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Use of inhaled and oral glucocorticoids, severity of inflammatory disease and risk of hip/femur fracture: a population-based case–control study

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Abstract. de Vries F, Pouwels S, Lammers JWJ, Leufkens HGM, Bracke M, Cooper C, van Staa TP (Utrecht Institute for Pharmaceutical Sciences and Utrecht Medical Center, Utrecht University, the Netherlands; University of Southampton, Southampton General Hospital, Southampton, UK; and General Practice Research Database, London, UK). Use of inhaled and oral glucocorticoids, severity of inflammatory disease and risk of hip/femur fracture: a population-based case–control study. *J Intern Med* 2007; **261:** 170–177.

Background. Patients using higher dosages of inhaled or oral glucocorticoids (GCs) have an increased risk of hip/femur fractures. The role of the underlying disease in the aetiology of this increased risk has not been widely studied.

Objective. To evaluate the contribution of the underlying disease to the risk of hip/femur fracture in patients using inhaled or oral GCs.

Design and subjects. A case–control study within the Dutch PHARMO-RLS database was conducted. Cases (n = 6763) were adult patients with a first hip/femur fracture during enrolment. Each case was matched to four controls by age, gender and region.

Results. The risk of hip/femur fracture increased with current use of inhaled GCs (crude OR 1.30, 95% CI: 1.16–1.47) and with current use of oral GCs (crude OR 1.66, 95% CI: 1.46–1.90). After adjustment for disease severity, the risk of hip/femur fracture was no longer statistically significantly increased in inhaled GC users (adjusted OR 1.08, 95% CI: 0.91–1.27), whilst it remained elevated in oral GC users (adjusted OR 1.43, 95% CI: 1.22–1.67). Patients using inhaled GCs without any exposure to oral GCs had no increased risk of fracture (adjusted OR 0.98, 95% CI: 0.79–1.22).

Conclusion. Inhaled GC users had no increased risk of femur/hip fracture after adjustment for underlying disease severity. Our data suggest that, even at higher dosages, inhaled GC use is not an independent risk factor for fracture. In contrast, oral GC use was associated with an increased risk of fracture, which was not fully explained by the underlying disease severity.

Keywords: 'lung diseases, obstructive', confounding factors (epidemiology), glucocorticoids, hip fractures.

Introduction

Oral and inhaled glucocorticoids (GCs) are frequently prescribed to patients with inflammatory disease such as obstructive airway disease, rheumatoid arthritis (RA) or inflammatory bowel disease (IBD) [1, 2]. Use of oral GCs has been found to decrease bone mineral density and increase the risk of fracture [3, 4]. These increases in the risk of fracture correlate with the daily dose of oral GCs [5, 6]. For inhaled

GCs decreases in bone mineral density and increases in the risk of fracture have also been reported.

However, there has been controversy about the aetiology of these increases in the risk of fracture in users of inhaled GCs [7–10]. Although these medications are administered locally, they undergo systemic absorption at higher dosages and may induce a suppression of plasma cortisol [11]. This may lead to low bone mineral density and increased risk of fracture. An alternative explanation for these effects on the bone may be the underlying obstructive airway disease [12–15]. A reanalysis of a study conducted in the UK with the General Practice Research Database (GPRD) found that a previously reported dose–response association between inhaled GC use and risk of fracture disappeared after adjustment for the severity of obstructive airways disease [7, 16]. The aim of this study was to evaluate the possible contribution of the underlying disease to the risk of hip/femur fracture in patients using inhaled GCs or oral GCs in a different population.

Methods

Study design

PHARMO Record Linkage System (RLS) (http://www.pharmo.nl) is a database that contains the pharmacy dispensing data for a population of about 1 million Dutch patients. These dispensing data are linked to a nation-wide hospital discharge register [17]. In the Netherlands, pharmacies maintain a virtually complete register of dispensed medications, which have been prescribed by specialists and general practitioners. Patients are included irrespective of their health insurance or socio-economic status, and represent about 7% of the general population. Several independent validation studies have shown that the PHARMO-RLS database has a high level of completeness and validity [18, 19].

Cases and control subjects

Within PHARMO-RLS, a case–control study was conducted. Cases were patients who were 18 years or older and who sustained a hip/femur fracture during the study period (1 January 1991 to 31 December 2002). Each case was matched to up to four control patients (PHARMO-RLS participants without any fracture during enrolment) by year of birth, gender and region. The date of the first hip/femur fracture was defined as the index date. Each control was assigned the index date of the matched case.

Exposure assessment

Current exposure was defined as the dispensing of at least one oral GC [predniso(lo)ne, dexamethsone, triamcinolone, hydrocortisone] or inhaled GC (fluticasone, beclomethasone, budesonide) in 4 months before the index date, because Dutch health insurance policies cover the dispensing of the majority of drugs for periods of 3 months. Past users were patients who received their last GC dispensing more than 4 months before the index date. For each current user, the cumulative exposure was calculated by summing the total amount of dispensing between enrolment in PHARMO-RLS and the index date. The average daily dose was calculated by dividing the cumulative exposure by the total treatment time. Using defined daily dosages, exposure was expressed as oral prednisone equivalents or inhaled beclomethasone equivalents [20].

Covariate assessment

For the inhaled GC analyses, we measured indicators of respiratory disease severity within 6 or 12 months before the index date, similar to previous studies [16, 21, 22]. These included asthma/Chronic Obstructive Pulmonary Disease (COPD) exacerbations and the use of inhaled anticholinergics, β-2 agonists, oral GCs, xanthine derivatives, acetylcystein, in the 6 months before the index date. Dispensings of antibiotics within ±3 days before or after an oral GC dispensing were considered an asthma/COPD exacerbation [23]. Hospitalizations for asthma/COPD in the 1 year before the index date and administration of nebulized respiratory medications in the 6 months before were also measured. Likewise, for the oral GC analyses, we determined indicators of inflammatory disease.

These included the respiratory disease severity indicators, exposure to DMARDs (methothrexate, azathioprine, mesasalazin, salazopyrin, gold preparations and penicillamin within 6 months before the index date in order to estimate prevalent disease), and a history of hospitalizations for IBD or RA/Polymyalgia Rheumatica/Bechterew's disease. The following general potential confounding factors were also determined: use of benzodiazepines within 3 months prior to the index date (under Dutch law, most benzodiazepines cannot be prescribed for longer than 30 days), use of antipsychotics, antidepressants, anticonvulsants, antidiabetic agents, β-blockers, hormone replacement therapy and ≥2 dispensings for a nonsteroidal anti-inflammatory drug (NSAID) within 6 months before index date and a history of hospitalizations for anaemia, mental disorders, endocrine disorders and cerebrovascular disease before index date.

Statistical analysis

Conditional logistic regression was used to estimate odds ratios (OR) for hip/femur fracture (SAS version 9.1.3, PHREG procedure). Two different adjustments were made in the regression analyses. The first analysis adjusted for indicators of the severity of the underlying respiratory disease (inhaled GC analysis), or inflammatory disease (oral GC analysis). The second analysis adjusted not only for disease severity indicators, but also for general risk factors of hip/femur fracture. Backward selection of variables was used in the regression analyses. We also used smoothing spline regression plots (SAS version 9.1.3) to visualize the longitudinal relationship of risk of fracture with time between the index date and last dispensing of GCs (recency of use), and cumulative GC exposure [24].

Results

We identified 6763 patients who suffered a hip/femur fracture. These cases were matched to 26 341 controls. The mean age was 75 years and 73% of the case patients were female. The majority of hip fractures (93%) occurred amongst subjects who were 50 years or older (Table 1). The mean period of time with prescription information prior to the index date was 4.1 years.

Indicators for the severity of the respiratory or inflammatory disease were associated with increased risk of hip/femur fracture. Hospitalizations for asthma/COPD

Table 1 Baseline characteristics

	Cases (n = 6763), n (%)	Controls (n = 26 341), n (%)	Crude odds ratio (95% CI)
Mean age (years)	75.7	75.3	
Females, n (%)	4929 (73)	19 138 (73)	
Use 6 months before the index date			
Short-acting β-2 agonists	388 (6)	1100 (4)	1.41 (1.25–1.59)
Long-acting β-2 agonists	148 (2)	488 (2)	1.21 (1.00–1.46)
Anticholinergics	323 (5)	1002 (4)	1.27 (1.12–1.45)
Xanthine derivatives	131 (2)	281 (1)	1.85 (1.50–2.29)
N-Acetylcystein	278 (4)	803 (3)	1.37 (1.19–1.57)
Inhaled GCs	437 (6)	1316 (5)	1.32 (1.18–1.48)
Oral GCs	366 (5)	918 (3)	1.59 (1.40–1.80)
DMARDs	115 (2)	202 (1)	2.27 (1.80–2.86)
Hospitalization for cardiovascular disease	359 (5)	1289 (5)	1.10 (0.98–1.25)
Hospitalization for cerebrovascular disease	296 (4)	565 (2)	2.12 (1.84–2.45)
Hospitalization for RA/Polymyalgia Rheumatica/Bechterew's disease	245 (4)	731 (3)	1.34 (1.16–1.56)

GC, glucocorticoid; RA, rheumatoid arthritis.

in the 1 year prior to the index date doubled the risk of hip/femur fracture [crude OR 2.17, 95% confidence interval (CI): 1.41–3.34)]. In addition, asthma/COPD exacerbations and the use of nebulized medications 6 months before the index date increased the risk of hip/femur fractures (crude ORs 1.67, 95% CI: 1.29–2.17 and 2.35, 95% CI: 1.39–3.96), respectively. Hospitalizations for IBD (crude OR 1.58, 95% CI: 1.39–1.79) and RA/Polymyalgia Rheumatica/Bechterew disease (crude OR 1.34, 95% CI: 1.16–1.56) were also associated with an increased risk of hip/femur fracture.

As shown in Table 2, the risk of hip/femur fracture increased with current use of inhaled GCs (crude OR 1.30, 95% CI: 1.16–1.47) and with current use of oral GCs (crude OR 1.66, 95% CI: 1.46–1.90; Table 3). After adjustment for indicators of severity of the underlying respiratory disease, the risk of hip/femur fracture was no longer statistically significantly increased with current use of inhaled GCs (adjusted OR 1.08, 95% CI: 0.91–1.27). In contrast, the risk of hip/femur fracture remained statistically significantly increased with use of oral GCs after additional adjustment for indicators of disease severity (adjusted OR 1.43, 95% CI: 1.22–1.67).

For current users of higher daily dosages of inhaled GCs, similar findings were demonstrated (≥1600 μg day^{-1}: crude OR 2.02, 95% CI: 1.24–3.29) or oral GCs (≥15 mg day^{-1}: crude OR 2.09, 95% CI: 1.42–3.07). The excess risk of hip/femur fracture substantially decreased after adjustment for indicators of underlying respiratory disease severity in inhaled GC users, and was no longer significantly increased compared with nonusers (adjusted OR 1.43, 95% CI: 0.85–2.41). In contrast, adjustment for indicators of disease severity did not substantially change the risk of hip/femur fracture in high-dose oral GC users (adjusted OR 1.87, 95% CI: 1.26–2.78).

There was no association between the time since the last dispensing of an inhaled GC and risk of hip/femur fracture (Fig. 1). Conversely, current oral GC users had an increased risk of hip/femur fractures, which slowly decreased to baseline after discontinuation of oral GCs (Fig. 2). The association between cumulative exposure to inhaled and oral GCs and risk

Table 2 Use of inhaled GCs and risk of hip/femur fracture

Inhaled GC use before	Cases (n = 6763), n (%)	Controls (n = 26 341), n (%)	Univariate analysis, odds ratio (95% CI)	Multivariate analysis I[b], odds ratio (95% CI)	Multivariate analysis II[c], odds ratio (95% CI)
Never use	6047 (89.4)	24 021 (91.2)	1.00	1.00	1.00
Past use	334 (4.9)	1145 (4.3)	1.17 (1.03–1.32)	1.08 (0.95–1.24)	1.02 (0.89–1.17)
Current use	382 (5.6)	1175 (4.5)	1.30 (1.16–1.47)	1.08 (0.91–1.27)	1.07 (0.91–1.27)
Average daily dose[a] (μg)					
≤400	94 (1.4)	315 (1.2)	1.19 (0.94–1.50)	1.04 (0.81–1.34)	1.03 (0.79–1.33)
401–800	124 (1.8)	409 (1.6)	1.23 (1.00–1.50)	1.04 (0.82–1.31)	1.04 (0.82–1.32)
801–1600	109 (1.6)	300 (1.1)	1.47 (1.17–1.83)	1.17 (0.89–1.53)	1.14 (0.87–1.50)
≥1600	26 (0.4)	49 (0.2)	2.02 (1.24–3.29)	1.43 (0.85–2.41)	1.51 (0.89–2.54)
Not classified[d]	29 (0.4)	102 (0.4)	1.15 (0.76–1.75)	1.04 (0.68–1.59)	1.07 (0.69–1.64)

[a]Average daily dose: cumulative exposure divided by the treatment time, expressed as μg inhaled beclomethasone equivalents.
[b]Adjusted for indicators of underlying respiratory disease severity (i.e. use of short- or long-acting β-2 agonists, anticholinergics, xanthines, acetylcystein, average daily dose of oral GCs, use of nebulized medications, ≥1 exacerbations, and ≥1 asthma/COPD hospitalizations).
[c]Adjusted for indicators of the underlying respiratory disease severity (listed under footnote (b)] and general risk factors for fracture (i.e. use of benzodiazepines, hormone replacement therapy, antipsychotics, antidepressants, β-blockers, anticonvulsants, antidiabetics, two or more NSAID dispensings, disease modifying antirheumatic drugs, anaemia, mental disorders, cerebrovascular disease, heart failure, endocrine disorders and IBD).
[d]Not classified: average daily dose could not be determined for current inhaled GC users with one prescription.
GC, glucocorticoid; IBD, inflammatory bowel disease; NSAID, nonsteroidal anti-inflammatory drug.

Table 3 Use of oral GCs and risk of hip/femur fracture

Oral GC use before	Cases (n = 6763), n (%)	Controls (n = 26 341), n (%)	Univariate analysis, odds ratio (95% CI)	Multivariate analysis I[b], odds ratio (95% CI)	Multivariate analysis II[c], odds ratio (95% CI)
Never use	5941 (87.9)	24 026 (91.2)	1.00	1.00	1.00
Past use	500 (7.3)	1527 (5.8)	1.34 (1.20–1.49)	1.25 (1.11–1.40)	1.18 (1.05–1.32)
Current use (4 months before)	322 (4.7)	788 (3.0)	1.66 (1.46–1.90)	1.43 (1.22–1.67)	1.32 (1.13–1.55)
Average daily dose[a] (mg)					
<7.5	153 (2.3)	405 (1.5)	1.54 (1.28–1.86)	1.31 (1.05–1.63)	1.23 (0.98–1.54)
7.5–15.0	87 (1.3)	154 (0.6)	2.30 (1.76–3.00)	1.98 (1.50–2.62)	1.76 (1.32–2.34)
≥15.0	40 (0.6)	77 (0.3)	2.09 (1.42–3.07)	1.87 (1.26–2.78)	1.69 (1.13–2.53)
Not classified[d]	42 (0.6)	152 (0.6)	1.12 (0.80–1.58)	1.00 (0.70–1.41)	0.95 (0.67–1.36)

[a]Average daily dose: cumulative exposure divided by the treatment time, expressed as mg oral prednisone equivalents.
[b]Adjusted for indicators of underlying respiratory disease severity (i.e. use of short- or long-acting β-2 agonists, anticholinergics, xanthines, acetylcystein, use of nebulized medications, ≥1 exacerbations and ≥1 asthma/COPD hospitalizations), and other indicators of underlying inflammatory disease (i.e. use of methothrexate, azathioprine, mesasalazin, salazopyrin, gold preparations and penicillamin, ≥1 IBD hospitalizations and ≥1 RA/Polymyalgia/Bechterew's disease hospitalizations).
[c]Adjusted for indicators of the underlying respiratory and inflammatory disease severity [listed under footnote (b)] and general risk factors for fracture (i.e. use of benzodiazepines, hormone replacement therapy, antipsychotics, antidepressants, β-blockers, anticonvulsants, antidiabetics, two or more NSAID dispensings, anaemia, mental disorders, cerebrovascular disease, heart failure and endocrine disorders).
[d]Not classified: average daily dose could not be determined for current oral GC users with one prescription.
GC, glucocorticoid; RA, rheumatoid arthritis; IBD, inflammatory bowel disease; NSAID, nonsteroidal anti-inflammatory drug.

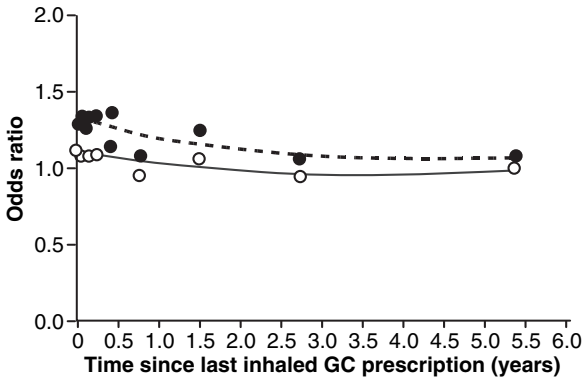

Fig. 1 Time since last inhaled glucocorticoid prescription and risk of hip/femur fracture. Closed dots, dashed line: crude odds ratios. Open dots, solid line: adjusted odds ratios. Adjusted for the same confounders as in Table 2.

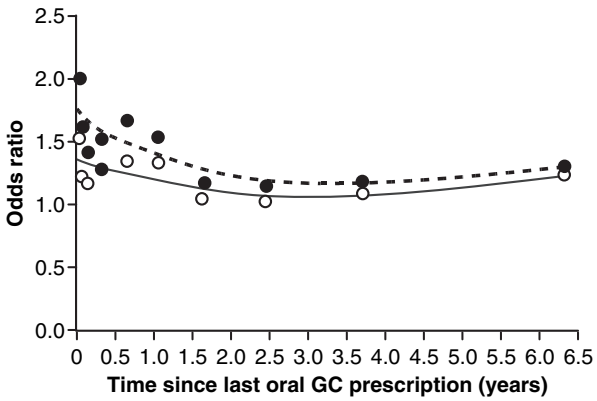

Fig. 2 Time since last oral glucocorticoid prescription and risk of hip/femur fracture. Closed dots, dashed line: crude odds ratios. Open dots, solid line: adjusted odds ratios. Adjusted for the same confounders as in Table 3.

of hip/femur fractures is illustrated in Figs 3 and 4. The risk of hip/femur fracture was increased after exposure to >1 g of oral GCs yielding an adjusted OR of 1.40 (95% CI: 1.18–1.66).

Table 4 shows that the risk of femur/hip fracture in oral GC users was independent of concomitant use of inhaled GCs. The adjusted OR was 1.57 (95% CI: 1.19–2.06) in patients who used oral GCs at a daily dose of 7.5 mg or more and who were never exposed to inhaled GCs. In those with current exposure to inhaled GCs, the adjusted OR was 1.25 (95% CI: 0.71–2.18). It was also found that users of

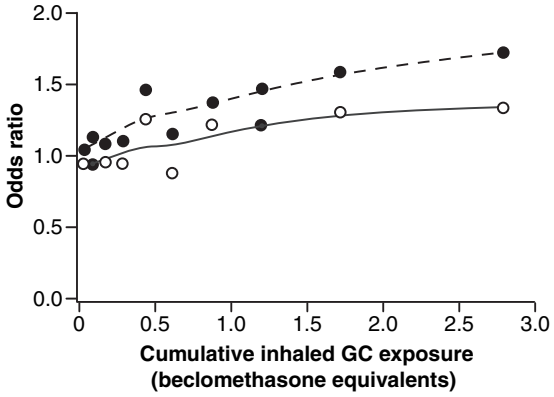

Fig. 3 Cumulative exposure to inhaled glucocorticoids amongst current users and risk of hip/femur fracture. Closed dots, dashed line: crude odds ratios. Open dots, solid line: adjusted odds ratios. Adjusted for the same confounders as in Table 2.

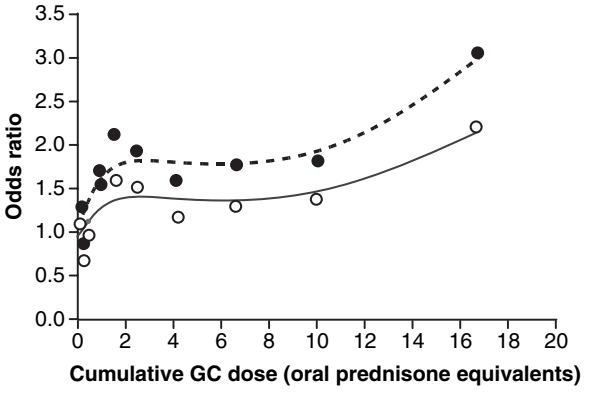

Fig. 4 Cumulative exposure to oral glucocorticoids amongst current users and risk of hip/femur fracture. Closed dots, dashed line: crude odds ratios. Open dots, solid line: adjusted odds ratios. Adjusted for the same confounders as in Table 3.

inhaled GCs had a fracture risk comparable with controls at all daily dosages when excluding subjects who had been exposed to oral GCs before index date. The adjusted OR was 0.93 (95% CI: 0.67–1.31) in inhaled GC users with a daily dose of ≤400 μg, 1.05 (95% CI: 0.75–1.46) with a daily dose of 401–800 μg, 0.92 (95% CI: 0.60–1.43) with a daily dose of 801–1600 μg and 1.29 (95% CI: 0.53–3.04) with a daily dose of ≥1600 μg beclomethasone equivalents.

Discussion

We found that current users of inhaled and oral GCs had increased risks of hip/femur fracture, especially at higher daily dosages. The excess risk amongst inhaled GC users mostly disappeared after adjustment for respiratory disease severity, whereas the risk of hip/femur fracture remained statistically elevated in oral GC users after adjustment for inflammatory disease severity. Patients without a history of use of oral GCs use were not at increased hip/femur fracture risk at all daily dosages of inhaled GC intake.

Our results of the crude risk of hip/femur fracture in inhaled GC users are consistent with previous large epidemiological studies [9, 16]. We clearly showed that patients using higher daily dosages of inhaled GCs had increased risks of hip/femur fracture. Several epidemiological studies have also reported reduced bone mineral density or increased hip fracture risk in patients using inhaled GCs [7, 8, 25]. However, none of these studies extensively adjusted for the severity of the underlying respiratory disease [12, 13]. We found that the excess fracture risk in inhaled GC users decreased substantially after adjustment for disease severity. This is in line with the results from a study in the UK that reported different results with and without adjustment for respiratory disease severity [7, 16]. These findings are supported by the observations in two studies that lung function and bone mineral density were inversely correlated, independent of GC use [14, 15].

Our results suggest an increased risk of hip/femur fracture in oral GC users and this is consistent with previous observational studies [5, 6, 26]. Our finding of a reduction in hip/femur fracture risk towards baseline levels after discontinuation of oral GCs is similar to that of a large study from the UK [5]. We also found that confounding by the underlying inflammatory disease played a small role in the association between oral GC use and risk of hip/femur fracture. Inflammatory diseases like RA and IBD have been associated with fracture risk regardless of oral GC use [27, 28]. However, a meta-analysis suggested that oral GC-induced fracture risk is at least partially related to oral GC therapy [3].

Table 4 Average daily dose of current users of inhaled GCs and risk of hip/femur fracture by average daily oral GC dose in the 4 months before the index date

	Current exposure to oral GCs											
	Never				ADD <7.5 mg day^{-1}				ADD ≥7.5 mg day^{-1}			
			Adjusted				Adjusted				Adjusted	
Use of inhaled GCs	Cases	Controls	OR[a]	95% CI	Cases	Controls	OR[a]	95% CI	Cases	Controls	OR[a]	95% CI
Never exposed[b]	5757	23 151	**1.00**		73	183	1.29	0.97–1.71	86	169	1.57	1.19–2.06
Current exposure to inhaled GCs	131	473	0.98	0.79–1.22	59	161	1.05	0.73–1.51	22	44	1.25	0.71–2.18
ADD ≤400 μg	46	177	0.93	0.67–1.31	12	64	1.13	0.57–2.23	4	9	1.82	0.60–5.54
ADD 401–800 μg	49	174	1.05	0.75–1.47	21	68	0.92	0.55–1.54	7	14	0.95	0.35–2.57
ADD 801–1600 μg	28	104	0.92	0.59–1.43	22	49	1.17	0.68–2.02	6	14	1.02	0.39–2.68
ADD ≥1600 μg	8	18	1.29	0.54–3.07	4	10	1.15	0.35–3.78	5	7	1.70	0.46–6.32

[a]See previous table [footnote (c)] for adjustments for disease severity indicators and general risk factors.
ADD, average daily dose; GC, glucocorticoid.
Data of current users with either one inhaled or oral GC prescription, and data of patients with combinations of past use of either inhaled or oral GC use is not shown. Therefore, adding up the numbers of cases and controls in this table results in lower numbers compared with Tables 2 and 3.
[b]Referent category: never exposed to inhaled and oral glucocorticoids.

Our study had a reasonable sample size to study the associations between GCs and risk of hip/femur fracture. It was population-based because drug dispensings were reimbursed regardless of socio-economic status or employment. Moreover, drug-dispensing data were routinely collected as 94% of Dutch patients collect their drug dispensings from the same pharmacy [29].

Limitations of this study included absence of data on body mass index, fat free mass, smoking status, exercise, high-impact trauma or an outpatient diagnosis of malignancy [30–34]. We could only control for more severe diagnoses that required an inpatient hospitalization, as computerized registers of general practitioner were unavailable. Adjustments for the severity of the underlying disease included proxy indicators such as use of a wide range of respiratory medications, DMARDs and exacerbations. For example, we did not have specific data on the lung function, symptoms like diarrhoea or rectal bleeding. Given the reduced lung function in inhaled GC users and the reported inverse association between lung function and bone mineral density [14, 15], it is likely that better adjustment for respiratory disease severity would further decrease the small excess risk of hip/femur fracture in inhaled GC users. Another limitation was that the statistical power was limited in the subgroup of high-dose inhaled GC user. However, our result of no association was consistent with those previously reported in the UK GPRD [16].

In conclusion, inhaled GC users had no increased risk of femur/hip fracture after adjustment for underlying disease severity. Our data suggest that, even at higher dosages, inhaled GC use is not an independent risk factor for fracture. In contrast, oral GC use was associated with an increased risk of fracture, which was not fully explained by the underlying disease severity.

Conflict of interest statement

The study was not funded. T. P. van Staa was previously employed by Procter & Gamble Pharmaceuticals.

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