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

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Patients with asthma are more likely to develop osteoporosis or sustain fragility fractures than the general population, with a particular concern in younger people and those more frequently using OCS or ICS https://bit.ly/2D8cjbm

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ABSTRACT

Introduction: Osteoporosis and fragility fractures 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 UK 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, sex and practice. Osteoporosis and fragility fracture incidence rates were calculated, and Cox regression was performed comparing hazard rates to the general population. We report the impact of age, sex, glucocorticoids and the risk of specific fractures.

Results: Patients with asthma had a higher risk of osteoporosis (adjusted hazard ratio (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 fragility fractures than the general population. Age modified the effect of asthma on osteoporosis and fragility fractures, such that the effect was stronger in younger people ($p_{interaction}<0.0001$). The vertebra (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 fragility fractures increased in those with six or more OCS courses per year. Regular use of inhaled corticosteroids (ICS) increased the risk of both bone conditions.

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

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This study is based on UK Clinical Practice Research Database (CPRD) data and is subject to a full licence agreement which does not permit data sharing outside of the research team. However, data can be obtained by applying to the 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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Introduction

Asthma is a common chronic inflammatory disease affecting 300 million people of all ages [1]. Inhaled corticosteroids (ICS) are considered the gold standard treatment, with oral corticosteroids (OCS) to be used in people with difficult asthma or for exacerbations [2]. Asthma is among 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 20 mg prednisolone equivalent and almost half of them receive up to 2000 µg ICS per day [5]. Although corticosteroids are the main asthma treatment, there are well-recognised deleterious effects [6–9].

Osteoporosis that can result in fragility fractures is the most common severe and preventable side-effect of steroid use [10]. Fragility fractures are associated with substantially increased healthcare costs, morbidity and mortality [11, 12]. In the general population, studies suggest an increased fragility fracture risk in patients exposed to both short (⩽3 months) and prolonged OCS use [8, 13]. Vertebra fracture risk increases by 55% with exposure at doses as low as 2.5 mg prednisone per day, whereas hip fracture risk increases by 77% in patients exposed to 2.5–7.5 mg prednisone per day [13]. ICS also carry risk; compared with 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 fragility fractures, less is known about the relationship between asthma and these bone conditions. 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 5 mg prednisolone per day are more likely to be diagnosed with osteoporosis (OR 6.53) and fracture (OR 1.65) compared with those without asthma [20]. A high prevalence of fractures in patients with steroid-dependent asthma has also been reported [21, 22]. However, knowledge is limited due to small sample sizes [21, 22] or a focus on specific asthma groups [20].

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

Methods

Source population

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

Study population

The study population included all adult patients (⩾18 years old) with a new Read code for asthma between April 1, 2004 (activation of Quality and Outcomes Framework score) and December 31, 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 with up to four randomly selected patients without asthma (not any record of Read code for asthma) by age (±1 year), sex and practice to generate 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 were 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) fragility fractures, separately. Patients with a previous history of osteoporosis and the specific fracture outcome under investigation before the index date were excluded. The fragility fractures were defined as a composite of vertebra, hip, forearm/wrist and humerus fractures. An additional category called "unspecified" was generated including fractures classified as fragility fractures without specifying the exact fracture location. We selected these locations as they are considered major fragility fractures 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 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 factors 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 COPD prior to the index date; at least one prescription of opioids, vitamin D and/or calcium or hormone replacement therapy 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 by the corresponding person-time of each 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 deviation or median and interquartile range (IQR) for those following a normal or skewed distribution, respectively. Categorical variables were summarised by frequency and percentages. We compared the baseline characteristics between asthma and nonasthma patients, performing a conditional logistic regression analysis using the matched set as the strata variable. Absolute incidence rates of osteoporosis and fragility fractures were calculated by dividing the number of incident diagnoses by follow-up person-years for both groups. The probability of experiencing fragility fractures 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 comparing the osteoporosis and fragility fracture risk between asthma and nonasthma patients. Then, we adjusted our model for *a priori* confounders (age and sex) and the other potential confounders listed earlier. These confounders were included in the model whether they altered the age–sex adjusted HR (aHR) between exposure and outcome by $\geqslant$5%. 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, sex, outcome and all confounders. Missing data for IMD were assigned a new category. A subgroup analysis by sex, age group and fracture location was performed. To test whether or not age or sex modified the effect of asthma on osteoporosis and fragility fractures, 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 fragility fracture risk was similar in different patient populations. We therefore conducted the main analysis 1) including patients with a history of osteoporosis before the index date and 2) excluding patients with any fracture before the index date.

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

All statistical analyses were performed using Stata version 16 (StataCorp, College Station, TX, USA)

Results

Baseline characteristics

The study included 138 123 patients with asthma and 520 626 age-, sex- and practice-matched nonasthma patients (controls) (table 1). The mean±SD age of patients with and without asthma was 52.0±17.9 and

TABLE 1 Baseline characteristics of asthma and nonasthma patients

	Asthma patients	Nonasthma patients	p-value[#]
Patients	138 123	520 626	
Age years	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	7917 (5.7)	28 299 (5.4)	
Sex			
Male	56 538 (40.9)	213 635 (41.0)	
Female	82 585 (59.1)	306 991 (59.0)	
Follow-up years			
Outcome: fragility fracture diagnosis	4.50 (2.1–7.9)	4.58 (2.1–8.0)	
Outcome: osteoporosis diagnosis	4.51 (2.1–7.9)	4.60 (2.1–8.0)	
IMD quintile			<0.0001
1 (least deprived)	16 026 (11.6)	62 026 (11.9)	
2	16 439 (11.9)	61 102 (11.7)	
3	16 030 (11.6)	58 013 (11.1)	
4	15 341 (11.1)	52 752 (10.1)	
5 (most deprived)	14 612 (10.5)	46 284 (8.8)	
Missing	59 675 (43.2)	240 339 (46.1)	
CCI score			<0.0001
1	113 950 (82.5)	447 602 (86.0)	
2	11 796 (8.5)	38 310 (7.4)	
3	6452 (4.7)	18 572 (3.6)	
4	2855 (2.1)	7790 (1.5)	
⩾5	3070 (2.2)	8352 (1.6)	
BMI kg·m^{-2}			<0.0001
<18.5 (underweight)	2214 (1.6)	6676 (1.3)	
18.5–24.9 (normal)	31 486 (22.8)	111 417 (21.4)	
25.0–29.9 (overweight)	37 110 (26.9)	109 519 (21.0)	
⩾30.0 (obese)	36 890 (26.7)	86 361 (16.6)	
Missing	30 423 (22.0)	206 653 (39.7)	
Smoking status			<0.0001
Never-smoker	62 095 (45.0)	254 418 (48.9)	
Ex-smoker	42 307 (30.6)	103 230 (19.8)	
Current smoker	30 760 (22.3)	103 729 (19.9)	
Missing	2961 (2.1)	59 249 (11.4)	
Alcohol consumption			<0.0001
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	20 109 (14.6)	118 653 (22.8)	
At least one prescription of			
Bisphosphonates	3923 (2.8)	11 628 (2.2)	<0.0001
Opioids	14 321 (10.4)	31 781 (6.1)	<0.0001
Vitamin D and/or calcium	4386 (3.2)	12 308 (2.4)	<0.0001
HRT	11 237 (8.1)	34 460 (6.6)	<0.0001
ICS	70 024 (50.7)	23 136 (4.4)	<0.0001
OCS	34 221 (24.8)	18 799 (3.6)	<0.0001
History of			
Falls	11 758 (8.5)	33 169 (6.4)	<0.0001
Any fracture	29 139 (21.1)	95 523 (18.3)	<0.0001
COPD	15 365 (11.1)	11 345 (2.2)	<0.0001

Data are presented as n, mean±SD, n (%) or median (interquartile range), unless otherwise stated; percentages have been rounded and may not total 100%. IMD: Index of Multiple Deprivation; CCI: Charlson Comorbidity Index; BMI: body mass index; HRT: hormone replacement therapy; ICS: inhaled corticosteroids; OCS: oral corticosteroids. [#]: p-values are based on the likelihood ratio test.

51.7±17.8 years, respectively. The median (IQR) follow-up time was 4.50 (2.1–7.9) years in asthma patients and 4.58 (2.1–8.0) years in nonasthma patients.

Patients with asthma compared with nonasthma were more likely to be obese (27% *versus* 17%; p<0.0001) and ex-smokers or current smokers (53% *versus* 40%; p<0.0001) (table 1). Furthermore, asthma patients had more comorbidities than controls (p<0.0001). More patients with asthma had at least one prescription of opioids (10% *versus* 6%; p<0.0001) before the index date than the nonasthma patients.

Osteoporosis risk

During the whole study period the incidence of osteoporosis was higher in the asthma than the nonasthma 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 sex modified the effect of asthma on osteoporosis, such that effect was stronger in younger people ($p_{interaction}$<0.0001) and slightly larger in males with asthma ($p_{interaction}$<0.0001), respectively. The risk stratified by age groups and sex is presented in supplementary table E1.

Osteoporosis risk among patients with asthma

Increasing OCS prescriptions raised the risk of osteoporosis, with patients exposed to nine or more prescriptions per year of follow-up found to be at higher risk than nonexposed patients (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 bisphosphonate prescription after OCS initiation during the follow-up (supplementary table E2). Risk of osteoporosis increased with regular use of ICS prescriptions 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).

Fragility fracture risk

A total of 4286 (3.1%) patients with asthma and 13 040 (2.5%) patients without asthma sustained a fragility fracture. The incidence rates were 5.99 (95% CI 5.81–6.17) in the asthma group and 4.77 (95% CI 4.69–4.85) in the nonasthma group per 1000 person-years (table 4). After adjusting for confounders, the fragility fracture risk was 12% higher in patients with asthma than those without asthma (aHR 1.12, 95% CI 1.07–1.16). The Kaplan–Meier plot also displayed a significantly higher probability of fracture during follow-up between the patients with and without asthma (log-rank test p<0.0001) (supplementary figure E1). The effect of asthma on fragility fracture risk was modified by age ($p_{interaction}$<0.0001), but not sex ($p_{interaction}$=0.9972). The risk stratified by age group and sex is presented in supplementary table E3. The forearm/wrist (aHR 1.21, 95% CI 1.13–1.30) and vertebra (aHR 1.19, 95% CI 1.10–1.28) were the sites with a higher risk (table 5). The risk of site-specific fragility fractures stratified by sex and age groups is summarised in supplementary table E4.

TABLE 2 Incidence rates and hazard ratios (HRs) for associations of osteoporosis with exposure to asthma

	Asthma patients		Nonasthma patients		Unadjusted HR (95% CI)	Adjusted HR[#] (95% CI)	p-value
	Patients with osteoporosis n	Rate per 1000 person-years	Patients with osteoporosis n	Rate per 1000 person-years			
Overall	3767	5.26	9911	3.23	1.45 (1.40–1.51)	1.18 (1.13–1.23)	<0.0001
Sex							
Male	768	2.60	1431	1.27	2.05 (1.88–2.24)	1.35 (1.22–1.50)	<0.0001
Female	2999	7.11	8480	4.37	1.35 (1.29–1.41)	1.14 (1.09–1.20)	<0.0001
Age years[¶]							
<40	55	0.28	126	0.17	1.67 (1.22–2.30)	1.54 (1.04–2.29)	0.032
40–49	208	1.48	496	0.93	1.59 (1.35–1.87)	1.29 (1.06–1.57)	0.013
50–59	678	5.06	1697	3.01	1.51 (1.38–1.65)	1.24 (1.12–1.39)	<0.0001
60–69	1195	8.97	3049	6.02	1.49 (1.39–1.59)	1.20 (1.10–1.29)	<0.0001
70–79	1182	15.04	3269	6.19	1.42 (1.33–1.52)	1.17 (1.08–1.26)	<0.0001
⩾80	449	15.99	1274	5.81	1.36 (1.22–1.52)	1.16 (1.02–1.32)	0.022

[#]: adjusted for age, sex, smoking, body mass index, Charlson Comorbidity Index score, inhaled corticosteroids, oral corticosteroids, Index of Multiple Deprivation and previous history (COPD and fractures), when not stratified by those variables; [¶]: age at the index date.

TABLE 3 Risk of osteoporosis within the 138 123 asthma patients stratified by well-known risk factors

	Patients with osteoporosis n	Rate per 1000 person-years	Unadjusted HR (95% CI)	Adjusted HR[#] (95% CI)	p-value
OCS prescriptions per person-year n (patients n)					<0.0001
0 (120 761)	2341	3.67	Reference	Reference	
1–2 (8489)	434	9.29	2.57 (2.31–2.86)	1.75 (1.57–1.95)	
3–5 (5797)	463	15.79	4.41 (3.97–4.89)	2.49 (2.24–2.77)	
6–8 (1652)	234	28.33	7.91 (6.92–9.18)	3.82 (3.28–4.44)	
⩾9 (1424)	295	54.03	15.36 (13.48–17.50)	6.11 (5.31–7.02)	
ICS prescriptions per person-year n (patients n)					<0.0001
0 (50 199)	1234	4.87	Reference	Reference	
1–8 (79 430)	1663	3.72	0.76 (0.70–0.81)	0.98 (0.92–1.05)	
9–13 (7068)	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)	
Sex					<0.0001
Male	768	2.61	Reference	Reference	
Female	2999	7.11	2.73 (2.52–2.95)	3.03 (2.80–3.28)	
Age years					<0.0001
⩽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	1195	8.97	32.31 (24.65–42.34)	31.27 (23.79–41.10)	
70–79	1182	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 status					<0.0001
Never-smoker	1435	4.37	Reference	Reference	
Ex-smoker	1381	6.39	1.10 (1.01–1.20)	1.14 (1.06–1.24)	
Current smoker	949	5.79	1.40 (1.27–1.55)	1.46 (1.34–1.59)	
BMI kg·m^{-2}					<0.0001
<18.5 (underweight)	253	14.18	1.48 (1.23–1.87)	1.50 (1.25–1.80)	
18.5–24.9 (normal)	1340	6.94	Reference	Reference	
25.0–29.9 (overweight)	1195	4.83	0.67 (0.62–0.73)	0.68 (0.63–0.74)	
⩾30.0 (obese)	880	3.21	0.49 (0.44–0.53)	0.50 (0.46–0.55)	
IMD quintile					<0.0001
1 (least deprived)	381	4.61	Reference	Reference	
2	401	4.96	1.08 (0.94–1.25)	1.01 (0.87–1.15)	
3	381	4.84	1.06 (0.92–1.22)	0.99 (0.86–1.14)	
4	370	4.95	1.08 (0.93–1.25)	1.02 (0.88–1.17)	
5 (most deprived)	429	6.17	1.35 (1.17–1.55)	1.36 (1.18–1.56)	
Not known	1805	5.47	1.18 (1.05–1.31)	1.21 (1.08–1.35)	

HR: hazard ratio; OCS: oral corticosteroids; ICS: inhaled corticosteroids; BMI: body mass index; IMD: Index of Multiple Deprivation. [#]: adjusted for age, sex, smoking, BMI, Charlson Comorbidity Index score, ICS, OCS, IMD and previous history (COPD and fractures).

Fracture risk among asthma patients

There were 17 233 (12.5%) and 87 675 (64%) distinct users with at least one OCS and ICS prescription per year of follow-up, respectively. The median (IQR) prescriptions per year of follow-up was 2 (1–4) for OCS and 5 (2–7) for ICS. The fragility fracture risk increased from the sixth 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 bisphosphonate 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).

Discussion

Overall, this study shows that asthma is associated with an increased risk of osteoporosis and fragility fractures. 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 for both bone conditions.

TABLE 4 Incidence rates and hazard ratios (HRs) for associations of fragility fractures with exposure to asthma

Variables	Asthma patients		Nonasthma patients		Unadjusted HR (95% CI)	Adjusted HR[#] (95% CI)	p-value
	Patients with fracture n	Rate per 1000 person-years	Patients with fracture n	Rate per 1000 person-years			
Overall	4286	5.99	13040	4.77	1.26 (1.21–1.30)	1.12 (1.07–1.16)	<0.0001
Sex							
Male	1107	3.76	3287	2.93	1.29 (1.21–1.39)	1.11 (1.02–1.20)	0.011
Female	3179	7.54	9753	6.06	1.25 (1.20–1.30)	1.11 (1.06–1.16)	<0.0001
Age years[¶]							
<40	388	1.98	1079	1.43	1.38 (1.23–1.55)	1.24 (1.07–1.44)	0.005
40–49	428	3.07	1171	2.21	1.39 (1.24–1.55)	1.33 (1.15–1.51)	<0.0001
50–59	636	4.74	1945	3.84	1.24 (1.13–1.35)	1.16 (1.04–1.28)	0.009
60–69	1052	7.87	3021	5.96	1.33 (1.24–1.42)	1.15 (1.05–1.25)	0.001
70–79	1128	13.36	3629	11.14	1.21 (1.13–1.29)	1.02 (0.95–1.11)	0.541
⩾80	654	23.41	2195	20.30	1.15 (1.06–1.26)	1.00 (0.90–1.10)	0.964

[#]: adjusted for age, sex, smoking, body mass index, Charlson Comorbidity Index score, inhaled corticosteroids, oral corticosteroids, Index of Multiple Deprivation and previous history (COPD and fractures), when not stratified by those variables; [¶]: age at the index date.

To the best of our knowledge, this is the largest study reporting the incidence and risk of osteoporosis and fragility fractures in asthma using a primary care database. Another strength of the study is the population-based setting, which means the findings are generalisable to the wider population. We captured osteoporosis and fragility fracture diagnoses for the general asthma population and not just for a specific subset, 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.

Data use from primary care databases has some limitations. First, there may be misclassification of asthma, osteoporosis and fragility fracture diagnoses, as we were reliant on how accurately GPs recorded these conditions. However, these diagnoses have been previously validated in the database, demonstrating a positive predictive value ∼90%; therefore, 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 them and would be recorded. However, vertebra 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, 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 healthcare datasets, our prescriptions were based on issued prescriptions without knowing whether or not they were dispensed.

The absolute incidence rate of each fragility fracture site in our general population is in accordance with another CPRD cohort study [30] and the incidence of hip fractures was additionally very similar to population statistics in the UK (10.8 *versus* 10.3 per 10000 person-years) [31]. The observed rate is consistent with the limited published studies examining osteoporosis and fracture risk in asthma. However, these studies were small (*e.g.* 105 patients *versus* 133 controls), lacked data on important confounders such

TABLE 5 Overall incidence rates and hazard ratios (HRs) for associations of site-specific fragility fractures with exposure to asthma

Fracture location	Asthma patients		Nonasthma patients		Unadjusted HR (95% CI)	Adjusted HR[#] (95% CI)	p-value
	Patients with fracture n	Rate per 1000 person-years	Patients with fracture n	Rate per 1000 person-years			
Forearm/wrist	1463	2.04	4363	1.59	1.28 (1.20–1.35)	1.21 (1.13–1.30)	<0.0001
Vertebra	685	0.96	1845	0.67	1.42 (1.30–1.55)	1.19 (1.10–1.28)	<0.0001
Hip	873	1.22	2954	1.08	1.13 (1.05–1.22)	1.01 (0.92–1.08)	0.905
Humerus	598	0.83	1842	0.67	1.24 (1.13–1.35)	1.05 (0.94–1.17)	0.371
Unspecified[¶]	667	0.93	2036	0.74	1.26 (1.16–1.38)	1.06 (0.95–1.17)	0.267

[#]: adjusted for age, sex, smoking, body mass index, Charlson Comorbidity Index score, inhaled corticosteroids, oral corticosteroids, Index of Multiple Deprivation and previous history (COPD and fractures), with nonasthma patients consider the reference group; [¶]: a mention that it was a fragility fracture without specifying the exact fracture location.

TABLE 6 Risk of fragility fractures within the 138 123 asthma patients stratified by well-known risk factors

	Patients with fracture n	Rate per 1000 person-years	Unadjusted HR (95% CI)	Adjusted HR# (95% CI)	p-value
OCS prescriptions per person-year n (patients n)					<0.0001
0 (120 890)	3515	5.54	Reference	Reference	
1–2 (8557)	326	7.62	1.37 (1.22–1.54)	0.97 (0.86–1.09)	
3–5 (5795)	251	9.23	1.66 (1.46–1.89)	1.00 (0.88–1.14)	
6–8 (1599)	105	14.28	2.60 (2.12–3.19)	1.35 (1.10–1.64)	
⩾9 (1282)	89	18.41	3.38 (2.71–4.21)	1.46 (1.16–1.83)	
ICS prescriptions per person-year n (patients n)					<0.0001
0 (50 448)	1766	7.05	Reference	Reference	
1–8 (79 692)	2174	4.99	0.70 (0.66–0.75)	0.92 (0.85–1.01)	
9–13 (6982)	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)	
Sex					<0.0001
Male	1107	3.76	Reference	Reference	
Female	3179	7.54	2.00 (1.86–2.14)	2.13 (1.98–2.28)	
Age years					<0.0001
⩽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	1052	7.87	3.98 (3.55–4.47)	4.13 (3.66–4.65)	
70–79	1128	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 status					<0.0001
Never-smoker	1736	5.29	Reference	Reference	
Ex-smoker	1517	7.04	1.34 (1.25–1.43)	1.09 (1.02–1.18)	
Current smoker	1033	6.19	1.17 (1.08–1.26)	1.35 (1.25–1.47)	
BMI kg·m^{-2}					<0.0001
<18.5 (underweight)	588	11.89	1.83 (1.51–2.21)	1.46 (1.19–1.79)	
18.5–24.9 (normal)	1257	6.34	Reference	Reference	
25.0–29.9 (overweight)	1296	5.80	0.92 (0.85–0.99)	0.83 (0.76–0.89)	
⩾30.0 (obese)	1145	5.08	0.82 (0.75–0.89)	0.71 (0.65–0.77)	
IMD quintile					<0.0001
1 (least deprived)	417	5.04	Reference	Reference	
2	479	5.93	1.18 (1.04–1.35)	1.11 (0.98–1.27)	
3	480	6.12	1.22 (1.07–1.39)	1.17 (1.03–1.33)	
4	394	5.28	1.05 (0.91–1.20)	1.02 (0.88–1.16)	
5 (most deprived)	409	5.87	1.17 (1.02–1.34)	1.15 (1.02–1.31)	
Not known	2107	6.39	1.25 (1.13–1.39)	1.27 (1.14–1.41)	

HR: hazard ratio; OCS: oral corticosteroids; ICS: inhaled corticosteroids; BMI: body mass index; IMD: Index of Multiple Deprivation. #: adjusted for age, sex, smoking, BMI, Charlson Comorbidity Index score, ICS, OCS, IMD and previous history (COPD and fractures).

as BMI and socioeconomic status or focused on specific asthma groups, providing little information about the risk in asthma [20, 22, 32]. Sweeney *et al.* [20] found a higher risk of osteoporosis and fracture compared with our study, which probably reflects the more severe asthma population. We found a greater risk of vertebra and forearm/wrist fractures, in accordance with reports that show 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] that did not find a reduced BMD at the 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 fragility fractures 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 fractures and are more likely in older people or females. Therefore, at younger ages and in males the main risk factor for osteoporosis will be steroids; hence, the stronger relationship. Lastly, males and younger people generally receive osteoporosis treatment less frequently than females and older people [35], and this was demonstrated in our findings. Knowledge that the effect of asthma on osteoporosis and fragility fractures is stronger in younger people is crucial in daily asthma practice in terms of the management of corticosteroid therapy and minimising the side-effects in subpopulations 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 also 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 (⩾0.7 mg per day) [14], with our findings confirming the negative effects on bone of ICS within the asthma population with regular use of ICS. It is best practice to review the 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 bisphosphonate 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. In particular, the British Thoracic Society/Scottish Intercollegiate Guidelines Network guideline on asthma management covers specific comorbidities including osteoporosis, but no specific bone protection guidance is given [2], and the National Institute for Health and Care Excellence asthma guideline does not mention osteoporosis at all [39]. Our results suggest that osteoporosis and fragility fractures should be addressed explicitly in future guideline updates.

Conclusions

Patients with asthma have an increased risk for osteoporosis and fragility fractures compared with the general population, particularly for vertebra and forearm/wrist fractures. An increased awareness of these bone condition comorbidities in asthma, particularly in the younger population, is needed. Reviewing corticosteroid dose and using the lowest dose possible to minimise the risk of these bone conditions in asthma is recommended.

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