Osteoporosis International (2024) 35:805–818
https://doi.org/10.1007/s00198-024-07023-6

ORIGINAL ARTICLE

Average daily glucocorticoid dose, number of prescription days, and cumulative dose in the initial 90 days of glucocorticoid therapy are associated with subsequent hip and clinical vertebral fracture risk: a retrospective cohort study using a nationwide health insurance claims database in Japan

Masayuki Iki[1,2] · Kenji Fujimori[3,2] · Shinichi Nakatoh[4,2] · Junko Tamaki[5,2] · Shigeyuki Ishii[6,2] · Nobukazu Okimoto[7,2] · Hironori Imano[1] · Sumito Ogawa[8,2]

Received: 25 May 2023 / Accepted: 15 January 2024 / Published online: 24 January 2024

Abstract

Purpose Fracture risk assessment is recommended at three months after glucocorticoid (GC) therapy initiation. This study aimed to assess whether GC exposure in the initial 90 days of GC therapy is associated with subsequent hip and clinical vertebral fracture risk using the nationwide health insurance claims database of Japan (NDBJ).

Methods Patients aged ≥ 50 years who were prescribed GC (≥ 70 mg prednisolone or equivalent; PSL) in the initial 90 days of GC therapy and were followed for hip and clinical vertebral fracture incidences for the subsequent 1080 days were selected from NDBJ. Associations of GC exposure with hip or clinical vertebral fracture risk were evaluated by Cox regression analysis adjusted for potential confounders.

Results We selected 316,396 women and 299,871 men for the GC-exposed group and 43,164 women and 33,702 men for the reference group. Higher GC doses and longer prescription days in the initial 90 days of GC therapy were significantly and dose-dependently associated with increased fracture risk relative to the reference group. Patients receiving GC ≥ 5 mg PSL/day had a significantly increased fracture risk in the stratum of 30–59 days of GC prescription. In addition, female patients who received GC (≥ 1 and < 2.5 mg PSL/day) for 90 days in the initial 90 days of GC therapy had a significantly increased fracture risk.

Conclusions GC exposure in the initial 90 days of GC therapy was dose-dependently associated with hip and clinical vertebral fracture risk. GC may increase fracture risk with lower doses for shorter durations than previously reported.

Summary Fracture risk assessment three months after glucocorticoid (GC) therapy initiation is recommended. We found that GC exposure in the initial 90 days of GC therapy at lower daily doses for shorter durations than previously reported were significantly and dose-dependently associated with fracture risk using a nationwide health insurance claims database.

Keywords Dose–response relationship · Glucocorticoid-induced osteoporosis · Hip fracture · Nationwide health insurance claims database study · Retrospective cohort study · Clinical vertebral fracture

Introduction

Patients on glucocorticoid (GC) therapy are at risk of a rapid loss of bone mineral density (BMD) [1, 2] and a rapid increase in vertebral and non-vertebral fracture risk [3, 4]. From 30 to 50% of patients on long-term GC therapy reportedly experience fractures [5], resulting in an increased risk of mortality [6] and decreased quality of life [7]. These adverse effects of GC are known as GC-induced osteoporosis (GIO), the most frequent type of secondary osteoporosis.

Since increased fracture risk is observed in the initial months of GC therapy [8, 9], most guidelines for GIO management recommend fracture risk assessment three months after the initiation of GC therapy [10–15]. Although the criteria for high fracture risk warranting the initiation of anti-osteoporosis medications (AOMs) vary from guideline to guideline, most guidelines include

Extended author information available on the last page of the article

a daily GC exposure of ≥ 5 or ≥ 7.5 mg (prednisolone or equivalent; PSL) in the criteria [10–15]. These criteria have been developed according to results from observational studies examining the association between GC doses and fracture risk [3, 5, 16–25, 26–28]. However, GC exposures assessed in those studies were not obtained from the initial three months of GC therapy but from longer durations. For example, van Staa et al. [23] conducted one of the largest cohort studies using data from the General Practice Research Database (GPRD), and reported a significant dose-dependent relationship between daily GC doses and vertebral or hip fracture risk. However, GC exposure in that study was obtained from the entire period of GC therapies ranging from 3 to 60 months. Given that physicians who conduct a fracture risk assessment three months after GC therapy initiation only know GC doses of the initial three months of GC therapy, evidence to support the validity of fracture risk assessment based on GC exposure in the initial three months of GC therapy is necessary.

In addition, it is unclear whether lower GC doses for shorter durations of GC therapy than 5 mg PSL/day for three months are associated with a significant increase in fracture risk. GC therapy at ≥ 2.5 mg PSL/day has been reported to be associated with increased hip and vertebral fracture risk in a cohort study comprising more than 244 thousand patients each for the GC-exposed and control groups using GPRD [22–24]. However, even such a large-scale study did not present results for women and men separately. Other studies reported that GC exposure ≥ 5 mg PSL/day was associated with elevated fracture risk [3, 16–20]. Previous studies may not have had sufficient power to evaluate the association between lower GC exposure and incidence of rare outcomes, such as hip fracture.

The Japanese Ministry of Health, Labour and Welfare (MHLW) has recently developed the National Database of Health Insurance Claims and Specific Health Checkups of Japan (NDBJ). This database has accumulated all monthly electronic health insurance claims since fiscal year 2012 on an individual patient basis [29]. Japan has a public health insurance system with nationwide coverage, and 97% of health insurance claims were submitted electronically in 2012, with the proportion increasing every year thereafter [30]. Thus, the NDBJ is one of the most exhaustive healthcare databases in the world [31].

We conducted a large-scale retrospective cohort study using NDBJ data to examine whether patients on GC therapy with an average daily dose of 5 mg PSL or lower for shorter durations than previously reported in the initial 90 days of GC therapy had a significantly increased risk of hip and clinical vertebral fractures in the 1080 days following GC therapy initiation by sex-specific analysis.

Methods

Database

The NDBJ contains information such as patient identification (ID) number, age, sex, date of consultation for outpatient service, dates of admission and discharge for inpatient service, as well as date, volume, and tariff of procedures and drugs provided to each patient, but not actual laboratory values [29]. The ID number is generated by an encrypting function to make data anonymous but combinable for the same patient. The NDBJ is open to researchers who have their study involving the use of NDBJ data approved by the MHLW. The present study protocol was approved by the MHLW on 2 October 2019, as well as the Ethics Committee of Kindai University Faculty of Medicine (Approval number: #31–065, 3 July 2019). The present study used NDBJ data from fiscal years 2012 to 2018 (1 April 2012 to 31 March 2019).

Patient selection (Fig. 1)

We selected women and men aged ≥ 50 years at baseline (initiation of GC therapy) who went 180 days without a GC prescription prior to GC therapy, and who were followed for 1080 days after the initiation of GC therapy (Fig. 1). We recorded the names of all GCs prescribed, as well as their doses, date of prescription, and number of prescription days in 90-day increments for the 1080 days of the observation period. GC doses were converted to mg PSL based on anti-inflammatory potency [32]. We selected patients who were prescribed cumulative doses of GC ≥ 70 mg PSL for at least 15 days in the initial 90 days of GC therapy.

We also recorded the prescription of AOMs (bisphosphonates, denosumab, teriparatides, specific estrogen receptor modulators (SERMs), and activated vitamin D_3 (AVD) analogs including alfacalcidol, calcitriol, and eldecalcitol), dose, and date and days of prescription for 180 days before and 1080 days after baseline (Fig. 1). Patients who received AOMs during the 180-day period before baseline were excluded. Patients who received AOMs during the 1080-day observation period were included in analyses.

Classification of patients according to GC exposure (Fig. 2)

Patients were divided according to the number of days of GC prescription (< 30 days, 30–59 days, 60–89 days, 90 days), cumulative doses of GC (< 150 mg PSL, ≥ 150 and < 250 mg PSL, ≥ 250 and < 500 mg PSL, ≥ 500 and < 1000 mg PSL, ≥ 1000 mg PSL), and average daily doses of GC (< 1

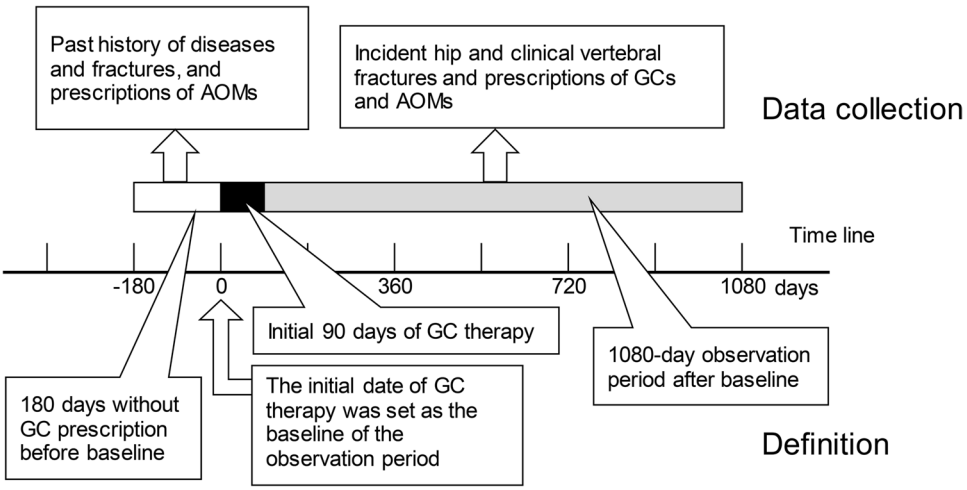

Fig. 1 Definition of eligible patients and data collection. AOM: anti-osteoporosis medication, GC: glucocorticoid

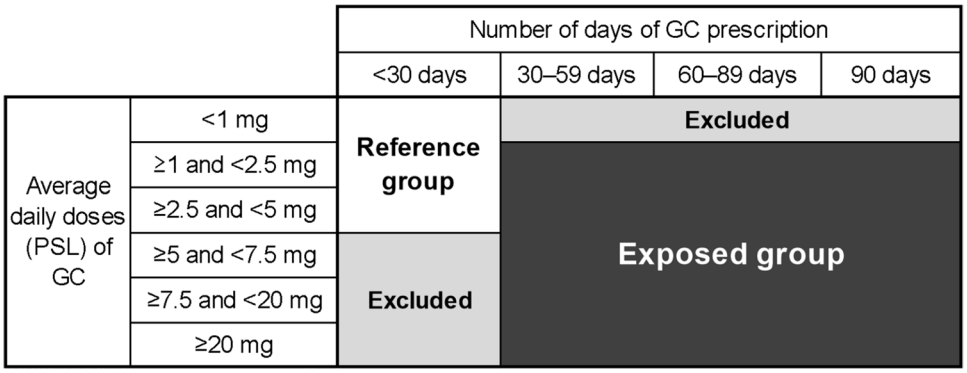

Fig. 2 Patient classification according to GC exposure in initial 90 days of GC therapy. GC: glucocorticoid, PSL: prednisolone or equivalent GC dose

mg PSL, ≥ 1 and <2.5mg PSL, ≥ 2.5 and <5 mg PSL, ≥ 5 and <75 mg PSL, ≥ 7.5 and <20 mg PSL, ≥ 20 mg PSL) in the initial 90 days of GC therapy. Average daily GC dose was calculated as cumulative GC dose divided by number of days of GC prescription. As shown in Fig. 2, we selected patients who were prescribed GC with average daily doses of ≥ 1 mg PSL for ≥ 30 days (GC-exposed group) and those with average daily GC doses of < 5 mg PSL for < 30 days (reference group), i.e., patients who were speculated to have no increase in fracture risk due to GC exposure.

Definition of outcome

Patients who suffered a hip or clinical vertebral fracture were defined as those who were registered as having had a femoral neck, trochanteric, intertrochanteric, or pertrochanteric fracture, or cervical, thoracic, or lumbar vertebral fracture, respectively, in the diagnosis field of the NDBJ for the first time in the 1080-day observation period (Fig. 1). However, those with pathologic, metastatic, tumorous, and suspicious fractures, as well as those with descriptions in a modifier field suggesting old fractures (e.g., previous, history, or postoperative) were not included in either hip or clinical vertebral fracture cases. In addition, fractures of the vertebral arch, transverse process, and spinous process were not included. To avoid the inclusion of prevalent vertebral fractures found incidentally on radiographs as incident vertebral fractures, patients who had been diagnosed with a vertebral fracture during the 180-day period before baseline were excluded in the analyses setting incident clinical vertebral fracture as the outcome. The date of the initial institutional visit due to fracture was adopted as the date of fracture occurrence. In patients with hip fractures, proof that the patient received hip surgery within 30 days from the date of fracture occurrence was additionally required. The endpoint was set as either the end of the 1080-day follow-up period or a hip or clinical vertebral fracture event, whichever came first.

According to a meta-analysis of studies validating hip fracture diagnosis according to hospital administrative claims data, there is convincing evidence to support the use of such data to identify hip fractures, with a sensitivity of 69–97% and a positive predictive value (PPV) of 63–96%. The validity was improved by combining diagnostic codes for hip fracture and procedural codes for hip surgeries, as was done in the present

study, with a sensitivity of 83–97% and a PPV of 86–98% [33]. However, there is insufficient evidence regarding the accuracy of clinical vertebral fracture identification using administrative data [33].

Covariates used for confounding adjustment

Diseases and bone fractures registered in the NDBJ during the 180-day period before baseline were obtained to evaluate their confounding effects on the association between GC and incident hip and clinical vertebral fractures. We identified type 1 and 2 diabetes mellitus, dementia, hip fracture, and clinical vertebral fracture as diagnoses which resulted in institutional visits or were found incidentally during institutional visits. Prescription of ≥ 7 different medications during the 90 days before and after the initiation of GC therapy was defined as polypharmacy according to the definition set forth by the Japanese National Health Insurance System.

Statistical analysis

Continuous variables are presented as mean and standard deviation (SD) or median and lower and upper quartile values according to the distribution. Dichotomous variables are presented as proportion (%). Trends of continuous or dichotomous variables with GC doses were tested by a linear regression test or Cochran-Armitage trend test. Cumulative incidence rates were calculated by the Kaplan–Meier method. Differences in cumulative incidence rates among groups stratified by GC exposure were evaluated by the generalized Wilcoxon trend test. Associations of baseline characteristics and GC therapy with incident hip or clinical vertebral fracture risk were evaluated by hazard ratios (HRs) derived from Cox proportional hazards regression analysis (PHREG procedure of the SAS system, release 9.40, SAS Institute, Cary, NC, USA). Confounding effects of baseline characteristics on the association between GC exposure and incident hip or clinical vertebral fracture risk were adjusted for by Cox proportional hazards models with the inverse probability weighting (IPW) method using propensity scores estimated by the logistic regression equation incorporating baseline characteristics (LOGISTIC procedure of the SAS system, release 9.40, SAS Institute, Cary, NC, USA). The propensity score was calculated as the probability of receiving GC with doses classified as the GC-exposed group in the analysis of the entire GC-exposed group and the reference group, and in the stratified analysis according to the GC prescription days.

Results

Baseline characteristics of patients (Table 1)

A total of 835,462 women and 610,323 men were selected from the NDBJ according to the inclusion criteria. We excluded 164,060 patients with AOM prescription before GC therapy initiation. Among the remaining 688,720 women and 593,005 men, 43,164 women and 33,702 men were classified into the reference group, and 316,396 women and 299,871 men into the GC-exposed group. Hip fractures occurred in 4040 women (incidence rate, 3.80/1000 person-years (PY)) and 1422 men (1.44/1000 PY), and clinical vertebral fractures in 15,697 women (14.8/1000 PY) and 9080 men (9.23/1000 PY).

As shown in Table 1, patients with higher daily doses of GC were older, had a history of more diseases, and had a higher proportion of polypharmacy and receiving AOMs. These trends were highly significant, except for the prevalence of hip fracture in men. Incidence rates of hip and clinical vertebral fractures increased with increasing daily GC doses.

Baseline characteristics and unadjusted fracture risk (Table 2 and Figs. 3and 4)

HRs of incident hip and clinical vertebral fractures during the 1080-day observation period were significantly increased even in the lowest daily or cumulative GC dose group and in the shortest GC prescription day group relative to the reference group (Table 2). Significant increasing trends of fracture risk were observed with increasing daily and cumulative GC doses and number of GC prescription days. These dose-dependent associations between GC exposure and fracture risk were observed in Kaplan–Meier cumulative incidence rate curves (Figs. 3 and 4). Baseline characteristics that were significantly associated with fracture risk were age, polypharmacy, comorbidities, and fracture history.

Male patients who received any AOM after GC therapy initiation had a significantly increased risk of incident hip and clinical vertebral fractures compared with patients who did not. An increase in fracture risk was also observed in female patients on bisphosphonates, teriparatides, and AVDs.

Table 1 Basic characteristics of patients on glucocorticoid (GC) therapy stratified by sex and average daily GC dose in initial 90 days of GC therapy

Basic characteristics	Women							P-value for trend	Men							P-value for trend
		Exposed group								Exposed group						
	Reference group		Classified by average daily GC dose (PSL) in initial 90 days of GC therapy						Reference group		Classified by average daily GC dose (PSL) in initial 90 days of GC therapy					
		All patients	≥1& < 2.5 mg	≥2.5& < 5 mg	≥5& < 7.5 mg	≥7.5& < 20 mg	20 mg			All patients	≥1& < 2.5 mg	≥2.5& < 5 mg	≥5& < 7.5 mg	≥7.5& < 20 mg	≥20 mg	
Number of patients	43,164	316,396	48,385	87,119	63,023	82,299	35,570	—	33,702	299,871	40,884	76,424	55,245	83,392	43,926	—
Daily GC dose in initial 90 days (mg PSL)	3.7 (3.7, 4.1)	5.4 (3.7, 11.1)	1.9 (1.9, 2.1)	3.7 (3.3, 4.0)	5.6 (5.2, 6.2)	11.3 (9.4, 14.8)	28.1 (23.2, 36.8)	< 0.001	3.7 (3.7, 4.1)	5.8 (3.7, 13)	1.9 (1.9, 2.1)	3.7 (3.4, 4)	5.6 (5.2, 6.4)	11.4 (9.6, 14.9)	28.9 (23.7, 37.9)	< 0.001
Cumulative GC dose in initial 90 days (mg PSL)	86 (78, 105)	341 (168, 754)	114 (86, 153)	195 (127, 273)	396 (240, 480)	795 (530, 1085)	2080 (1560, 2747)	< 0.001	86 (78, 108)	378 (174, 912)	114 (88, 155)	196 (133, 275)	380 (240, 480)	807 (535, 1100)	2165 (1690, 2870)	< 0.001
Cumulative days of GC prescription in initial 90 days (days)	23 (21, 28)	64 (43, 89)	59 (45, 80)	54 (36, 83)	69 (42, 90)	78 (45, 90)	83 (50, 90)	< 0.001	15 (0, 130)	65 (43, 89)	59 (45, 79)	54 (36, 80)	65 (41, 89)	78 (46, 90)	84 (55, 90)	< 0.001
GC after initial 90 days (%)	53.0	77.8	77.2	75.5	78.5	77.2	84.7	< 0.001	51.3	77.6	76.2	74.6	77.3	77.5	85.0	< 0.001
Cumulative GC dose after initial 90 days (mg PSL)	18 (0, 123)	345 (25, 2201)	116 (11, 427)	172 (5, 737)	504 (40, 2586)	895 (30, 3904)	3227 (417, 7165)	< 0.001	15 (0, 130)	383 (26, 2371)	120 (7, 420)	180 (0, 730)	431 (28, 2324)	868 (32, 3834)	3 (0.4, 7.2)	< 0.001
Age at GC therapy initiation (years)	65.1 ± 10.0	67.6 ± 10.9	65.8 ± 10.7	66.5 ± 10.7	68.6 ± 11.1	69.2 ± 11.0	67.4 ± 10.0	< 0.001	66.2 ± 9.8	68.5 ± 10	66.8 ± 10.1	67.5 ± 10	69 ± 10.1	69.7 ± 10	68.6 ± 9.4	< 0.001
Polypharmacy at GC therapy initiation (%)	5.83	13.7	8.52	9.72	13.6	15.6	26.7	< 0.001	6.5	14.4	8.25	9.08	12.3	15.8	29.1	< 0.001
Comorbidities in 180 days preceding GC therapy (%)																< 0.001
Type 1 diabetes mellitus	0.15	0.31	0.19	0.21	0.26	0.38	0.65	< 0.001	0.19	0.38	0.23	0.26	0.35	0.42	0.69	< 0.001
Type 2 diabetes mellitus	9.14	15.7	9.74	11.1	13.8	19.1	30.2	< 0.001	14.7	23.1	15.5	17.3	20.3	26.1	38.4	< 0.001
Dementia	4.06	6.81	4.96	5.67	7.67	8.64	6.36	< 0.001	3.58	5.24	4.43	4.68	5.67	5.92	5.13	< 0.001
Hip fracture	0.10	0.17	0.09	0.14	0.23	0.19	0.15	< 0.001	—[A]	0.05	0.05	0.03	0.07	0.06	0.04	0.042

Table 1 (continued)

Basic characteristics	Women							P-value for trend	Men							P-value for trend
		Exposed group								Exposed group						
	Reference group		Classified by average daily GC dose (PSL) in initial 90 days of GC therapy						Reference group		Classified by average daily GC dose (PSL) in initial 90 days of GC therapy					
		All patients	≥1& < 2.5 mg	≥2.5& < 5 mg	≥5& < 7.5 mg	≥7.5& < 20 mg	20 mg			All patients	≥1& < 2.5 mg	≥2.5& < 5 mg	≥5& < 7.5 mg	≥7.5& < 20 mg	≥20 mg	
Clinical vertebral fracture	0.21	0.46	0.31	0.35	0.58	0.56	0.49	< 0.001	0.15	0.27	0.17	0.23	0.30	0.33	0.27	< 0.001
Initiation of anti-osteoporosis medications after GC therapy initiation (%)																
Bisphosphonates	6.35	24.4	8.60	11.9	21.6	34.4	61.3	< 0.001	1.29	14.8	1.88	3.46	7.87	19.7	49.5	< 0.001
Denosumab	0.51	1.27	0.62	0.95	1.59	1.64	2.67	< 0.001	0.05	0.34	0.11	0.19	0.35	0.44	1.02	< 0.001
Teriparatides	0.54	1.42	0.85	1.02	1.64	1.90	2.92	< 0.001	0.12	0.37	0.19	0.21	0.39	0.49	0.81	< 0.001
SERMs	1.21	1.83	1.39	1.62	2.13	2.18	2.06	< 0.001	–[B]	–[B]	–[B]	–[B]	–[B]	–[B]	–[B]	–[B]
AVDs	4.34	10.29	5.69	6.82	10.4	14.5	24.5	< 0.001	1.28	5.67	1.70	2.39	4.25	8.09	18.40	< 0.001
Incidence rate of fracture after GC therapy initiation (per 1000 PY)																
Hip fracture	2.04	4.04	2.97	3.33	4.76	4.60	4.67	< 0.001	0.76	1.52	1.13	1.29	1.62	1.74	1.73	< .0001
Vertebral fracture	7.82	15.8	10.1	11.4	16.4	19.8	24.2	< 0.001	5.18	9.69	5.77	6.80	9.8	11.7	14.5	< 0.001

Values represent median lower and upper quartile values, mean ± SD, or proportion (%)

Reference patients were those who were prescribed GC with average daily GC doses < 5 mg PSL for less than 30 days

PSL: prednisolone or equivalent GC dose

PY: person-years

SERM: specific estrogen receptor modulator

AVD: activated vitamin D_3 analog

–[A]Prevalence proportion of hip fracture in the corresponding cell is not shown because it may contain proportions derived from less than 10 patients, which would not comply with the NDBJ privacy protection policy of the Ministry of Health, Labour and Welfare

–[B]SERMs were not prescribed to men

Table 2 Unadjusted hazard ratios (HRs) of incident hip and clinical vertebral fractures for glucocorticoid (GC) exposure and basic characteristics of patients

Basic characteristics	Women				Men			
	Hip fracture		Clinical vertebral fracture		Hip fracture		Clinical vertebral fracture	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Daily GC dose (PSL) in initial 90 days (compared with reference group)								
≥1 and < 2.5 mg	1.46	(1.25, 1.70)	1.29	(1.19, 1.40)	1.49	(1.12, 1.97)	1.12	(1.00, 1.25)
≥2.5 and < 5 mg	1.64	(1.42, 1.88)	1.46	(1.36, 1.57)	1.69	(1.31, 2.18)	1.32	(1.19, 1.45)
≥5 and < 7.5 mg	2.35	(2.04, 2.69)	2.12	(1.98, 2.28)	2.13	(1.65, 2.75)	1.90	(1.72, 2.10)
≥7.5 and < 20 mg	2.27	(1.98, 2.60)	2.58	(2.41, 2.76)	2.28	(1.79, 2.91)	2.28	(2.07, 2.50)
≥20 mg	2.30	(1.98, 2.68)	3.19	(2.96, 3.43)	2.28	(1.75, 2.95)	2.85	(2.58, 3.14)
P-value for trend	p < 0.001		p < 0.001		p < 0.001		p < 0.001	
Cumulative GC dose (PSL) in initial 90 days (compared with reference group)								
≥150 and < 250 mg	1.44	(1.26, 1.65)	1.26	(1.18, 1.35)	1.44	(1.12, 1.84)	1.10	(1.00, 1.21)
≥250 and < 500 mg	2.20	(1.92, 2.52)	2.02	(1.89, 2.17)	2.15	(1.68, 2.76)	1.84	(1.67, 2.02)
≥500 and < 1000 mg	2.58	(2.24, 2.96)	2.59	(2.41, 2.78)	2.52	(1.96, 3.24)	2.36	(2.14, 2.60)
≥1000 mg	2.38	(2.07, 2.73)	3.37	(3.14, 3.61)	2.32	(1.81, 2.97)	2.86	(2.61, 3.15)
P-value for trend	p < 0.001		p < 0.001		p < 0.001		p < 0.001	
Cumulative days of GC prescription in initial 90 days (compared with reference group)								
30—59 days	1.45	(1.27, 1.66)	1.36	(1.27, 1.45)	1.54	(1.21, 1.96)	1.26	(1.15, 1.38)
60—89 days	2.34	(2.05, 2.67)	2.39	(2.23, 2.56)	2.19	(1.72, 2.78)	2.14	(1.95, 2.35)
90 days	2.57	(2.25, 2.94)	2.93	(2.74, 3.14)	2.58	(2.02, 3.29)	2.72	(2.48, 2.99)
P-value for trend	p < 0.001		p < 0.001		p < 0.001		p < 0.001	
Cumulative GC dose after initial 90 days (per 1000 mg PSL)	1.08	(1.08, 1.09)	1.13	(1.13, 1.13)	1.05	(1.04, 1.07)	1.11	(1.11, 1.11)
Age at GC therapy initiation (per 5 year increase)	1.73	(1.71, 1.76)	1.45	(1.44, 1.46)	1.68	(1.63, 1.73)	1.52	(1.51, 1.54)
Polypharmacy at GC therapy initiation (absence as reference)	2.53	(2.36, 2.71)	2.45	(2.36, 2.54)	2.47	(2.20, 2.77)	2.34	(2.24, 2.46)
Comorbidities in 180 days preceding GC therapy (absence as reference)								
Type 1 diabetes mellitus	1.97	(1.31, 2.97)	1.59	(1.27, 2.01)	1.77	(0.92, 3.40)	1.45	(1.09, 1.93)
Type 2 diabetes mellitus	2.04	(1.91, 2.19)	1.81	(1.75, 1.88)	1.81	(1.62, 2.02)	1.53	(1.46, 1.60)
Dementia	6.40	(5.98, 6.84)	2.92	(2.80, 3.05)	6.24	(5.53, 7.03)	3.21	(3.03, 3.41)
Hip fracture	6.28	(4.56, 8.65)	2.86	(2.24, 3.64)	7.46	(3.11, 17.9)	5.33	(3.48, 8.18)
Vertebral fracture	3.61	(2.80, 4.65)	–-[A]		5.94	(3.86, 9.13)	–-[A]	
Initiation of AOM after GC therapy initiation (no AOM as reference)								
Bisphosphonates	1.23	(1.14, 1.32)	1.14	(0.98, 1.32)	2.09	(2.01, 2.16)	1.87	(1.77, 1.97)
Denosumab	1.01	(0.71, 1.44)	1.16	(0.43, 3.09)	2.76	(2.43, 3.13)	3.93	(3.12, 4.96)
Teriparatides	2.59	(2.10, 3.20)	3.48	(2.01, 6.00)	8.73	(8.11, 9.40)	14.9	(13.1, 16.8)
SERMs	0.84	(0.61, 1.15)	–-[B]		1.87	(1.65, 2.11)	–-[B]	
AVDs	1.24	(1.11, 1.39)	1.46	(1.18, 1.81)	2.13	(2.02, 2.24)	2.41	(2.24, 2.60)

95% CI: 95% confidence interval

PSL: prednisolone or equivalent GC dose

AOM: anti-osteoporosis medication

SERM: specific estrogen receptor modulator

AVD: activated vitamin D_3 analog

–-[A]Patients with a history of vertebral fracture were excluded

–-[B]SERMs were not prescribed to men

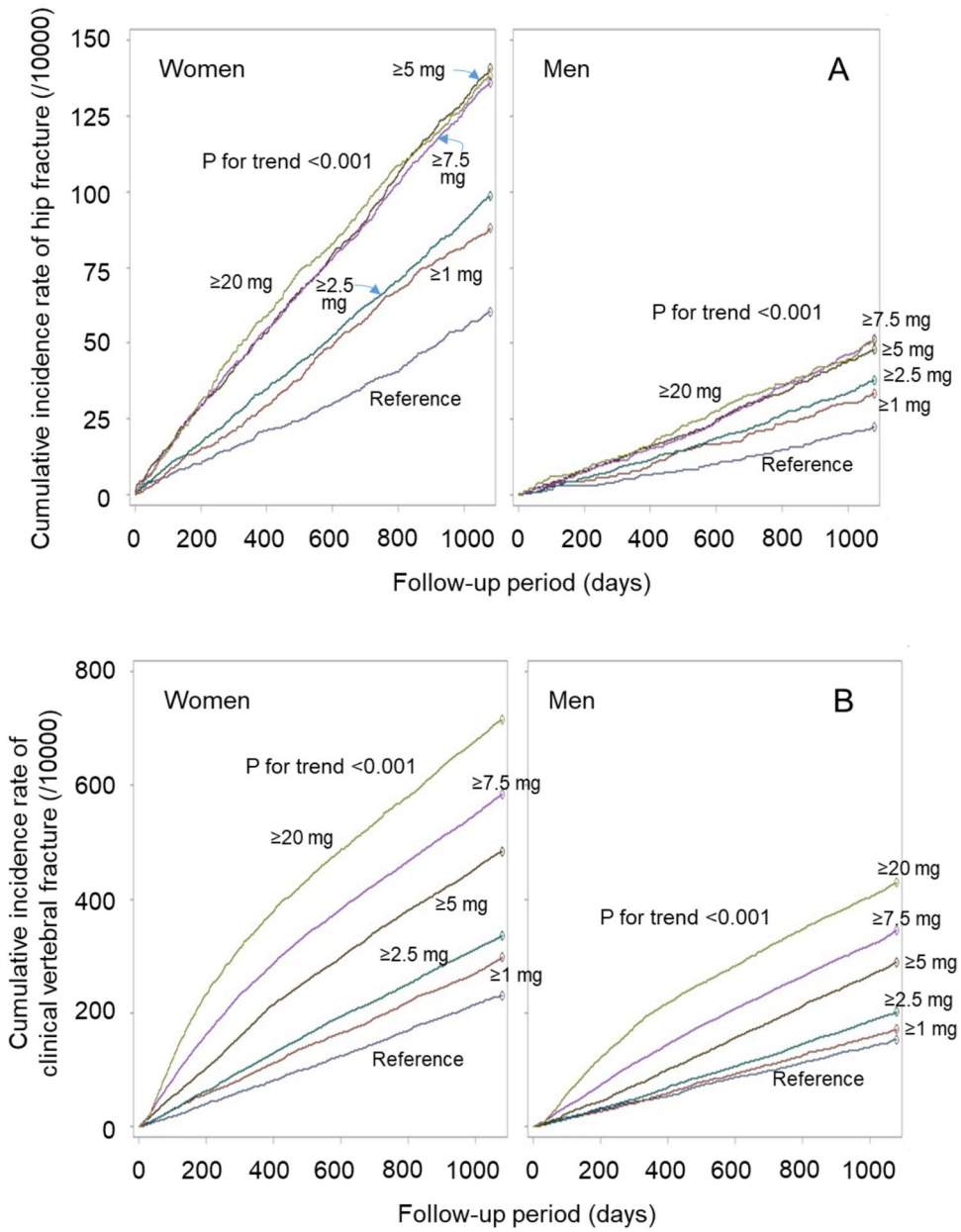

Fig. 3 Kaplan–Meier cumulative incidence rate curves of hip fracture (A) and clinical vertebral fracture (B) in patients on glucocorticoid (GC) therapy according to average daily GC dose in the initial 90 days of GC therapy

Daily and cumulative GC doses and adjusted fracture risk (Table 3, 4, 5, S1-S5)

Associations between average daily GC doses in the initial 90 days of GC therapy and hip or clinical vertebral fracture risk are shown in Table 3 and 4, respectively, after adjusting for covariates at baseline by IPW using propensity scores. Equations of the propensity score model for receiving GC are presented in Tables S1 (for hip fracture as outcome) and S2 (for clinical vertebral fracture as outcome). C-statistics of the equations were 0.596 and 0.599, respectively. As shown in Tables S3 and S4, standardized differences in baseline characteristics with IPW using propensity scores between the GC exposure groups (in the entire group and groups stratified by GC prescription days) and the reference group were less than 0.1 SD, suggesting that baseline characteristics were well-balanced between groups. All patients in the GC-exposed group showed significant dose-dependent increases in hip fracture risk compared with the reference group, and the HR was significant even in the lowest exposure group (≥1 and < 2.5 mg PSL) (Table 3).

When patients were stratified by number of days of GC prescription in the initial 90 days of GC therapy, a significantly increased risk of hip fracture was observed in groups with daily doses ≥5 and < 7.5 mg PSL for the stratum of 30–59 day prescription, and in groups with daily doses ≥1

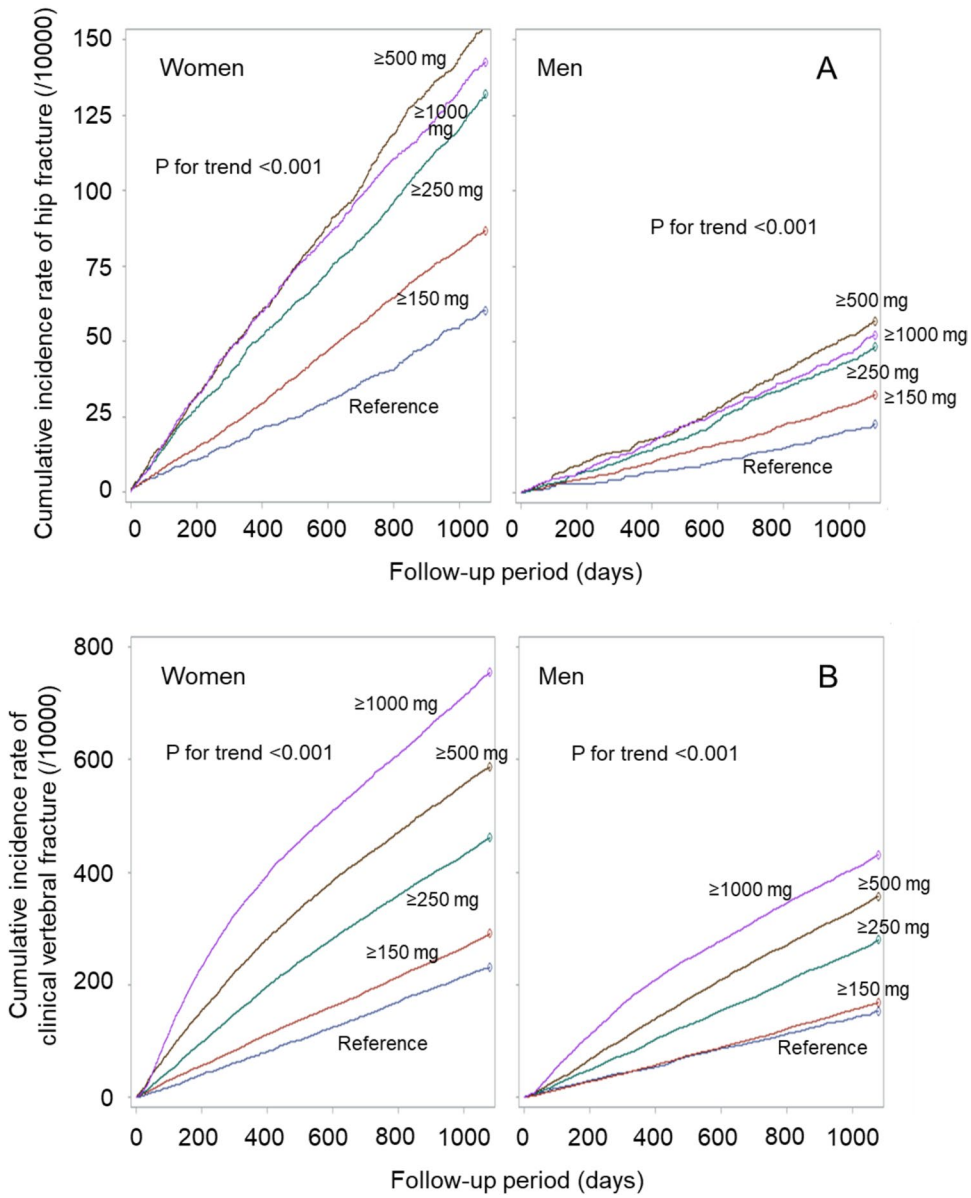

Fig. 4 Kaplan–Meier cumulative incidence rate curves of hip fracture (A) and clinical vertebral fracture (B) in patients on glucocorticoid (GC) therapy according to cumulative GC dose in the initial 90 days of GC therapy

and < 2.5 mg PSL for the stratum of 90 day prescription in women (Table 3). As for the risk of clinical vertebral fracture, results were similar to those regarding the risk of hip fracture in women, whereas a more modest association was observed in men (Table 4).

In addition, a significant dose-dependent association between cumulative GC doses in the initial 90 days of GC therapy and hip and clinical vertebral fractures were observed after adjusting for baseline characteristics by IPW using propensity scores (Table 5). Baseline characteristics were well-balanced between patients in all GC-exposed groups and the reference group (Tables S3 and S4).

Discussion

In this large-scale retrospective cohort study using a nationwide health insurance claims database, higher GC doses and longer prescription days in the initial 90 days of GC therapy were significantly and dose-dependently associated with increased fracture risk in the subsequent 1080 days. Patients receiving GC at ≥ 5 mg PSL/day had significantly increased fracture risk in the stratum of 60–89 day GC prescription. In addition, patients who received GC for 90 days in the initial 90 days of GC therapy had

Table 3 Multivariate-adjusted hazard ratios (HRs) of incident hip fracture for patients on glucocorticoid (GC) therapy classified by average daily GC dose in all GC-exposed patients or in each stratum according to number of days of GC prescription in the initial 90 days of GC therapy compared with reference patients

	Average daily GC dose (PSL) in initial 90 days of GC therapy	All patients in GC-exposed group		Stratified by number of days of GC prescription in initial 90 days of GC therapy					
				30–59 days		60–89 days		90 days	
Women	≥1 and < 2.5 mg	1.15	(1.04, 1.27)	1.10	(0.94, 1.28)	1.13	(0.98, 1.31)	1.47	(1.22, 1.77)
	≥2.5 and < 5 mg	1.18	(1.09, 1.27)	1.11	(0.99, 1.23)	1.24	(1.10, 1.40)	1.45	(1.26, 1.67)
	≥5 and < 7.5 mg	1.31	(1.22, 1.41)	1.21	(1.07, 1.36)	1.45	(1.29, 1.63)	1.49	(1.31, 1.69)
	≥7.5 and < 20 mg	1.17	(1.09, 1.25)	1.26	(1.13, 1.41)	1.17	(1.05, 1.31)	1.24	(1.10, 1.39)
	≥20 mg	1.52	(1.38, 1.67)	1.55	(1.32, 1.82)	1.67	(1.44, 1.92)	1.52	(1.30, 1.78)
	P-value for trend	< 0.001		< 0.001		< 0.001		0.245	
Men	≥1 and < 2.5 mg	1.28	(1.08, 1.53)	1.21	(0.93, 1.57)	1.38	(1.07, 1.78)	1.41	(0.96, 2.08)
	≥2.5 and < 5 mg	1.36	(1.20, 1.55)	1.20	(0.997, 1.45)	1.52	(1.24, 1.86)	1.76	(1.36, 2.27)
	≥5 and < 7.5 mg	1.46	(1.27, 1.66)	1.36	(1.10, 1.68)	1.47	(1.18, 1.83)	1.81	(1.43, 2.28)
	≥7.5 and < 20 mg	1.44	(1.29, 1.61)	1.57	(1.32, 1.88)	1.44	(1.20, 1.73)	1.51	(1.23, 1.85)
	≥20 mg	1.57	(1.36, 1.82)	1.57	(1.21, 2.03)	1.68	(1.34, 2.1)	1.65	(1.29, 2.10)
	P-value for trend	< 0.001		< 0.001		< 0.001		0.005	

Values represent HRs and 95% confidence intervals (95% CIs)

PSL: prednisolone or equivalent GC dose

HRs and 95% CIs were calculated for all GC-exposed patients or for each stratum according to number of days of GC prescription in the initial 90 days of GC therapy after adjusting for age at GC therapy initiation, presence of type 1 diabetes mellitus, type 2 diabetes mellitus, dementia, hip fracture, and vertebral fracture during 180 days prior to GC therapy, polypharmacy at GC therapy initiation, and cumulative GC dose after the initial 90 days of GC therapy in addition to inverse-probability weighting using propensity scores

Table 4 Multivariate-adjusted hazard ratios (HRs) of incident clinical vertebral fracture for patients on glucocorticoid (GC) therapy classified by average daily GC dose in all GC-exposed patients or in each stratum according to number of days of GC prescription in the initial 90 days of GC therapy compared with reference patients

	Average daily GC dose (PSL) in initial 90 days of GC therapy	All patients in GC-exposed group		Stratified by number of days of GC prescription in initial 90 days of GC therapy					
				30–59 days		60–89 days		90 days	
Women	≥1 and < 2.5 mg	1.07	(1.01, 1.12)	1.03	(0.96, 1.12)	1.09	(1.01, 1.18)	1.26	(1.13, 1.41)
	≥2.5 and < 5 mg	1.14	(1.1, 1.19)	1.04	(0.99, 1.1)	1.27	(1.19, 1.36)	1.37	(1.27, 1.48)
	≥5 and < 7.5 mg	1.38	(1.33, 1.44)	1.17	(1.1, 1.25)	1.51	(1.42, 1.61)	1.67	(1.56, 1.79)
	≥7.5 and < 20 mg	1.59	(1.54, 1.65)	1.29	(1.22, 1.37)	1.70	(1.61, 1.8)	1.96	(1.85, 2.08)
	≥20 mg	2.23	(2.13, 2.33)	1.92	(1.78, 2.07)	2.39	(2.23, 2.55)	2.65	(2.47, 2.84)
	P-value for trend	< 0.001		< 0.001		< 0.001		< 0.001	
Men	≥1 and < 2.5 mg	0.95	(0.88, 1.02)	0.86	(0.77, 0.96)	1.03	(0.92, 1.14)	1.13	(0.96, 1.33)
	≥2.5 and < 5 mg	1.06	(1.01, 1.12)	0.98	(0.91, 1.06)	1.12	(1.02, 1.22)	1.32	(1.18, 1.47)
	≥5 and < 7.5 mg	1.34	(1.27, 1.41)	1.12	(1.03, 1.23)	1.47	(1.35, 1.61)	1.63	(1.48, 1.78)
	≥7.5 and < 20 mg	1.50	(1.44, 1.57)	1.32	(1.23, 1.42)	1.63	(1.52, 1.75)	1.66	(1.54, 1.79)
	≥20 mg	1.97	(1.87, 2.07)	1.61	(1.46, 1.78)	2.14	(1.97, 2.32)	2.25	(2.06, 2.44)
	P-value for trend	< 0.001		< 0.001		< 0.001		< 0.001	

Values represent HRs and 95% confidence intervals (95% CIs)

PSL: prednisolone or equivalent GC dose

HRs and 95% CIs were calculated for all GC-exposed patients or for each stratum according to number of days of GC prescription in the initial 90 days of GC therapy after adjusting for age at GC therapy initiation, presence of type 1 diabetes mellitus, type 2 diabetes mellitus, dementia, and hip fracture during 180 days prior to GC therapy, polypharmacy at GC therapy initiation, and cumulative GC dose after the initial 90 days of GC therapy in addition to inverse-probability weighting using propensity scores

Table 5 Multivariate-adjusted hazard ratios (HRs) of incident hip and clinical vertebral fractures for patients on glucocorticoid (GC) therapy classified by cumulative GC dose in the initial 90 days of GC therapy compared with reference patients

	Cumulative GC dose (PSL) in initial 90 days of GC therapy	Hip fracture		Clinical vertebral fracture	
Women	≥150 and < 250 mg	1.16	(1.08, 1.24)	1.08	(1.04, 1.12)
	≥250 and < 500 mg	1.28	(1.19, 1.37)	1.36	(1.31, 1.42)
	≥500 and < 1000 mg	1.25	(1.16, 1.35)	1.55	(1.49, 1.61)
	≥1000 mg	1.31	(1.21, 1.41)	2.12	(2.05, 2.20)
	P-value for trend	< 0.001		< 0.001	
Men	≥150 and < 250 mg	1.27	(1.13, 1.43)	0.98	(0.93, 1.03)
	≥250 and < 500 mg	1.48	(1.31, 1.67)	1.32	(1.25, 1.38)
	≥500 and < 1000 mg	1.55	(1.36, 1.75)	1.52	(1.45, 1.60)
	≥1000 mg	1.48	(1.30, 1.67)	1.85	(1.77, 1.94)
	P-value for trend	< 0.001		< 0.001	

Values represent HRs and 95% confidence intervals (95% CIs)

PSL: prednisolone or equivalent GC dose

HRs and 95% CIs for hip fracture were calculated after adjusting for age at GC therapy initiation, presence of type 1 diabetes mellitus, type 2 diabetes mellitus, dementia, hip fracture, and clinical vertebral fracture during 180 days prior to GC therapy, polypharmacy at GC therapy initiation, and cumulative GC dose after the initial 90 days of GC therapy in addition to inverse-probability weighting using propensity scores

HRs and 95% CIs for clinical vertebral fracture were calculated after adjusting for the same variables as those for hip fracture except for previous clinical vertebral fracture

a significant increase in fracture risk even with doses ≥1 and < 2.5 mg PSL/day.

Our results support the recommendation of the GIO management guidelines to perform fracture risk assessment at three months after GC therapy initiation, with a valid association between daily GC doses in the initial 90 days of GC therapy and fracture risk. We do not believe, however, that GC exposure in the initial 90 days of GC therapy increases fracture risk in the subsequent 1080 days regardless of GC exposure after 90 days of GC therapy. In the present study, 77.8% of patients in the GC-exposed group continued GC therapy after the initial 90 days, and this proportion significantly increased with the increase in daily GC doses in the initial 90 days of GC therapy (Table 1). Since GC exposure after the initial 90 days was also associated with an increase in fracture risk (Table 2), the association between daily GC doses in the initial 90 days and fracture risk may partly be explained by GC exposure after the initial 90 days. However, GC doses after 90 days of GC therapy are not available at the time of fracture risk assessment conducted at three months after GC therapy initiation. The present study thus underscores the need for physicians to perform fracture risk assessment three months after GC therapy initiation according to GC exposure information in the initial 90 days of GC therapy.

A meta-analysis including 23 observational studies on the association between GC exposure and fracture risk concluded that GC exposure ≥ 5 mg PSL/day was associated with a significant increase in fracture risk [5]. Another review concluded that GC exposure ≥ 7.5 mg PSL/day increased fracture risk [8]. However, a large-scale cohort study using GPRD reported that a significant increase in hip fracture was observed in the 2.5–7.4 mg PSL/day group, and in vertebral fracture in an even lower exposure stratum, i.e., < 2.5 mg PSL/day [23]. In the GPRD study, however, the fracture risk increase in relation to GC exposure was not separately presented for women and men, even though the prevalence of osteoporosis and incidence of fractures significantly differ between sexes. The present study is the first to report that GC exposure as low as ≥1 and < 2.5 mg PSL/day was significantly associated with increased fracture risk in both women and men when patients received GC for 90 days in the initial 90 days of GC therapy.

There were significant increases in hip and clinical vertebral fracture risk in patients who received AOMs relative to those who did not (Table 2). This is possibly due to confounding by indication [34], that is, physicians might have selected patients who were at increased risk of fracture to administer AOMs. For example, if a physician selected a patient with a four-fold higher risk of fracture based on clinical risk factors and laboratory tests for osteoporosis, a two-fold higher risk of fracture would still remain even though the use of AOMs reduced the fracture risk by half. In the analyses shown in Table 3 and 4, we did not adjust the association between GC exposure and fracture risk for AOM use since the imbalance in AOM use (i.e., higher AOM use in higher GC exposure group) might have led to an underestimation of the effect of GC on fracture risk in higher daily dose groups, resulting in a reduced significance of the overall association.

The potential effects of confounding by underlying diseases should also be considered. We did not have data on underlying diseases that had led to GC therapy as well as increased fracture risk, such as rheumatoid arthritis (RA), chronic obstructive pulmonary diseases (COPD), and inflammatory bowel diseases. Patients with severe diseases are more likely to have received higher doses of GC and may have had higher fracture risk due to underlying diseases. This may have resulted in overestimating the association between GC exposure and fracture risk. However, GC is not a first-line medication for RA or COPD. Hence, the effects of these diseases on the association studied may not have been large. In addition, the GPRD study reported that fracture risk was similar across underlying diseases [5]. Imbalance of baseline characteristics observed in the present study was adjusted for by Cox regression with IPW using propensity scores, resulting in well-balanced baseline characteristics. However, baseline characteristics incorporated in the logistic equations for propensity score were limited and the C-statistics of the equations were not optimal. We acknowledge that the observed association between GC exposure and fracture risk might be explained in part by confounding due to underlying diseases.

The strength of the present study is the use of NDBJ data, which include all electronic health insurance claims data submitted in Japan under a public health insurance system with nationwide coverage. To our knowledge, the present study is the largest-scale cohort study ever conducted in Japan, and the obtained results are representative of the entire population in real-world settings.

There are also some limitations worth noting. First, the NDBJ does not provide detailed information on fracture events (e.g., how the fracture occurred). Therefore, hip and vertebral fractures caused by high-energy impact may have been included in the analyzed data. In addition, we could not completely exclude prevalent vertebral fractures found incidentally on radiographs taken for other purposes due to a lack of information needed to distinguish between old and new vertebral fractures in the diagnosis field of the NDBJ. Moreover, since we did not extract data on fractures of skeletal sites other than the hip and vertebra, we could not evaluate the association between GC exposure and non-vertebral fractures or major osteoporotic fractures. Second, the definition of hip fracture in this study included hip fracture diagnosis and hip surgery within 30 days from a fracture event. This resulted in exclusion of patients with hip fractures treated conservatively, which account for 6% of all hip fracture cases in Japan [35]. Third, many asymptomatic vertebral fractures may have been missed, since two-thirds of vertebral fractures are asymptomatic and patients do not always seek medical attention [36]. Thus, our results may be limited to clinically manifested vertebral fractures. It is important, however, to reduce clinical vertebral fractures, as they deteriorate quality of life [7] and increase morbidity and mortality [6]. Fourth, the reference group consisted of patients with the least GC exposure, i.e., a cumulative GC dose < 150 mg PSL in the initial 90 days. Such a small GC exposure would not have increased fracture risk, and even if it did, the association between GC exposure and fracture risk would be underestimated. Fifth, the NDBJ does not contain data on BMD, laboratory tests, radiological examinations including vertebral fracture assessment, and risk factors for hip and vertebral fractures, including low body weight, frailty status, fall history, smoking and drinking habits, inadequate diet, and low physical activity. Therefore, we could not adjust the association between GC prescription and fracture risk for these factors. Finally, the present study used a retrospective cohort design and thus could not completely eliminate confounding effects, such as confounding by indication.

In conclusion, the present retrospective cohort study using NDBJ data revealed that average daily doses of GC in the initial 90 days of GC therapy were significantly and dose-dependently associated with subsequent hip and clinical vertebral fracture risk. A significant increase in fracture risk was observed in patients on GC therapy with lower daily doses and fewer days of prescription than previously reported.

Supplementary information The online version contains supplementary material available at https://doi.org/10.1007/s00198-024-07023-6.

Acknowledgements The authors thank the personnel of the Osteoporosis Foundation who supported the present study.

Funding Financial support for the present study was provided by a 52nd Taiju Life Social Welfare Foundation Medical Research Grant 2019, a Japan Osteoporosis Foundation Grant for Bone Research 2019, and a 28th Pfizer Health Research Grant 2019. The funding bodies had no role in designing the study, collecting, analyzing, or interpreting the data, writing the manuscript, or deciding where to submit the manuscript for publication.

Data availability Data cannot be shared with researchers who are not approved to access them by the Ministry of Health, Labour and Welfare of Japan.

Code availability Codes for data analysis will be made available on request.

Declarations

Ethics approval The study protocol was approved by the Ethics Committee of Kindai University Faculty of Medicine (Approval Number: 31–065).

Consent to participate We analyzed data provided by the Ministry of Health, Labour and Welfare which were completely anonymous. Therefore, informed consent from each patient was not required.

Consent for publication Publication of the present manuscript was approved by the Ministry of Health, Labour and Welfare and all authors.

Conflicts of interest Nobukazu Okimoto has received consulting fees from Asahi-Kasei Pharmaceutical Co., Ltd. and Teijin Pharma Ltd., and payments for lectures, including speakers' bureau fees, from Asahi-Kasei Pharmaceutical Co., Ltd., Amgen K.K., Chugai Pharmaceutical Co., Daiichi-Sankyo Co., Ltd., Eli Lilly Japan, and Teijin Pharma Ltd. Shinichi Nakatoh has received payments for lectures, including speakers' bureau fees, from Asahi-Kasei Pharmaceutical Co., Ltd., Amgen K.K., and Daiichi-Sankyo Co., Ltd. Shigeyuki Ishii has received honorarium from Teijin Pharma Ltd., and has written manuscripts for Asahi Kasei Pharma Ltd. Masayuki Iki, Kenji Fujimori, Junko Tamaki, and Sumito Ogawa declare that they have no conflict of interest.

Trial registration number The present study is not registered.

References

1. LoCascio V, Bonucci E, Imbimbo B, Ballanti P, Adami S, Milani S, Tartarotti D, DellaRocca C (1990) Bone loss in response to long-term glucocorticoid therapy. Bone Miner 8(1):39–51. https://doi.org/10.1016/0169-6009(91)90139-q
2. Laan RF, van Riel PL, van de Putte LB, van Erning LJ, van't Hof MA, Lemmens JA, (1993) Low-dose prednisone induces rapid reversible axial bone loss in patients with rheumatoid arthritis. A randomized, controlled study. Ann Int Med 119(10):963–968. https://doi.org/10.7326/0003-4819-119-10-199311150-00001
3. Steinbuch M, Youket TE, Cohen S (2004) Oral glucocorticoid use is associated with an increased risk of fracture. Osteoporos Int 15(4):323–328. https://doi.org/10.1007/s00198-003-1548-3
4. Kanis JA, Johansson H, Oden A, Johnell O, de Laet C, Melton IL, Tenenhouse A, Reeve J, Silman AJ, Pols HA, Eisman JA, McCloskey EV, Mellstrom D (2004) A meta-analysis of prior corticosteroid use and fracture risk. J Bone Miner Res 19(6):893–899. https://doi.org/10.1359/jbmr.040134
5. van Staa TP, Leufkens HG, Cooper C (2002) The epidemiology of corticosteroid-induced osteoporosis: a meta-analysis. Osteoporos Int 13(10):777–787. https://doi.org/10.1007/s001980200108
6. Cauley JA, Thompson DE, Ensrud KC, Scott JC, Black D (2000) Risk of mortality following clinical fractures. Osteoporos Int 11(7):556–561. https://doi.org/10.1007/s001980070075
7. Peeters CM, Visser E, Van de Ree CL, Gosens T, Den Oudsten BL, De Vries J (2016) Quality of life after hip fracture in the elderly: A systematic literature review. Injury 47(7):1369–1382. https://doi.org/10.1016/j.injury.2016.04.018
8. Buckley L, Humphrey MB (2018) Glucocorticoid-Induced Osteoporosis. N Engl J Med 379(26):2547–2556. https://doi.org/10.1056/NEJMcp1800214
9. Chotiyarnwong P, McCloskey EV (2020) Pathogenesis of glucocorticoid-induced osteoporosis and options for treatment. Nat Rev Endocrinol 16(8):437–447. https://doi.org/10.1038/s41574-020-0341-0
10. Lee TH, Song YJ, Kim H, Sung YK, Cho SK (2020) Intervention Thresholds for Treatment in Patients with Glucocorticoid-Induced Osteoporosis: Systematic Review of Guidelines. J Bone Metab 27(4):247–259. https://doi.org/10.11005/jbm.2020.27.4.247
11. Buckley L, Guyatt G, Fink HA, Cannon M, Grossman J, Hansen KE, Humphrey MB, Lane NE, Magrey M, Miller M, Morrison L, Rao M, Robinson AB, Saha S, Wolver S, Bannuru RR, Vaysbrot E, Osani M, Turgunbaev M, Miller AS, McAlindon T (2017) 2017 American College of Rheumatology Guideline for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis. Arthritis Rheumatol 69(8):1521–1537. https://doi.org/10.1002/art.40137
12. Suzuki Y, Nawata H, Soen S, Fujiwara S, Nakayama H, Tanaka I, Ozono K, Sagawa A, Takayanagi R, Tanaka H, Miki T, Masunari N, Tanaka Y (2014) Guidelines on the management and treatment of glucocorticoid-induced osteoporosis of the Japanese Society for Bone and Mineral Research: 2014 update. J Bone Miner Metab 32(4):337–350. https://doi.org/10.1007/s00774-014-0586-6
13. Compston J, Cooper A, Cooper C, Gittoes N, Gregson C, Harvey N, Hope S, Kanis JA, McCloskey EV, Poole KES, Reid DM, Selby P, Thompson F, Thurston A, Vine N (2017) UK clinical guideline for the prevention and treatment of osteoporosis. Arch Osteoporos 12(1):43. https://doi.org/10.1007/s11657-017-0324-5
14. Hoes JN, Jacobs JW, Boers M, Boumpas D, Buttgereit F, Caeyers N, Choy EH, Cutolo M, Da Silva JA, Esselens G, Guillevin L, Hafstrom I, Kirwan JR, Rovensky J, Russell A, Saag KG, Svensson B, Westhovens R, Zeidler H, Bijlsma JW (2007) EULAR evidence-based recommendations on the management of systemic glucocorticoid therapy in rheumatic diseases. Ann Rheum Dis 66(12):1560–1567. https://doi.org/10.1136/ard.2007.072157
15. Lekamwasam S, Adachi JD, Agnusdei D, Bilezikian J, Boonen S, Borgström F, Cooper C, Diez Perez A, Eastell R, Hofbauer LC, Kanis JA, Langdahl BL, Lesnyak O, Lorenc R, McCloskey E, Messina OD, Napoli N, Obermayer-Pietsch B, Ralston SH, Sambrook PN, Silverman S, Sosa M, Stepan J, Suppan G, Wahl DA, Compston JE (2012) A framework for the development of guidelines for the management of glucocorticoid-induced osteoporosis. Osteoporos Int 23(9):2257–2276. https://doi.org/10.1007/s00198-012-1958-1
16. Amiche MA, Abtahi S, Driessen JHM, Vestergaard P, de Vries F, Cadarette SM, Burden AM (2018) Impact of cumulative exposure to high-dose oral glucocorticoids on fracture risk in Denmark: a population-based case-control study. Arch Osteoporos 13(1):30. https://doi.org/10.1007/s11657-018-0424-x
17. Bours S, de Vries F, van den Bergh JPW, Lalmohamed A, van Staa TP, Leufkens HGM, Geusens PPP, Drent M, Harvey NC (2016) Risk of vertebral and non-vertebral fractures in patients with sarcoidosis: a population-based cohort. Osteoporos Int 27(4):1603–1610. https://doi.org/10.1007/s00198-015-3426-1
18. Kim D, Cho SK, Park B, Jang EJ, Bae SC, Sung YK (2018) Glucocorticoids Are Associated with an Increased Risk for Vertebral Fracture in Patients with Rheumatoid Arthritis. J Rheumatol 45(5):612–620. https://doi.org/10.3899/jrheum.170054
19. Lee E, Lee MJ, Park B, Park I (2020) Risk of fracture according to glucocorticoid use after renal biopsy: a nationwide population-based study. Sci Rep 10(1):13846. https://doi.org/10.1038/s41598-020-70935-w
20. Robinson DE, van Staa TP, Dennison EM, Cooper C, Dixon WG (2018) The limitations of using simple definitions of glucocorticoid exposure to predict fracture risk: A cohort study. Bone 117:83–90. https://doi.org/10.1016/j.bone.2018.09.004
21. van Staa TP (2006) The pathogenesis, epidemiology and management of glucocorticoid-induced osteoporosis. Calcif Tissue Int 79(3):129–137. https://doi.org/10.1007/s00223-006-0019-1
22. van Staa TP, Abenhaim L, Cooper C, Zhang B, Leufkens HG (2001) Public health impact of adverse bone effects of oral corticosteroids. Br J Clin Pharmacol 51(6):601–607. https://doi.org/10.1046/j.0306-5251.2001.1385.x
23. Van Staa TP, Leufkens HG, Abenhaim L, Zhang B, Cooper C (2000) Use of oral corticosteroids and risk of fractures. J Bone Miner Res 15(6):993–1000. https://doi.org/10.1359/jbmr.2000.15.6.993
24. van Staa TPLH, Abenhaim L, Zhang B, Cooper C (2000) Oral corticosteroids and fracture risk: relationship to daily and cumulative doses. Rheumatology 39:1383–1389

25. Vestergaard P, Rejnmark L, Mosekilde L (2005) Fracture risk associated with systemic and topical corticosteroids. J Intern Med 257(4):374–384. https://doi.org/10.1111/j.1365-2796.2005.01467.x
26. Balasubramanian A, Wade SW, Adler RA, Lin CJF, Maricic M, O'Malley CD, Saag K, Curtis JR (2016) Glucocorticoid exposure and fracture risk in patients with new-onset rheumatoid arthritis. Osteoporos Int 27(11):3239–3249. https://doi.org/10.1007/s00198-016-3646-z
27. Ozen G, Pedro S, Wolfe F, Michaud K (2019) Medications associated with fracture risk in patients with rheumatoid arthritis. Ann Rheum Dis 78(8):1041–1047. https://doi.org/10.1136/annrheumdis-2019-215328
28. Koh JW, Kim J, Cho H, Ha YC, Kim TY, Lee YK, Kim HY, Jang S (2020) Effects of Systemic Glucocorticoid Use on Fracture Risk: A Population-Based Study. Endocrinol Metab 35(3):562–570. https://doi.org/10.3803/EnM.2020.659
29. Matsuda S, Fujimori K (2012) The claim database in Japan. Asian Pac J Dis Manag 6(3–4):55–59
30. Ministry of Health Labour, and Welfare (2016) Proportion of electronic claims in the Japanese health insurance system. Ministry of Health, Labour, and Welfare. https://www.mhlw.go.jp/file/06-Seisakujouhou-12400000-Hokenkyoku/0000099002.pdf. Accessed 16 November, 2023
31. Ministry of Health Labour, and Welfare (2017) NDB open data. Ministry of Health, Labour, and Welfare. https://www.mhlw.go.jp/file/06-Seisakujouhou-12400000-Hokenkyoku/0000193322.pdf. Accessed 16 November, 2023
32. Liu D, Ahmet A, Ward L, Krishnamoorthy P, Mandelcorn ED, Leigh R, Brown JP, Cohen A, Kim H (2013) A practical guide to the monitoring and management of the complications of systemic corticosteroid therapy. Allergy Asthma Clin 9(1):30. https://doi.org/10.1186/1710-1492-9-30
33. Hudson M, Avina-Zubieta A, Lacaille D, Bernatsky S, Lix L, Jean S (2013) The validity of administrative data to identify hip fractures is high–a systematic review. J Clin Epidemiol 66(3):278–285. https://doi.org/10.1016/j.jclinepi.2012.10.004
34. Kyriacou DN, Lewis RJ (2016) Confounding by Indication in Clinical Research. JAMA 316(17):1818–1819. https://doi.org/10.1001/jama.2016.16435
35. The Japanese Orthopaedic Association (2019) Results of national survey of hip fracture in 2019. https://www.joa.or.jp/member/committee/osteoporosis/pdf/femur19.pdf. Accessed 16 November, 2023
36. Cooper C, Atkinson EJ, O'Fallon WM, Melton LJ 3rd (1992) Incidence of clinically diagnosed vertebral fractures: a population-based study in Rochester, Minnesota, 1985–1989. J Bone Miner Res 7(2):221–227. https://doi.org/10.1002/jbmr.5650070214

Authors and Affiliations

Masayuki Iki[1,2] · Kenji Fujimori[3,2] · Shinichi Nakatoh[4,2] · Junko Tamaki[5,2] · Shigeyuki Ishii[6,2] · Nobukazu Okimoto[7,2] · Hironori Imano[1] · Sumito Ogawa[8,2]

✉ Masayuki Iki
masa@med.kindai.ac.jp

1 Department of Public Health, Kindai University Faculty of Medicine, 377-2 Oono-Higashi, Osaka-Sayama, Osaka 589-8511, Japan

2 National Database Japan-Osteoporosis Management (NDBJ-OS) Study Group, Department of Public Health, Kindai University Faculty of Medicine, 377-2 Oono-Higashi, Osaka-Sayama, Osaka 589-8511, Japan

3 Department of Health Administration and Policy, Tohoku University School of Medicine, 2-1 Seiryo-Machi, Aoba-Ku, Sendai, Miyagi 980-8575, Japan

4 Department of Orthopedic Surgery, Asahi General Hospital, 477 Tomari, Asahimachi, Shimo-Nikawa-Gun, Toyama 939-0798, Japan

5 Department of Hygiene and Public Health, Osaka Medical and Pharmaceutical University, 2-7 Daigakumachi, Takatsuki, Osaka 569-8686, Japan

6 Department of Regulatory Science, School of Pharmacy, Tokyo University of Pharmacy and Life Sciences, 1432-1 Horinouchi, Hachiouji, Tokyo 193-0392, Japan

7 Okimoto Clinic, 185-4 Kubi, Yutaka-Machi, Kure, Hiroshima 734-0304, Japan

8 Department of Geriatric Medicine, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-Ku, Tokyo 113-8655, Japan