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Full Length Article

Use of high-dose intermittent systemic glucocorticoids and the risk of fracture in patients with chronic obstructive pulmonary disease



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ABSTRACT

Introduction: Chronic obstructive pulmonary disease (COPD) is characterised by persistent airflow obstruction and respiratory symptoms. While short course systemic GCs are prescribed in patients with acute COPD exacerbations, little is known of the risk of fractures with intermittent exposure to high-dose GC and the effect of proxies of disease severity.

Methods: A case-control study was conducted using the Danish National Hospital Discharge Registry (NHDR) between January 1996 to December 2011. Conditional logistics regression models were used to derive adjusted odds ratios (OR) risk of fractures in subjects with COPD stratified by intermittent high-dose, and proxies of disease severity.

Result: A total of 635,536 cases and the same number of controls were identified (mean age 67.5 ± 13.8 , 65% female). COPD patients with intermittent use of high average daily dose oral glucocorticoids did not have an increased risk of any, osteoporotic, hip or clinically symptomatic vertebral fracture compared to non-COPD patients (adj. OR 0.65; 95% CI: 0.50–0.86, 0.70; 95% CI: 0.70–0.99, 1.17; 95% CI: 0.59–2.32, 1.98; 95% CI: 0.59–6.65 respectively). We identified an elevated risk of osteoporotic fracture among patients who visited the emergency unit (adj. OR 1.47; 95% CI 1.20–1.79) or were hospitalised in the past year for COPD (adj. OR 1.76; 95% CI 1.66–1.85). Current GC use among COPD patients was associated with an increased risk of osteoporotic, hip and clinically symptomatic vertebral fractures compared to patients without COPD.

Conclusion: Intermittent high-dose GCs was not associated with an increased risk of any, osteoporotic, hip or clinically symptomatic vertebral fractures in patients with COPD. Current GC use was however associated with an increased risk of hip and clinically symptomatic vertebral fractures. Therefore, emphasis on prophylactic treatment of fractures may not be essential in patients with COPD receiving intermittent dose of GCs, whereas this should be considered for high-dose long-term users with advanced COPD disease stage, postmenopausal women and men over 40 years.

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1. Introduction

Chronic obstructive pulmonary disease (COPD) is characterised by persistent airflow obstruction and respiratory symptoms. It is projected to be the third leading cause of morbidity and mortality by 2030 [1,2]. Pharmacologic management of stable COPD consists of short- and long-acting bronchodilators, as well as inhaled and oral glucocorticoids (GCs) [3]. In patients with acute COPD exacerbations, short courses of

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systemic GCs are prescribed in order to reduce exacerbations, shorten recovery time and reduce length of hospital stay [3]. Although not recommended by current international guidelines, a proportion of COPD patients are chronically treated with low-dose oral GCs [4].

The detrimental effects of GCs on bone mineral density (BMD), resulting in an increased (hip or vertebral) fracture risk, are well established [5–9]. While elevated fracture risk may be caused by several factors related to disease severity which negatively influences bone structure, fracture risk remains elevated in patients using oral GCs even after adjustment for proxy indicators of disease severity [10–12]. Consequently, GC use is included in risk prediction tools such as FRAX [8] and international clinical guidelines on the prevention of GC-induced osteoporosis [13].

Fracture risk associated with oral GC use increases rapidly, particularly during the first 3 months of treatment, and is partially independent of a decreased BMD [14]. The increase in fracture risk is directly, and linearly, related to the daily, and possibly also to cumulative, dose of oral GCs; yet the relative relationship between the two is not consistent [5–7,15]. Thus clinicians suggest the use of intermittent dosing of GCs to mitigate and manage GC-induced adverse effects, such as fractures [16]. De Vries et al. evaluated the risk of fracture with intermittent use of high-dose oral GC and found a small increased risk of osteoporotic fractures among patients with various disease conditions requiring GC use [7]. They defined intermittent high dose exposure as daily dose ≥ 15 mg and cumulative dose exposure ≤ 1 g (for instance 30 mg prednisolone equivalents per day for 2–4 weeks).

While the risk of fracture in patients with obstructive airways disease exposed to intermittent high-dose oral GC was examined by de Vries et al. in a large British population, little is known of this risk in COPD patients in other settings. Therefore the objective of the present study was to investigate the effects of intermittent high-dose glucocorticoid use on fracture risk in patients with COPD, the impact of proxy indicators of disease severity and the effect of dose, compared to patients without COPD.

2. Methods

2.1. Design and source population

A population-based case-control study was conducted using healthcare records from Danish National databases. In Denmark, separate registers of computerized medical records on all contacts to hospitals and on the use of drugs can be linked for the entire population (approximately 5.5 million inhabitants). The register was founded in 1977 and covers all inpatients contacts from 1977 to 1994, and from 1995 onwards also includes all outpatient visits to hospitals, outpatient clinics and emergency rooms. After discharge, the physician enters the reason for the contact according to the International Classification of Diseases (ICD) system. The register has nationwide coverage of public health facilities with an almost 100% completeness of recordings and a high precision of diagnoses [17,18], particularly for fracture diagnoses [6].

The Danish Medicines Agency keeps a nationwide prescription database, the Register of Medicinal Product Statistics, with information on prescriptions for refundable drugs. The database includes information on the patient's civil registry number, the type and amount of drug prescribed in accordance to the Anatomical Therapeutic Chemical (ATC) classification system [2] and the date when the prescription was filled by the patient. This permits an evaluation of the average daily dose and cumulative exposure. All registers can be interconnected through the use of the civil registry number that is assigned to all Danes [19].

2.2. Study population/outcome

Cases were identified as patients aged 45 years and older who had sustained a fracture between January 1996 and December 2011.

Fractures considered included a fracture of the hip (ICD10 code S72.0–S72.2), clinical symptomatic vertebrae (S12, S22.0–S22.1, S32.0–S32.2, S32.7, S32.8, T08), osteoporotic (defined as a fracture of the hip, clinical symptomatic vertebrae, radius/ulna [S52] or humerus [S42.2–S42.4] according to the World Health Organisation's (WHO) definition [20]). Any fracture was determined by the following International Classification of Diseases and Related Health Problems (ICD)-10 codes: S02, S12, S22, S32, S42, S52, S62, S72, S82, S92, T02, T08, T10 and T12. For each case, one control patient (who had not sustained a fracture) was matched by gender and year of birth using incidence-density sampling [21]. The date of the first fracture defined the index date for cases, and controls were assigned the index date of their matched cases.

2.3. Exposure

Presence of COPD before the index date was defined based on ICD-10 code J43 or J44. Individuals without an ICD-10 code for COPD were categorized as non-COPD patients and used as the reference category in all analyses. Furthermore, among COPD patients we evaluated oral glucocorticoid (GC) use before the index date. Based on the time since the most recent GC dispensing from the index date patients was classified as current (1–91 days), recent (92–182), past (183–364 days) or distant (over 364 days) users. For each current user, the cumulative and average daily GC exposure was estimated. The average daily dose was calculated by dividing the cumulative GC exposure by the treatment time (i.e. the time between the first GC dispensing and the index date). Intermittent high-dose of GC was defined as daily dose ≥ 15 mg and cumulative exposure < 1 g [7]. This roughly corresponds to 30 mg prednisolone per day for 2–4 weeks. It is recommended that patients with COPD receive of 30 mg of prednisolone for 7–14 days and no longer that in the event of an exacerbation (ref). The cumulative dose was calculated by adding up all previous GC dispensing using the defined daily dosages (DDD). The average daily dose was calculated by dividing the cumulative GC exposure by the treatment time (i.e. the time between the first GC dispensing and the index date). GC exposure was expressed as oral prednisolone equivalents.

2.4. Confounders

We considered the following potential confounders before the index date: history of fracture, rheumatoid arthritis, inflammatory bowel disease (IBD), secondary osteoporosis (type 1 diabetes, hyperthyroidism, hypogonadism and renal failure), dementia, type 2 diabetes mellitus, cerebrovascular disease, pneumonia, malignancies (excluding non-melanoma skin cancer) and gout. These potential confounders have been related to fractures and COPD in previous studies [11,22]. Other potential confounders included a dispensing in the six months before the index date of the following drugs: inhaled cromoglycates, xanthine derivatives, bisphosphonates, vitamin D, calcium, raloxifene, strontium, denosumab, calcitonin, parathyroid hormone, hormone replacement therapy, antipsychotics, antidepressants, hypnotics/anxiolytics, anti-convulsants, anti-parkinson drugs, antihypertensive drugs and proton pump inhibitors. Proxy indicators of respiratory disease severity variables included a dispensing of inhaled corticosteroids, long-acting beta-2 agonists, short-acting beta-2 agonists, long-acting anticholinergics, short-acting anticholinergics, roflumilast, oxygen and the number of accident & emergency registrations or hospitalisations for COPD in the previous year [11].

2.5. Statistical analysis

Conditional logistic regression was used to estimate odds ratios (ORs) for fracture risk (SAS 9.3). Final regression models were determined by stepwise backward elimination using a significance level of 0.05. Patients without COPD were the reference category, and among COPD patients. Analyses were stratified by intermittent GC exposure,

proxies of disease severity and average daily and cumulative dose exposure for specific fracture sites. Proxies of disease severity considered include hospitalisation and emergency visits for COPD in previous year. All results were presented as OR with corresponding 95% confidence intervals (CIs).

3. Results

The study population consisted of 635,536 cases and the same number of controls. Baseline characteristics of the study participants are shown in Table 1. The mean age at index date was 67.5 ± 13.8 and 65% were female. Approximately 18% of the cases ($n = 113,553$) and 15% of the controls ($n = 97,460$) used GCs in the six months before the index date. There was a history of fracture among 24.4% of the cases and 8% of the controls. A higher proportion of cases had used anticonvulsants, hypnotics, anxiolytics and antidepressants in the six months prior to index date. There were 38,013 (6%) patients with COPD among the cases and 28,490 (4.5%) among controls.

Table 2 presents the adjusted fracture risk among COPD patients currently exposed to oral glucocorticoid compared with patients without COPD. COPD patients with intermittent use of high average daily dose oral glucocorticoids did not have an increased risk of any, osteoporotic, hip or clinically symptomatic vertebral fracture compared to patients without COPD (adj. OR 0.65; 95% CI: 0.50–0.86, 0.70; 95% CI:

0.70–0.99, 1.17; 95% CI: 0.59–2.32, 1.98; 95% CI: 0.59–6.65 respectively). However, the risk of osteoporotic fractures was significantly increased among long time heavy users receiving a cumulative dose between 1 and 4.9 g (adj. OR: 1.46; 95% CI: 1.07–1.20), and the risk of hip fracture increased among COPD patients with cumulative dose of 5.0–9.9 g (adj. OR: 2.88; 95% CI: 1.27–6.57).

As a proxy for disease severity, we further stratified COPD patients by patients with an emergency visit or hospitalisation for COPD in the year prior to fracture (Table 3). We identified an elevated risk of osteoporotic fracture among patients who visited the emergency unit (adj. OR 1.47; 95% CI 1.20–1.79) or were hospitalised in the past year for COPD (adj. OR 1.76; 95% CI 1.66–1.85), as compared to patients without COPD (Table 3). Similarly the risk of hip fracture was elevated in hospitalised patients (adj. OR: 2.47; 95% CI: 2.26–2.70) and those who visited the emergency unit (adj. OR: 2.13; 95% CI: 1.49–3.04) in the past year, compared to non-COPD patients. The risk of clinically symptomatic vertebral fractures showed a 3-fold increase among COPD patients following hospitalisation and emergency visit in the past year when compared to patients without COPD. We also noticed an increased risk of any fracture in patients with emergency visits or hospitalisation for COPD.

The individual breakdown of average daily dose and cumulative dose by fracture type among COPD patients, compared to non-COPD patients, is provided in Table 4. Current GC use among COPD patients was associated with an increased risk of osteoporotic (adj. OR: 1.12; 95% CI: 1.05–1.20), hip (adj. OR: 1.23; 95% CI: 1.10–1.37) and clinically symptomatic vertebral fractures (adj. OR: 1.87; 95% CI: 1.52–2.31) as compared to patients without COPD except risk for any fracture. The risk of hip and clinically symptomatic vertebral fractures increased with increasing average daily doses, with patients exposed to 7.5–15 mg/day having the greatest risk. Cumulative dose of 5.0–9.9 g was associated with and increased risk of clinically symptomatic vertebral fractures (adj. OR: 2.26; 95% CI: 1.52–3.35).

4. Discussion

In the current study, we found that exposure to intermittent high-dose glucocorticoid was not associated with an increased risk of any, osteoporotic, hip and clinically symptomatic vertebral fracture in COPD patients compared to patients without COPD. Furthermore, we showed that proxies of disease severity (hospitalisation and emergency visit for COPD in the past year) were associated with an increased risk of any, osteoporotic, hip and clinically symptomatic vertebral fractures among patients with COPD compared to patients without COPD.

This study extends previous knowledge from large population based studies [5,6]. A cohort study by de Vries et al. [7], showed that intermittent high-dose of glucocorticoid among patients with various diseases requiring GC use was associated with a small increased risk of osteoporotic and vertebral fractures, but no increased risk of hip fractures. In their study, intermittent use of GC was defined as daily dose ≥ 15 mg and cumulative exposure ≤ 1 g similar to our study. However, they employed a cohort study design adjusting for covariates time-dependently. This might explain the absence of the small increased risk of osteoporotic and vertebral fractures with intermittent exposure in our study. Another study among patients with COPD, found no increased risk of vertebral fracture with intermittent use of systemic GC [23]. The investigators defined intermittent use of GC as exposure to prednisolone for an average of 4 months during the patient's lifetime and the study population was comprised of men over 50 years. Additionally, intermittent use of GCs (daily dose ≥ 10 mg and cumulative dose ≤ 1 g) did not change the BMD in patients with COPD [24] this might explain our result. However, COPD patients exposed to continuous GC use were 2.4 times more likely to have one or more vertebral fracture [23].

In our study we defined emergency visits and hospitalisations for COPD in the past year as proxies for disease severity. Patients with

Table 1
Baseline characteristics^a.

| Characteristics | Cases <i>n</i> = 635,536 | | Controls <i>n</i> = 635,536 | |
|---|-----------------------------|---------|--------------------------------|---------|
| | <i>n</i> | % | <i>n</i> | % |
| | Male sex | 224,182 | 35.3 | 224,182 |
| Mean age at index date (years, SD) | 67.5 | 13.8 | 67.5 | 13.8 |
| 45–60 | 220,166 | 34.6 | 220,158 | 34.6 |
| 60–74 | 194,647 | 30.6 | 194,664 | 30.6 |
| 75+ | 220,723 | 34.7 | 220,714 | 34.7 |
| History of co-morbidities | | | | |
| Fracture | 154,923 | 24.4 | 49,742 | 7.8 |
| COPD | 38,013 | 5.9 | 28,490 | 4.5 |
| Pneumonia | 21,106 | 3.3 | 15,771 | 2.5 |
| Rheumatoid arthritis | 12,245 | 1.9 | 9133 | 1.4 |
| Inflammatory bowel disease | 12,962 | 2.0 | 10,005 | 1.6 |
| Secondary osteoporosis | 32,275 | 5.1 | 25,041 | 3.9 |
| Type 1 diabetes mellitus | 13,897 | 2.2 | 8439 | 1.3 |
| Type II diabetes mellitus | 31,252 | 4.9 | 25,535 | 4.0 |
| Hyperthyroidism | 13,934 | 2.2 | 13,614 | 2.1 |
| Hypogonadism | 612 | 0.1 | 408 | 0.1 |
| Renal failure | 5570 | 0.9 | 3496 | 0.6 |
| Dementia | 16,572 | 2.6 | 9251 | 1.5 |
| Cerebrovascular disease | 54,999 | 8.7 | 41,511 | 6.5 |
| Malignancies (excl. non-melanoma skin cancer) | 71,393 | 11.2 | 62,780 | 9.9 |
| Drug use within six months before index date | | | | |
| Oral glucocorticoids | 113,553 | 17.9 | 97,460 | 15.3 |
| Inhaled corticosteroids | 21,550 | 3.4 | 19,236 | 3.0 |
| Inhaled bronchodilators | 44,096 | 6.9 | 37,105 | 5.8 |
| Xanthine derivates | 5427 | 0.9 | 4653 | 0.7 |
| Bisphosphonates | 16,941 | 2.7 | 10,211 | 1.6 |
| Vitamin D | 740 | 0.1 | 627 | 0.1 |
| Calcium | 8535 | 1.3 | 5777 | 0.9 |
| Raloxifene | 747 | 0.1 | 493 | 0.1 |
| Hormone replacement therapy | 45,381 | 7.1 | 55,626 | 8.8 |
| Antipsychotics | 31,258 | 4.9 | 20,080 | 3.2 |
| Antidepressants | 89,941 | 14.2 | 53,689 | 8.5 |
| Hypnotics/anxiolytics | 72,682 | 11.4 | 54,384 | 8.6 |
| Anticonvulsants | 21,443 | 3.4 | 10,456 | 1.7 |
| Anti-Parkinson drugs | 7030 | 1.1 | 3987 | 0.6 |
| Antihypertensive drugs | 228,310 | 35.9 | 227,776 | 35.8 |
| Proton pump inhibitors | 56,646 | 8.9 | 41,382 | 6.5 |
| COPD related Emergency visit in past year | 588 | 0.1 | 302 | 0.1 |
| COPD related hospitalization in past year | 9658 | 1.5 | 4252 | 0.7 |

Abbreviations: SD: standard deviation; COPD: chronic obstructive pulmonary disease.

^a Data are number (%) of patients, unless stated otherwise.

Table 2
Adjusted risk fractures among COPD patients compared to patients without COPD stratified by current GC use.

| | Any fracture Adj. OR ^{a,b} | Osteoporotic fracture Adj. OR ^{a,b} | Hip fracture Adj. OR ^{a,b} | Clinical symptomatic vertebral Adj. OR ^{a,b} |
|---|-------------------------------------|--|-------------------------------------|---|
| No COPD | 1.00 (Reference) | 1.00 (Reference) | 1.00 (Reference) | 1.00 (Reference) |
| COPD | 1.06 (1.04–1.08) | 1.03 (1.00–1.06) | 1.08 (1.03–1.13) | 1.31 (1.20–1.44) |
| By GC exposure | | | | |
| Current use | 1.01 (0.96–1.06) | 1.12 (1.05–1.20) | 1.23(1.10–1.37) | 1.87(1.52–2.31) |
| By average daily dose ≥ 15 mg/day (oral prednisone equivalents) | | | | |
| <1 g | 0.65 (0.50–0.86) | 0.70 (0.49–0.99) | 1.17 (0.59–2.32) | 1.98 (0.59–6.65) |
| 1.0–4.9 g | 1.14 (0.90–1.43) | 1.46 (1.07–2.00) | 1.61 (0.95–2.73) | 2.43 (0.95–6.22) |
| 5.0–9.9 g | 1.36 (0.97–1.89) | 1.40 (0.91–2.16) | 2.88 (1.27–6.57) | 0.93 (0.35–2.44) |
| ≥10 g | 1.07 (0.84–1.36) | 1.19 (0.85–1.65) | 1.59 (0.89–2.87) | 1.25 (0.52–3.00) |

Abbreviations: OR: odds ratio; GC: glucocorticoid; COPD: chronic obstructive pulmonary disease.
Current GC use: most recent GC dispensing with 1–91 days before index date.

^a Values are the adjusted odds ratios (95% confidence interval).

^b Adjusted for: prior fracture, history of pneumonia, inhaled corticosteroids, inhaled bronchodilators, antidepressants, hypnotics/anxiolytics, proton pump inhibitors, emergency visit for COPD, hospitalisation for COPD, never, distant, past, and recent use of oral GCs.

COPD who were hospitalised or who visited the emergency unit in the past year had an increased risk of hip, osteoporotic and clinically symptomatic vertebral fractures. The severity of the disease may influence the dose and duration of GC administered [9]. However, severity of pulmonary disease was shown to be inversely proportional to BMD [11]. Our findings are in line with a population-based case-control study of Danish patients with fractures exposed to corticosteroids (*n* = 124,655), reporting that overall fracture risk increased with the number of days in which COPD patients were hospitalised [14]. While hospitalisation was identified as an important proxy for disease severity, the duration of disease has been found not to correlate with fracture risk, as it does not reflect severity of disease [14]. Adjustment for disease severity is limited in fracture studies [5,25,26]. In our study we adjusted the primary analysis for proxies of disease severity. Furthermore, studies have identified the importance of disease severity on fracture risk in patients exposed to GC. Consequently, adequate adjustments should be made when studying the risk of fractures in COPD patients [11].

The present results are in line with a previous observational study, which evaluated cumulative/daily dose and the risk of fractures using the CPRD. The researchers found an increased risk of hip and vertebral fractures with higher daily doses of oral corticosteroids compared to patients using lower doses [10]. Our findings are also supported by a large case-control study which reported an increased risk of hip fractures with increasing average daily dose [10]. Vestergaard et al. [14] also reported a dose-dependent increased risk of fractures, with the greatest risk of hip fractures observed at a dose of ≥7.5 mg/day. Their study was carried out in a subset of our population. In our study, an increased risk of osteoporotic, clinically symptomatic vertebral and hip fractures was observed at a dose of 7.5–15-mg/day compare to patients without

COPD. The perceived increased risk of hip and osteoporotic fracture with increasing cumulative dose seems to disappear after adjustment for various confounders. However, the risk of GC related fractures was reported to be strongly associated with daily dose than with cumulative dose [6,27]. This may be due to misclassification of exposures to GC as participant's exposures were ascertained by interviews and prone to recall bias. Researchers have emphasised the importance of daily dose monitoring in patients exposed to GC, as risk of fracture have been seen to return towards baseline following termination of GC therapy irrespective of cumulative dose [6].

Several mechanisms have been suggested for the possible relationship between COPD and fracture. GC use has been associated to the reduction in bone mineral density and increased fracture risk via a number of mechanisms which include inhibition of steroid synthesis and inhibition over reduced calcium absorption from the gut and increased loss of osteoclast, osteoblast, insulin like growth factor and collagen [28,29]. It has been suggested that factors associated with COPD itself may contribute to loss of bone mineral density [30,31]. Similarly, low dietary calcium is correlated with low BMD and increase fracture risk [25]. However, the risk of fracture among patients receiving oral GCs is somewhat independent of decreased bone mineral density [7]. Damage to the micro-architecture of the trabecular bone has been attributed to deformities of the vertebrae [32]. Furthermore, it is been reported that cumulative exposure to GCs correlates with the degree of the trabecular network of bones [33]. Furthermore, smoking remains a major risk for COPD and may induce osteoporosis via various mechanism which include the alteration of metabolism of calciotropic hormone; dysregulation in the production, metabolism, and binding of estradiol; altered metabolism of adrenal cortical hormone and bone angiogenesis [34].

Table 3
Adjusted risk of fracture among COPD patients stratified by proxies of disease severity compared to patients without COPD.

| | Any fracture Adj. OR ^{a,b} | Osteoporotic fracture Adj. OR ^{a,b} | Hip fracture Adj. OR ^{a,b} | Clinical symptomatic vertebral Adj. OR ^{a,b} |
|---------------------------------------|-------------------------------------|--|-------------------------------------|---|
| No COPD | 1.00 (Reference) | 1.00 (Reference) | 1.00 (Reference) | 1.00 (Reference) |
| COPD | 1.05 (1.03–1.07) | 1.03 (1.00–1.06) | 1.08 (1.03–1.13) | 1.31 (1.20–1.44) |
| Proxy indicators of disease | | | | |
| Emergency visit in past year for COPD | | | | |
| No | 1.05 (1.03–1.07) | 1.03 (1.00–1.06) | 1.08 (1.03–1.13) | 1.31 (1.20–1.44) |
| Yes | 1.47 (1.27–1.71) | 1.47 (1.20–1.79) | 2.13 (1.49–3.04) | 3.15 (1.64–6.07) |
| Hospitalisation in past year for COPD | | | | |
| No | 1.07 (1.05–1.10) | 1.06 (1.03–1.08) | 1.11 (1.06–1.17) | 1.35 (1.23–1.48) |
| Yes | 1.66 (1.60–1.73) | 1.76 (1.66–1.85) | 2.47 (2.26–2.70) | 3.08 (2.57–3.69) |

Abbreviations: OR: odds ratio; GC: glucocorticoid; COPD: chronic obstructive pulmonary disease.
Current GC use: most recent GC dispensing with 1–91 days before index date.

^a Values are the adjusted odds ratios (95% confidence interval).

^b Adjusted for previous fracture, history of pneumonia, inflammatory bowel disease, cerebrovascular disease, inhaled corticosteroids, inhaled bronchodilators, antidepressants, hypnotics/anxiolytics, proton pump inhibitors, hospitalizations for COPD, emergency visits for COPD, and previous use of oral GCs.

Table 4

Adjusted risk of fracture among COPD patients compared to patients without COPD stratified by average daily and cumulative exposure.

| | Any Fracture Adj. OR ^{a,b} | Osteoporotic fracture Adj. OR ^{a,b} | Hip Fracture Adj. OR ^{a,b} | Clinical Symptomatic Vertebral Adj. OR ^{a,b} |
|---|-------------------------------------|--|-------------------------------------|---|
| No COPD | 1.00 (Reference) | 1.00 (Reference) | 1.00 (Reference) | 1.00 (Reference) |
| COPD | 1.06 (1.04–1.08) | 1.03 (1.00–1.06) | 1.08 (1.03–1.13) | 1.31 (1.20–1.44) |
| By GC exposure | | | | |
| Current use | 1.01 (0.96–1.06) | 1.12 (1.05–1.20) | 1.23(1.10–1.37) | 1.87(1.52–2.31) |
| By average daily dose (oral prednisone equivalents) | | | | |
| <7.5 mg/day | 0.98 (0.92–1.04) | 1.08 (0.99–1.17) | 1.16 (1.01–1.34) | 1.53 (1.18–1.99) |
| 7.5–15 mg/day | 1.08 (0.99–1.17) | 1.20 (1.07–1.34) | 1.23 (1.02–1.47) | 2.98 (2.05–4.33) |
| ≥15 mg/day | 1.01 (0.89–1.15) | 1.15 (0.96–1.37) | 1.66 (1.21–2.28) | 1.55 (0.94–2.54) |
| By cumulative dose (oral prednisone equivalents) | | | | |
| <1.0 g | 0.87 (0.77–0.99) | 1.01 (0.86–1.18) | 1.19 (0.89–1.59) | 1.96 (1.10–3.46) |
| 1.0–4.9 g | 0.96 (0.89–1.04) | 1.09 (0.98–1.22) | 1.21 (1.01–1.45) | 1.60 (1.15–2.24) |
| 5.0–9.9 g | 1.11 (1.00–1.22) | 1.15 (1.02–1.31) | 1.23 (0.99–1.53) | 2.26 (1.52–3.35) |
| ≥ 10 g | 1.06 (0.98–1.15) | 1.18 (1.06–1.31) | 1.26 (1.06–1.51) | 1.87 (1.33–2.64) |

Abbreviations: OR: odds ratio; GC: glucocorticoid; COPD: chronic obstructive pulmonary disease.

Current GC use: most recent GC dispensing with 1–91 days before index date.

^a Values are the adjusted odds ratios (95% confidence interval).^b Adjusted for previous fracture, history of pneumonia, inhaled corticosteroids, inhaled bronchodilators, antidepressants, hypnotics/anxiolytics, proton pump inhibitors, hospitalizations for COPD, emergency visits for COPD, and previous use of oral GCs.

The main strength of our study was the large sample size among cases and controls. This was possible because our study was conducted using the Danish National database with roughly 5 million anonymised patient records from across Denmark [17]. We considered hospitalisation and emergency visit in the past year as proxies for disease severity [14]. Although we adjusted our analyses for these proxies this might not have completely corrected for the severity of the disease. Our limitations included the lack of information on smoking, alcohol use, inflammatory markers, muscle mass or strength and BMD as such we could not adjust for these potential confounders in our analysis. There is also the problem of diagnosis of vertebral fracture, which is mostly done by clinical and radiological assessment, as such asymptomatic vertebral fractures are most likely to go undetected [6]. We could not independently confirm the predictive values of cases diagnosed with fractures by the general practitioner. Although, a high positive predictive value (93%) of diagnosis of fractures has been reported in the Danish database [26]. This limits the possibility of non-differential misclassification. As with most observational studies, we could not rule out the possibility of misclassification of exposure to GCs. Information on potential treatment received prior to entry into the Danish national database was also not available. We also lacked information on severity of COPD as such there may be confounding by indication [9].

In conclusion, intermittent high-dose GCs was not associated with an increased risk of any, osteoporotic, hip or clinically significant vertebral fractures in patients with COPD. Current GC use however was associated with an increased risk of hip and clinically symptomatic vertebral fracture. It is important to also note that COPD alone increases the risk of fracture compared to those without COPD, especially among patients with history of hospitalisation or emergency room visit for COPD. Therefore, emphasis on prophylactic treatment of fractures may not be essential in patients with COPD receiving intermittent dose of GCs, whereas this should be considered for high-dose long-term users with advanced COPD disease stage, postmenopausal women and men over 40 years.

Competing interest

AMB's salary is supported by a Canadian Institutes of Health Research (CIHR) fellowship (2014–2017). All other authors have nothing to declare.

Acknowledgement and author contributions

Conception or design: all authors equally contributed.

Analysis of data: OAO, AMB

Interpretation of data: all authors equally contributed.

Drafting the work OAO, FV, FF, AMB

Revising the work critically for important intellectual content: all authors equally contributed.

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All authors who are affiliated to Utrecht University are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The other authors are accountable for all aspects of the work that are not related to data analysis.

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