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Use of Oral Corticosteroids and Risk of Fractures

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ABSTRACT

Treatment with oral corticosteroids is known to decrease bone density but there are few data on the attendant risk of fracture and on the reversibility of this risk after cessation of therapy. A retrospective cohort study was conducted in a general medical practice setting in the United Kingdom (using data from the General Practice Research Database [GPRD]). For each oral corticosteroid user aged 18 years or older, a control patient was selected randomly, who was matched by age, sex, and medical practice. The study comprised 244,235 oral corticosteroid users and 244,235 controls. The average age was 57.1 years in the oral corticosteroid cohort and 56.9 years in the control cohort. In both cohorts 58.6% were female. The most frequent indication for treatment was respiratory disease (40%). The relative rate of nonvertebral fracture during oral corticosteroid treatment was 1.33 (95% confidence interval [CI], 1.29–1.38), that of hip fracture 1.61 (1.47–1.76), that of forearm fracture 1.09 (1.01–1.17), and that of vertebral fracture 2.60 (2.31–2.92). A dose dependence of fracture risk was observed. With a standardized daily dose of less than 2.5 mg prednisolone, hip fracture risk was 0.99 (0.82–1.20) relative to control, rising to 1.77 (1.55–2.02) at daily doses of 2.5–7.5 mg, and 2.27 (1.94–2.66) at doses of 7.5 mg or greater. For vertebral fracture, the relative rates were 1.55 (1.20–2.01), 2.59 (2.16–3.10), and 5.18 (4.25–6.31), respectively. All fracture risks declined toward baseline rapidly after cessation of oral corticosteroid treatment. These results quantify the increased fracture risk during oral corticosteroid therapy, with greater effects on the hip and spine than forearm. They also suggest a rapid offset of this increased fracture risk on cessation of therapy, which has implications for the use of preventative agents against bone loss in patients at highest risk. (*J Bone Miner Res* 2000;15:993–1000)

Key words: osteoporosis, corticosteroids, hip fracture, epidemiology

INTRODUCTION

ORAL CORTICOSTEROIDS have been widely used in medical practice for over 50 years and play a major role in the treatment of asthma, inflammatory joint disorders, and other diseases affecting the gastrointestinal tract and central nervous system. Although often effective in these conditions, osteoporosis is one of the most serious complications of oral corticosteroid treatment. Several studies have reported decreases in bone mineral density during oral corticosteroid

treatment irrespective of the disease being treated. This bone loss, which can be substantial and rapid, is related to the dose of oral corticosteroid therapy and occurs more rapidly in trabecular than in cortical bone.^(1,2) However, it has been suggested that the patient's bone density and the degree of loss during corticosteroid therapy do not always predict the magnitude of the risk of fractures. In one study, vertebral fractures occurred in asthmatic oral corticosteroid users at higher bone density levels compared with fracture cases with involutional osteoporosis.⁽³⁾ Fracture risk may be

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greater for a given degree of bone loss with oral corticosteroid treatment than with postmenopausal osteoporosis.

A few, generally small, epidemiological studies have examined the association between oral corticosteroids and fracture risk. In the two largest of these, the risk of fracture was increased between 50% and 100% in oral corticosteroid users.^(4,5) These studies do not provide information on the relationship between dose and duration of oral corticosteroid use and fracture risk. The effect of discontinuing oral corticosteroid treatment on any excess fracture risk because of oral corticosteroids also remains unknown. The objective of this study was to evaluate, in a representative general medical practice setting, the fracture risks of patients exposed to oral corticosteroids.

MATERIALS AND METHODS

Data resource

The information in this study was obtained from the General Practice Research Database (GPRD), which comprises the computerized medical records of general practitioners (GP). GPs play a key role in the U.K. health care system because they are responsible for primary health care and specialist referrals. Patients are semipermanently affiliated to a practice, which centralizes the medical information not only from the GPs themselves but also from specialist referrals and hospitalizations. The current study included 683 practices from different geographic areas in the United Kingdom. The data recorded in the GPRD include demographic information, prescription details, clinical events, preventive care provided, specialist referrals, hospital admissions, and their major outcomes.⁽⁶⁻¹¹⁾ Clinical data are stored and retrieved by means of Oxford Medical Information Systems (OXMIS) codes for diseases that are cross-referenced to the International Classification of Diseases (ICD-9).^(7,10) Each entry into GPRD is validated internally by cross-checking within the practice and by comparisons with external statistics.⁽⁶⁻¹¹⁾ 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 GPRD.⁽¹²⁻¹⁵⁾ The GPRD is owned by the Department of Health in the United Kingdom.

Study population and outcome assessment

A retrospective cohort study was conducted comparing patients using oral corticosteroids with controls. The oral corticosteroid users were defined as permanently registered patients aged 18 years or older who received one or more prescriptions for oral corticosteroids during the period of time from the enrollment date of their practice in GPRD up to the end of the study (December 1997). The controls were adult patients who received nonsystemic corticosteroid prescriptions (topical, aural, ophthalmic, or nasal); they were matched by age (within 5 years or, if no patient found, within 10 years), gender, and, if possible, medical practice. Topical corticosteroids were the most frequently used non-

systemic corticosteroid in the control group (78.0% of the control group). The baseline date for each oral corticosteroid user was defined as the date of the first oral corticosteroid prescription after their practice's enrollment date in GPRD.

Each oral corticosteroid user was followed from baseline until they sustained a fracture or until 91 days after the last oral corticosteroid prescription or until the patient's change of practice, death, or the end of the study (whichever date came first). Control patients were followed from a randomly selected baseline date until the fracture or until the patient's change of practice, death, or end of study.

In a separate analysis of reversibility of fracture risk after cessation of oral corticosteroids, each user who stopped therapy before the end of the study was followed from 91 days after the last oral 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. Thus, any apparent change in fracture rate could not be attributed to censorship at first fracture.

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's (9th revision) categories. Thus, the coding of hip fracture included ICD-820, forearm fracture 813, vertebral fracture 805-806, and nonvertebral fracture 800-804 and 807-829. As part of this study, the general practitioners were requested to confirm the diagnosis and to provide discharge summaries or diagnostic reports for 150 hip fracture cases 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 confirmed by radiographic report in 76.3% of cases. According to the GP, 96.4% of the vertebral fractures were diagnosed radiographically.

Factors associated with fractures and considered as potential confounding variables included diabetes mellitus, rheumatoid arthritis, hyperthyroidism, congestive heart failure, seizures, anemia, dementia, depression, psychotic disorder, cerebrovascular accident, falls, and a history of fractures and back pain before baseline. Prescriptions during follow-up for anticonvulsants, methotrexate, thiazide diuretics, anxiolytics, antipsychotics, antidepressants, anti-Parkinson drugs, hormone replacement therapy, bisphosphonates, vitamin D, and calcitonin also were considered potential confounding variables.^(16,17)

For the oral corticosteroid users, the daily corticosteroid dose over the total treatment period was estimated by dividing the total amount of prescribed prednisolone (or equivalent dose) in milligrams by the treatment time.⁽¹⁸⁾ The treatment time was taken as the time between the first oral corticosteroid prescription up to 31 days after the last prescription (the median supply was for 31 days of treatment). Three dose categories were assigned: low dose (less than 2.5 mg/day), medium (2.5-7.5 mg/day), and high dose (7.5 mg/day or more).

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Statistical methods

Incidence rates of fractures were calculated by dividing the number of cases by the total number of patient-years of follow-up.⁽¹⁹⁾ Adjusted relative rates were estimated using Cox proportional hazards models that included age, gender, and selected confounding variables. Construction of these final regression models consisted of three steps. Confounding variables that either caused a change in the crude rate of at least 10% or were strongly associated with the development of a fracture (unadjusted relative rate of >1.50 or <0.67 in this data set) were first included, together with interaction terms between the confounding variables and age and gender.⁽²⁰⁾ The final regression model was then determined by backward selection using a significance level of 0.25. Martingale and deviance residuals were used to check the model and time-dependent covariates were examined to ensure the proportional hazards assumption of the model. In an analysis of fracture risk over duration of corticosteroid discontinuation, a nonparametric cubic spline regression model was used to adjust for risk factor changes over time.⁽²¹⁻²⁴⁾

RESULTS

Oral corticosteroids were prescribed to 244,235 patients. The oral corticosteroid cohort was followed for a mean period of 1.3 years per person, for a total duration of 325,623 person-years, and received a mean of 6.8 oral corticosteroid prescriptions per person. All the oral corticosteroid users were matched by gender and age (within 10 years); 94% of the oral corticosteroid users were matched by age (within 5 years), gender, and medical practice.

Table 1 summarizes baseline characteristics of the oral corticosteroid and control groups. As expected, the age and gender distributions of these two groups were similar: their mean age was around 57 years and 58.6% were female. Oral corticosteroid users were more likely to have a history of rheumatoid arthritis (4.1% of oral corticosteroid users vs. 0.9% of the control patients). The most frequently recorded indication was respiratory disease: around 40% of the patients had respiratory diseases recorded and 13% had associated respiratory symptoms. Skin and musculoskeletal disorders were recorded in about 6% of the oral corticosteroid users. A history of nonvertebral fractures in the year before follow-up was present in 1.6% of the oral corticosteroid group and 1.3% of the controls.

In the oral corticosteroid group, the incidence of nonvertebral fractures was 2.0 per 100 person-years as compared with an incidence of 1.3 in the control group (Table 2). After adjustment for potential confounding variables (coexisting disease, concomitant drug treatment, and a baseline history of fracture or back pain), the rate of nonvertebral fractures was significantly higher among oral corticosteroid users compared with control patients (relative rate [RR] = 1.33; 95% confidence interval [CI] 1.29-1.38). Oral corticosteroid users also had a significantly higher rate of hip fracture than control (RR = 1.61; 95% CI, 1.47-1.76). Vertebral fracture incidence was increased more than 2-fold

TABLE 1. CHARACTERISTICS OF ORAL CORTICOSTEROID AND CONTROL GROUP

	Corticosteroid group (n = 244,235)	Control group (n = 244,235)
Follow-up		
Total duration (person-years)	325,623	664,016
Mean duration of follow-up per subject (years)	1.3	2.7
Median duration of follow-up per subject (years)	0.3	2.4
Age (years)		
Mean	57.1	56.9
Median	60	60
Medical condition		
Back pain year before	21,630 (8.9%)	16,993 (7.0%)
Rheumatoid arthritis	9966 (4.1%)	2159 (0.9%)
Falls year before	3874 (1.6%)	3271 (1.3%)
Drug history in year before baseline		
NSAIDs	64,709 (26.5%)	52,790 (21.6%)
Hormone replacement therapy	11,217 (4.6%)	11,390 (4.7%)
Fracture history in year before baseline		
Nonvertebral fracture	3809 (1.6%)	3242 (1.3%)
Vertebral fracture	376 (0.2%)	150 (0.1%)

NSAIDs, nonsteroidal anti-inflammatory drugs.

in the oral corticosteroid group (RR = 2.60; 95% CI = 2.31-2.92).

Table 3 shows a comparison of the incidence of fractures in the three corticosteroid dose groups. A significant dose response was found for all fracture types with the exception of the forearm. The relative rate of nonvertebral fractures increased from 1.17 in the lowest dose group to 1.36 in the intermediate group and to 1.64 in the highest dose group. For vertebral fracture, the relative rates were 1.55, 2.59, and 5.18, respectively. The rate of hip fracture was similar among the low-dose corticosteroid users and controls but increased by 77% with a daily oral corticosteroid dose of 2.5-7.5 mg and by 127% with doses of 7.5 mg or higher.

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 at age 85+ years, the incidence was 4.5 per 100 person-years. There was a progressive increase in fracture incidence in females using high doses of oral corticosteroids. 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 greater doses of oral corticosteroids.

TABLE 2. INCIDENCE OF FRACTURES AMONG SUBJECTS USING ORAL CORTICOSTEROIDS AND CONTROLS

	Corticosteroid group (n = 244,235)		Control group (n = 244,235)		Adjusted relative rate	95% confidence interval
	No. of cases	Rate (%)	No. of cases	Rate (%)		
Nonvertebral	6395	2.0	8595	1.3	1.33	1.29–1.38
Forearm	1338	0.4	2190	0.3	1.09	1.01–1.17
Hip	1072	0.3	1102	0.2	1.61	1.47–1.76
Vertebral	1033	0.3	465	0.1	2.60	2.31–2.92

TABLE 3. FRACTURE RISK ACCORDING TO DOSE OF ORAL CORTICOSTEROIDS

	Low dose (n = 50,649)		Medium dose (n = 104,833)		High dose (n = 87,949)	
	No. of cases	Adjusted relative rate (95% CI)	No. of cases	Adjusted relative rate (95% CI)	No. of cases	Adjusted relative rate (95% CI)
Nonvertebral	2192	1.17 (1.10–1.25)	2486	1.36 (1.28–1.43)	1665	1.64 (1.54–1.76)
Forearm	531	1.10 (0.96–1.25)	526	1.04 (0.93–1.17)	273	1.19 (1.02–1.39)
Hip	236	0.99 (0.82–1.20)	494	1.77 (1.55–2.02)	328	2.27 (1.94–2.66)
Vertebral	191	1.55 (1.20–2.01)	440	2.59 (2.16–3.10)	400	5.18 (4.25–6.31)

Figure 2 shows the incidence of fractures before, during, and after oral corticosteroid treatment. The incidence of nonvertebral fractures was 1.6 per 100 person-years in the year before commencement of oral corticosteroid treatment and increased to 2.0 over the first 3 months of treatment. Fracture incidence then remained stable during oral corticosteroid treatment. Nonvertebral fracture rates were 2.0 per 100 person-years in the first year and 2.2 in the fifth year. Similar patterns were found for hip, vertebral, and forearm fractures. A spline regression analysis (to adjust for risk factor changes over time) confirmed the finding of a rapid increase in fracture risk after commencement of oral corticosteroid therapy, which remained stable over duration of use.

Figure 2 also shows that there was a sharp decline in fracture incidence after cessation of oral corticosteroid use. This effect was most pronounced for vertebral fractures but was also apparent for hip and all nonvertebral fractures. The number of nonvertebral fractures after cessation of oral corticosteroid therapy was sufficient to examine this trend using spline regression. The results of this analysis are illustrated in Fig. 3 and show that most of the excess risk disappeared within 1 year of stopping oral corticosteroids. The numbers of vertebral, hip, and forearm fractures after cessation of oral corticosteroids was too small to permit stable estimates to be derived from the spline regression model.

The pattern of fracture risks in the patients who had stopped oral corticosteroids and who had a history of over 6 months of high corticosteroid dose was analyzed separately. It was found that in this group of 7095 patients the fracture risks also decreased over time after cessation of the oral corticosteroids. The nonvertebral fracture rate was 2.4 per 100 person-years (100 cases) in the first year and 1.8 in the second year or later (41 cases) after stopping treatment. The

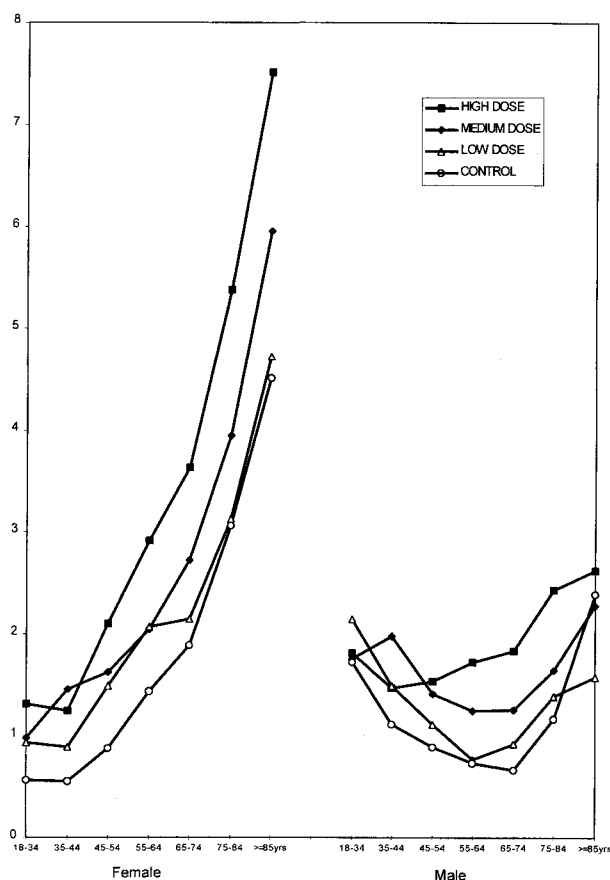


FIG. 1. Incidence of nonvertebral fractures stratified by daily corticosteroid dose, age, and gender.

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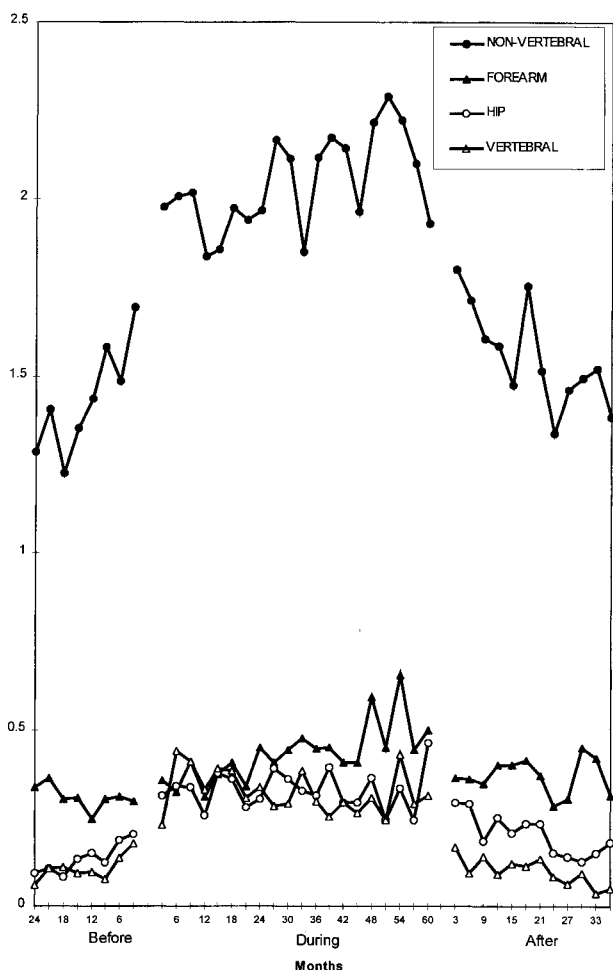


FIG. 2. Incidence of nonvertebral, forearm, hip, and vertebral fracture before, during, and after oral corticosteroid treatment.

rate of nonvertebral fractures was 2.6 per 100 person-years during corticosteroid use in the high-dose group. A similar pattern of decreasing fracture risk after stopping corticosteroids was observed in patients with a prior cumulative oral corticosteroid dose of 10 g or more (rate of 2.7 during use). In 6993 patients who had this cumulative exposure and who had stopped oral corticosteroids, the incidence of nonvertebral fractures decreased to 2.0 per 100 person-years in the first year after stopping (61 cases). In the second year after stopping, the rate was 1.6 per 100 person-years (14 cases).

DISCUSSION

The results of this study suggest that the risk of fractures, particularly those of the vertebral body and proximal femur, is increased during oral corticosteroid treatment and the magnitude of this risk increase is related directly to the standardized daily dose of oral corticosteroid. It also was observed that fracture risk increases rapidly after the commencement of oral corticosteroid therapy but reverses

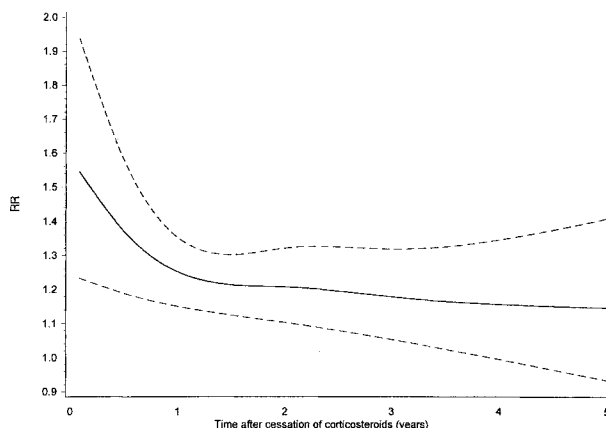


FIG. 3. Adjusted relative rate (and 95% CI) of nonvertebral fracture after discontinuation of oral corticosteroids.

sharply toward baseline levels after discontinuation of oral corticosteroids.

Although there have been numerous studies evaluating bone density change during oral corticosteroid treatment, there have been only a few studies that examined the clinically more relevant endpoint of fractures. The largest study, a case-control study in the general population, found a doubling in hip fracture risk.⁽⁴⁾ However, after adjustment for confounding variables, this increased relative risk did not reach statistical significance. The magnitude of excess hip fracture risk in oral corticosteroid users was similar in our study and in that population-based case-control study. Of the other published studies that analyzed at least 100 oral corticosteroid patients all found increased fracture rates among oral corticosteroid users compared with control patients, but the magnitude of excess risk and the statistical significance of the findings varied.⁽²⁵⁻²⁹⁾ None of these studies provided detail on the relationship to oral corticosteroid dose or on the reversibility of fracture risk after corticosteroid discontinuation.

This study shows that the increase in fracture risk after commencement of oral corticosteroid therapy is rapid, with significant increases in risk of nonvertebral fracture becoming apparent within the first 3 months of treatment. A possible explanation could be the osteoblast and osteocyte apoptosis induced by corticosteroids.⁽³⁰⁾ An alternative interpretation would be that a marked alteration in bone turnover, through induction of microarchitectural changes in bone quality, was responsible for the rapid change in fracture risk. This observation would be in accord with recent studies of bisphosphonates, which suggest a protective effect against fracture despite relatively small increases in bone mineral density.⁽³¹⁾ The only previous study to examine the mode of onset of corticosteroid-induced fractures was one performed in cardiac transplant patients.⁽³²⁾ Again, fractures were found to occur early during the treatment course, but the doses of corticosteroid used were high and there were attendant immunosuppressive agents utilized as part of the therapeutic regimen. Finally, it is possible that corticosteroids also influence fracture risk through nonskel-

etal mechanisms. One potential mechanism would be through an increased risk of falling. Although this was not a principal objective of this study, we examined the incidence rate of falls in our cohort. Rates increased rapidly after commencement of oral corticosteroid therapy (1.6 per 100 person-years in the year before baseline and 2.8 in the first 3 months of corticosteroid treatment). In addition, the rates decreased to baseline values fairly rapidly after stopping corticosteroid therapy. Although previous studies examining the relationship between corticosteroid use and fracture risk have not directly examined the frequency of falling, the Southampton case control study did suggest that corticosteroid users had increased levels of frailty, physical inactivity, and immobility.⁽⁴⁾ An early effect on both bone strength and propensity to trauma, with a more persistent effect on bone strength, might explain the observed pattern of fracture incidence in oral corticosteroid users.

An important observation in this study was the finding of reversibility of fracture risks after discontinuation of oral corticosteroid treatment. Fracture risks decreased toward baseline value after corticosteroids were stopped. This decrease in excess fracture risk mostly occurred within the first year of stopping. It has been debated in the literature whether corticosteroid-induced osteoporosis and its consequences are fully reversible.^(2,33-35) Studies in patients who were cured of Cushing's syndrome have observed normal bone density.⁽³⁶⁻³⁹⁾ Studies in patients with rheumatoid arthritis and sarcoidosis report increases in bone density after cessation of corticosteroid use.⁽⁴⁰⁻⁴²⁾ This study is the first that evaluated the reversibility of fracture risks rather than bone density. When looking at the small number of patients who stopped long-term high-dose corticosteroids, a decline in fracture rates also was observed. These data support the reversibility of fracture risk after discontinuing treatment. Because several agents are now licensed for the prevention and treatment of corticosteroid-induced osteoporosis, our findings suggest that their most appropriate use is during oral corticosteroid use, especially during periods when high doses are being utilized.

The control group in this study consisted of users of nonsystemic corticosteroids. We wished to select a control group in which patients were matched by age, gender, and practice. However, documented prescription was a means of ensuring active registration at any general practice within the GPRD. We therefore selected users of nonsystemic corticosteroids as controls, in the knowledge that we would conservatively (in a downward direction) bias any estimate of risk associated with oral corticosteroids. The exclusion of control patients with frequent prescribing of nonsystemic corticosteroids, which might have been absorbed with frequent use, did not substantially alter the results. Furthermore, the age- and gender-specific overall fracture incidence in our control group was very close to that observed in the entire population sample included in the GPRD (Table 4).⁽⁴³⁾ The incidence of hip fractures in the control group also was comparable to data from a recent U.K. population study.⁽⁴⁴⁾

There are several possible limitations of this study. The first is the possible role of underlying disease in the causation of fractures. It has been reported that patients with

TABLE 4. AGE- AND GENDER-SPECIFIC INCIDENCE (PER 100 PERSON-YEARS) OF ALL FRACTURES IN THE CONTROL GROUP ADOPTED FOR THIS STUDY AND THE ENTIRE GPRD POPULATION SAMPLE⁴³

Age (years)	Men		Women	
	Control group	GPRD	Control group	GPRD
18-34	1.74	1.72	0.59	0.57
35-44	1.13	1.08	0.57	0.62
45-54	0.91	0.88	0.90	0.79
55-64	0.75	0.78	1.50	1.50
65-74	0.71	0.77	1.97	1.94
75-84	1.25	1.26	3.28	3.02
≥85	2.53	2.08	4.79	4.48

rheumatoid arthritis have an increased fracture risk, even people not using corticosteroids.⁽⁴⁾ However, exclusion of patients with musculoskeletal disease did not modify the results substantively, and the relative rate of fractures in oral corticosteroid users compared with controls was similar among patient groups with different types of underlying disease. The 40% of subjects in the oral corticosteroid group with documented respiratory disease had a relative rate of nonvertebral fractures, which was 1.29 (95% CI = 1.23-1.36); the comparable rate among oral corticosteroid users with documented arthropathies was 1.33 (95% CI = 1.24-1.43). Another possible limitation is the possibility of detection bias. Physicians may have been more likely to diagnose fractures because of awareness of the adverse bone effects of corticosteroids. However, we did not find major differences in case characteristics (proportion of hospitalizations and deaths) and the validation of vertebral and hip fracture reporting indicated similar rates of recording among corticosteroid users and controls. The use of bone-active medication also was very low among oral corticosteroid users (5.0% used hormone replacement therapy and 1.8% bisphosphonates during follow-up). The third limitation concerned the characterization of oral corticosteroid dose. Because the prescribed daily dose was not recorded systematically by the GPs, the corticosteroid dose was averaged over the time period between the first and last oral corticosteroid prescription. For patients using oral corticosteroids intermittently, this time period included periods without corticosteroid use. This may have resulted in an underestimate of the excess fracture risk but also an underestimate of the oral corticosteroid dose. Several analyses were conducted to review the sensitivity of the 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. Limiting the length of follow-up of control patients to the length of follow-up of the corticosteroid user or exclusion of various types of patients (e.g., control patients with heavy use of nonsystemic corticosteroids) also did not modify the results.

In conclusion, these results indicate an increased risk of fractures during oral corticosteroid treatment, with greater effects on the hip and vertebral body than on the forearm.

The magnitude of the risk of corticosteroid-induced fractures was related to daily corticosteroid dose. These fracture risks increased shortly after the start of oral corticosteroid treatment and reversed toward baseline levels after the discontinuation of oral corticosteroids.

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