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Use of sodium-glucose co-transporter 2 inhibitors, changes in body mass index and risk of fracture: A population-based cohort study

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ABSTRACT

Aims: Sodium-glucose co-transporter-2 (SGLT-2) inhibitor-induced weight loss might play a role in the debated elevated fracture risk with these agents. The aim of the current study was to investigate the association between SGLT-2 inhibitor use, changes in body mass index (BMI) and fracture risk.
Methods: A retrospective cohort study was conducted using data from the UK Clinical Practice Research Datalink (CPRD) GOLD (2013–2018). The study population (N = 34,960) consisted of adults with diabetes initiating a sulphonylurea or SGLT-2 inhibitor. Cox proportional hazards models estimated hazard ratios (HRs) for major osteoporotic fracture with SGLT-2 inhibitor use versus sulphonylurea use, stratified by change in BMI, average daily dose and cumulative dose. Analyses were adjusted for age, sex, lifestyle variables, comorbidities, and concomitant drug use.
Results: SGLT-2 inhibitor use was not associated with an increased fracture risk compared to sulphonylurea use (adjusted HR 1.19; 95% confidence interval (CI): 0.80–1.79). This finding remained consistent after stratification by BMI change. However, the highest cumulative dose category was associated with an increased fracture risk (adjusted HR: 2.10, 95 %CI: 1.11–3.99).
Conclusion: SGLT-2 inhibitor use was not associated with increased osteoporotic fracture risk, irrespective of change in BMI. However, a high cumulative dose could be an important risk factor.

1. Introduction

Sodium-glucose co-transporter-2 (SGLT-2) inhibitors have emerged as glucose-lowering drugs with beneficial effects on heart failure, atherosclerotic cardiovascular disease and renal complications in not only patients with diabetes, but also individuals without [1,2].

Despite these obvious benefits, there is an on-going debate about the SGLT-2 inhibitor-associated risk of fractures. The SGLT-2 inhibitor

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canagliflozin has been associated with an increase of several bone turnover markers and a decrease of hip bone mineral density (BMD) [3]. Although several meta-analyses of randomised controlled trials (RCTs) and observational studies have shown that the overall risk of fractures was not increased in SGLT-2 inhibitor users [4–8], a pooled analysis of 9 trials showed an increased overall risk of bone fractures in users of canagliflozin [9].

The use of SGLT-2 inhibitors also induces an average weight loss of 2 to 3 kg, even up to 5 kg in some patients [10,11]. This weight loss might affect fracture risk, since weight loss and a lower body mass index (BMI) are associated with an increased risk of fractures [12]. To date, however, this change in BMI has not been taken into account in the fracture risk analyses.

Therefore, the aim of the current study was to investigate the association between the use of SGLT-2 inhibitors and the risk of major osteoporotic fractures, and the role of a change in BMI herein.

2. Methods

2.1. Data source

We conducted a retrospective, population-based cohort study using data from the Clinical Practice Research Datalink (CPRD) GOLD. The CPRD GOLD contains primary healthcare information on approximately 7% of the population in the United Kingdom (UK). The recorded data include information on patient demographics, medical history, laboratory test results, prescription details, specialist referrals, lifestyle (e.g., smoking and alcohol use), hospital admissions and major outcomes since 1987, with on-going data collection [13]. Data in CPRD GOLD have been shown to be valid and of high quality for a wide range of diseases, including fractures [13,14]. The study protocol was approved by the Interdisciplinary Scientific Advisory Committee for Medicines and Healthcare products Regulatory Agency database research, protocol number 18_314R2.

2.2. Study population

All patients aged $\geq$ 18 years starting treatment with metformin only between 01-01-1998 and 30-06-2018 were included in a base cohort. Individuals needed to have at least one year of valid data collection before the first metformin prescription to be included. From this base cohort, we selected all patients with a first ever prescription for a SGLT-2 inhibitor, sulphonylurea, or dipeptidyl peptidase 4 (DPP-4) inhibitor between 01-01-2013 (date of introduction of the SGLT-2 inhibitors in the UK) and 30-06-2018. The index date was defined as the date of the first prescription for a SGLT-2 inhibitor, sulphonylurea, or DPP-4 inhibitor. Individuals with no BMI record in the 3 years before the index date were excluded.

2.3. Study outcome

Patients were followed from their index date until the date of registration of the outcome of interest, disenrollment, death, or end of study period, whichever occurred first. The primary outcome of interest was a first major osteoporotic fracture (hip, radius/ulna, humerus or clinical symptomatic vertebral fracture), defined by Read codes. Secondary outcomes included a fracture of the hip, radius/ulna, and vertebrae individually.

2.4. Exposure to glucose-lowering agents

Follow-up time was divided into fixed intervals of 30 days, starting from the index date. Based on the time since the most recent non-insulin glucose-lowering agent prescription, an interval was classified as 'current use' or 'past use'. 'Current use' was defined as at least one prescription in the 90 days before the start of the interval, whereas 'past use' was defined as the most recent prescription more than 90 days before the start of the interval. 'Current use' was further stratified into the following mutually exclusive exposure groups: current use of SGLT-2 inhibitors, current use of sulphonylureas, current use of DPP-4 inhibitors, current concomitant use of a SGLT-2 inhibitor and/or a sulphonylurea and/or a DPP-4 inhibitor, and current use of another non-insulin glucose-lowering agent. Patients could move between current and past use intervals during follow-up.

In order to study the association between change in BMI and fracture risk, we stratified current use of SGLT-2 inhibitors by change in BMI since the index date. The most recent BMI measurement was determined at the start of each interval. In addition, we stratified current use of SGLT-2 inhibitors by cumulative dose and average daily dose, as weight changes might be related to the treatment dose [15]. The cumulative dose and the average daily dose were calculated using defined daily doses (DDDs) and expressed in dapagliflozin equivalents, using the WHO ATC/DDD index [16]. The cumulative dose was calculated by summing the amount of prescribed SGLT-2 inhibitor DDDs and was subsequently categorised into three groups: (1) $<$ 1.82 g dapagliflozin equivalents, (2) 1.82–6.29 g dapagliflozin equivalents, or (3) $\geq$ 6.30 g dapagliflozin equivalents. The average daily dose of the SGLT-2 inhibitor was calculated by dividing its cumulative dose by the treatment time and was subsequently categorised into four groups: (1) no average daily dose, (2) $<$ 6.6 mg dapagliflozin equivalents/day, (3) 6.6–9.9 mg dapagliflozin equivalents/day, or (4) $\geq$ 10 mg dapagliflozin equivalents/day.

2.5. Covariates

Potential risk factors related to the outcome (major osteoporotic fractures) and to the exposure of interest were selected based on literature. Potential confounders assessed at baseline included sex, smoking status (non-smoker, current smoker, former smoker or unknown), and alcohol use (yes, no or unknown). The following potential confounders were determined time-dependently at the start of each 30-day interval: age, most recent BMI record; duration of diabetes; most recent glycosylated haemoglobin A1c (HbA1c) measurement in the last year; most recent estimated glomerular filtration rate (eGFR) in the last year; falls in the 7–12 months before an interval; and a history of fractures, hyperthyroidism, hypothyroidism, COPD, heart failure, cancer, rheumatoid arthritis, retinopathy, secondary osteoporosis, neuropathy, diabetic foot ulcers, or albuminuria (urine albumin-to-creatinine ratio $\geq$ 30 mg/g). Most recent eGFR was evaluated using laboratory test data and CPRD Read codes (stages of chronic kidney disease). When multiple eGFR values were reported on one day, we used the mean value.

In addition, a prescription of the following drugs in the 6 months before an interval was considered as a potential confounder: insulin, oral glucocorticoids, statins, antiarrhythmics, antidepressants, anti-Parkinson agents, antipsychotics, hypnotics/anxiolytics, antihypertensives, bisphosphonates, raloxifene, vitamin D, calcium, strontium ranelate and hormone replacement therapy.

2.6. Data analysis

Time-dependent Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for major osteoporotic fractures associated with current use of SGLT-2 inhibitors, compared with current use of sulphonylureas. Sulphonylureas were chosen as the reference group as both SGLT-2 inhibitors and sulphonylureas are second line treatment options for type 2 diabetes in the UK [17]. Current SGLT-2 inhibitor use was further stratified by sex, age, type of fracture, average daily dose, cumulative dose, and change in BMI according to the following categories: loss or gain of $\leq$ 0.50 kg/m^2, loss of $\geq$ 0.51 kg/m^2, and gain of $\geq$ 0.51 kg/m^2. We performed an additional analysis to study the association between changes in BMI and risk of osteoporotic fractures, irrespective of SGLT-2 inhibitor use. In this analysis, we determined the HR for major osteoporotic fracture for

current users of all non-insulin glucose-lowering agents, stratified by change in BMI (measured time-dependently), versus patients with no change in BMI. No change in BMI was defined as loss or gain of ≤ 0.50 kg/m^2.

HRs were adjusted for age, sex and potential confounders that showed a > 5% change in the beta-coefficient of an age- and sex-adjusted analysis, or when consensus about inclusion existed within the team of researchers, supported by clinical evidence from literature. An indicator variable was used to account for missing data.

2.7. Sensitivity analyses

We conducted multiple sensitivity analyses. The first sensitivity analysis investigated the influence of reference group. In this analysis, we changed the reference group from current sulphonylurea use (used in our primary analysis) to current DPP-4 inhibitor use (another second-line treatment option). In a second sensitivity analysis, we only considered change in BMI in current SGLT-2 inhibitor users if the most recent BMI measurement was recorded in the year before the start of an interval. As weight loss is mainly expected in the first year of SGLT-2 inhibitor therapy, we also studied the association between SGLT-2 inhibitor use and change in BMI during the first year after SGLT-2 inhibitor initiation. In the final sensitivity analysis, we studied the number of BMI recordings after index date to examine whether this was regularly measured. All statistical analyses were performed using SAS statistical software, version 9.4 (SAS Institute, Inc, NC, USA).

3. Results

3.1. Patient characteristics

Supplemental Figure 1 shows the selection of the study population from the base cohort. The final study population included 34,960 initiators of SGLT-2 inhibitors, sulphonylureas and DPP-4 inhibitors. Table 1 shows the baseline characteristics of the included patients. At baseline, there were 6,579 SGLT-2 inhibitor users, 13,767 sulphonylurea users and 14,488 DPP-4 inhibitor users, with a median duration of follow-up of 2.4, 3.4 and 3.1 years, respectively. The mean age of SGLT-2 inhibitor users was 58.2 years and 43.0% (N = 2,830) were female. The mean age of sulphonylurea users was 62.0 years and 42.7% (N = 5,877) were female. SGLT-2 inhibitor users had a longer median diabetes duration (6.4 versus 2.4 years), were more obese (mean BMI 35.8 kg/m^2 versus 32.0 kg/m^2), had more diabetes-related comorbidities (e.g. retinopathy and neuropathy), were more likely to use insulin (13.1% vs. 0.8%), were less likely to have other comorbidities (e.g. COPD and congestive heart failure), and were less likely to use oral glucocorticoids (6.9% vs. 11.2%), calcium (2.1% vs. 4.5%), and bisphosphonates (1.0% vs. 3.3%) when compared to sulphonylurea users. 67% of all SGLT-2 inhibitor prescriptions during follow-up were for dapagliflozin, 19% for empagliflozin, and 14% for canagliflozin (data not shown).

3.2. SGLT-2 inhibitors, change in BMI and risk of major osteoporotic fractures

There was no difference in risk of major osteoporotic fractures between current SGLT-2 inhibitor users and current sulphonylurea users (adjusted [adj.] HR: 1.22, 95% CI 0.81–1.83) (Table 2). This finding remained consistent after stratification of current SGLT-2 inhibitor use by sex, age, and fracture type.

When current use of SGLT-2 inhibitors was stratified according to change in BMI since index date, BMI decrease was not associated with an increased risk of major osteoporotic fractures (Table 3). The risk of major osteoporotic fractures was comparable in patients with a BMI loss or gain of ≤ 0.50 kg/m^2 (adj. HR 1.26, 95% CI: 0.76–2.23), patients losing ≥ 0.51 kg/m^2 (adj. HR 1.11, 95% CI: 0.64–1.93), and patients gaining ≥ 0.51 kg/m^2 (adj. HR 1.30, 95% CI: 0.47–3.58) when compared to current use of sulphonylureas. The mean change in BMI in these groups was: −0.02 kg/m^2 (SD 0.17 kg/m^2); +2.1 kg/m^2 (SD 2.1 kg/m^2); and −2.5 kg/m^2 (SD 1.9 kg/m^2) respectively.

3.3. SGLT-2 inhibitor dose and risk of major osteoporotic fractures

Stratification of current SGLT-2 inhibitor use by average daily dose did not demonstrate a significant difference in risk of major osteoporotic fractures in the different average daily dose groups compared to current sulphonylurea use (Table 4). However, stratification by cumulative dose categories indicated an increased risk of major osteoporotic fractures in the highest cumulative dose category (adj. HR: 2.10, 95% CI 1.11–3.99). We also found greater mean BMI decreases in the highest cumulative dose category (−1.9 kg/m^2, standard deviation [SD] 2.8 kg/m^2) compared to the lower cumulative dose categories of 1.82–6.29 g (−1.3 kg/m^2, SD 2.2 kg/m^2) or < 1.82 g (−0.4 kg/m^2, SD 1.4 kg/m^2).

3.4. Non-insulin glucose lowering agents, change in BMI and risk of major osteoporotic fractures

When comparing all current users of non-insulin glucose-lowering agents with BMI decrease (≥0.51 kg/m^2 loss) to those with no BMI change (≤0.50 kg/m^2 gain or loss), BMI decrease was not associated with an increased risk of major osteoporotic fracture (Table 5). However, patients with a gain in BMI of >1.0 kg/m^2 had a statistically significant decreased risk of a major osteoporotic fracture (adj. HR: 0.70, 95% CI 0.51–0.97) compared to those with no change in BMI. Mean change in BMI was −2.6 kg/m^2 (SD 1.9) in users with a loss of BMI ≥ 1.00 kg/m^2; −0.7 kg/m^2 (SD 0.1) in users with a loss of BMI 0.51–0.99 kg/m^2; 0.0 (SD 0.2) in users with no change in BMI; +0.7 kg/m^2 (SD 0.1) in users with a gain of BMI 0.51–0.99 kg/m^2; +2.3 kg/m^2 (SD 1.7) in users with a gain of BMI ≥ 1.00 kg/m^2.

3.5. Sensitivity analyses

The first sensitivity analysis, in which DPP-4 inhibitor use was used as the reference group instead of sulphonylurea use, did not lead to different findings. The fully adjusted HR for major osteoporotic fracture in current SGLT-2 inhibitor use compared to current DDP-4 inhibitor use was 1.30 (95% CI 0.86–1.97). Moreover, the results were not substantially altered in the sensitivity analysis in which the change in BMI was only considered if the most recent BMI measurement was within one year before the start of an interval. Finally, studying BMI change only in the first year of SGLT-2 inhibitor treatment did not substantially alter the results either (data not shown).

4. Discussion

The results of this large, population-based study showed that current use of SGLT-2 inhibitors was not associated with an increased risk of major osteoporotic fractures when compared to current use of sulphonylureas. Furthermore, a decrease in BMI in users of SGLT-2 inhibitors or other non-insulin glucose-lowering agents was not associated with an increased risk of major osteoporotic fractures either. Stratification by sex, age, type of fracture or average daily dose revealed no association. Interestingly, current use of SGLT-2 inhibitors with a cumulative dose exposure of ≥ 6.30 g dapagliflozin equivalents showed an increased risk of major osteoporotic fractures.

Recently published meta-analyses of RCTs and observational studies comparing use of SGLT-2 inhibitors with placebo or an active comparator also did not observe an increased risk of fractures in users of SGLT-2 inhibitors [4–8,18]. Nevertheless, the results of the CANagliflozin cardioVascular Assessment Study (CANVAS) suggested that the use of canagliflozin might be associated with an increased risk of fractures [19]. This finding was replicated in a pooled analysis of the results of the CANVAS study and 8 non-CANVAS studies. However, the results may

Table 1
Baseline characteristics of SGLT-2 inhibitor users, sulphonylurea users and DPP-4 inhibitor users.[a,b]

Characteristic	SGLT-2 inhibitor users (N = 6,579)		Sulphonylurea users (N = 13,767)		DPP-4 inhibitor users (N = 14,488)	
Median follow-up time (years (IQR))	2.4	(1.2–3.4)	3.4	(2.1–4.6)	3.1	(1.7–4.4)
Median diabetes duration (years (IQR))	6.4	(3.0–9.5)	2.4	(0.6–5.2)	4.6	(2.0–7.9)
Number of women	2,830	(43.0)	5,877	(42.7)	6,032	(41.6)
Age at index date						
Mean age (years (SD))	58.2	(10.2)	62.0	(12.9)	64.0	(12.4)
18–49 years	3,569	(54.2)	5,853	(42.5)	5,259	(36.3)
50–59 years	2,125	(32.3)	3,881	(28.2)	4,245	(29.3)
60–69 years	805	(12.2)	2,835	(20.6)	3,436	(23.7)
70–79 years	77	(1.2)	1,103	(8.0)	1,409	(9.7)
80+ years	<5	(0.0)	95	(0.7)	139	(1.0)
BMI (most recent record in the 3 years before index date)						
Mean BMI (kg/m^2 (SD))	35.8	(6.9)	32.0	(6.7)	32.8	(6.5)
<20.0 kg/m^2	<5	(0.0)	50	(0.4)	25	(0.2)
20.0–24.9 kg/m^2	149	(2.3)	1,559	(11.3)	1,092	(7.5)
25.0–29.9 kg/m^2	1,093	(16.6)	4,213	(30.6)	4,175	(28.8)
30.0–34.9 kg/m^2	2,098	(31.9)	4,165	(30.3)	4,652	(32.1)
≥35 kg/m^2	3,236	(49.2)	3,780	(27.5)	4,544	(31.4)
Smoking status at index date						
Never	1,782	(27.1)	3,766	(27.4)	3,847	(26.6)
Current	1,028	(15.6)	2,393	(17.4)	2,140	(14.8)
Ex	3,766	(57.2)	7,593	(55.2)	8,495	(58.6)
Missing	<5	(0.0)	15	(0.1)	6	(0.0)
Alcohol use at index date						
No	1,890	(28.7)	4,285	(31.1)	4,563	(31.5)
Yes	4,587	(69.7)	9,217	(66.9)	9,694	(66.9)
Missing	102	(1.6)	265	(1.9)	231	(1.6)
HbA1c (most recent record in the year before index date)						
Mean HbA1c (% (SD))	8.8	(1.6)	8.6	(1.7)	8.4	(1.5)
Mean HbA1c (mmol/mol (SD))	73	(13.3)	70	(13.8)	68	(12.1)
<6.0% (42 mmol/mol)	50	(0.8)	170	(1.2)	152	(1.0)
6.0–6.9% (42–52 mmol/mol)	603	(9.2)	1,763	(12.8)	2,091	(14.4)
7.0–7.9% (53–63 mmol/mol)	1,579	(24.0)	3,684	(26.8)	4,540	(31.3)
8.0–8.9% (64–74 mmol/mol)	1,567	(23.8)	2,712	(19.7)	3,341	(23.1)
≥9.0% (75 mmol/mol)	2,556	(38.9)	4,314	(31.3)	3,960	(27.3)
Missing	224	(3.4)	1,124	(8.2)	404	(2.9)
eGFR (most recent record in the year before index date)						
<15 ml/min/1.73 m^2	<5	(0.0)	7	(0.1)	19	(0.13)
15–29 ml/min/1.73 m^2	<5	(0.0)	139	(1.0)	245	(1.7)
30–59 ml/min/1.73 m^2	227	(3.5)	1,683	(12.2)	2,320	(16.0)
60–89 ml/min/1.73 m^2	3,615	(54.9)	6,992	(50.8)	7,427	(51.3)
≥90 ml/min/1.73 m^2	2,582	(39.2)	4,449	(32.3)	14,227	(29.2)
Missing	154	(2.3)	497	(3.6)	250	(1.7)
Falls in the 7–12 months before	38	(0.6)	117	(0.8)	153	(1.1)
History of comorbidities ever before						
Fracture	1787	(27.2)	3,489	(25.3)	3,789	(26.2)
Hyperthyroidism	67	(1.0)	186	(1.4)	191	(1.3)
Hypothyroidism	620	(9.4)	1,298	(9.4)	1,407	(9.7)
COPD	379	(5.8)	1,117	(8.1)	1,082	(7.5)
Congestive heart failure	144	(2.2)	537	(3.9)	624	(4.3)
Cancer	1,879	(28.5)	4,162	(30.2)	4,426	(30.5)
Rheumatoid arthritis	103	(1.6)	278	(2.0)	265	(1.8)
Retinopathy	1,676	(25.4)	2,329	(16.9)	3,426	(23.6)
Secondary osteoporosis	678	(10.3)	1,262	(9.2)	1,252	(8.6)
Neuropathy	429	(6.5)	623	(4.5)	855	(5.9)
Albuminuria	2667	(40.5)	4255	(30.9)	5471	(37.8)
Drugs used within 6 months before						
Insulins	864	(13.1)	104	(0.8)	374	(2.6)
Oral glucocorticoids	451	(6.9)	1,540	(11.2)	1,172	(8.1)
Statins	5,043	(76.7)	9,559	(69.4)	11,194	(77.3)
Antiarrhythmics	54	(0.8)	177	(1.3)	199	(1.4)
Antidepressants	1,946	(29.6)	3,456	(25.1)	3,499	(24.2)
Anti-Parkinson agents	31	(0.5)	84	(0.6)	93	(0.6)
Antipsychotics	159	(2.4)	399	(2.9)	337	(2.3)
Hypnotics/anxiolytics	432	(6.6)	1,092	(7.9)	970	(6.7)
Antihypertensives	4,669	(71.0)	9,062	(65.8)	10,533	(72.7)
Bisphosphonates	67	(1.0)	448	(3.3)	379	(2.6)
Raloxifene	<5	(0.0)	<5	(0.0)	<5	(0.0)
Vitamin D	25	(0.4)	103	(0.7)	134	(0.9)
Calcium	139	(2.1)	613	(4.5)	634	(4.4)
Strontium ranelate	<5	(0.0)	5	(0.0)	<5	(0.0)
Hormone replacement therapy	31	(0.5)	55	(0.4)	55	(0.4)

Abbreviations: BMI: body mass index; COPD: chronic obstructive pulmonary disease; DPP-4: dipeptidyl peptidase 4; HbA1c: glycosylated haemoglobin type A1c; IQR: inter quartile range; SD: standard deviation; SGLT-2: sodium-glucose co-transporter 2; eGFR: estimated glomerular filtration rate.

[a] Data are presented as number (%) of individuals, unless stated otherwise.

[b] Combined users (N = 126) are not shown.

Table 2
Risk of major osteoporotic fractures in past and current users of non-insulin glucose-lowering agents compared to current sulphonylurea use, for current SGLT-2 inhibitor use stratified by sex, age and type of fracture.

Exposure to glucose-lowering agents	Number of MOFs (N = 415)	IR (/1000 PY)	Age/sex adjusted HR (95% CI)	Age/sex/BMI adjusted HR (95% CI)	Fully adjusted HR[a] (95% CI)
Past use of glucose-lowering agents	27	0.88	0.16 (0.10–0.24)	0.16 (0.10–0.24)	0.35 (0.22–0.56)
Current use of glucose-lowering agents					
Sulphonylureas	124	5.28	Reference	Reference	Reference
DPP-4 inhibitors	94	5.16	0.93 (0.71–1.22)	0.94 (0.72–1.23)	0.92 (0.70–1.21)
Combined use[b]	104	5.09	1.01 (0.78–1.32)	1.03 (0.79–1.34)	1.09 (0.83–1.43)
Other glucose-lowering agents[c]	33	4.47	0.89 (0.60–1.31)	0.88 (0.59–1.29)	0.84 (0.57–1.25)
SGLT-2 inhibitors	33	4.53	1.22 (0.82–1.82)	1.26 (0.84–1.87)	1.21 (0.80–1.81)
By sex[d]					
Males	13	3.16	1.12 (0.59–2.09)	1.11 (0.59–2.09)	1.03 (0.54–1.98)
Females	20	6.32	1.32 (0.79–2.20)	1.37 (0.82–2.28)	1.32 (0.78–2.22)
By age at index date[e]					
<50 years	<5	2.80	1.72 (0.45–6.56)	1.68 (0.44–6.52)	1.86 (0.46–7.47)
50–59 years	7	2.62	0.83 (0.34–2.04)	0.88 (0.36–2.18)	0.84 (0.33–2.14)
60–69 years	15	6.37	1.27 (0.68–2.37)	1.25 (0.67–2.35)	1.37 (0.71–2.62)
70+ years	7	8.57	1.35 (0.61–2.96)	1.37 (0.62–3.03)	1.19 (0.53–2.65)
By type of fracture					
Hip	7	0.96	1.92 (0.80–4.57)	2.16 (0.90–5.16)	2.08 (0.86–5.06)
Vertebral	5	0.68	0.83 (0.31–2.19)	0.87 (0.33–2.33)	0.87 (0.32–2.35)
Radius/ulna	13	1.78	1.37 (0.71–2.64)	1.35 (0.70–2.60)	1.41 (0.72–2.77)

Abbreviations: BMI: body mass index; CI: confidence interval; DPP-4: dipeptidyl peptidase-4; HR: hazard ratio; IR: incidence rate; MOF: major osteoporotic fracture; PY: person years; SGLT-2: sodium-glucose co-transporter 2.
Note: all groups in this table were mutually exclusive. Current use (1–90 days) or past use (>90 days) were defined by the time since the most recent prescription.
[a] Adjusted for age, sex, body mass index, alcohol use, diabetes duration, history of fracture, chronic obstructive pulmonary disease, congestive heart failure, cancer, eGFR, albuminuria, history of falls in the previous 7–12 months and the use of the following drugs in the previous 6 months: insulin, antidepressants, anxiolytics/hypnotics, bisphosphonates, calcium, and glucocorticoids.
[b] Combined use of at least two of the following glucose-lowering agents: a sulphonylurea and/or DPP-4 inhibitor and/or SGLT-2 inhibitor.
[c] No sulphonylurea, DPP-4 inhibitor or SGLT-2 inhibitor.
[d] Compared with controls of the same sex.
[e] Compared with controls in the same age category.

have been driven by the participants of the CANVAS study, as they were of great influence on the study results of this pooled analysis and participants differed substantially from the study populations of the non-CANVAS studies (e.g. with regard to age, race, kidney function and risk of cardiovascular events) [9]. In a RCT assessing the effects of canagliflozin on bone mineral density, a small but statistically significant decrease in total hip bone mineral density over 104 weeks was found, but not at other sites measured [3]. The authors suggested that it was likely the result of increased bone turnover due to weight loss. An alternative hypothesis is that the use of canagliflozin results in increased phosphate reabsorption, which triggers secretion of fibroblast growth factor 23 (FGF23), which eventually leads to decreased production of 1,25-dihydroxyvitamin D (the biologically active form of vitamin D) and increased secretion of parathyroid hormone (PTH) [20].

In our current study, we did not observe an increased risk of major osteoporotic fractures in SGLT-2 inhibitor users with a BMI decrease of>0.50 kg/m^2. It is well established that a low BMI increases the risk of fractures. Possible explanations include increased bone turnover, decreased bone formation and bone mineral density as a result of reduced mechanical loading, frailty in elderly, and muscle loss [12,21,22]. There are several meta-analyses and studies that underline the increased risk of fractures in patients with weight loss [23–25]. The

Table 3
Risk of major osteoporotic fractures in past and current users of non-insulin glucose-lowering agents compared to current sulphonylurea use, for current SGLT-2 inhibitor use stratified by change in BMI since index date.

Exposure to glucose-lowering agents	Number of MOFs (N = 415)	IR (/1000 PY)	Age/sex adjusted HR (95% CI)	Fully adjusted HR[a] (95% CI)
Past use of glucose-lowering agents	27	0.88	0.16 (0.10–0.24)	0.35 (0.22–0.57)
Current use of glucose-lowering agents				
Sulphonylureas	124	5.28	Reference	Reference
DPP-4 inhibitors	94	5.16	0.93 (0.71–1.22)	0.92 (0.70–1.21)
Combined use[b]	104	5.09	1.01 (0.78–1.32)	1.08 (0.82–1.41)
Other glucose-lowering agents[c]	33	4.47	0.89 (0.60–1.31)	0.85 (0.58–1.26)
SGLT-2 inhibitors	33	4.53	1.22 (0.82–1.82)	1.18 (0.78–1.76)
By change in BMI since index				
Loss or gain of ≤ 0.50 kg/m^2	14	4.85	1.32 (0.76–2.32)	1.25 (0.71–2.21)
Loss of ≥ 0.51 kg/m^2	15	4.09	1.09 (0.63–1.89)	1.09 (0.62–1.89)
Gain of ≥ 0.51 kg/m^2	<5	5.54	1.50 (0.55–4.09)	1.30 (0.47–3.59)

Abbreviations: BMI, Body Mass Index; CI: confidence interval; DPP-4: dipeptidyl peptidase-4; HR: hazard ratio; IR: incidence rate; MOF: major osteoporotic fracture; PY: person years; SGLT-2: sodium-glucose co-transporter 2.
Note: all groups in this table were mutually exclusive. Current use (1–90 days) or past use (>90 days) were defined by the time since the most recent prescription.
[a] Adjusted for sex, age, alcohol use, diabetes duration, history of fracture, chronic obstructive pulmonary disease, congestive heart failure, cancer, eGFR, albuminuria, history of falls in the 7–12 months before and the use of the following drugs in the 6 months before: insulin, antidepressants, anxiolytics/hypnotics, bisphosphonates, calcium and glucocorticoids.
[b] Combined use of at least two of the following glucose-lowering agents: a sulphonylurea and/or DPP-4 inhibitor and/or SGLT-2 inhibitor.
[c] No sulphonylurea, DPP-4 inhibitor or SGLT-2 inhibitor.

Table 4
Risk of major osteoporotic fractures in past and current users of non-insulin glucose-lowering agents compared to current sulphonylurea use, for current SGLT-2 inhibitor use stratified by average daily dose exposure and cumulative dose exposure.

Exposure to glucose-lowering agents	Number of MOFs (N = 415)	IR (/1000 PY)	Age/sex adjusted HR (95% CI)	Fully adjusted HR[a] (95% CI)
Past use of glucose-lowering agents	27	0.88	0.16 (0.10–0.24)	0.35 (0.22–0.56)
Current use of glucose-lowering agents				
Sulphonylureas	124	5.28	Reference	Reference
DPP-4 inhibitors	94	5.16	0.93 (0.71–1.22)	0.92 (0.70–1.21)
Combined use[b]	104	5.09	1.01 (0.78–1.32)	1.09 (0.83–1.43)
Other glucose-lowering agents[c]	33	4.47	0.89 (0.60–1.31)	0.84 (0.57–1.25)
SGLT-2 inhibitors	33	4.53	1.22 (0.82–1.82)	1.21 (0.80–1.81)
By average daily dose exposure[d]				
6.60 mg/day	8	4.39	1.15 (0.56–2.37)	1.10 (0.53–2.28)
6.60–9.99 mg/day	11	5.53	1.53 (0.82–2.86)	1.51 (0.80–2.84)
≥10.00 mg/day	11	3.50	0.95 (0.51–1.76)	0.95 (0.51–1.78)
No average daily dose	<5	9.20	2.58 (0.82–8.15)	2.49 (0.79– 7.88)
By cumulative dose exposure[d]				
<1.82 g	12	4.31	1.18 (0.65–2.15)	1.15 (0.63– 2.10)
1.82–6.29 g	10	3.22	0.87 (0.45–1.67)	0.87 (0.45– 1.68)
≥6.30 g	11	7.93	2.09 (1.11–3.93)	2.10 (1.11– 4.00)

Abbreviations: CI: confidence interval; DPP-4: dipeptidyl peptidase-4; HR: hazard ratio; IR: incidence rate; MOF: major osteoporotic fracture; PY: person years; SGLT-2: sodium-glucose co-transporter 2.
Note: all groups in this table were mutually exclusive. Current use (1–90 days) or past use (>90 days) were defined by the time since the most recent prescription.
[a] Adjusted for age, sex, body mass index, alcohol use, diabetes duration, history of fracture, chronic obstructive pulmonary disease, congestive heart failure, cancer, eGFR, albuminuria, history of falls in the previous 7–12 months and the use of the following drugs in the previous 6 months: insulin, antidepressants, anxiolytics/hypnotics, bisphosphonates, calcium, and glucocorticoids.
[b] Combined use of at least two of the following glucose-lowering agents: a sulphonylurea and/or DPP-4 inhibitor and/or SGLT-2 inhibitor.
[c] No sulphonylurea, DPP-4 inhibitor or SGLT-2 inhibitor.
[d] In dapagliflozin equivalents (1 Defined Daily Dose = 10 mg).

Table 5
Risk of major osteoporotic fractures in current users of non-insulin glucose-lowering agents by change in BMI since index date compared to loss or gain of ≤ 0.5 kg/m^2.

Exposure to glucose-lowering agents	Number of MOFs (N = 415)	IR (/1000 PY)	Age/sex adjusted HR (95% CI)	Fully adjusted HR[a] (95% CI)
Past use of glucose-lowering agents	27	0.88	0.14 (0.09–0.21)	0.31 (0.19–0.49)
Current use of glucose-lowering agents				
By change in BMI since index				
Loss or gain of ≤ 0.50 kg/m^2	201	5.63	Reference	Reference
Loss of 0.51–0.99 kg/m^2	25	4.77	0.85 (0.56–1.29)	0.86 (0.57–1.31)
Loss of ≥ 1.00 kg/m^2	97	4.83	0.84 (0.65–1.07)	0.81 (0.63–1.03)
Gain of 0.51–0.99 kg/m^2	16	3.90	0.72 (0.43–1.19)	0.72 (0.43–1.19)
Gain of ≥ 1.00 kg/m^2	49	4.20	0.76 (0.55–1.04)	0.70 (0.51–0.97)

Abbreviations: BMI: body mass index; CI: confidence interval; HR: hazard ratio; IR: incidence rate; MOF: major osteoporotic fracture; PY: person years.
Note: all groups in this table were mutually exclusive. Current use (1–90 days) or past use (>90 days) were defined by the time since the most recent prescription.
[a] Adjusted for age, sex, alcohol use, diabetes duration, history of fracture, chronic obstructive pulmonary disease, congestive heart failure, cancer, eGFR, albuminuria, history of falls in previous 7–12 months and the use of the following drugs in the previous 6 months: insulin, antidepressants, anxiolytics/hypnotics, bisphosphonates, calcium and glucocorticoids.

percentage of weight loss (i.e. the amount of weight loss relative to initial bodyweight) that occurs during SGLT-2 inhibitor use might not be sufficient to increase the risk of fractures. Studies investigating the risk of hip fractures related to weight loss in men and women found that at least 10% weight loss was required to increase the risk of hip fractures [26,27]. The use of SGLT-2 inhibitors is associated with an average weight loss of 2 to 3 kg [10], which is probably not enough to cause an increased fracture risk. Moreover, it is possible that other mechanisms, not related to weight loss, are responsible for an increased risk of fractures. Use of SGLT-2 inhibitors can result in postural hypotension due to volume depletion, which might lead to an increased risk of falls and thereby an increased risk of fractures. Furthermore, orthostatic hypotension and syncope were reported in patients using canagliflozin [28]. A high BMI, conversely, is associated with a protective effect against fractures [12,29]. In line with this well-established association, we observed a reduced fracture risk in users of non-insulin glucose-lowering agents with ≥ 1.0 kg/m^2 BMI gain compared to those with no BMI change.

One of our most interesting findings is that we observed an increased risk of major osteoporotic fractures in SGLT-2 inhibitor users in the highest cumulative dose category (≥6.30 g dapagliflozin equivalents, corresponding with 630 DDDs). No increased risk was observed in patients using a high average daily dose. This observation suggests that the duration of use of SGLT-2 inhibitors might influence the risk of major osteoporotic fractures. To some extent, this is in line with the meta-analysis by Cheng et al [5], in which a beneficial effect on the risk of fractures was found in users of SGLT-2 inhibitors, but this beneficial effect disappeared when the treatment period was longer than one year. Potentially, a longer duration of SGLT-2 inhibitor use increases the risk of major osteoporotic fractures by altered calcium/phosphate homeostasis [30–32]. The results of the current study suggest an increased risk of fracture after SGLT-2 inhibitor use for at least 630 DDDs, which could correspond to approximately 1.7 years of continuous use (630/365 days). Future studies with substantial follow-up time are required to explore the potential effect of a longer duration of SGLT-2 inhibitor use. Although we found greater mean BMI decreases in the highest cumulative dose category, it is unlikely that this potentially increased risk of fractures is related to weight loss as we observed no association with BMI in our primary analysis.

This population-based study has several strengths. As CPRD GOLD

contains information on a wide range of confounding factors, such as lifestyle factors, comorbidities, and drug use, we were able to statistically adjust our results for potential important confounders in a time-dependent way. Another strength is the fact that data are collected prospectively, which minimalizes the risk of recall bias. In addition, it has been shown that the CPRD fracture data has high validity [14]. Finally, our main results remained consistent in several sensitivity analyses, including an analysis in which we only considered change in BMI if the most recent BMI measurement was within a year before the start of the interval. It has been demonstrated that CPRD recorded BMI measurements have good concordance with the Health Survey for England when BMI measurements recorded within the last 3 years are used [33].

Due to the observational study design, certain limitations need to be considered when interpreting the results of the current study. The relatively short median follow-up time of 2.4 to 3.4 years is a concern. Weight loss due to SGLT-2 inhibitor use is generally observed in the first year after the start of the treatment [34], but it remains uncertain by which pathway SGLT-2 inhibitor use might affect fracture risk. Therefore, the time until a potential effect may occur is unknown, and so is the study duration required to observe a potentially altered fracture risk with SGLT-2 inhibitors. As we observed an increased fracture risk with a higher cumulative dose but not with a higher daily dose, a longer duration of SGLT-2 inhibitor use could be an important risk factor. Although the follow-up time in the current study was longer than that in most previous work, future studies with a longer follow-up are required to examine the effect of longer continuous duration of SGLT-2 inhibitor use. Another limitation is the effect of unmeasured confounders. Although the CPRD contains information of a wide range of confounding factors, the influence of potential unmeasured confounders cannot be discounted. For example, we were unable to correct for diet and exercise, which might have been associated with our identified outcomes. Moreover, hypoglycaemia is a well-known side effect of sulphonylureas, but not of SGLT-2 inhibitors, and could potentially increase the risk of falls and subsequent fractures. The absence of adjustment for hypoglycaemia could have introduced bias in favour of SGLT-2 inhibitors. Nevertheless, our sensitivity analysis in which use of DPP-4 inhibitors was the reference group showed similar results as the main analysis.

It should also be noted that SGLT-2 inhibitor users were more likely to have diabetes-related comorbidities and generally appeared to be less healthy than sulphonylurea users, our reference group. While we could correct for diabetes duration as well as insulin use, the results may still have been influenced by the potentially more advanced diabetes stage of SGLT-2 inhibitor users. Noteworthy, the use of glucocorticoids was relatively high in both groups. Finally, due to the low number of events, we were unable to stratify change in BMI into more categories or study individual SGLT-2 inhibitors separately.

In conclusion, the present study has demonstrated that current use of SGLT-2 inhibitors, independent of change in BMI related to the use of these drugs, does not appear to be associated with an increased risk of major osteoporotic fractures when compared to current use of sulphonylureas. Moreover, when results were stratified by sex, age, type of fracture, or average daily dose, we also showed that use of SGLT-2 inhibitors was not associated with an increased risk of fractures. However, exposure to high cumulative doses of SGLT-2 inhibitors does appear to be associated with an increased risk of major osteoporotic fractures. Other mechanisms than weight loss might be of influence and further research is warranted to clarify this.

5. Contributors

BR, JD and JB initiated the study and were responsible for the study concept and design. JvD and NW did the literature review and wrote the first draft of the paper. JD analysed the data. JvD, NW, JB, MB and JD participated in the interpretation of the data. All authors had full access to all data in the study, critically revised the paper for intellectual content and approved the final version to be published. JD can take responsibility for the integrity of the data and accuracy of the data analyses.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2022.109993.

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