

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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Supplements

Supplementary Methods

Dealing with implausible and missing values of ICS and OCS

Once all possible values about the quantity, prescribed number of tablets per day of each prescription had been estimated using the data provided by CPRD, the method to check for implausible results and fill in missing data was as follows.

- Define implausible number of tablets/puffs prescribed per day and quantity to these were defined using the 99th centile for each value and were defined as (OCS: 8 and 200; ICS: 4 and 400, respectively)
- Identify prescriptions with implausible quantity
- Replace those with implausible quantity with
 - mean of patient for that that specific drug, or if not available
 - mean of all patients for that specific drug
- Identify prescriptions with implausible number of tablets prescribed per day
- Replace those with implausible number of tablets prescribed per day with
 - mean of patient for that that specific drug, or if not available
 - mean of all patients for that specific drug
- Calculate prednisolone for OCS and beclomethasone for ICS equivalent dose per day of all prescriptions.

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](https://zenodo.org/record/1405937/files/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 Table E1. Equivalent doses to prednisolone and beclomethasone for oral and inhaled corticosteroids, respectively.

Oral corticosteroids	
Prednisolone 5mg	Betamethasone 0,75mg
	Deflazacort 6mg
	Dexamethasone 0,75mg
	Hydrocortisone 20mg
	Methylprednisolone 4mg
	Prednisone 5mg
Inhaled corticosteroids	
Beclomethasone 0.4mg	Budesonide 0.4mg
	Fluticasone 0.2mg
	Ciclesonide 0.16mg

Supplementary Results

Long-term exposure

Risk of osteoporosis

Supplementary Table E2. Association between Oral (OCS) / Inhaled (ICS) Exposure as rate per year up to 10 years prior to the Index Date and Risk of Osteoporosis.

Type of exposure	Cases		Controls		Unadjusted OR (95%CI)	Adjusted ^a OR (95%CI)	<i>p</i> -value [*]
	n	%	n	%			
No OCS use (reference)	578	36.9	1,751	52.8	1.00	1.00	
OCS prescriptions per year							<.0001
1	265	16.9	560	16.9	1.52 (1.26-1.82)	1.21 (0.99-1.48)	
2-3	212	13.6	468	14.1	1.59 (1.30-1.94)	1.18 (0.95-1.47)	
4-8	241	15.4	335	10.1	2.58 (2.08-3.19)	1.81 (1.44-5.13)	
≥9	268	17.2	199	6.1	4.68 (3.71-5.89)	3.13 (2.44-6.11)	
OCS cumulative dose (mg) per year							<.0001
≤500	332	21.2	746	22.5	1.49 (1.25-1.76)	1.15 (0.96-1.39)	
501-1000	155	9.9	308	9.3	1.69 (1.35-2.12)	1.28 (1.01-1.63)	
1001-2500	180	11.5	274	8.3	2.35 (1.86-2.97)	1.70 (1.31-2.18)	
>2500	319	20.4	234	7.1	4.78 (3.84-5.95)	3.26 (2.57-4.14)	
No ICS use (reference)	335	22.7	1,247	37.7	1.00	1.00	
ICS prescriptions per year							<.0001
1-6	557	35.6	1,014	30.6	2.13 (1.79-2.53)	1.43 (1.19-1.74)	
7-10	350	22.4	492	14.9	2.70 (2.22-3.30)	1.42 (1.15-1.76)	
≥11	302	19.3	560	16.9	1.99 (1.64-2.43)	1.64 (1.32-2.04)	
ICS cumulative dose (mg) per year							<.0001
≤40	201	13.4	432	13.6	1.90 (1.52-2.38)	1.27 (0.98-1.62)	
41-80	430	28.0	703	21.8	2.40 (1.99-2.90)	1.52 (1.23-1.87)	
81-120	277	18.3	427	13.5	2.63 (2.13-3.25)	1.50 (1.20-1.88)	
>120	301	19.8	504	15.8	2.27 (1.85-2.77)	1.63 (1.29-2.05)	

^a Adjusted for smoking, BMI, social class, Charlson Comorbidity Index score, any previous fracture, any previous fall, bisphosphonate, and number of ICS or OCS prescriptions accordingly.
Percentages have been rounded and might not total 100.

^{*}*P*-values for trend. The *p*-values are referred to the adjusted model.

Supplementary Table E3. Association between Oral (OCS) / Inhaled (ICS) Exposure as rate per year from the Asthma to the Index Date and Risk of Osteoporosis.

Type of exposure	Cases		Controls		Unadjusted OR (95%CI)	Adjusted ^a OR (95%CI)	p-value [*]
	n	%	n	%			
No OCS use (reference)	548	35.0	1,652	49.9	1.00	1.00	
OCS prescriptions per year							<.0001
1	254	14.2	586	17.7	1.39 (1.16-1.68)	1.10 (0.90-1.35)	
2-3	226	14.5	478	14.4	1.68 (1.38-2.06)	1.27 (1.02-1.58)	
4-8	233	14.9	363	11.0	2.36 (1.90-2.91)	1.66 (1.32-2.09)	
≥9	303	19.4	234	7.1	4.65 (3.71-5.82)	3.14 (2.46-4.00)	
OCS cumulative dose (mg) per year							<.0001
≤500	326	20.8	779	23.5	1.39 (1.17-1.65)	1.07 (0.89-1.30)	
501-1000	160	10.2	324	9.8	1.71 (1.36-2.15)	1.31 (1.03-1.67)	
1001-2500	179	11.4	292	8.8	2.25 (1.78-2.84)	1.58 (1.23-2.02)	
>2500	351	22.4	266	8.0	4.64 (3.75-5.74)	3.20 (2.54-4.03)	
No ICS use (reference)	456	29.2	1,543	46.6	1.00	1.00	
ICS prescriptions per year							<.0001
1-6	427	27.3	774	23.4	2.22 (1.86-2.66)	1.52 (1.25-1.85)	
7-10	346	22.1	454	13.7	2.95 (2.42-3.59)	1.61 (1.31-1.98)	
≥11	335	21.4	542	16.4	2.35 (1.95-2.84)	1.77 (1.43-2.19)	
ICS cumulative dose (mg) per year							<.0001
≤40	215	13.8	416	12.6	2.13 (1.71-2.64)	1.48 (1.17-1.87)	
41-80	305	19.5	475	14.3	2.60 (2.12-3.18)	1.54 (1.25-1.90)	
81-120	277	17.7	398	12.0	2.71 (2.21-3.33)	1.68 (1.35-2.09)	
>120	319	20.4	509	15.4	2.41 (1.98-2.93)	1.74 (1.40-2.18)	

^a Adjusted for smoking, BMI, social class, Charlson Comorbidity Index score, any previous fracture, any previous fall, bisphosphonate, and number of OCS or ICS prescriptions accordingly.
Percentages have been rounded and might not total 100.

^{*}P-values for trend. The p-values are referred to the adjusted model.

*Risk of fragility fractures***Supplementary Table E4.** Association between Oral (OCS) / Inhaled (ICS) Exposure as rate per year up to 10 years prior to the Index Date and Risk of Fragility Fractures.

Type of exposure	Cases		Controls		Unadjusted OR (95%CI)	Adjusted ^a OR (95%CI)	<i>p</i> -value [*]
	n	%	n	%			
No OCS use (reference)	1,153	54.1	2,639	59.6	1.00	1.00	
OCS prescriptions per year							.0005
1	336	15.8	750	17.0	1.02 (0.88-1.20)	0.94 (0.80-1.09)	
2-3	257	12.1	472	10.7	1.32 (1.11-1.58)	1.15 (0.95-1.38)	
4-8	211	9.9	358	8.1	1.43 (1.17-1.74)	1.25 (1.02-1.53)	
≥9	174	8.2	202	4.6	1.96 (1.56-2.48)	1.58 (1.25-2.00)	
OCS cumulative dose (mg) per year							<.0001
≤500	419	19.7	953	21.6	1.03 (0.89-1.19)	0.92 (0.80-1.07)	
501-1000	187	8.8	307	6.9	1.46 (1.18-1.80)	1.26 (0.98-1.55)	
1001-2500	186	8.7	290	6.6	1.56 (1.26-1.93)	1.37 (1.10-1.70)	
>2500	186	8.7	232	5.3	1.82 (1.46-2.27)	1.48 (1.18-1.86)	
No ICS use (reference)	781	36.7	1,998	45.2	1.00	1.00	
ICS prescriptions per year							.002
1-6	630	29.6	1,191	26.9	1.41 (1.23-1.63)	1.20 (1.03-1.40)	
7-10	353	16.6	556	12.6	1.68 (1.41-2.00)	1.27 (1.07-1.53)	
≥11	367	17.2	676	15.3	1.47 (1.24-1.73)	1.38 (1.14-1.65)	
ICS cumulative dose (mg) per year							.0006
≤40	283	13.3	535	12.3	1.38 (1.15-1.65)	1.17 (0.96-1.42)	
41-80	412	19.4	782	17.8	1.42 (1.21-1.68)	1.19 (1.01-1.41)	
81-120	293	14.0	472	11.0	1.70 (1.41-2.05)	1.31 (1.10-1.57)	
>120	361	17.1	636	14.5	1.54 (1.30-1.82)	1.38 (1.13-1.69)	

^a Adjusted for smoking, BMI, social class, Charlson Comorbidity Index score, any previous fracture, any previous fall, bisphosphonates and number of OCS or ICS prescriptions accordingly.

Percentages have been rounded and might not total 100.

^{*}*P*-values for trend. The *p*-values are referred to the adjusted model.

Supplementary Table E5. Association between Oral (OCS) / Inhaled (ICS) Exposure as rate per year from the asthma to the Index Date and Risk of Fragility Fractures.

Type of exposure	Cases		Controls		Unadjusted OR (95%CI)	Adjusted ^a OR (95%CI)	<i>p</i> -value [*]
	n	%	n	%			
No OCS use (reference)	1,111	52.1	2,541	57.5	1.00	1.00	
OCS prescriptions per year							.0003
1	346	16.2	765	17.3	1.03 (0.89-1.21)	0.94 (0.80-1.10)	
2-3	260	12.2	498	11.3	1.25 (1.05-1.50)	1.10 (0.91-1.32)	
4-8	225	10.6	386	8.7	1.42 (1.17-1.72)	1.23 (1.02-1.50)	
≥9	189	8.9	231	5.2	1.89 (1.51-2.36)	1.53 (1.21-1.92)	
OCS cumulative dose (mg) per year							<.0001
≤500	433	20.3	979	22.1	1.02 (0.89-1.18)	0.92 (0.81-1.07)	
501-1000	187	8.8	327	7.4	1.35 (1.10-1.66)	1.17 (0.95-1.45)	
1001-2500	193	9.1	310	7.0	1.54 (1.25-1.90)	1.35 (1.08-1.67)	
>2500	207	9.7	264	6.0	1.80 (1.45-2.22)	1.46 (1.18-1.82)	
No ICS use (reference)	958	45.0	2,415	54.6	1.00	1.00	
ICS prescriptions per year							<.0001
1-6	481	22.6	902	20.4	1.46 (1.25-1.71)	1.23 (1.04-1.46)	
7-10	321	15.1	495	11.2	1.76 (1.47-2.10)	1.42 (1.19-1.70)	
≥11	371	17.4	609	13.8	1.67 (1.41-1.98)	1.44 (1.20-1.75)	
ICS cumulative dose (mg) per year							.0014
≤40	237	11.4	452	10.4	1.46 (1.20-1.77)	1.22 (0.99-1.50)	
41-80	313	14.9	518	11.9	1.69 (1.41-2.02)	1.40 (1.15-1.69)	
81-120	297	14.2	507	11.6	1.65 (1.38-2.96)	1.39 (1.14-1.66)	
>120	327	15.6	536	12.3	1.66 (1.39-1.96)	1.40 (1.15-1.68)	

^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.
Percentages have been rounded and might not total 100.

^{*}*P*-values for trend. The *p*-values are referred to the adjusted model.

Sensitivity analysis

*Risk of osteoporosis***Supplementary Table E6.** Association between Oral (OCS) / Inhaled (ICS) Corticosteroids Exposure in the Year prior to the Index Date and Risk of Osteoporosis Including Only Patients with at Least One ICS Prescription.

Type of exposure	Cases		Controls		Unadjusted OR (95%CI)	Adjusted ^a OR (95%CI)	<i>p</i> -value*
	n	%	n	%			
No OCS use (reference)	378	55.3	682	64.8	1.00	1.00	
OCS prescriptions per year							<.0001
1	86	12.3	187	17.8	0.82 (0.61-1.12)	0.79 (0.58-1.10)	
2-3	75	11.0	108	10.3	1.33 (0.95-1.88)	1.15 (0.80-1.63)	
4-8	95	13.9	58	5.5	3.34 (2.29-4.87)	3.38 (2.27-5.03)	
≥9	50	7.3	17	1.6	5.57 (3.07-10.1)	4.52 (2.39-8.60)	
OCS cumulative dose (mg) per year							<.0001
≤500	119	17.3	244	23.1	0.88 (0.67-1.16)	0.81 (0.61-1.07)	
501-1000	55	8.0	60	5.7	1.79 (1.17-2.77)	1.73 (1.10-2.71)	
1001-2500	81	11.8	49	4.6	3.61 (2.41-5.42)	3.36 (2.19-5.18)	
>2500	51	7.4	19	1.8	5.70 (3.19-10.2)	5.50 (2.93-10.3)	
ICS prescriptions per year							.0099
1	73	10.6	152	14.4	1.00	1.00	
2-6	331	48.2	555	52.6	1.25 (0.91-1.72)	1.21 (0.86-1.69)	
7-10	157	22.8	193	18.3	1.77 (1.23-2.55)	1.55 (1.04-2.28)	
≥11	126	18.3	155	14.7	1.87 (1.26-2.80)	1.58 (1.06-2.41)	
ICS cumulative dose (mg) per year							.0025
≤40	146	21.4	279	26.5	1.00	1.00	
41-80	146	21.4	250	23.8	1.13 (0.83-1.52)	1.13 (0.83-1.56)	
81-120	119	17.4	193	18.4	1.17 (0.85-1.60)	1.01 (0.72-1.41)	
>120	273	39.6	330	31.4	1.63 (1.24-2.13)	1.57 (1.18-2.10)	

^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.
Percentages have been rounded and might not total 100.

**P*-values for trend. The *p*-values are referred to the adjusted model.

Supplementary Table E7. Association between Inhaled corticosteroids (ICS) Exposure in the year prior to the Index Date and Risk of Osteoporosis after restricting the individuals not in receipt of OCS within the database records.

Type of exposure	Cases		Controls		Unadjusted OR (95%CI)	Adjusted ^a OR (95%CI)	<i>p</i> -value [*]
	n	%	n	%			
No ICS use (reference)	286	28.2	579	34.9	1.00	1.00	
ICS prescriptions							.0252
1-6	413	40.7	683	41.1	1.10 (0.87-1.40)	0.94 (0.73-1.21)	
7-10	170	16.8	220	13.3	1.59 (1.19-2.13)	1.25 (1.02-1.56)	
≥11	146	14.4	179	10.7	2.04 (1.47-2.84)	1.54 (1.06-2.17)	
ICS type							
Beclomethasone	271	26.7	497	29.9	1.08 (0.85-1.40)	1.00 (0.75-1.31)	.703**
Budesonide	151	14.9	204	12.3	1.44 (1.05-1.98)	1.23 (1.06-1.72)	.034**
Fluticasone	295	29.0	372	22.4	1.58 (1.22-2.04)	1.26 (1.04-1.66)	.007**
Ciclesonide	9	0.9	8	0.5	1.72 (0.53-5.61)	2.07 (0.72-6.94)	.234**
ICS cumulative dose (mg)							.0201
≤40	128	12.6	257	15.5	0.97 (0.69-1.29)	0.82 (0.60-1.14)	
41-80	163	16.0	245	14.8	1.24 (0.93-1.82)	0.94 (0.67-1.33)	
81-120	138	13.6	212	12.8	1.23 (1.01-1.86)	1.07 (0.77-1.48)	
>120	299	29.4	365	22.0	1.85 (1.06-1.84)	1.41 (1.07-1.88)	

^a Adjusted for smoking, BMI, social class, Charlson Comorbidity Index score, any previous fracture, any previous fall, and bisphosphonates.

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

*Risk of fragility fractures***Supplementary Table E8.** Association between Oral (OCS) / Inhaled (ICS) Corticosteroids Exposure in the Year prior to the Index Date and Risk of Fragility Fractures Including Only Patients with at Least One ICS Prescription.

Type of exposure	Cases		Controls		Unadjusted OR (95%CI)	Adjusted ^a OR (95%CI)	<i>p</i> -value [*]
	n	%	n	%			
No OCS use (reference)	466	64.7	728	68.7	1.00	1.00	
OCS prescriptions per year							.0181
1	114	15.8	175	16.5	1.08 (0.82-1.42)	1.05 (0.80-1.38)	
2-3	62	8.6	75	7.1	1.37 (0.94-1.99)	1.29 (0.88-1.83)	
4-8	53	7.4	65	5.8	1.47 (1.03-2.13)	1.37 (1.02-2.01)	
≥9	25	3.5	21	2.0	1.93 (1.05-3.53)	1.72 (1.08-3.21)	
OCS cumulative dose (mg) per year							.0323
≤500	151	21.0	212	20.0	1.18 (0.92-1.51)	1.14 (0.89-1.48)	
501-1000	34	4.7	48	4.5	1.12 (0.69-1.80)	1.04 (0.64-1.72)	
1001-2500	44	6.1	49	4.6	1.55 (1.21-2.41)	1.37 (1.06-2.16)	
>2500	25	3.5	23	2.2	1.84 (1.29-3.34)	1.76 (1.18-3.06)	
ICS prescriptions per year							.0404
1	94	13.1	153	14.4	1.00		
2-6	358	49.7	564	53.2	1.06 (0.95-1.16)	0.98 (0.89-1.09)	
7-10	159	22.1	205	19.3	1.30 (1.05-1.54)	1.16 (1.02-1.31)	
≥11	109	15.1	138	13.0	1.47 (1.14-1.73)	1.20 (1.04-1.37)	
ICS cumulative dose (mg) per year							.0422
≤40	170	23.4	298	28.2	1.00	1.00	
41-80	166	23.1	230	21.7	1.28 (0.96-1.70)	1.21 (0.90-1.63)	
81-120	136	18.9	195	18.4	1.26 (1.02-1.69)	1.15 (0.85-1.56)	
>120	247	34.5	335	31.7	1.34 (1.13-1.74)	1.24 (1.04-1.63)	

^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.
Percentages have been rounded and might not total 100.

^{*}*P*-values for trend. The *p*-values are referred to the adjusted model.

Supplementary Table E9. Association between Inhaled corticosteroids (ICS) Exposure in the year prior to the Index Date and Risk of Fragility Fracture after restricting the individuals not in receipt of OCS within the database records.

Type of exposure	Cases		Controls		Unadjusted OR (95%CI)	Adjusted ^a OR (95%CI)	<i>p</i> -value [*]
	n	%	n	%			
No ICS use (reference)	319	31.3	651	34.6	1.00	1.00	
ICS prescriptions							.032
1-6	424	41.6	813	43.2	1.14 (0.99-1.45)	1.10 (0.86-1.41)	
7-10	154	15.1	245	13.0	1.37 (1.01-1.88)	1.29 (0.93-1.78)	
≥11	123	12.1	171	9.2	1.64 (1.14-2.36)	1.51 (1.11-2.20)	
ICS type							
Beclomethasone	302	29.6	557	29.6	1.10 (0.85-1.44)	1.05 (0.80-1.38)	.703**
Budesonide	130	12.8	224	11.9	1.34 (0.96-1.88)	1.21 (0.85-1.72)	.284**
Fluticasone	257	25.2	429	22.8	1.43 (1.09-1.89)	1.27 (0.94-1.70)	.117**
Ciclesonide	12	1.2	19	1.0	0.85 (0.25-2.89)	0.91 (0.26-3.23)	.895**
ICS cumulative dose (mg)							.0194
≤40	145	14.2	319	16.9	0.94 (0.69-1.29)	0.89 (0.96-1.42)	
41-80	170	16.7	286	15.2	1.30 (0.93-1.82)	1.19 (0.84-1.67)	
81-120	127	12.5	226	12.0	1.37 (1.01-1.86)	1.36 (0.98-1.87)	
>120	256	25.1	396	21.1	1.40 (1.06-1.84)	1.34 (1.04-1.79)	

^a Adjusted for smoking, BMI, social class, Charlson Comorbidity Index score, any previous fracture, any previous fall, and bisphosphonates.

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