

TITLE PAGE

Title: Real world antidiabetic drug use and fracture risk in 12,277 patients with type 2 diabetes mellitus: a nested case-control study

Short running title: Antidiabetic drug use and fracture risk

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Summary: We conducted a nested case-control study to study the association between antidiabetic treatments (alone or in combination) use and fracture risk amongst incident type 2 Diabetes mellitus patients. We found an increased risk of bone fracture with insulin therapy compared to metformin monotherapy.

ABSTRACT (256 words)

Introduction: Patients with type 2 diabetes mellitus (T2DM) have an increased risk of fragility fractures, to which antidiabetic therapies may contribute. We aimed to characterize the risk of fracture associated with different antidiabetic treatments as usually prescribed to T2DM patients in actual practice conditions.

Research design and methods: A case-control study was nested within a cohort of incident T2DM patients registered in 2006-2012 in the Information System for Research Development in Primary Care (Catalan acronym, SIDIAP), a database which includes records for >5.5 million patients in Catalonia (Spain). Each case (incident major osteoporotic fracture) was risk-set matched with up to five same-sex controls by calendar year of T2DM diagnosis and year of birth (± 10 years). Study exposure included previous use of all antidiabetic medications (alone or in combination), as dispensed in the six months before the index date, with metformin (MTF) monotherapy, the most commonly used drug, as a reference group (active comparator).

Results: Data on 12,277 T2DM patients (2,049 cases and 10,228 controls) were analysed. Insulin use was associated with increased fracture risk (adjusted OR 1.63 [95% CI 1.30-2.04]), as was the combination of MTF and sulfonylurea (SU) (adjusted OR 1.29 [1.07-1.56]), compared with MTF monotherapy. Sensitivity analyses suggest possible causality for insulin therapy but not for the MTF+SU combination association.

No significant association was found with any other antidiabetic medications.

Conclusions: Insulin monotherapy was associated with an increased fracture risk compared to MTF monotherapy in T2DM patients. Fracture risk should be taken into account when starting a glucose-lowering drug as part of T2DM treatment.

KEYWORDS: Epidemiology, Type 2 diabetes mellitus, Fracture risk, General Population.

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Author contributions: ELG, BS, MSA, DM and DPA were responsible for the study concept and design. ELG, BS, MSA DM and DPA acquired and analysed the data and all authors interpreted the data. All authors drafted the manuscript and critically revised it for intellectual content. MSA, DPA, ELG and BS were responsible for the statistical analysis. DM and DPA supervised the study and DPA is the guarantor.

TEXT

INTRODUCTION

Patients with type 2 diabetes mellitus (T2DM) have an increased risk of bone fractures [1-5] despite a normal to high bone mineral density (BMD) [6,7], compared with non-diabetic patients. The mechanisms underlying this excess fracture risk are unclear, but may be explained by the presence of impaired structural properties that compromise bone quality and ultimately lead to bone fragility in T2DM patients [8,9]. The causes are multifactorial, including disease duration [10], chronic diabetes microvascular complications [11,12], episodes of hypoglycaemia and increased risk of falls [13], poor glycaemic control [14], and the use of antidiabetic medications. The use of glucose-lowering drugs may have an impact on bone metabolism and fracture risk.

Metformin (MTF), the first line treatment for T2DM [15], has been associated with a reduced [1,5,16] or neutral effect [17-18] on fracture risk. Conversely, it is known that glitazones have a detrimental effect on bone, resulting in an increased risk of fractures in women and possibly in men [19-21] who use this class of medications. However, there are controversial data about the fracture risk associated with sulfonylurea (SU) [1,5,17,18,20,22,23], insulin [1,4,11,18,24], and incretin treatments [25-28]) in T2DM patients.

In summary, currently available data on the effects of antidiabetic treatments on fracture risk are scarce and controversial, except for glitazones. There is a need for data on T2DM-specific fracture risk factors, including the potential effect/s of different antidiabetic treatments on bone metabolism. Moreover, few studies have assessed the impact of antidiabetic drug combinations used in actual practice on fracture risk.

The aim of this study was to compare the risk of fracture among T2DM patients, stratified by use of various antidiabetic treatments as monotherapy or in usual combinations, in real-world practice conditions.

RESEARCH DESIGN AND METHODS

The study was a nested case-control study within a cohort of newly diagnosed T2DM participants from the Information System for Research Development in Primary Care database (Catalan acronym, SIDIAP). SIDIAP contains the primary care electronic medical records of more than 5 million patients (80% of the total population of Catalonia, in Northeast Spain). Clinical and referral events registered by primary care administrative staff and health professionals (GPs and nurses) are incorporated in the database, as well as demographic information, prescriptions and the corresponding pharmacy invoicing data, specialist referrals, primary care laboratory test results, hospital admissions, and major patient outcomes.

Cases and controls

We screened the SIDIAP database for patients who had a recorded diagnosis of T2DM between January 1st 2006 and December 31th 2012, and followed them up to death, transfer out, or December 31th 2013 (end of study). Patients with a T2DM diagnosis date before January 1st 2006 (i.e., prevalent cases), within the final year of the study period (2013), or before the registration date with the primary care practice participating in SIDIAP were excluded. Additional exclusion criteria were use of antidiabetic medication >1 month before T2DM diagnosis (likely pre-existing diabetes), advanced chronic kidney failure [estimated glomerular filtration rate (eGFR) ≤ 15], <40 years of age on the date of T2DM diagnosis (potentially misclassified type 1 diabetes mellitus) and bone fracture before study inclusion.

Cases were identified as those in the cohort who experienced a fracture during follow-up, and the date when such fracture was recorded in SIDIAP was defined as the index date. Each case was then risk-set matched by sex, 10-year age category, and calendar year of cohort entry with up to 5 controls at risk of developing fracture. Controls can become case at later point in time and were selected using incidence density sampling.

Fractures of any of the following sites were included as major bone fracture cases for analysis: hip, clinical spine, pelvis, tibia, multiple rib, proximal humerus, and wrist/forearm. All fracture events were ascertained from primary care and hospital data using previously validated lists of ICD-10 codes [29,30].

Exposures

Pharmacy dispensation of antidiabetic medications was identified from the official regional reimbursement database (*Facturació de Farmàcia CatSalut* in Catalan) using national product codes, mapped to the WHO Anatomic Therapeutic Classification (ATC) codes and SIDIAP data. Patients were considered exposed if they had filled prescriptions for one or more antidiabetic treatment/s, in monotherapy or in combination, in the six months prior to the index date. Five classes of drugs were considered in monotherapy: MTF, insulin, SU, dipeptidyl peptidase-4 inhibitors (DPP4i), and alpha-glucosidase inhibitors. We also considered double or triple combinations commonly used in clinical practice: insulin+MTF, insulin+SU, insulin+MTF+SU, insulin+MTF+DPP4i, MTF+SU, MTF+IDPP4i, MTF+glitazone, MTF+SU+DPP4i. Insulin and MTF+SU combination duration of uses was stratified by tertiles and SU monotherapy use was stratified by halves to assess the effect of duration of use on the risk of fracture. In all the analyses, we used MTF monotherapy users as a reference group, as this is the first line therapy according to local and international guidelines [15]. In a sensitivity analysis to assess the timing of use on the risk of fracture, we

also looked at antidiabetic medication use in the 6 months, 6-12 months, 12-18 months, and 18-24 months before the index date.

Confounders

Potential confounders of an antidiabetic treatment and bone fracture association were pre-defined based on clinical knowledge and a literature search for data pertaining to T2DM patients. Known variables included age, sex, socioeconomic status (MEDEA deprivation index) (31), body mass index (BMI), smoking status, and alcohol use. For BMI, smoking, and alcohol, only the value recorded nearest to T2DM diagnosis in the 5 years preceding the index date was used. We noted medications affecting fracture risk (statins, antihypertensive drugs) and osteoporosis treatment (parathyroid hormone, hormone replacement therapy, selective oestrogen receptor modulators, calcium supplements, calcium plus vitamin D, and bisphosphonates). These medications were considered potential confounders in the 6 months prior to the outcome date. We also considered previous conditions affecting fracture risk (transitory ischemic attack, stroke, angina, myocardial infarction, falls, cataracts and knee, hip, humerus/ wrist osteoarthritis), eGFR, and most recent HbA_{1c} value in the year prior to T2DM diagnosis.

Ethics

All data analysis was carried out in accordance with current and relevant guidelines and regulations. The study was approved by the Institut d'Investigació d'Atenció Primària Jordi Gol (IDIAP Jordi Gol) ethics committee (CEIC) and the SIDIAP Scientific Committee. No active patient involvement activities were applicable and written informed consent was not required because all data obtained from the SIDIAP database are anonymized.

Statistical analysis

Missing data on BMI, smoking, alcohol use, eGFR measurement, and HbA_{1c} level were handled using multiple imputations with chained equation, as implemented in the “mice” package in R {A}. We included all available confounders, antidiabetic medication use, and outcome status in the imputation. Multivariate models were adjusted for all anti-diabetic treatments use.

Odds ratios (ORs) and 95% confidence intervals (Cis) were estimated using conditional logistic regression analysis stratifying on the matched sets. We adjusted for all covariates except sex that were associated with fracture risk. All analyses were run in R version 3.4.0 {B} and we implemented the “Epi” package in R to run the conditional logistic regression {C}.

RESULTS

We identified 166,106 patients diagnosed with T2DM in SIDIAP. After excluding prevalent T2DM cases (N=90,183) and applying all other pre-specified exclusion criteria, a total of 62,087 T2DM patients fulfilled inclusion and exclusion criteria. Of these, 2,049 (3%) were identified as cases (i.e., major osteoporotic fracture), and 10,228 (16%) as matched controls (no fracture) throughout the study period [Figure 1]. Cases and matched controls showed similar baseline characteristics for most variables [Table 1].

The risk of major osteoporotic fracture in insulin monotherapy users was 126/546 (23.1%) compared with 625/4,079 (15.3%) in MTF users. The unadjusted OR for bone fracture was 1.65 (95% CI 1.33-2.06). After adjustment for potential confounders (as described in Methods section), no changes were observed in the size of the association [adjusted OR (aOR) 1.63 (1.30-2.04)] [Table 2]. Additionally, insulin monotherapy was associated with an increased risk in longer-term users, with aOR 1.93 (1.42-2.61) in the second tertile. However,

insulin monotherapy was not associated with an increased fracture risk in the third tertile [aOR 1.55 (0.88-2.72)] of duration of use, compared to MTF [Table 3]. Finally, an analysis of timing of use showed that current use of insulin (at the time of fracture or in the previous 6 months) was associated with an increased bone fracture risk [aOR 1.52 (1.19-1.93)], whilst previous use (more than 6 months before index date) showed no association [Table 4].

In parallel, users of a combination of MTF+SU showed a risk of major osteoporotic fractures of 177/946 (18.7%) compared with MTF monotherapy (625/4,079, 15.3%). The unadjusted OR 1.28 (1.06-1.54) and aOR 1.29 (1.07-1.56) confirmed an association between this drug combination and an increased risk of fractures. No other antidiabetic therapy (alone or in double or triple combination) observed in actual practice conditions showed any significant associations with fracture risk (compared with MTF monotherapy use) (Table 2). However, higher cumulative use was not associated with higher fracture risk: only users of MTF+SU combination in the first tertile of treatment duration [aOR 1.46 (1.09-1.95)] had an increased fracture risk compared to MTF users [Table 3], and no association was found between timing of use and risk of bone fracture/s [Table 4].

DISCUSSION

We report a significantly higher risk of major osteoporotic fractures, before and after adjusting for potential confounders, in T2DM patients treated with insulin monotherapy or with MTF+SU combination treatment, compared to T2DM patients treated with MTF. No differences in risk fracture were found when we compared other T2DM users of different glucose-lowering drugs in monotherapy or in actual clinical-practice combinations. The observed association with insulin use was further confirmed in timing and dose-dependency analyses, where higher doses and more recent use were again associated with higher fracture risk. None of these findings held true for the observed association with the MTF+SU

combination, where no gradient was observed with cumulative use and no relationship was seen with more recent drug use.

Metformin use was considered as the reference group because it is the first line therapy for T2DM in international guidelines (15). However, MTF treatment has some contraindications and secondary effects that may reduce its use as initial treatment. Nevertheless, MTF as the reference group allows comparisons with oral combined antidiabetic drugs that include MTF or with stepped therapy that included progressively different drugs to improve poor glycaemic control.

Our results on insulin are consistent with a recent propensity score-matched cohort study published by our group [24] and with most previous observational studies in which insulin therapy has been related to a higher risk of hip and major bone fractures [4,11]. It has been suggested that this increased fracture risk is caused more by the characteristics of T2DM patients treated with insulin, such as a longer duration or higher severity of the disease [32], rather than being a direct effect of insulin on the bone. Nevertheless, in the present study the higher risk of fracture is detected in patients with newly diagnosed T2DM treated with insulin and a short disease duration, suggesting an effect of insulin treatment rather than a disease progression or diabetes chronic complications effect on risk fracture. Insulin fracture risk may be caused by an increased risk of hypoglycaemia and a consequent increase in falls [13] or the detrimental effect of insulin in bone described in experimental models [33]. Furthermore, only patients with current use of insulin treatment were associated with an increased risk of fracture in our study. Similar results were found in a previous Italian case-control study [18], where short-term insulin use was also related to an increased fracture risk in men but not in women. Moreover, a higher risk of hypoglycaemia at the beginning of insulin treatment has been described, and attributed to the insulin dose titration and to a deficiency in the patient education provided [34].

It is remarkable that we found an increased risk of bone fractures with the MTF+SU combination but not with SU monotherapy or in combination with other glucose-lowering drugs (including insulin). The most widely used combination of glucose-lowering drugs in clinical practice in some countries is MTF+SU [35], although the use of SU has declined over the last few years in developed countries [36]. Until the present study, no data attributed an increased risk to this drug combination. There are controversial data of the effect of SU on bone. Although no preclinical evidence of detrimental effect of this drug on bone cells is available, most recent studies describe a trend to an increased risk of fracture in SU users. In a Danish cohort, current use of SU (within 90 days) was associated with hip fractures [22], and a 30% excess risk of fracture has been described by Rajpathak *et al.* in elderly men and women with T2DM treated with SU [23]. The most widely accepted hypothesis is that SU may increase fracture risk by increasing the risk of hypoglycaemia-induced falls. However, this increased risk with the combination of MTF+SU was not supported in our results after sensitivity analysis. No relation with current/recent use at time of fracture or dose gradient with higher cumulative use was present. Moreover, no pathophysiological hypothesis can explain the neutral, or even protective, effect of the combination with MTF, which showed an increased risk that was not present with SU alone or in combination with insulin. These data suggest that causality is less likely to support this association. In summary, our data does not support any increased risk of fracture related with SU use.

We did not observe any association between bone fracture and the use of incretin therapies, whether as monotherapy or in double or triple combinations. Due to prescription restrictions in our primary care system for economic reasons during the study period, a very low number of patients were treated with glucagon-like peptide 1 receptors agonists (GLP1RA); therefore, DPP4i drugs were the only incretin therapy included in our analysis. A meta-analysis of results from randomized controlled trials showed a 40% reduction in fracture risk

with the use of DPP4i [28]. Nevertheless, a more recent meta-analysis of population-based clinical data concluded that current use of DPP4i was not associated with a decreased risk of fractures [26]. Indeed, large randomized clinical trials, such as TECOS or SAVOR-TIMI, showed no increase in fracture risk with the use of sitagliptin and saxagliptin, respectively [37,38]. Therefore, the effects of DPP4i treatment on bone fracture risk in T2DM patients remain unclear.

Our study has several limitations beyond those inherent to observational studies. The main limitation is the lack of validation of each individual fracture. However, previous validation of fractures as recorded in SIDIAP has shown the database to be very precise (>90% accuracy for all fracture sites), compared with prospective cohort and hospital admissions data [30,39]. Another limitation was that the date of recorded T2DM diagnosis might not reflect the actual time of disease onset, which could have occurred months before a diagnosis was made and recorded. An unresolved issue was the potential for residual confounding secondary to unobserved variables. Our database lacked important risk factors for osteoporosis such as bone mineral density status or the use of other medications that may impact fracture risk, such as antidepressants, sedatives, corticosteroids, and antipsychotics. It is, however, unlikely that these would be true confounders in our analyses, as there is no clinical guidance on the use of antidiabetic treatments according to bone density or the concomitant use of any of these therapies with the exception of corticosteroids. Other information lacked in the database was the presence of some diabetic complications such as retinopathy, nephropathy with albuminuria determination or neuropathy that could affect in the preponderance of choosing insulin or in the fracture risk. No pathophysiological information (circulating levels of insulin or other parameters potentially involved in bone health such as bone turnover markers, IGF-1, osteocalcin, and others) was available, nor were the number of hypoglycaemic readings or falls in each study group. These data would be interesting and

would have helped to better understand the physiopathology behind our results; however, this information is not usually available in primary care databases and its assessment was not the purpose of this observational study.

Finally, the current study was not adequately powered to study the association between fracture risk and any of the following drugs/combinations: DPP4i alone or in combination (14, 7, 36 and 18 fracture outcomes), glitazones, Insulin + SU, or any triple combinations

Our study also has several strengths. The quality of the data used in this investigation has been confirmed in recent studies showing the representativeness of the SIDIAP database for the Catalan population [29]. Inclusion of only incident T2DM cases enabled a more accurate assessment by reducing the effect of differences in time from T2DM onset. Furthermore, the use of MTF as a reference value enabled a better understanding of treatment effect in real-world data. The analysis of double or triple combinations of glucose-lowering drugs gives information about their effect on bone fracture in actual cases. The definition of drug exposure used in the present study was based on pharmacy data showing drugs actually dispensed. The use of these data is a strength of our study because pharmacy data are more reliable than prescription data in determining adherence to therapy. It is therefore reasonable to assert that patients used most of the dispensed doses; however, this could not be verified.

In conclusion, our study evaluated the fracture risk of real-world clinical use of antidiabetic treatment in newly diagnosed T2DM patients. We observed a higher risk of osteoporotic bone fractures in T2DM patients with insulin or with combined MTF+SU treatment, compared to T2DM patients treated with MTF monotherapy. Our sensitivity analyses suggest possible causality for the first (insulin) but not the latter (MTF+SU combination) association. As these results could be relevant in clinical practice, fracture risk should be considered at the time of starting insulin therapy in T2DM patients.

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	Cases	Controls
Age [years, Mean (sd)]	72.90 (11.40)	72.86 (11.36)
Sex [female, N (%)]	1457 (0.71)	7277 (0.71)
Stroke [N (%)]	171 (0.08)	605 (0.06)
Transient ischemic attack [N (%)]	63 (0.03)	207 (0.02)
Ischaemic heart disease [N (%)]	145 (0.07)	612 (0.06)
Angina pectoris [N (%)]	74 (0.04)	322 (0.03)
Cataracts [N (%)]	375 (0.18)	1723 (0.17)
Hip osteoarthritis [N (%)]	92 (0.04)	484 (0.05)
Knee osteoarthritis [N (%)]	382 (0.19)	1757 (0.17)
Hand/wrist osteoarthritis [N (%)]	22 (0.01)	137 (0.01)
Unspecific osteoarthritis [N (%)]	188 (0.09)	845 (0.08)
Poly-articular osteoarthritis [N (%)]	198 (0.01)	915 (0.09)
Statins [N (%)]	845 (0.41)	4439 (0.43)
ACEi [N (%)]	695 (0.34)	3280 (0.32)
Calcium channel blockers [N (%)]	413 (0.2)	1987 (0.19)
Thiazides [N (%)]	349 (0.17)	1884 (0.18)
Beta-blockers [N (%)]	433 (0.21)	1999 (0.2)
Teriparatide [N (%)]	8 (0)	26 (0)
Vitamin D [N (%)]	51 (0.02)	225 (0.02)
Calcium supplements [N (%)]	71 (0.03)	247 (0.02)
Calcium + Vitamin D [N (%)]	384 (0.19)	1296 (0.13)
Selective oestrogen receptor modulators [N (%)]	16 (0.01)	98 (0.01)
Anti-vitamin K anticoagulants [N (%)]	194 (0.09)	871 (0.09)
Oral bisphosphonate/s [N, (%)]	278 (0.14)	907 (0.09)
Strontium ranelate [N (%)]	31 (0.02)	101 (0.01)

HbA _{1c} [%, Mean (sd)]	6.65 (1.28)	6.65 (1.24)
HbA _{1c} [mmol/mol, Mean (sd)]	49 (14)	49 (14)
eGFR [ml/min, Mean (sd)]	75.32 (23.86)	74.04 (22.64)
BMI [kg/m ² , Mean (sd)]	30.25 (5.2)	30.7 (5.17)
Socioeconomic status (MEDEA index), [Mean (sd)]	0.77 (0.98)	0.79 (0.95)
Alcohol consumption [N (%)]		
None/Mild	1772 (0.86)	8777 (0.86)
Moderate	942 (0.46)	4852 (0.47)
Severe	741 (0.36)	3617 (0.35)
Smoking [N (%)] grade		
Never	1941 (0.95)	9732 (0.95)
Current	1738 (0.85)	8647 (0.85)
Former	1756 (0.86)	8739 (0.85)

Table 1. Baseline characteristics of osteoporotic fracture cases and controls
HbA_{1c}: glycated haemoglobin; eGFR: estimated glomerular filtration rate; BMI: body mass index; MEDEA index (31)

P value is NS for all

	Total (N=12,277)	Cases (N=2,049)	Unadjusted			Adjusted		
			Odds Ratio	95% CI		Odds Ratio	95% CI	
MTF	4,079	625	1.00			1.00		
Non-users	5,089	842	1.10	0.98	1.23	1.09	0.97	1.23
Insulin	546	126	1.65	1.33	2.06	1.63	1.30	2.04
SU	697	119	1.14	0.92	1.42	1.13	0.91	1.41
DPP4i	77	14	1.23	0.68	2.20	1.21	0.67	2.19
AGI	44	6	0.89	0.37	2.11	0.81	0.34	1.94
Insulin + MTF	329	58	1.18	0.88	1.59	1.22	0.89	1.65
Insulin + SU	33	5	0.99	0.38	2.56	1.07	0.41	2.80
Insulin + MTF + SU	58	11	1.32	0.68	2.58	1.41	0.72	2.79
Insulin + MTF + DPP4i	32	7	1.53	0.66	3.56	1.47	0.63	3.47
MTF + SU	946	177	1.28	1.06	1.54	1.29	1.07	1.56
MTF + DPP4i	218	36	1.10	0.76	1.59	1.12	0.77	1.62
MTF + Glitazone	27	5	1.27	0.48	3.36	1.25	0.47	3.34
MTF + SU + DPP4i	102	18	1.19	0.71	2.15	1.27	0.75	2.15

Table 2. Unadjusted and adjusted association between different antidiabetic medications and risk of fracture

OR: odds ratio; CI: confidence interval; MTF: metformin; SU: sulfonylurea; DPP4i: dipeptidyl peptidase-4 inhibitor; AGI: alpha-glucosidase inhibitor

	Total (N=12,27)	Cases (N=2,049)	aOR	95% CI	
MTF (reference)	4,079	625	1.00		
Non-users	5,089	842	1.09	0.97	1.23
Insulin 1 st tertile	212	41	1.32	0.93	1.89
Insulin 2 nd tertile	256	68	1.93	1.42	2.61
Insulin 3 rd tertile	78	17	1.55	0.88	2.72
SU 1 st half	200	33	1.12	0.76	1.66
SU 2 nd half	497	86	1.14	0.88	1.47
DPP4i	77	14	1.21	0.67	2.2
AGI	44	6	0.80	0.33	1.92
Insulin + MTF	329	58	1.22	0.90	1.66
Insulin + SU	33	5	1.07	0.41	2.81
Insulin + MTF + SU	58	11	1.42	0.72	2.81
Insulin + MTF + DPP4i	32	7	1.47	0.62	3.46
MTF + SU 1 st tertile	311	65	1.46	1.09	1.95
MTF + SU 2 nd tertile	29	5	1.21	0.46	3.20
MTF + SU 3 rd tertile	606	107	1.21	0.96	1.53
MTF + DPP4	218	36	1.11	0.77	1.62
MTF + Glitazone	27	5	1.26	0.47	3.38
MTF + SU + DPP4i	102	18	1.26	0.74	2.14

Table 3. Association between different antidiabetic medications and risk of fracture (Insulin and metformin + sulphonylurea use were stratified by tertiles of duration of use, sulphonylurea monotherapy use was stratified by halves of duration of use)

aOR: Adjusted odds ratio; CI: Confidence interval; MTF: metformin; SU: sulfonylurea;
DPP4i: dipeptidyl peptidase-4 inhibitor; AGI: alpha-glucosidase inhibitor

	Insulin Users				SU Users			
	Total	Cases	aOR	95% CI	Total	Cases	aOR	95% CI
Never users	3,933	666	1.00		3,933	666	1.00	
Current users	470	116	1.52	1.19-1.93	48	5	0.56	0.22-1.44
Recent users	78	14	1.02	0.57-1.85	154	25	0.93	0.60-1.45
Past users	37	7	1.19	0.51-2.74	98	14	0.81	0.46-1.45
Previous past users	22	2	0.46	0.10-2.00	90	16	1.06	0.61-1.85

Table 4. Timing of use and risk of hip fracture in insulin and sulfonylurea users

SU: sulfonylurea; aOR: adjusted odds ratio; CI: confidence interval; Never users: no use during the previous 24 months; Current users: use during the previous 6 months; Recent users: use between the previous 6 and 12 months; Past users: use between the previous 12 and 18 months; Previous past users: use between the previous 18 and 24 months.

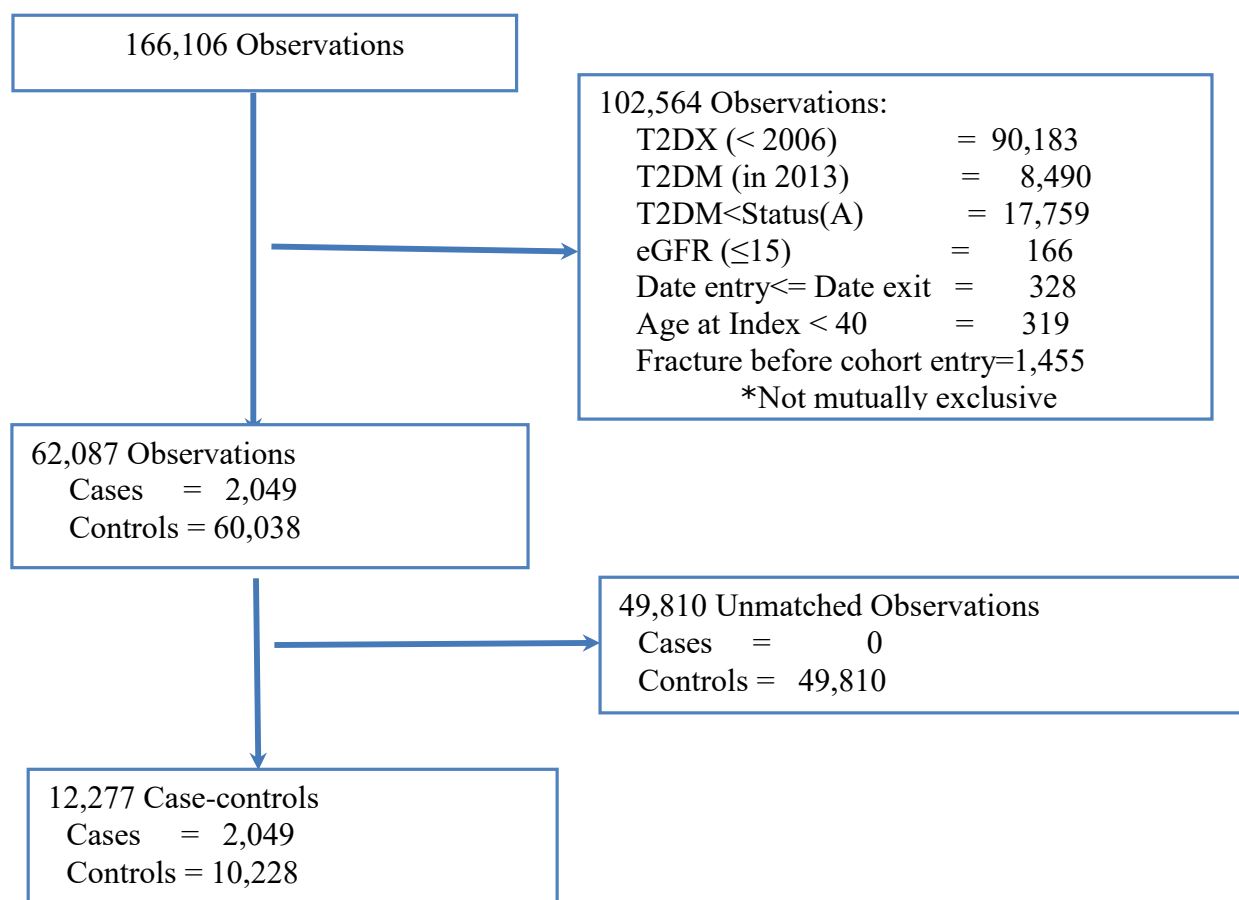


Figure 1. Population flowchart