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

Supplements

Supplementary Methods

Assessment of Body Mass Index (BMI) status in CPRD

Initially, the BMI was calculated using weights and heights recorded data (weight in kg and height in m) from the additional CPRD file. Weights less than 20 kg or more than 450kg and heights less than 1.21m or above 2.14m set to missing data. The measurement remained the same in case of only one weight and height measurement per day, otherwise the difference between multiple measurements on the same date was calculated getting the mean weight and height of the day. Then, the median height was used as least affected by outliers. The weight difference between visits was calculated. Random intercepts model was fitted regressing weight on time, adjusting for age and gender (grouping: patient) and calculate standardised residuals. Any weight measurements where the residuals are outliers unless the data point is within 10 kg of the preceding (n-1) or subsequent (n+1) measurement by date, was dropped. The modelling process was repeated using the cleaned data (once or twice more until no extras are removed) to ensure outlier residuals are removed. Measurements with an inter-date weight change of > 5 kg per day was removed if patient only has weight measurements for two visits. The BMI was calculated based on the WHO classification. Any BMI less than 10 set to missing data. Additionally, BMI status was extracted using Read codes for patients with a missing BMI status. The algorithm that used to define smoking status is available to download (1).

1. Ruth Costello. BmiAlgorithm (STATA): an algorithm to calculate body mass index (BMI) in patients of the UK Clinical Practice Research Datalink (CPRD) (Version v.1.0.1). Zenodo Mar 2017. https://zenodo.org/record/1405937 - .XhDB8C2Q01I

Assessment of alcohol consumption status in CPRD

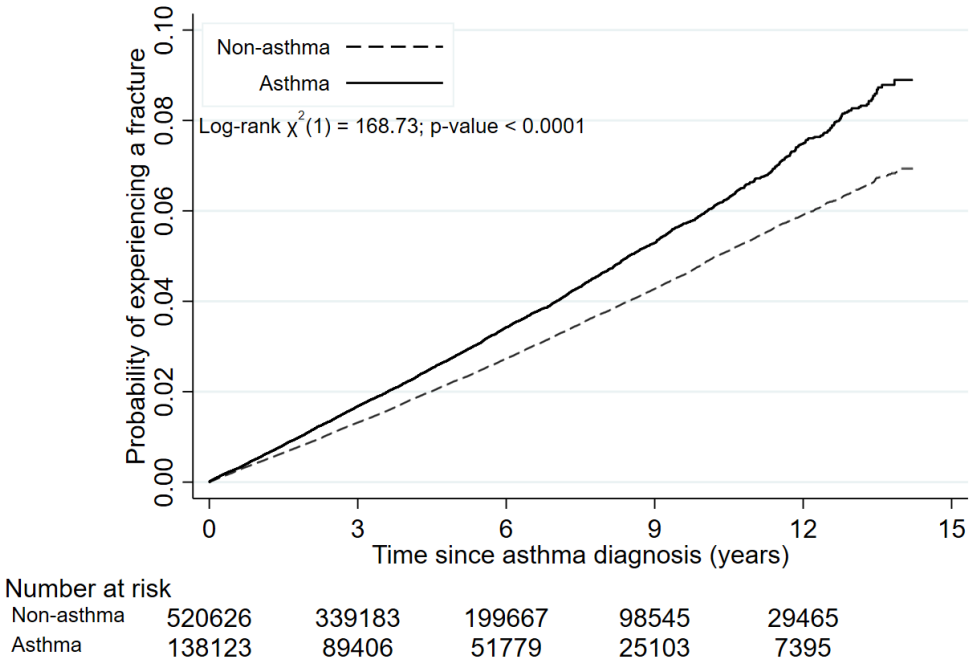
Self-reported alcohol consumption was collected prospectively and coded by general practitioners or practice nurses on the consultation date in CPRD. The most recent alcohol consumption record prior the index date was used to classify participants drinking behaviour. Four categories were defined including: (1) non-drinkers (Read codes such as "Non-drinker alcohol"), (2) former drinkers (Read codes such as "stopped drinking alcohol"), (3) occasional drinkers (Read codes such as "drinks rarely"), and (4) current drinkers (Read codes such as “drinks wine”, and “alcohol misuse”). We also extracted data based on the alcohol status and the alcohol units per week from the additional file of CPRD to define patients in the above categories, where available. The information about the alcohol status helped us to include more patients as “non-drinkers” or “former-drinkers”, and if a patient had more than 0 alcohol units per week classified as “current drinker”. We reclassified non-drinkers as former drinkers if they had any record of drinking recorded in their entire clinical record entered on CPRD prior to study entry, otherwise their category remained the same.

Assessment of smoking status in CPRD

Smoking status was defined as the CPRD record of smoking status using the nearest measurement ever prior to the index date and categorised as never-smoker, former-smoker, or current-smoker. Smoking status was determined from the CPRD datasets based on Read codes, additional clinical information and prescriptions for smoking cessation therapy. If never-smokers had a previous record indicating smoking in their entire CPRD history, they were counted as a former-smoker. The algorithm that used to define smoking status is available to download (2).

(2). Joseph RM, Movahedi M. SmokingDefinition v1.1 (STATA): an algorithm to define smoking status in patients of the UK Clinical Practice Research Datalink (CPRD). Zenodo Mar 2017. https://zenodo.org/record/1405937 - .XhDB8C2Q01I

Supplementary Results



Supplementary Figure E1. Kaplan-Meier plot showing the probability of experiencing a fracture during the follow-up between asthma and non-asthma patients. The long-rank test is also presented.

Supplementary Table E1. Incidence rates and hazard ratios (HR) for associations of osteoporosis with exposure to asthma stratified by gender and age groups.

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			
Males							
Age[a]							
<40	15	0.20	28	0.10	2.06 (1.10-3.86)	1.01 (0.42-2.39)	.995
40-49	39	0.72	64	0.31	2.31 (1.55-3.45)	1.36 (0.81-2.27)	.238
50-59	142	2.49	176	0.82	3.04 (2.43-3.79)	1.76 (1.33-2.33)	<.0001
60-69	252	4.19	455	1.99	2.11 (1.81-2.46)	1.31 (1.10-1.57)	<.0001
70-79	236	6.53	508	3.60	1.82 (1.56-2.13)	1.24 (1.04-1.48)	.02
≥80	84	7.54	200	4.71	1.60 (1.24-2.07)	1.20 (0.89-1.63)	.226
Females							
Age[a]							
<40	40	0.33	98	0.21	1.57 (1.08-2.26)	1.73 (1.10-2.71)	.016
40-49	169	1.97	432	1.33	1.48 (1.24-1.77)	1.26 (1.01-1.58)	.033
50-59	536	6.95	1,521	4.37	1.34 (1.21-1.48)	1.16 (1.03-1.31)	.012
60-69	943	12.89	2,594	9.34	1.38 (1.28-1.49)	1.16 (1.06-1.21)	.001
70-79	946	19.88	2,761	7.94	1.32 (1.23-1.43)	1.15 (1.06-1.28)	.001
≥80	365	21.53	1,074	6.07	1.33 (1.18-1.49)	1.14 (0.98-1.31)	.072

[a] Age at the index date.

[b] Adjusted for age, gender, smoking, BMI, Charlson score, ICS, OCS, IMD, previous: COPD, fractures; when not stratified by those.

Supplementary Table E2. Overall and stratified by gender prevalence of patients using at least one BP prescription after OCS initiation during the follow-up.

	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 per year of follow-up						
Overall						
1-2	982	8,489	12	980	8,557	11
3-5	1,393	5,797	24	1,390	5,795	24
6-8	769	1,652	46	730	1,599	45
≥9	795	1,424	55	682	1,282	53
Male						
1-2	288	3,224	9	258	3,305	8
3-5	476	2,318	21	444	2,345	19
6-8	275	651	42	261	655	40
≥9	341	597	57	303	578	52
Female						
1-2	901	5,262	17	735	5,253	14
3-5	1,062	3,479	30	975	3,443	28
6-8	575	1,001	57	498	944	53
≥9	561	827	68	428	704	60

BP, Bisphosphonate; OCS, Oral Corticosteroid.

Supplementary Table E3. Incidence rates and hazard ratios (HR) for associations of fragility fractures with exposure to asthma stratified by gender and age groups.

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			
Males							
Age[a]							
<40	136	1.79	467	1.60	1.12 (0.92-1.35)	0.94 (0.73-1.20)	.632
40-49	145	2.68	360	1.74	1.53 (1.26-1.86)	1.53 (1.21-1.95)	<.0001
50-59	155	2.72	423	1.97	1.38 (1.14-1.65)	1.28 (1.03-1.61)	.032
60-69	252	4.19	728	3.19	1.32 (1.14-1.52)	1.06 (0.89-1.25)	.501
70-79	265	7.34	831	5.91	1.26 (1.10-1.44)	1.00 (0.85-1.17)	.999
≥80	154	13.99	478	11.37	1.25 (1.04-1.50)	1.01 (0.81-1.26)	.892
Females							
Age[a]							
<40	252	2.09	612	1.32	1.58 (1.25-1.83)	1.47 (1.22-1.78)	<.0001
40-49	283	3.31	811	2.50	1.32 (1.15-1.51)	1.25 (1.06-1.47)	.010
50-59	481	6.23	1,522	5.19	1.20 (1.08-1.33)	1.12 (0.98-1.26)	.079
60-69	800	10.87	2,293	8.20	1.33 (1.22-1.44)	1.17 (1.06-1.29)	.001
70-79	863	17.86	2,798	15.10	1.19 (1.10-1.28)	1.03 (0.94-1.12)	.526
≥80	500	29.53	1,717	25.97	1.13 (1.03-1.25)	0.99 (0.89-1.13)	.989

[a] Age at the index date.

[b] Adjusted for age, gender, smoking, BMI, Charlson score, ICS, OCS, IMD, previous: COPD, fractures; when not stratified by those.

Supplementary Table E4. Adjusted Hazard ratios (HR) for associations of site-specific fracture with exposure to asthma stratified by gender and age groups.

Variables		aHR[a] (95% CI) comparing the risk of fracture in those with and without asthma				
		Vertebral fractures	**Forearm-wrist fractures**	**Hip fractures**	**Humerus fractures**	**Unspecified[b] fractures**
Gender						
	Male	1.16 (1.04-1.39)	1.12 (1.02-1.24)	1.08 (0.92-1.26)	1.14 (0.92-1.41)	1.16 (0.89-1.51)
	Female	1.13 (1.02-1.29)	1.24 (0.15-1.35)	0.96 (0.87-1.08)	1.02 (0.89-1.16)	1.03 (0.93-1.16)
Age[c]						
	<40	1.58 (1.15-2.17)	1.30 (1.09-1.55)	1.27 (0.62-2.60)	0.90 (0.58-1.40)	0.80 (0.22-2.88)
	40-49	1.59 (1.10-2.34)	1.31 (1.08-1.59)	1.26 (0.76-2.09)	1.21 (0.88-1.67)	1.39 (0.93-2.08)
	50-59	1.26 (0.92-1.71)	1.12 (0.94-1.33)	1.35 (0.98-1.86)	1.15 (0.89-1.48)	1.05 (0.79-1.39)
	60-69	1.16 (0.94-1.44)	1.31 (1.13-1.52)	0.91 (0.75-1.13)	1.22 (1.00-1.50)	1.05 (0.87-1.27)
	70-79	1.07 (0.89-1.28)	1.06 (0.90-1.25)	0.94 (0.82-1.09)	0.95 (0.76-1.20)	1.09 (0.91-1.31)
	≥80	1.02 (0.79-1.31)	1.12 (0.87-1.45)	1.02 (0.88-1.20)	0.65 (0.45-0.93)	1.05 (0.80-1.37)

[a] Adjusted for age, gender, smoking, BMI, Charlson score, ICS, OCS, IMD, previous: COPD, fractures.
[b] Just a mention that it was a fragility fracture without specifying the exact fracture location.
[c] Age at the index date.

Sensitivity analyses

When the outcome was the occurrence of a fragility fracture, the main analysis approach, in which we only excluded those with a previous history of the specific fracture outcome under investigation, assumes that a fracture will only affect subsequent fracture probability in the same bone. However, a fracture in one bone can affect fracture risk in another bone. To test this, we repeated the main analysis after additionally excluding those with a history of any previous fracture. Similarly, osteoporosis affects the fracture risk, so we included those with a history of osteoporosis (2.8% vs 2.2%).

Supplementary Table E5. Incidence rates and hazard ratios (HR) for associations of fragility fractures with exposure to asthma after conducting a series of sensitivity analyses.

	Unadjusted HR (95%CI)	**Adjusted HR[c] (95%CI)**	***p*-value**
Overall[a]	1.26 (1.21-1.30)	1.12 (1.07-1.17)	<.0001
Overall[b]	1.28 (1.23-1.33)	1.14 (1.08-1.20)	<.0001

[a] Patients with an osteoporosis diagnosis prior the asthma diagnosis have been included.
[b] Patients with an any fracture diagnosis prior the asthma diagnosis have been excluded.
[c] Adjusted for age, gender, smoking, BMI, Charlson score, ICS, OCS, IMD, previous: COPD, fractures osteoporosis; when not stratified by those.