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ORIGINAL ARTICLE

Long-term effects of inhaled corticosteroids on bone mineral density in older women with asthma or COPD: a registry-based cohort study

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Abstract

Summary We assessed the association between long-term inhaled corticosteroid (ICS) use and bone mineral density (BMD) in older women with chronic respiratory disease. Women with > 50% adherence to ICS use had very slightly accelerated BMD loss at the total hip compared with those with lower or ICS use.

Introduction This study evaluated the impact of long-term ICS therapy on bone loss in older women with asthma or chronic obstructive pulmonary disease (COPD).

Methods We used a population-based bone densitometry registry linked with administrative health data covering the province of Manitoba, Canada (1999–2013), to identify women aged > 40 years who had diagnosed asthma or COPD. ICS exposure was defined as cumulative dispensed days and medication possession ratio (MPR). Associations were examined both cross-sectionally and longitudinally, and results were covariate adjusted.

Results Among 6561 women with asthma and/or COPD (mean age 65 years [SD = 11]), compared to no ICS treatment, those in the highest tertile of prior ICS use (≥ 720 days) had lower BMD at the femoral neck (− 0.09 T-score, 95% CI − 0.16, − 0.02) and total hip (− 0.14 T-score, 95% CI − 0.22, − 0.05), but not at the lumbar spine. Over a mean of 5 years of follow-up, the highest tertile of ICS exposure (MPR > 0.5) was associated with a − 0.02 SD/year (95% CI − 0.04, − 0.01) greater decline in total hip BMD relative to non-users, with no significant effect at the femoral neck or lumbar spine. Middle and lower tertiles of ICS use were not associated with baseline or longitudinal change in BMD.

Conclusions The highest tertile of ICS use was associated with a slightly lower hip BMD at baseline and slightly greater reduction in total hip BMD over time in older women with asthma or COPD. No adverse effects on BMD were seen from low to moderate ICS exposure.

Keywords Women · Bone mineral density · Inhaled corticosteroids · Asthma · Chronic obstructive pulmonary disease · Osteoporosis

Wenjia Chen and Kate M. Johnson are co-first authors.

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Introduction

Inhaled corticosteroids (ICS) are the first-line of treatment for asthma. Through suppression of airway inflammation, ICS can control symptoms, prevent exacerbations, and improve quality of life in asthma patients [1]. ICS is also frequently used in patients with chronic obstructive pulmonary disease (COPD). The benefits of ICS in these patients are less well established, but it has been shown to reduce exacerbations in moderate to severe COPD, especially in combination with a long-acting beta agonist [2, 3].

Despite its efficacy and common usage, the safety of long-term ICS use remains contentious. Systematic reviews have suggested an increased risk of fractures in long-term ICS users with COPD [4], but not in children and young adults with asthma [5]. The relationship between ICS and bone mineral density (BMD) is generally found to be dose-dependent [6–8]; however, the dosage that is typically assessed is high. Further, the impact of ICS use on BMD is likely to depend on the age and sex of the patient [8–11]. COPD is a common chronic disease among the elderly, and older women with asthma suffer the highest burden of morbidity [12] while also constituting the vast majority of osteoporosis cases [13], thus the safety of ICS should be particularly elucidated in this potentially more susceptible population. However, the existing evidence in older women is limited to small studies [7, 14]. A population-based assessment of long-term ICS use, in terms of both duration and amount, on bone loss in older women with chronic respiratory diseases would be relevant from both a pathophysiological perspective and to clinicians making treatment decisions that must balance safety and efficacy. It may also help patients in making treatment decisions that require contrasting the safety of ICS to oral corticosteroids (OCS).

The objective of this study was to examine the impact of ICS on BMD loss in older women with asthma or COPD in routine clinical practice. We tested for dose-response associations both cross-sectionally and longitudinally. We hypothesized that among older women with asthma or COPD, BMD would be lower in those exposed to high-dose ICS as compared with unexposed women, and that BMD would decline more rapidly with increasing exposure to ICS.

Methods

Data sources

The province of Manitoba, Canada, provides universal health care to its population of 1.3 million residents [15]. The needs of maintaining the public health care system have resulted in the creation of centralized administrative health care databases, which comprehensively capture information about hospital discharges, physician billing claims, prescription medication dispensations, as well as demographics, registration, and vital statistics. These databases have low rates of missing data and high validity [16–18]. The current study was based on bone densitometry services provided between April 1, 1999 and March 31, 2013 under a province-wide bone densitometry program [19]. The population-based clinical BMD registry records information related to all bone densitometry services in the province (completeness and accuracy ≥ 99%) [20]. 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 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 retrospective cohort study had both cross-sectional and longitudinal components. Figure 1 displays the schematic presentation of the study design. The study population consisted of women who were at least 40 years of age, had continuous health care coverage for at least 3 years prior to undergoing their first BMD test, and had a previous diagnosis of asthma or COPD. These diagnoses were identified by the presence of one or more hospitalizations or two or more physician claims with diagnostic codes for asthma or COPD during the 3-year period prior to the first BMD test. Asthma-specific inpatient and outpatient encounters were determined based on International Classification of Diseases, 9th Edition (ICD-9) codes of 493.x, and 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 primary respiratory diagnosis for each patient was determined based on the majority of diagnosis codes. For each patient, the *index date* was defined as the date of first (baseline) BMD measurement.

Outcomes

The major sites for BMD measurement were at the femoral neck, total hip, and lumbar spine (L1–4). Femoral neck BMD is the reference standard for the description of osteoporosis diagnosis and for fracture risk assessment [21], while total hip BMD has the best test-retest precision and is the least affected by age-related degenerative artifact [22]. BMD testing was performed using dual-energy X-ray absorptiometry scans of the hip and spine with a pencil-beam instrument (Lunar DPX; GE Lunar, Madison WI, USA) prior to 2000 and fan-beam instruments (Lunar Prodigy or iDXA; GE Lunar) afterwards. The program's quality assurance is under

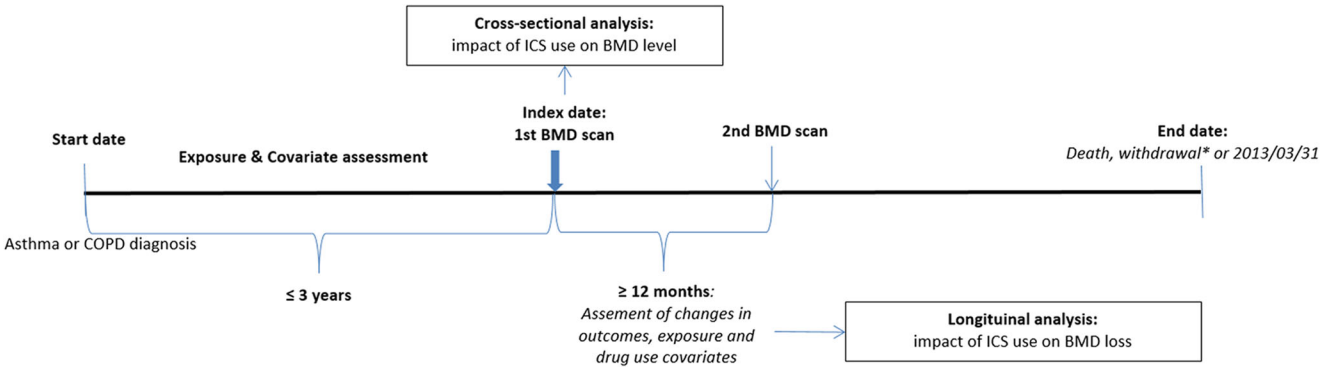

Fig. 1 Schematic study design. *BMD* bone mineral density, *COPD* chronic obstructive pulmonary disease, *ICS* inhaled corticosteroids

strict supervision by a medical physicist [19]. Instruments were cross-calibrated and no clinically significant differences were detected [20]. The instruments used for this study exhibited stable long-term performance (coefficient of variation < 0.5%). All reporting physicians and supervising technologists are required to maintain DXA certification with the International Society for Clinical Densitometry (ISCD).

The first analysis examined the association between prior ICS exposure and BMD at baseline (cross-sectional analysis). The dependent variable was BMD T-score (i.e., the number of standard deviations above or below the mean of a healthy young adult white female [23]). Hip T-scores were calculated using U.S. National Health and Nutrition Examination Survey (NHANES) III reference values [21]. Lumbar spine T-score were calculated using manufacturer's reference data [24]. In the subset of the sample with a second bone scan at least 12 months apart from the baseline scan, we performed a second analysis to examine the change in BMD between the first and second scans (longitudinal analysis). For consistency with the cross-sectional analysis, BMD loss per year was expressed as the change in BMD T-score divided by the time in years between the two scans.

Exposures

All exposure measures were obtained from the provincial pharmacy system using data from the Drug Program Information Network (DPIN) [17]. The definition of ICS exposure considered both the duration and amount to comprehensively capture its effects. For the cross-sectional analysis, we measured the total dispensed ICS days (i.e., duration, the primary exposure) as well as total dispensed ICS quantity in μg of beclomethasone-equivalent (i.e., amount, the secondary exposure) prior to the first BMD scan. For the longitudinal analyses, the dispensed days of ICS between the first and second BMD scans (primary exposure) was expressed as the medication possession ratio (MPR), defined as the proportion of days a patient was on ICS divided by the total number of observed days for that patient. Additionally, we measured the dispensed quantity of ICS between the two scans (secondary exposure) normalized for time by dividing by the time interval between the two scans. As such, both longitudinal exposure variables were independent of the length of the time window. For each exposure definition, ICS use was classified into four categories: no use (referent), lowest, middle, and highest tertile (for ICS users).

The cross-sectional and longitudinal analyses were adjusted for baseline factors that could affect bone loss, including the primary respiratory diagnosis (COPD or asthma) and its severity (the number of asthma/COPD-related hospitalizations and physician visits in the 3 years prior to the index date). We also adjusted for fracture risk factors as characterized by the Fracture Risk Assessment Tool [25] and measured on the index date (age, body mass index, self-reported parental hip fracture, current smoking), as well as diagnoses from ICD codes (one or more hospitalizations or two or more physician claims) for rheumatoid arthritis or high alcohol intake (defined as alcohol/substance abuse diagnosis) in the 3 years prior to the index date, or prior non-traumatic major fracture since 1987 (using validated national surveillance definitions [26, 27]). Finally, we adjusted for the total number of dispensed days of oral corticosteroids and anti-osteoporosis medication use (bisphosphonates, calcitonin, systemic estrogen products, raloxifene, teriparatide) measured in the 3 years prior to the index date for the cross-sectional analysis, or as the total days of use between the first and second BMD scan for the longitudinal analysis. We classified medication use into four groups: none, lowest, middle, and highest tertile for both analyses. Although we adjusted for oral corticosteroid use, this study was not designed to assess the impact of oral corticosteroids on BMD loss because a previous study using the same provincial bone densitometry registry has already investigated this question [28].

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.

In the cross-sectional analysis, we used analysis of covariance (ANCOVA) to estimate the association between prior ICS exposure and baseline BMD T-scores for the femoral neck, total hip, and lumbar spine sites. Separate analyses were conducted for the primary (total dispensed days) and secondary (total dispensed quantity) ICS exposure indicators. We tested for an interaction between disease diagnosis (COPD or asthma) and ICS use on BMD loss in an exploratory analysis.

In the longitudinal analysis, we repeated the ANCOVA on the annualized change in BMD between the first and second BMD tests (expressed as T-score/year for consistency with the cross-sectional analysis), and examined the effects of both primary (MPR) and secondary (time-normalized dispensed quantity) exposures. Separate analyses were performed for changes across all three BMD measurement sites.

Sensitivity analysis

To eliminate the effects of bone-protective medications, we repeated the longitudinal analyses in the subgroup of individuals who did not have any estrogen or osteoporosis medication exposure during the observation period.

Results

Cross-sectional analysis of ICS exposure and BMD

The study sample included 6561 older women, 63% with a primary diagnosis of COPD and 37% with a primary diagnosis of asthma, respectively (Table 1). The average age at baseline was 65.2 years (SD = 10.8). Approximately 51% of patients had received ICS therapy prior to BMD testing. These patients were divided into three tertiles based on total days of usage (lowest tertile 1–155 days of use, middle 156–719 days, highest ≥ 720 days). Compared to ICS users, women who did not use ICS prior to the first BMD scan were significantly more likely to have a primary diagnosis of COPD rather than asthma (86 vs 47%), had lower body mass index (27.2 vs 28.6 kg/m^2), a higher prevalence of smoking (26 vs 18%) and lower baseline BMD measurements (Appendix Table 1). Additionally, half (50%) of the patients had also used oral corticosteroids. The mean T-scores for the femoral neck, total hip, and lumbar spine at baseline were − 1.5, − 1.0, and − 1.1, respectively. Based on the lowest score across all sites, osteoporosis was present in 31% of patients at baseline.

For the primary exposure, the highest tertile of days of ICS use (≥ 720 days) was associated with lower T-scores in the femoral neck and total hip (− 0.093 [95% CI − 0.163, − 0.023, $p = 0.009$], − 0.136 [95% CI − 0.219, − 0.052, $p = 0.001$], respectively), but not the lumbar spine (type III analysis of overall effects, $p = 0.12$), compared with non-users after adjustment for oral corticosteroid use and other covariates (Fig. 2). The BMD effects associated with the lowest and middle tertiles of ICS days were not significantly different

Table 1 Descriptive characteristics of the study sample for the cross-sectional analysis

	Overall sample ($N = 6561$)
Diagnosis, *n%*	
COPD	4110 (62.6)
Asthma	2451 (37.4)
Disease severity: hospitalizations, *n%*	
0	5556 (84.7)
1	691 (10.5)
≥ 2	314 (4.8)
Disease severity: physician claims, *n%*	
0–2	2234 (34.0)
3–5	2517 (38.4)
≥ 6	1810 (27.6)
Age, years	65.2 ± 10.8
Body mass index, kg/m^2	28.0 ± 6.3
Prior fracture, *n%*	1119 (17.1)
Rheumatoid arthritis, *n%*	251 (3.8)
High alcohol intake, *n%*	380 (5.8)
Current smoker, *n%*	936 (21.1)
Parental hip fracture, *n%*	565 (12.7)
Days of prior ICS use, *n%*	
None	2626 (40.0)
Lowest tertile (1–155 days)	1323 (20.2)
Middle tertile (156–719 days)	1301 (19.8)
Highest tertile (> 719 days)	1311 (20.0)
Quantities of prior ICS use[a], *n%*	
None	2626 (40.0)
Lowest tertile (1–160,000 μg)	1351 (20.6)
Middle tertile (160,001–840,000 μg)	1273 (19.4)
Highest tertile (> 840,000 μg)	1311 (20.0)
Days of prior OCS use, *n%*	
None	3274 (49.9)
Lowest tertile (1–90 days)	1149 (17.5)
Middle tertile (91–365 days)	1052 (16)
Highest tertile (> 366 days)	1086 (16.6)
Any osteoporosis drug use	3427 (52.2)
Lumbar spine T-score	− 1.1 ± 1.5
Femoral neck T-score	− 1.5 ± 1.0
Total hip T-score	− 1.0 ± 1.3
Minimum site osteoporotic[b]	2050 (31.2)

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

COPD chronic obstructive pulmonary disease, *ICS* inhaled corticosteroids, *OCS* oral corticosteroids

[a] ICS quantities were calculated as beclomethasone equivalent

[b] Osteoporosis was defined as − 2.5 or lower in T-scores based on the minimum T-score obtained from the three sites

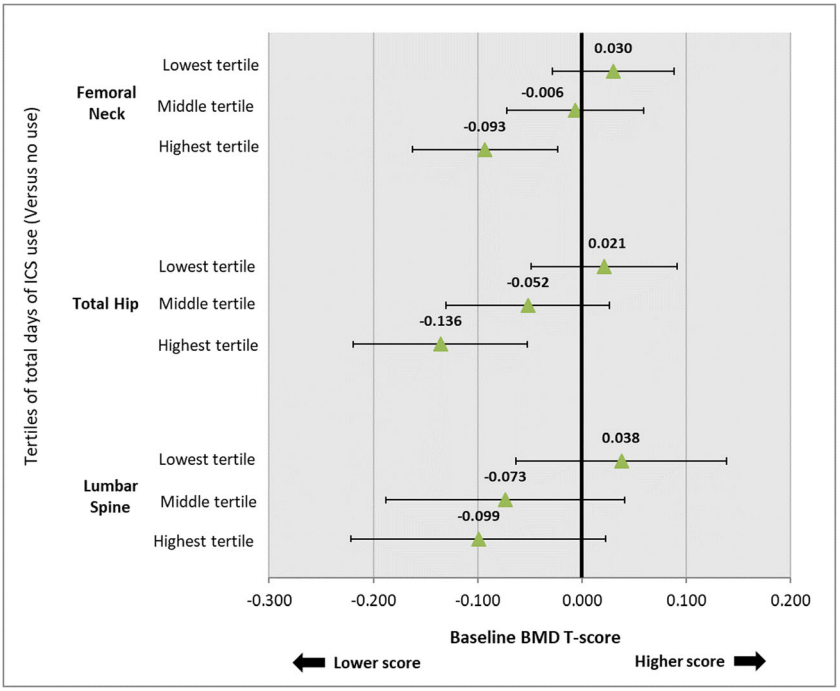

Fig. 2 Cross-sectional association between prior inhaled corticosteroid (ICS) exposure and baseline bone mineral density (BMD) T-scores for the (top) femoral neck, (middle) total hip, and (bottom) lumbar spine. Total number of dispensed days of ICS was categorized into tertiles (reference group no use): lowest tertile 1–155 days, middle tertile 156–719 days, highest tertile ≥ 720 days. Results are covariate adjusted. Error bars are 95% confidence intervals

from non-users for the three measurement sites. Although unadjusted baseline BMD was lower in patients with COPD as the primary diagnosis compared with asthma (Appendix Table 2), the effect of prior ICS exposure on baseline T-scores was similar ($p = 0.52$ for the interaction term between diagnosis and ICS use).

Similar effects were seen for the secondary exposure: the highest tertile of total dispensed ICS quantity (> 840,000 μg of beclomethasone-equivalent) was associated with lower baseline T-scores for the femoral neck (− 0.092 [95% CI − 0.164, − 0.023, $p = 0.006$]) and total hip (− 0.150 [95% CI − 0.234, − 0.065, $p < 0.001$]), but not for the lumbar spine ($p = 0.110$), compared to no use after adjustment for oral corticosteroid use and other covariates. The middle and lowest tertiles of total dispensed ICS quantity were not associated with BMD loss for the three measurement sites.

Longitudinal analysis of ICS exposure and BMD

From the overall sample, we identified 1807 women (59% COPD, 41% asthma) who received a second BMD scan at least 12 months after the baseline scan (Table 2). The average time interval between the first and second scans was 4.8 years (SD = 2.4). ICS were used in 51% of patients between the two scans, with each tertile of ICS MPR comprising 17% of patients (lowest < 0.16, middle 0.16–0.50, highest > 0.50). Oral corticosteroid exposure was identified in 38% of subjects during the same period. Mean femoral neck and total hip T-scores decreased between the two scans (− 0.027 T-score/year and − 0.025 T-score/year, respectively), but lumbar spine T-score increased (+ 0.011 T-score/year) (Table 2). Unadjusted hip BMD loss was not affected by the primary diagnosis, but the increase in spine BMD was greater among those with COPD compared with asthma (Appendix Table 2).

For the primary exposure, Fig. 3 shows the longitudinal change in BMD T-scores across tertiles of ICS exposure adjusted for other covariates. Compared to no use, the highest tertile of ICS MPR was associated with a significant decline in total hip T-score (− 0.024 T-score/year [95% CI − 0.040, − 0.008], $p = 0.003$), whereas the lowest and middle tertiles of MPR had no significant effects. The highest tertile of MPR also led to a borderline decline in lumbar spine T-score (− 0.024 T-score/year [95% CI − 0.047, 0.000], $p = 0.050$), although overall the effect was not significant in a type III analysis of effects ($p = 0.25$). The lower and middle tertiles of MPR again had no effect. The effect of ICS exposure on longitudinal bone loss across the three measurement sites did not significantly differ in patients with COPD compared with asthma (*p*-values for the interaction term between diagnosis and ICS use: total hip 0.33, lumbar spine 0.30, femoral neck 0.08).

Similar effects were seen for the secondary exposure: only the highest tertile of dispensed ICS quantity (> 124,875 μg/year of beclomethasone equivalent) was associated with BMD decline in total hip compared to no use (− 0.020 T-score/year [95% CI − 0.035, − 0.004], $p = 0.016$) after adjustment for oral corticosteroid use and other covariates, whereas ICS quantity

Table 2 Descriptive characteristics of the subsample for the longitudinal analysis

	Longitudinal subsample ($N = 1807$)
Diagnosis, *n%*	
COPD	1066 (59.0)
Asthma	741 (41.0)
Disease severity: hospitalizations, *n%*	
0	1614 (89.3)
1	139 (7.7)
≥ 2	54 (3.0)
Disease severity: physician claims, *n%*	
0–2	647 (35.8)
3–5	678 (37.5)
≥ 6	482 (26.7)
BMD interval, years	4.8 ± 2.4
Age, years	63.2 ± 9.9
Body mass index, kg/m^2	27.4 ± 5.9
Prior fracture, *n%*	271 (15.0)
Rheumatoid arthritis	63 (3.5)
High alcohol intake	90 (5.0)
Current smoker	262 (15.6)
Parental hip fracture	240 (14.3)
Adherence to ICS, MPR, *n%*	
None	890 (49.3)
Lowest tertile (≤ 0.16)	302 (16.7)
Middle tertile (0.17–0.50)	303 (16.8)
Highest tertile (> 0.50)	301 (16.7)
Yearly ICS quantities[a], *n%*	
None	890 (49.3)
Lowest tertile (1–30,897 μg/year)	302 (16.7)
Middle tertile (30,898–124,785 μg/year)	302 (16.7)
Highest tertile (> 124,785 μg/year)	302 (16.7)
Adherence to OCS, MPR, *n%*	
None	1127 (62.4)
Lowest tertile (< 0.008)	235 (13.0)
Middle tertile (0.008–0.067)	213 (11.8)
Highest tertile (> 0.067)	221 (12.2)
Any osteoporosis drug use, *n%*	1113 (61.6)
Change in lumbar spine T-score/year	0.011 ± 0.156
Change in femoral neck T-score/year	− 0.027 ± 0.098
Change in total hip T-score/year	− 0.025 ± 0.112
Any OCS use, *n%*	680 (37.6%)

Values are mean ± standard deviation or n (%)

COPD chronic obstructive pulmonary disease, *ICS* inhaled corticosteroids, *MPR* medication possession ration, *OCS* oral corticosteroids

[a] ICS quantities were calculated as beclomethasone equivalent

had no significant effect on other sites or at lower tertiles of ICS quantity.

Sensitivity analysis: ICS effects in women with no use of bone-conserving medications

In a subsample of 800 women who had two BMD scans and did not use any estrogen or osteoporosis medications (mean age 62.3 years [SD = 10.0]), results remained consistent with the original analysis: compared to no use, the highest tertile of ICS MPR (≥ 0.5) was still associated with a similar loss in total hip BMD T-scores (− 0.026 T-score/year [95% CI − 0.051, 0.000], $p = 0.047$), but not in other sites or for lower tertiles of exposure. For the secondary exposure, the dispensed ICS quantity was no longer significantly associated with BMD change in any site or for any tertiles of exposure.

Discussion

Overall, only the highest tertile of ICS exposure was associated with bone loss in this population-based registry of older women with asthma or COPD. Our results are adjusted for the potentially confounding effects of respiratory disease diagnosis and severity, age, smoking, oral corticosteroids, and anti-osteoporosis medications. In the cross-sectional analysis, previous ICS use of more than 2 years and cumulative ICS exposure of more than 840,000 μg (beclomethasone equivalent) were both associated with approximately − 0.1 T-score lower BMD at the femoral neck and total hip. Longitudinally, high ICS use (MPR over 50% and above 124,875 μg per year) was associated with a − 0.02 T-score decline in total hip bone density. These effects are statistically significant but nonetheless relatively weak. This level of effect would need to be sustained for about 50 years to produce one standard deviation reduction in total hip BMD.

Our results are generally in line with previous observations of a dose-dependent relation between ICS use and BMD loss [6–8]. In general, the patients in our study were receiving low-dose ICS therapy; 85% of patients were dispensed less than five puffs (100 μg/puff) of beclomethasone-equivalent per day, although actual medication intake is likely even lower [29]. It is possible that the doses observed here were too low to have a strongly negative effect on BMD; however, our sample is likely to be representative of patients in routine clinical practice who are deemed to be at increased risk for osteoporosis due to a wide range of risk factors. Of note, the impact of ICS use on BMD also varied between bone sites. The hip was the only site at which we observed an effect in both the cross-sectional and longitudinal analyses. BMD at the lumbar spine was not significantly affected by ICS use in the cross-sectional analysis, but we observed a borderline effect of ICS use in the longitudinal analysis. These differences may be due to age-related degenerative changes, which are particularly common in the lumbar spine. For example, the mean

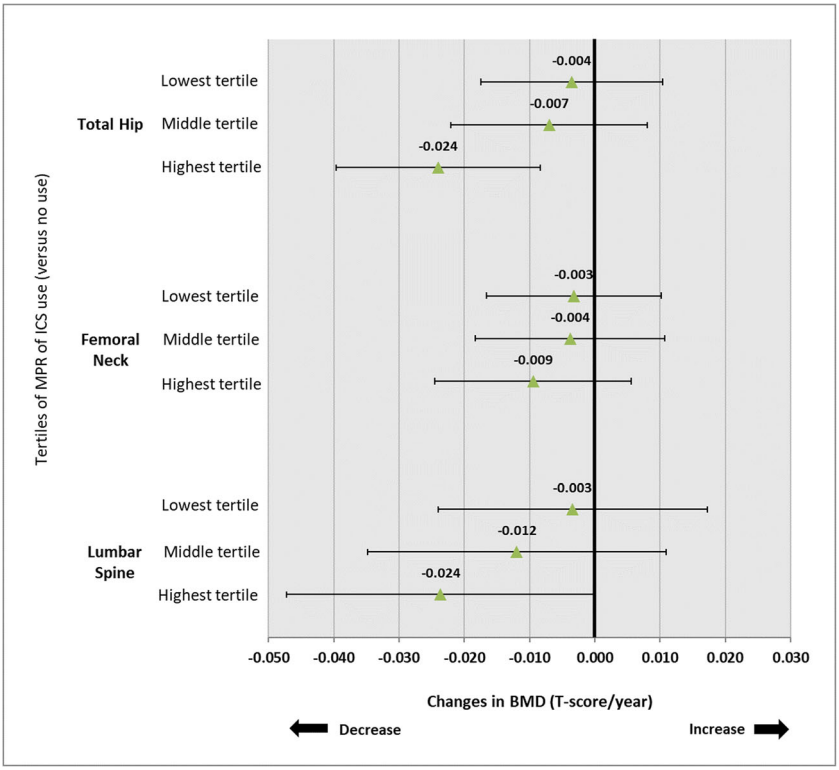

Fig. 3 Longitudinal effects of inhaled corticosteroid (ICS) medication possession ratio (MPR) on annualized changes in bone mineral density (BMD) T-scores for the (top) total hip, (middle) femoral neck, and (bottom) lumbar spine. MPR of ICS use was determined for the interval between the baseline and second BMD scan and categorized into tertiles (reference group no use): lowest tertile < 0.16, middle tertile 0.16–0.50, highest tertile > 0.50. Results are covariate adjusted. Error bars are 95% confidence intervals

lumbar spine T-score actually increased over the follow period, whereas mean T-scores at the other sites decreased.

Our findings indicate that long-term ICS use is unlikely to cause a clinically significant increase in osteoporosis in most patients. These results are in contrast to previous studies suggesting ICS may not be safe in older women [12, 14, 30]. However, those studies either did not control for confounding and were small in size [14], or did not take into account the effects of disease severity and historical oral corticosteroid exposure [30]. In fact, oral corticosteroids were almost as commonly used as ICS in our sample, and the use of oral corticosteroids is consistently shown to be associated with an increased fracture risk [28, 31, 32]. In this regard, routine use of ICS can be viewed as a safe substitute for oral corticosteroids in older women with asthma or COPD [33]. However, it is possible that the positive impact of ICS therapy on patient mobility and respiratory function offset its negative impact on BMD, resulting in a smaller effect that would have otherwise been observed. Testing this hypothesis would require a comparison of fracture risk among respiratory patients both with and without ICS use to healthy controls, as performed by van Staa et al. [34].

Our study has several strengths. First, both the cross-sectional and longitudinal analyses used a population-based registry, which offered a very robust sample size compared to previous studies [7, 14, 35]. The registry-based nature of the study sample reduces many issues associated with sample representativeness that are common in cohort studies, including low participation rates, self-selection, and participants lost to follow-up. In addition, ICS was objectively measured using a prescription drug database, which eliminates bias due to self-reporting. To the best of our knowledge, our study is the first to apply a longitudinal design to a registry-based sample to assess the association between ICS use and BMD. Further, we determined the impact of ICS independent of well-established fracture risk factors, as well as other important predictors of bone density including smoking history and the use of osteoporosis drugs or oral corticosteroids. In addition, unobserved, time-fixed confounding effects were accounted for in the longitudinal analysis because BMD comparisons were made within patients, which support the causal effects of ICS use on progressive BMD loss.

However, our study also has several limitations. First, we were unable to perform adjustment for lung function or the level of systemic inflammation as potentially important confounders because these parameters were unavailable. These factors can change rapidly over time and might independently affect BMD. However, we did adjust for disease severity based on the intensity of resource use for respiratory conditions, which might account for part of the longitudinal variation in lung function and inflammation. Second, the overall sample consisted of older women for whom a BMD scan was requested by their physician, and the longitudinal subsample consisted of patients who received more than one scan. Thus, our sample might have preferentially selected patients who were at a greater osteoporosis risk and whose physicians were more

conservative about prescribing ICS as a result. If this bias exists, it would reduce the generalizability of our findings; however, it would also have resulted in a more homogeneous group of patients with a similar risk of fracture before considering ICS use. Third, the average follow-up time in the longitudinal analysis was 5 years, which might not be long enough to capture the cumulative effects of low-dose ICS use on BMD.

In conclusion, our study used cross-sectional and longitudinal designs with multiple confounder adjustments to show that long-term ICS use does not lead to clinically important bone decline in older women with asthma or COPD, particularly at low to moderate exposures. ICS is the cornerstone of disease management in asthma [36, 37], and it is associated with a reduction in exacerbations in certain subgroups of COPD patients [38]. As such, it is important to balance concerns for the safety of ICS therapy with its effectiveness, as improper disease management can result in exposure to more bone-damaging treatments, which is especially a concern in older women. Future studies should characterize the association between ICS use and the risk of fractures over a long follow-up period, as this is the final endpoint most relevant to the health of this population.

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Author contributions WDL, MS, and JMF formulated the study idea. WDL designed the study and performed all data analyses. JMF and MS contributed to the study design and interpretation of findings. WC and KJ wrote the first draft of the manuscript (they are co-first authors). All authors critically commented on the manuscript and approved the final version. WDL is the guarantor of the manuscript.

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Compliance with ethical standards

Conflict of interest JMF has served on advisory boards for Novartis, Pfizer, AstraZeneca, Boehringer-Ingelheim, and Merck. He has also been a member of speakers' bureaus for AstraZeneca, Boehringer-Ingelheim, Novartis, and Merck. He has received research funding paid directly to the University of British Columbia from AstraZeneca, GlaxoSmithKline, Boehringer-Ingelheim, Merck, Sanofi, and Novartis. Dr. FitzGerald is a member of the Global Initiative for Asthma (GINA) Executive and Science Committees. Dr. Sadatsafavi receives salary support from the Canadian Institutes of Health Research and Michael Smith Foundation for Health Research. WDL, MS, KJ, and WC have no conflicts to declare.

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