Risk of osteoporosis and fragility fractures in asthma due to oral and inhaled corticosteroids: Two population-based nested case-control studies.

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WORD COUNT: 3,149

ABSTRACT

Background

Inhaled (ICS) and oral (OCS) corticosteroids are used widely in asthma; however, the risk of osteoporosis and fragility fracture (FF) due to corticosteroids in asthma is not well-established.

Methods

We conducted two nested case-control studies using linked data from the Clinical Practice Research Datalink (CPRD) and Hospital Episode Statistics (HES) databases. Using an asthma cohort, we separately identified patients with osteoporosis or FF and gender-, age-, and practice-matched controls. Conditional logistic regression was used to determine the association between ICS and OCS exposure, and the risk of osteoporosis or FF. The prevalence of patients receiving at least one bisphosphonate was also calculated.

Results

There was a dose-response relationship between both cumulative dose and number of OCS/ICS prescriptions within the previous year, and risk of osteoporosis or FF. After adjusting for confounders, people receiving more OCS prescriptions (≥9 vs 0) had a 4.50 (95%CI: 3.21-6.11) and 2.16 (95%CI: 1.56-3.32) increased risk of osteoporosis and FF, respectively. For ICS (≥11 vs 0) the odds ratios were 1.60 (95%CI: 1.22-2.10) and 1.31 (95%CI: 1.02-1.68). The cumulative dose had a similar impact, with those receiving more OCS or ICS being at greater risk. The prevalence of patients taking ≥9 OCS and at least one bisphosphonate prescription was just 50.6% and 48.4% for osteoporosis and FF, respectively.

Conclusion

The findings suggest that exposure to OCS or ICS is an independent risk factors for bone health in patients with asthma. Steroid administration at the lowest possible level to maintain asthma control is recommended.

KEY MESSAGES

What is the key question?

- What is the impact of oral and inhaled corticosteroid treatment on osteoporosis and fragility fracture risk among people with asthma?

What is the bottom line?

- Exposure to OCS or ICS is an independent risk factor for bone health in patients with asthma. There is a clear dose-response relationship between cumulative dose and prescriptions of OCS/ICS, and risk of osteoporosis and fragility fractures.

Why read on?

- The use of ICS in asthma is likely to increase with the recent change in GINA guidance recommending combined long-acting-β_2-agonists with ICS at step 1 and the prescribing of OCS follows an upward trend. Additionally, current guidelines on asthma do not fully cover the management of bone comorbidities and no specific bone protection guidance is given. This large study using primary and secondary care data provides pragmatic guidance to clinicians by stratifying bone health risk by dose, number of prescriptions, and type of OCS and ICS.

INTRODUCTION

Asthma is one of the most common chronic, non-communicable disease affecting around 334 million people worldwide.(1) Inhaled and oral corticosteroids play a crucial role in the control of airway inflammation in asthma.(2) The Global Initiative for Asthma (GINA) guidelines suggest a stepwise approach with low to high-dose ICS alone or in combination with long-acting-β_2-agonists as the first line treatment for patients with moderate to severe asthma, and use of OCS for patients experiencing exacerbations or having severe asthma.(3) Both ICS and OCS are known to cause well-recognised side effects.(4–7)

One of the most frequent adverse effects is osteoporosis which can lead to fragility fractures.(8–10) FF are associated with substantial increased health care costs, morbidity, and mortality.(11,12) Studies investigating the adverse effects of corticosteroids on bone health based on change in bone mineral density (BMD) in patients with asthma have contradictory findings. Laatikainen et al. did not find statistically significant differences in BMD between three groups of patients with asthma (ICS (n=26) vs OCS (n=65) vs non-exposed (n=28)).(13) Similarly, a 4-year longitudinal study assessing lumbar spine BMD in people with asthma receiving low (n=26) and high (n=9) dose of ICS as well as sporadic (n=26) and frequent (n=9) OCS did not reveal any change in BMD ($p > .05$).(14) This might be a result due to small sample size in both studies. In contrast, Wong et al. showed that cumulative dose of ICS (median, 876 mg) was negatively associated with BMD ($p < 0.05$) in young patients with asthma.(15) Sivri et al. also found a significantly lower BMD in female patients with asthma exposed to regular use of ICS (750 to 1500µg/d for at least 3 months).(16) Few studies have quantified the risk between corticosteroids and bone health in patients with asthma, mostly examining the effects of OCS.(17–19) However, these studies have been limited by their small size and focus on severe asthma.

Given that the use of ICS in asthma is likely to increase with the recent change in GINA guidance recommending combined long-acting-β_2-agonists with ICS at step 1 (3) and the upward trend in prescribing of OCS,(20) we sought to clarify the link between steroids,

osteoporosis and FF in patients with asthma stratifying the risk by dose, number of courses, and type of steroids.

METHODS

Source population

We conducted a population-based nested case-control study utilising the Clinical Practice Research Datalink GOLD, a large longitudinal primary care database,(21) linked to the Hospital Episode Statistics database.(22) We used the July 2018 dataset which covers more than 15.4 million patients from 738 practices across the UK. The percentage of patients is approximately 7% of the UK population and they are representative with respect to age, gender and ethnicity of the wider UK people. HES is a secondary care database consisting of all hospitalisations in England, consequently only 60% of CPRD patients have linked data. The study was approved by the Independent Scientific Advisory Group of the CPRD (ISAC protocol number 19_041RA).

Cohort definition

The study population included all adult patients (≥18 years old) with a Read code for asthma between 1st April 2004 (activation of Quality and Outcomes Framework score) to 31th December 2017, with at least 1 year of data collection prior to the diagnosis of asthma date ensuring that only 'incident' cases were picked.(23) We included patients classed as "acceptable" research quality data and registered to an up-to standard practice according to CPRD's recommendations.

Cases, controls, and outcomes definition

We conducted two nested case-control studies using CPRD linked HES data, with cases defined by the first-recorded diagnosis of 1) osteoporosis and 2) fragility fracture (as separate outcomes). The databases were linked using an identifier variable (same in both databases) called "patid", and then we looked for the earliest diagnosis in both databases by using either the Read or ICD-10 code, depending on the database. The date of the first diagnosis of 1) osteoporosis and 2) fragility fracture served as the index date for the cases. Each case was

matched with up to four randomly selected patients from the remaining patients with asthma by age (±1 year), gender and practice. We assigned the same index date to controls and cases.

Vertebral, hip, forearm-wrist, and humeral fractures are considered common sites of fragility fractures, and are associated with morbidity and mortality.(12,24) A composite of these fracture sites was used to define the presence of FF. Any fracture described as an “open fracture” was excluded, since this type usually occurs via a high-energy event, and is not related to frailty. The code list was reviewed by a clinician to identify appropriate fractures that were unlikely to be osteoporotic in nature.

Potential confounders

For each participant in this study, we retrieved information on the following variables which are well-established risk for fracture or thought to have an impact on osteoporosis or fracture risk and are also likely to be recorded within the databases: age at the index date; sex, including only those clearly classified as male or female; body mass index (BMI) using the nearest measurement prior the index date and categorised according to the World Health Organization (See Online Supplements); smoking and alcohol status using the nearest measurement ever prior to the index date (See Online Supplements); socioeconomic status measured by using the patient-level Index of Multiple Deprivation (IMD) 2015 in quintiles, with quintile 1 being the least and quintile 5 the most deprived; osteoporosis (only when the outcome was FF), any fracture (not those considered as an outcome) or falls prior the index date; bisphosphonates, Vitamin D and Calcium supplements the year prior the index date. The comorbidities were also summarised using the Charlson comorbidity index score.(25) If there was no record for a medication or diagnosis, patients were assumed to have not had the exposure.

Exposure assessment

Corticosteroid use was categorised in a number of ways. Initially, a 1-year period prior to index date was used to identify the exposure status. OCS and ICS use were examined as the number of prescriptions filled. It was not possible to categorise the OCS use by type since 97% of individuals received prednisolone. ICS was grouped according to type as follows: beclomethasone dipropionate, budesonide, fluticasone propionate, and ciclesonide. Where the type of ICS was changed during the year, we considered the most frequently prescribed. We also assessed the OCS and ICS as cumulative dose in milligrams (mg) over the previous year. To calculate the cumulative OCS and ICS dose, we used information from tablet strength (e.g. 5mg) or the dose of drug delivered with each inhalation (e.g. 0.1mg) and prescribed quantity, multiplying the quantity by strength for each prescription, and then all doses per patient were summed. We dealt with missing or implausible values using a recognised algorithm (See Online Supplements).(26) We additionally looked for the exposure in different time periods. Thus, the cumulative dose and number of OCS and ICS prescriptions were calculated as a rate per year, identifying prescriptions up to 10 years prior the index date (median patients' record time prior the index date), as well as from the asthma to the index date. The reference category for all analyses was no steroid exposure. To account for differences in potency of different types of corticosteroids, we converted dosages into prednisolone and beclomethasone equivalent for OCS and ICS, respectively (See Online Supplements).

Statistical analysis

Descriptive statistics were used to summarise the characteristics of the cases and controls. To account for the matched design, we used conditional logistic regression deriving unadjusted and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) assessing the effect of OCS and ICS exposure on the first osteoporosis and FF diagnosis after the asthma date, separately. Firstly, we performed a univariate analysis between the exposure and

outcome of interest to establish the unadjusted OR. Our *a priori* confounders were BMI and smoking status. The next step was to fit the conditional logistic regression model including the exposure of interest and the *a priori* confounders. Then we added into the model, one at a time, each of the other potential confounding variables, removing this potential confounder before adding the next. We examined how the OR of the exposure of interest changed as we added each potential confounder. If the inclusion of the confounder changed the effect of the exposure of interest by more than 5% then it was an important confounder and should be placed in the fully adjusted model. Missing data for BMI and smoking status were assumed as missing at random and imputed using chained equations. Ten imputations were generated, and the imputed model consisted of all listed confounders, OCS and ICS exposure, and the case-control indicator. Missing data for IMD were assigned a new category. The prevalence of those receiving at least one bisphosphonate (BP) prescription per steroid prescription category after their initiation the year prior to the index dates was also calculated. Sensitivity analyses was also conducted restring the samples only to patients with at least one ICS prescription the year prior to the index dates as a stricter definition of asthma as well as restricting the samples only to individuals not in receipt of OCS within the database records examining the relationship between ICS and bone comorbidities eliminating any confounding due to OCS. All analyses were performed in Stata v16.

RESULTS

Characteristics of the study populations

We identified 1,564 patients with asthma and osteoporosis, and 3,313 control subjects as well as 2,131 patients with asthma and fractures and 4,421 control subjects from a cohort of 69,074 people with asthma (Table 1, 2). The vast majority were women and the mean age were 69.4 years (range, 26-95 years) for osteoporosis and 66.4 years (range, 18-94 years) for fractures. Patients with asthma and both osteoporosis and fracture were more likely to smoke, had more comorbid illness, and were from a lower social class compared with control subjects. The cases were more likely to have a previous diagnosis of fall or fracture and had more prescriptions of bisphosphonates in the previous year than their controls.

Table 1. Characteristics of Patients with Osteoporosis and Control Subjects

Characteristic	Cases (N=1564) n (%)	Controls (N=3313) n (%)	Unadjusted OR (95%CI)
Age[a] (mean±SD), y	69.4±10.7	68.1±10.4	-
Sex			
Male	303 (19.4)	619 (18.7)	-
Female	1,261 (80.6)	2,694 (81.3)	-
Smoking status			
Never	584 (37.3)	1,438 (43.4)	1.00
Former	584 (37.3)	1,267 (38.3)	1.17 (1.02-1.35)
Current	381 (24.4)	574 (17.3)	1.95 (1.62-2.33)
Missing status	15 (01.0)	34 (1.0)	0.93 (0.37-2.32)
BMI status			
Underweight (<18.5)	76 (04.9)	48 (01.5)	2.25 (1.50-3.36)
Normal (18.5 - 24.9)	481 (30.7)	654 (19.7)	1.00
Overweight (25 - 29.9)	435 (27.8)	990 (29.9)	0.56 (0.47-0.67)
Obese (≥30)	322 (20.6)	1,099 (33.2)	0.39 (0.32-0.46)
Missing status	250 (16.0)	522 (15.8)	0.63 (0.51-0.79)
Alcohol status			
Non-drinker	187 (12.0)	323 (09.8)	1.00
Ex-drinker	181 (11.6)	402 (12.1)	0.81 (0.62-1.05)
Current drinker	1,052 (67.3)	2,315 (69.9)	0.85 (0.69-1.04)
Missing status	144 (9.2)	273 (8.2)	1.02 (0.76-1.37)
IMD (Social Class)			
1 (least deprived)	295 (18.9)	653 (19.7)	1.00
2	324 (20.8)	688 (20.8)	1.12 (0.91-1.40)
3	318 (20.3)	710 (21.4)	1.13 (0.90-1.41)
4	319 (20.4)	665 (20.1)	1.21 (0.96-1.53)
5 (most deprived)	306 (19.6)	597 (18.0)	1.36 (1.06-1.74)
Charlson comorbidity index			
1	717 (45.8)	1,847 (55.8)	1.00
2	258 (16.5)	523 (15.8)	1.27 (1.06-1.52)
3	274 (17.5)	447 (13.5)	1.51 (1.25-1.81)
4	151 (9.7)	250 (7.6)	1.54 (1.21-1.94)
≥5	164 (10.5)	246 (7.4)	1.62 (1.27-2.06)
Drug use in the year prior the index date			
Bisphosphonates	851 (54.5)	162 (4.9)	25.11 (19.38-32.53)
Vitamin D and/or Calcium	418 (26.8)	243 (7.3)	4.47 (3.69-5.40)
History of a diagnosis ever prior the index date			
Fall	450 (28.8)	575 (17.4)	1.95 (1.65-2.27)
Any fracture	478 (31.0)	533 (16.1)	2.38 (1.98-2.68)

Abbreviations: BMI, body mass index; IMD, Index of Multiple Deprivation.
Percentages have been rounded and might not total 100.
[a] Age at the index date.

Table 2. Characteristics of Patients with Fragility Fractures and Control Subjects.

Characteristic	Cases (N=2131) n (%)	Controls (N=4421) n (%)	Unadjusted OR (95%CI)
Age[a] (mean±SD), y	65.1±14.9	64.0±14.1	-
Sex			
Male	633 (29.8)	1,215 (27.5)	-
Female	1,497 (70.2)	3,206 (72.5)	-
Smoking status			
Never	813 (38.2)	1,870 (42.3)	1.00
Former	767 (36.0)	1,693 (38.3)	1.04 (0.92-1.18)
Current	513 (24.0)	806 (18.2)	1.53 (1.32-1.77)
Missing status	38 (01.8)	52 (01.2)	1.81 (0.94-3.49)
BMI status			
Underweight (<18.5)	79 (3.7)	62 (1.4)	2.28 (1.57-3.29)
Normal (18.5 - 24.9)	507 (23.8)	905 (20.5)	1.00
Overweight (25 - 29.9)	588 (27.6)	1,291 (29.2)	0.80 (0.68-0.93)
Obese (≥30)	538 (25.2)	1,389 (31.3)	0.72 (0.61-0.84)
Missing status	419 (19.6)	774 (17.5)	0.95 (0.80-1.13)
Alcohol status			
Non-drinker	203 (09.5)	396 (09.0)	1.00
Ex-drinker	211 (09.9)	467 (10.6)	0.91 (0.72-1.17)
Current drinker	1,506 (70.7)	3,156 (71.4)	0.99 (0.82-1.20)
Missing status	211 (9.9)	402 (9.1)	1.07 (0.82-1.38)
IMD (Social Class)			
1 (least deprived)	382 (18.0)	893 (20.2)	1.00
2	468 (22.0)	916 (20.8)	1.25 (1.04-1.50)
3	442 (20.8)	952 (21.5)	1.16 (0.95-1.40)
4	418 (19.7)	819 (18.5)	1.26 (1.04-1.55)
5 (most deprived)	420 (19.7)	840 (19.0)	1.23 (1.04-1.52)
Charlson comorbidity index			
1	1,195 (56.1)	2,786 (63.0)	1.00
2	319 (15.0)	643 (14.5)	1.17 (0.99-1.38)
3	256 (12.0)	460 (10.4)	1.33 (1.11-1.59)
4	157 (7.4)	268 (6.1)	1.39 (1.11-1.75)
≥5	204 (9.6)	264 (6.0)	1.71 (1.37-2.13)
Drug use in the year prior the index date			
Bisphosphonates	255 (12.0)	217 (4.9)	2.57 (2.10-3.15)
Vitamin D and/or Calcium	194 (9.1)	260 (5.9)	1.54 (1.25-1.91)
History of a diagnosis ever prior the index date			
Fall	577 (27.1)	607 (13.7)	2.44 (2.11-2.81)
Osteoporosis	261 (12.3)	202 (4.6)	2.82 (2.29-3.46)
Any fracture	707 (33.2)	662 (15.0)	2.94 (2.57-3.36)

Abbreviations: BMI, body mass index; IMD, Index of Multiple Deprivation.
Percentages have been rounded and might not total 100.
[a] Age at the index date.

Corticosteroids and risk of osteoporosis

A dose-response relationship was observed between the number of prescriptions and cumulative dose the year prior and risk of osteoporosis. Two to three OCS prescriptions were linked with larger odds of osteoporosis, with those receiving more OCS prescriptions (≥9 vs 0 prescriptions; aOR=4.50, 95%CI: 3.21-6.11) and cumulative doses (≥2500 vs 0 mg; aOR=4.79, 95%CI: 3.38-6.79) being at greater risk (Table 3).

ICS exposure was associated with osteoporosis, but the effect was less strong than with OCS. Patients prescribed eleven or more prescriptions were 1.6 times more likely to be diagnosed with osteoporosis than controls (aOR=1.60, 95%CI: 1.22-2.10), after adjusting for confounders. However, the risk was slightly increased with cumulative doses more than 120mg the year prior the index date (≥120 vs 0 mg; aOR=1.63, 95%CI: 1.33-1.99). The risk was similar across ICS type, but budesonide had the strongest effect (aOR=1.56, 95%CI: 1.23-1.98) (Table 3).

Table 3. Association between Oral (OCS) / Inhaled (ICS) Corticosteroids Exposure in the Year prior to the Index Date and Risk of Osteoporosis.

	Cases		Controls		Unadjusted OR	Adjusted[a] OR	
Type of exposure	**n**	**%**	**n**	**%**	**(95%CI)**	**(95%CI)**	***p*-value[*]**
No OCS use (reference)	992	63.4	2,607	78.8	1.00	1.00	
OCS prescriptions							<.0001
1	188	12.0	371	11.1	1.44 (1.19-1.77)	1.12 (0.90-1.40)	
2-3	123	7.9	189	5.7	1.88 (1.45-2.42)	1.34 (1.12-1.66)	
4-8	161	10.3	98	3.0	4.74 (3.58-6.28)	3.80 (2.81-5.13)	
≥9	100	6.4	48	1.5	5.37 (3.69-7.82)	4.50 (3.21-6.11)	
OCS cumulative dose (mg)							<.0001
≤500	244	15.6	475	14.4	1.47 (1.23-1.77)	1.21 (1.03-1.43)	
501-1000	83	5.3	99	3.0	2.44 (1.75-3.41)	2.05 (1.57-2.68)	
1001-2500	148	9.5	86	2.6	4.77 (3.59-6.40)	4.04 (3.12-5.12)	
>2500	95	6.1	44	1.3	6.10 (4.15-8.98)	4.79 (3.38-6.79)	
No ICS use (reference)	569	36.4	1,742	52.6	1.00	1.00	
ICS prescriptions							<.0001
1-6	605	38.7	1,053	31.2	1.87 (1.61-2.17)	1.35 (1.14-1.59)	
7-10	220	14.1	294	8.9	2.49 (2.01-3.07)	1.51 (1.20-1.92)	
≥11	170	10.9	224	6.8	2.66 (2.08-3.39)	1.60 (1.22-2.10)	
ICS type							
Beclomethasone	423	27.1	783	23.6	1.75 (1.49-2.06)	1.29 (1.08-1.54)	.007**
Budesonide	207	13.2	300	09.1	2.27 (1.82-2.83)	1.56 (1.23-1.98)	<.0001**
Fluticasone	352	22.5	475	14.3	2.44 (2.04-2.96)	1.44 (1.18-1.77)	<.0001**
Ciclesonide	12	0.9	12	0.5	2.55 (1.13-5.75)	1.80 (0.76-4.27)	.179**
ICS cumulative dose (mg)[b]							<.0001
≤40	209	13.4	433	13.1	1.60 (1.37-2.01)	1.18 (0.95-1.47)	
41-80	232	14.8	363	10.1	2.07 (1.62-2.40)	1.26 (0.98-1.60)	
81-120	180	11.5	282	08.5	2.02 (1.74-2.72)	1.50 (1.21-1.87)	
>120	370	23.7	488	14.7	2.55 (2.01-2.97)	1.63 (1.33-1.99)	

[a] Adjusted for smoking, BMI, IMD, Charlson Comorbidity Index score, any previous fracture, any previous fall, bisphosphonates, and number of ICS or OCS prescriptions accordingly.
[b] Was not able to determine cumulative dose in 9 individuals.
Percentages have been rounded and might not total 100.
[*] *P*-values for trend unless otherwise stated. The *p-values are* referred to the adjusted model.
** *P*-values from the Wald's test

Corticosteroids and risk of fragility fracture

There was an effect of OCS on risk of FF, however the effect size was smaller than on osteoporosis. More than nine OCS prescriptions in the previous year had a significant impact on risk (≥9 vs 0 prescriptions; aOR=2.16, 95%CI: 1.56-3.38), whereas OCS cumulative doses at more than 1000 mg led to an increased risk in the previous year, with the risk to be greater at higher doses in comparison to controls (≥2500 vs 0 mg; aOR=1.99, 95%CI: 1.30-3.04) (Table 4).

Eleven or more ICS prescriptions were associated with an increased risk of fracture (≥11 vs 0 prescriptions; aOR=1.31, 95%CI: 1.02-1.68) (Table 4). Patients exposed to cumulative doses at more than 120 mg in the year prior to the FF were 1.2 times more likely to sustain FF (aOR=1.20, 95%CI: 1.08-1.42). No significant association between any ICS type and fragility fracture was found.

Table 4. Association between Oral (OCS) / Inhaled (ICS) Exposure in the year prior to the Index Date and Risk of Fragility Fracture.

	Cases		Controls		Unadjusted OR	Adjusted[a] OR	
Type of exposure	**n**	**%**	**n**	**%**	**(95%CI)**	**(95%CI)**	***p*-value***
No OCS use (reference)	1,663	78.0	3,676	83.1	1.00	1.00	
OCS prescriptions							.0002
1	219	10.3	410	9.3	1.23 (1.03-1.48)	1.11 (0.91-1.34)	
2-3	112	5.3	171	3.9	1.43 (1.10-1.85)	1.24 (0.95-1.62)	
4-8	85	4.0	123	2.8	1.56 (1.16-2.10)	1.31 (1.12-1.77)	
≥9	52	2.4	41	1.0	2.70 (1.75-4.17)	2.16 (1.56-3.38)	
OCS cumulative dose (mg)							.0001
≤500	279	13.1	507	11.5	1.25 (1.06-1.48)	1.11 (0.92-1.32)	
501-1000	60	2.8	98	2.2	1.39 (0.98-1.96)	1.20 (0.84-1.70)	
1001-2500	79	3.7	93	2.1	1.84 (1.33-2.55)	1.54 (1.10-2.14)	
>2500	50	2.4	47	1.1	2.36 (1.56-3.59)	1.99 (1.30-3.04)	
No ICS use (reference)	1,081	50.7	2,527	57.1	1.00	1.00	
ICS prescriptions							.010
1-6	678	31.8	1,330	30.1	1.19 (1.05-1.35)	1.02 (0.89-1.17)	
7-10	219	10.3	340	7.7	1.51 (1.24-1.84)	1.24 (1.01-1.53)	
≥11	153	7.2	224	5.1	1.66 (1.30-2.11)	1.31 (1.02-1.68)	
ICS type							
Beclomethasone	510	23.9	984	22.3	1.21 (1.06-1.40)	1.10 (0.94-1.28)	.213**
Budesonide	176	08.3	333	7.5	1.29 (1.04-1.59)	1.14 (0.90-1.44)	.269**
Fluticasone	341	16.0	548	12.4	1.38 (1.16-1.63)	1.04 (0.85-1.26)	.679**
Ciclesonide	16	0.8	24	0.5	2.21 (1.09-4.48)	1.75 (0.82-3.75)	.145**
ICS cumulative dose (mg)[b]							.021
≤40	257	12.1	560	12.7	1.06 (0.89-1.26)	0.94 (0.78-1.31)	
41-80	248	11.6	433	9.8	1.35 (1.12-1.62)	1.13 (0.93-1.63)	
81-120	194	9.1	332	7.5	1.35 (1.10-1.65)	1.14 (0.90-1.78)	
>120	348	16.3	564	12.8	1.47 (1.25-1.74)	1.20 (1.08-1.42)	

[a] Adjusted for smoking, BMI, social class, Charlson Comorbidity Index score, any previous fracture, any previous fall, bisphosphonates, and number of ICS or OCS prescriptions accordingly.
[b] Was not able to determine cumulative dose in 29 individuals.
Percentages have been rounded and might not total 100.
[*] *P*-values for trend unless otherwise stated. The *p-values are* referred to the adjusted model.
** *P*-values from the Wald's test

Long-term exposure

The odds ratios in different period analyses were similar to those found when a 1-year period prior to index date was used to identify the exposure status. (Supplementary Tables E2-E5).

Sensitivity analysis

When only patients with at least one ICS prescription before the index dates were included, the risk of both osteoporosis and fragility fractures were similar compared to the main analysis (Supplementary Tables E6 & E8). After including the patients who never had OCS exposure within the database records, the relationship between ICS, osteoporosis, and FF still held (Supplementary Tables E7 & E9).

Bisphosphonate use

The prevalence of OCS users receiving at least one bisphosphonate prescription was 31.4% and 21.4% for osteoporosis and FF, respectively (Table 5). When ICS users without an OCS prescription in the year prior to the index date were included, the percentage of patients receiving at least one bisphosphonate prescription decreased further by around 2%. Only around 50% of patients receiving nine or more OCS prescriptions had at least one BP prescription.

Table 5. Prevalence of patients using at least one bisphosphonate prescription after the OCS and ICS initiation in the Year prior to the Osteoporosis and Fragility Fractures Diagnosis.

	Osteoporosis			Fragility Fractures		
	Patients with at least a BP prescription	Patients per corticosteroid category	Prevalence	Patients with at least a BP prescription	Patients per corticosteroid category	Prevalence
	n	n	%	n	n	%
OCS prescriptions						
Overall	401	1,275	31.4	259	1,208	21.4
1	108	559	19.3	92	629	14.6
2-3	99	309	31.7	50	283	17.6
4-8	119	259	45.9	72	208	35.5
≥9	75	148	50.6	45	93	48.4
ICS prescription						
Overall	868	2,566	33.8	573	2,944	19.4
1-6	532	1,658	32.0	348	2,008	17.3
7-10	191	514	37.1	120	559	21.4
≥11	145	394	36.8	105	377	27.8
ICS prescription*						
Overall	467	1,579	29.5	314	1,685	18.6
1-6	314	1,100	28.5	203	1,434	14.2
7-10	90	280	32.1	63	348	18.1
≥11	63	199	31.6	48	217	22.1

BP, Bisphosphonate; ICS, Inhaled Corticosteroids; OCS, Oral Corticosteroid.
* ICS users without an OCS prescription the year prior the index date.

DISCUSSION

Our findings provide evidence that both OCS and ICS exposure have deleterious effects on bone health. We found a clear dose-response relationship, with higher cumulative doses and number of OCS and ICS prescriptions being associated with increased odds of osteoporosis and fragility fracture. The percentage of patients receiving bisphosphonates after OCS initiation was low.

Our findings are similar to the limited literature. Bloechliger et al. reported a significant dose-response association between first episode of a bone-related condition and cumulative OCS dose in patients with asthma using a nested case-control design, but they did not report the odds for osteoporosis and fractures separately.(27) Similarly, a cross-sectional study found that OCS were associated with an increased OR for osteoporosis (OR=6.55; 95%CI 4.64-9.21) and fractures (OR=1.65; 95%CI 1.14-2.39) when comparing patients with severe asthma requiring regular OCS treatment with non-asthma controls.(18) Our study adds more details by defining the exposure based on the number of prescriptions and cumulative dose, capturing both the short- and long-term users. Cumulative doses more than 1000mg within a year had a significant effect. Price et al. examined the risk of osteoporosis and osteoporotic fractures in patients with asthma exposed to OCS and found similar estimates for cumulative doses (28). Our data are also in line with a study reporting that the odds of developing bone and muscle-related complications increased significantly in a dose-dependent manner with OCS use (29). We also found that the number of prescriptions within a year (i.e. intermittent use rather than regular) was associated with adverse bone effects, supporting the view that even short courses of OCS are harmful to bone health.(5)

Although the benefits of ICS in asthma are well-documented,(3) the detrimental effects of ICS on bones have been less clearly quantified with the majority of the limited literature to be relevant to the general population and not to asthma. A Canadian study of elderly women failed to detect a high risk of hip fracture (rate ratio = 0.92; 95% CI, 0.75-1.12).(30) Suissa et al. found no increased risk of fracture at recommended doses of ICS, but they reported a rate

ratio of fracture equal to 1.61 (95% CI, 1.04-2.50) for ≥ 2000μg of ICS per day,(31) although this study included only older people (≥65 yrs) who were already at a higher risk of fractures. Hubbard et al. used CPRD data to reveal a dose-response relationship and increased odds of hip fracture of 1.19 (95% CI, 1.10-1.28) when adjusting for annual prescriptions of OCS which is similar to the odds ratios found in our study.(32) Another study, comparing ICS users with non-users, found increased hazard ratios for fracture ranging from 1.13 to 1.51 depending on the fracture site.(33) Our study adds to the literature by providing estimates not only about the risk of osteoporosis, which are lacking, but also of fragility fractures, capturing a wide range of of severity of asthma, whilst adjusting for important confounders.

The low percentage of bisphosphonate use after the first OCS prescription in the year prior the osteoporosis or FF diagnoses is disappointing as this class of drugs is considered the most effective bone protective agent. There is guidance on the prevention of bone loss due to OCS in the general population, suggesting BP treatment for adults taking, for more than 3 months, any dose (34,35) or ≥2.5mg of prednisone daily (36). There is no current recommendation for BP therapy among ICS users. We found that only a minor percentage of ICS users at high risk had at least one bisphosphonate prescription after the first ICS prescription in the year prior to the osteoporosis or FF date.

Current guidelines on asthma do not cover the management of bone comorbidities in detail. Although the British Thoracic Society / Scottish Intercollegiate Guidelines Network and the Global Initiative for Asthma guidelines on asthma management cover specific co-morbidities including osteoporosis, no specific bone protection guidance is given (2,3) and the asthma guideline from the National Institute for Health Care and Excellence does not mention osteoporosis at all.(37) Our results suggest that risk and prevention of osteoporosis and FF should be addressed explicitly in future guideline updates.

The main strengths of our study are the large study size and use of linked data. By using linked data, we have been able to provide more complete estimates of osteoporosis and fractures incidence, capturing not only those recorded in primary care as vertebral fractures or osteoporosis often do not come to clinical attention in primary care, and people might not be

aware of these conditions (38) before a hospitalisation. Our study reports separately the risk stratifying data by dose, number of prescriptions, and type of OCS and ICS providing pragmatic guidance to clinicians. The dose-response relationship between ICS, osteoporosis, and fractures held, even after excluding each individual with a previous OCS exposure within the databse records. The population-based setting means the findings are generalizable to the wider population.

This study has some limitations. Diagnostic misclassification may occur, as we were reliant on general practitioners recording these conditions. However, these diagnoses have been previously validated in the database demonstrating a positive predictive value around 90%.(39,40) Because of the nature of our data, we may have included some non-fragility fractures, however we acted properly to minimize as much as possible this bias. The dose response relationship may need to include number of years on OCS or ICS; however, the patients' medical records do not go back indefinitely. Patients may have been using a drug prescribed before the examined index periods; however, this would bias the results towards the null hypothesis. Inhalers can be difficult to use correctly, and adherence is unlikely to be perfect, leading to lesser intake of actual dose underestimating the relationship between a prescribed ICS dose and bone health. Our exposure was defined based on corticosteroid prescriptions and not on actual compliance.

Conclusion

In summary, both OCS and ICS are associated with an increased risk of osteoporosis and fragility fracture in people with asthma. The use of OCS and ICS should be kept to the minimum necessary to treat symptoms and should be stepped down if symptoms and exacerbations are well-managed. Bisphosphonate co-medication should be considered according to guidelines for bone protection.

AUTHOR CONTRIBUTIONS

C.V.C. had full access to all the study data and takes full responsibility for the integrity of the data and the accuracy of the data analysis. Conception and design: C.V.C., D.E.S., T.M.M.; acquisition of data: C.V.C.; analysis of data: C.V.C.; interpretation of data: C.V. C., D.E.S., T.M.M.; drafting the article: C.V.C.; revision for important intellectual content and approval of the version to be published: C.V.C., D.E.S., T.M.M.

FUNDING

The study was funded by a research award from the British Medical Association (BMA).

COMPETING INTEREST

The authors declare no competing interests.

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