Incidence of osteoporosis and fragility fractures in asthma: a UK population-based matched cohort study

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ABSTRACT

Background

Osteoporosis and fragility fractures (FF) are associated with corticosteroids which are the mainstay treatment for asthma; however, these bone comorbidities within asthma need to be better described.

Methods

A matched cohort study was conducted using the Clinical Practice Research Database (CPRD). Adults with an incident asthma code were identified and matched, with up to four randomly selected people without asthma, by age, gender, and practice. Osteoporosis and FF incidence rates were calculated, and Cox regression was performed comparing hazard rates to the general population. We report the impact of age, gender, glucocorticoids, and the risk of specific fractures.

Results

Patients with asthma had a higher risk of osteoporosis (aHR = 1.18, 95% CI: 1.13-1.23) and were 12% (aHR = 1.12, 95% CI: 1.07-1.16) more likely to sustain FF than the general population. Age modified the effect of asthma on osteoporosis and FF, such that effect to be stronger in younger people ($p_{interaction}$<.0001). Vertebral (aHR = 1.40, 95% CI: 1.33-1.48), and forearm-wrist (aHR = 1.27, 95% CI: 1.22-1.32) were the sites linked with a larger incidence. A dose-response relationship between oral corticosteroids (OCS) and osteoporosis was observed, whereas the risk of FF increased in those with 6 or more OCS courses per year. Regular use of inhaled corticosteroids (ICS) increased the risk of both bone conditions.

Conclusion

Patients with asthma are more likely to develop osteoporosis or sustain FF than the general population with a particular concern in younger people and those more frequently using OCS and ICS.

INTRODUCTION

Asthma is a common chronic inflammatory disease affecting 300 million people of all ages (1). ICS are considered the gold-standard treatment, with OCS to be used in people with difficult asthma, or for exacerbations (2). Asthma is amongst the most common indications for prolonged (≥ 3 months) OCS therapy (3). Additionally, 17% of people with asthma have difficult-to-treat asthma (4) and 30% of them receive up to the equivalent of 20mg prednisolone equivalent and almost half of them receive up to over 2000 μg of ICS per day (5). Although corticosteroids are the main asthma treatment, there are well-recognised deleterious effects (6–9).

Osteoporosis which can result in FF is the most common severe and preventable side effect of steroid use (10). FF are associated with substantially increased health care costs, morbidity, and mortality (11,12). In a general population, studies suggest an increased fragility fracture risk in patients exposed to both short (≤ 3 months) and prolonged OCS use (8,13). Vertebral fracture risk increases by 55% with exposure at doses as low as prednisone 2.5mg per day, whereas hip fracture risk increases by 77% in patients exposed to 2.5 - 7.5mg per day (13). ICS also carry risk; compared to controls, people with an airway disease exposed to ICS have a higher fracture risk ranging from 15% to 51% depending on the fracture location (14).

Although there is a clear link between OCS and ICS use, and the risk of osteoporosis and FF, less is known about the relationship between asthma and these bone diseases. Some studies have examined this relationship, but they have used as outcome any change in the bone mineral density (BMD) with conflicting findings (15–19). Patients with severe asthma exposed to 5mg of prednisolone per day are more likely to be diagnosed with osteoporosis (OR=6.53) and fracture (OR=1.65) compared to those without asthma (20). A high prevalence of fractures in patients with steroid dependent asthma has been also reported (21,22). However, knowledge is limited due to small sample size (21,22) or focus on specific asthma groups (20).

The aim of this study was to estimate the incidence and risk of osteoporosis and FF among patients with asthma, when compared to the general population. We reported the impact of age, gender, glucocorticoids, and the risk of specific fractures.

METHODS

Source population

We conducted a matched cohort study utilising the Clinical Practice Research Datalink, a large longitudinal primary care database. We used the July 2018 dataset which covers more than 15.4 million patients from 738 practices across the UK. The percentage of acceptable active patients is approximately 7% of the UK population and data are representative with respect to age, gender and ethnicity to the wider UK people (23). The study was approved by the Independent Scientific Advisory Group of the CPRD (ISAC protocol number 19_041RA).

Study population

The study population included all adults patients (≥18 years old) with a new 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 index date (24). We assigned an index date equal to a new Read code for asthma to each patient with asthma. Each patient with asthma was matched up to four randomly selected patients without asthma (not any record of Read code for asthma) by age (±1 year), gender and practice generating a matched cohort. We assigned to patients without asthma the same index date as their matched patients. Only patients classed as “acceptable” research quality data and registered to an up to standard practice according to CPRD’s recommendations included.

Definition of outcomes

The outcomes of interest were the time from the index date to the first Read code for 1) osteoporosis and 2) FF, separately. Patients with a previous history of osteoporosis and the specific fracture outcome under investigation before the index date were excluded. The FF were defined as composite of vertebral, hip, forearm-wrist and humerus fractures. An additional category called “unspecified” was generated including fractures classified as FF without specifying the exact fracture location. We selected these locations as they are considered major FF sites and are associated with morbidity and mortality (12,25). Any

fracture described as an “open fracture” was excluded, since this type usually occurs via a high-energy event, and is not associated with frailty.

Follow-up

The index date was the start date of the follow-up and the end date was defined as the date of the patient’s death, the date of the last collection of the practice, the date of the patient transferred out of the practice, the date of the first Read coded outcome of interest or the end of the dataset, whichever came earliest.

Potential confounders

For each participant in this study, we retrieved information on the following variables, all of which are well-established risk fractures or thought to have an impact on osteoporosis or fracture risk and are also likely to be recorded within the database: age at the index date; sex, including only those clearly classified as male or female; body mass index (BMI) using the nearest measurement prior to the index date and categorised according to the World Health Organization (supplementary material); smoking and alcohol status using the nearest measurement prior to the index date (supplementary material); socioeconomic status measured by using the patient-level Index of Multiple Deprivation (IMD) 2015 in quintiles (with quintile 1 being the least deprived and quintile 5 being the most deprived; history of any fracture (not those considered as an outcome), fall or chronic obstructive pulmonary disease (COPD) prior to the index date; at least one prescription of opioids, vitamin D and calcium, and hormone replacement therapy (HRT) in the year prior to the index date. The comorbidities were also summarised using the Charlson Comorbidity Index score (26).

Exposure to OCS, ICS and bisphosphonates was calculated in two ways. We calculated their use in the year before the index date. Then, the OCS and ICS prescription rates per patient per year of follow-up were also estimated by dividing the total number of prescriptions of each patient during the follow-up period to the corresponding person- time of each one patient Furthermore, among OCS users during the follow-up, the prevalence of patients taking at least

one bisphosphonate prescription after OCS initiation was calculated. If there was no record for a medication or diagnosis, we assumed that the patient did not have the exposure.

Statistical analysis

All continuous demographic and lifestyle variables were summarised using mean and standard or median and interquartile range for those following normal or skewed distribution, respectively. Categorical variables were summarised by frequency and percentages. We compared the baseline characteristics between asthma and non-asthma patients performing a conditional logistic regression analysis using the matched set as the strata variable. Absolute incidence rates of osteoporosis and FF were calculated by dividing the number of incident diagnosis by follow-up person-years for both groups. The probability of experiencing FF during the follow-up time was presented with a plot using the Kaplan-Meier method and the log-rank test examined any difference between the groups. Performing a Cox regression analysis, stratified by matched set, we calculated the hazard ratio (HR) estimates and 95% confidence intervals (CI) comparing the osteoporosis and FF risk between asthma and non-asthma patients. Then, we adjusted our model for a priori confounders (age and gender) and the other potential confounders listed above. These confounders were included in the model whether they altered the age-gender adjusted HR between exposure and outcome by 5% or more. The Cox model assumption was tested using Schoenfeld residuals. Missing data for BMI, smoking status, and alcohol status were assumed as missing at random and imputed using chained equations. Ten imputations were generated, and the imputed model consisted of age, gender, outcome, and all confounders. Missing data for IMD were assigned a new category. A subgroup analysis by gender, age group, and fracture location was performed. To test whether or not age or gender modified the effect of asthma on osteoporosis and FF, we used the likelihood ratio test to examine for statistical evidence of effect modification.

To test the robustness of our findings, we also conducted two sensitivity analyses to determine whether the overall FF risk was similar in different patient populations. We therefore conducted

the main analysis (a) including patients with a history of osteoporosis before the index date, and (b) excluding patients with any fracture before the index date.

After excluding the patients without asthma, we investigated the effect on osteoporosis and FF of some well-known risk factors within asthma group, including ICS and OCS prescriptions during the follow-up, by estimating aHR.

All statistical analyses were performed using Stata v16

RESULTS

Baseline characteristics

The study included 138,123 patients with asthma and 520,626 age-, sex- and practice-matched non-asthma patients. The mean age of people with and without asthma was 52.0±17.9 and 51.7±17.8, respectively (Table 1). The median follow-up time was 4.50 (IQR: 2.1-7.9) in asthma and 4.58 (IQR: 2.1-8.0) in non-asthma patients.

Patients with asthma compared to non-asthma were more likely to be obese (27% vs 17%, $p<.0001$) and ex- or current smokers (53% vs 40%, $p<.0001$) (Table 1). Furthermore, patients had had more comorbidities than controls ($p<.0001$). More patients with asthma had at least one prescription of opioids (10% vs 6%, $p<.0001$) before the index date than the non-asthma.

Table 1. Baseline characteristics of asthma and non-asthma patients.

Descriptor	Asthma patients n=138,123	%*	Nonasthma patients n=520,626	%*	*p*-value**
Age y, mean ± SD	52.0±17.9		51.7±17.8		
<40	39,043	28.3	149,685	28.7	
40-49	24,998	18.1	95,308	18.3	
50-59	23,974	17.4	90,549	17.4	
60-69	24,774	17.9	92,478	17.8	
70-79	17,417	12.6	64,307	12.3	
≥80	7,917	5.7	28,299	5.4	
Gender					
Male	56,538	40.9	213,635	41.0	
Female	82,585	59.1	306,991	59.0	
Follow-up y, median (IQR)[a]	4.50 (2.1-7.9)		4.58 (2.1-8.0)		
Follow-up y, median (IQR)[b]	4.51 (2.1-7.9)		4.60 (2.1-8.0)		
IMD					<.0001
Least Deprived	16,026	11.6	62,026	11.9	
-	16,439	11.9	61,102	11.7	
-	16,030	11.6	58,013	11.1	
-	15,341	11.1	52,752	10.1	
Most deprived	14,612	10.5	46,284	8.8	
Missing status	59,675	43.2	240,339	46.1	
CCI score					<.0001
1	113,950	82.5	447,602	86.0	
2	11,796	8.5	38,310	7.4	
3	6,452	4.7	18,572	3.6	
4	2,855	2.1	7,790	1.5	
≥5	3,070	2.2	8,352	1.6	
BMI (kg/m^2)					<.0001
Underweight (<18.5)	2,214	1.6	6,676	1.3	
Normal (18.5 - 24.9)	31,486	22.8	111,417	21.4	
Overweight (25 - 29.9)	37,110	26.9	109,519	21.0	
Obese (≥30)	36,890	26.7	86,361	16.6	
Missing status	30,423	22.0	206,653	39.7	
Smoking status					<.0001
Never	62,095	45.0	254,418	48.9	
Former	42,307	30.6	103,230	19.8	
Current	30,760	22.3	103,729	19.9	
Missing status	2,961	2.1	59,249	11.4	
Alcohol consumption					<.0001
Never	13,759	10.0	46,968	9.1	
Former	11,734	8.5	33,039	6.3	
Occasional	18,102	13.1	60,005	11.5	
Current	74,419	53.9	261,961	50.3	
Missing status	20,109	14.6	118,653	22.8	
At least one prescription of					
Bisphosphonates	3,923	2.8	11,628	2.2	<.0001
Opioids	14,321	10.4	31,781	6.1	<.0001
Vitamin D and/or Calcium intake	4,386	3.2	12,308	2.4	<.0001
HRT	11,237	8.1	34,460	6.6	<.0001
ICS	70,024	50.7	23,136	4.4	<.0001
OCS	34,221	24.8	18,799	3.6	<.0001
History of					
Falls	11,758	8.5	33,169	6.4	<.0001
Any fracture	29,139	21.1	95,523	18.3	<.0001
COPD	15,365	11.1	11,345	2.2	<.0001

Abbreviations: BMI, body mass index; CCI, Charlson comorbidity index; COPD, chronic obstructive pulmonary disease; HRT, hormone replacement therapy; ICS, inhaled corticosteroids; IMD, Index of Multiple Deprivation; OCS, oral corticosteroids.
[a] The outcome was a fragility fracture diagnosis

[b] The outcome was an osteoporosis diagnosis
[*]Percentages have been rounded and might not total 100.
[**]*P*-values based on likelihood ratio test.

Osteoporosis risk

During the whole study period the incidence of osteoporosis was higher in asthma than non-asthma group. The incidence rates were 5.26 (95% CI: 5.09-5.42) and 3.23 (95% CI: 3.16-3.29) per 1000 person-years for patients with and without asthma, respectively (Table 2). An association between asthma and osteoporosis was observed (aHR = 1.18, 95% CI: 1.13-1.23). Age and gender modified the effect of asthma on osteoporosis, such that effect to be stronger in younger people ($p_{interaction}$<.0001) and slightly larger in men with asthma ($p_{interaction}$<.0001), respectively. The risk stratified by age groups and gender is presented in the Supplementary Table E1.

Table 2. Incidence rates and hazard ratios (HR) for associations of osteoporosis with exposure to asthma.

Variables	Asthma patients		Non-asthma patients		Unadjusted HR (95%CI)	Adjusted HR[b] (95%CI)	*p*-value
	Number with osteoporosis	Rate per 1000 person-years	Number with osteoporosis	Rate per 1000 person-years			
Overall	3,767	5.26	9,911	3.23	1.45 (1.40-1.51)	1.18 (1.13-1.23)	<.0001
Gender							
Male	768	2.60	1,431	1.27	2.05 (1.88-2.24)	1.35 (1.22-1.50)	<.0001
Female	2,999	7.11	8,480	4.37	1.35 (1.29-1.41)	1.14 (1.09-1.20)	<.0001
Age[a]							
<40	55	0.28	126	0.17	1.67 (1.22-2.30)	1.54 (1.04-2.29)	.032
40-49	208	1.48	496	0.93	1.59 (1.35-1.87)	1.29 (1.06-1.57)	.013
50-59	678	5.06	1,697	3.01	1.51 (1.38-1.65)	1.24 (1.12-1.39)	<.0001
60-69	1,195	8.97	3,049	6.02	1.49 (1.39-1.59)	1.20 (1.10-1.29)	<.0001
70-79	1,182	15.04	3,269	6.19	1.42 (1.33-1.52	1.17 (1.08-1.26)	<.0001
≥80	449	15.99	1,274	5.81	1.36 (1.22-1.52)	1.16 (1.02-1.32)	.022

[a] Age at the index date.
[b] Adjusted for age, gender, smoking, BMI, Charlson score, ICS, OCS, IMD, and previous: COPD, fractures; when not stratified by those.

Osteoporosis risk among patients with asthma

Increasing OCS prescriptions raised the risk with patients exposed to nine or more prescriptions per year of follow-up to be at higher risk than non-exposed (aHR = 6.11, 95% CI 5.31-7.02) (Table 3). Nevertheless, only 55% of patients exposed to nine or more OCS courses had at least one BP prescription after OCS initiation during the follow-up (Supplementary Table E2). Risk of osteoporosis increased with regular use of ICS prescription per year, however a substantial increase was observed after the 17th prescription per year of follow-up (aHR = 10.66, 95% CI 8.20-12.05) (Table 3).

Table 3. Risk of osteoporosis within asthma patient stratified by well-known risk factors.

	Asthma patients (n=138,123)				
Predictive variables	**Number with osteoporosis**	**Rate per 1000 person-years**	**Unadjusted HR (95%CI)**	**Adjusted HR[a] (95%CI)**	**p-value**
OCS prescriptions per person-year (n)					<.0001
0 (120,761)	2,341	3.67	Reference	Reference	
1-2 (8,489)	434	9.29	2.57 (2.31-2.86)	1.75 (1.57-1.95)	
3-5 (5,797)	463	15.79	4.41 (3.97-4.89)	2.49 (2.24-2.77)	
6-8 (1,652)	234	28.33	7.91 (6.92-9.18)	3.82 (3.28-4.44)	
≥9 (1,424)	295	54.03	15.36 (13.48-17.50)	6.11 (5.31-7.02)	
ICS prescriptions per person-year (n)					<.0001
0 (50,199)	1,234	4.87	Reference	Reference	
1-8 (79,430)	1,663	3.72	0.76 (0.70-0.81)	0.98 (0.92-1.05)	
9-13 (7,068)	429	11.51	2.51 (2.22-2.85)	1.72 (1.52-1.94)	
14-16 (980)	254	41.41	9.94 (7.99-12.35)	5.48 (4.41-6.82)	
≥17 (446)	187	79.11	16.24 (12.70-18.12)	10.66 (8.20-12.05)	
Gender					<.0001
Male	768	2.61	Reference	Reference	
Female	2,999	7.11	2.73 (2.52-2.95)	3.03 (2.80-3.28)	
Age					<.0001
≤40	55	0.28	Reference	Reference	
40-49	208	1.48	5.29 (3.93-7.13)	5.43 (4.03-7.32)	
50-59	678	5.05	18.06 (13.72-23.78)	18.00 (13.66-23.73)	
60-69	1,195	8.97	32.31 (24.65-42.34)	31.27 (23.79-41.10)	
70-79	1,182	14.12	51.71 (39.46-67.76)	45.34 (34.43-59.72)	
≥80	449	15.99	60.66 (45.83-80.29)	47.13 (35.36-62.79)	
Smoking					<.0001
Never	1,435	4.37	Reference	Reference	
Former	1,381	6.39	1.10 (1.01-1.20)	1.14 (1.06-1.24)	
Current	949	5.79	1.40 (1.27-1.55)	1.46 (1.34-1.59)	
BMI (kg/m^2)					<.0001
Underweight (<18.5)	253	14.18	1.48 (1.23-1.87)	1.50 (1.25-1.80)	
Normal (18.5 - 24.9)	1,340	6.94	Reference	Reference	

	Overweight (25 - 29.9)	1,195	4.83	0.67 (0.62-0.73)	0.68 (0.63-0.74)	
	Obese (≥30)	880	3.21	0.49 (0.44-0.53)	0.50 (0.46-0.55)	
IMD						<.0001
	Least deprived	381	4.61	Reference	Reference	
	-	401	4.96	1.08 (0.94-1.25)	1.01 (0.87-1.15)	
	-	381	4.84	1.06 (0.92-1.22)	0.99 (0.86-1.14)	
	-	370	4.95	1.08 (0.93-1.25)	1.02 (0.88-1.17)	
	Most deprived	429	6.17	1.35 (1.17-1.55)	1.36 (1.18-1.56)	
	Not known IMD	1,805	5.47	1.18 (1.05-1.31)	1.21 (1.08-1.35)	

Abbreviations: BMI, body mass index; CCI, Charlson comorbidity index; ICS, Inhaled Corticosteroids; IMD, Index of Multiple Deprivation; OCS, Oral corticosteroids
[a] Adjusted for age, gender, smoking, BMI, Charlson score, ICS, OCS, IMD, previous: COPD, fractures.

Fragility fracture risk

A total of 4286 (3.1%) patients with asthma and 13040 (2.5%) without asthma sustained a FF. The incidence rates were 5.99 (95% CI 5.81-6.17) in asthma and 4.77 (95% CI 4.69-4.85) in non-asthma group per 1000 person-years (Table 4). After adjusting for confounders, the FF risk was 12% higher in patients with asthma than those without asthma (aHR = 1.12, 95% CI 1.07-1.16). The Kaplan-Meier graph also displayed a significantly higher probability of fracture during the follow-up between the patients with and without asthma (Log-rank test, $p < .0001$) (Supplementary Figure E1). The effect of asthma on FF risk was modified by age ($p_{interaction}<.0001$), but not gender ($p_{interaction}=.9972$). The risk stratified by age groups and gender is presented in the Supplementary Table E3. Forearm-wrist (aHR = 1.21, 95% CI 1.13-1.30) and vertebral (aHR = 1.19, 95% CI 1.10-1.28) were the sites with a higher risk (Table 5). The risk of site-specific FF stratified by gender and age groups is summarised in Supplementary Table E4.

Table 4. Incidence rates and hazard ratios (HR) for associations of fracture with exposure to asthma.

Variables	Asthma patients		Non-asthma patients		Unadjusted HR (95%CI)	Adjusted HR[b] (95%CI)	*p*-value
	Number with a fracture	Rate per 1000 person-years	Number with a fracture	Rate per 1000 person-years			
Overall	4,286	5.99	13,040	4.77	1.26 (1.21-1.30)	1.12 (1.07-1.16)	<.0001
Gender							
Male	1,107	3.76	3,287	2.93	1.29 (1.21-1.39)	1.11 (1.02-1.20)	.011
Female	3,179	7.54	9,753	6.06	1.25 (1.20-1.30)	1.11 (1.06-1.16)	<.0001
Age[a]							
<40	388	1.98	1,079	1.43	1.38 (1.23-1.55)	1.24 (1.07-1.44)	.005
40-49	428	3.07	1,171	2.21	1.39 (1.24-1.55)	1.33 (1.15-1.51)	<.0001
50-59	636	4.74	1,945	3.84	1.24 (1.13-1.35)	1.16 (1.04-1.28)	.009
60-69	1,052	7.87	3,021	5.96	1.33 (1.24-1.42)	1.15 (1.05-1.25)	.001
70-79	1,128	13.36	3,629	11.14	1.21 (1.13-1.29)	1.02 (0.95-1.11)	.541
≥80	654	23.41	2,195	20.30	1.15 (1.06-1.26)	1.00 (0.90-1.10)	.964

[a] Age at the index date.
[b] Adjusted for age, gender, smoking, BMI, Charlson score, ICS, OCS, IMD, and previous: COPD, fractures; when not stratified by those.

Table 5. Overall incidence rates and hazard ratios (HR) for associations of site-specific fracture with exposure to asthma.

Fracture location	Asthma patients		Non-asthma patients		Unadjusted HR (95%CI)	Adjusted HR[b] (95%CI)	*p*-value
	Number with a fracture	Rate per 1000 person-years	Number with a fracture	Rate per 1000 person-years			
Forearm-Wrist	1,463	2.04	4,363	1.59	1.28 (1.20-1.35)	1.21 (1.13-1.30)	<.0001
Vertebra	685	0.96	1,845	0.67	1.42 (1.30-1.55)	1.19 (1.10-1.28)	<.0001
Hip	873	1.22	2,954	1.08	1.13 (1.05-1.22)	1.01 (0.92-1.08)	.905
Humerus	598	0.83	1,842	0.67	1.24 (1.13-1.35)	1.05 (0.94-1.17)	.371
Unspecified[a]	667	0.93	2,036	0.74	1.26 (1.16-1.38)	1.06 (0.95-1.17)	.267

[a] Just a mention that it was a fragility fracture without specifying the exact fracture location.
[b] Non-asthma patients consider the reference group. Adjusted for age, gender, smoking, BMI, Charlson score, ICS, OCS, IMD, previous: COPD, fractures.

Fracture risk among asthma patients

There were 17 233 (12.5%) patients with a median of 2 (IQR 1–4) and 87 675 (64%) distinct users with at least one OCS and ICS prescription per year of follow-up, respectively. The median prescriptions per year of follow-up were 2 (IQR: 1-4) for OCS and 5 (IQR: 2-7) for ICS. The fragility fracture risk increased from the 6th OCS course per year of follow-up (6-8 courses; aHR = 1.35, 95% CI 1.10-1.64), but only 45% had at least one BP prescription after the OCS initiation during the follow-up in this category (Supplementary Table E2). A larger risk due to ICS appeared after the 17th prescription per year of follow-up (aHR = 6.15, 95% CI 2.37-13.21) (Table 6).

Sensitivity analyses

The results remained consistent in the sensitivity analyses (Supplementary Table E5).

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Table 6. Risk of fragility fracture within asthma patients stratified by well-known risk factors.

	Asthma patients (n=138,123)				
Predictive variables	**Number with a fracture**	**Rate per 1000 person-years**	**Unadjusted HR (95%CI)**	**Adjusted HR[a] (95%CI)**	**p-value**
OCS prescriptions per person-year (n)					<.0001
0 (120,890)	3,515	5.54	Reference	Reference	
1-2 (8,557)	326	7.62	1.37 (1.22-1.54)	0.97 (0.86-1.09)	
3-5 (5,795)	251	9.23	1.66 (1.46-1.89)	1.00 (0.88-1.14)	
6-8 (1,599)	105	14.28	2.60 (2.12-3.19)	1.35 (1.10-1.64)	
≥9 (1,282)	89	18.41	3.38 (2.71-4.21)	1.46 (1.16-1.83)	
ICS prescriptions per person-year (n)					<.0001
0 (50,448)	1,766	7.05	Reference	Reference	
1-8 (79,692)	2,174	4.99	0.70 (0.66-0.75)	0.92 (0.85-1.01)	
9-13 (6,982)	252	9.43	1.34 (1.18-1.53)	0.95 (0.83-1.08)	
14-16 (812)	56	27.87	4.15 (3.17-5.41)	2.45 (1.93-3.20)	
≥17 (189)	20	67.26	10.01 (5.41-18.81)	6.15 (2.37-13.21)	
Gender					<.0001
Male	1,107	3.76	Reference	Reference	
Female	3,179	7.54	2.00 (1.86-2.14)	2.13 (1.98-2.28)	
Age					<.0001
≤40	388	1.98	Reference	Reference	
40-49	428	3.06	1.54 (1.34-1.77)	1.58 (1.38-1.81)	
50-59	636	4.74	2.34 (2.09-2.70)	2.46 (2.17-2.80)	
60-69	1,052	7.87	3.98 (3.55-4.47)	4.13 (3.66-4.65)	
70-79	1,128	13.36	6.88 (6.12-7.72)	6.72 (5.95-7.59)	
≥80	654	23.41	12.58 (11.09-14.27)	11.34 (9.91-12.98)	
Smoking					<.0001
Never	1,736	5.29	Reference	Reference	
Former	1,517	7.04	1.34 (1.25-1.43)	1.09 (1.02-1.18)	
Current	1,033	6.19	1.17 (1.08-1.26)	1.35 (1.25-1.47)	
BMI (kg/m^2)					<.0001
Underweight (<18.5)	588	11.89	1.83 (1.51-2.21)	1.46 (1.19-1.79)	
Normal (18.5 - 24.9)	1,257	6.34	Reference	Reference	

	Overweight (25 - 29.9)	1,296	5.80	0.92 (0.85-0.99)	0.83 (0.76-0.89)	
	Obese (≥30)	1,145	5.08	0.82 (0.75-0.89)	0.71 (0.65-0.77)	
IMD						<.0001
	Least deprived	417	5.04	Reference	Reference	
	-	479	5.93	1.18 (1.04-1.35)	1.11 (0.98-1.27)	
	-	480	6.12	1.22 (1.07-1.39)	1.17 (1.03-1.33)	
	-	394	5.28	1.05 (0.91-1.20)	1.02 (0.88-1.16)	
	Most deprived	409	5.87	1.17 (1.02-1.34)	1.15 (1.02-1.31)	
	Not known IMD	2,107	6.39	1.25 (1.13-1.39)	1.27 (1.14-1.41)	

Abbreviations: BMI, body mass index; CCI, Charlson comorbidity index; ICS, Inhaled Corticosteroids; IMD, Index of Multiple Deprivation; OCS, Oral corticosteroids.
[a] Adjusted for age, gender, smoking, BMI, Charlson score, ICS, OCS, IMD, previous: COPD, fractures

DISCUSSION

Overall, this study shown that asthma is associated with an increased risk of osteoporosis and FF. This association was stronger in the younger age groups. Among patients with asthma, a single OCS course raised the osteoporosis risk, and greater use of ICS increased the risk of both bone diseases.

To the best of our knowledge, this is the largest study reporting the incidence and risk of osteoporosis and FF in asthma using a primary care database. Other strength is the population-based setting that means the findings are generalizable to the wider population. We captured osteoporosis and fragility fracture diagnoses for the general population of asthma and not just for a specific one such as people with severe asthma. We were able to adjust for a wide range of potentially confounding factors. Our results were also robust to sensitivity analyses.

The data use from primary care databases has some limitations. Firstly, there may be misclassification of asthma, osteoporosis, and FF diagnoses, as we were reliant on how accurately general practitioners record these conditions. However, these diagnoses have been previously validated in the database demonstrating a positive predictive value around 90%; therefore, the existence of any diagnosis misclassification in our study should be very unlikely (27,28). In addition, most fractures are painful and medical treatment would be sought for it and it be recorded, however, vertebral fractures or osteoporosis often do not come to clinical attention, and people might not be aware of these conditions (29); this may result in the underestimation of their coding and as a result of their risk. Nevertheless, we do not think this underestimation would be different in people with asthma than people who do not have asthma. As in all health care datasets, our prescriptions were based on issued prescriptions without knowing whether or not they were dispensed.

The absolute incidence rate of each FF site in our general population is in accordance with another CPRD cohort study (30), and the incidence of hip fractures was additionally identical

to population statistics in the UK (10.8 vs 10.3 per 10,000 person-years) (31). The observed rate is consistent with the limited published studies examining the osteoporosis and fracture risk in asthma. However, these studies were small (e.g. 105 patients vs 133 controls), lacked data on important confounders such as BMI, socioeconomic status, or focused on specific asthma group providing a little information about the risk in asthma (20,22,32). Sweeney et al. found a higher risk of osteoporosis and fracture compared to our study which probably reflects the more severe asthma population (20). We found greater risk of spine and forearm fractures in accordance with reports shown a lower BMD at these sites in patients with asthma (7,18,33), but not a significant risk of hip fractures in agreement with a meta-analysis (34) which did not find a reduced BMD at femur/hip between patients with asthma and controls.

Our study found the effect of asthma on osteoporosis is stronger in younger people and males and on FF in younger people. This observation may be due to other factors such as previous fractures, low oestrogen level, comorbidities, and other medications which have a bigger impact on the risk of osteoporosis and fragility fracture and are more likely in older people or women. Therefore, at younger ages and in men the main risk factor for osteoporosis will be steroids, hence the stronger relationship. Lastly, men and younger generally receive osteoporosis treatment less frequently than women and older people (35), as this was demonstrated in our findings. Knowledge that the effect of asthma on osteoporosis and FF is stronger in younger people is crucial in daily asthma practice in terms of the management of corticosteroid therapy minimising the side effects in subpopulation being at higher risk. Furthermore, as the effect of asthma on osteoporosis is stronger in males a high awareness is recommended not only in female but in male patients with asthma

Previous studies have reported an increase in fracture risk in relation to daily and cumulative OCS use, and our study shows that even one prescription per year increases the risk (13,20,36). Concerns about the negative impact of ICS on bones are recognised with long-term use (≥0.7mg/day) (14), with our findings confirming the negative effects on bone of ICS within asthma population at regular use of ICS. It is best practice to review OCS and ICS dose

and use the lowest dose possible to maintain asthma control (37). Although there is clear guidance on OCS and bisphosphonate therapy in the general population, there is no current recommendation for BP therapy for ICS users, despite evidence supporting fractures-related to ICS (14,38).

Current UK guidelines on asthma do not cover the management of these bone comorbidities appropriately due to the very few studies specific to asthma. Specifically, the BTS/SIGN guideline on asthma management cover specific co-morbidities including osteoporosis, but not specific bone protection guidance is given (2), and the NICE asthma guideline does not mention osteoporosis at all (39). Our results suggest that osteoporosis and FF should be addressed explicitly in future guideline updates.

Conclusion

Patients with asthma have an increased osteoporosis and FF risk compared to the general population, in particular vertebral and humerus fractures. An increased awareness of these bone disease comorbidities in asthma, particularly in the younger population, is needed. Reviewing corticosteroid dose and using the lowest dose possible minimising the risk of these bone conditions in asthma is recommended.

CONTRIBUTORS

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., T.M.M., D.E.S.; acquisition of data: C.V.C.; analysis of data: C.V.C.; interpretation of data: C.V. C., T.M.M., D.E.S.; drafting the article: C.V.C.; revision for important intellectual content and approval of the version to be published: C.V.C., T.M.M., D.E.S.

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COMPETING INTERESTS

The authors declare no competing interests.

DATA AVAILABILITY

This study is based on CPRD data and is subject to a full license agreement which does not permit data sharing outside of the research team. However, data can be obtained by applying to CPRD (enquiries@cprd.com) for any replication of the study. The Read codes used are available from the corresponding author upon a reasonable request.

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