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ORIGINAL ARTICLE

Effects of long-term inhaled corticosteroid treatment on fragility fractures in older women: the Manitoba BMD registry study

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Abstract

Summary The effects of inhaled corticosteroids (ICS) on fracture risk in older women with chronic respiratory diseases are not well established. Our results indicate long-term ICS use in this population does not increase the risk of major osteoporotic fracture. This finding further elucidates the long-term safety of ICS in older women.

Introduction Inhaled corticosteroids (ICS) are frequently used in older women with chronic respiratory diseases. There is insufficient evidence regarding the association between long-term ICS use and the risk of fragility fractures in this population.

Methods We used linked Manitoba health administrative databases and the provincial bone mineral density (BMD) registry (1996–2013) to identify women ≥ 40 years of age with asthma and/or chronic obstructive pulmonary disease (COPD) within 3 years preceding the baseline BMD test. We followed them until the first major osteoporotic fracture or end of study, whichever came first. ICS use, stratified by exposure tertiles, was measured within the 12-month period following the baseline BMD test (by total days and quantity, primary outcome), and over the entire follow-up period (by medication possession ratio (MPR) and average annual dose, secondary outcome). The hazard ratio of fracture with ICS use was estimated using a Cox proportional hazards model, controlling for baseline determinants of fracture.

Results Of 6880 older women with asthma (38%) or COPD (62%), 810 (12%) experienced a major osteoporotic fracture over a mean follow-up of 7.7 years (SD = 3.9). ICS use at any tertile was not associated with an increased risk of fracture (dispensed days, $p = 0.90$; dispensed quantity, $p = 0.67$). Similarly, ICS use at any tertile during the entire follow-up period was not associated with an increased risk of fracture (MPR, $p = 0.62$; average annual dose, $p = 0.58$).

Conclusion Our findings do not support an increased risk of major osteoporotic fracture in older women with chronic respiratory diseases due to long-term ICS use.

Keywords Asthma · Chronic obstructive pulmonary disease · Fracture · Inhaled corticosteroids · Osteoporosis · Women

Introduction

Chronic respiratory diseases, primarily asthma and chronic obstructive pulmonary disease (COPD), are leading causes of morbidity and mortality for older women globally [1, 2]. Asthma and COPD are both characterized by chronic inflammation of the airways and a constant, low-level systemic inflammation [3]. Many studies have reported various extra-pulmonary manifestations, including osteoporosis and fragility fractures, in COPD [4].

Evidence-based guidelines recommend anti-inflammatory medications such as inhaled corticosteroids (ICS) as the mainstay treatment for asthma [5]. ICS, in combination with long-acting beta agonists and/or long-acting muscarinic agents, are also commonly used to reduce exacerbation rate in moderate and severe COPD [6, 7]. Previous evidence suggests that anti-

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inflammatory medications used to treat asthma and COPD may elicit a dose-dependent increased risk of bone fracture [8, 9]. However, the assessed dosage in these studies was typically high [8], or the studies included predominantly male populations [9].

Older women are disproportionately affected by osteoporotic fractures [10]. Due to hormonal changes leading to bone loss [11] and the risk of glucocorticoid-induced osteoporosis [12], extra attention to the safety of ICS treatment regimens is required in this vulnerable population. Current evidence in asthma regarding the long-term safety of ICS use on bone fracture is mainly focused on children and young adults [13]; evidence in older women is scarce. In COPD, a recent study showed a slightly increased risk of fracture in older patients who use ≥ 1000 μg (fluticasone-equivalent) of ICS daily for more than 4 years [14]. However, this study could not fully consider the confounding effect of pre-existing risk factors for fracture. Characterizing the real-world longitudinal relationship between intensity of ICS use and fragility fractures in older women, while controlling for confounding factors, is required to inform treatment decisions in this patient population.

Using a population-based bone densitometry registry, linked with provincial administrative health data in the province of Manitoba, Canada, we investigated the association between ICS use and the long-term risk of fracture in older women with asthma and/or COPD. ICS use was characterized by both days of use and dispensed quantity across a wide range of intensities.

Methods

Data sources

The province of Manitoba, Canada, provides universal health care to its population of 1.3 million (as of 2016) residents [15]. The need to maintain the public health care system has resulted in the creation of centralized administrative databases which comprehensively captures information about hospital discharges, physician billing claims, and prescription medication dispensations, as well as demographics, registration, and vital statistics. These databases have low rates of missing data and high accuracy [16–18].

The population-based clinical bone mineral density (BMD) registry records information related to all bone densitometry services in the province (completeness and accuracy ≥ 99%) [19]. The BMD registry was linked at the individual level with other population-based provincial health care data held by the Manitoba Centre for Health Policy Data Repository via an encrypted personal health number.

The current study was based on bone densitometry services provided between April 1, 1996, and March 31, 2013, under a province-wide bone densitometry program [20]. The study was approved by the Human Research Ethics Board of the University of Manitoba. Data access permission was obtained from the Manitoba Health Information Privacy Committee.

Study population

This was a retrospective cohort study. Figure 1 displays a schematic presentation of the study design. The study population consisted of women who were at least 40 years of age with a baseline BMD test between April 1, 1996, and March 31, 2013. Subjects must have had continuous health care coverage for at least 3 years prior to the baseline BMD test with a previous diagnosis of asthma or COPD, and have remained registered with the health care system for at least 12 months after the baseline BMD test. The previous diagnosis of asthma and COPD was identified by the presence of one or more hospitalizations or two or more physician claims with relevant diagnostic codes during the 3-year period prior to the baseline BMD test. Asthma-specific inpatient and outpatient encounters were determined based on International Classification of Diseases, 9th Revision (ICD-9) codes of 493.x and ICD, 10th Revision (ICD-10) codes of J45.x, J46.x. COPD-specific encounters were determined by ICD-9 codes of 491.x, 492.x, 493.x, 496.x, and ICD-10 codes of J43.x, J44.x. The major respiratory diagnosis for each patient was determined based on the majority of diagnosis codes. Each patient was followed from the *index date*, defined as the date of baseline BMD measurement, until the date of the first non-traumatic fracture, death, migration, or end of study period, whichever came first.

Assessment of incident fractures

The primary outcome was the time to first incident non-traumatic fracture of the hip, clinical vertebral, humerus, or forearm (collectively designated "major osteoporotic" fractures). The secondary outcome was the time to first incident non-traumatic clinical vertebral fracture. We assessed Manitoba Health records for presence of major osteoporotic fractures using previously validated algorithms [21], and identified any diagnosis of clinical fragility fractures not associated with trauma codes from hospital discharge abstracts and physician billing claims. We required that hip and forearm fracture codes be associated with site-specific fracture reduction, fixation, or casting codes, to enhance specificity for an acute fracture event. To minimize misclassification of prior incident fracture, we conservatively required that there be no hospitalization or physician visits with the same type of fracture in the 6 months preceding an incident fracture diagnosis.

Assessment of ICS use

All exposure measures were obtained from the provincial pharmacy system using data from the Drug Program

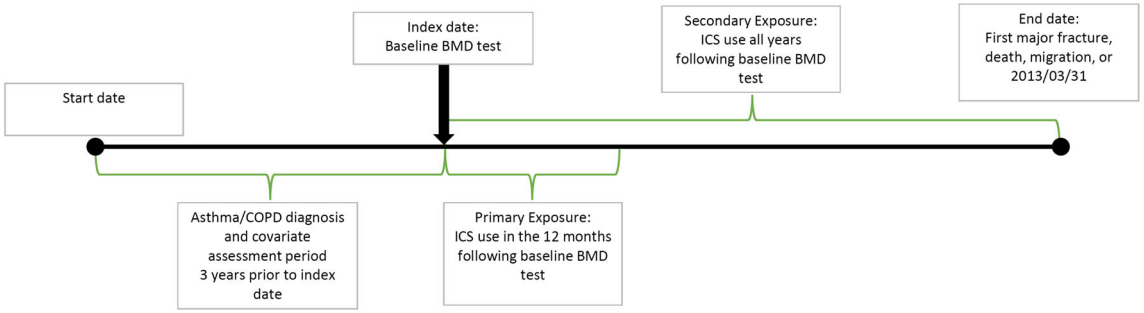

Fig. 1 Schematic representation of study design. BMD bone mineral density, COPD chronic obstructive pulmonary disease, ICS inhaled corticosteroids

Information Network. The definition of ICS exposure considered both the duration and amount to comprehensively capture its effects and included exposure to any drug within the ICS class, converted to mcg of beclomethasone equivalent according to relative anti-inflammatory activity [22]. The primary exposure was the total use of ICS within the 12 months following the index date, characterized by total dispensed days and total dispensed quantity, where the latter was expressed in mcg of beclomethasone equivalent. The secondary exposure was ICS use following the index date until the end of follow-up. The secondary exposure was again measured by both duration and quantity of use. The intensity of exposure was expressed as the medication possession ratio (MPR), calculated as the proportion of days a patient was on ICS divided by the total number of observed days for that patient [23]. The quantity of use was calculated as the yearly dispensed quantities in mcg/year of beclomethasone equivalent.

For each exposure definition, ICS use was classified into four categories: no use (reference), and lowest, middle, and highest tertile.

Statistical analyses

All analyses were performed with Dell Statistica (Version 13.0, Dell Inc. 2015). A 2-sided p value of 0.05 was set as the threshold for assessing statistical significance.

We used Cox proportional hazards models to estimate the association between ICS use following the baseline BMD test and the long-term rates of major osteoporotic fracture (primary outcome) and clinical vertebral fracture (secondary outcome). We reported hazard ratios (HRs) and 95% confidence intervals for change in fracture rates, and performed type 3 tests to examine the overall effects across different levels of the exposure variable. The analyses were adjusted for baseline confounding factors between ICS use and bone loss, including the major respiratory diagnosis (COPD or asthma) and two indices of respiratory disease severity: the number of asthma/COPD-related hospitalizations, and the number of asthma/COPD-related medical claims, all in the 3 years prior to the index date. In addition, we further adjusted for fracture risk factors as used by the validated Fracture Risk Assessment Tool (FRAX®) tool [24], which is based on well-established risk factors including age, body mass index (BMI), self-reported parental hip fracture, current smoking, femoral neck T-score, diagnosis of rheumatoid arthritis (confirmed by one or more hospitalizations or two or more physician claims), and high alcohol intake (defined as alcohol/substance abuse ICD diagnosis). All these variables were measured in the 3 years prior to the index date, as well as prior non-traumatic major fractures since 1987. Finally, we adjusted for the intensity of oral corticosteroid and anti-osteoporosis medication use during the exposure assessment period for the primary analysis (first year following the index date) and secondary analysis (all observation years following the index date). These anti-osteoporosis medications were bisphosphonates, calcitonin, systemic estrogen products, raloxifene, and teriparatide, classified according to dispensed days (none, lowest, middle, and highest tertile).

Results

We included 6880 older women (62.1% COPD, 37.9% asthma) with characteristics shown in Table 1. The mean age on the index date was 64.6 (SD = 11.1), and the average follow-up time was 7.7 years (SD = 3.9). ICS medications were used in 40.2% of patients in the year following the index date and in 59.6% of patients at some point during follow-up (Table 1). Oral corticosteroid and anti-osteoporosis medication use was identified in 20.1% and 48.4% of participants in the first year following the index date, and in 48.1% and 57.7% at some point following the index date, respectively. A major osteoporotic fracture was confirmed in 810 (11.8%) participants during the study period, including 228 (3.3%) vertebral, 239 (3.5%) hip, 157 (2.3%) humerus, and 302 (4.4%) forearm (Table 1).

Primary outcomes: risk of major osteoporotic fracture

Table 2 presents adjusted HRs of the association between ICS use in the first year following the index date and long-term risk of major osteoporotic fracture.

Compared to participants with no ICS use, there were no significant differences in the risk of major osteoporotic fractures

Table 1 Descriptive characteristics of the study sample

	Overall sample ($N = 6880$)
Diagnosis, n%	
COPD	4275 (62.1)
Asthma	2605 (37.9)
Observation time, years	7.7 (3.9)
Age at baseline, years	64.6 ± 11.1
BMI, kg/m^2	27.9 ± 6.2
Prior fracture, n%	1119 (16.3)
Rheumatoid arthritis, n%	295 (4.3)
High alcohol intake, n%	371 (5.4)
Current smoker, n%	881 (12.8)
Parental hip fracture, n%	592 (8.6)
ICS use in the first year following baseline BMD test, n%	2765 (40.2)
Osteoporosis drug use in the first year following baseline BMD test, n%	3331 (48.4)
OCS use in the first year following baseline BMD test, n%	1380 (20.1)
ICS use during all years following baseline BMD test, n%*	4099 (59.6)
Osteoporosis drug use during all years following baseline BMD test, n%*	3972 (57.7)
OCS use during all years following baseline BMD test, n%*	3307 (48.1)
Incident major osteoporotic fractures, n%*	810 (11.8)
Incident clinical vertebral fractures, n%	228 (3.3)

Values are mean ± standard deviation or *n* (%)

BMD bone mineral density, *BMI* body mass index, *COPD* chronic obstructive pulmonary disease, *ICS* inhaled corticosteroids, *MPR* medication possession ratio, *OCS* oral corticosteroids

*Measured from the baseline bone mineral density test until end of follow-up

for any tertile of ICS dispensed days measured during the first year following the index date (overall $p = 0.90$, vs no use, HR [95% CI], lowest tertile, 1.07 [0.86, 1.32], middle tertile, 1.06 [0.84, 1.35], highest tertile, 1.08 [0.85, 1.36]). In contrast, the highest tertile of OCS use in the first year following the index date was associated with a 57% increased risk of major osteoporotic fracture (Supplementary Table 1, HR 1.57 [1.22, 2.02]). Of note, our results were unaffected by the respiratory diagnosis (interaction between ICS use and disease diagnosis, $p = 0.50$). Between the two indices of disease severity, previous asthma- or COPD-related medical claims were not associated with the outcome (overall $p = 0.83$). On the other hand, greater number of hospitalizations for asthma and/or COPD in the preceding 3 years was associated with an increased risk of major osteoporotic fracture (overall $p = 0.03$).

Similarly, ICS dispensed quantity across all tertiles, measured during the first year following the index date, was not associated with a significantly elevated risk of major osteoporotic fracture as compared with participants with no ICS use (overall $p = 0.67$, vs no use, HR [95% CI], lowest tertile, 1.05 [0.84, 1.30], middle tertile, 1.03 [0.82, 1.29], highest tertile, 1.17 [0.91, 1.49]).

Table 3 presents the association between long-term ICS use during follow-up and the risk of major osteoporotic fracture.

There were no significant differences in risk of major osteoporotic fractures between the lowest, middle, and highest tertiles of ICS exposure over all observation years following the index date compared to participants with no ICS use (overall $p = 0.62$, vs no use, HR [95% CI], lowest tertile, 1.02 [0.84, 1.26], middle tertile, 1.14 [0.93, 1.41], highest tertile, 1.05 [0.84, 1.32]). In comparison, the highest tertile of OCS adherence was associated with a 32% increased risk of major osteoporotic fracture (Supplementary Table 3, HR 1.32 [1.08, 1.61]). Our results were unaffected by the respiratory condition diagnosis (interaction between ICS use and disease diagnosis, $p = 0.38$). Greater number of previous asthma- or COPD-related medical claims was not associated with the outcome (overall $p = 0.79$), but greater number of previous hospitalizations for asthma or COPD was associated with an increased risk of major osteoporotic fracture (overall $p = 0.02$).

Likewise, ICS use at different yearly quantities was not associated with a significantly elevated risk of major osteoporotic fractures compared with participants with no use (overall $p = 0.58$, vs no use, HR [95% CI], lowest tertile, 1.03 [0.84, 1.26], middle tertile, 1.15 [0.93, 1.42], highest tertile, 1.03 [0.82, 1.30]).

Secondary outcome: risk of vertebral fracture

Table 4 presents the effects of ICS use on clinical vertebral fractures. Compared to non-users, there were no significant differences in the risk of clinical vertebral fractures between

Table 2 Results of the adjusted Cox proportional hazards models of incident major osteoporotic fractures, by ICS use in the year following baseline bone mineral density test

	Major osteoporotic fracture†		
	HR (95% CI)	*p* value	*p* value (overall effect)
ICS dispensed days			
None	Referent		0.90
Lowest tertile	1.07 (0.86, 1.32)	0.56	
Middle tertile	1.06 (0.84, 1.35)	0.60	
Highest tertile	1.08 (0.85, 1.36)	0.54	
ICS dispensed quantity*			
None	Referent		0.67
Lowest tertile	1.05 (0.84, 1.30)	0.68	
Middle tertile	1.03 (0.82, 1.29)	0.81	
Highest tertile	1.17 (0.91, 1.49)	0.22	

HR hazard ratio, *ICS* inhaled corticosteroids

ICS dispensed days was categorized into tertiles (reference group no use): lowest tertile, 0–100, middle tertile 101–223, highest tertile > 223. ICS dispensed quantity was categorized into tertiles (reference group no use): lowest tertile, 0–54,793 mcg, middle tertile 54,794–164,384 mcg, highest tertile > 164,384 mcg. Results adjusted for age, BMI, self-reported parental hip fracture, current smoking, rheumatoid arthritis, high alcohol intake, prior fracture, femur neck T-score, respiratory diagnosis (COPD vs asthma) and severity indices, OCS use, anti-osteoporosis drug use (bisphosphonates, calcitonin, systemic estrogen products, raloxifene, teriparatide)

*ICS quantity calculated as beclomethasone equivalent

† Major osteoporotic fractures include clinical vertebral, hip, humerus, and forearm fractures

Table 3 Results of the adjusted Cox proportional hazards models of incident major osteoporotic fractures, by ICS use over all years following baseline bone mineral density test

	Major osteoporotic fracture†		
	HR (95% CI)	*p* value	*p* value (overall effect)
Exposure to ICS, MPR			
None	Referent		0.62
Lowest tertile	1.02 (0.84, 1.26)	0.82	
Middle tertile	1.14 (0.93, 1.41)	0.20	
Highest tertile	1.05 (0.84, 1.32)	0.65	
Yearly ICS quantity*			
None	Referent		0.58
Lowest tertile	1.03 (0.84, 1.26)	0.76	
Middle tertile	1.15 (0.93, 1.42)	0.19	
Highest tertile	1.03 (0.82, 1.30)	0.78	

HR hazard ratio, *ICS* inhaled corticosteroids, *MPR* medication possession ratio

Exposure to ICS was categorized into tertiles (reference group no use): lowest tertile, 0–0.13, middle tertile 0.14–0.49, highest tertile > 0.49. Yearly ICS quantity was categorized into tertiles (reference group no use): lowest tertile, 0–30,227 mcg/year, middle tertile 30,228–133,159 mcg/year, highest tertile > 133,159 mcg/year. Results adjusted for age, BMI, self-reported parental hip fracture, current smoking, rheumatoid arthritis, high alcohol intake, prior fracture, femur neck T-score, respiratory diagnosis (COPD vs asthma) and severity indices, OCS use, anti-osteoporosis drug use (bisphosphonates, calcitonin, systemic estrogen products, raloxifene, teriparatide)

*ICS quantity calculated as beclomethasone equivalent

† Major osteoporotic fractures include clinical vertebral, hip, humerus and forearm fractures

the lowest, middle, and highest tertiles of ICS use measured in the first year following the index date (dispensed days $p = 0.73$, dispensed quantities $p = 0.67$), or ICS use over all observation years following the index date (MPR $p = 0.56$, yearly quantities $p = 0.65$).

Discussion

In this retrospective cohort study of older women with asthma and/or COPD, we investigated the association between ICS use at a wide range of doses, in terms of both days of use and dispensed quantity, and the long-term risk of major osteoporotic fracture. ICS use, at all intensities of days use or dispensed dose, was not associated with an increased fracture risk compared to not using ICS. Our results were controlled for potential confounders including disease severity indices, age, BMI, parental hip fractures, smoking status, femoral neck T-score, diagnosis of rheumatoid arthritis, high alcohol intake, prior fractures, and oral corticosteroid and anti-osteoporosis medications. These findings complement our previous study using similar methodology, which found that the highest tertile of ICS exposure was associated with a modest reduction in hip bone density in older women with asthma and COPD, without adverse effects from low to moderate ICS exposure [25].

Our results are generally in line with previous studies [9, 13, 14, 26]. Gonzalez and colleagues [14] studied the long-term use of ICS in COPD patients and found that, consistent with our findings, "any" ICS use was not associated with an increased rate of fracture in men and postmenopausal women. However, prolonged ICS use (≥ 4 years) at high doses (≥ 1000 μg in fluticasone equivalents) was associated with a 10% increase in hip or upper extremity fracture. This inconsistency may be due to differences in patient composition, as their study population was older at baseline compared to our study (≥ 65 vs ≥40 years). Also, our analysis adjusted for additional confounders including parental hip fractures, BMI, high alcohol use, smoking status, and femoral T-neck score. Of note, our study cohort had a relatively higher prevalence of anti-osteoporosis medication use (48%) compared to Gonzalez and colleagues [14] (7% bisphosphonate and 6% calcium/vitamin D). Thus, not observing an increase in fracture risk at higher intensities of ICS use could in part reflect protective effects of concomitant anti-osteoporosis treatments. On the other hand, a meta-analysis on ICS use and fracture

Table 4 Results of the adjusted Cox proportional hazards models of incident clinical vertebral fractures, by ICS use following baseline bone mineral density test

	Vertebral fracture		
	HR (95% CI)	*p* value	*p* value (overall effect)
ICS use in the first year following baseline BMD test[†]			
ICS dispensed days			
None	Referent		0.73
Lowest tertile	0.99 (0.65, 1.51)	0.96	
Middle tertile	1.14 (0.74, 1.79)	0.54	
Highest tertile	1.24 (0.82, 1.89)	0.31	
ICS dispensed quantity*			
None	Referent		0.67
Lowest tertile	1.07 (0.71, 1.62)	0.75	
Middle tertile	1.02 (0.66, 1.58)	0.94	
Highest tertile	1.30 (0.84, 2.01)	0.24	
ICS use during all years following baseline BMD test[‡]			
Exposure to ICS, MPR			
None	Referent		0.56
Lowest tertile	0.79 (0.52, 1.18)	0.24	
Middle tertile	0.84 (0.56, 1.27)	0.41	
Highest tertile	0.99 (0.66, 1.50)	0.98	
Yearly ICS quantity*			
None	Referent		0.65
Lowest tertile	0.82 (0.55, 1.22)	0.33	
Middle tertile	0.82 (0.54, 1.24)	0.35	
Highest tertile	0.96 (0.64, 1.45)	0.86	

HR hazard ratio, *ICS* inhaled corticosteroids, *MPR* medication possession ratio

*ICS quantity calculated as beclomethasone equivalent

[†] ICS dispensed days was categorized into tertiles (reference group no use): lowest tertile, 0–102, middle tertile 103–223, highest tertile > 223. ICS dispensed quantity was categorized into tertiles (reference group no use): lowest tertile, 0–54,793 mcg, middle tertile 54,794–164,384 mcg, highest tertile > 164,384 mcg. Results adjusted for age, BMI, self-reported parental hip fracture, current smoking, rheumatoid arthritis, high alcohol intake, prior fracture, femur neck T-score, respiratory diagnosis (COPD vs asthma) and severity indices, OCS use, anti-osteoporosis drug use (bisphosphonates, calcitonin, systemic estrogen products, raloxifene, teriparatide)

[‡] Exposure to ICS was categorized into tertiles (reference group no use): lowest tertile, 0–0.13, middle tertile 0.14–0.49, highest tertile > 0.49. Yearly ICS quantity was categorized into tertiles (reference group no use): lowest tertile, 0–30,227 mcg/year, middle tertile 30,228–133,159 mcg/year, highest tertile > 133,159 mcg/year. Results adjusted for age, BMI, self-reported parental hip fracture, current smoking, rheumatoid arthritis, high alcohol intake, prior fracture, femur neck T-score, respiratory diagnosis (COPD vs asthma) and severity indices, OCS use, anti-osteoporosis drug use (bisphosphonates, calcitonin, systemic estrogen products, raloxifene, teriparatide)

risk in COPD demonstrated a dose-dependent increase in fracture risk with long-term ICS exposure [9]; however, this finding was driven by a single large study in a male-predominant COPD population, and most of the other included studies showed a non-significant effect [9]. Further, the above-mentioned meta-analysis included studies that lacked adjustment for important baseline variables and potential effect modifiers, such as parental hip fractures, comorbidities, and anti-osteoporosis drug use. As for asthma, the majority of literature on ICS use and fracture risk is in pediatric and younger adult populations [13]. Although one study concluded ICS use was not associated with change in BMD in postmenopausal women with asthma [27], the study was limited by sample size and adjustment for a limited set of baseline risk factors. Our findings support the skeletal safety of long-term ICS use, regardless of the days of use and dispensed dose, in older women with asthma and COPD.

There are several strengths to this study. We used population-based registry-linked health administrative data in a unique patient population. The data combined population-based representation of administrative health data and nuanced information from a patient registry, limiting biases generated from self-reporting for diagnosis, prescription information, and outcome assessment, as well as minimizing the risk of confounding. We used several measures of ICS use intensity to establish the longitudinal association between ICS use and subsequent fracture risk. Further, we controlled for many risk factors that could affect both the exposure and outcome, which other studies could not include in their analyses [9, 13, 14].

On the other hand, our study has some limitations. First, prescription records derived from administrative health data may not equate with actual medication intake. However, while this concern is relevant for short-term prescription patterns, filling prescriptions over extended periods likely correlates with actual intake. Second, we only adjusted for disease severity indices based upon numbers of COPD/asthma hospitalizations and medical claims. We were unable to measure other indicators of disease severity such as pulmonary function, and as such, residual confounding by disease severity cannot be ruled out. However, residual confounding would be expected to generate positive associations between ICS use and fracture risk; as such, our negative findings are unlikely to be explained by disease severity. Third, we included older women referred for BMD measurement. Our sample may therefore overrepresent patients at risk for osteoporosis, which could result in conservative ICS and OCS prescribing, with greater use of anti-osteoporotic medications. Fourth, we acknowledge that the upper bounds of the 95% confidence interval are compatible with a modestly increased risk for fracture. Finally, administrative health care data do not capture information on the use of over-the-counter medications and supplements, such as calcium and vitamin D, which could modify fracture risk. Likewise, we could not assess the use of pulse corticosteroids, as medication use was aggregated by years.

In conclusion, our study adds to the few previous studies evaluating the impact of ICS use on fracture risk in older

women, particularly in asthma [13]. Overall, these results do not support an association between long-term ICS use across a range of intensities, in terms of both days of use and dispensed quantity, and an increase in major osteoporotic fracture risk in older women with asthma and/or COPD.

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Compliance with ethical standards

The study was approved by the Human Research Ethics Board of the University of Manitoba.

Conflicts of interest None.

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