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Use of Inhaled Corticosteroids and Risk of Fractures

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ABSTRACT

Treatment with systemic corticosteroids is known to increase the risk of fractures but little is known of the fracture risks associated with inhaled corticosteroids. A retrospective cohort study was conducted using a large UK primary care database (the General Practice Research Database [GPRD]). Inhaled corticosteroid users aged 18 years or older were compared with matched control patients and to a group of noncorticosteroid bronchodilator users. Patients with concomitant use of systemic corticosteroids were excluded. The study comprised 170,818 inhaled corticosteroid users, 108,786 bronchodilator users, and 170,818 control patients. The average age was 45.1 years in the inhaled corticosteroid, 49.3 years in the bronchodilator, and 45.2 years in the control groups. In the inhaled corticosteroid cohort, 54.5% were female. The relative rates (RRs) of nonvertebral, hip, and vertebral fractures during inhaled corticosteroid treatment compared with control were 1.15 (95% CI, 1.10–1.20), 1.22 (95% CI, 1.04–1.43), and 1.51 (95% CI, 1.22–1.85), respectively. No differences were found between the inhaled corticosteroid and bronchodilator groups (nonvertebral fracture RR = 1.00; 95% CI, 0.94–1.06). The rates of nonvertebral fractures among users of budesonide (RR = 0.95; 95% CI, 0.85–1.07) and fluticasone propionate (RR = 1.03; 95% CI, 0.71–1.49) were similar to the rate determined for users of beclomethasone dipropionate. We conclude that users of inhaled corticosteroids have an increased risk of fracture, particularly at the hip and spine. However, this excess risk may be related more to the underlying respiratory disease than to inhaled corticosteroid. (J Bone Miner Res 2001;16:581–588)

Key words: osteoporosis, corticosteroid, epidemiology, fracture, inhaled

INTRODUCTION

INHALED CORTICOSTEROIDS are known to be effective in reducing inflammation of the bronchial mucosa and have become an integral component in the treatment of inflammatory respiratory disorders such as asthma.[1] Current guidelines for the management of asthma advocate early intervention with inhaled corticosteroids as a first-line treatment.[2] Although safer than systemic corticosteroids, inhaled corticosteroids have been associated (particularly at higher doses) with adrenal suppression and unwanted systemic effects such as skin thinning, bruising, and cataract.[3,4] Oral corticosteroid therapy is an established cause of osteoporosis. In a previous study, we showed that the use of oral corticosteroids led to substantial increases in fracture risk. Among people using doses of 7.5 mg prednisolone daily or more, the risk of hip fracture was doubled and that of vertebral fracture was increased 4-fold.[5] Previous studies have suggested that inhaled corticosteroid treatment induces short-term changes in biochemical markers of bone turnover, although the clinical relevance of these findings is unknown.[6,7] Studies addressing changes in bone density have yielded conflicting results.[8–19] Generally, these have been cross-sectional surveys; they report significant dose-dependent decreases in bone density among patients using inhaled corticosteroids.[10,11,16,19] However, there are few data on the effect of inhaled corticosteroids on fracture risk. Because these fractures are associated with considerable

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morbidity and mortality[21] and because the frequency of utilization of inhaled corticosteroids has risen steeply in recent decades, it is important to address this issue.

We therefore performed a retrospective cohort study using a population-based British registration system in which around 1.8% of all adults were registered users of inhaled corticosteroids. Our objective was to contrast the fracture risks of patients exposed to inhaled corticosteroids, those with obstructive airway disease or asthma using nonsteroid inhaled bronchodilators only, and control subjects.

MATERIALS AND METHODS

The data used in this retrospective cohort study was obtained from the General Practice Research Database (GPRD), owned by the Medicines Control Agency in the United Kingdom. This database comprises the entire computerized medical records of a sample of general practitioners (GPs) in the country. GPs play an essential role in the UK health care system because they are responsible for primary health care and specialist referrals. All members of the population are registered with a single practice, which centralizes the medical information not only from the GPs themselves but also from specialist referrals and hospital attendances. The current study included all 683 practices currently incorporated in the GPRD and thereby comprised a 6% sample of the UK population. The data recorded in the GPRD included demographic information, prescription details, clinical events, preventive care provided, specialist referrals, hospital admissions, and their major outcomes.[22–27] Clinical data are stored and retrieved by means of the Oxford Medical Information Systems (OXMIS) codes for diseases that are cross-referenced to the International Classification of Diseases (ICD-9).[23,26] Each entry into the GPRD is validated internally by cross-checking within the practice and by comparisons with external statistics.[22–27] Only data from practices that pass this quality control are compiled to form the GPRD. Several independent validation studies have confirmed a high level of completeness and validity of the GPRD, specifically with regard to recording of hip and other limb fractures.[28–31]

Study sample

A nonconcurrent (retrospective) cohort study was conducted comparing patients using inhaled corticosteroids with control patients. The inhaled corticosteroid users were defined as permanently registered patients aged 18 years or older who received one or more prescriptions for inhaled corticosteroids during the period of time from the enrollment date of their practice in the GPRD up to the end of data collection (December 1997). Inhaled corticosteroid users who received a prescription for oral corticosteroids in the period of time from 6 months before to 91 days after the last inhaled corticosteroid prescription were excluded from the analysis. Two comparison groups were selected: (a) a bronchodilator group, which included adult patients who received nonsystemic corticosteroid prescriptions (topical, aural, ophthalmic, or nasal) and bronchodilators (British National Formulary [BNF] category 3.1) but never used inhaled or systemic corticosteroids; and (b) a control group who received nonsystemic corticosteroid prescriptions (topical, aural, ophthalmic, or nasal) but never used inhaled or systemic corticosteroids, bronchodilators, or cromoglycate (BNF, 3.1–3.3).[32] We selected these two comparison groups to evaluate the effects of underlying respiratory disease on fracture incidence.[33] The control patients were matched by age (within 5 years and, if no patient was found, within 10 years), gender, and medical practice. Topical corticosteroids were the most frequently used nonsystemic corticosteroid in both comparison groups (75% of the bronchodilator and 76% of the control groups). The age- and gender-specific fracture incidence in the control group was similar to that of the general population in the GPRD.[34]

Follow-up

The baseline date for each inhaled corticosteroid user was defined as the date of the first inhaled corticosteroid prescription after their practice enrollment date in GPRD. Each inhaled corticosteroid user was followed from baseline until they sustained a fracture; until 91 days after the last inhaled corticosteroid prescription; or until the patient's change of practice, death, or the end of the study (whichever date came first). Bronchodilator users were followed from the first bronchodilator prescription until they sustained a fracture; until 91 days after the last bronchodilator prescription; or until the patient's change of practice, death, or the end of the study (whichever date came first). The control patients were followed from a randomly selected baseline.

In an analysis of the reversibility of fracture risk after cessation of inhaled corticosteroids, each user who stopped therapy before the end of study was followed from 91 days after the last inhaled corticosteroid prescription until they sustained a fracture or were censored. Patients were included in this analysis whether or not they had sustained previous fractures during follow-up.

Fracture assessment

We identified all patients who had a nonvertebral or vertebral fracture recorded in their medical records during follow-up. The classification of fractures was based on ICD (ninth revision) categories. In an earlier study on oral corticosteroids, GPs were requested to confirm the diagnosis and to provide discharge summaries or diagnostic reports for 150 hip and 150 vertebral fracture cases. The hip fracture was confirmed by the GP on the questionnaire in 91.0% of cases and by discharge summary in 85.2% of cases. The vertebral fracture was confirmed on the GP questionnaire in 88.1% of cases and by radiographic report in 76.3% of cases. According to the GPs, 96.4% of the vertebral fractures were diagnosed radiographically.[5] Factors associated with fracture and considered as potential confounding variables included a history of previous fracture, rheumatoid arthritis, hyperthyroidism, congestive heart failure, diabetes mellitus, seizures, anemia, dementia, depression, psychotic disorder, cerebrovascular accident, back pain, or falls before baseline. Prescriptions during follow-up for anticonvul-

TABLE 1. DEMOGRAPHIC AND MEDICAL CHARACTERISTICS OF INHALED CORTICOSTEROID AND COMPARISON GROUPS

	Inhaled corticosteroid group (n = 170,818)	*Bronchodilator group (n = 108,786)*	*Control group (n = 170,818)*
Follow-up			
Total duration (person-years)	292,102	124,660	454,448
Mean duration of follow-up per subject (years)	1.7	1.1	2.7
Median duration of follow-up per subject (years)	0.9	0.2	2.3
Number of women	93,055 (54.5%)	65,824 (60.5%)	93,055 (54.5%)
Age (years)			
Mean	45.1	49.3	45.2
Median	42	47	42
Medical Condition			
Back pain year before	10,718 (6.3%)	9312 (8.6%)	10,601 (6.2%)
Diabetes mellitus	4030 (2.4%)	3764 (3.5%)	4435 (2.6%)
Emphysema	2110 (1.2%)	557 (0.5%)	130 (0.1%)
Rheumatoid arthritis	1109 (0.6%)	779 (0.7%)	1045 (0.6%)
Falls year before	1248 (0.7%)	1250 (1.1%)	1180 (0.7%)
Drug history in year prior to baseline			
NSAIDs	25,986 (15.2%)	23,467 (21.6%)	28,810 (16.9%)
Hormone replacement therapy	6455 (3.8%)	4773 (4.4%)	6511 (3.8%)
Fracture history in year prior to baseline			
Nonvertebral fracture	1969 (1.2%)	1358 (1.2%)	1895 (1.1%)
Vertebral fracture	87 (0.05%)	61 (0.06%)	71 (0.04%)

NSAIDs, nonsteroidal anti-inflammatory drugs.

sants, methotrexate, thiazide diuretics, anxiolytics, antipsychotics, antidepressants, anti-Parkinson drugs, hormone replacement therapy, bisphosphonates, vitamin D, and calcitonin also were considered as potential confounding variables.[35,36]

Assessment of inhaled corticosteroid dose

For each inhaled corticosteroid user who received at least two prescriptions during follow-up, the daily corticosteroid dose over the total treatment period was estimated by dividing the total dose of prescribed beclomethasone dipropionate or equivalent (in micrograms) by the treatment time. Budesonide was considered dose-equivalent to beclomethasone. Fluticasone propionate was considered to be twice as potent as either budesonide or beclomethasone.[32] The treatment time was taken as the time from the first inhaled corticosteroid prescription until the last recorded supply date after the last prescription. Three dose categories were assigned: low dose (less than 300 μg/day), medium dose (300–700 μg/day), and high dose (700 μg/day or more).

Statistical methods

Incidence rates for fractures were calculated by dividing the number of cases by the total number of person-years of follow-up.[37] Adjusted relative rates (RRs) were estimated using Cox proportional hazards models that included age, gender, and selected confounding variables.

RESULTS

Inhaled corticosteroids were prescribed to 284,733 patients, of whom 170,818 did not receive systemic corticosteroids concomitantly. The inhaled corticosteroid cohort (without concomitant use of systemic corticosteroids) was followed for a mean period of 1.7 years per person, for a total duration of 292,102 person-years, and received a mean of 7.9 inhaled corticosteroid prescriptions per person. Beclomethasone dipropionate was the most frequently prescribed inhaled corticosteroid (86.4% of all prescriptions). Budesonide (11.1%) and fluticasone propionate (2.4%) were prescribed less frequently. The group of bronchodilator users included 108,786 patients, followed for a mean duration of 1.1 years per person, and the control group 170,818 subjects followed for a mean of 2.7 years per person.

Table 1 summarizes baseline characteristics of the inhaled corticosteroid and comparison groups. As expected, the age and gender distributions of inhaled corticosteroid and control groups were similar: the mean age was 45 years and 54.5% were female. The bronchodilator group was slightly older (average of 49 years) and included more women (60.5%). There were no major differences between the three groups in baseline fracture history. Around 1% in each cohort reported a history of nonvertebral fractures in the year before baseline.

During follow-up, the incidence of nonvertebral fractures was 1.4 fractures per 100 person-years in the inhaled corticosteroid group, 1.4 in the bronchodilator group, and 1.1 in the control group (Table 2). After adjustment for potential

TABLE 2. INCIDENCE OF FRACTURES AMONG INHALED CORTICOSTEROID USERS, CONTRASTED BY COMPARISON GROUP WITH USERS OF NONSTEROID BRONCHODILATORS AND CONTROLS

	Inhaled corticosteroid group (n = 170,818)		*Bronchodilator control group (n = 108,786)*			*Control group (n = 170,818)*		
	No. of cases	*Rate*	*No. of cases*	*Rate*	*Adjusted RR (95% CI)*	*No. of cases*	*Rate*	*Adjusted RR (95% CI)*
Nonvertebral	3936	1.4	1752	1.4	**1.00 (0.94–1.06)**	4811	1.1	**1.15 (1.10–1.20)**
Forearm	846	0.3	382	0.3	**1.02 (0.90–1.15)**	1061	0.2	**1.13 (1.03–1.25)**
Hip	299	0.1	178	0.1	**1.20 (0.99–1.45)**	331	0.1	**1.22 (1.04–1.43)**
Vertebral	195	0.1	119	0.1	**0.90 (0.71–1.14)**	192	0.04	**1.51 (1.22–1.85)**

Figures in bold are relative rates for fracture after adjusting for age, sex, coexisting disease, concomitant drug treatment, and a baseline history of fracture and back pain.

confounding variables (coexisting disease, concomitant drug treatment, and a baseline history of fracture or back pain), the rate of nonvertebral fractures was significantly elevated among inhaled corticosteroid users when compared with control patients (RR = 1.15; 95% CI, 1.10–1.20). No difference was apparent in nonvertebral fracture risk between the inhaled corticosteroid and bronchodilator groups (RR = 1.00; 95% CI, 0.94–1.06). The crude RR in the inhaled corticosteroid group compared with the bronchodilator group was 0.95 (95% CI, 0.90–1.01) and the RR adjusted for age and gender was 0.99 (95% CI, 0.94–1.05). Inhaled corticosteroid users also had a significantly higher rate of hip fracture than controls (RR = 1.22; 95% CI, 1.04–1.43); again the rate was similar to that of the bronchodilator group (RR = 1.20; 95% CI, 0.99–1.45). The rate of nonvertebral fractures among users of budesonide (RR = 0.95; 95% CI, 0.85–1.07) and fluticasone propionate (RR = 1.03; 95% CI, 0.71–1.49) was similar to that of beclomethasone dipropionate. The average age of subjects who only used beclomethasone dipropionate (n = 143,436) was 45 years and 53.8% were female. Among those who used fluticasone propionate only (n = 2322), the mean age was 44 years and 56.6% were female. Finally, those only using budesonide (n = 17,284) were aged 47 years on average and 58.3% were female.

Figure 1 shows the age-specific incidence rates of nonvertebral fracture among men and women in the cohort according to their oral corticosteroid use. Fracture rates in women rose exponentially with advancing age among the control patients such that for women aged 85 years or more, the incidence was 4.5 per 100 person-years. The incidence among female users of inhaled corticosteroids was higher at most ages relative to women in the control group, but it was comparable with female users of bronchodilators. Among men, nonvertebral fracture incidence fell to a nadir in midlife but rose more steeply after 65 years of age. Again, incidence rates tended to be greater among those using inhaled corticosteroids and bronchodilators compared with the control group. These differences in incidence were most pronounced in younger subjects and were not apparent above age 75 years.

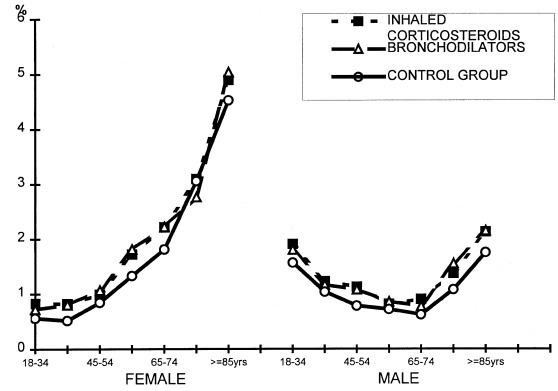

FIG. 1. Age- and gender-specific incidence rates of nonvertebral fracture among users of inhaled corticosteroids, nonsteroid bronchodilators, and controls.

Table 3 compares the incidence of fractures in the three inhaled corticosteroid dose categories (for patients who received at least two prescriptions). Comparing the inhaled corticosteroid users with the control group, a dose response was found for hip and vertebral fractures. With a standardized daily dose of <300 μg beclomethasone per day, hip fracture risk was 0.95 (95% CI, 0.67–1.34), rising to 1.06 (95% CI, 0.80–1.40) at doses of 300–700 μg, and 1.77 (95% CI, 1.31–2.40) at doses of 700 μg/day or more. Vertebral fracture showed a similar dose-related risk gradient with the highest risk in the high-dose inhaled corticosteroid group compared with the control patients (RR of 2.50). There was no consistent trend in the rate of fractures among inhaled corticosteroids users compared with the bronchodilator users.

Figure 2 shows the incidence of fractures before, during, and after inhaled corticosteroid and bronchodilator treat-

TABLE 3. INCIDENCE OF FRACTURES ACCORDING TO INHALED CORTICOSTEROID DOSE

	Low dose (n = *46,797*)			*Medium dose* (n = *43,070*)			*High dose* (n = *28,815*)		
	No. of cases	*Inhaled corticosteroid versus bronchodilator group Adjusted RR (95% CI)*	*Inhaled corticosteroid versus control group Adjusted RR (95% CI)*	*No. of cases*	*Inhaled corticosteroid versus bronchodilator group Adjusted RR (95% CI)*	*Inhaled corticosteroid versus control group Adjusted RR (95% CI)*	*No. of cases*	*Inhaled corticosteroid versus bronchodilator group Adjusted RR (95% CI)*	*Inhaled corticosteroid versus control group Adjusted RR (95% CI)*
Nonvertebral	1643	0.98 (0.91–1.05)	**1.11 (1.03–1.20)**	1315	0.99 (0.92–1.06)	**1.16 (1.07–1.26)**	806	1.09 (1.00–1.19)	**1.28 (1.15–1.42)**
Forearm	327	0.98 (0.84–1.15)	**1.06 (0.90–1.24)**	306	1.06 (0.91–1.24)	**1.19 (1.00–1.41)**	188	1.14 (0.96–1.37)	**1.15 (0.94–1.42)**
Hip	67	0.93 (0.69–1.24)	**0.95 (0.67–1.34)**	110	1.06 (0.83–1.36)	**1.06 (0.80–1.40)**	107	1.59 (1.24–2.03)	**1.77 (1.31–2.40)**
Vertebral	63	0.77 (0.56–1.06)	**1.31 (0.89–1.92)**	110	0.80 (0.59–1.09)	**1.39 (0.95–2.04)**	61	1.23 (0.90–1.68)	**2.50 (1.63–3.83)**

Figures in bold show adjusted relative rate for fracture when subjects using inhaled corticosteroids were compared with control subjects.

FIG. 2. Incidence of nonvertebral fracture before, during, and after inhaled corticosteroid or nonsteroid bronchodilator treatment stratified by dose.

ment. The incidence of nonvertebral fractures was similar among the three dose groups of inhaled corticosteroids and the bronchodilator group before commencement of treatment. The largest increase in fracture incidence during treatment was observed in the high-dose inhaled corticosteroid group (rate of 1.7 cases per 100 person-years in the first year of treatment compared with 1.3 in the year before). Similar patterns were found for hip, vertebral, and forearm fractures. The rates in the bronchodilator group also increased after commencement of treatment (from 1.3 in the year before to 1.6 during the first year of treatment). After cessation of treatment with either bronchodilators or inhaled corticosteroids, the rates declined toward baseline levels in all groups. The rate of fractures did not vary over time in the control group (rate of 1.1 in the first year of follow-up and 1.0 in the fifth year).

DISCUSSION

In this cohort study we have examined fracture incidence among patients who used inhaled corticosteroids, patients with respiratory disease using noncorticosteroid inhaled bronchodilators, and a control population sample not using inhaled treatment. The results point to an increased risk of fracture (particularly at the hip and vertebral body) among patients who used inhaled corticosteroids, as well as those who used inhaled noncorticosteroid bronchodilators, when compared with patients not using these drugs. Fracture risks tended to decline after cessation of inhaled corticosteroid or bronchodilator treatment. The findings suggest that low-dose inhaled corticosteroid therapy, at the doses included in this study, is not associated with an increased risk of fracture; however, patients with chronic respiratory disease who use any inhaled therapy appear to be at increased risk when compared with a population control group.

Previous studies examining the effects of inhaled corticosteroid therapy on bone density give conflicting results with limited information on the risk of fractures.[8–20] This

study shows that users of inhaled corticosteroids have a fracture risk which is comparable with that of users of nonsteroid bronchodilators. Furthermore, users of different types of inhaled corticosteroids have similar fracture risks in this study, despite differences in systemic bioavailability.[3,4,6] Other studies have found that fluticasone and budesonide show less effect on bone metabolism than beclomethasone.[38–41] Two prospective studies observed that fluticasone was associated with higher bone density levels compared with beclomethasone.[42,43] The nature of the inhaler device also has been reported to affect the deposition of the inhaled corticosteroids and their systemic bioavailability.[3,6] However, this study found no consistent difference in fracture risk between users of dry-powder delivery system and metered-dose inhalers.

We found no differences in fracture risk between the various types of bronchodilator drugs (72% of the bronchodilator prescriptions were for β_2-adrenoceptor stimulants, 7% were for ephedrine or orciprenaline, 13% were for theophylline, and 6% were for antimuscarinic bronchodilators). Users of ephedrine or orciprenaline had a nonvertebral fracture RR of 1.04 compared with users of selective β_2-adrenoceptor stimulants (95% CI, 0.86–1.26). For theophylline users, the RR was 1.08 (95% CI, 0.85–1.36) and for users of antimuscarinic bronchodilators, the RR was 1.01 (95% CI, 0.77–1.34). With respect to the possible role of these drugs in causing fracture, theophylline has been associated with increases in serum calcium concentration and urinary calcium excretion[44,45] and osteoporotic changes in tail vertebrae have been reported in rats subjected to long-term parenteral theophylline.[46] The clinical relevance of these findings to fracture risk in routine clinical practice is unknown. However, the consistency of the fracture risks over different types of respiratory disease treatment suggests that the underlying disease itself (reversible airway obstruction) rather than a heterogeneous group of drugs is the true reason for the small increase in the risk of fracture.

Whether patients with reversible airways obstruction develop fractures independently of the drugs used to treat them is not yet clear. In patients with chronic lung disease not using corticosteroids, Praet reported decreases in bone density that were not confirmed by the findings of Reid and Riancho.[14,47,48] All three studies were small and the severity of lung disease may have varied considerably. It is also possible that reversible airways obstruction influences the risk of fracture through nonskeletal mechanisms.[49] For example, physical inactivity with concomitant muscle weakening and reduced coordination may increase the risk of falling.[50] Although not the principal objective of this study, we examined the incidence rate of falls in our cohort. Rates increased rapidly after commencement of inhaled corticosteroid treatment (1.2 per 100 person-years in the year before baseline in the high-dose group compared with 1.6 in the first 6 months of treatment). These findings necessitate further research, given the high prevalence of chronic respiratory disease and our observation of a significant contribution to fracture risk.

The classification of inhaled corticosteroid dose was based on an averaging over the time period between the first and last inhaled corticosteroid prescription because the prescribed daily dose was not recorded systematically by the GPs and patients' use may have been intermittent. The time period of follow-up may have included periods without inhaled corticosteroid use. This may have resulted in an underestimate of any excess fracture risk, as well as an underestimate of the inhaled corticosteroid dose. It has been postulated that adverse skeletal effects only occur at doses over 1500 μg beclomethasone equivalent per day when used for long periods.[4] In this study, there were 3311 (1.9%) patients who were using these higher doses for over 6 months. Given this relatively small number of patients, the possibility of a more pronounced increase in fracture risk at these higher doses of inhaled corticosteroids cannot be excluded. However, any impact in actual clinical practice is likely to be small because of the low prevalence of utilization of these doses.

The control group in our study consisted of users of nonsystemic corticosteroids. The age- and gender-specific overall fracture incidence in the control group was very close to that of the general population in GPRD.[34] We wished to select a control group similar in age, gender, and practice to the treatment group. However, documented prescription was a means of ensuring active registration at the practice. Therefore, we selected users of nonsystemic corticosteroids as controls, because this would conservatively (downwards) bias any estimate of risk associated with oral corticosteroids. The exclusion of control patients with frequent prescribing of nonsystemic corticosteroids, which may be absorbed with frequent use, did not modify the results.

A possible weakness of this study is the comparability of the inhaled corticosteroid and bronchodilator groups. Control for confounding was restricted to age, gender, and a variety of medical diagnoses and treatments. A number of potential confounders, such as physical activity and baseline bone density, were not available. However, adjustments for known confounders had little effect on the comparison of nonvertebral fracture rates between inhaled corticosteroid and bronchodilator users. In addition, there was evidence to suggest that inhaled corticosteroid users had, on average, more severe respiratory disease than the users of bronchodilator drugs. The recorded duration of respiratory disease, number of visits to the GP for respiratory complaints, and the prevalence of emphysema were all higher among the inhaled corticosteroid users. Despite this potential selection bias, the incidence of nonvertebral fractures was comparable in the two groups. Another possible limitation of the study is that lifetime data on corticosteroid use were not available, because information was restricted to the period of GPRD data collection. Some patients may have received oral corticosteroids before data collection. However, a previous study using the GPRD suggested that a substantial proportion of the excess fracture risk caused by oral corticosteroids might wane within 6 months of stopping treatment.[5] Also, analyses on patients with more than 2 years of data before commencement of inhaled corticosteroid therapy showed similar results to those in the cohort as a whole. The RR of nonvertebral fracture in the inhaled corticosteroid group compared with the bronchodilator group was 0.96 (95% CI, 0.85–1.08) in this analysis; for the low-dose

group, it was 0.93 (95% CI, 0.79–1.10); for the medium-dose group it was 0.96 (95% CI, 0.81–1.13); and for the high-dose group it was 1.13 (95% CI, 0.93–1.38). We also did not have information on the precise time-course of inhaled corticosteroid use by individual patients. They were followed from the first prescription to 91 days after the last prescription for inhaled corticosteroids. For patients using these drugs intermittently, follow-up would have included periods without treatment as evidenced by the average 7.9 inhaler prescriptions annually. This may have resulted in an underestimate of the excess fracture risk.

Several analyses were conducted to review the sensitivity of these results to the method of analysis and control selection. Results did not materially change when adjustments were made for calendar year of follow-up or alcohol use, smoking, and body mass index (BMI). Limiting the length of follow-up of control patients to the length of follow-up of the inhaled corticosteroid users also did not modify the results. Finally, the observation that fracture risk declined after cessation of inhaled therapy (whether corticosteroid or not) suggests possible ascertainment bias for fractures during treatment. However, we have previously shown that nonspine fracture identification has 90% accuracy in this cohort.[5]

In conclusion, the results of this study suggest that users of inhaled corticosteroids and other bronchodilators have an increased risk of fractures, particularly at the hip and spine; this excess risk is more likely to be related to the underlying respiratory disease than to the inhaled corticosteroid use.

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