fracture risk in patients with RA using the CPRD. In **Chapter 6**, the association between concomitant use of oral GCs and PPIs in RA and risk of OP fractures in the CPRD has been investigated. In **Chapter 7**, we aimed to compare OP fracture risk with use of bDMARDs to no treatment with biologicals in patients with RA using the nationwide Danish registries. The thesis is concluded with **Chapter 8**, as the general discussion of the main findings of the accomplished studies, their methodological evaluations, clinical implications, and suggestions for future research.

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SECTION 1

Osteoporotic fractures in the general population

CHAPTER 2

Secular trends in major osteoporotic fractures among 50+ adults in Denmark between 1995 and 2010

Shahab Abtahi

Johanna H M Driessen

Peter Vestergaard

Joop P van den Bergh

Annelies Boonen

Frank de Vries

Andrea M Burden

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a. Abstract

Background

The trend in osteoporotic fractures is varied across the globe, and there is no updated information in the case of Denmark for all major osteoporotic fractures (MOFs). Thus, we investigated the incidence rates (IRs) of MOFs among 50+ adults in Denmark over the period 1995–2010.

Methods

A series of cross-sectional analyses was done using the Danish National Health Service Register. Participants were 50+ adults in the full country Denmark with a MOF between 1995 and 2010. Gender-specific IRs of MOFs per 10,000 person years (PYs) were estimated, in addition to IRs of individual fracture sites (hip, vertebrae, humerus, and radius/ulna), and women-to men IR ratios for MOFs.

Results

A general decline was observed in IRs of MOFs for the whole population (from 169.8 per 10,000 PYs in 1995, to 148.0 in 2010), which was more pronounced among women. Thirty-one and nineteen percent of decline was observed in hip fracture rates among women and men, respectively. The trend in clinical vertebral fracture was slightly decreasing for women and increasing for men. The women-to-men rate ratio of MOFs decreased noticeably from 2.93 to 2.72 during study period.

Conclusions

We observed declining trends in MOFs and hip fracture for both sexes. However, a lower rate of decrease of hip fracture and an increasing trend in vertebral fracture was noticed among men. Considering our observations and the major economic burden that accompanies this devastating disease, more attention should be paid to MOFs, especially in men.

b. Introduction

This article was published in error in Archives of Osteoporosis and has now been retracted.[1] Osteoporosis is a systemic metabolic skeletal disease where reduced bone mineral density would make patients susceptible to fractures, called osteoporotic (OP) fractures. Based on literature consensus, major osteoporotic fractures (MOFs) include mostly hip, clinical vertebral, humerus, and forearm (radius/ulna) fractures, which altogether are a leading cause of morbidity and mortality worldwide.[2] OP fractures incurred 5.8 million lost Disability-Adjusted Life Years (DALYs) worldwide in the year 2000, of which 51% was represented by two WHO world regions Europe and the Americas.[3] The occurrence of a MOF would not only impact the well-being and function of a patient, including an elevated mortality risk, but also has substantial economic consequences.[4-9] It is estimated that in the year 2011, the associated costs of OP fractures were €36 billion in Europe, and €1.6 billion in Denmark (including both direct and productivity costs), and these costs are estimated to double by 2050.[10,11]

The predicted increase in OP fractures has been reported in numerous countries, including the USA, China, and in worldwide projections (especially developing countries), and is in large part due to the impending ageing trajectory.[12-14] A recent study in the UK with a relatively long follow-up time (1990–2012) revealed mostly a rising or steady trend for most OP fractures in both men and women.[15] However, despite the expected increase, a number of studies have identified a levelling, or decline in hip fractures in recent years.[16-21] This led the International Osteoporosis Foundation (IOF) working group on fracture to request for updates on secular trends in hip and other OP fracture incidence rates (IRs).[22] In Danish studies, age-adjusted hip fracture IRs increased between 1977 and 1999, yet a decline, particularly in women, has been observed since 1997.[23-25] This trend of increasing fractures up to the 1990s, with a levelling of fracture rates in the past two decades, has been noted by others.[18,19,26] Apart from two single year studies which surveyed the IRs of forearm and OP fractures in 2010 and 2011, respectively, and two reports on hip fracture trend until 2006 and 2010, there has never been a country-specific report on secular incidence trends in all OP fractures for Denmark.[24,25,27,28] Thus, the aim of this study was to investigate the IRs of MOFs among adults aged 50 years or older in Denmark over the period 1995–2010.

c. Methods

Data Source

We used data from the registry of the Danish National Health Service. The extensive registers in Denmark cover all contacts to the health sector for all citizens, without age restriction. This includes approximately 5.2 million individuals in 1995 and 5.5 million in 2010.[29] The unique 10-digit civil registry number allocated to each Danish citizen was used to link the population-based registries and generate a complete hospital discharge history for each patient. Data on vital status for the Danish population have been collected since 1968 in the Civil Registration System, and all inpatient contacts have been registered in the Danish National Hospital Discharge Register (NHDR) since 1977.[30] The NHDR covers all inpatient contacts since 1977, and beginning in 1995, the NHDR captures also all outpatient visits to hospitals, outpatient clinics, and emergency room visits. The validity of the Danish National fracture records has been previously verified.[31]

Study Design

We included patients, aged 50 years or older, who were diagnosed with a fracture in the period between 1995 and 2010. MOFs were identified in accordance with the WHO/FRAX definition as hip, clinical symptomatic vertebral, humerus, or forearm (radius/ulna) fracture.[32,33] They were clustered by site using the following International Classification of Diseases and Related Health Problems 10th Edition (ICD-10) codes: hip (S72.0-S72.2), clinical symptomatic vertebral (S12, S22.0, S22.1, S32.0, T08), humerus (S42.2-S42.4), and forearm (S52). As it is possible that the original fracture and follow-up visits or procedures may have the same ICD-10 code, we introduced a washout period to avoid double counting fractures in individuals. As 1995 was the first year of observation, we also applied a 1-year washout period prior to 1995. Thus, if a patient had a hip fracture code (ICD-10 S72.2) in 1995 and also had the same code in 1994, we did not include this in our analysis as we could not be certain that it was a new hip fracture or a recurring follow-up. After 1995, we took the first recorded fracture code in each calendar year and assessed if the patient had a previous code for the same fracture, or unspecified fracture, in the prior 365 days. If there were no codes for a prior fracture of the same type, or unspecified, in the prior 365 days, it was deemed an eligible new fracture, otherwise it was excluded. Additionally, for MOF, the first occurrence of a hip, clinical symptomatic vertebral, humerus, or forearm fracture was selected.

Statistical Analysis

Population demographics for the background population in calendar years 1995–2010 were obtained online from Statistics Denmark.[29] IRs (number of fractures/10,000 person years [PYs]), and corresponding 95% confidence intervals (95% CI), were calculated by dividing all cases of first recorded fractures during the calendar year over the average number of persons alive in that calendar year. For example, to calculate the denominator for the year 2010, we first summed the number of people alive on 1 January 2010 and those alive on 1 January 2011, then divided this sum by two. Gender-specific IRs were estimated in addition to site-specific fracture rates. While we did not produce age-specific rates, we were able to standardise the IRs to the annual Danish population over the age 50, using the Statistics Denmark data. This permits a comparison to a similar age distribution. Women-to-men incidence rate ratios (IRRs) were calculated for MOFs and determined by dividing the IR for women over the IR for men. The IRs were plotted over time both for MOFs, as well as specific fracture sites, and the plots were examined by visual assessment. Data were analysed using SAS version 9.3 (SAS Institute Inc. Cary, NC, USA).

d. Results

We identified a total of 422,380 MOFs in Danish adults over 50 between 1995 and 2010, where a sum of 101,177 fractures occurred among men, and 321,203 cases among women (Table 2.1); thus, females sustained 76.0% of all MOFs. There was a 4.5% relative increase in the total number of MOFs from 1995 to 2010, although apart from a spike in 2010, the numbers were dropping until 2009. The mean age at first occurrence of a MOF was 74.1 years, and the age distribution was constant across all years.

A general decline was observed in the IRs of MOFs for the whole population, where IRs dropped from 169.8 per 10,000 PYs in 1995 to 148.0 in 2010 (Table 2.1), as visualised in Figure 2.1. Among women, the rates for the MOF dropped during this 16-year study period from 242.8 to 211.5; however, it is worth mentioning that the rates had dropped even lower in the years 2008 and 2009 (IRs 188.3 and 186.2, respectively). For men, the MOF rates exhibited a smaller decrease from 82.9 in 1995 to 77.6 in 2010. The women-to-men rate ratio of MOFs decreased noticeably from 2.93 (95% CI, 2.85–3.01) in 1995 to 2.72 (95% CI, 2.65–2.80) in 2010 (Table 2.1).

Table 2.1. Absolute number and incidence rates of major osteoporotic fractures among Danish adults aged 50+, stratified by sex and calendar year (1995-2010).

	Total				Men				Women				W/M Ratio		
Calendar year	Number of fractures	IR per 10,000 PYs	95% CI		Number of fractures	IR per 10,000 PYs	95% CI		Number of fractures	IR per 10,000 PYs	95% CI		IRR W/M	95% CI	
1995	28,351	169.8	166.9	172.6	6323	82.9	80.0	85.9	22,028	242.8	238.2	247.4	2.93	2.85	3.01
1996	27,215	160.1	157.4	162.9	5908	75.8	73.1	78.6	21,307	231.5	227.1	236.0	3.05	2.97	3.14
1997	25,856	149.5	146.9	152.2	5850	73.5	70.9	76.3	20,006	214.3	210.1	218.6	2.91	2.83	3.00
1998	25,823	147.1	144.6	149.7	5850	72.2	69.6	74.9	19,973	211.3	207.1	215.5	2.93	2.84	3.01
1999	26,314	148.1	145.5	150.7	6141	74.7	72.1	77.4	20,173	211.3	207.1	215.5	2.83	2.75	2.91
2000	25,007	139.2	136.8	141.7	5925	71.1	68.6	73.7	19,082	198.1	194.1	202.2	2.79	2.71	2.87
2001	25,797	142.1	139.7	144.6	6004	71.1	68.6	73.7	19,793	203.8	199.8	207.9	2.87	2.78	2.95
2002	25,698	140.2	137.8	142.7	6211	72.7	70.2	75.3	19,487	199.3	195.3	203.3	2.74	2.66	2.82
2003	25,192	136.1	133.7	138.5	6198	71.6	70.0	75.2	18,994	192.7	188.8	196.7	2.69	2.61	2.77
2004	26,196	140.0	137.6	142.5	6446	73.6	71.0	76.2	19,750	198.6	194.7	202.6	2.70	2.63	2.78
2005	26,687	141.1	138.7	143.5	6603	74.4	71.8	77.0	20,084	200.2	196.2	204.2	2.69	2.62	2.77
2006	26,739	139.8	137.4	142.2	6558	72.8	70.4	75.4	20,181	199.2	195.4	203.2	2.74	2.66	2.81
2007	25,804	133.4	131.1	135.7	6538	71.6	69.2	74.2	19,266	188.5	184.7	192.3	2.63	2.56	2.71
2008	26,001	132.9	130.6	135.2	6569	71.0	68.6	73.5	19,432	188.3	184.6	192.2	2.65	2.58	2.73
2009	26,076	131.8	129.5	134.1	6681	71.3	68.9	73.8	19,395	186.2	182.5	190.0	2.61	2.54	2.69
2010	29,624	148.0	145.6	150.4	7372	77.6	75.1	80.2	22,252	211.5	207.5	215.5	2.72	2.65	2.80
Total	422,380				101,177				321,203						

CI: Confidence interval, IR: Incidence rate, IRR W/M: women to men ratio of incidence rate, PYs: Person years.

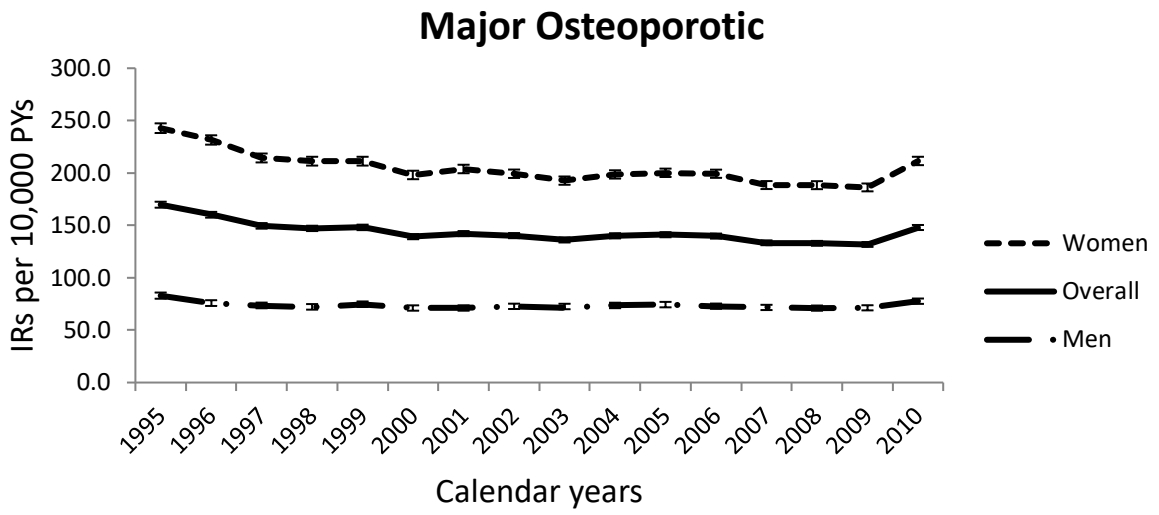

Figure 2.1. Incidence rates of major osteoporotic fractures for Danish adults aged 50+, stratified by sex and calendar year, 1995-2010. 95% confidence intervals are shown by small bars for each graph line and calendar year.
IR: incidence rates, PYs: person years.

Regarding hip fractures, a total of 152,571 cases were identified, where 72.3% (110,349) of all hip fractures occurred in women, and 27.7% (42,222) occurred in men. The mean age for occurrence of hip fracture among the whole population was 80.0 years. The overall hip fracture IRs decreased during the study period, i.e., 1995 to 2010 from 64.1 per 10,000 PYs to 45.5, respectively, and this decrease was more prominent in women (Figure 2.2a). We observed a 31% decline in hip fracture rates (from 87.2 to 59.9 per 10,000 PYs) among women and 19% decline (from 36.5 to 29.6 per 10,000 PYs) among men.

The IRs over time for the other MOF subsites are provided in Figure 2.2b–d. The trend for clinical vertebral fracture remained steady between 1995 and 2010, yet there was a slightly decreasing trend for women and an increasing trend for men (Figure 2.2b). Overall, humerus fracture rates remained stable, and this steady state was observed among both men and women (Figure 2.2c). Regarding forearm fractures, there is a declining trend for the whole study population from 1995 to 2009 (IRs dropped from 73.0 in 1995 to 55.5 in 2009), but there was a spike in 2010 (IRs 69.1) (Figure 2.2d). Women followed a similar trend to the overall trend regarding radius/ulna fracture, while for men, a smaller decrease was observed. The mean age of occurrence was 72.4 years for clinical vertebral fracture, 73.6 years for humerus fracture, and 69.6 years for radius/ulna fracture. Furthermore, females sustained 61.5% of all clinical vertebral fractures, 76.4% of all humerus fractures, and 82.1% of all radius/ulna fractures.

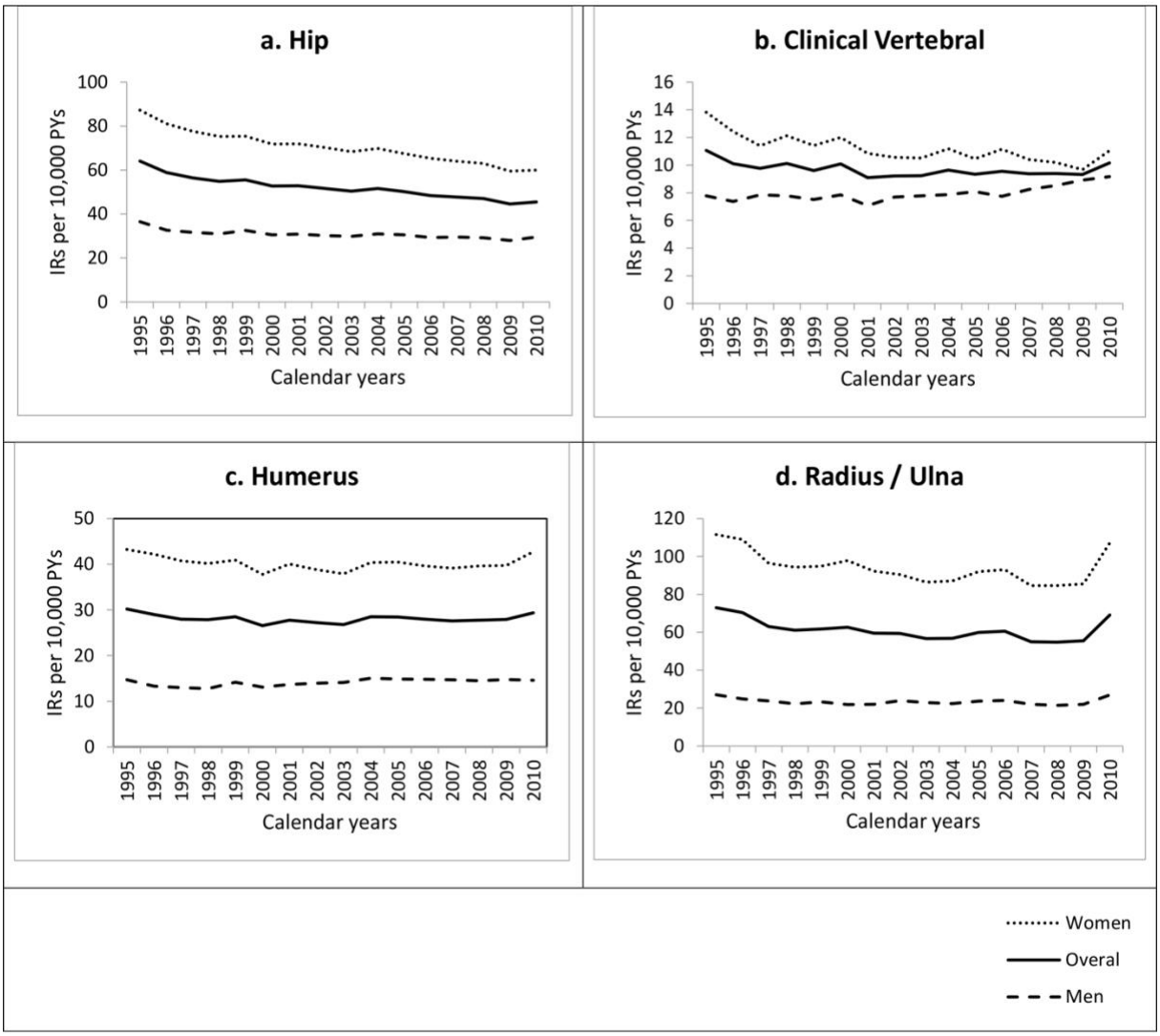

Figure 2.2. Incidence rates of major osteoporotic fracture subsites (a hip, b clinical vertebral, c humerus, d radius/ulna) for Danish adults aged 50+, stratified by sex and calendar year, 1995–2010.
IR: incidence rates, PYs: person years.

e. Discussion

In this study, we observed a reduction in IRs of MOFs from 1995 to 2010 in 50+ adults in Denmark, where the striking finding was a reduction in hip fracture rates in both men and women. Among women, the IRs of all MOFs have been declining, with exception of a rather steady state for humerus. But in men, apart from the gradually reducing hip and forearm fracture rates, steady rates for humerus fracture and a rising trend in vertebral fracture were noticed. The results of study by Driessen et al. in 2011 complement our observed decreasing trend in MOFs for Denmark.[28] Considering the ageing population, these findings are interesting, as we identify a decreasing incidence of MOFs between

1995 and 2011. Yet, importantly, there appears to be differences between males and females, particularly for hip fractures, in Denmark.

In general, our findings are in line with the present literature affirming a decrease in hip fracture rates in both men and women. We observed a 31% decline (from 87.2 to 59.9 per 10,000 PYs) among women and 19% decline (from 36.5 to 29.6) among men. Driessen et al. estimated even lower IRs for hip fracture in Denmark in the year 2011, as 57.1 per 10,000 PYs for women, and 29.2 for men.[28] In numerous studies from different countries, a levelling or decrease in age- and sex-specific hip fracture rates especially in the past two decades has been noticed too.[16-21,24] For instance, Leslie et al. showed that there was a 32% reduction in hip fracture rates among women in Canada (118.6 to 80.9 per 100,000 PYs), and 25% in men (68.2 to 51.1) between 1985 and 2005.[16] Additionally, Brauer et al. reported dropped rates from 964.2 per 100,000 PYs in 1986 to 793.5 in 2005 among 65+ women, and from 392.4 to 369.0 among 65+ men in the USA.[17] In most cases as we observed, the decrease was more profound among women, which could be hypothesised due to the higher number of women under anti-osteoporotic treatment or who received lifestyle modifications.

There are few studies that have looked at both hip and other MOFs. A study in the USA made comparisons after 20 years (1989–1991 and 2009–2011), and the reported decrease in hip fracture rates in both sexes and an increase in vertebral fractures in men were concordant with our results.[34] Another study in Canada (1986–2006) identified a similar result to ours regarding a global decrease in hip fracture rates and a decrease of forearm fractures among women.[35]

On the other hand, there are studies whose results are not concordant with our findings. Van der Velde et al. reported an increase of hip fracture rates in men and a steady state for women in the UK;[15] the differences could be due to a different version of ICD used for fracture classification (ICD-9 vs. 10) or a different kind of database (medical record-based Clinical Practice Research Datalink [CPRD]). A Japanese study showed not only substantially lower rates for limb OP fractures, and higher rates of vertebral cases, but also an increasing trend in hip fractures since the 1990s.[36] Two other studies from Japan and Singapore showed similar results with increasing tendencies for hip fracture over the 1990s and 2000s.[37,38] Interestingly, there was a notable difference between East and West regarding change of rates of hip fracture in the past decades, where the exact reason for these trend discrepancies is not clear.[39,40]

Our study period (i.e., the 1990s and 2000s) was a crucial time span as it saw extensive developments in management of osteoporosis, including bisphosphonates coming to the market, awareness of osteoporosis management grew, and treatment guidelines underwent a number of revisions.[41,42] Based on the guidelines for osteoporosis treatment in Denmark, the suggested daily intake of calcium for men with osteoporosis is lower than postmenopausal women at risk (800–1000 mg vs. 1000–1200 mg, respectively), but the first line treatment for both sexes is alendronate, and in case of severe disease, anabolic treatment is indicated.[43,44] Nevertheless, osteoporosis has been traditionally considered a women's only disease, and it could be hypothesised that a decrease in hip fractures due to preventive medication may be stronger among women than men. Numerous studies have already shown the effectiveness of anti-osteoporotic therapy (including bisphosphonates) on fracture prevention; however, there are studies which reported only a small role of these medication in the reduction of hip fracture rates.[24,45-47] So, the extent to which anti-osteoporotic therapy may affect rates of OP fractures, or whether it could have a role in the present discrepancies among men and women, requires further investigation.

Beside anti-osteoporotic therapy, there might be other factors which contributed to the mostly declining OP fracture trend in Denmark. An increasing proportion of 50+ individuals was born after the World War II, and grew up under better nutritional states and physical activities (sport classes introduced at schools, etc.), which might help to improve their peak bone mass. Also, the next generations are being guided by physicians on the importance of bone health as we age, and this could end up in positive effects including better use of Ca/Vit D supplements, and more adherence to anti-osteoporotic therapies. These among others resulted in a lower rate of fracture despite an ageing population. Still, interventions such as more ubiquitous use of devices that reduce risk of falling in frail and elderly, such as walk aids, could play a role. These hypothesised factors are beyond the scope of this study and need further investigation.

As stated above, the economic burden of OP fractures is substantial and many reports suggest this will increase over the coming years mostly because of an ageing population.[2,4-9] Studies showed that healthcare expenditures associated with an OP fracture in the USA are twice as high compared to patients only affected with osteoporosis and are threefold higher compared to the general population.[9] It has also been shown that the hospital costs of OP fractures were higher compared to similar ageing ailments such as myocardial infarction, stroke, or breast cancer.[5] From €1.6 billion total costs of OP fractures in Denmark in 2011, just €628 million (40.2%) was spent for

men;[10] but based on our results, there was an increase in the total number of fractures in Denmark, the OP fracture rates are not declining among men with the same rate observed in women, and the women to men ratio for MOF rates were noticeably decreased from 2.93 to 2.72 between 1995 and 2010. Considering all these, it could be expected that healthcare expenditures for osteoporosis and OP fractures among men might be a more serious burden in the near future.

This study had many strengths. The database used provided the opportunity of studying all fracture cases reported to hospitals in Denmark in this time period, and it has already proved to be reliable and valid.[31] This is one of the few studies that examined not only hip but all MOFs. Again, the duration of study is one of the longest in literature with 16 years of follow- up time. We were also able to stratify IRs by fracture sites. All these resulted in a comprehensive study that could be used for national and international policy-making purposes, including improvements of healthcare services, and better estimation of OP fracture-associated costs.

We had also some limitations in this study. To minimise double counting, we excluded fractures of the same type within 1 year. While this decision was made to improve the likelihood that we would capture new fractures as opposed to follow-up visits, we recognise that this may have resulted in an underestimation of the true fracture rate as we may have excluded some new fractures. In case of clinical vertebral fracture, this underestimation could be even worse, as the evidence suggests the majority of vertebral fractures do not immediately come to clinical attention.[48] On the other hand, there is this possibility that we overestimated the clinical vertebral fractures, because with advancement of spine imaging utilisation in recent years, there are more chances to detect old previously unrecognised fractures, and so, some prevalent vertebral fracture might be misclassified as incident fractures. Also, our IRs were not adjusted beyond the factors explained in this article, as we were not able to examine the influence of any further mediating or confounding factor on the observed trends. Similarly, we have limited explanatory information for seemingly anomalous spikes. For example, the only explanation for the spike observed in trends of radius/ulna fracture in the year 2010 (Figure 2.2d) was the record-breaking freezing winter happened in Europe in 2010 (potentially resulting in higher number of falls),[49] as no other coding or reporting issue was detected.

In conclusion, we did a series of cross-sectional analyses showing the secular trends of MOF rates in Denmark between 1995 and 2010. The results showed a general decline in MOF rates and a decreasing trend in hip fracture rates for both men and women, which is

in line with the study by Driessen et al. in Denmark for the year 2011, and many other studies in Nordic and Western countries. Also, we noticed a lower rate of decrease of hip fracture trends and an increasing trend in rates of vertebral fracture among men, which was accompanied by a reducing women-to-men IRR in the study period. Considering these observations and the major economic burden that accompanies this devastating disease, more attention should be paid to MOFs, especially in men.

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CHAPTER 3

The association of oral bisphosphonate use with mortality risk following a major osteoporotic fracture in the United Kingdom: population-based cohort study

Shahab Abtahi

Andrea M Burden

Piet Geusens

Joop P van den Bergh

Tjeerd P van Staa

Frank de Vries

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a. Abstract

Background

Bisphosphonates (BPs) might have extra benefits in reducing mortality because of their anti-atherosclerotic effects, but studies reported conflicting results. We investigated the association between oral BP use and mortality risk following a major osteoporotic fracture (MOF) in the United Kingdom.

Methods

This was a population-based cohort study. In total, 163,273 adults aged 50 years and older with a MOF were included between 2000 and 2018 from the Clinical Practice Research Datalink in the United Kingdom. Cox proportional-hazards models were used to estimate the risk of all-cause mortality in current (0–6 months), recent (7–12 months), and past (>1 year) exposures to oral BPs after non-hip MOF and hip fracture. In addition, stratification by sex, BP type, and duration of follow-up was performed.

Results

Compared with never users of oral BPs, current BP use was associated with a 7% higher all-cause mortality risk after non-hip MOF, whereas a 28% lower all-cause mortality risk was observed after hip fracture. Past BP exposure was associated with a 14% and 42% lower risk after non-hip MOF and hip fracture, respectively. When considering only the first 5 years of follow-up, mortality risk associated with current BP use was significantly lower for both fracture groups, and the greatest reduction in mortality risk was observed within the first year. Women had slightly lower risk compared with men.

Conclusions

We found a slight increased risk of all-cause mortality with current BP exposure after a non-hip MOF; however, a protective effect was observed following a hip fracture. Both the timing and the effect size of an association based on the anti-atherosclerotic hypothesis of BPs are not supported by our results. The decreasing trend of the mortality risk with shorter durations of follow-up suggests that the observed association is likely due to unknown distortion or unknown pleiotropic properties of BPs.

b. Introduction

Major osteoporotic fractures (MOFs) are the main consequence of osteoporosis, with devastating results for the affected patients, including a significant increased risk of mortality.[1] Occurrence of a hip fracture markedly increases the risk of subsequent fractures (relative risks of 2–7 compared with the general population).[2,3] This may increase mortality after fracture even more.[4] Approximately 33% of men and 22% of women suffering a hip fracture will die within 1 year, and 51% of men and 39% of women sustaining an MOF will die within 5 years.[5-7] But the reasons of this high mortality risk and the ways to prevent it are still not fully understood.

Secondary fracture prevention with anti-osteoporotic treatment, such as bisphosphonates (BPs), can prevent subsequent fractures.[8,9] Given the strong association between fracture and mortality in older individuals, it has been hypothesised that use of BPs may lower the risk of mortality after a fracture. Apart from preventing secondary fractures, the main underlying potential mechanism that could explain the mortality-reducing benefits of BPs is protection against cardiovascular events. This may mostly be the result of lowering lipid profile and decreasing arterial wall calcification.[10-14] However, data from randomised clinical trials (RCTs) yield conflicting evidence.[15,16] Although a *post hoc* analysis of the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) trial showed a 28% statistically significant mortality reduction among users of zoledronic acid after hip fracture,[15] the design, analysis, and conduct of this study have been heavily criticised.[17]

Because the underlying mechanism for mortality reduction is likely similar for various BPs, we sought to further test the hypothesis of an association between all-cause mortality and the initiation of oral BPs following a MOF in a large representative real-life cohort study. Thus, the aim of this study was to examine if oral BP treatment was associated with a lower all-cause mortality risk after a non-hip MOF or hip fracture.

c. Methods

Data Source

This was a cohort study using the Clinical Practice Research Datalink (CPRD; www.cprd.com). The CPRD contains medical records of 674 practices in the United Kingdom (UK) representing approximately 6.9% of the total population.[18] Recorded data

includes patient demographics, lifestyle parameters, medical history, laboratory test results, prescription details, specialist referrals, hospital admissions, and major outcomes since 1987. Previous studies showed a high validity of using CPRD data regarding MOFs.[19]

Study Population

The study population included all patients aged 50 years and older with a record of their first fracture between 01 January 2000 and 31 December 2018. The index date (start of study follow-up) was defined as the date of first recorded MOF (i.e., a fracture of the hip/femur, vertebrae, humerus, or radius/ulna). We further classified fractures by hip or non-hip MOF (i.e., vertebral, humerus, radius/ulna, or femur excluding hip). Patients with any fracture prior to age 50 years and those with use of oral BPs prior to the index date were excluded (adhering to new-user design). Also, to allow for at least 1 year of follow-up, we excluded those with an index fracture in 2018.

Exposure and Outcome

The exposure of interest was the use of oral BPs after index date, which was assessed time-dependently. First, the total follow-up time for each patient was established by considering the time he/she had entered the study (i.e., index date) and the time follow-up ends, which could be the end of study period, the date of transfer out of the practice area, or death (the outcome of interest), whichever came first. The total follow-up time was then divided into 180-day "periods" starting from the index date. Exposure status to BPs was defined as the following: "current exposure" means that the patient has received his most recent BP prescription during the past 6 months before the start of a period. "Recent exposure" means that the patient has taken his most recent BP prescription 7–12 months before, and "past exposure" means that the patient has stopped taking BPs for >1 year before. Using this model, patient exposure is then classified in a dynamic time-dependent manner, meaning they can move between exposure groups (current, recent, past) throughout time. However, once a patient is classified as a current user, he cannot return to the never user group. The total person-time in each category is accounted for and contributes to the Cox proportional-hazards model. In addition, BP use was broken down into nitrogen-containing BPs (n-BP, alendronate, and risedronate) and the non-nitrogen-containing BP (non-n-BP) etidronate. The outcome of interest was all-cause mortality as recorded -in the CPRD.

Potential Confounders

Age was considered time dependently, whereas sex, smoking status, alcohol use, and body mass index were determined at index date. A history of the following comorbidities was assessed at the start of each interval: cerebrovascular disease, chronic kidney disease, chronic obstructive pulmonary disease, dementia, diabetes mellitus, epilepsy, heart failure, ischaemic heart disease, major infections (sepsis, meningitis, upper and lower respiratory tract infections), or malignant neoplasms (excluding nonmelanoma skin cancers). In addition, the use of following medications in the 6 months prior was included: antihypertensives, anti-Parkinson's medications, glucocorticoids, loop diuretics, psychotropic drugs (antipsychotics, anxiolytics, hypnotics, and sedatives), and statins. Confounders were included in the final model if they changed the beta coefficient of the association >5% or based on expert opinion. Collinearity between potential confounders was assessed.

Statistical Analysis

Cox proportional-hazards models were used to assess the risk of all-cause mortality following fracture associated with current BP use vs never use (using the SAS PHREG procedure). To avoid immortal time bias, all patient time in each exposure status was incorporated into the model and all patient time prior to first BP use was defined as never use. Analyses were stratified by index fracture type (non-hip MOF vs hip) and sex.

In secondary analyses, current BP exposure was stratified by type of oral BP (n-BP or non-n-BP). A sensitivity analysis assessed 1-year and 5-year all-cause mortality risk, censoring the total follow-up period at 1 or 5 years, respectively.

Data were analysed using SAS v 9.3 (SAS Institute Inc, Cary, NC). This study was reviewed and approved by the Independent Scientific Advisory Committee of the Clinical Practice Research Datalink (reference 18_115), which is responsible for reviewing protocols for scientific quality.

d. Results

A total of 163,273 patients were included in our cohort with a first MOF between 2000 and 2018 (Figure 3.1). Of the eligible fractures, 119,107 (72.9%) were non-hip MOF and 44,166 (27.1%) were hip fractures (Table 3.1). The mean age of patients with a non-hip

MOF and hip fracture were 70 and 81 years, respectively. Female patients accounted for 74% of the non-hip MOF and 69% of hip fracture patients. A similar pattern of smoking was observed among both fracture groups, with less than one quarter of patients being current smokers. Frequent comorbidity and comedication included major infections and antihypertensives. The non-hip MOF comprised 16,378 vertebral fractures (13.8%), 5294 femur fractures (4.4%), 33,665 humerus fractures (28.3%), and 63,770 radius/ulna fractures (53.5%). The follow-up time for BP users was 7.6 years in the non-hip MOF and 5.7 years in the hip fracture group. The average duration of BP use was 3.3 years among non-hip MOF patients and 2.7 years among hip fracture patients.

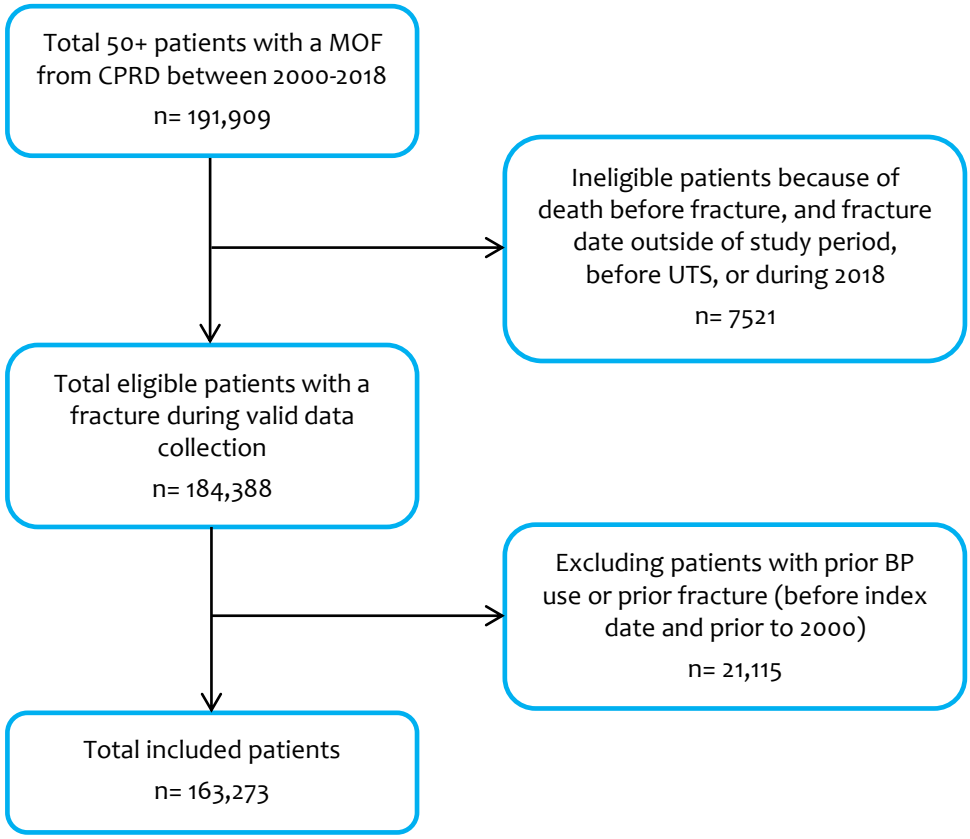

Figure 3.1. Flowchart on establishment of patient population. All patients aged over 50 years from the CPRD in the UK who had a major osteoporotic fracture between 2000 and 2018, and started bisphosphonate use after the (index, first) fracture are included in the study.
50+ patients: patients aged over 50 years, UTS: up to standard time of the CPRD practice.

Table 3.1. Baseline characteristics of participants according to index fracture site.

	Non-hip MOF		Hip fracture	
	N	% - SD	N	% - SD
Number of events	119,107		44,166	
Mean follow-up (years, SD)	6.7	4.8	3.9	4.0
Mean age (SD)	70.1	11.9	80.5	10.3
Female	88,415	74.2	30,645	69.4
Mean BMI (SD)	26.6	5.5	24.3	4.9
Smoking status				
Never	70,241	59.0	25,593	57.9
Past	17,856	15.0	6878	15.6
Current	29,056	24.4	9443	21.4
Missing	1954	1.6	2252	5.1
Alcohol use				
Yes	80,188	67.3	22,786	51.6
No	28,937	24.3	13,921	31.5
Missing	9982	8.4	7459	16.9
Comorbidities*				
Cerebrovascular disease	10,825	9.1	7908	17.9
Chronic kidney disease	11,168	9.4	7850	17.8
COPD	8269	6.9	4198	9.5
Dementia	4395	3.7	6142	13.9
Diabetes mellitus	12,820	10.8	6247	14.1
Epilepsy	3630	3.0	1520	3.4
Heart failure	3284	2.8	2626	5.9
Ischaemic heart disease	15,268	12.8	8218	18.6
Major infection	31,928	26.8	10,660	24.1
Malignant neoplasm	14,816	12.4	7568	17.1
Prior fracture	0	0.0	0	0.0
Medications†				
Antihypertensives‡	49,832	41.8	22,195	50.3
Anti-Parkinson's	1428	1.2	1325	3.0
BP history	0	0.0	0	0.0
Loop diuretics	13,933	11.7	9790	22.2
Glucocorticoids	5944	5.0	2325	5.3
Psychotropics	16,299	13.7	9580	21.7
Statins	30,354	25.5	11,820	26.8
Fracture at baseline				
Hip	n/a	n/a	44,166	100
Vertebral	16,378	13.8	n/a	n/a
Femur	5294	4.4	n/a	n/a
Humerus	33,665	28.3	n/a	n/a
Radius/Ulna	63,770	53.5	n/a	n/a

BMI: body mass index, BP: bisphosphonates, COPD: Chronic obstructive pulmonary disease, MOF: Major osteoporotic fracture, SD: Standard deviation.

* Disease comorbidities happened ever before.

† Medications taken 6 months before index fracture.

‡ Excluding loop diuretics

Table 3.2 shows that current use of oral BPs was associated with a 7% higher risk of all-cause mortality among patients with an index non-hip MOF compared with never use (adjusted hazard ratio [adj. HR] 1.07, 95% confidence interval [CI] 1.03–1.10). Mortality risk in the recent exposure group was also higher compared with the reference group (adj. HR 1.25, 95% CI 1.16–1.36), but past exposure was associated with statistically significant lower risk (adj. HR 0.86, 95% CI 0.83–0.90). Among patients who had sustained a hip fracture, current BP exposure was associated with a significant 28% lower mortality risk compared with never BP exposure (adj. HR 0.72, 95% CI 0.70–0.75), whereas recent and past exposures were associated with 21% and 42% lower risk, respectively. The HR of past exposure was statistically lower compared with recent and current exposure. In general, mortality risk tended to be slightly lower among women as compared with men.

Stratifying our analysis by nitrogen-containing BPs showed similar results to the primary analysis. Analyses with the non-n-BP etidronate lacked statistical power due to low frequency of exposure (data not shown).

The 5-year analysis showed a significant reduction in mortality risk with current BP exposure after non-hip MOF (adj. HR 0.91, 95% CI 0.87–0.95) compared with never use (Table 3.3). Following a hip fracture, all-cause mortality risk associated with current exposure shifted further from the null value with a significant 39% reduction compared to never use (adj. HR 0.61, 95% CI 0.59–0.64).

The 1-year mortality risk (data not shown) in the non-hip MOF group showed a 34% lower risk of all-cause mortality with current BP exposure (adj. HR 0.66, 95% CI 0.60–0.72), whereas it was not lower with recent exposure (adj. HR 0.23, 95% CI 0.03–1.61). The 1-year risk of all-cause mortality among hip fracture patients was considerably lower for current BP exposure (adj. HR 0.41, 95% CI 0.37–0.44), but not for recent (adj. HR 0.79, 95% CI 0.33–1.90).

Table 3.2. Risk of all-cause mortality following an index fracture (non-hip MOF and hip), stratified by fracture type, gender and oral BP exposure status.

	Events	IR per 1000 PYs	Age (/Sex) adjusted Analysis HR (95%CI)*	Final adjusted Model HR (95%CI)†
Non-hip MOF				
BP Never exposure‡	21,940	34.6	Reference	Reference
BP Past exposure	2341	36.1	**0.85 (0.81-0.89)**	**0.86 (0.83-0.90)**§
BP Recent exposure	627	57.9	**1.40 (1.30-1.52)**	**1.25 (1.16-1.36)**§
BP Current exposure¶	5219	57.4	**1.32 (1.28-1.37)**	**1.07 (1.03-1.10)**§
Females**				
BP Never exposure	14,535	31.4	Reference	Reference
BP Past exposure	1933	33.2	**0.82 (0.78-0.86)**	**0.85 (0.81-0.89)**§
BP Recent exposure	480	50.2	**1.30 (1.19-1.43)**	**1.19 (1.09-1.31)**§
BP Current exposure¶	4003	50.1	**1.25 (1.21-1.30)**	**1.04 (1.01-1.08)**§
Males**				
BP Never exposure	7405	43.2	Reference	Reference
BP Past exposure	408	61.7	0.93 (0.84-1.03)	**0.88 (0.80-0.98)**§
BP Recent exposure	147	115.1	**1.81 (1.53-2.13)**	**1.47 (1.25-1.73)**§
BP Current exposure¶	1216	109.7	**1.61 (1.52-1.72)**	**1.14 (1.07-1.21)**§
Hip Fracture				
BP Never exposure‡	16,977	152.3	Reference	Reference
BP Past exposure	1440	62.5	**0.51 (0.48-0.53)**	**0.58 (0.55-0.62)**
BP Recent exposure	398	96.2	**0.75 (0.68-0.83)**	**0.79 (0.71-0.87)**††
BP Current exposure¶	3778	103.5	**0.76 (0.73-0.78)**	**0.72 (0.70-0.75)**††
Females**				
BP Never exposure	10,942	145.1	Reference	Reference
BP Past exposure	1123	59.3	**0.50 (0.47-0.54)**	**0.58 (0.54-0.61)**§
BP Recent exposure	305	91.8	**0.76 (0.68-0.85)**	**0.81 (0.72-0.90)**§
BP Current exposure¶	2738	92.4	**0.71 (0.68-0.74)**	**0.69 (0.66-0.72)**§
Males**				
BP Never exposure	6035	167.5	Reference	Reference
BP Past exposure	317	77.0	**0.49 (0.43-0.55)**	**0.58 (0.52-0.65)**
BP Recent exposure	93	114.5	**0.69 (0.56-0.85)**	**0.73 (0.59-0.89)**
BP Current exposure¶	1040	151.2	**0.87 (0.81-0.93)**	**0.80 (0.75-0.85)**††

BP: Bisphosphonate, CI: Confidence interval, HR: hazard ratio, IR: Incidence rate, MOF: Major osteoporotic fracture, PYs: person years. Statistically significant hazard ratios are shown in bold.

* Adjusted only for age where stratified by sex.

† Adjusted for sex, body mass index, smoking status and alcohol use at baseline, and the following variables time-dependently: age and use of antihypertensives, anti-Parkinson's medications, loop diuretics, glucocorticoids, psychotropics, statins in the previous 6-months, and history of malignant neoplasm, dementia (for hip fracture group), and chronic obstructive pulmonary disease (for non-hip MOF group).

‡ Never exposure denotes to no known use of oral BPs, whereas past, recent, and current exposures refer to taking oral BPs in the time window >12 months, 6-12 months, and 0-6 month prior to the start of a period, respectively.

§ HR from each BP exposure status is statistically different from the other exposure status in the same model, by Wald test, P <0.05.

¶ Not stratified by nitrogen containing agents due to small cell sizes and reporting restrictions in the CPRD for privacy reasons.

** Patients from each sex are compared only with same sex cohorts.

†† HR is statistically different from the past exposure status, by Wald test, P <0.05.

Table 3.3. Five-year risk of all-cause mortality following an index fracture (non-hip MOF and hip), by oral BP exposure status.

	Events	IR per 1000 PYs	Age/Sex adjusted Analysis HR (95%CI)	Final adjusted Model* HR (95%CI)
Non-hip MOF				
BP Never exposure†	16,162	42.5	Reference	Reference
BP Past exposure	753	43.2	**0.73 (0.68-0.79)**	**0.76 (0.70-0.82)**
BP Recent exposure	342	55.9	1.00 (0.90-1.12)	0.98 (0.88-1.09)‡
BP Current exposure	3135	56.5	1.03 (0.99-1.07)	**0.91 (0.87-0.95)**‡
Hip Fracture				
BP Never exposure†	14,946	183.1	Reference	Reference
BP Past exposure	644	75.7	**0.43 (0.40-0.47)**	**0.50 (0.47-0.55)**
BP Recent exposure	279	95.7	**0.56 (0.50-0.64)**	**0.62 (0.55-0.70)**‡
BP Current exposure	2831	103.3	**0.60 (0.58-0.63)**	**0.61 (0.59-0.64)**‡

BP: Bisphosphonate, CI: Confidence interval, HR: hazard ratio, IR: Incidence rate, MOF: Major osteoporotic fracture, PYs: person years. Statistically significant hazard ratios are shown in bold.

* Adjusted for sex, body mass index, smoking status and alcohol use at baseline, and the following variables time-dependently: age and use of antihypertensives, anti-Parkinson's medications, loop diuretics, glucocorticoids, psychotropics, statins in the previous 6 months, and history of malignant neoplasm, dementia (for hip fracture group), and chronic obstructive pulmonary disease (for non-hip MOF group).

† Never exposure denotes to no known use of oral BPs, while past, recent, and current exposures refer to taking oral BPs in the time window >12 months, 6-12 months, and 0-6 month prior to the start of a period, respectively.

‡ HR is statistically different from the past exposure status, by Wald test, P <0.05.

e. Discussion

This study identified that current oral BP exposure was associated with a 7% higher all-cause mortality risk after a non-hip MOF and with a 28% lower mortality risk after a hip fracture. When the follow-up time was censored at 1 and 5 years, a significant protective effect was observed in both fracture groups, with a trend away from the null with decreasing follow-up time: mortality risk with current BP use in the non-hip MOF group first dropped to a 9% reduction in the 5-year and then to 34% reduction in the 1-year analysis. In the case of hip fracture, mortality risk with current BP use first dropped to a 39% reduction in the 5-year and then to 59% in the 1-year analysis.

Our finding of a higher mortality risk among non-hip MOF patients with current BP exposure is not in line with findings from 2 meta-analyses of RCTs in 2010 (n=25,072) and 2018 (n=63,371), which showed no association between all-cause mortality and BP use vs placebo, yielding a pooled relative risk of 0.91 (95% CI 0.80–1.03) and 0.95 (95% CI 0.86–1.04), respectively.[20,21] However, the 28% lower mortality risk after hip fracture with current BP exposure in our study could be in line with those from the HORIZON trial, which showed a 28% reduced risk of all-cause mortality after 16 months of zoledronic acid use (HR 0.72; 95% CI 0.56–0.93), and was included in both meta-analyses.[15] However, RCTs

have normally evaluated BP use in individual patients in a time-fixed model, while we assessed person-time within exposure states in a time-dependent analysis.

Our results in patients with hip fractures are in line with those from other observational studies in the field. In a recent cohort study by van Geel et al, a 21% reduction in mortality risk (HR 0.79, 95% CI 0.64–0.97) was reported with oral BP use compared to calcium and vitamin D use among fracture patients.[22] Using Danish national health register data, Bondo et al observed survival benefits for patients who had taken BP both before and after hip fracture, although their results may be distorted due to channelling or immortal time bias.[23] Sambrook et al found 27% mortality reduction for oral BP use compared to no use in frail older people (mean age=86 years), and an even higher reduction (80%) in those only after hip fracture, although the number of BP users was very low (n=17).[24,25]

However, BPs are not always found in literature to be beneficial on mortality risk reduction. Steinbuch et al reported no significant risk reduction in all-cause mortality for risedronate in patients with a history of vertebral or hip fracture or with low bone mass, although there were some benefits in case of stroke and cardiovascular events reduction.[14] In "primary prevention arm" of the HORIZON trial, Black et al reported a small but not statistically significant increase in death numbers by using zoledronic acid and raised risk of serious atrial fibrillation adverse events.[16] This might be comparable with our findings regarding the 7% higher mortality risk with current BP use in non-hip MOF patients. Although similar results regarding atrial fibrillation events have been reported from the Fracture Intervention Trial by using alendronate, this unconfirmed association has no apparent biologic plausibility, and we do not expect this happening to our patients.[26]

There is some evidence from the literature regarding the anti-atherosclerotic effects of BPs, such as lowering low-density lipoprotein (LDL) cholesterol levels, decreasing arterial wall calcification, enhancing endothelial nitric oxide production, and reducing monocytes and platelets interactions with epithelial cells.[12,13,27-30] If cardiovascular effects of BPs would be comparable to those of statins, there should be (indirect) evidence of comparability of the timing and size of the effect. Large RCTs showed that the statin-induced reductions of mortality occurred after 11–24 months of use, which suggests that the mortality reduction starting after 16 months of BP use in the HORIZON trial may be plausible.[31-34] If we assume this timing to be true, part of our observations, such as the lower mortality among hip fracture patients (with 2.7 years of BP use) might be in line with the explained anti-atherosclerotic hypothesis of BPs. However, even among hip fracture patients, we observed the lowest mortality risk within 1-year analysis, which does

not support this hypothesis as the proper timing has not been met. Also, the expected effect size is not comparable: large meta-analyses of RCTs comparing statin use with placebo reported an overall 13% reduction of all-cause mortality, or 9% mortality reduction per 1.0 mmol/L reduction of LDL cholesterol.[35,36] BPs have been shown to lower LDL in a range from no effect up to a reduction of approximately 0.34 mmol/L, after 6–12 months of use.[12,37,38] In the best-case scenario, this would then translate into a 3% lower risk of all-cause mortality,[36] which is around 9 times lower than the observed 28% reduction in the HORIZON trial and results of our study in the hip fracture patients.[15] Nevertheless, BPs could have other anti-atherosclerotic effects. A meta-analysis showed BPs have decreased aortic calcification by 11.2% compared with untreated individuals,[13] and coronary artery calcification is a well-known risk factor for all-cause mortality.[39,40]

Although some causal effect of BPs on all-cause mortality cannot be excluded, it is more likely that unmeasured distortion explains the largest proportion of the observed risk reductions in the HORIZON trial and our study. The HORIZON trial was later criticised because of some inconsistencies regarding the interpretation of data, early termination of the trial, and the high number of withdrawal or loss to follow-up.[17] Observational studies may have been confounded by selective prescribing of BPs to patients at lower risk of mortality.[41] Physicians rarely prescribe oral BPs to very ill and hospitalised patients. This can culminate in a spurious survival benefit for exposure drug as the very ill patients are unlikely to receive preventative medication. Moreover, healthy user and healthy adherer bias could also play a role.[42,43] Previous studies have suggested that patients who start a preventative medication or who are more adherent are generally healthier than patients who are not, and therefore may be at lower risk of mortality.[44] These bias scenarios, in addition to the high mortality rates in the early days after a fracture, could best explain the lowest HRs with 1-year analysis and the observed decreasing trend of HRs with shorter durations of follow-up. Moreover, assuming these bias scenarios, the generally lower HRs among the hip fracture patients, compared with the non-hip MOF patients, could be partly explained by longer hospitalisation and higher mortality rates after a hip fracture compared with other MOFs.[45] Hip fracture patients are generally sicker with higher chance of mortality and, hence, are less likely to receive BPs.

Our study had several strengths. First, we used the CPRD for data collection, which is one of the world's largest primary care databases. Second, as our study period was relatively long (i.e., 19 years [2000-2018]), we could include more than 163,000 patients in the study cohort, which is by far the largest study sample among observational studies in this topic. Also, we considered not only hip but all MOFs, making this the first study to our

knowledge to evaluate the mortality after non-hip MOF with BP use. Furthermore, the statistical analysis was performed time-dependently, which means it incorporated all person time, avoiding immortal time bias.[46] Moreover, we used different approaches to test the underlying hypothesis of a causal effect,[47] such as assessing the same research question in two cohorts with different fracture sites and testing the underlying pharmacologic hypothesis with analyses that evaluated the onset and ending of the effect, which the other observational studies did not do.[14,22-25]

This study had also some limitations. One objective was to differentiate between n-BP or non-n-BP respecting their effect on mortality reduction, which was not feasible due to low numbers of non-n-BP use in the UK. As mentioned above, we could not exclude those dying shortly after having a fracture, and this could result in distortion (i.e., higher estimates of drug effect than what it should be, especially with shorter durations of follow-up). Moreover, we could not measure or adjust for healthy user or healthy adherer effect, and we had no information about the cause of death, socioeconomic status of patients, or other similar indicators from CPRD. Nonetheless, we tried to overcome this by running multiple analyses that tested the same hypothesis indirectly in different ways, taking into account the hypothesised pharmacologic effect.

In conclusion, although we found a higher risk of all-cause mortality with current BP exposure after non-hip MOF, a protective effect was observed with 1 and 5 years of follow-up. After a hip fracture, current BP exposure was associated with lower mortality risk in all analyses. Compared to statin studies and the effect of BPs on LDL reduction or arterial calcification, both the timing and the effect size of such an association is not supported by our results. Rather, the substantially lower mortality risk in the 1-year analysis and the decreasing trend of HRs with shorter durations of follow-up suggest that the vast majority of the observed association between BP use and mortality risk after fracture is explained by unknown distortion or unknown pleiotropic properties of BPs. We recommend that future studies focus on evaluation of these hypotheses to elucidate alternative mechanisms of potential pleiotropic effects of BPs, and on explaining potential unmeasured distortion.

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CHAPTER 4

Impact of cumulative exposure to high-dose oral glucocorticoids on fracture risk in Denmark: a population-based case-control study

M Amine Amiche

Shahab Abtahi

Johanna H M Driessen

Peter Vestergaard

Frank de Vries

Suzanne M Cadarette

Andrea M Burden

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a. Abstract

Background

The effect of cumulative exposure to high daily doses of oral glucocorticoids on fracture risk remains debated. We therefore aimed to examine the hip fracture risk associated with short courses and heavy use of high-dosed oral glucocorticoids.

Methods

We conducted a population-based case-control study using the Danish National Health Service data, 1996–2011. Cases were those aged ≥18 years who sustained a hip (primary outcome) fracture (n=81,342). Vertebral and forearm fractures were considered in secondary analyses. Controls (matched 1:1) were those without a fracture. Average daily dose (DD) and total cumulative dose (CD) were calculated among current oral glucocorticoid users. Among patients with a high daily dose (DD ≥15 mg), we identified short-course users as those with a CD <1 g and heavy users as those with a CD ≥1 g. We estimated adjusted odds ratio (adj. OR) of fracture with current glucocorticoid use compared to never-use, using conditional logistic regression.

Results

A high DD (≥15 mg) and high CD (≥1 g) were independently associated with an increased hip fracture risk (adj. OR 2.5; 95% CI 2.2–2.9; adj. OR 1.6; 95% CI 1.5–1.8, respectively). However, the risk was substantially increased among heavy users (DD ≥15 mg and CD ≥1 g: adj. OR 2.9; 95%CI 2.5–3.4) as compared to short-course users (DD ≥15 mg and CD <1 g: adj. OR 1.4; 95%CI 1.1–1.9). Associations were stronger for vertebral fractures, yet little association was identified for forearm fractures.

Conclusions

Among patients receiving a high DD (≥15 mg), heavy users (≥1 g CD) showed the most substantial increase in hip fracture risk. Among those receiving high DD, a threshold of 1 g CD may identify heavy users that are candidates for focused fracture management services.

b. Introduction

Oral glucocorticoids (GCs) are widely prescribed drugs with established clinical benefits for patients with chronic inflammatory and autoimmune diseases, such as chronic respiratory disease, inflammatory arthritis, and dermatologic disease.[1–3] It is estimated that the prevalence of oral GC use among adults ranges between 1.5 and 3% worldwide.[4] Unfortunately, oral GC use is limited by significant side effects that usually appear after an extended period of exposure.[5–7] GC-induced musculoskeletal disorders, such as osteoporosis, are a major problem and a well-documented side effect.[8–13] Indeed, it is estimated that oral GCs are associated with a 30 to 120% increased risk of hip fracture and 2- to 3-fold increase in vertebral fracture risk compared with non-use.[14–16] For inflammatory conditions, short courses of high doses with tapering regimens are often required for symptom management. While it is well-known that oral GC-induced bone loss and fracture risk is dose-dependent,[15,17] the relationship with the cumulative exposure is less well established.[15,17]

To minimise fracture risk, clinical practice guidelines recommend that osteoporosis pharmacotherapy should be given to patients that are expected to receive a daily dose of 5 to 7.5 mg of prednisone equivalent for 3–6 months.[10,18–20] However, in a real-world setting, patients with inflammatory conditions often receive intermittent short courses (7–14 days) of high doses (40–60 mg per day), or a continuous low dose (5–10 mg per day) for longer periods until remission of the underlying disease.[21–23] In both cases, this may result in a similar cumulative exposure; however, the impact on bone and fracture may differ due to the daily dose.

To date, data related to the risk of bone fracture associated with these different patterns of exposure are limited, and it is often difficult to examine different cumulative and daily dose exposure patterns in database research. Thus, in this study using population-level data from Denmark, we sought to examine the association between the daily dose and cumulative exposure to oral GCs and the risk of fracture. Hip fracture is the most burdensome osteoporotic (OP) fracture, and its identification using hospital and physician diagnosis codes is accurate compared to other common OP fractures.[24,25] In particular, we focus on the effect of "short courses" or "heavy use" of high daily doses of oral GCs and hip fracture risk. Additionally, as the association of oral GC exposure with other fractures (forearm and vertebra) is not yet clear, we further examined other fracture sites in secondary analyses.

c. Methods

Data Source

We utilised data from the Danish National Health Service Register that covers all contacts with the health sector for over five million individuals in Denmark.[26] The National Health Service Register captures all contacts with general practitioners. The National Hospital Discharge Register includes information on hospital admissions since 1977 and all outpatient and emergency department visits since 1995.[27] All diagnoses are coded using the International Classification of Diseases and Related Health Problems (ICD) system, with high precision for diagnoses, particularly for fractures.[28] The vital status for the entire Danish population is identified from the Civil Registration System. The Danish Medicines Agency Register of Medicinal Product Statistics is a nationwide prescription database that uses the Anatomical Therapeutic Chemical Classification (ATC) system and includes information on the type, amount, and prescription date. All registers can be linked at the patient level using the unique 10-digit civil registry number assigned to all Danish citizens.[29]

Study Design

We completed a population-based case-control study. Cases were all patients aged 18 years or older, who sustained the first ever hip, vertebral, or forearm fracture between 1 January 1996, and 31 December 2011. The primary fracture of interest was hip fracture (ICD-10 codes: S72.0–S72.2). We further identified patients with clinical symptomatic vertebral fractures (ICD-10 codes: S12, S22.0, S22.1, S32.0, T08) and forearm fractures: radius or ulna (ICD-10 code: S52).

We randomly selected a control for each case, matched on age and year of birth, using incidence density sampling. Controls had no fracture during the study period. The date of the first fracture was used as the index date for the cases, and controls were assigned the index date of their matched case.

Exposure

We defined oral GC exposure based on most recent GC prescription prior to the index date: current (within 91 days), recent (92–182 days), past (183–364 days), and distant past (≥365 days). Patients with no GC prescriptions prior to the index date were classified as never users and were the reference category in all analyses.

Average daily dose (DD) and the cumulative dose (CD) of oral GCs were calculated among current users and expressed as prednisone equivalents. The average DD was calculated by dividing CD by the treatment time (days between the first GC prescription to the index date) and categorised into three groups: low (<7.5 mg), moderate (7.5–14.9 mg), and high (≥15 mg). CD was calculated by summing defined daily doses of GC prescriptions prior to the index date, according to the World Health Organisation. The primary exposure categories of interest were defined as follows: CD was categorised as low (<1 g CD) or high (≥1 g CD) (Figure 4.1). In a secondary analysis, we defined high CD as ≥5 or ≥10 g, with relevant sub-groups of CD (1.0–4.9 g, and 5.0–9.9 g), where appropriate.

To examine fracture risk associated with different patterns of GC exposure, we further stratified exposure by both DD and CD to capture short-course and heavy users of high DD (≥15 mg) oral GCs. Among these patients with a high DD, we defined "short-course users" as those with <1 g CD, while "heavy users" were those with a CD ≥1 g. These definitions were used as a heavy user would be a patient receiving 2–3 months of 15 mg daily, or more than a 30-day exposure to 40–60 mg daily.

Covariates

A history of the following comorbidities were identified if they occurred any time before a patient's index date: secondary osteoporosis (type 1 diabetes mellitus, hypogonadism, or premature menopause), fracture (prior to 1996), rheumatoid arthritis, gout, inflammatory bowel disease, chronic obstructive pulmonary disease, alcoholism, cerebrovascular disease, congestive heart failure, pneumonia, type 2 diabetes mellitus, hyperthyroidism, hypothyroidism, malignancies (excluding non-melanoma skin cancer), dementia, and retinopathy. All potential confounders were identified using ICD-8 or ICD-10 codes. In the 6 months before the index date, we identified the following prescriptions as potential confounders: bone-sparing drugs (bisphosphonates, vitamin D, calcium, calcitonin, denosumab, raloxifene, and strontium ranelate), hormone replacement therapy, parathyroid hormone, antidepressants, antipsychotics, hypnotics/ anxiolytics, anticonvulsants, anti-Parkinson drugs, inhaled bronchodilators, inhaled corticosteroids, xanthine derivatives, antihypertensive drugs, and proton pump inhibitors.

Statistical Analysis

Conditional logistic regression was used to estimate the association between the use of oral GCs and fracture risk. All results are presented as odds ratios (ORs) with the

corresponding 95% confidence intervals (95% CIs). Analyses were stratified by DD, CD, and the DD stratified by CD (i.e., short-course vs. heavy use). Final regression models were determined using stepwise backward elimination using a significance level of 0.05. We completed an additional analysis that adjusted the final model for osteoporosis medications in addition to identified significant covariates. Separate models were run for hip (primary outcome), clinical symptomatic vertebral, and forearm fracture. Analyses were conducted using SAS software version 9.3 (SAS Institute Inc., Cary, NC).

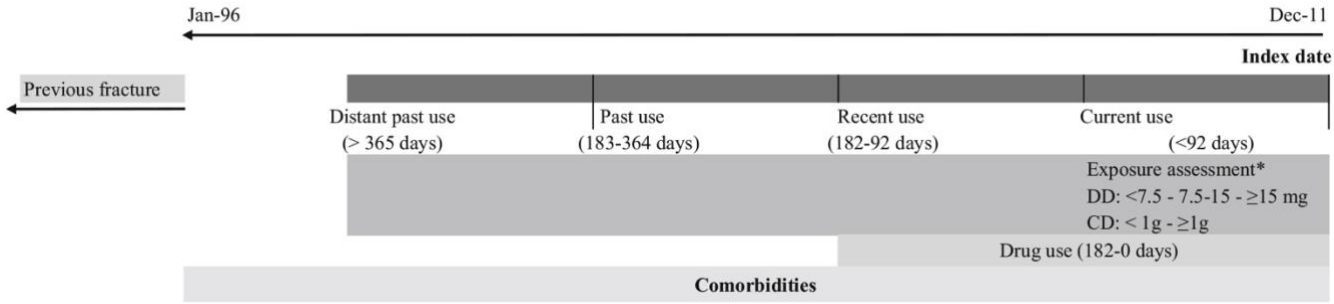

Figure 4.1. Study design diagram.
*DD: average daily dose in milligrams of prednisone equivalent measured among current users. CD: cumulative exposure in grams of prednisone equivalent measured among current users. Notes: index date defined as the first fracture occurring between 1996 and 2011. Oral glucocorticoid exposure based on most recent glucocorticoid prescription prior to the index date: current (within 91 days), recent (92–182 days), past (183–364 days), and distant past (>364 days). Comorbidities: any diagnoses code prior to the index date. Drug use: any drug prescription within 6 months prior to the index date. Previous fracture: any fracture prior to January 1996.

d. Results

Primary fracture site: hip fracture

We identified 81,342 cases of hip fracture who were well matched to controls on age (mean 78.6 years, standard deviation 12 years) and sex (women 68.6%) (Table 4.1). Compared with controls, a higher proportion of cases had comorbidities, such as the history of fracture (27 cases vs. 11% controls), chronic obstructive pulmonary disease (10 cases vs. 7% controls), and secondary osteoporosis (8 cases vs. 5% controls). Drug use in the 6 months prior to the index date was higher among the fracture cases, as compared to controls: bisphosphonates (3.5 vs. 2.4%), antipsychotics (9.3 vs. 4.3%), anticonvulsants (4.5 vs. 1.9%), and antidepressants (22.3 vs. 10.8%) (Table 4.1).

Table 4.1. Baseline characteristics of cases of hip fracture and controls.

	Cases (n=81,342)		Controls (n=81,342)		
	N	%	N	%	*P* value
Women	55,776	68.6	55,776	68.6	1
Mean age in years (SD)	78.6	(12.0)	78.6	(12.0)	0.99
Age group					
18–49 years	2237	2.8	2240	2.8	0.99
50–59 years	3791	4.7	3794	4.7	0.99
60–69 years	8565	10.5	8578	10.6	0.91
70–79 years	21,513	26.5	21,545	26.5	0.86
80+ years	45,236	55.6	45,185	55.6	0.8
History of comorbidities*					
COPD	7986	9.8	5293	6.5	<0.001
Fracture (prior to 1996)	21,653	26.6	8672	10.7	<0.001
Rheumatoid arthritis	2318	2.9	1452	1.8	<0.001
Inflammatory bowel disease	1998	2.5	1405	1.7	<0.001
Secondary osteoporosis†	6189	7.6	3951	4.9	<0.001
Drug use 6 months before index date					
Bisphosphonates	2868	3.5	1917	2.4	<0.001
Vitamin D	156	0.2	122	0.2	<0.05
Calcium	1718	2.1	1109	1.4	<0.001
Raloxifene	104	0.1	62	0.1	<0.01
Strontium ranelate	37	0.1	19	0.0	0.01
Denosumab	8	0.0	–	–	–
Parathyroid hormone	30	0.0	20	0.0	0.16
Hormone replacement therapy	4306	5.3	5875	7.2	<0.001
Inhaled corticosteroids	2948	3.6	2625	3.2	<0.001
Inhaled bronchodilators	7020	8.6	5436	6.7	<0.001
Antipsychotics	7552	9.3	3496	4.3	<0.001
Antidepressants	18,138	22.3	8783	10.8	<0.001
Hypnotics/ Anxiolytics	13,053	16.1	8734	10.7	<0.001
Anticonvulsants	3660	4.5	1539	1.9	<0.001
Anti-Parkinson drugs	2124	2.6	841	1.0	<0.001

COPD: Chronic obstructive pulmonary disease, SD: Standard deviation. Cells <6 are not reported.
* Comorbidities: any diagnoses code (ICD-8 or ICD-10) recorded prior to the index date.
† Secondary osteoporosis defined as a diagnosis of type 1 diabetes mellitus, hypogonadism, or premature menopause.

A total of 16,606 patients with hip fracture (20.4%) and 13,763 controls (16.9%) had used oral GCs prior to the index fracture (Supplementary Table S4.1). Current use of oral GCs was associated with an increased risk of hip fracture (adjusted [adj.] OR 1.56, 95% CI [1.48–1.65]), as compared to never users of oral GCs (Figure 4.2). Among current users, a dose-response relationship was observed with increasing DD: <7.5 mg (adj. OR 1.37 [95% CI 1.28–1.47]), 7.5–14.9 mg (adj. OR 1.53 [95% CI 1.39–1.68]), and ≥15 mg (adj. OR 2.5 [95% CI 2.19–2.85]) (Supplementary Table S4.1). Likewise, a higher CD was associated with an increased hip fracture risk. A CD <1 g was associated with a 1.3-fold increased hip fracture risk (adj. OR 1.28 [95% CI 1.14–1.44]), while a 1.6-fold increased risk was observed for CD ≥1

g (adj. OR 1.64 [95% CI 1.54–1.74]), CD ≥5 g (adj. OR 1.61 [95% CI 1.50–1.74]), and CD ≥10 g (adj. OR 1.57 [95% CI 1.42–1.73]).

To examine the association between "heavy" and "short-course" users of high-dosed oral GCs, the DD was further stratified by the CD (Figure 4.2). Among short-course users (DD ≥15 mg and CD <1 g), a 42% increase in hip fracture risk was observed (adj. OR 1.42 [95% CI 1.08–1.86]). In contrast, "heavy" use of high doses (DD ≥15 mg and CD ≥1 g) resulted in a tripled risk of hip fracture (adj. OR 2.94 [95% CI 2.52–3.42]). When CD exceeded 5 or 10 g, among those with a high DD, the hip fracture risk was similar (CD ≥5 g: adj. OR 2.86 [95% CI 2.29–3.58] and CD ≥10 g: adj. OR 2.55 [95% CI 1.84–3.55]).

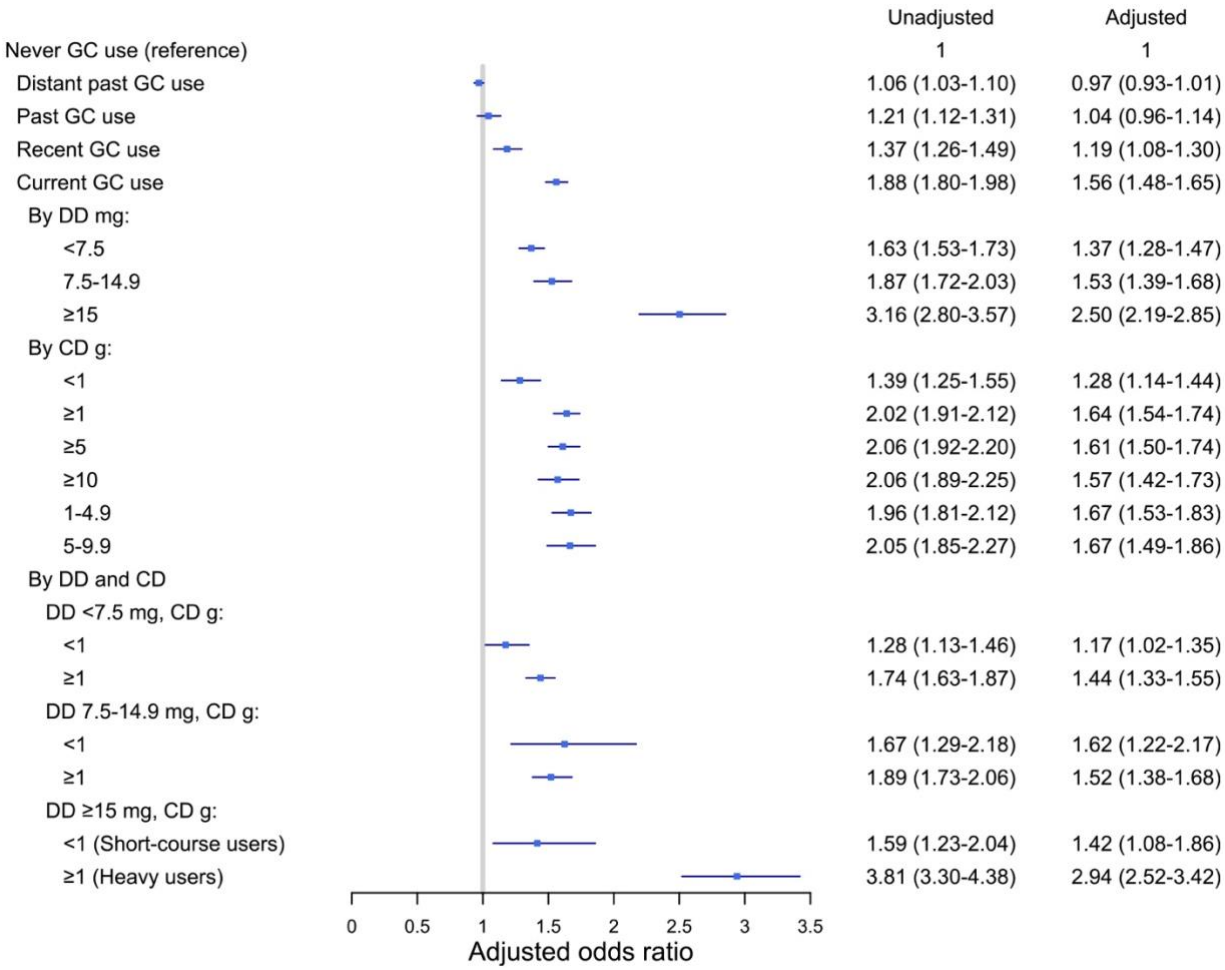

Figure 4.2. Odds ratio of hip fracture by glucocorticoid use (vs. never).

CD: cumulative dose, DD: average daily dose, GC: glucocorticoid.

Oral GC exposure based on most recent GC prescription prior to the index date: current (within 91 days), recent (92–182 days), past (183–364 days), and distant past (>364 days). DD and CD were calculated among current users. Adjusted for history of chronic obstructive pulmonary disease, fracture (prior to 1996), rheumatoid arthritis, inflammatory bowel disease, secondary osteoporosis, antidepressants, anxiolytics and hypnotics, anticonvulsants, bone-sparing drugs, and inhaled bronchodilators.

Secondary fracture sites: vertebral and forearm fractures

Figure 4.3 and Supplementary Table S4.2 present the ORs of clinical symptomatic vertebral fracture by GC exposure. Current use of oral GCs was associated with doubled risk of clinical vertebral fracture (adj. OR 2.36 [95% CI 2.15–2.60]). A high DD (≥15 mg/day) was associated with a 3.8-fold increased clinical vertebral fracture risk (adj. OR 3.76 [95% CI 2.97–4.77]), and a CD ≥1 g was associated with a 2.6-fold increased risk (adj. OR 2.57 [95% CI 2.30–2.87]). Among the high DD users, short-course use was associated with a doubled risk of clinical symptomatic vertebral fracture risk (adj. OR 2.13, 95% CI 1.30–3.49), while "heavy" use was associated with a more than 4-fold increased risk (adj. OR 4.36, 95% CI 3.32–5.72) (Figure 4.3 and Supplementary Table S4.2).

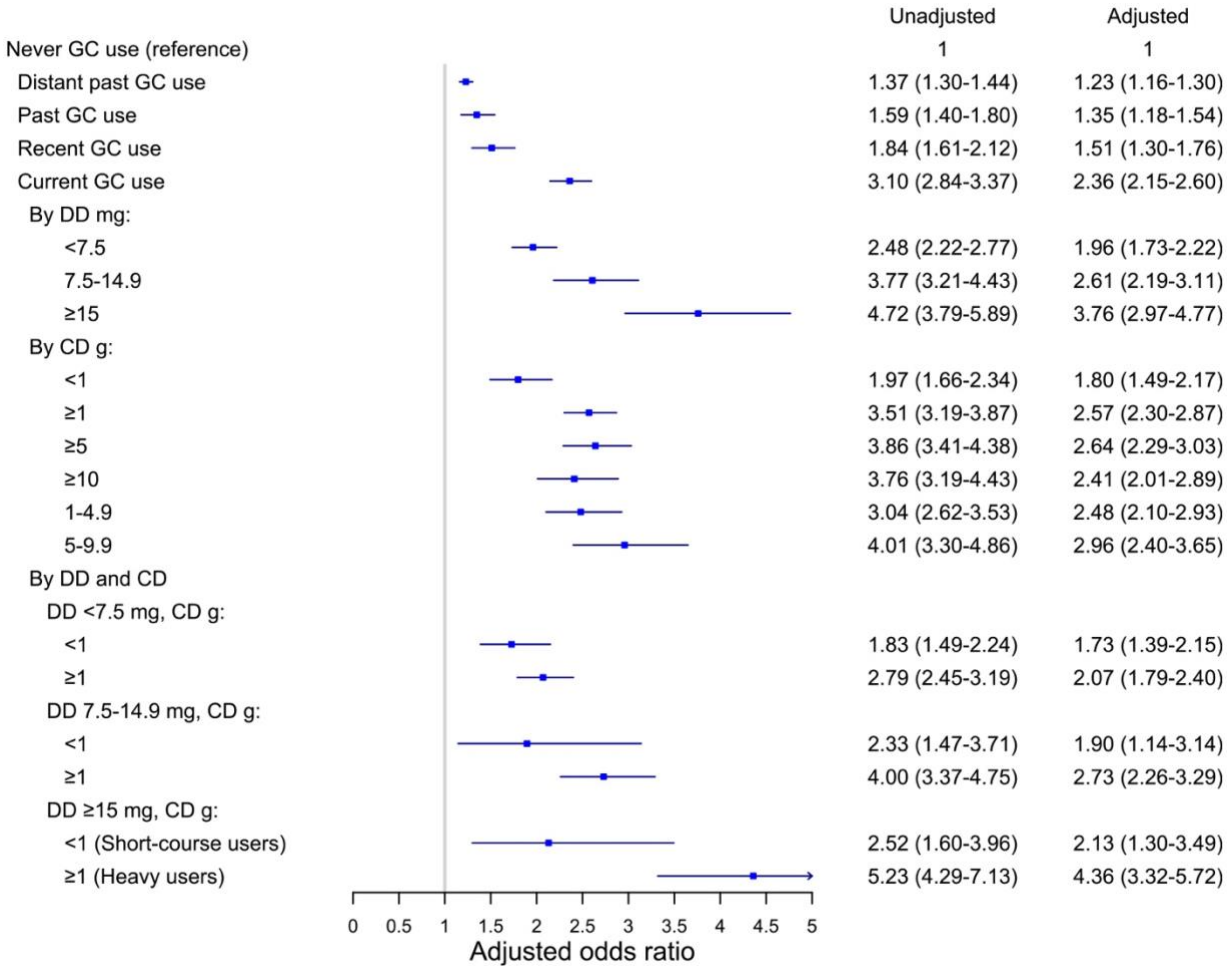

Figure 4.3. Odds ratio of vertebral fracture by glucocorticoid dose (vs. never).

CD: cumulative dose, DD: average daily dose, GC: glucocorticoid.

Oral GC exposure based on most recent GC prescription prior to the index date: current (within 91 days), recent (92–182 days), past (183–364 days), and distant past (>364 days). DD and CD were calculated among current users. Adjusted for history of chronic obstructive pulmonary disease, fracture (prior to 1996), rheumatoid arthritis, inflammatory bowel disease, secondary osteoporosis, antidepressants, anxiolytics and hypnotics, anticonvulsants, bone-sparing drugs, and inhaled bronchodilators.

Among patients with forearm fractures, the analysis showed minimal to no association with oral GC exposure (Figure 4.4). No dose-response of forearm fracture risk was observed (Figure 4.4 and Supplementary Table S4.3).

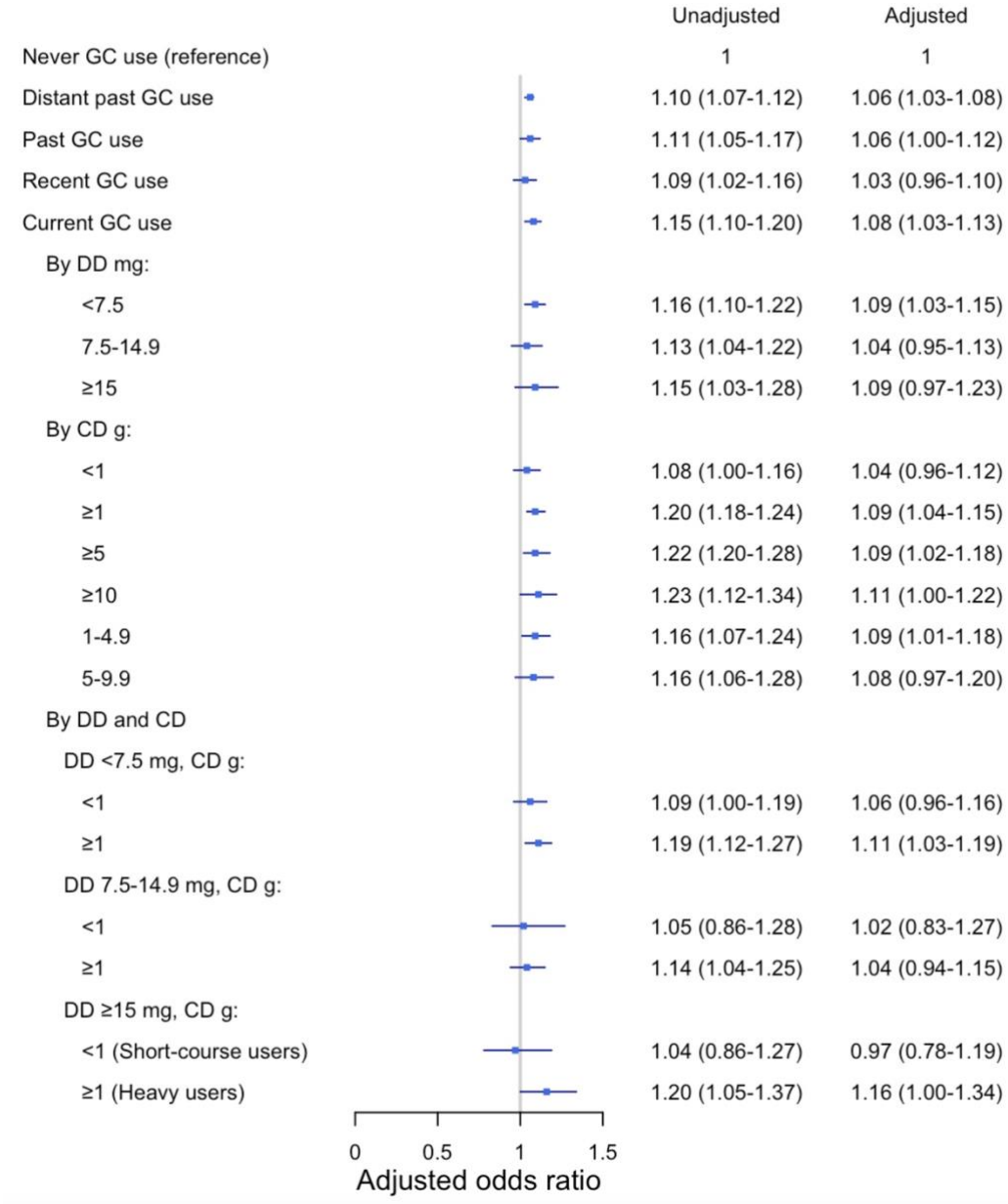

Figure 4.4. Odds ratio of forearm fracture by glucocorticoid dose (vs. never).
CD: cumulative dose, DD: average daily dose, GC: glucocorticoid.
Oral GC exposure based on most recent GC prescription prior to the index date: current (within 91 days), recent (92–182 days), past (183–364 days), and distant past (>364 days). DD and CD were calculated among current users. Adjusted for history of chronic obstructive pulmonary disease, fracture (prior to 1996), rheumatoid arthritis, inflammatory bowel disease, secondary osteoporosis, antidepressants, anxiolytics and hypnotics, anticonvulsants.

e. Discussion

In this population-based case-control study, we identified that heavy use (high DD and high CD) of oral GCs was associated with a 3-fold increased hip fracture risk, which was substantially higher as compared to short-course users. While both the DD and CD were independently associated with hip fracture risk, our results suggest that hip fracture risk was modified by the CD among patients receiving a high DD of oral GCs. This association was not observed among patients with a low to moderate DD, thereby suggesting that heavy users of high DD oral GCs are a distinct patient group with substantially elevated fracture risk.

Interestingly, in our study, we did not observe an incremental increase in hip fracture risk among patients receiving CD exceeding 1 g of prednisone equivalent (≥5 or ≥10 g). This result may indicate a threshold effect for the CD, which may be used to guide clinical decision making to determine patients in need of fracture/osteoporosis management. Our study further showed that the odds of sustaining fractures among GC users were stronger for clinical symptomatic vertebral fracture than hip fracture, while forearm fracture risk was minimal to non-significant among current users and across dose categories.

Systemic GCs cause considerable inhibition of bone formation and bone resorption, but particularly when given at higher doses and longer durations. Additionally, systemic GCs impair renal and intestinal calcium absorption, reduce sexual hormone secretion, and cause muscle atrophy and gait impairment, which in turn increase bone loss and fracture risk.[5] These pleiotropic effects significantly increase fracture risk, and we speculate that it is the high daily and cumulative doses which can explain the effect modification that we observed. Our finding is also in line with a previous cohort study in the UK.[15]

In clinical practice, treatment with bisphosphonates for osteoporosis management is often suboptimal among patients receiving oral GCs, particularly those receiving short courses as they do not reach the guideline recommendation of 7.5 mg per day for a duration of 3 months. As a result, these patients remain at high risk for potentially devastating hip fractures. Since the cycle of bone remodelling takes on average 3 months, [30] multiple short courses are likely to hinder bone metabolism by preventing the skeleton to completely regenerate. Indeed, data have shown that fracture risk can persist up to 1 year after oral GC cessation.[15,17] However, the association between a more intermittent exposure to high DD and fracture remains controversial. Moreover, the

effect of a CD of oral GCs, particularly in relation to the DD, on fracture risk remains debated.

While it is well established that a DD exceeding 15 mg is associated with a significant increase in fracture risk, our study highlighted that the magnitude of fracture risk associated with a high DD differed depending on the CD thresholds. We observed that patients receiving short courses (<1 g CD) of high DD had an elevated hip and clinical symptomatic vertebral fracture risk, yet heavy users (≥1 g CD) of high DD had a tripled risk of hip fracture, and a 4.5-fold increase in clinical symptomatic vertebral fracture risk. Interestingly, we observed that fracture risk reached a plateau starting at a CD ≥1 g. Prior studies have shown that GC daily dose is a stronger predictor than the cumulative dose.[12,15,16] However, our results suggest that high DD with low CD does not confer higher risk of fractures, and therefore, we assume that there is a threshold duration of exposure or a minimum number of high daily doses that are causing the highest risk of fracture. Our results support that a clinical threshold of 1 g prednisone equivalent may be useful to guide therapeutic interventions to prevent OP fracture. Indeed, clinical practice guidelines use various oral GC exposure thresholds to consider anti-fracture treatment, yet no agreement between guidelines is established.[10,18–20]

When placing our results in the context of the literature, we note that the most comparable study to ours is a large cohort study conducted by de Vries et al., using the UK primary care data (Clinical Practice Research Datalink) to examine fracture risk among GC users covering the period between 1987 and 1997.[15] In their study, de Vries et al. examined similar GC DD and CD exposure to our study, and showed a 49% increase in relative risk of hip and femur fracture, and more than 3-fold risk increase of vertebral fracture. The authors showed similar dose-response patterns for the average DD and CD and OP fracture overall. However, contrary to our study, de Vries et al. assessed fracture risk by disease at baseline, limiting the direct comparison with our study. Additionally, the comparator group in the study by de Vries et al. were those with past use of GCs, while never users were compared in our study. Thus, a larger overall effect of current use in our study would be expected.

Additionally, a case-control study in the Netherlands investigated inhaled and oral GC users from 1991 to 2002, identifying cases of 366 hip or femur fracture among current oral GC users.[31] This study examined daily dose-response and showed lower overall risk than identified in our study. However, this study did not consider the total CD of GCs, which is an important factor to estimate differential fracture risk. Consequently, we are unable to make a direct comparison regarding the effect of heavy or short-term use on fracture

risk. Finally, Vestergaard et al. showed that the highest increase in hip fracture risk by cumulative dose was among patients receiving ≥1500 mg prednisone equivalent in the year preceding the fracture (OR 4.2, 95% CI 1.96–9.00 vs. OR 1.89, 95% CI 1.62–2.21 for patients receiving 500–1499 mg prednisone equivalent).[32] However, this analysis was not stratified by GC daily dose.

Other observational studies have examined the association of short courses of GC exposure and support our findings of a moderately increased fracture risk. A cohort study using administrative healthcare databases reported a similar increase in hip fracture risk (60%) among all GC users, and RR of hip fracture equal to 1.26 (95% CI 0.87–1.83) among patients with short courses of oral GCs (<90 days). A lack of statistical power is likely to cause the non-significant results for short courses. Another cohort study reported increased risk of hip fracture among oral GC users (RR 1.87, 95% CI 1.19–2.94).[16] In addition, increases in daily dose and duration were significantly associated with hip and clinical symptomatic vertebral fracture risk. This study showed that short duration of oral GC exposure also increased fracture risk.

In interpreting our data, we are mindful of some limitations. By design, the case-control study is not able to provide an absolute risk. We used a density sampling technique which allowed us to interpret the odds ratio as risk ratio since controls were selected based on the person-time duration corresponding to each case.[33] There remains debate of the thresholds of GC exposure resulting in fracture risk. Consequently, our definition of dose and duration thresholds may be debatable. Many guidelines recommend treatment among patients receiving a planned systemic GC dose ≥7.5 mg prednisone equivalent daily and a duration of 3 months.[19,34] However, the patterns of GC exposure are often complex, requiring multiple courses and may therefore not meet guidelines for treatment, leaving many patients at risk. While the definition of high GC daily doses is debated, doses <7.5 mg/day prednisone equivalent are often considered as low doses in clinical trials of oral GCs.[35,36] While our study did not identify significant differentiation between those receiving <7.5 mg daily and those receiving 7.5–14.9 mg daily, there was a significant increased hip and vertebral fracture risk among those receiving ≥15 mg daily.

Additionally, there may be limitations regarding our definition of short-course and heavy users of high DD oral GCs. In this study, we assumed patients with a DD ≥15 mg and CD <1 g may have received intermittent use (short-courses) of oral GC therapy, as this would suggest that a patient received two or fewer 30-day courses of 15 mg per day. Conversely, the heavy users with ≥1 g CD were more likely to have received more prolonged exposure to oral GC therapy. Using a combination of CD and DD to describe patterns of exposure

may not be the most optimal choice. In many clinical cases, dosing schedule of oral GCs consists of a high DD and a short duration. In this study, we assumed that less than 1 g of prednisone equivalent before the fracture event is indicative of short-course or intermittent use for acute symptom management. This would correspond to one or two 30-day courses of 15 mg per day. However, it is possible that intermittent users may accumulate more than 1 g of exposure if a DD exceeded 30 mg. Nonetheless, we expect that this is likely to happen in very few cases only.

Additionally, while we adjusted for common GC indications, we did not stratify our results by the specific disease indications. Similarly, while we adjusted comorbidities and drug use, residual confounding remains a limitation. We recognise that other risk factors have not been captured in our data and therefore not adjusted for. These include patient body mass index, smoking status, and bone mineral density values. However, we note that de Vries et al. reported similar results using UK data, which adjusted for these variables, and there is evidence showing that the fracture risk could be partly independent from the diminished bone density in patients who take oral GCs.[37]

Another limitation was the possibility of misclassification bias in the Danish database. Vertebral fractures can be asymptomatic and likely have a low predictive value when defined using claims data.[38] This may have resulted in an underestimated effect in our vertebral fracture results. However, we believe there is little chance of differential misclassification and commonly used codes for OP fracture were identified. Additionally, misclassification of exposure is possible with GCs as information was derived from pharmacy claims, and we cannot be assured that the pills were taken as prescribed. Indeed, GCs may be prescribed on a "take as needed" basis, and therefore may have been collected at the pharmacy and not taken. In this study, the average daily dose was used, yet we acknowledge that this method has limitations with oral GCs, particularly when the GC regimen requires adjustment and gradual tapering for long exposure periods.[39] This may result in underestimating the DD. However, the CD may partially adjust for this by estimating the overall exposure.

There are several strengths to our current study. We used the Danish nationwide population register, which is a large population-based register that permitted the examination of a large number of cases and controls. In Denmark, all residents receive universal medical and prescription services. Thus, the data are complete and collected longitudinally. This data also permitted the inclusion of many important confounders. Additionally, the prescription data in Denmark are claims-based and collected longitudinally, permitting us to calculate a reliable cumulative and average daily dose.

Moreover, all data on fractures have been validated,[40] minimising the effect of misclassification.

Clinical implication

The literature is consistent with respect to increases in fracture risk related to oral GC exposure, yet the independent and combined effects of DD and CD on fracture risk remains controversial. According to the underlying condition, patients are faced with various instructions regarding GC exposure - including tapering over time, alternate day use, and "take as needed" instructions. Thus, defining an exposure threshold to initiate osteoporosis treatment is ambiguous, and difficult to assess in research using population-based data. In general, the literature shows suboptimal osteoporosis management among oral GC users, where up to 70% of eligible users have no bone protection treatment.[3,41] Many oral GC users may not fall under clinical guidelines' eligibility criteria to receive osteoporosis management.

The results of this study, therefore, provide additional evidence that a high DD (≥15 mg/day) and a CD exceeding 1 g is likely to cause the greatest risk of hip and clinical symptomatic vertebral fracture. Thus, while patients receiving short courses of high DD should continue to be monitored, focused attention for fracture management and osteoporosis pharmacotherapy should be given to patients with heavy use. These results may help clinical guidance to elaborate an evidence-based strategy for bone protection among oral GC users.

Conclusion

In conclusion, heavy use of high-dosed oral GCs is associated with a substantial 3-fold increase in hip fracture risk. Therefore, while short courses or more intermittent use of high-dosed oral GCs do increase fracture risk, primary attention should be paid to patients with heavy use - defined as those receiving multiple short or prolonged courses of high GC doses that result in a cumulative exposure exceeding 1 g prednisone equivalent. Knowing a patients' prescription history to identify the cumulative exposure to high daily doses of oral GCs may help clinicians to identify patients that are at high risk of fractures. These patients should then be targeted for osteoporosis management strategies to minimise fracture risk.

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g. Supplementary material

Table S4.1. Results for hip fracture.

	N of cases (n=81,342)	N of controls (n=81,342)	Unadjusted OR	95% CI		Adjusted OR*	95% CI		Adjusted OR†	95% CI	
Never GC use	64,736	67,579	1.00	Reference		1.00	Reference		1.00	Reference	
Ever GC use	16,606	13,763	1.28	1.25	1.32	1.12	1.08	1.15	1.11	1.08	1.15
Distant past GC use	8639	8610	1.06	1.03	1.10	0.96	0.93	1.00	0.97	0.93	1.01
Past GC use	1407	1213	1.21	1.12	1.31	1.04	0.96	1.14	1.04	0.96	1.14
Recent GC use	1330	1023	1.37	1.26	1.49	1.19	1.09	1.30	1.19	1.08	1.30
Current GC use	5230	2917	1.88	1.80	1.98	1.59	1.50	1.67	1.56	1.48	1.65
By average daily dose (oral prednisolone equivalents)											
<7.5 mg/day	2628	1699	1.63	1.53	1.73	1.39	1.29	1.49	1.37	1.28	1.47
7.5 -14.9 mg/day	1548	869	1.87	1.72	2.03	1.56	1.42	1.72	1.53	1.39	1.68
≥15 mg/day	1054	349	3.16	2.80	3.57	2.54	2.23	2.90	2.50	2.19	2.85
By cumulative dose (oral prednisolone equivalents)											
<1 g	812	608	1.39	1.25	1.55	1.28	1.14	1.43	1.28	1.14	1.44
≥1 g	4418	2309	2.02	1.91	2.12	1.67	1.58	1.77	1.64	1.54	1.74
≥5 g	2666	1370	2.06	1.92	2.20	1.66	1.54	1.79	1.61	1.50	1.74
≥10 g	1519	780	2.06	1.89	2.25	1.62	1.47	1.79	1.57	1.42	1.73
1-4.9 g	1752	939	1.96	1.81	2.12	1.69	1.55	1.84	1.67	1.53	1.83
5-9.9 g	1147	590	2.05	1.85	2.27	1.70	1.53	1.90	1.67	1.49	1.86
By average daily dose & cumulative dose											
DD <7.5 mg/day											
CD <1 g	513	418	1.28	1.13	1.46	1.17	1.02	1.35	1.17	1.02	1.35
CD ≥1 g	2115	1281	1.74	1.63	1.87	1.46	1.35	1.58	1.44	1.33	1.55
CD ≥5 g	1233	731	1.78	1.62	1.95	1.46	1.32	1.62	1.42	1.28	1.58
CD ≥10 g	648	400	1.71	1.51	1.95	1.39	1.21	1.60	1.35	1.18	1.55
CD 1-4.9 g	882	550	1.70	1.52	1.89	1.46	1.30	1.64	1.46	1.29	1.64
CD 5-9.9 g	585	331	1.86	1.63	2.14	1.55	1.33	1.79	1.51	1.30	1.75
DD 7.5-14.9 mg/day											
CD <1 g	145	90	1.67	1.29	2.18	1.61	1.20	2.14	1.62	1.22	2.17
CD ≥1 g	1403	779	1.89	1.73	2.06	1.56	1.41	1.72	1.52	1.38	1.68
CD ≥5 g	997	526	2.00	1.79	2.22	1.62	1.44	1.82	1.58	1.40	1.77
CD ≥10 g	673	327	2.18	1.91	2.49	1.71	1.48	1.97	1.65	1.42	1.91
CD 1-4.9 g	406	253	1.67	1.42	1.95	1.43	1.21	1.70	1.40	1.18	1.67
CD 5-9.9 g	324	199	1.70	1.42	2.03	1.48	1.22	1.80	1.45	1.19	1.76

Table S4.1. (continued)

DD ≥15 mg/day											
CD <1 g	154	100	1.59	1.23	2.04	1.41	1.07	1.84	1.42	1.08	1.86
CD ≥1 g	900	249	3.81	3.30	4.38	3.00	2.58	3.50	2.94	2.52	3.42
CD ≥5 g	436	113	4.09	3.32	5.03	2.95	2.35	3.68	2.86	2.29	3.58
CD ≥10 g	198	53	3.93	2.90	5.33	2.66	1.92	3.70	2.55	1.84	3.55
CD 1-4.9 g	464	136	3.58	2.95	4.33	3.06	2.49	3.75	3.01	2.45	3.69
CD 5-9.9 g	238	60	4.23	3.18	5.64	3.20	2.36	4.35	3.15	2.32	4.28

CD: Cumulative dose, CI: Confidence interval, DD: daily dose, GC: Glucocorticoid, OR: Odds ratio.

Oral GC exposure based on most recent GC prescription prior to the index date: current (within 91-days), recent (92-182 days), past (183-364 days), and distant past (>364 days). DD and CD were calculated among current users.

* Adjusted for: history of COPD, fracture, rheumatoid arthritis, inflammatory bowel disease, secondary osteoporosis, inhaled bronchodilators, antidepressants, hypnotics/ anxiolytics and anticonvulsants.

† Adjusted for confounders in model A plus bone medications (bisphosphonates, raloxifene, strontium, denosumab, calcium, vitamin D), calcitonin, and hormone replacement therapy.

Table S4.2. Results for clinical symptomatic vertebral fracture.

	N of cases (n=37,144)	N of controls (n=37,144)	Unadjusted OR	95% CI		Adjusted OR*	95% CI		Adjusted OR†	95% CI	
Never GC use	30,044	32,463	1.00	Reference		1.00	Reference		1.00	Reference	
Ever GC use	7100	4681	1.72	1.65	1.79	1.49	1.42	1.56	1.44	1.38	1.52
Distant past GC use	3745	3103	1.37	1.30	1.44	1.24	1.17	1.32	1.23	1.16	1.30
Past GC use	637	450	1.59	1.40	1.80	1.38	1.20	1.57	1.35	1.18	1.54
Recent GC use	555	338	1.84	1.61	2.12	1.61	1.38	1.87	1.51	1.30	1.76
Current GC use	2163	790	3.10	2.84	3.37	2.54	2.31	2.79	2.36	2.15	2.60
By average daily dose (oral prednisolone equivalents)											
<7.5 mg/day	1060	485	2.48	2.22	2.77	2.07	1.84	2.34	1.96	1.73	2.22
7.5 -14.9 mg/day	673	201	3.77	3.21	4.43	2.89	2.43	3.44	2.61	2.19	3.11
≥15 mg/day	430	104	4.72	3.79	5.89	4.01	3.17	5.07	3.76	2.97	4.77
By cumulative dose (oral prednisolone equivalents)											
<1 g	376	212	1.97	1.66	2.34	1.81	1.50	2.18	1.80	1.49	2.17
≥1 g	1034	459	3.51	3.19	3.87	2.81	2.52	3.13	2.57	2.30	2.87
≥5 g	1129	331	3.86	3.41	4.38	2.98	2.60	3.42	2.64	2.29	3.03
≥10 g	641	192	3.76	3.19	4.43	2.80	2.34	3.35	2.41	2.01	2.89
1-4.9 g	658	247	3.04	2.62	3.53	2.57	2.18	3.03	2.48	2.10	2.93
5-9.9 g	488	139	4.01	3.30	4.86	3.23	2.63	3.98	2.96	2.40	3.65
By average daily dose & cumulative dose											
DD <7.5 mg/day											
CD <1 g	257	156	1.83	1.49	2.24	1.74	1.40	2.16	1.73	1.39	2.15
CD ≥1 g	803	329	2.79	2.45	3.19	2.24	1.93	2.59	2.07	1.79	2.40
CD ≥5 g	462	174	3.04	2.55	3.63	2.43	2.01	2.95	2.16	1.78	2.63
CD ≥10 g	234	98	2.73	2.15	3.48	2.21	1.70	2.88	1.88	1.44	2.46
CD 1-4.9 g	341	155	2.51	2.07	3.05	2.02	1.63	2.49	1.97	1.59	2.44
CD 5-9.9 g	228	76	3.43	2.64	4.45	2.71	2.04	3.59	2.51	1.89	3.34
DD 7.5-14.9 mg/day											
CD <1 g	56	27	2.33	1.47	3.71	1.90	1.15	3.15	1.90	1.14	3.14
CD ≥1 g	617	174	4.00	3.37	4.75	3.06	2.54	3.68	2.73	2.26	3.29
CD ≥5 g	451	117	4.33	3.53	5.33	3.19	2.56	3.99	2.78	2.23	3.48
CD ≥10 g	295	73	4.55	3.51	5.88	3.18	2.42	4.19	2.75	2.09	3.63
CD 1-4.9 g	166	57	3.31	2.44	4.50	2.76	1.98	3.86	2.60	1.86	3.64
CD 5-9.9 g	156	44	3.98	2.82	5.60	3.21	2.23	4.61	2.84	1.97	4.11

Table S4.2. (continued)

DD ≥15 mg/day											
CD <1 g	63	29	2.52	1.60	3.96	2.17	1.33	3.55	2.13	1.30	3.49
CD ≥1 g	367	75	5.23	4.29	7.13	4.69	3.59	6.14	4.36	3.32	5.72
CD ≥5 g	216	40	6.11	4.32	8.65	4.64	3.22	6.69	4.18	2.88	6.04
CD ≥10 g	112	21	5.72	3.58	9.14	3.96	2.42	6.49	3.41	2.07	5.62
CD 1-4.9 g	151	35	4.88	3.35	7.09	4.76	3.20	7.08	4.58	3.08	6.83
CD 5-9.9 g	104	19	6.60	3.94	11.07	5.52	3.22	9.47	5.19	2.99	9.00

CD: Cumulative dose, CI: Confidence interval, DD: daily dose, GC: Glucocorticoid, OR: Odds ratio.

Oral GC exposure based on most recent GC prescription prior to the index date: current (within 91-days), recent (92-182 days), past (183-364 days), and distant past (>364 days). DD and CD were calculated among current users.

* Adjusted for: history of COPD, fracture, rheumatoid arthritis, inflammatory bowel disease, secondary osteoporosis, inhaled bronchodilators, antidepressants, a hypnotics/ anxiolytics and anticonvulsants.

† Adjusted for confounders in model A plus bone medications (bisphosphonates, raloxifene, strontium, denosumab, calcium, vitamin D), calcitonin, and hormone replacement therapy.

Table S4.3. Results for forearm (radius/ulna) fracture.

	N of cases (n=201,963)	N of controls (n=201,963)	Unadjusted OR	95% CI		Adjusted OR*	95% CI		Adjusted OR†	95% CI	
Never GC use	172,692	174,940	1.00	Reference		1.00	Reference		1.00	Reference	
Ever GC use	29,271	27,023	1.11	1.08	1.13	1.06	1.03	1.08	1.06	1.04	1.08
Distant past GC use	19,160	17,862	1.10	1.07	1.12	1.05	1.03	1.08	1.06	1.03	1.08
Past GC use	2961	2719	1.11	1.05	1.17	1.05	0.99	1.11	1.06	1.00	1.12
Recent GC use	2085	1949	1.09	1.02	1.16	1.03	0.96	1.10	1.03	0.96	1.10
Current GC use	5065	4493	1.15	1.10	1.20	1.09	1.05	1.14	1.08	1.03	1.13
By average daily dose (oral prednisolone equivalents)											
<7.5 mg/day	3161	2785	1.16	1.10	1.22	1.10	1.04	1.16	1.09	1.03	1.15
7.5 -14.9 mg/day	1229	1111	1.13	1.04	1.22	1.08	0.99	1.18	1.04	0.95	1.13
≥15 mg/day	675	597	1.15	1.03	1.28	1.10	0.98	1.24	1.09	0.97	1.23
By cumulative dose (oral prednisolone equivalents)											
<1 g	1440	1356	1.08	1.00	1.16	1.03	0.96	1.12	1.04	0.96	1.12
≥1 g	3625	3137	1.20	1.18	1.24	1.12	1.06	1.81	1.09	1.04	1.15
≥5 g	2015	1718	1.22	1.20	1.28	1.15	1.07	1.23	1.09	1.02	1.18
≥10 g	1133	946	1.23	1.12	1.34	1.18	1.07	1.30	1.11	1.00	1.22
1-4.9 g	1610	1419	1.16	1.07	1.24	1.09	1.01	1.18	1.09	1.01	1.18
5-9.9 g	882	772	1.16	1.06	1.28	1.11	1.00	1.23	1.08	0.97	1.20
By average daily dose & cumulative dose											
DD <7.5 mg/day											
CD <1 g	1040	969	1.09	1.00	1.19	1.05	0.95	1.15	1.06	0.96	1.16
CD ≥1 g	2121	1816	1.19	1.12	1.27	1.12	1.05	1.20	1.11	1.03	1.19
CD ≥5 g	1105	912	1.24	1.13	1.35	1.19	1.08	1.31	1.14	1.04	1.26
CD ≥10 g	569	464	1.26	1.11	1.42	1.24	1.09	1.42	1.17	1.03	1.34
CD 1-4.9 g	1016	904	1.15	1.05	1.25	1.06	0.96	1.17	1.07	0.97	1.18
CD 5-9.9 g	536	448	1.22	1.08	1.38	1.13	0.99	1.29	1.11	0.97	1.27
DD 7.5-14.9 mg/day											
CD <1 g	197	190	1.05	0.86	1.28	1.04	0.84	1.28	1.02	0.83	1.27
CD ≥1 g	1032	921	1.14	1.04	1.25	1.09	0.99	1.20	1.04	0.94	1.15
CD ≥5 g	701	615	1.16	1.04	1.30	1.09	0.97	1.23	1.03	0.91	1.16
CD ≥10 g	464	384	1.24	1.08	1.41	1.14	0.98	1.32	1.05	0.91	1.22
CD 1-4.9 g	331	306	1.10	0.94	1.28	1.08	0.91	1.27	1.07	0.90	1.26
CD 5-9.9 g	237	231	1.04	0.87	1.25	1.02	0.84	1.24	0.98	0.81	1.19

Table S4.3. (continued)

DD ≥15 mg/day											
CD <1 g	203	197	1.04	0.86	1.27	0.97	0.79	1.19	0.97	0.78	1.19
CD ≥1 g	472	400	1.20	1.05	1.37	1.18	1.02	1.36	1.16	1.00	1.34
CD ≥5 g	209	191	1.12	0.92	1.36	1.12	0.91	1.39	1.08	0.87	1.34
CD ≥10 g	100	98	1.04	0.79	1.37	1.05	0.78	1.42	0.99	0.73	1.34
CD 1-4.9 g	263	209	1.28	1.06	1.53	1.22	1.00	1.48	1.23	1.01	1.49
CD 5-9.9 g	109	93	1.20	0.91	1.58	1.20	0.89	1.62	1.18	0.87	1.59

CD: Cumulative dose, CI: Confidence interval, DD: daily dose, GC: Glucocorticoid, OR: Odds ratio.

Oral GC exposure based on most recent GC prescription prior to the index date: current (within 91-days), recent (92-182 days), past (183-364 days), and distant past (>364 days). DD and CD were calculated among current users.

* Adjusted for: history of COPD, fracture, rheumatoid arthritis, inflammatory bowel disease, secondary osteoporosis, inhaled bronchodilators, antidepressants, hypnotics/ anxiolytics and anticonvulsants.

† Adjusted for confounders in model A plus bone medications (bisphosphonates, raloxifene, strontium, denosumab, calcium, vitamin D), calcitonin, and hormone replacement therapy.

SECTION 2

Osteoporotic fracture risk with medication use in rheumatoid arthritis

CHAPTER 5

Low-dose oral glucocorticoid therapy and risk of osteoporotic fractures in patients with rheumatoid arthritis: a cohort study using the Clinical Practice Research Datalink

Shahab Abtahi

Johanna H M Driessen

Andrea M Burden

Patrick C Souverein

Joop P van den Bergh

Tjeerd P van Staa

Annelies Boonen

Frank de Vries

Rheumatology (Oxford). (first published on 13 July 2021; in press)

a. Abstract

Background

Clinical trials have shown that low-dose glucocorticoid therapy in patients with rheumatoid arthritis (RA) reduces bone loss in hands or hip, but the effect on osteoporotic fractures is not yet clear. Therefore, we investigated the use of low-dose oral glucocorticoids and risk of osteoporotic fractures among patients with RA.

Methods

This was a cohort study including patients with RA aged 50+ years from the Clinical Practice Research Datalink between 1997 and 2017. Exposure to oral glucocorticoids was stratified by the most recent prescription in current (<6 months), recent (7-12 months), and past (>1 year) use, and average daily and cumulative doses. Risk of incident osteoporotic fractures (including hip, vertebrae, humerus, forearm, pelvis, and ribs) was estimated by time-dependent Cox proportional-hazards models, adjusted for life-style parameters, comorbidities, and comedications. Secondary analyses assessed osteoporotic fracture risk with a combination of average daily and cumulative doses of oral glucocorticoids.

Results

Among 15,123 patients with RA (mean age 68.8 years, 68% females), 1640 osteoporotic fractures occurred. Current low-dose oral glucocorticoid therapy (≤7.5 mg prednisolone equivalent/day) in patients with RA was not associated with overall risk of osteoporotic fractures (adjusted hazard ratio 1.14, 95% CI 0.98-1.33) compared with past glucocorticoid use, but was associated with an increased risk of clinical vertebral fracture (adjusted hazard ratio 1.59, 95% CI 1.11-2.29). Results remained unchanged regardless of a short-term or a long-term use of oral glucocorticoids.

Conclusions

Clinicians should be aware that even in RA patients who receive low daily glucocorticoid doses, the risk of clinical vertebral fracture is increased.

b. Introduction

Osteoporotic (OP) fractures are a major complication among patients with rheumatoid arthritis (RA).[1-3] The reason for this increased susceptibility of OP fractures in RA is the underlying chronic inflammation of the disease, and the pharmacotherapy that patients with RA receive, most importantly oral glucocorticoids (GCs). Short-term GC therapy is part of the European Alliance of Associations for Rheumatology (EULAR) recommendations 2019 update for RA management, and around a quarter of RA patients are treated with GCs in the UK.[1,4] GC therapy leads to decreased bone mineral density (BMD) and increased fracture risk from early in the treatment course, by mediating a reduction in bone formation and an increase in bone resorption.[5-8]

Low-dose GC therapy, especially in chronic inflammatory diseases, could also have positive effects on bone loss, where it suppresses the underlying deleterious inflammation and improves the functional status of patient.[9-14] The randomised controlled trial (RCT) by Haugeberg et al reported a statistically significant reduced bone loss in hands after 1- and 2-years in RA patients who were taking 7.5 mg prednisolone once daily compared to placebo.[9] However, extrapolation of this local beneficial effect in hands to the generalised bone loss in RA and the resulting risk of OP fracture is questionable. On the other hand, observational studies have reported higher fracture rates with low-dose oral GC use (i.e., ≤7.5 mg prednisolone equivalent dose [PED] per day) in RA compared to non-use,[13,15,16] although these findings may be confounded by indication or disease severity. Additionally, the results of a review by an EULAR task force regarding the risk of harm (including osteoporosis and OP fractures) of long-term GC therapy in RA was inconclusive for dosages between 5-10 mg PED/day.[17] These conflicting findings and the uncertainty over any possible beneficial effect of low daily doses of oral GCs on fracture risk in RA justifies a more detailed examination of this association using real-world data. Thus, the objective of this study was to investigate the use of low-dose oral GCs and risk of OP fractures among patients with RA.

c. Methods

Database

This is a retrospective cohort study using data from the Clinical Practice Research Datalink, GOLD (CPRD; www.cprd.com). CPRD is one of the world's largest primary care databases. It contained medical records of 674 practices in the United Kingdom in 2013,

representing 4.4 million active patients that equalled to 6.9% of the total population.[18] It includes data on patient demographics, life-style parameters, clinical diagnoses, prescription details, laboratory test results, specialist referrals, and major outcomes since 1987, with continuing data collection. The CPRD has been well validated for a wide range of diseases, including hip and vertebral fractures.[19,20]

Study Population

The study population comprised all adults aged 50+ years diagnosed with RA in the CPRD between 01 January 1997 and 31 December 2017. We used a validated algorithm that detected 86% of the true RA cases among people with an RA Read code in the CPRD (Supplementary Table S5.1).[21,22] The date of the first RA diagnosis during the period of valid data collection (considering up to standard time of the CPRD practice) defined the index date (i.e., start of follow-up). Each patient was then followed from the index date until the occurrence of the intended outcome, the end of study period, moving out of the practice area, death, or last data collection date of the CPRD practice, whichever came first. Follow-up time was broken down into 30-day periods. Patients with a history of oral GC use during the 1 year before the index date, and those with an OP fracture prior to the index date were excluded.

Exposure and Outcome

The exposure of interest was the use of oral GCs, which was assessed time-dependently in 30-day periods. At the start of each 30-day period, we identified prescribing of oral GCs in a retrospective manner. A period was defined as current, recent, or past use when the most recent prescription of oral GCs was issued within 6 months before, 7-12 months before, and >12 months before, respectively.[6,23] Non-use was defined as all other follow-up time without a history of oral GC exposure.

Current GC use was further broken down into subcategories based on average daily and cumulative dose. All oral GC prescriptions were retrieved, and the prescribed quantity was extracted and converted into PED, using the World Health Organisation Anatomical Therapeutic Chemical classification system of defined daily doses (ATC/DDD).[24] Values for missing data on prescribed quantity were assigned the median value of all prescriptions. The cumulative amount of the drug prescribed in each follow-up period was estimated by summing all consecutive prescriptions since the index date. The average daily dose in each follow-up period was calculated by dividing the cumulative amount prescribed by

the treatment time (i.e., the time between the first oral GC prescription and the start date of a period of current use). The composite outcome in this study was the occurrence of a first OP fracture in patients with RA after the index date, including the hip, clinically symptomatic vertebral, humerus, forearm, pelvic, and rib fractures, through relevant Read codes.[1,16,19,23,25,26]

Potential Confounders

Sex, body mass index (BMI), smoking status and alcohol use were assessed at the index date. During follow-up, we determined age, and a history of asthma, chronic obstructive pulmonary disease, ischaemic heart disease (including myocardial infarction), cerebrovascular disease, congestive heart failure, anaemia, peripheral arterial disease, gastroesophageal reflux disease, peptic ulcer disease, inflammatory bowel disease (Crohn disease and ulcerative colitis), Coeliac disease, hyperthyroidism, hypothyroidism, type 1 and 2 diabetes mellitus, osteomalacia, hypopituitarism, Cushing's disease, bilateral orchidectomy or oophorectomy, chronic renal failure, ankylosing spondylitis, muscular dystrophy, dementia, Parkinson's disease, spinal cord injury, anorexia nervosa, major infections (i.e., sepsis, meningitis, upper and lower respiratory tract infections), malignant neoplasms (excluding non-melanoma skin cancers), and organ transplantation.[27] Falls were determined in 7-12 months before each period. The use of comedications in six months prior was determined and included antihypertensives, anticoagulants, proton pump inhibitors, calcium/vitamin D, bisphosphonates, hormone replacement therapy, anticonvulsants, hypnotics/anxiolytics, antidepressants and antipsychotics. The following medications were measured at the same time-windows and were considered as indicators of the underlying severity of RA: non-selective non-steroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase-2 selective inhibitors, paracetamol, tramadol, opioids (stronger than tramadol), and conventional synthetic disease-modifying antirheumatic drugs (csDMARDs).

Statistical Analysis

Time-dependent Cox proportional-hazards models estimated the risk of OP fracture in RA patients with current use of low-dose oral GCs (average daily dose ≤7.5 mg PED/day [based on EULAR definitions][4]) versus past use. We selected past use as the reference category - instead of non-use, to have the most comparable control group and to reduce confounding by indication. Also, medium and high average daily use of oral GCs (7.6-14.9

mg PED/day and ≥15.0 mg PED/day, respectively) were compared with past use. All these exposure subcategories under current GC use were statistically compared with a Wald test. Additionally, separate analyses were conducted for various OP fracture sites. Any of the potential confounders were incorporated in the model if they changed the beta coefficient of the association >5% or based on literature following authors' assessment. Collinearity between potential confounders was assessed.

In secondary analyses, cumulative use of oral GCs and its combination with average daily doses of oral GCs in RA patients were compared with past use. Furthermore, four sensitivity analyses were conducted. First, OP fracture risk in RA was assessed in various other cut-offs for low GC use (i.e., ≤5.0 mg PED/day and ≤2.5 mg PED/day). Second, we repeated a Cox model to estimate the risk of OP fracture with low-dose oral GC use by removing csDMARDs as confounder, since we thought csDMARDs, as a measure of RA disease severity, might lie in the causal pathway of this association.[4,28] In the third sensitivity analysis, we repeated the main model, only after excluding those patients with a prior OP fracture in 1 year before the index date. Fourthly, we ran a Cox model by comparing current use of low-dose oral GCs to non-use of GCs. Finally, a *post hoc* analysis was performed to evaluate the association between a GC daily dose of 5.1-7.5 mg PED/day and OP fractures in patients with RA. Data were analysed using SAS version 9.4 (SAS Institute Inc. Cary, NC, USA). This study was approved by the Independent Scientific Advisory Committee for Medicines and Healthcare products Regulatory Agency database research (protocol 19_201).

d. Results

The study population consisted of 15,123 RA patients aged 50+ years (Figure 5.1). Table 5.1 shows a mean follow-up time of 8.1 years for GC users (N=7039), and 6.2 years for non-users (N=8084). The average duration of GC use was 3.7 years. The mean age of GC users at the index date was 68.4 years and of non-users was 69.1 years. Females constituted 67% of GC users and 70% of non-users. Around one third of both exposure groups had a normal-range BMI (25-30 kg/m^2). While 23% of GC users were current smokers, only 19% of non-users were smokers at the index date. The most frequent comorbidities among GC users were major infections and asthma, and major infections and anaemia among non-users. Around 30% of GC users and >35% of non-users were concomitantly taking csDMARDs at the index date.

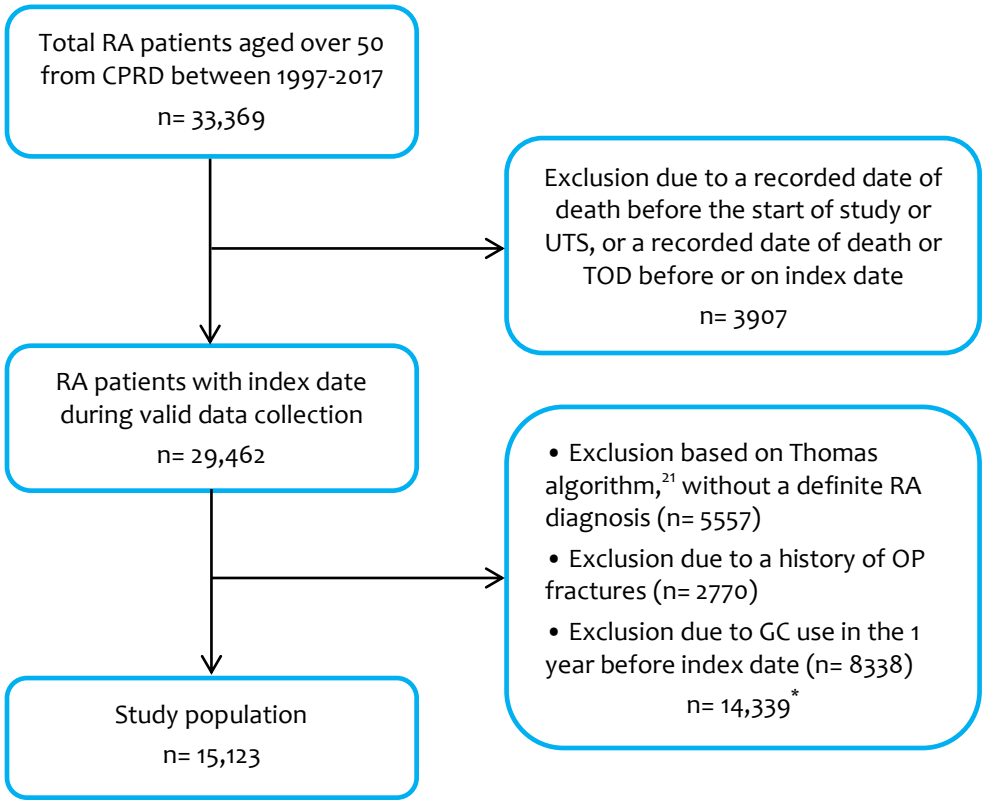

Figure 5.1. Flowchart on establishment of patient population.
CPRD: Clinical Practice Research Datalink, GC: glucocorticoid, OP: osteoporotic, RA: rheumatoid arthritis, TOD: transfer out of database date (i.e., date the patient transferred out of the practice), UTS: Up to standard time (i.e., date at which the practice data is deemed to be of research quality).
* The numbers for specific exclusion criteria would not add up to the total excluded number as there was some overlap between the exclusion categories.

Table 5.1. Baseline characteristics of patients with rheumatoid arthritis, stratified by oral glucocorticoid therapy status during follow-up (N=15,123).

	Oral Glucocorticoid users (N=7039)*		Non-users (N=8084)	
	N	% - SD	N	% - SD
Mean duration of follow-up (years, SD)	8.1	4.9	6.2	4.7
Age(years)†				
Mean (SD)	68.4	8.6	69.1	8.7
50-59	1150	16.3	1211	15.0
60-69	2842	40.4	3052	37.8
70-79	2312	32.8	2817	34.8
80+	735	10.4	1004	12.4
Number of Females	4687	66.6	5654	69.9
BMI (kg/m²)†				
Mean (SD)	26.5	5.2	26.3	5.2
<20.0	481	6.8	568	7.0
20.0-24.9	2279	32.4	2642	32.7
25.0-29.9	2432	34.6	2687	33.2
30.0-34.9	1003	14.2	1039	12.9
≥35.0	394	5.6	435	5.4

Table 5.1. (continued)

Missing	450	6.4	713	8.8
Smoking status†				
Non	2488	35.3	3132	38.7
Current	1609	22.9	1557	19.3
Past	2856	40.6	3183	39.4
Missing	86	1.2	212	2.6
Alcohol use†				
No	2058	29.2	2205	27.3
Yes	4464	63.4	5125	63.4
Missing	517	7.3	754	9.3
History of comorbidities†				
Asthma	942	13.4	536	6.6
COPD	544	7.7	263	3.3
Ischaemic heart disease (including myocardial infarction)	940	13.4	987	12.2
Cerebrovascular disease	399	5.7	470	5.8
Congestive heart failure	192	2.7	254	3.1
Anaemia	923	13.1	1126	13.9
Peripheral arterial disease	364	5.2	416	5.1
Gastroesophageal reflux disease	585	8.3	596	7.4
Peptic ulcer disease	66	0.9	64	0.8
Coeliac disease	22	0.3	26	0.3
Inflammatory bowel disease	75	1.1	66	0.8
Hyperthyroidism	48	0.7	46	0.6
Hypothyroidism	558	7.9	619	7.7
Diabetes mellitus type 1	51	0.7	54	0.7
Diabetes mellitus type 2	425	6.0	560	6.9
Chronic renal failure	363	5.2	394	4.9
Ankylosing spondylitis	9	0.1	18	0.2
Dementia	34	0.5	65	0.8
Parkinson's disease	14	0.2	47	0.6
Major infections‡	1437	20.4	1414	17.5
Malignant neoplasms (excluding non-melanoma skin cancers)	651	9.2	747	9.2
Falls (7-12 months before)	47	0.7	71	0.9
Comedications use (6 months before)†				
Antihypertensives	2597	36.9	3141	38.9
Anticoagulants	218	3.1	237	2.9
Proton pump inhibitors	1756	24.9	2006	24.8
Calcium/vitamin D	380	5.4	574	7.1
Bisphosphonates	280	4.0	385	4.8
Hormone replacement therapy	233	3.3	231	2.9
Anticonvulsants	118	1.7	159	2.0
Hypnotics/ Anxiolytics	647	9.2	589	7.3
Antidepressants	916	13.0	967	12.0
Antipsychotics	67	1.0	77	1.0
Disease severity indicators				
Non-selective NSAIDs	4057	57.6	4344	53.7
COX-2 selective inhibitors	711	10.1	669	8.3
Paracetamol	3603	51.2	3811	47.1
Tramadol	541	7.7	513	6.3
Opioids (stronger than tramadol)	430	6.1	392	4.8
csDMARDs	2104	29.9	2849	35.2

Table 5.1. (continued)

BMI: body mass index, COPD: chronic obstructive pulmonary disease, COX-2: cyclooxygenase-2, csDMARDs: conventional synthetic disease-modifying antirheumatic drugs, NSAIDs: non-steroidal anti-inflammatory drugs, SD: standard deviation.
Data on a history of osteomalacia, hypopituitarism, Cushing's disease, bilateral orchidectomy/ oophorectomy, muscular dystrophy, spinal cord injury, anorexia nervosa, and organ transplantation are not shown due to a small number of patients in both cohorts.
* Oral glucocorticoid users are patients who had at least 1 prescription of an oral glucocorticoid during follow-up.
† At the index date (and start of follow-up).
‡ Major infections included sepsis, meningitis, upper and lower respiratory tract infections.

Current use of low-dose oral GCs (≤7.5 mg PED/day) was not associated with overall risk of OP fractures among patients with RA compared with past GC use (adjusted hazard ratio [adj. HR] 1.14, 95% CI 0.98-1.33), (Table 5.2). However, current use of higher daily dosages of oral GCs incurred a 38% increased (adj. HR of 1.38, 95% CI 1.11-1.73 for 7.6-14.9 mg PED/day) or an 84% increased risk (adj. HR of 1.84, 95% CI 1.23-2.74 for ≥15.0 mg PED/day) of OP fractures. The increased fracture risk with high-dose oral GCs was statistically different from low-dose oral GC use (Wald test, *P* <0.05). Sensitivity analyses showed that current use of lower dosages of oral GCs shifted the association further towards null, yielding an adj. HR of 1.07 (95% CI 0.89-1.29) for an average daily dose ≤5.0 mg PED/day, and an adj. HR of 1.00 (95% CI 0.77-1.31) for an average daily dose ≤2.5 mg PED/day for OP fracture risk (Supplementary Table S5.2).

Table 5.3 shows that treatment with low daily doses of oral GCs in patients with RA was associated with a 59% increased risk of clinical vertebral fracture, compared with past GC use (adj. HR 1.59, 95% CI 1.11-2.29). Nonetheless, the risk of other individual OP fracture sites, i.e., hip, humerus, forearm, pelvic and rib fractures, was not associated with low-dose oral GC use versus past use.

Patients with RA who were current users of low-dose oral GCs had no increased risk of OP fracture, regardless of a short-term (≤1.0 g PED) or a long-term (>1.0 g PED) use (Table 5.4). In contrast, high-dose (≥7.5 mg PED/day) long-term oral GC users had a 1.5-fold increased risk of OP fracture compared to patients who had stopped taking oral GCs for >1 year, yielding an adj. HR of 1.52 (95% CI 1.22-1.89).

When csDMARDs were removed from the Cox model as confounder, we observed similar estimates of OP fracture risk with the various daily doses of oral GCs (Supplementary Table S5.3). However, exclusion of patients with a prior fracture only in 1 year before the index date (N=16,450) resulted in associations shifting away from the null

(Supplementary Table S5.4). Finally, a comparison of current use of oral GCs to non-use, instead of past GC use, resulted in a statistically significant 21% increased risk of OP fracture with low-dose oral GC use (ad. HR of 1.21, 95% CI 1.05-1.39) (data not shown). Finally, 136 OP fractures occurred among those RA patients who used a GC daily dose of 5.1-7.5 mg PED/day, with an incidence rate (IR) of 23.2 per 1000 person years (PYs). Current use of oral GCs with a dose of 5.1-7.5 mg PED/day in RA incurred a 24% increased risk of OP fractures (adj. HR 1.24, 95% CI 1.02-1.51), compared to past GC use.

Table 5.2. Use of oral glucocorticoids and risk of osteoporotic fracture in patients with rheumatoid arthritis, by average daily dose.

Oral Glucocorticoid Use By recency of use	OP fractures (N=1640)*	IR per 1000 PYs	Age/Sex adjusted Hazard Ratio (95% CI)	Fully adjusted Hazard Ratio† (95% CI)
Current use‡	428	21.3	**1.36 (1.18-1.56)**	**1.22 (1.06-1.40)**
Mean daily dose ≤7.5 mg PED/day	301	20.3	**1.26 (1.08-1.46)**	1.14 (0.98-1.33)
Mean daily dose 7.6-14.9 mg PED/day	101	23.3	**1.60 (1.29-2.00)**	**1.38 (1.11-1.73)**
Mean daily dose ≥15.0 mg PED/day	26	27.9	**2.09 (1.40-3.11)**	**1.84 (1.23-2.74)**§
Recent use‡	36	11.1	0.76 (0.54-1.06)	0.71 (0.51-1.00)
Past use‡	375	15.7	Reference	Reference
Non-use	801	12.6	0.90 (0.80-1.02)	0.94 (0.83-1.07)

CI: confidence interval, IR: incidence rate, OP: Osteoporotic, PED: prednisolone equivalent dose, PYs: person years. Statistically significant hazard ratios are shown in bold.

* 1640 OP fracture events among all included patients.

† Adjusted at baseline for sex, body mass index, smoking status and alcohol use, and during follow-up for age, a history of ankylosing spondylitis, chronic obstructive pulmonary disease, dementia, falls (in the past 7-12 months), inflammatory bowel disease, and the use in the past 6-months of antidepressants, antihypertensives, proton pump inhibitors, paracetamol, non-selective non-steroidal anti-inflammatory drugs, cyclooxygenase-2 selective inhibitors, tramadol, opioids stronger than tramadol and conventional synthetic disease-modifying antirheumatic drugs.

‡ Current, recent and past use refer to the last prescription within 6 months, 7-12 months, and >12 months before a period, respectively.

§ Statistically different from low daily GC use (≤7.5 mg PED/day), Wald test $P < 0.05$.

Table 5.3. Use of oral glucocorticoids and risk of osteoporotic fracture in patients with rheumatoid arthritis, by fracture type and average daily dose.

Oral Glucocorticoid Use By recency of use	Hip (N=642)		Clinical vertebral (N=267)		Humerus (N=426)		Forearm (N=340)	
	IR per 1000 PYs	Fully adjusted Hazard Ratio* (95% CI)	IR per 1000 PYs	Fully adjusted Hazard Ratio† (95% CI)	IR per 1000 PYs	Fully adjusted Hazard Ratio* (95% CI)	IR per 1000 PYs	Fully adjusted Hazard Ratio‡ (95% CI)
Current use**	8.4	1.20 (0.96-1.50)	4.5	**1.75 (1.25-2.45)**	4.4	1.00 (0.76-1.34)	3.1	0.94 (0.68-1.30)
Mean daily dose ≤7.5 mg PED/day	8.1	1.14 (0.90-1.45)	4.1	**1.59 (1.11-2.29)**	4.5	1.01 (0.75-1.38)	2.9	0.84 (0.58-1.21)
Mean daily dose 7.6-14.9 mg PED/day	9.1	1.34 (0.95-1.90)	5.4	**2.15 (1.33-3.48)**	4.1	0.96 (0.59-1.58)	3.4	1.17 (0.68-2.01)
Mean daily dose ≥15.0 mg PED/day	9.3	1.62 (0.82-3.18)	6.1	**2.68 (1.15-6.26)**	4.1	1.06 (0.39-2.89)	5.1	1.89 (0.76-4.67)
Recent use**	5.3	0.92 (0.56-1.50)	1.2	0.53 (0.19-1.46)	1.8	0.44 (0.19-1.00)	2.9	0.85 (0.44-1.65)
Past use**	6.0	Reference	2.2	Reference	4.0	Reference	3.3	Reference
Non-use	4.5	0.89 (0.73-1.09)	1.7	1.02 (0.73-1.41)	3.4	0.96 (0.75-1.22)	2.7	0.98 (0.74-1.28)

AD: antidepressants, AS: ankylosing spondylitis, BMI: body mass index, CI: confidence interval, COPD: chronic obstructive pulmonary disease, COX-2: cyclooxygenase-2, csDMARDs: conventional synthetic disease-modifying antirheumatic drugs, GC: glucocorticoid, IBD: inflammatory bowel disease, IR: incidence rate, NSAIDs: non-selective non-steroidal anti-inflammatory drugs, OPI: opioids stronger than tramadol, PED: prednisolone equivalent dose, PPI: proton pump inhibitors, PYs: person years. Statistically significant hazard ratios are shown in bold.

* Adjusted at baseline for sex, BMI, smoking status, and alcohol use, and during follow-up for age, a history of AS, COPD, dementia, falls (in the past 7-12 months), IBD, and use in the past 6-months of ADs, antihypertensives, PPIs, paracetamol, NSAIDs, COX-2 selective inhibitors, tramadol, OPI, csDMARDs.

† Adjusted at baseline for sex, BMI, smoking status, and alcohol use, and during follow-up for age, a history of COPD, dementia, falls (in the past 7-12 months), IBD, and use in the past 6-months of ADs, antihypertensives, hypnotics/anxiolytics, PPIs, paracetamol, non-selective NSAIDs, COX-2 selective inhibitors, tramadol, OPI, csDMARDs.

‡ Adjusted at baseline for sex, BMI, smoking status, and alcohol use, and during follow-up for age, a history of asthma, COPD, dementia, falls (in the past 7-12 months), IBD, and use in the past 6-months of ADs, antihypertensives, anticoagulants, anticonvulsants, hypnotics/anxiolytics, PPIs, paracetamol, non-selective NSAIDs, COX-2 selective inhibitors, tramadol, OPI, csDMARDs.

** Current, recent, and past use refer to the last prescription within 6 months, 7-12 months, and >12 months before a period, respectively.

Table 5.3. (Continued)

Oral Glucocorticoid Use By recency of use	Pelvis (N=135) IR per 1000 PYs	Pelvis (N=135) Fully adjusted Hazard Ratio[§] (95% CI)	Rib (N=92) IR per 1000 PYs	Rib (N=92) Fully adjusted Hazard Ratio[¶] (95% CI)
Current use[**]	2.0	**1.78 (1.08-2.94)**	1.2	1.07 (0.62-1.86)
Mean daily dose ≤7.5 mg PED/day	1.8	1.59 (0.93-2.73)	1.1	1.08 (0.59-1.98)
Mean daily dose 7.6-14.9 mg PED/day	2.3	**2.22 (1.08-4.55)**	1.7	1.50 (0.67-3.34)[††]
Mean daily dose ≥15.0 mg PED/day	3.1	**3.57 (1.07-11.89)**	-	N/A
Recent use[**]	1.4	1.53 (0.58-3.99)	0.6	0.59 (0.14-2.48)
Past use[**]	1.0	Reference	1.0	Reference
Non-use	0.9	1.29 (0.81-2.07)	0.6	0.61 (0.37-1.01)

[§] Adjusted at baseline for sex, and during follow-up for age, and use in the past 6-months of ADs, antihypertensives, PPIs, paracetamol, tramadol, OPI, csDMARDs.
[¶] Adjusted at baseline for sex, and during follow-up for age, and use in the past 6-months of PPIs and paracetamol.
[††] Due to no rib fracture in the high daily GC use (≥15.0 mg PED/day) group, this group was lumped together with users of medium oral GCs, together representing a mean daily dose >7.5 mg/day.

Table 5.4. Use of oral glucocorticoids and risk of osteoporotic fracture in patients with rheumatoid arthritis, by cumulative and average daily dose.

Oral Glucocorticoid Use By recency of use	OP fractures (N=1640)[*]	IR per 1000 PYs	Age/Sex adjusted Hazard Ratio (95% CI)	Fully adjusted Hazard Ratio[†] (95% CI)
Current use[‡]	428	21.3	**1.36 (1.18-1.56)**	**1.22 (1.06-1.40)**
❶Cumulative use ≤1.0 g PED	70	17.4	1.20 (0.93-1.55)	1.11 (0.86-1.44)
-Mean daily dose ≤7.5 mg PED/day	53	17.2	1.18 (0.88-1.57)	1.10 (0.83-1.47)
-Mean daily dose >7.5 mg PED/day	17	18.0	1.27 (0.78-2.06)	1.15 (0.71-1.87)
❷Cumulative use >1.0 g PED	358	22.3	**1.39 (1.21-1.61)**	**1.24 (1.07-1.44)**
-Mean daily dose ≤7.5 mg PED/day	248	21.2	**1.27 (1.09-1.50)**	1.15 (0.98-1.35)
-Mean daily dose >7.5 mg PED/day	110	25.5	**1.77 (1.43-2.20)**	**1.52 (1.22-1.89)**[§]
Past use[‡]	375	15.7	Reference	Reference
Non-use	801	12.6	0.90 (0.80-1.02)	0.94 (0.83-1.07)

CI: confidence interval, IR: incidence rate, OP: Osteoporotic, PED: prednisolone equivalent dose, PYs: person years.
Statistically significant hazard ratios are shown in bold.
[*] 1640 OP fracture events among all included patients.
[†] Adjusted at baseline for sex, body mass index, smoking status and alcohol use, and during follow-up for age, a history of ankylosing spondylitis, chronic obstructive pulmonary disease, dementia, falls (in the past 7-12 months), inflammatory bowel disease, and use in the past 6-months of antidepressants, antihypertensives, proton pump inhibitors, paracetamol, non-selective non-steroidal anti-inflammatory drugs, cyclooxygenase-2 selective inhibitors, tramadol, opioids stronger than tramadol, conventional synthetic disease-modifying antirheumatic drugs, and recent use of oral glucocorticoids.
[‡] Current, recent and past use refer to the last prescription within 6 months, 7-12 months, and >12 months before a period, respectively.
[§] Statistically different from low daily GC use (≤7.5 mg PED/day) within the same stratum of cumulative use, Wald test *P* <0.05.

e. Discussion

We found that current low-dose oral GC use (≤7.5 mg PED/day) in patient with RA was not associated with an increased risk of OP fractures compared to past GC use. Similar

findings were revealed for lower daily doses, i.e., ≤5.0 mg PED/day and ≤2.5 mg PED/day. Nevertheless, low-dose oral GC therapy was associated with an increased risk of clinical vertebral fracture, while the risk of other individual OP fracture sites was not increased. Additionally, the main results remained unchanged regardless of a short-term or a long-term use.

There is evidence from RCTs reporting that GC therapy in RA especially in low-doses might have local protective effects on bone health, probably by suppressing the inflammatory process of the disease.[9,10] Apart from the reduced hand bone loss in RA by once daily 7.5 mg prednisolone reported by Haugeberg et al.,[9] another RCT from the Better Anti-Rheumatic FarmacOTherapy (BARFOT) study group showed conservation of BMD at the hip, but not in the spine, by taking 7.5 mg prednisolone daily for two years in patients with active RA compared to no prednisolone treatment.[10] However, there was no statistically significant difference in BMD changes at the hip or lumbar spine between the treatment groups in the latter study.[10] Our findings of no higher risk of non-vertebral OP fractures with an average daily dose of ≤7.5 mg/day was to some extent comparable to the findings of these RCTs. The only fracture in our study with an observed increased risk with low daily GC use was the clinical vertebral (adj. HR 1.59). We know that vertebral fracture risk is markedly increased in RA,[1,29] and it is well-known that GC therapy in particular affects trabecular bone, which is abundantly present in lumbar vertebrae.[5] Therefore, we can hypothesise that the beneficial effect of low-dose GC therapy on suppressing the background inflammation of RA could probably be enough to offset its negative effect on bone synthesis in most fracture sites but not in vertebrae.

When comparing our findings to those of RCTs several points need further clarification. First, BMD changes associated with GC therapy cannot be directly translated into changes in fracture risk. A meta-analysis of observational studies showed that the increase in hip and vertebral fractures after GC use is higher than the rate estimated based on BMD decrease alone.[5] This may be due to GC-induced micro-architectural changes at specific active sites in bone, which were not reflected by the lowered BMD.[8] Second, the choice of past users as the comparator in our study might not fully mimic the placebo group in the RCTs,[9,10] as past users could have already reduced levels of disease activity, hence an improved bone health and a reduced fracture risk. Moreover, as any possible beneficial effect of GCs on bone is thought to be through reduction of RA's background inflammation, adjusting for csDMARDs in analyses (which was intended to minimise confounding) might have annihilated this beneficial effect through overadjustment.[4,28] But, removing csDMARDs from the Cox model produced similar estimates compared to

the main model (Supplementary Table S5.3). This shows that csDMARD use was not perhaps a strong indicator of the disease severity and the background inflammation.

Conflicting results have been reported from observational studies. Our findings were partly in line with those from a recently conducted study that used the same data source, but with a different study design and underlying hypothesis.[16] Robinson and colleagues found no increased OP fracture risk in RA patients taking an average daily dose up to 5.0 mg PED/day, but increased risks with daily doses ≥5.0 mg PED/day compared to non-users.[16] Our *post hoc* analysis showed conformity with these findings, as we observed an increased risk of OP fractures with a GC dose of 5.1-7.5 mg PED/day, and comparable IRs of OP fracture between this daily dose group (23.2 per 1000 PYs) and that of the next stratum, i.e., 7.6-14.9 mg PED/ day (23.3 per 1000 PYs). While we both studied cohorts of RA patients in CPRD, the age limit of included patients (50+ in our study vs. 18+ in Robinson et al.[16]) and the comparator group (past use vs. non-use) were different.

Higher fracture rates with low-dose GC therapy (<7.5 mg/day) were also found in two other studies that compared current GC users to non-users. These included US patients who had a mix of autoimmune diseases including RA and Danish patients from the general population.[15,30] The choice of non-users as the comparator group without adjustment for additional indicators of RA severity in these studies could have possibly introduced confounding by indication. This might have led to an overestimation of the associations between GC use and OP fractures in these studies and the observed discrepancy to our main findings in Table 5.2. The statistically significant association between low daily GC use and OP fracture risk only against non-use in our study and not against past GC use supports such hypothesis. We observed no increased OP fracture risk with cumulative GC use ≤1.0 g PED, even for doses >7.5 mg PED/day. This is in line with the results from a paper that used older data from the same data source (1987-1997) and reported no increased OP fracture rates in patients with arthropathy with a cumulative GC use ≤1.0 g and an average daily dose ≥15.0 mg/day compared to past use.[23] This suggests that short-term intermittent high-dose GC therapy had no considerable effect on fracture risk.

Our study had several strengths. We used data from CPRD, which is one of the world's largest primary care databases. Validated definitions of RA were used in this study by means of a previously verified algorithm.[21,22] Moreover, an on-treatment study design was utilised, allowing for relatively fair and flexible assessment of changes in onset and offset of oral GC exposure, which also helped to avoid time-related biases. Also, by complying with the new-user design, we could tackle biases that would arise from inclusion of

prevalent users.[31] Furthermore, we statistically adjusted for a wide range of potential confounders including well-established risk factors of fractures.

This study had also limitations. Disease-severity indicators of RA, such as the Disease Activity Score in 28 joints (DAS28),[32] and the use of biological drugs were not available from the CPRD. This may have resulted in confounding by disease severity. Patients with a more severe RA have higher odds of receiving GCs and are at higher risk of having an OP fracture.[1,16] Also, the 1.9-year difference in follow-up time between GC users and non-users could be due to inclusion of more patients with a shorter follow-up and less severe RA. However, we incorporated five analgesics and csDMARDs into the Cox model to also consider the effect of RA disease severity on the observed association. Another limitation was a potential misclassification of exposure with oral GCs, as we had only prescribing information from CPRD, which is roughly two steps behind actual drug use by patients.[33] Non-adherence with medication and an "as needed" order for oral GCs might lead to overestimation of drug use by patients and underestimation of the association between oral GCs and fracture risk in our study. However, an average duration of GC use of 3.7 years was an indication of actual use. On the other hand, as our primary care data was not linked to Hospital Episodes Statistics, covering outpatient and admitted patient care by specialist teams at hospitals, we might have missed information on some short episodes of GC therapy during hospitalisations. Furthermore, detection bias might explain at least part of the finding of an increased risk of clinical vertebral fracture in our study.[33] In contrast to other fracture types, about two thirds of all vertebral fractures remain undetected in clinical practice as asymptomatic fractures, and hence their IRs would be underestimated when using large databases.[34-36] Patients who have more frequent visits to medical doctors, e.g. because of complaints that require prescriptions of oral GCs may discuss complaints of back pain more often and may have higher odds to be referred for further diagnosis.

In conclusion, we found an increased risk of clinical vertebral fracture with low-dose GC therapy in RA patients compared with past GC use, while the risk of non-vertebral OP fractures was not increased. Our results are partly in line with findings from RCTs reporting a local beneficial effect of low-dose GC therapy on BMD in various anatomical sites. Clinicians should be aware that even in RA patients who receive low daily GC doses, the risk of clinical vertebral fracture is increased.

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g. Supplementary material

Table S5.1. Criteria from Thomas et al. algorithm to detect true cases of rheumatoid arthritis in the General Practice Research Database, also used in the updated version by Muller et al.[21,22]

Criterion 1	At least one diagnostic Read code for RA and at least one appropriate prescription of a DMARD with no alternative indication for the DMARD;
OR	
Criterion 2	all three of the following: a) two or more diagnostic Read codes for RA (on different dates). b) no alternative diagnosis after the final RA code. c) RA code in group 1 (seropositive or erosive RA) or group 2 ('rheumatoid arthritis' codes e.g., RA of knee), opposed to only group 3 (systemic manifestations of RA) or group 4 (seronegative RA or other weak evidence of RA).

DMARD: disease-modifying antirheumatic drugs, RA: rheumatoid arthritis.

Table S5.2. Sensitivity analysis 1, evaluating use of oral glucocorticoids and risk of osteoporotic fracture in patients with rheumatoid arthritis, by different definitions of average daily dose.

Oral Glucocorticoid Use By recency of use	OP fractures (N=1640)*	IR per 1000 PYs	Age/Sex adjusted Hazard Ratio (95% CI)	Fully adjusted Hazard Ratio† (95% CI)
Current use‡				
Mean daily dose ≤2.5 mg PED/day	63	16.8	1.09 (0.84-1.42)	1.00 (0.77-1.31)
Mean daily dose >2.5 mg PED/day	365	22.4	**1.42 (1.23-1.64)**	**1.27 (1.09-1.47)**
Mean daily dose ≤5.0 mg PED/day	165	18.5	1.16 (0.97-1.40)	1.07 (0.89-1.29)
Mean daily dose >5.0 mg PED/day	263	23.6	**1.52 (1.30-1.78)**	**1.34 (1.14-1.57)**§
Past use‡	375	15.7	Reference	Reference
Non-use	801	12.6	0.90 (0.80-1.02)	0.94 (0.83-1.07)

CI: confidence interval, IR: incidence rate, OP: Osteoporotic, PED: prednisolone equivalent dose, PYs: person years.
Statistically significant hazard ratios are shown in bold.
* 1640 OP fracture events among all included RA patients.
† Adjusted at baseline for sex, body mass index, smoking status and alcohol use, and during follow-up for age, a history of ankylosing spondylitis, chronic obstructive pulmonary disease, dementia, falls (in the past 7-12 months), inflammatory bowel disease, and use in the past 6-months of antidepressants, antihypertensives, proton pump inhibitors, paracetamol, non-selective non-steroidal anti-inflammatory drugs, cyclooxygenase -2 selective inhibitors, tramadol, opioids stronger than tramadol, conventional synthetic disease-modifying antirheumatic drugs, and recent use of oral glucocorticoids.
‡ Current, recent, and past use refer to the last prescription within 6 months, 7-12 months, and >12 months before a period, respectively.
§ Statistically different from mean daily dose ≤5.0 mg/day, Wald test P <0.05.

Table S5.3. Sensitivity analysis 2, use of oral glucocorticoids and risk of osteoporotic fracture in patients with rheumatoid arthritis, by average daily dose, after removing conventional synthetic disease-modifying antirheumatic drugs as confounder from the Cox model.

Oral Glucocorticoid Use By recency of use	OP fractures (N=1640)*	IR per 1000 PYs	Age/Sex adjusted Hazard Ratio (95% CI)	Fully adjusted Hazard Ratio† (95% CI)
Current use‡	428	21.3	**1.36 (1.18-1.56)**	**1.22 (1.06-1.40)**
Mean daily dose ≤7.5 mg PED/day	301	20.3	**1.26 (1.08-1.46)**	1.14 (0.98-1.33)
Mean daily dose 7.6-14.9 mg PED/day	101	23.3	**1.60 (1.29-2.00)**	**1.38 (1.11-1.73)**
Mean daily dose ≥15.0 mg PED/day	26	27.9	**2.09 (1.40-3.11)**	**1.83 (1.23-2.74)**§
Recent use‡	36	11.1	0.76 (0.54-1.06)	0.71 (0.51-1.00)
Past use‡	375	15.7	Reference	Reference
Non-use	801	12.6	0.90 (0.80-1.02)	0.94 (0.83-1.07)

CI: confidence interval, IR: incidence rate, OP: Osteoporotic, PED: prednisolone equivalent dose, PYs: person years.
Statistically significant hazard ratios are shown in bold.
* 1640 OP fracture events among all included patients.
† Adjusted at baseline for sex, body mass index, smoking status and alcohol use, and during follow-up for age, a history of ankylosing spondylitis, chronic obstructive pulmonary disease, dementia, falls (in the past 7-12 months), inflammatory bowel disease, and the use in the past 6-months of antidepressants, antihypertensives, proton pump inhibitors, paracetamol, non-selective non-steroidal anti-inflammatory drugs, cyclooxygenase-2 selective inhibitors, tramadol and opioids stronger than tramadol.
‡ Current, recent and past use refer to the last prescription within 6 months, 7-12 months, and >12 months before a period, respectively.
§ Statistically different from low daily GC use (≤7.5 mg PED/day), Wald test *P* <0.05.

Table S5.4. Sensitivity analysis 3, use of oral glucocorticoids and risk of osteoporotic fracture in patients with rheumatoid arthritis, by average daily dose, only by excluding those patients with a prior fracture in 1 year before the index date (N=16,450).

Oral Glucocorticoid Use By recency of use	OP fractures (N=1883)*	IR per 1000 PYs	Age/Sex adjusted Hazard Ratio (95% CI)	Fully adjusted Hazard Ratio† (95% CI)
Current use‡	491	22.8	**1.38 (1.21-1.57)**	**1.24 (1.09-1.42)**
Mean daily dose ≤7.5 mg PED/day	342	21.6	**1.27 (1.10-1.46)**	**1.16 (1.00-1.33)**
Mean daily dose 7.6-14.9 mg PED/day	122	26.3	**1.71 (1.40-2.09)**	**1.49 (1.21-1.82)**§
Mean daily dose ≥15.0 mg PED/day	27	27.0	**1.90 (1.29-2.80)**	**1.66 (1.13-2.46)**
Recent use‡	40	11.4	0.74 (0.53-1.02)	**0.70 (0.50-0.96)**
Past use‡	424	16.5	Reference	Reference
Non-use	928	13.7	0.93 (0.83-1.04)	0.98 (0.87-1.10)

CI: confidence interval, IR: incidence rate, OP: Osteoporotic, PED: prednisolone equivalent dose, PYs: person years.
Statistically significant hazard ratios are shown in bold.
* 1883 OP fracture events among all included patients.
† Adjusted at baseline for sex, body mass index, smoking status and alcohol use, and during follow-up for age, a history of ankylosing spondylitis, chronic obstructive pulmonary disease, dementia, falls (in the past 7-12 months), inflammatory bowel disease, and the use in the past 6-months of antidepressants, antihypertensives, proton pump inhibitors, paracetamol, non-selective non-steroidal anti-inflammatory drugs, cyclooxygenase-2 selective inhibitors, tramadol, opioids stronger than tramadol and conventional synthetic disease-modifying antirheumatic drugs.
‡ Current, recent and past use refer to the last prescription within 6 months, 7-12 months, and >12 months before a period, respectively.
§ Statistically different from low daily GC use (≤7.5 mg PED/day), Wald test *P* <0.05.

CHAPTER 6

Concomitant use of oral glucocorticoids and proton pump inhibitors and risk of osteoporotic fractures among patients with rheumatoid arthritis: a population-based cohort study

Shahab Abtahi

Johanna H M Driessen

Andrea M Burden

Patrick C Souverein

Joop P van den Bergh

Tjeerd P van Staa

Annelies Boonen

Frank de Vries

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a. Abstract

Background

Patients with rheumatoid arthritis (RA) commonly use oral glucocorticoids (GCs) and proton pump inhibitors (PPIs), both associated with osteoporotic fractures. We investigated the association between concomitant use of oral GCs and PPIs and the risk of osteoporotic fractures among patients with RA.

Methods

This was a cohort study including patients with RA aged 50+ years from the Clinical Practice Research Datalink between 1997 and 2017. Exposure to oral GCs and PPIs was stratified by the most recent prescription as current use (<6 months), recent use (7–12 months) and past use (>1 year); average daily and cumulative dose; and duration of use. The risk of incident osteoporotic fractures (including hip, vertebrae, humerus, forearm, pelvis, and ribs) was estimated by time-dependent Cox proportional-hazards models, statistically adjusted for lifestyle parameters, comorbidities and comedications.

Results

Among 12,351 patients with RA (mean age of 68 years, 69% women), 1411 osteoporotic fractures occurred. Concomitant current use of oral GCs and PPIs was associated with a 1.6-fold increased risk of osteoporotic fractures compared with non-use (adjusted HR: 1.60, 95% CI: 1.35 to 1.89). This was statistically different from a 1.2-fold increased osteoporotic fracture risk associated with oral GC or PPI use alone. Most individual fracture sites were significantly associated with concomitant use of oral GCs and PPIs. Among concomitant users, fracture risk did not increase with higher daily dose or duration of PPI use.

Conclusions

There was an interaction in the risk of osteoporotic fractures with concomitant use of oral GCs and PPIs. Fracture risk assessment could be considered when a patient with RA is co-prescribed oral GCs and PPIs.

b. Introduction

Rheumatoid arthritis (RA) is a common chronic musculoskeletal inflammatory disease with many complications, including an elevated risk of osteoporotic (OP) fractures.[1,2,3] The contributors to increased fracture risk include the inflammatory process of RA and the pharmacologic treatment of the disease, most importantly oral glucocorticoids (GCs). About one-quarter of RA patients in the UK are current users of oral GCs.[1] Patients with RA taking oral GCs have reduced bone mineral density (BMD) at the hip and vertebrae and up to a 35% increased 5-year fracture risk.[1,4] This higher fracture risk with GCs is independent of the disease process and by known mechanisms, such as decreased bone formation, elevated bone resorption, and ultimately reduced bone density.[5-9]

Apart from GCs, patients with RA frequently use other medications that could also be associated with fragility fractures. Non-steroidal anti-inflammatory drugs (NSAIDs) are routinely prescribed for patients with RA as analgesics, and proton pump inhibitors (PPIs) may be co-prescribed to reduce the gastrointestinal side effects. A randomised, double-blind, crossover trial showed that fractional ^{45}calcium absorption was significantly decreased among elderly women using omeprazole (3.5%) versus placebo (9.1%), possibly because of hypochlorhydria.[10] Observational studies have reported conflicting results. Some reported an increased risk of hip and vertebral fractures with PPI use suggesting a causal effect,[11-15] whereas others could not match the shape of the hazard function of PPI-induced fracture risk to calcium absorption hypothesis.[16,17] Other mechanisms such as an increased fall risk due to hypomagnesemia, or explanations such as unmeasured confounding were also proposed to explain this association.[16-20]

A population-based study reported a 2.4-fold increased risk of hip fracture among concomitant users of both PPIs and high-dose oral GCs (≥15 mg prednisolone equivalent dose [PED]).[16] But, to our knowledge, no studies have evaluated the effects of simultaneous use of both drugs on fracture risk in patients with RA, particularly in elderly patients who are regular users of PPIs.[21,22] Thus, we sought to investigate the association between concomitant use of oral GCs and PPIs and the risk of OP fractures among patients with RA.

c. Methods

Data Source

This was a retrospective cohort study based on the Clinical Practice Research Datalink (CPRD) GOLD database (http://www.cprd.com). The CPRD is one of the largest databases of primary care data in the world, which contained medical records of 674 practices in the UK in 2013, representing 4.4 million active patients, which equalled 6.9% of the total population.[23] It includes data on patient demographics, clinical diagnoses, prescription details, laboratory test results, specialist referrals and major outcomes since 1987, with continuing data collection. The CPRD has been well validated for a wide range of diseases, including hip and vertebral fractures.[24,25]

Study Population

The study cohort included adults aged 50+ years and diagnosed with RA between 1 January 1997 and 31 December 2017. We used a validated algorithm to identify definite RA cases in the CPRD, which can detect 86% of the true RA cases (Supplementary Table S6.1).[26,27] The date of the first RA diagnosis during valid data collection defined the index date. Patients were followed until the occurrence of the outcome, the end of the study period, a patient's transfer out of practice, death, or the end of data collection, whichever came first. Following a new-user design, patients with a history of GC/PPI use during the 1 year before the index date and those with an OP fracture prior to the index date were excluded.

Exposure and Outcome

Oral GCs and PPIs were the exposures of interest. From the RA index date, follow-up was divided into consecutive 30-day periods and exposure status was assessed time-dependently at the start of each period. A period was defined as current, recent, or past use when the most recent prescription of oral GCs/PPIs was issued within 6 months, 7–12 months and >12 months before a period, respectively.[7,11,12,16,28] Follow-up time was defined as non-use if no oral GC/PPI had ever been prescribed. Patients were allowed to move between exposure states during follow-up. Once a non-user had taken oral GCs/PPIs, he could never become a non-user again.

To evaluate a dose–response relationship and to replicate previous similar studies,[11,17,28] current use of both drugs was further stratified in average daily and cumulative dose, and

duration of treatment. All oral GC and PPI prescriptions were retrieved, and the prescribed quantity was extracted and converted into PED for GCs and omeprazole equivalent dose (OED) for PPIs using the WHO Anatomical Therapeutic Chemical classification system.[29] Values for missing data on prescribed quantity were assigned the median value of all prescriptions. The cumulative amount of the drug prescribed in each follow-up period was estimated by summing all consecutive prescriptions since the index date. The average daily dose in each follow-up period was calculated by dividing the cumulative amount prescribed by the treatment time (i.e., the time between the first oral GC/PPI prescription and the start date of a period of current use). Continuous duration of PPI use was determined at each period of current use using the prescribed quantity and written dosage information, allowing a gap of 30 days after the expected end date of a prescription.[30] The outcome in this study was a first OP fracture after the RA index date, which included hip, clinically symptomatic vertebral, humerus, forearm, pelvic and rib fractures.[1,28,31,32]

Potential Confounders

Body mass index (BMI), smoking status and alcohol use were determined at the index date. Age and history of comorbidities and comedications were determined time-dependently. Comorbidities included asthma, chronic obstructive pulmonary disease, ischaemic heart disease (including myocardial infarction), cerebrovascular disease, congestive heart failure, anaemia, peripheral vascular disease, gastro-oesophageal reflux disease, peptic ulcer disease, inflammatory bowel diseases (Crohn's disease and ulcerative colitis), coeliac disease, hyperthyroidism, hypothyroidism, type 1 and 2 diabetes mellitus, chronic renal failure, ankylosing spondylitis, dementia, Parkinson's disease, major infections (i.e., sepsis, meningitis, and upper and lower respiratory tract infections) and malignant neoplasms (excluding non-melanoma skin cancers).[33] Falls were measured in the 7–12 months prior to a period. Use of comedications in the 6 months prior included antihypertensives, anticoagulants, calcium/vitamin D, bisphosphonates, hormone replacement therapy, anticonvulsants, hypnotics/anxiolytics, antidepressants and antipsychotics. The following proxy indicators of RA severity were included: use of non-selective NSAIDs, cyclo-oxygenase-2 selective inhibitors, paracetamol, tramadol, opioids (stronger than tramadol) or conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) in the past 6 months.

Statistical Analysis

Time-dependent Cox proportional-hazards models estimated the risk of OP fracture in patients with RA with concomitant current use of oral GCs and PPIs versus non-use. Also, the use of oral GCs alone and PPIs alone, and the recent and past use of oral GCs and PPIs (regardless of the use of the other drug) were compared with non-use. Individual exposure categories were statistically compared with a Wald test to detect between-group significance. Stratified analyses were conducted for various OP fracture sites. Potential confounders were incorporated into the model if the beta coefficient of the association changed by >5% or based on expert opinion.

Secondary analyses focused on average daily and cumulative dose of current GC use in relation to average daily dose and continuous duration of PPI use. Furthermore, three sensitivity analyses were performed. First, calcium/vitamin D and bisphosphonates were added to the model as confounders. They were not considered in the main analysis because of the accompaniment of their prescriptions with those of oral GCs and as we expected them to lie in the causal pathway of the intended association as mediators.[34-36] Second, the main association was re-evaluated by including the prevalent users of GCs and PPIs. Finally, the association between PPI use and OP fractures was assessed among the primary cohort of patients with RA, by excluding only those with PPI use during the 1 year before the index date. Data were analysed using SAS V.9.4 (SAS Institute).

This study was reviewed and approved by the Independent Scientific Advisory Committee of the Clinical Practice Research Datalink (reference 19_018R), which is responsible for reviewing protocols for scientific quality.

d. Results

The study population included 12,351 patients with RA (Figure 6.1). The mean age of concomitant users of oral GCs and PPIs at the index date was 67.5 years, 1.5 years younger than non-users (Table 6.1). The mean duration of follow-up was 9.1 years for concomitant users and 5.1 years for non-users. About two-thirds of patients with RA were women (concomitant users: 67%; non-users: 70%). More than one-third of concomitant users were overweight, whereas 34% of non-users had a normal BMI. In the 6 months before the index date, 54% of concomitant users and 48% of non-users had taken non-selective NSAIDs. The average duration of drug use was 3.3 years for concomitant and single GC users, and 4.1 years for single PPI users.

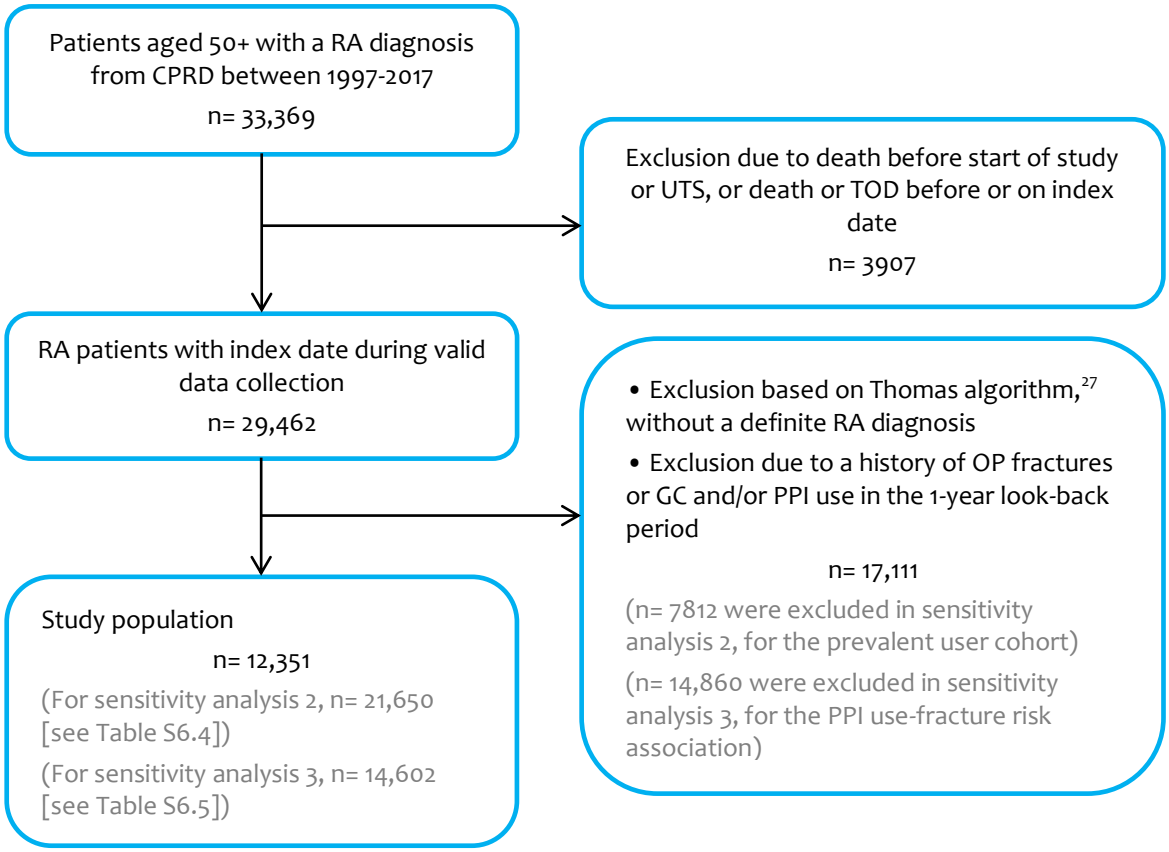

Figure 6.1. Flowchart on establishment of patient population.
CPRD: Clinical Practice Research Datalink, GC: glucocorticoid, OP: osteoporotic, PPI: proton pump inhibitor, RA: rheumatoid arthritis, TOD: transfer out of database date (i.e., date the patient transferred out of the practice), UTS: Up to standard time (i.e., date at which the practice data is deemed to be of research quality).

Table 6.1. Baseline characteristics of study population at index date, stratified by oral GC and PPI therapy status during follow-up (N=12,351).

	Concomitant users of oral GCs and PPIs* (N=4254)		Users of oral GCs alone† (N=2136)		Users of PPIs alone‡ (N=2823)		Non-users (N=3138)	
	N	%	N	%	N	%	N	%
Mean duration of follow-up (years, SD)	9.1	5.0	7.5	4.9	8.4	5.0	5.1	4.3
Age(years)§								
Mean (SD)	67.5	8.4	68.3	8.8	67.5	8.5	69.0	9.2
50-59	802	18.9	390	18.3	540	19.1	550	17.5
60-69	1763	41.4	813	38.1	1190	42.2	1102	35.1
70-79	1328	31.2	699	32.7	842	29.8	1055	33.6
80+	361	8.5	234	11.0	251	8.9	431	13.7
Number of Females	2837	66.7	1443	67.6	2003	71.0	2190	69.8
BMI (kg/m^2)§								
Mean (SD)	26.4	5.1	26.2	5.0	26.2	5.1	25.9	5.1
<20.0	304	7.1	146	6.8	200	7.1	222	7.1
20.0-24.9	1384	32.5	735	34.4	937	33.2	1079	34.4
25.0-29.9	1482	34.8	698	32.7	981	34.8	965	30.8

Table 6.1. (continued)

30.0-34.9	586	13.8	279	13.1	377	13.4	328	10.5
≥35.0	234	5.5	109	5.1	142	5.0	151	4.8
Missing	264	6.2	169	7.9	186	6.6	393	12.5
Smoking status[§]								
Non	1560	36.7	805	37.7	1158	41.0	1252	39.9
Current	988	23.2	522	24.4	571	20.2	646	20.6
Past	1670	39.3	770	36.0	1058	37.5	1104	35.2
Missing	36	0.8	39	1.8	36	1.3	136	4.3
Alcohol use[§]								
No	1249	29.4	559	26.2	780	27.6	795	25.3
Yes	2720	63.9	1380	64.6	1819	64.4	1969	62.7
Missing	285	6.7	197	9.2	224	7.9	374	11.9
History of comorbidities								
Asthma	573	13.5	277	13.0	170	6.0	207	6.6
COPD	321	7.5	161	7.5	65	2.3	102	3.3
Ischaemic heart disease (including myocardial infarction)	503	11.8	234	11.0	278	9.8	323	10.3
Cerebrovascular disease	234	5.5	109	5.1	139	4.9	152	4.8
Congestive heart failure	98	2.3	70	3.3	61	2.2	115	3.7
Anaemia	520	12.2	262	12.3	338	12.0	399	12.7
Peripheral arterial disease	200	4.7	103	4.8	132	4.7	139	4.4
Gastroesophageal reflux disease	198	4.7	94	4.4	130	4.6	110	3.5
Peptic ulcer disease	38	0.9	15	0.7	21	0.7	15	0.5
Coeliac disease	10	0.2	5	0.2	9	0.3	6	0.2
Inflammatory bowel disease	45	1.1	19	0.9	28	1.0	19	0.6
Hyperthyroidism	24	0.6	13	0.6	16	0.6	15	0.5
Hypothyroidism	289	6.8	149	7.0	206	7.3	213	6.8
Diabetes mellitus type 1	25	0.6	17	0.8	17	0.6	15	0.5
Diabetes mellitus type 2	230	5.4	101	4.7	164	5.8	172	5.5
Chronic renal failure	144	3.4	68	3.2	81	2.9	110	3.5
Ankylosing spondylitis	6	0.1	<5	<0.3	5	0.2	7	0.2
Dementia	17	0.4	11	0.5	19	0.7	28	0.9
Parkinson's disease	10	0.2	4	0.2	9	0.3	20	0.6
Malignant neoplasms (excl. non-melanoma skin cancers)	371	8.7	173	8.1	248	8.8	244	7.8
Major infections[¶]	812	19.1	397	18.6	468	16.6	452	14.4
Falls (7-12 months before)	38	0.9	10	0.5	16	0.6	21	0.7
Comedications use (6 months before)								
Antihypertensives	1383	32.5	718	33.6	905	32.1	1117	35.6
Anticoagulants	118	2.8	70	3.3	45	1.6	104	3.3
Calcium/vitamin D	290	6.8	105	4.9	133	4.7	190	6.1
Bisphosphonates	260	6.1	87	4.1	108	3.8	119	3.8
Hormone replacement therapy	184	4.3	65	3.0	107	3.8	81	2.6
Anticonvulsants	51	1.2	29	1.4	37	1.3	46	1.5
Hypnotics/ Anxiolytics	356	8.4	168	7.9	184	6.5	189	6.0
Antidepressants	498	11.7	237	11.1	275	9.7	290	9.2

Table 6.1. (continued)

Antipsychotics	36	0.8	19	0.9	17	0.6	40	1.3
Disease severity indicators								
Non-selective NSAIDs	2309	54.3	1202	56.3	1514	53.6	1518	48.4
COX-2 selective inhibitors	409	9.6	205	9.6	255	9.0	191	6.1
Paracetamol	2117	49.8	987	46.2	1147	40.6	1328	42.3
Tramadol	263	6.2	113	5.3	148	5.2	138	4.4
Opioids (stronger than tramadol)	241	5.7	105	4.9	114	4.0	118	3.8
csDMARDs	1323	31.1	637	29.8	915	32.4	1091	34.8

BMI: body mass index, COPD: chronic obstructive pulmonary disease, COX-2: cyclooxygenase-2, csDMARDs: conventional synthetic disease-modifying antirheumatic drugs, GC: glucocorticoid, NSAIDs: non-steroidal anti-inflammatory drugs, PPI: proton pump inhibitor, SD: standard deviation.

[*] Concomitant users of oral GCs and PPIs are patients who had at least one co-prescription of an oral GC and PPI during follow-up.

[†] Users of oral GCs alone are patients who had at least one prescription of an oral GC during follow-up without having prescribed PPI and excluding concomitant users.

[‡] Users of PPIs alone are patients who had at least one prescription of a PPI during follow-up without having prescribed oral GCs and excluding concomitant users and users of oral GCs alone.

[§] At the index date.

[¶] Major infections included sepsis, meningitis, and upper and lower respiratory tract infections.

Concomitant current use of oral GCs and PPIs in patients with RA was associated with a 1.6-fold increased risk of OP fractures compared with non-use of both drugs (adjusted HR (adj. HR): 1.60, 95% CI: 1.35 to 1.89; Table 6.2). Both oral GC and PPI use alone had a 1.2-fold increased risk of OP fracture (adj. HR: 1.23, 95% CI: 1.03 to 1.47 (oral GC use alone); adj. HR: 1.22, 95% CI: 1.05 to 1.42 (PPI use alone)). The OP fracture risk associated with the current use of oral GCs or PPIs alone was statistically different from concomitant use. There was no significant increase in OP fracture risk in those patients who had stopped taking oral GCs or PPIs for more than 6 months (recent and past users) versus non-use. Considering calcium/vitamin D and bisphosphonates as confounders reduced the association to a 1.4-fold increased fracture risk for concomitant users and to a statistically non-significant risk for oral GC use alone versus non-use (Supplementary Table S6.3).

Table 6.3 shows that among patients with RA, most OP fracture sites were statistically significantly associated with concomitant current use of oral GCs and PPIs versus non-use. With concomitant current use of oral GCs and PPIs, we observed a 1.5-fold increased risk of hip fracture, a 2.8-fold increased risk of clinical vertebral fracture, a 2.5-fold increased risk of pelvic fracture and a 4-fold increased risk of rib fracture. Risks of fracture of the humerus or forearm were not increased.

Table 6.4 shows the stratification of concomitant oral GC and PPI use by average daily doses of GCs and then substratification by average daily doses and continuous duration of PPI use. There was no increased fracture risk with increasing PPI daily doses. Under all strata of GC use, short-term PPI use (≤1 year) was associated with higher fracture risk, but there was no association between long-term PPI use (>1 year) and OP fractures. When concomitant use of GCs and PPIs was stratified by cumulative GC use and then substratified by PPI use, similar associations were observed (Supplementary Table S6.2).

The second sensitivity analysis including prevalent users of GCs and PPIs (N=21,650) resulted in similar estimates to the main analyses (Supplementary Table S6.4). In the third sensitivity analysis (N=14,602), current PPI use was associated with a 1.3-fold increased risk of OP fractures (adj. HR: 1.30, 95% CI: 1.15 to 1.47) versus non-use (Supplementary Table S6.5).

Table 6.2. OP fracture risk by concomitant use of oral GCs and PPIs in patients with rheumatoid arthritis.

By recency of use	Number of OP fractures (N=1411)*	IR per 1000 PYs	Age/Sex adjusted Hazard Ratio (95% CI)	Fully adjusted Hazard Ratio† (95% CI)
Non-use of GCs and PPIs	325	10.5	Reference	Reference
Current use‡				
GCs and PPIs concomitantly	264	24.4	**1.93 (1.65-2.27)**	**1.60 (1.35-1.89)**
GCs alone	178	15.5	**1.34 (1.12-1.59)**	**1.23 (1.03-1.47)**§
PPIs alone	324	16.7	**1.32 (1.14-1.54)**	**1.22 (1.05-1.42)**§
Recent GC use‡ ¶	34	11.0	0.87 (0.62-1.23)	0.82 (0.58-1.16)
Recent PPI use‡ ¶	49	16.0	1.21 (0.90-1.62)	1.17 (0.87-1.57)
Past GC use‡ ¶	339	15.6	**1.16 (1.01-1.33)**	1.13 (0.98-1.29)
Past PPI use‡ ¶	219	13.5	0.96 (0.82-1.13)	0.94 (0.80-1.10)

CI: confidence interval, GCs: glucocorticoids, IR: incidence rate, OP: osteoporotic, PPIs: proton pump inhibitors, PYs: person years. Statistically significant hazard ratios are shown in bold.

* 1411 OP fracture events among all included patients with RA. The number of events in exposure groups do not sum to this total due to the overlap between recent and past use of GCs and PPIs.

† Adjusted at baseline for sex, body mass index, smoking status, and alcohol use; during follow-up for age, a history of ankylosing spondylitis, chronic obstructive pulmonary disease, dementia, falls (in the past 7–12 months) and inflammatory bowel disease; and use in the past 6 months of antidepressants, paracetamol, non-selective non-steroidal anti-inflammatory drugs, cyclo-oxygenase-2 selective inhibitors, tramadol, opioids, and conventional synthetic disease-modifying antirheumatic drugs.

‡ Current, recent and past use refer to the last prescription within 6 months, 7–12 months and >12 months before a period, respectively.

§ Statistically different from concomitant GC and PPI use, Wald test P <0.05.

¶ Regardless of the use of the other drug.

Table 6.3. OP fracture risk by concomitant use of oral GCs and PPIs in patients with rheumatoid arthritis, stratified by fracture type.

By recency of use	Hip (N=541)		Clinical vertebral (N=224)		Humerus (N=372)		Forearm (N=302)	
	IR per 1000 PYs	Fully adjusted Hazard Ratio* (95% CI)	IR per 1000 PYs	Fully adjusted Hazard Ratio† (95% CI)	IR per 1000 PYs	Fully adjusted Hazard Ratio‡ (95% CI)	IR per 1000 PYs	Fully adjusted Hazard Ratio§ (95% CI)
Non-use of GCs and PPIs	3.8	Reference	1.0	Reference	2.9	Reference	2.5	Reference
Current use††								
GCs and PPIs concomitantly	9.0	**1.45 (1.11-1.91)**	5.4	**2.84 (1.87-4.32)**	5.8	1.29 (0.93-1.78)	2.9	0.87 (0.57-1.32)
GCs alone	6.0	1.26 (0.95-1.66)	1.8	1.31 (0.79-2.16)‡‡	3.3	0.99 (0.69-1.43)	3.2	1.17 (0.81-1.70)
PPIs alone	5.9	1.10 (0.86-1.41)	3.1	**1.78 (1.20-2.65)**‡‡	4.5	1.17 (0.88-1.55)	3.3	0.98 (0.71-1.37)
Recent GC use†† §§	5.9	1.25 (0.78-2.01)	1.2	0.59 (0.22-1.63)	1.5	0.42 (0.17-1.03)	3.1	1.00 (0.52-1.91)
Recent PPI use†† §§	5.3	1.00 (0.60-1.65)	2.8	1.73 (0.85-3.54)	3.4	0.93 (0.50-1.72)	3.7	1.09 (0.60-2.00)
Past GC use†† §§	5.5	1.08 (0.86-1.35)	2.4	1.12 (0.78-1.59)	3.7	0.98 (0.75-1.27)	3.6	1.19 (0.90-1.58)
Past PPI use†† §§	5.4	0.98 (0.76-1.27)	1.9	1.11 (0.71-1.74)	2.7	0.72 (0.51-1.01)	3.0	0.86 (0.61-1.21)

AD: antidepressants, AS: ankylosing spondylitis, BMI: body mass index, CI: confidence interval, COPD: chronic obstructive pulmonary disease, COX-2: cyclo-oxygenase-2, csDMARDs: conventional synthetic disease-modifying antirheumatic drugs, GCs: glucocorticoids, IBD: inflammatory bowel disease, IR: incidence rate, NSAIDs: non-steroidal anti-inflammatory drugs, OP: Osteoporotic, OPI: opioids stronger than tramadol, PPIs: proton pump inhibitors, PYs: person years. Statistically significant hazard ratios are shown in bold.

* Adjusted at baseline for sex, BMI, smoking status, and alcohol use; during follow-up for age, a history of anaemia, AS, COPD, dementia, falls (in the past 7–12 months) and IBD; and use in the past 6 months of AD, hypnotics/anxiolytics, paracetamol, non-selective NSAIDs, COX-2 selective inhibitors, tramadol, OPI and csDMARDs.

† Adjusted at baseline for sex, BMI, smoking status, and alcohol use; during follow-up for age, a history of COPD, falls (in the past 7–12 months) and IBD; and use in the past 6 months of AD, anticonvulsants, paracetamol, non-selective NSAIDs, COX-2 selective inhibitors, tramadol, OPI and csDMARDs.

‡ Adjusted at baseline for sex, BMI, smoking status, and alcohol use; during follow-up for age, a history of anaemia, AS, COPD, dementia, falls (in the past 7–12 months) and IBD; and use in the past 6 months of AD, paracetamol, non-selective NSAIDs, COX-2 selective inhibitors, tramadol, OPI and csDMARDs.

§ Adjusted at baseline for sex, BMI, smoking status, and alcohol use; during follow-up for age, a history of anaemia, type 2 diabetes mellitus, COPD, dementia, falls (in the past 7–12 months), gastro-oesophageal reflux disease and IBD; and use in the past 6 months of AD, anticoagulants, anticonvulsants, antihypertensives, paracetamol, non-NSAIDs, COX-2 selective inhibitors, tramadol, OPI and csDMARDs.

†† Current, recent and past use refer to the last prescription within 6 months, 7–12 months and >12 months before a period, respectively.

‡‡ Statistically different from concomitant GC and PPI use within the same fracture type, Wald test $P < 0.05$.

§§ Regardless of the use of the other drug.

Table 6.3. (Continued)

By recency of use	Pelvis (N=116)		Rib (N=90)	
	IR per 1000 PYs	Fully adjusted Hazard Ratio[¶] (95% CI)	IR per 1000 PYs	Fully adjusted Hazard Ratio[**] (95% CI)
Non-use of GCs and PPIs	0.6	Reference	0.6	Reference
Current use[††]				
GCs and PPIs concomitantly	2.9	**2.47 (1.41-4.34)**	1.7	**4.03 (2.13-7.63)**
GCs alone	0.9	1.07 (0.54-2.14)[‡‡]	1.2	**2.28 (1.17-4.46)**
PPIs alone	1.6	**1.93 (1.11-3.34)**	0.8	1.24 (0.66-2.34)[‡‡]
Recent GC use[††] [§§]	1.2	0.97 (0.35-2.72)	0.6	1.21 (0.29-5.14)
Recent PPI use[††] [§§]	0.9	1.16 (0.35-3.87)	1.5	2.17 (0.83-5.62)
Past GC use[††] [§§]	0.8	0.64 (0.37-1.11)	1.2	**2.43 (1.39-4.22)**
Past PPI use[††] [§§]	0.9	1.17 (0.62-2.20)	0.6	0.86 (0.43-1.75)

[¶] Adjusted at baseline for sex, during follow-up for age and use in the past 6 months of AD, paracetamol and OPI.
[**] Adjusted at baseline for sex and during follow-up for age.
[††] Current, recent and past use refer to the last prescription within 6 months, 7–12 months and >12 months before a period, respectively.
[‡‡] Statistically different from concomitant GC and PPI use within the same fracture type, Wald test *P* <0.05.
[§§] Regardless of the use of the other drug.

e. Discussion

Concomitant use of oral GCs and PPIs was associated with an increased risk of OP fractures compared with non-use in patients with RA. This was significantly higher when compared with the single use of oral GCs or PPIs. Increased fracture risk associated with concomitant GC and PPI use was observed for fractures of the hip, clinical vertebrae, pelvis and ribs, but not for those of the humerus or forearm. Among concomitant users, there was no increased OP fracture risk with higher daily dose or longer duration of PPI use.

This is the first study, to our knowledge, that looked into the association between concomitant use of GCs and PPIs and the risk of OP fracture in patients with RA. A Dutch population-based study found a 1.3-fold to 2.4-fold increased risk of hip/femur fracture with concomitant use of PPIs and various daily doses of oral GCs.[16] This is in line with our finding for the concomitant current use of GCs and PPIs (adj. HR: 1.60) and most of the strata of concomitant use in Table 6.4. However, their reference group was different and limited to never PPI users. Moreover, they focused on 18+ general population, whereas we included patients with RA aged 50+ years with higher baseline fracture risks.

Table 6.4. OP fracture risk by average daily dose of oral GC use in rheumatoid arthritis patients, stratified by average daily dose and continuous duration of PPI use.

By recency of use	OP fractures (N=1411)*	IR per 1000 PYs	Age/Sex adjusted Hazard Ratio (95% CI)	Fully adjusted Hazard Ratio† (95% CI)
Non-use of GCs and PPIs	325	10.5	Reference	Reference
Current use of GCs and PPIs concomitantly‡	264	24.4	**1.93 (1.65-2.27)**	**1.60 (1.35-1.89)**
❶*Low GC use (DD ≤7.5 mg PED/day)*				
+ Low-dose PPI use (DD <20 mg OED/day)	142	23.2	**1.75 (1.44-2.13)**	**1.42 (1.16-1.74)**
+ Medium-dose PPI use (DD 20–35 mg OED/day)	39	24.9	**1.93 (1.39-2.69)**	**1.54 (1.10-2.16)**
+ High-dose PPI use (DD >35 mg OED/day)	8	34.2	**2.72 (1.35-5.47)**	**2.10 (1.04-4.24)**
+ Short-term continuous PPI use (≤1 year)	89	25.7	**2.00 (1.59-2.52)**	**1.60 (1.26-2.04)**
+ Long-term continuous PPI use (>1 year)	71	20.3	**1.49 (1.15-1.93)**	1.18 (0.91-1.53)
+ No continuous duration of PPI§	29	30.4	**2.36 (1.62-3.45)**	**2.00 (1.36-2.93)¶**
❷*Medium GC use (DD 7.6–14.9 mg PED/day)*				
+ Low-dose PPI use (DD <20 mg OED/day)	43	25.0	**2.22 (1.62-3.04)**	**1.76 (1.27-2.43)**
+ Medium-dose PPI use (DD 20–35 mg OED/day)	19	27.7	**2.41 (1.52-3.82)**	**1.92 (1.20-3.05)**
+ High-dose PPI use (DD >35 mg OED/day)	<5	17.2	1.46 (0.36-5.86)	1.26 (0.31-5.07)
+ Short-term continuous PPI use (≤1 year)	36	30.2	**2.70 (1.92-3.80)**	**2.20 (1.55-3.11)**
+ Long-term continuous PPI use (>1 year)	23	20.9	**1.78 (1.17-2.72)**	1.37 (0.89-2.10)
+ No continuous duration of PPI§	5	22.3	2.00 (0.83-4.84)	1.67 (0.69-4.03)
❸*High GC use (DD ≥15.0 mg PED/day)*				
+ Low-dose PPI use (DD <20 mg OED/day)	5	21.1	1.92 (0.79-4.64)	1.58 (0.65-3.81)
+ Medium-dose PPI use (DD 20–35 mg OED/day)	<5	38.8	**3.77 (1.41-10.09)**	**3.05 (1.13-8.18)**
+ High-dose PPI use (DD >35 mg OED/day)	<5	41.1	3.83 (0.95-15.37)	3.30 (0.82-13.26)
+ Short-term continuous PPI use (≤1 year)	9	34.1	**3.21 (1.66-6.21)**	**2.72 (1.40-5.27)**
+ Long-term continuous PPI use (>1 year)	<5	11.3	0.99 (0.14-7.08)	0.72 (0.10-5.15)
+ No continuous duration of PPI§	<5	27.1	2.65 (0.37-18.90)	2.38 (0.33-16.97)

CI: confidence interval, DD: average daily dose, GCs: glucocorticoids, IR: incidence rate, OED: omeprazole equivalent dose, OP: osteoporotic, PED: prednisolone equivalent dose, PPIs: proton pump inhibitors, PYs: person years. Statistically significant hazard ratios are shown in bold.

* 1411 OP fracture events among all included patients with RA. The number of fractures in exposure groups do not sum to this total due to not reporting the current only use and recent and past use of GCs and PPIs.

† Adjusted at baseline for sex, body mass index, smoking status, and alcohol use; during follow-up for age, a history of anaemia, ankylosing spondylitis, chronic obstructive pulmonary disease, dementia, falls (in the past 7–12 months) and inflammatory bowel disease; use in the past 6 months of antidepressants, paracetamol, non-selective non-steroidal anti-inflammatory drugs, cyclo-oxygenase-2 selective inhibitors, tramadol, opioids and conventional synthetic disease-modifying antirheumatic drugs; and current only use and recent and past use of oral GCs and PPIs.

‡ Concomitant current use refers to the most recent prescription of both oral GCs and PPIs in the 6 months before the start of a period.

§ This represents fracture events that happened during a current period of PPI use but not eligible for a continuous duration of use calculation (i.e., up to 6 months after the last PPI prescription, but after 1-month threshold gap of our definition for the continuous duration of PPI use).

¶ Statistically different from long-term continuous PPI use within the same category, Wald test P <0.05.

Our results regarding the higher fracture risk with PPI use are partly in line with several previous observational studies.[11,12,15-17] A meta-analysis of observational studies in non-RA patients reported increased risk of hip and spine fracture with PPI use (relative risks of 1.30 and 1.56, respectively),[14] which is comparable with adj. HR of 1.30 for current PPI use

and OP fractures in our study. However, a recent study in patients with RA did not reveal a higher risk of OP fractures with PPI use, which was attributed to higher use of bisphosphonates among PPI users.[22] Previous studies found stronger associations with higher daily doses of PPIs,[11] or with 7 years of PPI use and fracture risk,[12] whereas another older study that used the same data source but a different reference group did not report any dose–response or duration–response relationships at all.[17] Our findings (i.e., no specific trend with longer duration or higher daily doses of PPI use) are comparable to the latter study.

Our findings in the single GC use group were generally consistent with the literature. Previous observational studies have reported increased OP fracture risks in patients with RA with current GC use between 43% and 70%, higher than the 23% increased risk that we found.[1,31] We used a different reference group (non-users of both GCs and PPIs), which may also explain the unexpected lack of statistical significance for a higher risk of clinical vertebral fracture with current GC use alone.

The magnitude of the association between concomitant GC and PPI use and the risk of OP fracture may indicate an additive effect of the individual drugs rather than a synergistic effect. This was suggested by a significantly higher fracture risk with concomitant GC and PPI use compared with monotherapy with either drug and as the observed HRs seem to be additive. This may be related to different biological mechanisms of GCs and PPIs acting on osteoporosis or falling. The effect of GCs on bone is mostly via decreased bone formation and interference with active bone remodelling sites.[1,6,8,9] But additionally, GCs might increase the fracture risk by inducing muscle atrophy or cataract especially with higher doses and in long-term use.[37-39] Previous studies have shown that the onset and offset of the effects of GCs on fracture risk are rather rapid, which is supported by our results.[7,31,40] Similar to GCs, the positive association of fracture risk with PPI use quickly subsided when the patient discontinued the treatment (after 6 months). But for PPIs, underlying pharmacological effects on fracture are not well understood.[41,42] The US Food and Drug Administration published a drug safety communication for a possible increased fracture risk with PPI use in 2011, which remained unchanged to date and was based on evidence from observational studies.[43] This was later criticised for not being supported by a clear biological mechanism.[44]

Various pharmacological mechanisms have been proposed to explain the PPI use and fracture risk association. Reduced intestinal absorption of calcium was previously suggested due to induced hypochlorhydria by PPI therapy and the effect on bone quality.[10] However, a more recent trial found no BMD changes after 52 weeks and non-

significant changes in bone turnover markers after 26 weeks with dexlansoprazole or esomeprazole use.[45] An alternative mechanism is an increased falling risk due to muscle weakness and drowsiness, caused by malabsorption of magnesium or vitamin B12.[18-20,46,47] Long-term PPI therapy (≥1 year) in elderly women was shown to significantly reduce serum vitamin B12 levels and double the 5-year risk of injurious falling-related and fracture-related hospitalisation.[46] But the design of this study did not consider proper timing of the exposure and outcome, which limits its interpretation. A third mechanism is effects on osteoclasts to increase bone resorption by PPIs.[48] Finally, methodological explanations for the observed associations include selection bias and/or unknown confounding.[16,17,44] Significant association only with short-term PPI use and no specific trend with increasing daily doses do not fit into any of the proposed mechanisms mentioned above. As we used different strategies in design and analysis to avoid potential sources of bias and to adjust for confounding, and when the GC findings are supported by previous literature with well-known biological mechanisms, the mere explanation of the PPI results by unmeasured confounding would be difficult. Hence, more research is recommended to elaborate on the exact biological mechanism of PPIs on bone.

This study had several strengths. We used data from the CPRD, which is one of the world's largest primary care databases. Our study had a substantial mean duration of follow-up (9.1 years for concomitant users). To bring more insight into the observed association, we stratified GC and PPI use by recency of use, average daily and cumulative dose, and duration of treatment. Furthermore, all analyses were performed time-dependently, incorporating all follow-up times, to avoid time-related biases. There were also several limitations. Biological therapies, especially during hospitalisation, and some RA severity indices (e.g., the disease activity score in 28 joints [DAS-28]) were not adequately captured in the CPRD as a general practice database, which might have introduced confounding by indication or disease severity. Patients with higher disease activity may have an elevated risk of fracture and be more prone to receive oral GCs/PPIs. Also, an improved clinical status might have led to both discontinuation of drug(s) and lower fracture rates. To partly overcome this, we statistically adjusted our analyses for six indicators of RA severity, including analgesics and csDMARDs. We cannot confirm the actual use of medications as we only had prescribing information, and GCs and PPIs are often prescribed on an "as needed" basis. The over-the-counter use of PPIs was also not captured. However, with an average duration of use of >3 years, repeated prescriptions are indicators of actual use. Finally, the number of vertebral fractures might be

underestimated, as some of them might not immediately come into clinical attention.[49,50] This might virtually increase the HRs for vertebral fractures due to detection bias.[35]

In conclusion, there was an interaction in the risk of OP fracture with concomitant use of oral GCs and PPIs. This increased risk seems to emerge from separate mechanisms of action of GCs and PPIs on bone or falling risk. Considering the increasing life expectancies and high consumption of PPIs among elderly patients, fracture risk assessment could be considered when a patient with RA is co-prescribed oral GCs and PPIs.

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g. Supplementary material

Table S6.1. Criteria from Thomas et al. algorithm to detect true cases of rheumatoid arthritis in the General Practice Research Database, also used in the updated version by Muller et al.[26,27]

Criterion 1	At least one diagnostic Read code for RA and at least one appropriate prescription of a DMARD with no alternative indication for the DMARD;
OR	
Criterion 2	all three of the following: a) two or more diagnostic Read codes for RA (on different dates). b) no alternative diagnosis after the final RA code. c) RA code in group 1 (seropositive or erosive RA) or group 2 ('rheumatoid arthritis' codes e.g., RA of knee), opposed to only group 3 (systemic manifestations of RA) or group 4 (seronegative RA or other weak evidence of RA).

DMARD: disease-modifying antirheumatic drugs, RA: rheumatoid arthritis.

Table S6.2. OP fracture risk by cumulative use of oral GCs in rheumatoid arthritis patients, stratified by average daily dose and duration of use of PPIs.

By recency of use	OP fractures (N=1411)*	IR per 1000 PYs	Age/Sex adjusted Hazard Ratio (95% CI)	Fully adjusted Hazard Ratio† (95% CI)
Non-use of GCs and PPIs	325	10.5	Reference	Reference
Current use of GCs and PPIs concomitantly‡	264	24.4	**1.93 (1.65-2.27)**	**1.60 (1.35-1.89)**
❶*Low GC use (CD ≤1.0 g PED)*				
+ Low-dose PPI use (DD <20 mg OED/day)	21	25.4	**2.10 (1.36-3.27)**	**1.79 (1.15-2.79)**
+ Medium-dose PPI use (DD 20–35 mg OED/day)	<5	15.3	1.33 (0.50-3.56)	1.10 (0.41-2.96)
+ High-dose PPI use (DD >35 mg OED/day)	<5	22.7	1.86 (0.46-7.46)	1.61 (0.40-6.47)
+ Short-term continuous PPI use (≤1 year)	18	26.4	**2.22 (1.38-3.56)**	**1.89 (1.17-3.03)**
+ Long-term continuous PPI use (>1 year)	<5	7.7	0.62 (0.15-2.47)	0.50 (0.12-2.01)
+ No continuous duration of PPI§	7	29.9	**2.54 (1.20-5.37)**	**2.25 (1.06-4.75)**
❷*Medium GC use (CD 1.1-4.9 g PED)*				
+ Low-dose PPI use (DD <20 mg OED/day)	61	29.5	**2.34 (1.79-3.07)**	**1.95 (1.48-2.57)**
+ Medium-dose PPI use (DD 20–35 mg OED/day)	19	27.0	**2.22 (1.40-3.52)**	**1.82 (1.15-2.90)**
+ High-dose PPI use (DD >35 mg OED/day)	<5	28.5	2.32 (0.87-6.22)	1.85 (0.69-4.97)
+ Short-term continuous PPI use (≤1 year)	50	30.8	**2.53 (1.89-3.40)**	**2.11 (1.57-2.84)**
+ Long-term continuous PPI use (>1 year)	21	23.2	**1.75 (1.12-2.71)**	1.41 (0.91-2.20)
+ No continuous duration of PPI§	13	34.1	**2.78 (1.60-4.84)**	**2.40 (1.38-4.17)**
❸*High GC use (CD ≥5.0 g PED)*				
+ Low-dose PPI use (DD <20 mg OED/day)	108	20.8	**1.61 (1.30-2.00)**	**1.26 (1.01-1.58)**
+ Medium-dose PPI use (DD 20–35 mg OED/day)	39	28.0	**2.22 (1.59-3.09)**	**1.72 (1.23-2.41)**
+ High-dose PPI use (DD >35 mg OED/day)	6	35.1	**2.94 (1.31-6.59)**	**2.28 (1.01-5.12)**
+ Short-term continuous PPI use (≤1 year)	66	25.3	**2.01 (1.54-2.62)**	**1.56 (1.19-2.05)**
+ Long-term continuous PPI use (>1 year)	72	20.4	**1.55 (1.20-2.01)**	1.20 (0.92-1.56)
+ No continuous duration of PPI§	15	25.0	**1.93 (1.15-3.24)**	1.59 (0.95-2.67)

Table S6.2. (Continued)

CI: confidence interval, CD: cumulative dose, DD: average daily dose, GCs: glucocorticoids, IR: incidence rate, OED: omeprazole equivalent dose, OP: osteoporotic, PED: prednisolone equivalent dose, PPIs: proton pump inhibitors, PYs: person years. Statistically significant hazard ratios are shown in bold. None of the Wald tests comparing exposure states within the same category were statistically significant.

* 1411 OP fracture events among all included RA patients. The number of fractures in exposure groups do not sum to this total due to not reporting the current only use and recent and past use of GCs and PPIs.

† Adjusted at baseline for sex, body mass index, smoking status and alcohol use, and during follow-up for age, a history of anaemia, ankylosing spondylitis, chronic obstructive pulmonary disease, dementia, falls (in the past 7-12 months), inflammatory bowel disease, and the use in the past 6-months of antidepressants, paracetamol, non-selective non-steroidal anti-inflammatory drugs, cyclooxygenase-2 selective inhibitors, tramadol, opioids, conventional synthetic disease modifying antirheumatic drugs, and current only use and recent and past use of oral glucocorticoids and proton pump inhibitors.

‡ Concomitant current use refers to the most recent prescription of both oral GCs and PPIs within the 6 months before the start of a period.

§ This represents fracture events that happened during a current period of PPI use but not eligible for a continuous duration of use calculation (i.e., up to 6 months after the last PPI prescription, but after 1-month threshold gap of our definition for the continuous duration of PPI use).

Table S6.3. Sensitivity analysis 1, the association between concomitant use of oral GCs and PPIs and OP fracture risk after adding calcium/vitamin D and bisphosphonates as confounders to the Cox model.

By recency of use	Number of OP fractures (N=1411)*	IR per 1000 PYs	Age/Sex adjusted Hazard Ratio (95% CI)	Fully adjusted Hazard Ratio† (95% CI)
Non-use of GCs and PPIs	325	10.5	Reference	Reference
Current use‡				
GCs and PPIs concomitantly	264	24.4	**1.93 (1.65-2.27)**	**1.39 (1.16-1.66)**
GCs alone	178	15.5	**1.34 (1.12-1.59)**	1.11 (0.92-1.33)§
PPIs alone	324	16.7	**1.32 (1.14-1.54)**	**1.20 (1.03-1.40)**§
Recent GC use‡ ¶	34	11.0	0.87 (0.62-1.23)	0.79 (0.56-1.12)
Recent PPI use‡ ¶	49	16.0	1.21 (0.90-1.62)	1.16 (0.86-1.56)
Past GC use‡ ¶	339	15.6	**1.16 (1.01-1.33)**	1.10 (0.96-1.27)
Past PPI use‡ ¶	219	13.5	0.96 (0.82-1.13)	0.93 (0.79-1.10)

CI: confidence interval, GCs: glucocorticoids, IR: incidence rate, OP: osteoporotic, PPIs: proton pump inhibitors, PYs: person years. Statistically significant hazard ratios are shown in bold.

* 1411 OP fracture events among all included patients with RA. The number of events in exposure groups do not sum to this total due to the overlap between recent and past use of GCs and PPIs.

† Adjusted at baseline for sex, body mass index, smoking status, and alcohol use, and during follow-up for age, a history of ankylosing spondylitis, chronic obstructive pulmonary disease, dementia, falls (in the past 7-12 months), inflammatory bowel disease, and the use in the past 6-months of calcium/vitamin D supplements, bisphosphonates, antidepressants, paracetamol, non-selective non-steroidal anti-inflammatory drugs, cyclooxygenase-2 selective inhibitors, tramadol, opioids, conventional synthetic disease modifying antirheumatic drugs.

‡ Current, recent and past use refer to the last prescription within 6 months, 7–12 months and >12 months before a period, respectively.

§ Statistically different from concomitant GC and PPI use, Wald test $P < 0.05$.

¶ Regardless of the use of the other drug.

Table S6.4. Sensitivity analysis 2, evaluating a prevalent user cohort instead of a new-user cohort (Table 6.2). OP fracture risk by concomitant use of oral GCs and PPIs in patients with rheumatoid arthritis (N=21,650).

By recency of use	Number of OP fractures (N=2384)*	IR per 1000 PYs	Age/Sex adjusted Hazard Ratio (95% CI)	Fully adjusted Hazard Ratio† (95% CI)
Non-use of GCs and PPIs	325	10.5	Reference	Reference
Current use‡				
GCs and PPIs concomitantly	613	25.0	**2.00 (1.76-2.26)**	**1.63 (1.43-1.85)**
GCs alone	363	16.8	**1.33 (1.17-1.52)**	**1.21 (1.06-1.38)**§
PPIs alone	622	16.5	**1.34 (1.19-1.51)**	**1.21 (1.07-1.37)**§
Recent GC use‡¶	66	11.7	0.85 (0.66-1.10)	0.81 (0.63-1.05)
Recent PPI use‡¶	93	17.3	**1.30 (1.04-1.62)**	**1.24 (1.00-1.55)**
Past GC use‡¶	541	15.3	1.07 (0.96-1.20)	1.05 (0.94-1.17)
Past PPI use‡¶	376	14.4	1.04 (0.91-1.18)	1.00 (0.88-1.14)

CI: confidence interval, GCs: glucocorticoids, IR: incidence rate, OP: osteoporotic, PPIs: proton pump inhibitors, PYs: person years. Statistically significant hazard ratios are shown in bold.

* 2384 OP fracture events among all included RA patients. The number of events in exposure groups do not sum to this total due to overlap between recent and past use of GCs and PPIs.

† Adjusted at baseline for sex, body mass index, smoking status, and alcohol use, and during follow-up for age, a history of ankylosing spondylitis, chronic obstructive pulmonary disease, dementia, falls (in the past 7-12 months), inflammatory bowel disease, and the use in the past 6-months of antidepressants, paracetamol, non-selective non-steroidal anti-inflammatory drugs, cyclooxygenase-2 selective inhibitors, tramadol, opioids, conventional synthetic disease modifying antirheumatic drugs.

‡ Current, recent and past use refer to the last prescription within 6 months, 7–12 months and >12 months before a period, respectively.

§ Statistically different from concomitant GC and PPI use, Wald test *P* <0.05.

¶ Regardless of the use of the other drug.

Table S6.5. Sensitivity analysis 3, OP fracture risk by use of PPIs in patients with rheumatoid arthritis (N=14,602).

By recency of use	Number of OP fractures (N=1629)*	IR per 1000 PYs	Age/Sex adjusted Hazard Ratio (95% CI)	Fully adjusted Hazard Ratio† (95% CI)
Non-use of PPIs	680	11.9	Reference	Reference
Current PPI use‡	626	19.8	**1.52 (1.35-1.70)**	**1.30 (1.15-1.47)**
Recent PPI use‡	58	17.0	**1.31 (1.00-1.72)**	1.23 (0.94-1.61)
Past PPI use‡	265	14.1	1.04 (0.90-1.21)	1.00 (0.86-1.16)

CI: confidence interval, IR: incidence rate, OP: osteoporotic, PPIs: proton pump inhibitors, PYs: person years. Statistically significant hazard ratios are shown in bold.

* 1629 osteoporotic fracture events among all included RA patients.

† Adjusted at baseline for sex, body mass index, smoking status and alcohol use, and during follow-up for age, a history of ankylosing spondylitis, chronic obstructive pulmonary disease, dementia, falls (in the past 7-12 months), inflammatory bowel disease, and the use in the past 6-months of oral glucocorticoids, antidepressants, paracetamol, non-selective non-steroidal anti-inflammatory drugs, cyclooxygenase-2 selective inhibitors, tramadol, opioids, conventional synthetic disease modifying antirheumatic drugs.

‡ Current, recent and past use refer to the last prescription within 6 months, 7–12 months and >12 months before a period, respectively.

CHAPTER 7

Biological disease-modifying antirheumatic drugs and osteoporotic fracture risk in patients with rheumatoid arthritis: a Danish cohort study with prevalent new-user design

Shahab Abtahi

René Cordtz

Lene Dreyer

Johanna H M Driessen

Annelies Boonen

Andrea M Burden

Submitted

CHAPTER 8

General Discussion

In this final chapter, first a summary of the main findings of each study will be provided, in the light of the existing knowledge gaps and the objective and sub-objectives of this thesis. The overall objective of this thesis was to study the osteoporotic (OP) fractures and their relation to mortality, medication use and rheumatoid arthritis (RA). The first sub-objective aimed to investigate various attributes of OP fractures in the general population, including a recent secular trend, the mortality after fracture in association with oral bisphosphonate (BP) use, and the association between various exposure patterns of oral glucocorticoids (GCs) and OP fracture risk. The second sub-objective was to evaluate the role of medications, including low-dose oral GCs, concomitant use of oral GCs and proton pump inhibitors (PPIs), and biological disease-modifying antirheumatic drugs (bDMARDs), in the risk of OP fractures among patients with RA. Following the summary, findings will be compared to those of the key published studies addressing the same research area/ topic. Then, a methodological evaluation of the studies in this thesis will be provided by introducing the major limitations of pharmacoepidemiological research, their examples in our studies, and the strategies that we adopted to avoid them. Finally, the clinical impact of our findings and some potential future ideas for research will be presented.

a. Main findings

The aim of **Section 1** was to evaluate various attributes of OP fractures in the general population. This included an investigation of recent secular trends in incidence rates (IRs) of OP fractures in the general population of Denmark in **Chapter 2**. In a series of contiguous cross-sectional analyses, we found a general decline in IRs of major OP fractures (MOF) for 50+ adults in Denmark between 1995 and 2010. The overall IR dropped from 169.8 per 10,000 person years (PYs) in 1995 to 148.0 per 10,000 PYs in 2010. The remarkable finding was the declining hip fracture rate among both men (from 36.5 in 1995 to 29.6 in 2010 per 10,000 PYs) and women (from 87.2 to 59.9 per 10,000 PYs). All other fracture sites (i.e., clinical vertebral, humerus, and forearm) were also declining in women. But in contrast, and with the exception of a gradual decrease in forearm fractures, increasing rates for clinical vertebral and steady rates for humerus fracture were observed in men. Another study using Danish data showed that the overall IR of hip and MOF in Denmark in 2011 was 43.8 and 142.0 per 10,000 PYs, respectively.[1] This obviously shows a continuous decreasing trend in hip and MOFs in Denmark from 1995 until 2011. Our findings were also in line with other studies from Denmark (from 1997 to

2006),[2] Canada (from 1985 to 2005),[3] US (from 1986 to 2005),[4] Minnesota, US (between 1989–1991 and 2009–2011),[5] and Manitoba, Canada (from 1986 to 2006),[6] respecting a generally declining trend in hip fracture rates in both sexes and an increasing trend in vertebral fractures especially among men.

The association between oral BP use and mortality risk following a MOF was evaluated in **Chapter 3**. Based on the evidence from the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) trial reporting a 28% mortality reduction with zoledronic acid use after hip fracture,[7] and some reported anti-atherosclerotic effects of BPs,[8,9] we hypothesised a reduced mortality rate with oral BP use after MOF in our study. To investigate this, we included all patients with a MOF in the UK Clinical Practice Research Datalink (CPRD) between 2000 and 2018. We observed a 7% increased risk of all-cause mortality after non-hip MOF, and a 28% reduced risk after hip fracture with current oral BP use versus never use. With the total follow-up time of BP use being 7.6 years in the non-hip MOF and 5.7 years in hip fracture group, censoring the follow-up time at 1- and 5-years shifted the association towards a stronger protective effect of BPs on mortality risk. In other words, the shorter the follow-up time, the greater the protective effect. This argues against anti-atherosclerotic properties of BPs, as both timing and effect size of the association revealed in our study do not support this hypothesis. Alternatively, unknown distortion due to healthy-user bias and selective prescribing, or unknown pleiotropic properties of BPs might be an explanation. Although, our finding of a 28% lower mortality with oral BP use after hip fracture was in line with a 28% mortality reduction observed in the HORIZON trial, the design, conduct and analysis of this trial was later criticised.[7,10] Furthermore, two meta-analyses of randomised controlled trials (RCTs), both including the HORIZON trial, did not find any association between all-cause mortality and BP use versus placebo.[11,12]

In **Chapter 4**, we explored the role of daily dose and cumulative exposure to oral GCs on OP fracture risk in the general population of Denmark. For doing this, we designed a case-control study using the Danish National Health Service data, which permitted us to include almost all patients with an OP fracture in Denmark between 1996 and 2011. Heavy users of oral GCs, defined as those taking oral GCs in high daily doses (≥15.0 mg prednisolone equivalent dose [PED] per day) and with a cumulative dose ≥1.0 g PED had a distinctive 2.9-fold increased risk of hip fracture and a 4.4-fold increased risk of clinical vertebral fracture, compared to non-use. This was in clear contrast to short-course users (taking oral GCs ≥15.0 mg PED/day but with a cumulative dose <1.0 g PED), who experienced a 1.4-fold increased risk of hip fracture and a 2.1-fold increased risk of clinical

vertebral fracture versus non-use. However, risk of forearm fracture was non-significant to slightly increased among current users of oral GCs in various dosages. Our findings were in line with an older study that showed a similar effect modification of the combination of daily and cumulative doses of oral GCs on hip/femur and vertebral fracture risk.[13] Presumably, the threshold for a marked increased fracture risk in high daily oral GC users is the cumulative use ≥1.0 g PED, which is a hallmark of long-term GC therapy.

The aim of **Section 2** was to investigate the risk of OP fracture with various medication use among patients with RA. The association between low-dose oral GC use (≤7.5 mg PED/day) and OP fracture risk in patients with RA was evaluated in **Chapter 5**. There is evidence from previous RCTs that 7.5 mg prednisolone once daily in early active RA could have a beneficial effect on bone loss in hands or hip.[14,15] Also, a review by the European Alliance of Associations for Rheumatology (EULAR) task force on the hazards of long-term GC therapy in RA was not decisive for risk of OP fracture with dosages between 5.0-10.0 mg PED, and concluded that the effect of low dose GC on bone was mostly dependent on patient-specific parameters.[16] We investigated this association in a retrospective cohort study using data from the UK CPRD between 1997 and 2017. Current use of low-dose oral GCs (≤7.5 mg PED/day) was not associated with overall risk of OP fractures (adjusted hazard ratio [adj. HR]: 1.14, 95% confidence interval [CI] 0.98-1.33) compared with past GC use. This lack of association between low-dose oral GC use and OP fracture risk was notwithstanding with an observed 22% increased risk with current oral GC therapy in our study and 49% to 70% increased risks reported by the previous literature.[13,17] There was no association between low-dose oral GC therapy and non-vertebral OP fracture sites versus past GC use; however, it incurred a 59% increased risk of clinical vertebral fracture. Within the limits of comparability, the elevated risk of clinical vertebral fracture with low-dose oral GC use in our study might be in line with lack of bone mineral density (BMD) conservation in the spine noticed in the RCT by Engvall et al.[15] It could be thought that any positive impact of low-dose GC on suppressing the chronic inflammation of RA is enough to offset its negative effect on bone resorption in most fracture sites but not in vertebrae.

The association between concomitant use of oral GCs and PPIs and OP fracture risk in patients with RA was studied in **Chapter 6**. Both drugs are commonly prescribed in RA, and both are associated with an increased fracture risk, albeit the biological mechanism is known for oral GCs but not yet for PPIs.[18-20] For conducting this study, we again used a cohort of RA patients from the UK CPRD between 1997 and 2017. We observed a 1.6-fold

increased risk of OP fractures with concomitant current use of oral GCs and PPIs in RA patients compared to non-use of both drugs. This was statistically different from a 1.2-fold increased fracture risk associated with single use of oral GCs or PPIs. Although, an interaction was suggested between oral GCs and PPIs in concomitant users on the risk of OP fracture, the interaction term, relative excess risk due to interaction (RERI), was not statistically significant.[21] Hence, there seems to be an additive effect of GCs and PPIs on bone and/or falling rather than a synergistic effect. We did not observe an increasing trend in fracture risk with higher daily doses or longer durations of PPI use, which is in contrast to older observational studies.[22,23] The timing and magnitude of our GC results were fairly in line with the previous literature,[17,24,25] explained by known effects of GCs on bone or falling, e.g. reduced bone formation, microarchitectural changes, and muscle atrophy.[18] In contrast, our PPI findings could not be mechanistically justified based on the few proposed biological mechanisms, such as hypochlorhydria and calcium malabsorption or an increased falling risk due to hypomagnesemia or malabsorption of vitamin B12.[26-28]

The last project in this thesis evaluated the association between use of bDMARDs and OP fracture risk in patients with RA compared with no biological treatment in **Chapter 7**. There is evidence from clinical trials reporting beneficial effects of bDMARDs on bone health in RA,[29-32] but the few observational studies have found no reduced fracture risk with biological drugs.[33-35] In order to investigate this, we conducted a retrospective cohort study using nationwide registries in Denmark with the possibility to include almost all RA patients under rheumatological care between 2006 and 2016.[36] This study has benefited from the novel prevalent new-user design, introduced by Suissa and colleagues in 2017,[37] which enabled us to match bDMARD users to bDMARD naïve patients by time-conditional propensity scores (PSs) in a pool of both incident and prevalent users of csDMARDs, as the first-line treatment in RA. We found no reduced risk of OP fractures with bDMARD use in patients with RA (HR 0.97, 95% CI 0.78-1.20), compared with no treatment with biologicals. The only known mechanism of action of bDMARDs on bone health is through the inflammatory cycle.[38] By using real-world data from a specialty clinical register, we can expect that the disease activity in bDMARD naïve patients has been also controlled during follow-up with a "treat-to-target" strategy of RA management by clinicians. Control of disease activity in both comparison groups could result in comparable beneficial effects on bone health and no observed reduction in fracture risk among bDMARD users compared with bDMARD naïve patients.

b. Methodological evaluation

The studies in this thesis were observational in design and used secondary healthcare data. Therefore, they are essentially prone to some inherent limitations of observational studies. A brief overview of the major limitations in observational research in general, and pharmacoepidemiological studies in particular, will be described in this part. Each limitation will be introduced and presented by examples that could have been occurred in the studies of this thesis. Then, the strategies that we adopted to avoid or minimise these limitations and their possible impact on the final results will be mentioned.

As previously mentioned in **Chapter 1**, pharmacoepidemiological studies complement RCTs by providing information on longer term or rarer adverse (or beneficial) effects of medications using real-world data. But both in theory and in practice, it is impossible to exactly reproduce the randomisation of an RCT in observational studies, in order to have two precisely identical comparing groups (beside the role of chance, and apart from the exposure and outcome of interest), and additionally to have internal and external validity generalisable to the source population.[39,40] This will be the source of two main types of methodological limitations in observational research including pharmacoepidemiological studies: confounding and bias. *Confounding* refers to the distortion of an estimated association between the exposure and outcome due to another determinant, which is associated with both the exposure and outcome but lies not in the causal pathway.[39,41] A *bias* signifies any systematic error in making an epidemiologic estimation (rather than a random error), which renders the findings of such study less valid.[40,41] Such a bias can occur in various stages of a scientific research such as in study design, data collection, analysis, reporting of the results, publication, or review of data.[42] It can result in differential (moving in either direction, away or towards the null) or non-differential (moving towards the null) distortion of the risk estimate. While we treat these two entities as separate methodological limitations in this thesis as per definition, there is a degree of overlap when classifying confounding and bias according to some authors.[43] Figure 8.1 shows a graphical depiction of different sorts of confounding and bias elaborated on in this chapter. A review of observational clinical studies based on large healthcare databases between 2000 and 2018 has shown that misclassification bias (under measurement [information] bias), confounding by indication (under confounding), and time-related biases were the most frequently reported limitations in pharmacoepidemiological studies.[44]

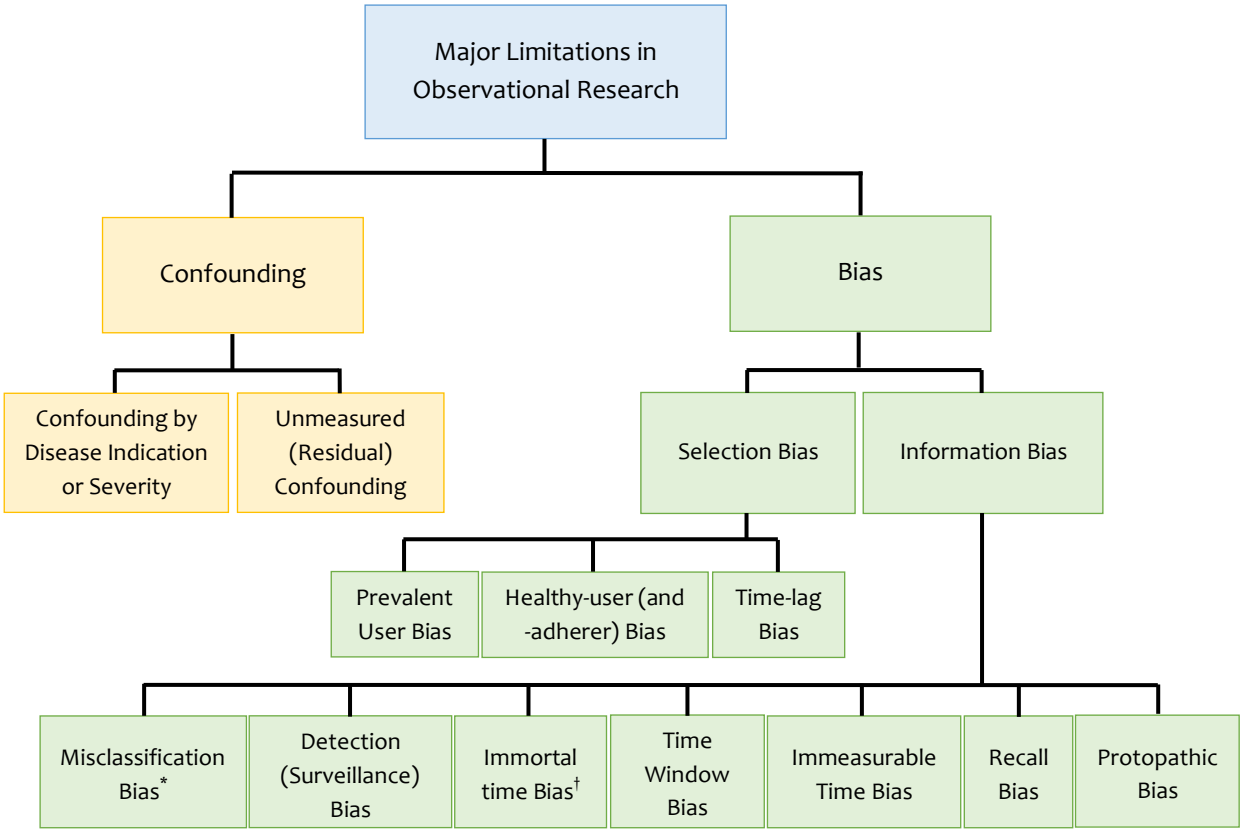

Figure 8.1. Major limitations in observational research.
* Misclassification bias is a broader term compared with other biases in this category and is usually considered to be equivalent to the information bias itself.
† If the misclassified time was excluded from the analyses, immortal time bias can be regarded as a kind of selection bias rather than information bias.

Confounding

Confounding by indication or disease severity is one of the most challenging pitfalls in pharmacoepidemiological studies. It occurs when some patients in the study population, who have a more severe disease with a poor prognosis, are also more likely to receive the exposure drug.[39,41] The result would be a higher risk estimate for the association between the exposure drug and the adverse outcome, compared to the true effect of the drug itself. This type of confounding might have existed in the studies in **Chapters 4, 5, 6, and 7** where patients who received oral GCs, PPIs, or bDMARDs may have a more severe background medical condition (such as RA) that would also result in a higher risk of fractures. Figure 8.2 depicts such a possible confounding effect from the RA's severity (or indication) on the association between oral GC use and OP fracture risk with a directed

acyclic graph. We tried to overcome this issue by better choices of the comparator group, such as selecting past users of oral GCs (who are more likely to also have a more severe disease course) instead of non-users in **Chapter 5**. Furthermore, we adjusted the analyses with some covariates as proxies of the disease severity, such as considering five analgesics and conventional synthetic DMARDs (csDMARDs) in the Cox regression model in **Chapters 5 and 6**, by adopting a PS matching model that included disease severity indicators (such as disease duration, Disease Activity Score in 28 joints, C-reactive protein, etc.) in **Chapter 7**, and by adjusting the analyses with a history of multiple comorbidities and various drug use as proxies of GC indications in **Chapter 4**. Nevertheless, we cannot exactly measure this type of confounding and its impact on our results, but comparability of our findings in each study to those of the previous literature would suggest only a small issue.

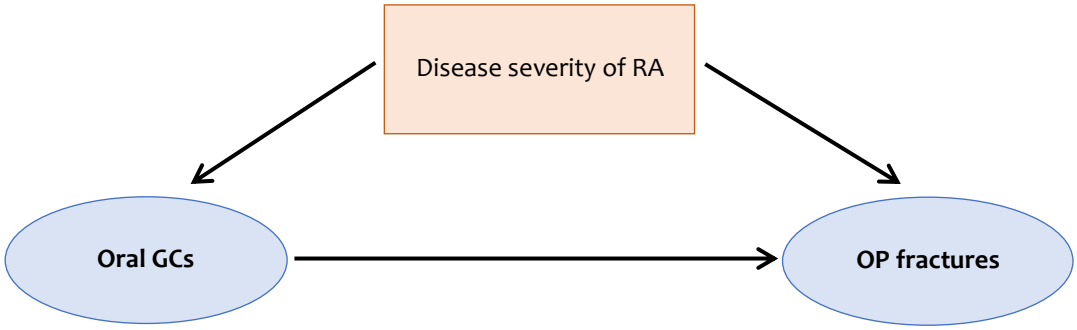

Figure 8.2. Confounding by disease severity (or indication) depicted by a directed acyclic graph in the association between oral GCs and OP fracture risk in patients with RA. A true confounder must be associated with both the exposure and the outcome but does not lie in the causal pathway of this association. In this example, a severe disease state might predispose to an imminent OP fracture, and at the same time requires higher use of anti-inflammatory medications, such as oral GCs. Thus, it can confound the true association between the drug and the outcome, if not considered and adjusted for in the analyses.
GCs: glucocorticoids, OP: osteoporotic, RA: rheumatoid arthritis.

Unmeasured or residual confounding is an ever-existing problem in observational research. This type of confounding is usually a problem of the data that we collect from a secondary healthcare data source, not necessarily collected for research purposes, for example in case of administrative or claims databases. Additionally, some covariates are usually not recorded (and perhaps are never measured) in electronic healthcare databases (EHDs) such as those we used as our data source, for instance exercise level, nutritional status, genetic factors, etc. In general, to minimise the confounding effect of

various covariates, we can take advantage of few strategies in design and analyses, including matching, stratification, and multivariable adjustment in analyses. We considered a long list of covariates including well-established risk factors of fracture in **Chapters 4, 5, 6 and 7**, where we studied the association between various drug use and OP fracture risk. In **Chapters 4, 5, and 6** multivariable adjustment was performed, and a PS matching model was designed for **Chapter 7**. Similarly, we used multivariable adjustment in **Chapter 3**, where we included important risk factors of all-cause mortality. In **Chapter 2**, we stratified fracture IRs by the fracture type and sex, and also stratified the analyses by calendar year including only a population of 50+ years. We expect that any remaining impact from the residual (unmeasured) confounding in our studies would be minimal. Nonetheless, we acknowledge that the produced risk estimates in our studies can never be free from such an impact.

Selection bias

Selection bias is a systematic divergence of study results due to inclusion of an unrepresentative group of patients due to a different pattern of exposure and/or outcome of interest in comparison with the source population.[39,41] It could be more of a concern with prospective study designs, such as in field studies, where voluntary referrals by clinicians or self-selection by subjects could lead to an unrepresentative study population.[45] However, this can also happen in retrospective studies using data from the EHDs, as highlighted by the following examples.

Prevalent user bias occurs when patients are entered into the study regardless of their starting date of the exposure drug, so many of them were actually prevalent users of the exposure drug when they were started to follow up (Figure 8.3).[39,46,47] When the hazard function of the exposure-outcome is varying over time, this could possibly distort the risk estimates, as the included prevalent users are probably the survivors of the early phase of the pharmacotherapy. This usually results in a protective/ beneficial effect of the exposure drug on the adverse outcome. This effect - especially with acute outcomes, has also been called *depletion of susceptibles*, such as in case of non-steroidal anti-inflammatory drug use and upper gastrointestinal bleeding.[48,49] The solution to this type of bias would be an incident new-user design.[46,47] With this design, one only includes patients with an incident (new) use of the exposure drug, so it would be possible to capture the whole period of hazard function for the exposed group, in order to have a fair comparison to the control group. Using EHDs with comprehensive data on

prescriptions, medical diagnoses, and other covariates with their exact start (and stop) date has made such a design easier in practice. We used an incident new-user design in the cohort studies in **Chapters 3, 5, and 6**, by excluding the exposure drug users before the index date. Furthermore, the case-control study in **Chapter 4** had a non-nested design that took into account all oral GC use times as current, recent, past, distant past or never use irrespective of the case accrual period, and also selected never users as the comparator.[46] Thus, we do not expect a prevalent user bias occurred in any of these studies.

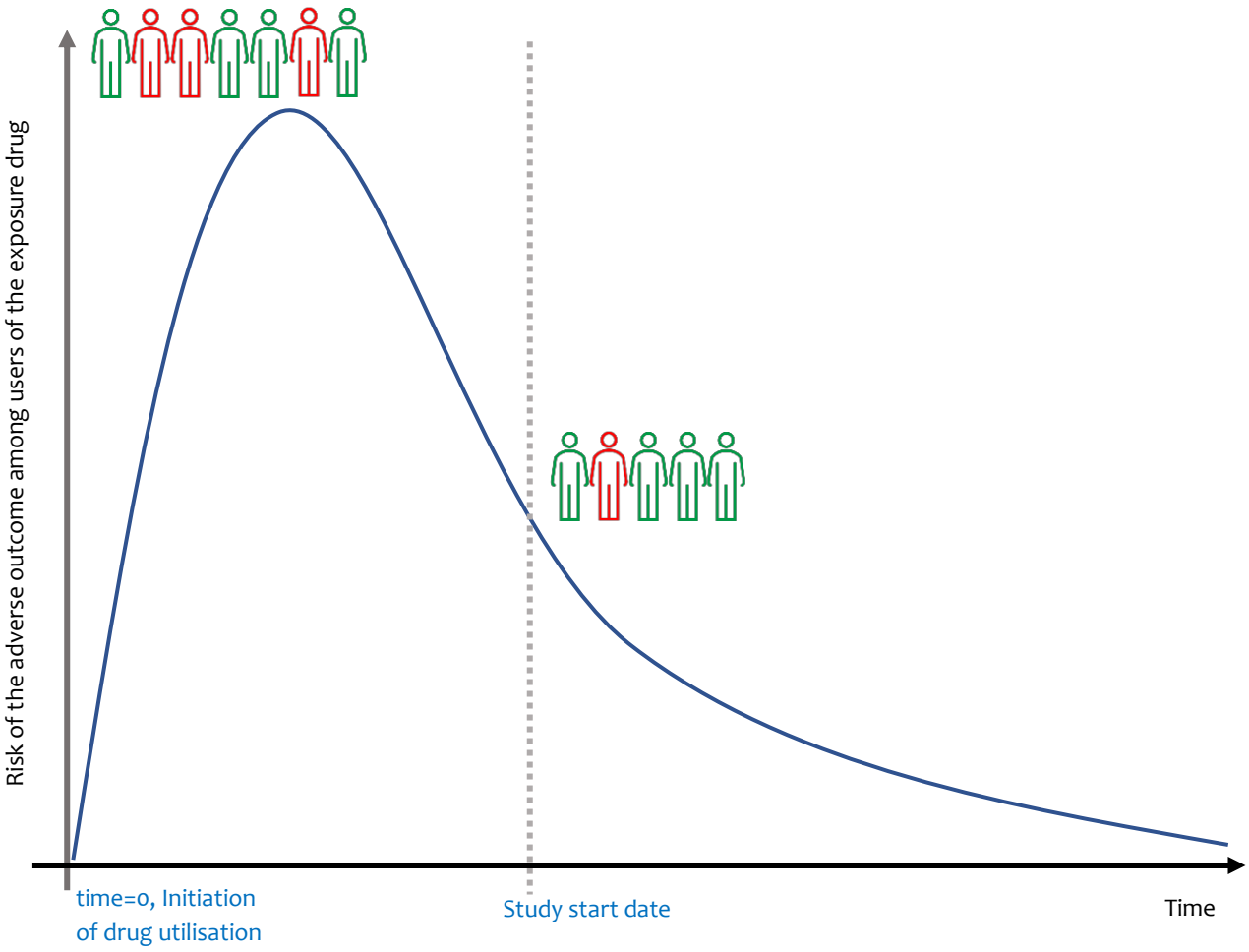

Figure 8.3. Prevalent user bias in pharmacoepidemiological studies. Hazard function of an adverse outcome for a given exposure drug is depicted in a hypothetical patient population. Susceptible patients who develop the adverse outcome after drug use are shown in red, while those who do not are shown in green. As drug utilisation starts at time=0, most of the adverse outcomes happen in the early phase of the pharmacotherapy. A study design that would include prevalent users of the exposure drug would intersect this hazard function at the middle, thus would only include survivors of the early phase who are not representative of the study population at time=0.

In **Chapter 7**, we profited from a novel study design called prevalent new-user design, in order to compare new use of bDMARDs in RA patients with no biological use respecting the effect on fracture risk among incident and prevalent users of csDMARDs.[37] This design would be beneficial in head-to-head comparison of two drugs that are normally prescribed in different stages of the same disease. The users of the study (newer) drug are allowed to be prevalent users of the comparator (older) drug, where the likelihood of receiving the study (new) drug would be estimated by means of time-conditional PSs allowing for appropriate matching with controls in the same stage of the disease course.[37] This design would also allow to tackle the issues related to the prevalent user bias, as the new (incident) use of the study drug (as either initiation or switch from the older dug) will be assessed, where the prevalent use of the older drug has been adequately matched and balanced among comparing groups.

Healthy-user bias can be deemed as a specific form of prevalent user bias under the category selection bias. It arises when healthier patients are more routinely treated with (especially preventative) medications, and due to their healthy behaviour, they would also have lower odds to have the outcome of interest.[50] If the point of divergence addresses the adherence with the medication, a similar bias would be ensued, called *healthy-adherer bias*.[50,51] Both these biases would result in an exaggeration of a beneficial effect of the (preventative) medication on the outcome of interest. A classic example was the apparently protective effect of hormone replacement therapy (HRT) against cardiovascular risk in postmenopausal women in observational studies, which later was found to be due to healthier HRT users in those studies.[52] We may suffer from healthy-use (and -adherer) bias in **Chapter 3**, where oral BP users could have been healthier patients who had taken this preventative medication more frequently (and more adherently) after having a MOF compared with the more fragile and sick patients who never took these medications. This could result in a spurious beneficial effect for oral BPs on all-cause mortality, especially with shorter durations of follow-up, as the biased effects are expected to be stronger in a shorter period. This can partly explain the mortality lowering effects that we observed with oral BPs in fracture patients in **Chapter 3**.

Time-lag bias is one of the time-related biases that lies under the selection bias. It can occur when patients in two different stages of the same disease are compared with each other because of using drugs that are specified as different lines of treatment for that disease (Figure 8.4).[53] The problem usually arises when the outcome of interest has a relatively long latency period (e.g., cancers) or when it is affected by the disease stage, as

in the case of fracture risk in RA. We know from previous literature that the risk of an imminent OP fracture increases when the RA advances.[17] This could be of concern in **Chapters 5, 6, and 7**, where the fracture risk was evaluated in cohorts of patients with RA, especially where we included both incident and prevalent cases of RA. In **Chapter 5**, current oral GC use was compared with past GC use in a time-dependent Cox regression model. This could be a fairer and more reasonable comparator group than non-users and thereby reducing the possibility of time-lag bias, considering an incident new-user design and as the person time from past GC use have been derived from the follow-up time of the same patients (i.e., those who stopped taking oral GCs for >1 year). If there was an impact from time-lag bias, we would expect higher fracture rates among our exposed patients and an artificially increased fracture risk with low-dose oral GC use. One sensitivity analysis in **Chapter 5** confirmed this hypothesis, where a comparison to non-use instead of past GC use shifted the associations away from the null. But in **Chapter 6**, the concomitant current use of oral GCs and PPIs has been compared to non-use of both drugs, and the mean follow-up time was around 4 years shorter for non-users (9.1 years, SD 5.0 years for concomitant users, and 5.1 years, SD 4.3 years for non-users). This might mean a less advanced disease and lower odds of fracture among non-users due to the inflammatory process of RA.[17] Thus, it might be deemed that part of the observed association was due to the time-lag bias. However, as past use of oral GCs or PPIs did not show any significant risk change compared to non-use of both drugs, and as this person time came from the same patients who contributed person time for concomitant use, an effect from time-lag bias was probably negligible. In **Chapter 7**, we used a PS matching model that considered covariates such as disease duration, and other disease severity indicators and medications. However, there was a 0.7-year difference in follow-up time between bDMARD users (4.4 years) and bDMARD naïve patients (3.7 years) after matching. This longer follow-up time could mean a more advanced RA disease course for bDMARD users and hence more fracture rates due to the inflammatory process of the disease. This might have masked a beneficial effect from bDMARDs on reducing OP fracture rates in this study.

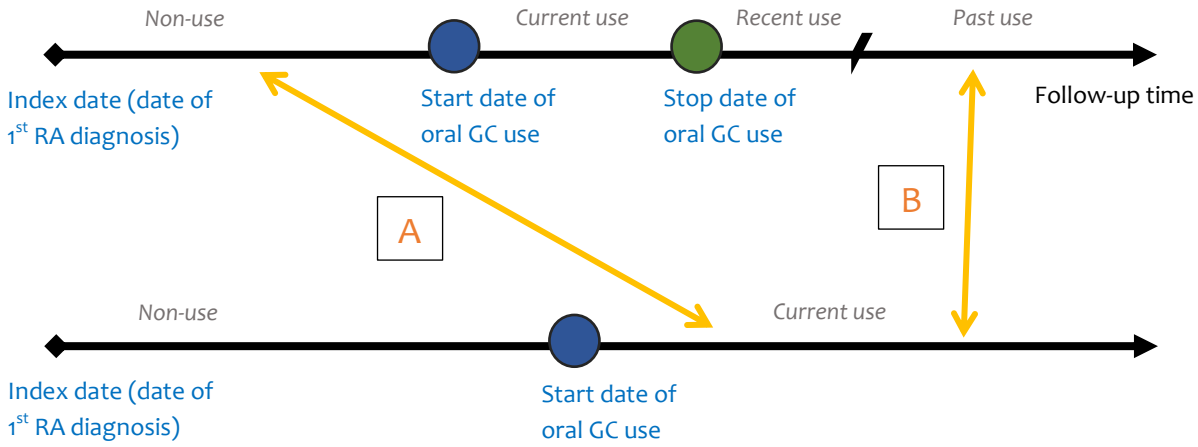

Figure 8.4. Time-lag bias in pharmacoepidemiological studies. The follow-up times of two random patients from our cohort studies in Chapters 5 or 6 are depicted here, with the exposure of interest being oral GCs. Follow-up time starts at the first date of a diagnosis of RA in the database during the valid data collection and study period. Two different approaches in analyses are shown. With the approach "A", a period of current use would be compared with a period of non-use, which might represent a very different stage of the disease, hence different odds for occurrence of an osteoporotic fracture due to advancement and inflammatory process of the disease. The other approach, "B", takes advantage of a comparison between a period of current use and a period of past use, which could be in a more similar disease stage, therefore similar chances for occurrence of an osteoporotic fracture due to advancement of the disease course.
GC: glucocorticoid, RA: rheumatoid arthritis.

Information bias

Information bias occurs when there is a systematic divergence of the study results due to flawed measuring and the resulting erroneous data on various study variables.[39,45] A synonymous term in literature is *misclassification bias*, which applies to any erroneous measurement and classification of the exposure drug, outcome, covariates, or disease diagnosis among the comparison groups in a pharmacoepidemiological study, which would lead to flawed study results.[39,42,54] In this part, first we will explain important examples of misclassification of exposure and outcome in our studies, then we will continue to introduce other potentially important cases of information bias in this thesis.

We expect some extent of *misclassification of exposure* in our studies, as we used data from the primary care, clinical, or specialty EHDs, such as the CPRD and Danish national registries. For instance, we had only information on drug prescriptions from the CPRD,

which is roughly two steps behind the actual drug use by patient; first, we had no information on the dispensation of the prescribed drug, and second, we did not know whether the prescribed (and dispensed) drug had been actually consumed by patient (i.e., adherence to medication).[39] Previous studies using data from the CPRD showed that above 20% of patients with diabetes mellitus and above 60% of patients with gout were not adherent to their therapies (i.e. glucagon-like peptide-1 receptor agonists and allopurinol, respectively).[55,56] Apart from the issue with non-adherence, some of our studied drugs were also available as over-the-counter, such as PPIs, and some were also prescribed in an "as needed" basis, for example in case of oral GCs. Non-adherence with the prescribed medication and an "as needed" order could lead to an overestimation of actual drug use in our analyses, while an over-the-counter use could lead to an underestimation of actual drug use. This would result in a differential distortion of our risk estimates, which has possibly underestimated the association for oral BP use and all-cause mortality in **Chapter 3**, the association of oral GC use and OP fracture risk in **Chapter 4**, and the association of low-dose oral GC use and OP fracture risk in **Chapter 5**. Following this rationale, the association between oral GC use alone and OP fracture risk in **Chapter 6** might be underestimated, while PPI use alone-OP fracture risk association could be overestimated (if we assume PPI users in our study had also more over-the-counter PPI use than the reference group). As the use of bDMARDs is principally parenteral, non-adherence would not be an issue for the exposure drug in **Chapter 7**. However, the same non-adherence issue with the mostly orally taken csDMARDs might have a differential impact on the final results, depending on the degree of non-adherence among the comparison groups, and the hypothetical effect of csDMARDs and bDMARDs on fracture risk.

Misclassification of outcome would be less of an issue in our studies, as the outcome of interest was either an OP fracture (in **Chapters 4, 5, 6, and 7**) or all-cause mortality (in **Chapter 3**), where both are clinically definitive endpoints and quite well recorded in an EHD.[57,58] However, one exception in our studies may be vertebral fracture, where two thirds of cases never come to clinical attention, and the only one third are normally found accidentally and due to other complaints.[59] Thus, not only we certainly underestimated IRs of vertebral fractures in our studies, but also the ascertainment of clinically symptomatic vertebral fracture in our studies might have suffered from *detection (surveillance) bias*. This occurs when patients with a given exposure have higher odds of detection of the outcome of interest, due to an associated symptom which leads to more screening or testing for that outcome.[39] In our studies, those patients who had received

oral GCs might have higher odds to be clinically examined or to undergo radiological imaging because of complaints such as a back pain or a stoop, which might end up in diagnosis of a vertebral fracture. For this reason, we expect a differential divergence, and an overestimation of risk estimates for the association between oral GC use and clinical vertebral fracture in **Chapters 4, 5 and 6**. This included increased vertebral fracture risks, such as an observed 4.4-fold with heavy GC use in **Chapter 4**, a 1.6-fold with low-dose oral GC use in **Chapter 5**, and a 2.8-fold with concomitant oral GC and PPI use in **Chapter 6**. So, it is not unlikely that at least part of these associations was due to detection bias.

Other forms of time-related biases, i.e., immortal time bias or time-window bias fall under the information bias. *Immortal time bias* refers to an improper handling of the follow-up time, when patients should have an "immortal" event-free period before the exposure drug could start (Figure 8.5).[49,53,60] It normally results in a beneficial (protective) effect for the exposure drug due to erroneous underestimation of the denominator in IRs of the unexposed (control) group. If the misclassified time was totally excluded from the analyses, immortal time bias can then be classified under selection bias. A typical example are the observational studies that found a protective role for metformin or statins in a wide range of outcome measures such as various cancers, or diabetes progression.[53,61] The solution is to implement a time-dependent design (instead of a time-fixed analysis) that carefully considers all the follow-up time of the included patients, for instance by considering the exact start dates of prescriptions. As we used time-dependent regression models by incorporating all person times in our analyses (**Chapters 3, 4, 5, and 6**), such a bias is not expected in these studies. The prevalent new-user design in **Chapter 7** might be prone to such a bias, where the index date of the comparator group is defined as the cohort entry date. However, we will not "look-into-the-future" for selecting the patients, also with an intention-to-treat analysis and a balanced state of prevalent use of csDMARDs among both comparison groups, we do not expect immortal time bias here.

Time-window bias occurs when there are different opportunities for having the outcome between the various exposure groups usually due to different follow-up times in a case-control study.[49,53,62] This often resulted in spurious protective effect of the medication (e.g. statins) on several adverse outcomes (such as various cancers), as the control group in those examples had a longer and different follow-up time and automatically higher odds to develop the outcome.[62] The ideal solution is a risk-set (or incidence density) sampling to allow for equal observation time for cases and controls. In our case-control study in **Chapter 4**, we used the date of first fracture as the index date for cases and the same date as the index date for their matched controls, where the comparison groups

were matched by year of birth and gender using incidence density sampling. Also, as the nationwide Danish databases covered all inhabitants with all data from a certain time point onward, there is unlikely that the comparison groups had different exposure opportunities. Moreover, unlike cancer outcome in the examples above, our outcome of interest (i.e., OP fracture) had not a long latency period after GC use. Hence, we expect relatively similar opportunities for cases and controls to have the exposure, and time-window bias was not an issue.

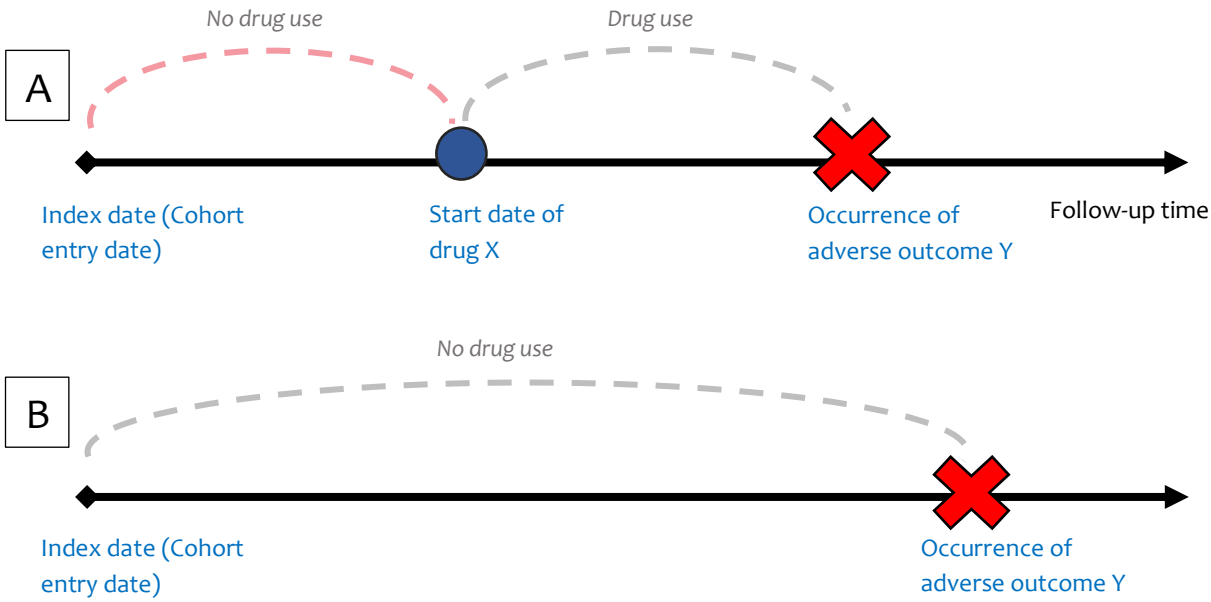

Figure 8.5. Immortal time bias in pharmacoepidemiological studies. The follow-up times of two random patients are depicted here in a hypothetical cohort study, which compares the risk of adverse outcome Y in patients who ever used drug X (such as Patient A) versus those who never used this drug (such as Patient B). The index date in such a design starts at the cohort entry date. As the exact start date of using drug X (e.g., the prescription dates) has not been taken into account, patients (such as Patient A) should survive enough without having the adverse outcome to be able to receive the exposure drug and counted as drug users, so there is an "immortal time" before the drug exposure in this group. The sole comparison of incidence rates of adverse outcome Y among ever users of drug X versus those of never users would usually result in a beneficial (protective) effect of the drug on the adverse outcome. This is because the time before start date of drug use among ever users (such as in Patient A, shown with pink patterned line) has been mistakenly considered as part of the denominator of the incidence rate of Y among the exposed group (drug users). This non-use time should be instead considered as part of the denominator of the incidence rates of the unexposed (control) group.

Immeasurable time bias concerns some differential recording of the exposure of interest between the two comparing groups because of some periods during follow-up, in which the exposure could not be recorded, mainly due to hospitalisation episodes that are not registered in the database (Figure 8.6).[49,63] It often happens when patients with a chronic debilitating disease are studied, where they need long periods of hospitalisation with no available information on any inpatient prescriptions. In **Chapters 5 and 6**, we focused on patients with RA, and we did not have information on any drug usage during hospitalisations from the CPRD. But it is unlikely that patients with RA need long periods of hospitalisation. Additionally, there is no indication that such hospitalisation periods and the resulting immeasurable time were different between the two comparing groups in each study. Moreover, our definitions for the classification of GC exposure in these studies, as current (<6 months before), recent (6-12 month before) and past (>1 year) use, would hamper a large effect from any hospitalisations. Thus, we do not expect an immeasurable time bias in this thesis.

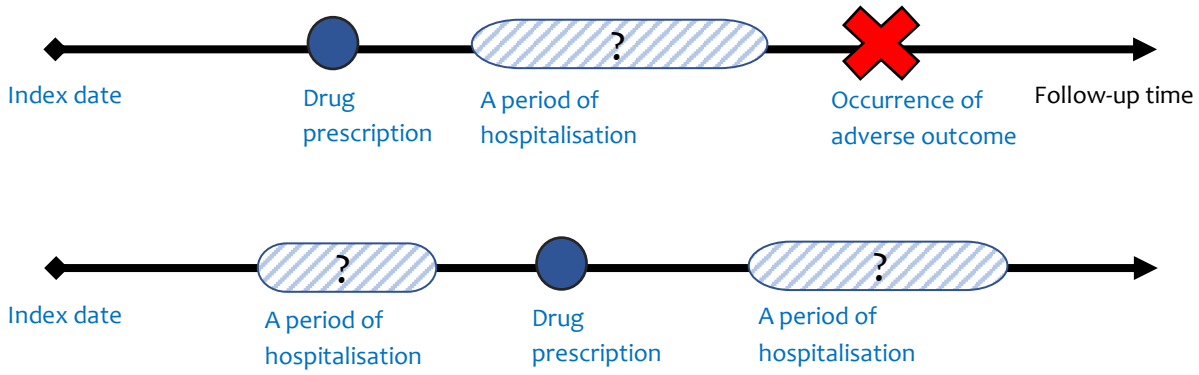

Figure 8.6. Immeasurable time bias in pharmacoepidemiological studies. The follow-up times of two random patients are shown in a hypothetical cohort study, where patients need long periods of hospitalisation (boxes with patterned lines) due to the background disease or its complications. This type of information bias might occur, when there is no information available from the data source for the hospitalisation periods on the exposure, outcome, death, or other study variables, which can end up in erroneous ascertainment of these attributes.

Recall bias is defined as differential remembrance of a past exposure among patients with different outcomes.[39,42,64] For example, patients with thromboembolism have been reported to recall more the use of oral contraceptives than healthy controls in a classic study.[65] We used data from the EHDs, such as the CPRD and Danish national registries, filled in by physicians and not from questionnaires, so in general it is unlikely that our data were affected by this bias. However, we used data from the DANBIO register in **Chapter 7**, and some of the variables have been entered into the DANBIO via patients, called patient-reported outcome measures, such as educational level, smoking status, and physical activity.[36] There is also a possibility that some few variables have been entered into the CPRD by physician or nurse but only after questioning the patient, such as previous falls, in **Chapters 3, 5, and 6**. In either case, the data have been collected prospectively and ideally before an outcome of interest. This reduces the risk and potential impact of recall bias on our findings.

Protopathic bias occurs when early symptoms of an outcome would affect prescribing of the exposure drug, thus leading to an erroneous positive association between the exposure and outcome.[39] With this bias, one normally observes a *reverse causality*, where it is actually the outcome that is causing the exposure of interest to befall. This type of bias might happen in the pharmacoepidemiological studies on cancer, as the outcome has a long latency period, for instance starting of antidiabetic drugs for treating diabetes mellitus that heralds an imminent pancreatic cancer.[66] However, the outcomes of interest in our studies, i.e., OP fractures or all-cause mortality, do not seem to be good candidates for predisposing to such a bias. One exception could be vertebral fracture, where two thirds of cases remain to be undiagnosed,[59] and a symptom or sign of the undetected fracture may induce the use of some medications such as analgesics. However, it sounds unlikely that even an undetected vertebral facture had caused prescribing of oral GCs, PPIs, or bDMARDs. So, we do not expect protopathic bias in this thesis.

In addition to the established study designs and a range of strategies that were embraced to tackle different sorts of bias and confounding, we also took advantage of running several *sensitivity analyses* in each study. The goal of these analyses was to further test the robustness of the observed association. Additionally, by running multiple sensitivity analyses we could indirectly evaluate the findings and their alignment with the presumed underlying pharmacological hypothesis.[67] An example was stratification of OP fracture sites as the outcome of interest in secondary analyses in **Chapters 4, 5, 6, and 7**, evaluating the association for the other cut-offs of low-dose oral GC use and fracture risk

in **Chapter 5**, or the impact of censoring the follow-up time after oral BP use on mortality reduction in **Chapter 3**.

c. Clinical implications & suggestions for future research

Before formulating the conclusions of this thesis, the relevance of the findings of our studies for patients, clinicians, and policymakers will be presented in this part. Furthermore, some novel ideas for future research in the studied topics will be introduced, which are inspired by the findings and limitations of our studies.

The first part of this thesis aimed to investigate various attributes of OP fractures in the general population. When exploring this, we found an overall declining trend in IRs of MOF in Denmark between 1995 and 2010, no beneficial effect for oral BPs against mortality after a MOF, and a marked increased risk of OP fractures with a cumulative oral GC use ≥1.0 g PED among high daily GC users as the hallmark of long-term GC therapy in the general population.

Aside from a generally declining trend in MOF rates, the important finding in **Chapter 2** was a lower rate of decrease of hip fractures among men compared with women, and an increasing trend in clinical vertebral fractures rates in men. Osteoporosis has been long considered a disease of postmenopausal women, and consistent with many other previous studies, we observed higher IRs of MOF among 50+ women (211.5 per 10,000 PYs in 2010) compared with 50+ men (77.6 per 10,000 PYs). But this intersexual gap is rapidly shrinking especially in some OP fractures such as the clinical vertebral. Some aetiologic factors have been proposed to explain the trend changes in general (e.g. higher BMD or higher frequency of overweight/ obese people due to a birth cohort effect, or urbanisation rates), and the differential changes between men and women (e.g. more anti-osteoporotic therapy among post-menopausal women), but there is no definite answer.[2,4,68,69] Our findings are important for clinicians and policymakers, as we recommend appropriate screening for OP fractures (by fracture risk assessment and BMD measurements),[70] in addition to appropriate use of anti-osteoporotic treatments not only in postmenopausal women, but also in older men. We think there is an urgent need for future research to investigate into the underlying reasons for the changes in the secular trends in OP fractures, and specifically into the differential changes between men and women. We also recommend an updated investigation of the secular trends in IRs of MOF not only in Northern Europe but also in the rest of the world to have more

comprehensive data from various countries with different levels of sun exposure, healthcare utilisation, and cultural and racial determinants.

Any potential beneficial effect of BPs on mortality is highly controversial in the bone research field. At least part of our positive findings in **Chapter 3**, i.e., oral BPs' effects on mortality reduction, could be explained by several bias scenarios, including the healthy-user bias or confounding by selective prescribing. But the observation of a mortality reduction as soon as the first year after a fracture strongly argues against the anti-atherosclerotic hypothesis of BPs. While there is some evidence supporting favourable effects of BPs on the cardiovascular outcomes or cancer incidence, a net benefit on the all-cause mortality has never been consolidated.[11,12,71] On the other hand, there is substantial evidence that BPs would prevent a recurrent fracture.[7,72,73] For this reason and aside from the still unknown beneficial effects on mortality, oral BP use is highly recommended as first-line treatment in patients with osteoporosis or those who already had an OP fracture, in order to avoid a future fracture.[74,75] To solve this ongoing and relevant discussion, we recommend conducting in vitro and in vivo studies that would elaborate on the alternative biological mechanisms or pleiotropic properties of BPs, which confer a mortality benefit.

Our findings in **Chapter 4** could be important to guide clinicians and possibly to inform the future guidelines in how and when to treat patients receiving oral GCs, who need long-term treatment due to a chronic inflammatory disease. The key finding was a clear distinction between a cumulative oral GC use ≥1.0 g PED and <1.0 g PED in marking a substantially elevated risk of hip and clinical vertebral fractures in patients who were using an average daily dose ≥15.0 mg PED. This group of heavy GC users (those taking an average GC daily dose ≥15.0 mg PED and a cumulative dose ≥1.0 g PED) are probably the most fragile group respecting the risk of OP fractures. Therefore, avoiding unnecessary high doses of oral GCs, adequate fracture assessment and timely anti-osteoporotic therapy are all recommended in order to avoid the catastrophic consequences of an imminent fracture. One research area would be a continued effort to develop new anti-inflammatory drugs, which can act more specifically at the inflammation site with less adverse impact on bone, such as those potential therapy targets found with the recent explorations in the new mechanisms of action of GCs.[76] Such new therapies could be more suitable for the long course of treatment of a chronic inflammatory disease.

The second part of this thesis aimed to address some knowledge gaps on the role of medications in the risk of OP fractures in patients with RA. We found an increased risk of clinical vertebral fracture with low-dose oral GC use in RA patients, but no association

with non-vertebral OP fractures. Furthermore, we found a significant increased risk of OP fractures with concomitant use of oral GCs and PPIs in patients with RA. Finally, we showed that bDMARD use was not associated with a reduced risk of OP fractures in RA.

The significantly increased risk of clinical vertebral fracture with low-dose oral GC use (≤7.5 mg PED/day) in RA was an important finding in **Chapter 5**. We already know from the previous literature that vertebrae are one of the most susceptible sites to GC therapy, culminating in highest fracture risks, presumably because of high proportion of trabecular bone.[77,78] We also acknowledge that a (small) part of this association in our study might have originated from the detection bias, as discussed earlier. However, our findings should warn clinicians that even with low daily doses of oral GCs, the patients are at risk of a vertebral fracture. This certainly comes along our other message that low-dose oral GC therapy does not pose a risk for non-vertebral OP fractures including the hip, making daily doses ≤7.5 mg PED perhaps a clinically safe exposure in RA patients respecting a non-vertebral fracture risk. A novel research idea in this topic would be a study design that investigates this association by means of a spline regression analysis to find a more exact cut-off point of a daily GC dose for a significantly elevated fracture risk in various sites. Another idea is to evaluate this association in various subgroups of patients with RA who had different baseline fracture risks, as recommended by the EULAR task force.[16]

On a same line, the key message in **Chapter 6** is relevant for clinicians and patients with RA. From our analyses it is understood that the OP fracture risk associated with concomitant use of oral GCs and PPIs has probably an additive nature, stemming from the individual risks related to each of these drugs. Therefore, more attention should be paid to those RA patients who are prescribed both drugs, with routine fracture risk assessment and proper preventative anti-osteoporotic therapies. This recommendation would be more important for elderly patients, possibly with a more advanced disease, who are at a higher risk of OP fractures due to other risk factors.[17] We could not unfortunately match the PPI findings with any of the previously proposed biological mechanisms of action of PPIs on bone or falling. This is still an unsolved enigma, and thus an interesting realm for future studies to find a clear and sound mechanism, which can hopefully explain the associations that we and others found in real-world data.

The results of the last project of this thesis in **Chapter 7** are also interesting for clinicians and patients with RA. In the past two decades, biological drugs have become a pivotal therapy for many chronic inflammatory diseases including RA,[79] but their comprehensive safety profile and any effect on the risk of OP fracture is still a matter of debate.[38] The negative findings of our study and other observational studies,[33-35] could be due to the

"treat-to-target" strategy of RA management in a real-world setting, which means comparable improvement of disease activity in both comparison groups in the study. We believe, this still conforms with the previously reported beneficial effects of bDMARDs on BMD identified in single-arm before-after trials.[30,32,80] Moreover, a side message of our study was evidence for the safety of bDMARDs regarding OP fracture risk, compared to the adverse effect of other anti-inflammatory drugs used in RA, in particular GCs. While biologicals were not associated with a reduced risk of OP fractures, they still did not incur an increased risk. There is also strong evidence from systematic reviews of RCTs that bDMARDs are efficacious therapies for those RA patients who were not responding to a first-line csDMARD to control the RA disease activity and progression.[81] As this is a relatively young research area, more investigation is needed to inform on alternative mechanisms or various pleiotropic effects that biologicals might have on different cytokines or bone active molecules.

d. Conclusion

In conclusion, there was an overall decreasing trend in IRs of MOFs in Denmark between 1995 and 2010. These changes were more pronounced in women, while there was a lower decrease of hip fracture and an increasing trend in clinical vertebral fracture among men. Oral BPs had apparently no beneficial effect on mortality reduction in patients with a MOF, although our results were probably impacted by healthy-user bias and confounding by selective prescribing. However, oral BPs are first-line treatment for osteoporosis and as preventative therapy for a recurrent OP fracture, as supported by strong evidence. Furthermore, we showed that the threshold for a marked increased risk of hip and clinical vertebral fracture in high daily oral GC users is the cumulative use ≥1.0 g PED, which is a hallmark of long-term GC therapy.

Low-dose oral GC therapy (≤7.5 mg PED/day) in RA patients was associated with an increased risk of clinical vertebral fracture, while there was no association with risk of non-vertebral OP fractures. Hence, more attention should be paid to an imminent vertebral fracture in patients with RA who receive low daily doses of GCs. We also showed that there was an increased and additive risk of OP fractures by concomitant use of oral GCs and PPIs in patients with RA, although the risk did not increase with increasing daily doses or longer duration of PPI use. Thus, we recommend adequate fracture risk assessment and anti-osteoporotic treatment for RA patients who are co-prescribed both oral GCs and PPIs. Finally, we found that bDMARDs had no independent beneficial effect

on reducing the risk of OP fractures in patients with RA. Nevertheless, bDMARDs are recommended as second-line pharmacotherapy in RA because of their potent effect on suppressing disease activity. Additionally, the combined data from clinical trials on BMD and observational studies on fracture risk point to their protective effect on bone health, presumably by suppressing the background inflammation of RA.

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APPENDICES

A

i. List of Abbreviations

ACPA	Anticitrullinated protein antibody
adj. HR	adjusted hazard ratio
ASBMR	American Society for Bone and Mineral Research
ATC	Anatomical Therapeutic Chemical
BARFOT	Better Anti-Rheumatic FarmacOTherapy
bDMARD	biological disease-modifying antirheumatic drug
BMD	Bone mineral density
BMI	Body mass index
BP	Bisphosphonate
CD	Cumulative dose
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
COX-2	Cyclooxygenase-2
CPRD	Clinical Practice Research Datalink
CRP	C-reactive protein
csDMARD	conventional synthetic disease-modifying antirheumatic drug
DALY	Disability-adjusted life year
DANBIO	Danish Biologics Register
DAS28	Disease Activity Score in 28 joints
DD	Average daily dose
DDD	Defined daily dose
DMARD	Disease-modifying antirheumatic drug
DNPR	Danish National Patient Registry
DXA	Dual-energy X-ray absorptiometry
EHD	Electronic healthcare database
ESR	Erythrocyte sedimentation rate
EULAR	The European Alliance of Associations for Rheumatology (previously the European League Against Rheumatism)
GC	Glucocorticoid
HAQ	Heath Assessment Questionnaire
HORIZON	Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly
HR	Hazard ratio
HRT	Hormone replacement therapy

ICD	International Classification of Diseases and Related Health Problems
ICPE	International Conference on Pharmacoepidemiology
IHD	Ischaemic heart disease
IL	Interleukin
IOF	International Osteoporosis Foundation
IR	Incidence rate
IRR	Incidence rate ratio
LDL	Low-density lipoprotein
MOF	Major osteoporotic fracture
NSAID	Non-steroidal anti-inflammatory drug
OED	Omeprazole equivalent dose
OP	Osteoporotic
OPG	Osteoprotegerin
OR	Odds ratio
PED	Prednisolone equivalent dose
PPI	Proton pump inhibitor
PS	Propensity score
PY	Person year
RA	Rheumatoid arthritis
RANKL	Receptor activator of nuclear factor-κB ligand
RCT	Randomised controlled trial
RERI	Relative excess risk due to interaction
RF	Rheumatoid factor
SD	Standard deviation
SMD	Standardised mean difference
TNF	Tumour necrosis factor
TOD	Transfer out of database date
tsDMARD	targeted synthetic disease-modifying antirheumatic drug
UTS	Up to standard time
VAS	Visual analogue scale
WHO	World Health Organisation

ii. Summary

General introduction

Osteoporosis is a chronic disease with loss of bone mass and increased risk of osteoporotic (OP) fractures. It is predominantly a disease of elderly or postmenopausal women, with substantial personal and societal impact, mainly because of the associated fractures. Osteoporosis and OP fractures can occur secondary to other morbidities (such as rheumatoid arthritis [RA]) or use of some medications (for instance, glucocorticoids [GCs]). Diagnosis of osteoporosis is based on measurements of bone mineral density (BMD) by dual-energy X-ray absorptiometry (DXA). Main OP fracture sites include hip, vertebrae, humerus, forearm, pelvis and ribs. Among the OP fractures, vertebral fracture is the most prevalent, and hip is the most problematic with high morbidity, mortality and societal costs.

Absolute number of OP fractures is increasing due to the global increase in life expectancies and the ageing trajectory. On the other hand, awareness about the disease, improved lifestyles and fracture prevention by anti-osteoporotic medications, might have resulted in reduced fracture rates. On that line, previous studies have shown a decrease in incidence rates (IRs) of hip fracture, especially in North European or North American countries in the past decades. However, there is little known about the secular trend in all OP fractures globally, not especially from a Northern European country with traditionally high incidence of OP fractures.

OP fractures are devastating outcomes due to their associated high morbidity and mortality rates. Previous literature has shown that anti-osteoporotic therapies (such as bisphosphonates [BPs]) can prevent a subsequent fracture. There is also evidence that BPs could have some anti-atherosclerotic effects, which might confer a mortality benefit. However, whether BPs would have a beneficial effect against mortality after a fracture is unsolved and highly controversial in the literature.

Oral GCs are one of the most potent anti-inflammatory medications with relatively high frequency of use in many chronic inflammatory diseases. Effects on bone quality and induction of an increased risk of OP fracture is one of the most established side effects of oral GCs. Previous literature has shown a role for daily or cumulative dose of oral GCs in developing an OP fracture. However, the association between various exposure patterns of oral GCs and risk of OP fractures is less clear, particularly in patients with a chronic inflammatory disease who need long-term GC therapy.

RA is a chronic inflammatory musculoskeletal disease, which is characterised by synovitis in the small joints of hands and feet, pain, morning stiffness, and limited range of motion. It is most prevalent among middle-aged and older women. A set of clinical signs and symptoms in physical examination, laboratory tests, and imaging determine the diagnosis of RA. Based on the European Alliance of Associations for Rheumatology (EULAR) recommendations, pharmacotherapy of RA includes conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) with or without short-term low-dose GC therapy in early disease, and biological DMARDs (bDMARD) and targeted synthetic DMARDs (tsDMARDs) in case of failure of csDMARDs. Patients with RA are at an increased risk of OP fractures compared to the general population due to the inflammatory process of the disease and reduced mobility.

Some of the medications that are recommended for use in RA have known and sometimes compound effects on fracture risk. For instance, oral GCs especially in low doses might have some local beneficial effects on bone by supressing the background inflammation and increasing the mobility of patient. But the effect of low-dose oral GCs (≤7.5 mg prednisolone equivalent dose [PED]/day) on OP fracture risk in RA is not yet clear. Furthermore, patients with RA, especially elderly patients, frequently use proton pump inhibitors (PPIs), which have been reported to increase the fracture risk in observational studies, although the exact mechanism has never been established. Thus, it would be of interest to investigate the effect of concomitant use of oral GCs and PPIs on OP fracture risk. Likewise, previous studies have shown that bDMARDs may have protective effects on BMD in patients with RA. But there are few studies who investigated the association between use of bDMARDs and OP fracture risk in RA.

Pharmacoepidemiology is an interdisciplinary field studying the effectiveness of medications and their adverse effects in real-world setting. The pharmacoepidemiological research is observational in essence, and generally uses previously collected anonymised patient data in electronic healthcare databases (EHDs). The randomisation performed in randomised controlled trials (RCTs) is lacking in pharmacoepidemiological studies and hence should be mimicked by means of complicated study designs. This can bring up major limitations, such as confounding and bias, in order to have a fair comparison between the studying groups. We took advantage of pharmacoepidemiological methodologies to investigate the above-mentioned knowledge gaps in the literature.

In this thesis, we aimed to study the OP fractures, and their relation to mortality, medication use and RA. The first section of this thesis evaluated various attributes of OP fractures in the general population, including a recent secular trend of OP fractures,

mortality after fracture with oral BP use, and the association between various exposure patterns of oral GCs and OP fracture risk. The second section focused on the role of medication use in risk of OP fractures among patients with RA, which included low-dose oral GCs, oral GCs and PPIs concomitantly, and bDMARDs.

Section 1, Osteoporotic fractures in the general population

An investigation of recent secular trends in IRs of OP fractures in the general population of Denmark was performed in Chapter 2. We found a general decline in IRs of major OP fractures (MOF) for 50+ adults in Denmark between 1995 and 2010 (from 169.8 to 148.0 per 10,000 person years). All OP fractures were decreasing in women, however, a lower decrease of hip fracture in addition to increasing rates for clinical vertebral and steady rates for humerus fracture were observed in men. Our observed trends were generally in line with previous studies from Denmark, Canada and US. Based on these findings, we recommend appropriate screening for OP fractures (by fracture risk assessment and BMD measurements if needed), in addition to proper use of anti-osteoporotic treatments not only in postmenopausal women, but also in older men.

The association between oral BP use and mortality risk following a MOF was evaluated in Chapter 3, using a cohort of patients with a MOF in the UK Clinical Practice Research Datalink (CPRD) between 2000 and 2018. We found a 7% increased risk of all-cause mortality after non-hip MOF, and a 28% reduced risk after hip fracture with current use of oral BPs versus never use. Both the timing and effect size of an association based on anti-atherosclerotic properties of BPs were not supported by our results. Instead, unknown distortion due to healthy-user bias and selective prescribing, or unknown pleiotropic properties of BPs might explain our findings. Future in vitro and in vivo studies are recommended to elaborate on the alternative mechanisms or pleiotropic properties of BPs, which confer a mortality benefit.

The role of daily and cumulative doses of oral GCs in OP fracture risk in the general population of Denmark was studied in Chapter 4, with a case-control study between 1996 and 2011. The remarkable finding was a distinctive elevated risk of hip and clinical vertebral fracture with heavy use of oral GCs, defined as average daily doses ≥15.0 mg PED/day and a cumulative use ≥1.0 g PED, as in clear contrast to short course users (those with high average daily doses but cumulative use <1.0 g PED). Presumably, the threshold for a marked increased fracture risk in high daily oral GC users is the cumulative use ≥1.0 g PED, which is the hallmark of long-term GC therapy. Therefore, avoiding unnecessary high

doses of oral GCs, adequate fracture assessment and timely anti-osteoporotic therapy are all recommended in patients with a chronic inflammatory disease who need long-term GC therapy, to avoid the catastrophic consequences of an imminent fracture.

Section 2, Osteoporotic fracture risk with medication use in rheumatoid arthritis

The association between low-dose oral GC use (≤7.5 mg PED/day) and OP fracture risk in patients with RA was evaluated in Chapter 5, in a cohort of patients with RA from the CPRD between 1997 and 2017. Current use of low-dose oral GCs was not associated with overall risk of OP fractures compared with past GC use; however, it incurred a 59% increased risk of clinical vertebral fracture. The main results remained unchanged regardless of a short-term (with a cumulative use <1 g PED) or a long-term (≥1 g PED) use. Apparently, the beneficial effect of low-dose GC therapy on suppressing the background inflammation of RA could probably be enough to offset its negative effect on bone synthesis in most fracture sites but not in vertebrae. Thus, clinicians should be aware that even in RA patients who use low daily doses of oral GCs, the risk of clinical vertebral fracture is increased.

The association between concomitant use of oral GCs and PPIs and OP fracture risk in patients with RA was studied in Chapter 6, using the CPRD with all RA patients from 1997 to 2017. We observed a 1.6-fold increased risk of OP fractures with concomitant current use of oral GCs and PPIs in RA patients compared to non-use of both drugs. This was statistically different from a 1.2-fold increased fracture risk associated with single use of oral GCs or PPIs. We did not observe an increasing trend in fracture risk with higher daily doses or longer durations of PPI use, which is in contrast to older observational studies. More attention should be paid to those RA patients who are prescribed both drugs, with routine fracture risk assessment and proper preventative anti-osteoporotic therapies. As we could not match the PPI findings with any of the previously proposed biological mechanisms of action of PPIs on bone or falling, more studies are recommended to investigate the associations that we and others found in real-world data.

The association between use of bDMARDs and OP fracture risk in patients with RA was evaluated in Chapter 7, using nationwide registries in Denmark including all RA patients between 2006 and 2016. We found no reduced risk of OP fractures with bDMARD use in patients with RA compared with no treatment with biologicals. The only known mechanism of action of bDMARDs on bone health is supposed to be through the inflammatory cycle. The negative findings of our study and other observational studies,

could be due to the "treat-to-target" strategy of RA management in a real-world setting, which means comparable control of disease activity in both comparison groups in the study. We believe, this still conforms with the previously reported beneficial effects of bDMARDs on BMD identified in single-arm before-after trials. More investigation is needed to inform on alternative mechanisms or various pleiotropic effects that biologicals might have on different cytokines or bone active molecules.

General discussion and conclusion

The main findings of the studies in this thesis, in addition to putting them into the broader context of the previous literature are presented in Chapter 8. Moreover, the major limitations in pharmacoepidemiological studies, i.e., confounding and bias, have been described with potential examples that we might have encountered in our studies, the strategies embraced to tackle them, and any possible impact on our results. Finally, the clinical implications of our findings and some novel ideas for future research have been presented.

In conclusion, there was an overall decreasing trend in IRs of MOFs in Denmark between 1995 and 2010, while there was an increasing trend in clinical vertebral fracture among men. Oral BPs had apparently no beneficial effect on mortality reduction in patients with a MOF, although our results were probably impacted by healthy-user bias and confounding by selective prescribing. Furthermore, we showed that the threshold for a marked increased risk of hip and clinical vertebral fracture in high daily oral GC users is the cumulative use ≥1.0 g PED, which is a hallmark of long-term GC therapy.

Low-dose oral GC therapy (≤7.5 mg PED/day) in RA patients was associated with an increased risk of clinical vertebral fracture, while there was no association with risk of non-vertebral OP fractures. We also found an increased and additive risk of OP fractures by concomitant use of oral GCs and PPIs in patients with RA, although the risk did not increase with increasing daily doses or longer duration of PPI use. Finally, we found that bDMARDs had no independent beneficial effect on reducing the risk of OP fractures in patients with RA.

iii. Impact Paragraph

The main objective of this thesis was to study the fragility or osteoporotic (OP) fractures, both in the general population and among the patients with rheumatoid arthritis (RA), and in relation to death after fracture and medication use.

Our key messages in **Chapters 5 and 6** are more relevant for the healthcare setting, clinicians and patients with RA, but also possibly for the future therapeutic guidelines. We found that low-dose oral glucocorticoid (GC) therapy was not associated with risk of non-vertebral OP fractures in patients with RA; however, it incurred a 59% increased risk of clinical vertebral fracture. This means an additional two clinical vertebral fractures per 1000 patients with RA in the UK who took low-dose oral GCs in one year. And we know that only one third of vertebral fractures would come into clinical attention, so another four vertebral fractures per 1000 patients with RA in the UK have been caused by low-dose GC therapy in a year and would have been missed in practice. This is an important finding, which warns clinicians that even in RA patients who take low daily GC doses, the risk of vertebral fracture is increased. Furthermore, we found that use of both oral GCs and proton pump inhibitors (PPIs, drugs that reduce stomach acid production) together incurred a 60% higher risk of OP fractures in patients with RA. This means an additional 14 OP fractures per 1000 patients with RA in the UK who took both drugs for one year, compared to non-use of both medications. Thus, more attention should be paid to those RA patients who are prescribed both drugs, with routine fracture risk assessment and proper preventative anti-osteoporotic therapies. This recommendation would be more important for elderly patients, possibly with a more advanced disease, who are at a higher risk of OP fractures due to other risk factors.

The main findings in **Chapters 2 and 4** could be more relevant for policymakers, clinicians and inclusion in therapeutic guidelines. Here, we found a decreasing trend for all four major OP fractures (MOFs) including hip, clinical vertebral, humerus and forearm among women between 1995 and 2010 in Denmark. A slower rate of decrease of hip fracture, steady rate for humerus, and an increasing rate for clinical vertebral fracture was observed among men. Thus, we recommend appropriate screening for OP fractures (by fracture risk assessment and bone mineral density [BMD] measurements if needed), in addition to proper use of anti-osteoporotic treatments not only in postmenopausal women, but also in older men. On the other hand, we showed that there was a clear distinction between long-term and short-term use of oral GCs in risk of hip and clinical

vertebral fracture, in those patients who were taking high daily doses. The threshold of cumulative GC use of 1.0 g prednisolone equivalent dose, as the hallmark of long-term GC therapy, is important for both the prescribing clinician and patients, who due to a chronic inflammatory disease, need long-term GC treatment in moderate to high average daily doses. Therefore, avoiding unnecessary high doses of oral GCs, adequate fracture risk assessment and timely anti-osteoporotic therapy are all recommended in order to avoid the catastrophic consequences of an imminent fracture in such patients.

The findings in **Chapters 3, 6 and 7** would ideally inspire the future research in the respecting field. Based on our findings, oral bisphosphonates (BPs) had apparently no beneficial effect on reducing the number of deaths in patients with a MOF. Oral BPs are highly recommended as first-line treatment in patients with osteoporosis or those who already had an OP fracture, in order to avoid a future fracture. However, our results did not support their hypothetical beneficial effect on hardening of the arteries. Instead, some limitations of the observational studies might explain our findings. Thus, we recommend further studies that could explain the alternative biological mechanisms or some properties of BPs that produce multiple effects, which confer a mortality benefit. Additionally, we did not observe an increasing fracture risk with higher daily doses or longer use of PPIs, which is in contrast to some previous observational studies. To date, few biological mechanisms have been proposed for an effect of PPIs on bone or falling, such as not enough production of stomach acid and calcium malabsorption, or an increased fall risk due to malabsorption of magnesium or vitamin B12, but our results did not support them. This is still an unsolved enigma, and thus an interesting realm for future studies to find a clear and sound mechanism, which can hopefully explain the associations that we and others found in real-world data. Furthermore, we found that biological disease-modifying antirheumatic drugs (bDMARDs) had no independent beneficial effect on reducing the risk of OP fractures in patients with RA. As the only known mechanism of biologic drugs for an effect on bone health is through the inflammatory cycle and considering a "treat-to-target" strategy of RA management in the real-world setting, our results are consenting with the protective effect of bDMARDs on BMD identified by clinical trials. However, more research is recommended to investigate the association between bDMARDs, BMD and OP fracture risk in patients with RA.

Our research projects had also considerable scientific impact. The results of the study in **Chapter 2** were published in one of the top journals in the bone field, i.e., *Osteoporosis International* in 2019. We also presented our findings in poster in the 34th International Conference on Pharmacoepidemiology (ICPE) in August 2018 at Prague, Czech Republic.

We published our results of **Chapter 3** in one of the top journals in the gerontology and geriatrics field, i.e., *Journal of the American Medical Directors Association* in 2020. This project was also orally presented at the Dutch Epidemiological Conference - WEON in July 2019 at Groningen, the Netherlands. The results of the project in **Chapter 4** have been published in *Archives of Osteoporosis* in 2018. The paper from **Chapter 5** has been published in one of the top ranked journals in the field of rheumatology, i.e., *Rheumatology (Oxford)* in 2021. The findings were also orally presented at the American Society for Bone and Mineral Research (ASBMR) 2020 Annual Meeting - virtual edition, oral presentation at the ASBMR Dutch days 2020 - virtual event, and in poster at the ICPE All Access 2020 - virtual event. We published our findings from **Chapter 6** in *Annals of the Rheumatic Diseases* in 2021, which is the rank 1 rheumatology journal in the world. This publication was followed by an especially tailored editorial in the same issue, a couple of correspondences published in the same journal, a lay summary in the British Medical Journal Patient Summaries Blog, and a wide media coverage in medical news services and online bulletins. This project was also presented in poster at the Dutch Epidemiological Conference - WEON in July 2019 in Groningen, the Netherlands, and also in poster at the ASBMR 2020 Annual Meeting - virtual edition. The project in **Chapter 7** has been currently submitted, with a list of target journals in the field of rheumatology, general medicine, and bone. The abstract has been also accepted for plenary poster presentation at the upcoming ASBMR 2021 Annual Meeting.

A

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v. List of Publications

The publications as parts of this thesis are marked with an asterisk.

***** Abtahi S, Driessen JHM, Burden AM, Souverein PC, van den Bergh JP, van Staa TP, Boonen A, de Vries F. Low-dose oral glucocorticoid therapy and risk of osteoporotic fractures in patients with rheumatoid arthritis: a cohort study using the Clinical Practice Research Datalink. *Rheumatology (Oxford).* 2021 Jul:keab548.

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vi. Curriculum Vitae

Shahab Abtahi was born in Tehran, Iran, on 19 May 1983. He went to the Moslem primary school in Tehranpars, before admitted to Allameh-Helli secondary and high schools as part of the National Organisation for Development of Exceptional Talents in Iran. At the final year of high school in 2000, he won the gold medal of 3rd National Biology Olympiad, followed a year later by winning the bronze medal of 12th International Biology Olympiad in Brussels, Belgium in 2001 as a member of Iran's national team. In doing this, he received scholarships from the Young Scholars Club and the Ministry of Education of Iran (2000-2001).

Shahab studied 'General Medicine' at the Tehran University of Medical Sciences and received his Medical Doctorate's degree (MD) in 2011. During these years and besides medical school, he was teaching biology to college and high school students across Iran, as well as strengthening his English and learning French and German. He received the First-Class Member's scholarship from the Iran's National Elites Foundation between 2004 and 2006. Furthermore, he received scholarship for and participated in the summer school for biomedical imaging at the Swiss Federal Institute of Technology- ETH Zurich in 2009.

After a few years of working as a general physician, teacher, and medical advisor in a pharmaceutical company, Shahab moved to the Netherlands in 2014 to enrol at the master course of 'Vitality and Ageing' at the Leyden Academy. For doing this, he benefited from a scholarship from the board of Academy. He obtained his Master of Science (MSc) in this discipline from the Leiden University in 2016. Shahab then started this PhD position in 'Pharmacoepidemiology' at the Department of Clinical Pharmacy and Toxicology of the Maastricht University Medical Center+ in 2017. Additionally, he was appointed as a visiting researcher at the Division of Pharmacoepidemiology and Clinical Pharmacology of the Utrecht Institute for Pharmaceutical Sciences, Utrecht University.

During his studies as a PhD candidate at the Maastricht University, he presented his works at several national and international conferences and symposia, for which he has also been awarded a few scholarships and prizes. These included the 34th International Conference on Pharmacoepidemiology (ICPE) in 2018 at Prague, the Dutch Epidemiological Conference - WEON 2019 in Groningen, and the American Society for Bone and Mineral Research (ASBMR) 2020 and 2021 Annual Meetings - virtual edition. He

also attended the Summer Course of Pharmacoepidemiology and Drug Safety at the Utrecht University in 2019.

Shahab is currently appointed as the 'Postdoctoral Fellow in Pharmacoepidemiology' at the Division of Pharmacoepidemiology and Clinical Pharmacology of the Utrecht Institute for Pharmaceutical Sciences, Utrecht University.