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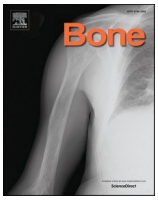

Full Length Article

Discrepancies in type of first major osteoporotic fracture and anti-osteoporotic therapy in elderly people with type 2 diabetes mellitus: A retrospective Danish cohort study

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ABSTRACT

Objective: Subjects with diabetes mellitus have an increased risk of fractures. We aimed to identify discrepancies in the first type of major osteoporotic fracture (MOF) and anti-osteoporotic therapy between subjects with type 2 diabetes (T2D) and subjects without diabetes.

Methods and research design.

We conducted a retrospective national cohort study by access to all discharge diagnoses (ICD-10 system) and redeemed drug prescriptions (ATC classification system). We included all subjects alive and Danish citizens in 2010 and identified subjects with T2D diagnosed after the age of 50 between 1998 and 2018. Only subjects with a MOF after the index date were included in the main analysis. The type of MOF was identified by diagnosis codes and categorized into Humerus, Forearm, Spine, and Hip. Multinomial logistic regression modeling was used to assess the predicted probability changes in MOF type between T2D and control subjects. Data on first anti-osteoporotic therapy after the MOF was assessed by redeemed drug prescriptions. Mortality and time to therapy after the MOF were evaluated by cox proportional hazards.

Result: We included 26,588 subjects with T2D and 97,982 subjects without diabetes. The mean age was age 69.33 (±10.34) for T2D and 69.85 (±10.19) for control subjects. The cohort was primarily females (67 %). Subjects with T2D had a higher probability of hip (3.98 % [95 % CI 3.29; 4.67]) and humerus (2.82 % [95 % CI 2.17; 3.46]) fractures as the first MOF compared to control subjects. However, the probability of forearm fractures as the first MOF was 6.77 % (95 % CI 6.08; 7.46) lower among subjects with T2D. The multiple adjusted hazard ratio for anti-osteoporotic treatment after the first MOF was 0.80 (95 % CI 0.77; 0.88) for T2D compared to controls among treatment-naïve subjects.

Conclusion: Forearm fractures were the most frequent type of MOF and were more prevalent in control subjects. Subjects with T2D had a significantly higher probability of hip and humerus fractures as the first MOF but had a 20 % lower chance of anti-osteoporotic treatment afterwards.

1. Introduction

Type 2 diabetes (T2D) and osteoporosis are major public health concerns related to aging and lifestyle that often co-exist in the elderly population [1–4]. The risk of fractures in subjects with diabetes has been investigated thoroughly in epidemiological studies throughout the last decades [5–8]. Despite the increasing evidence of the association, it is still debated whether T2D per se should be recognized as an independent risk factor for osteoporosis and fractures [9,10].

Fracture risk assessment is generally performed in the hip and other non-vertebral fractures and a recent meta-analysis found a 30 % increased hip (RR 1.33 [1.19; 1.49]) and 20 % increased non-vertebral (RR 1.19 [1.11; 1.28]) fracture risk in subjects with T2D [7]. These findings agree with previous studies and meta-analyses [5,6,8,11]. The fracture risk in subjects with diabetes differs according to site [12–14]. Lower arm fractures are in general the most frequent type of fractures in subjects with and without T2D but did not differ between the two groups as was reported for the foot, upper arm, spine, and hip in particular

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[12–14]. It has been reported that for a given T-score and age, the hip fracture risk is higher in subjects with T2D compared to subjects without diabetes [15]. It is possible that the routine diagnostic method does not assess bone quality and strength properly in these subjects. If so, more advanced diagnostic tools are needed to enable early detection of bone fragility in subjects with type 2 diabetes. Information on the first fracture site and any potential discrepancy from subjects without diabetes could provide useful information for future research when assessing site-specific bone quality to prevent fractures.

Up to 20 % of patients die in the first year after a hip or spine fracture with a significantly higher risk among subjects with T2D, and only a few regain the previous level of function [16–19]. This knowledge emphasizes the importance of early detection and treatment of poor bone health in subjects with T2D. Current anti-osteoporotic treatment is found just as effective in subjects with T2D as in subjects without diabetes [20]. However, diagnosing bone fragility in subjects with T2D is challenging and so, we speculate whether subjects suffering from T2D are diagnosed and treated with anti-osteoporotic medications to the same extent as subjects without T2D.

In this nation-based retrospective Danish cohort study, we aimed to estimate the differences in the first MOF according to site after T2D diagnosis compared to control subjects. Furthermore, we aimed to determine the proportion of osteoporosis diagnosis and anti-osteoporotic drug therapy after the first MOF.

2. Research design and methods

The STROBE statement guideline for reports of observational studies was followed (a STROBE checklist can be found in Supplemental Table S1) [21].

2.1. Data sources

All data were provided and anonymized by Statistics Denmark (*Danmarks Statistik*, project identifier no. 703382) and were obtained through the National Danish registry. In Denmark, all citizens are assigned a unique 10-digit personal identification number (PIN) which ensures a complete medical history of all contacts to the Danish health care system and drug redemptions [22–24]. The PIN has been anonymized and linked to all registers used in this study. All Danish citizens have equal and free access to health care, hospitalizations, and partial compensation for drug expenses provided by the Danish National Health Service.

Data on diagnoses were obtained from the Danish National Patient Register [23]. The register covers all contacts to the hospitals on both in- and outpatient basis. The data include all relevant physician-assigned discharge diagnoses on the individual level, coded according to the International Classification of Diseases, Tenth Revision (ICD-10). Information on drug prescriptions were coded according to the Anatomical Therapeutical Chemical (ATC) classification and recorded from 1996 by the Danish National Health Service Prescription Register [24,25].

Data on sex and date of birth as well as emigration and death (if applicable) were retrieved from the Danish Civil Registration system, which ensures high-fidelity subject identification with respect to emigration and death [26,27].

2.2. Study design and setting

We conducted a retrospective nationwide cohort study. We made sure that all subjects where alive and living in Denmark on January 1, 2010, to ensure a proper follow-up time over a study period of 2 decades for both diabetes and control subjects (Supplemental Fig. 1). The data was available between 1996 and 2018 and we identified all subjects with diagnosed with T2D between January 1, 1998; and December 31, 2018 (Supplemental Figs. S1 and S2). We chose 1998 to ensure proper data registration as the definition of T2D (see below) was based on redeemed drug prescriptions that became available in 1996. We then collected covariates and outcomes by identification of diagnosis codes and drug prescriptions at and after the index date, respectively. The index date (from 1998 to 2018 if alive and Danish citizens in 2010) was set at the date of T2D diagnosis and a "dummy" date was chosen for control subjects by Statics Denmark with respect to diabetes subjects, emigration and death, i.e., control subjects had to be alive, Danish residents and at risk at the time of the index date to be included. Subjects with T2D and control subjects were followed from their index date until the date of death, date of emigration or end of study period (December 31, 2018), whichever came first. All subjects with a diagnosis MOF after the index date was included in the analysis.

2.3. Identification of type 2 diabetes subjects

Based on a previously published algorithm (Supplemental Table S2) [20,28,29] we identified subjects with diabetes mellitus either by any ICD-10 code (main or secondary) related to diabetes or by an ATC code of glucose-lowering drugs used in diabetes. The T2D diagnosis and concordance between actual use and prescription of diabetes related medications are in general high [30–33]. Consequently, all subjects with diabetes were defined either from a hospital visit or by redemption of glucose-lowering drugs. In Denmark, all subjects with type 1 diabetes (T1D) will eventually be in contact with the hospital and no other glucose-lowering drugs than insulin were recommended in the study period. Consequently, T1D was defined by at least one E10 ICD-10 code (T1D) and at least one A10A ATC code (insulins and analogs) and no A10B ATC code (blood glucose-lowering drugs exclusive insulins); all other subjects with diabetes were classified as T2D subjects.

2.4. Study population

The primary study population included subjects alive and residing in Denmark without any emigration history on January 1, 2010, and with a MOF diagnosis after the index date (Supplemental Figs. S1 and S2 and Supplemental Tables S2 and S3).

We excluded subjects with classified diabetes before January 1, 1998, those with T1D, Paget's disease, polycystic ovary disease and subjects of age below 50 years at the index date (Supplemental Fig. S2). Women with polycystic ovary syndrome are often treated with clomifene and metformin, and to avoid the inclusion of these, women who received clomifene before the age of 40 years were excluded. In addition, we excluded subjects with an emigration date before the index date as this potentially provides a period of information bias, i.e., if the subject were not registered by diagnoses and drug redemptions in the Danish registers due to an emigration period. We chose a 50-year age cut off, as the average age for menopause in Denmark is 51.7 years with a corresponding increase of postmenopausal osteoporosis [34]. Thus, the final cohort consisted of adults with T2D and age $\geq$ 50 years after year 1998 and a control population, all alive and Danish citizens in year 2010.

2.5. Outcome

The primary outcome was first type of MOF after the index date, identified by primary or secondary diagnoses during hospitalization by ICD-10 codes (Supplemental Table S3) in the study period (between 1998 and 2018). MOF was categorized into the specific type, i.e., fracture of the Humerus, Forearm, Spine, and Hip [9].

The secondary outcome was time to anti-osteoporotic treatment following the first MOF after the index date evaluated by cox proportional hazards in treatment-naïve subjects from the cohort. To further explore any differences between T2D subjects and control subjects following a MOF, we evaluated differences in mortality as well as in osteoporotic diagnosis.

2.6. Identification of covariates

Covariates at baseline (index date) were identified by ICD-10 and ATC codes in the period from start date of data collection (January 1, 1996) until the index date (Supplemental Table S2) as published previously [20,28,29]. Age at baseline was calculated based on the date of birth and the index date. When evaluating characteristics of the treated and untreated population after the first MOF, we identified the covariates at/before the date of the first MOF after the index date.

As a proxy for smoking status, we used ICD-10 codes related to lung diseases, of which some were directly and others indirectly associated with tobacco exposure, as well as nicotine poisoning and psychiatric tobacco-related diagnoses. In addition, we identified ATC codes corresponding to treatments for tobacco dependence (ever), e.g., nicotine replacement therapy, or initiation of drugs for obstructive airway diseases after the age of 40. Due to potential underestimation, we classified this factor as *heavy smoking*.

We evaluated alcohol consumption by either one relevant ICD-10 or ATC code covering diseases and drugs with direct affiliation to alcohol, e.g., intoxication, alcohol abuse, alcoholic liver disease, alcoholic cardiomyopathy, alcoholic polyneuropathy, alcoholic gastritis, alcohol-induced pancreatitis or alcohol related psychiatric disorders etc. [35,36]. We classified this factor as *alcohol abuse*.

Obesity was evaluated by ICD-10 codes of obesity or use of anti-obesity pharmaceuticals by ATC codes. Information on chronic and acute pancreatitis were obtained from ICD-10 codes. Hyper- and hypothyroidism were assessed by either ICD-10 or ATC codes.

Hypertension was defined by any ICD-10 code related to hypertension and/or prescription of any antihypertensive drug. Hypoglycemia was assessed by a related ICD-10 code.

Comorbidity was assessed by use of Charlson Comorbidity Index (CCI) [37] based on discharge diagnoses registered by ICD-10 codes with a general high accuracy (Supplemental Table S3) [38]. However, we excluded diabetes from the index date and grouped CCI in 3 according to score (0, 1 and >2).

A history of MOF, other fractures than MOF, osteoporosis diagnosis and anti-osteoporotic treatment was identified by ICD-10 and ATC codes at the index date.

In addition, we identified any prescription of insulins, statins, opioids, glucocorticoids, and anxiolytics by ATC codes at the index date.

Data on socioeconomic status was also obtained from Statistics Denmark. We assessed income as the amount of DKK (Danish kroner) from the year preceding the year of the index date and adjusted for inflation to a 2018 level using the consumer price index from Statistics Denmark. Lastly, we converted the income to euro € at a rate of 1 € = 7.467 DKK (exchange rate December 2018).

Marital status was available through the Danish Civil Registration System and assessed from the year prior to the year of the index date. It was defined and grouped according to the classification from Statistics Denmark: married, divorced, widowed or unmarried.

2.7. Statistical analysis

Baseline characteristics in tables are presented by descriptive statistics as numbers (n) and percentages (%), means and standard deviations (SD), or medians and interquartile range (IQR). In addition, 95 % confidence intervals (CI) were calculated, either from means of continues outcomes or proportions of binary outcomes and presented in the result section. Unpaired *t*-test, Chi-square test, Wilcoxon Mann-Whitney median test and relative risk ratios (RR) were performed and calculated to compare continuous and dichotomous characteristics between T2D and controls. We grouped relevant quantitative variables, e.g., age, CCI score, and the index year.

We performed a multinomial logistic regression [39] to predict the probability of the first type of MOF as the dependent categorical variable between T2D and control subjects set as a binary independent "exposure" variable and added several other independent covariables in the adjusted analysis, i.e., sex, age, follow up time (from the index date to MOF, e.g., diabetes duration), history of any MOF, history of other fractures, history of osteoporosis diagnosis, history of anti-osteoporotic treatment, use of anxiolytics/opioids, dyslipidemia, smoking, alcohol, obesity, systemic glucocorticoid use, hypertension, rheumatoid arthritis, pancreatitis, hyperthyroidism, hypothyroidism, CCI category, income and marital status. We evaluated multicollinearity by assessing the variance inflation factor (VIF) between all independent covariables and no VIF exceeded a value of 2 (5 was set as threshold). We tested the assumption of independence of Irrelevant Alternatives between outcome categories, IIA, by Hausman-McFadden test, and no MOF type violated the assumption. We tested the assumption of independent variables by likelihood-ratio test and omitted the independent variables *pancreatitis*, *hyperthyroidism*, and *hypothyroidism* from the adjusted model. Consequently, the adjusted model included the following independent variables: sex, age, follow up time (from the index date to the MOF, e.g., diabetes duration), history of any MOF, history of other fractures, history of osteoporosis diagnosis, history of anti-osteoporotic treatment, use of anxiolytics/opioids, dyslipidemia, smoking, alcohol, obesity, systemic glucocorticoid use, hypertension, rheumatoid arthritis, CCI category, income and marital status. We evaluated the effect of each independent variable by discrete (binary variables) and marginal (continuous variables) changes for each MOF type and visualized results by plotting the log coefficients, factor changes and predicted probabilities (log view not shown). Interactions were evaluated and found significant between sex and age. Thus, we made a subgroup analysis stratified by sex and age categories and included the main and interaction (sex * age) effect in the multiple adjusted analysis. To see which model fits better, we performed a likelihood ratio test. For all outcomes it gave a significant better fit, estimated by BIC test, when adding the adjustments instead of the crude model (data not shown) and so, only results from the adjusted models are presented in the tables and figures. Missing data were only found in marital status and these subjects (34 controls and 29 T2D) were assigned to the marital status with the highest frequency in both groups, i.e., "married".

We evaluated mortality risk in the entire cohort and time to treatment by first anti-osteoporotic drug redemption in treatment-naïve subjects, by cox proportional hazard functions and plotted the analyses by 1-Kaplan-Meier cumulative incidence curves. In the mortality analysis, censoring was set to emigration date, death date or end of study period (December 31, 2018), whichever came first. In the time to treatment analysis, censuring was set to emigration date, death date, start of anti-osteoporotic treatment or end of study period (December 31, 2018), which ever came first. Crude and adjusted hazard rate ratios (HR) with 95 % CI were estimated for each outcome. We examined the assumption of proportionality by graphical log-log plots, and no violation was identified. We performed a multiple adjustment with respect to multicollinearity (none were identified). Interactions were evaluated, the simple slopes were visualized, and no significant interaction was identified in the analysis of mortality or time to treatment. Moreover, the time to treatment analysis was further evaluated as a competing risk regression analysis fitted by Fine and Gray's proportional subdistribution hazard models [40] with death as a competitive event to examine any difference from the original analysis.

2.8. Sensitivity analyses

We performed several sensitivity analyses on primary outcome data (type of first MOF). First, we excluded subjects with <2 years of follow-up, i.e., diabetes duration (Sensitivity analysis 1). Additionally, we excluded all participants with a history of MOF before the index date (Sensitivity analysis 2), anti-osteoporotic treatment/osteoporosis diagnosis before the index date (Sensitivity analysis 3) or both (Sensitivity analysis 4).

After evaluation of the secondary outcome, i.e., time to anti-

osteoporotic treatment after first MOF, we stratified data by age at MOF and gender. Moreover, we performed several sensitivity analyses on the treatment naïve subjects by only including: female subjects (Sensitivity analysis 1), subjects with Hip and Spine fractures (Sensitivity analysis 2), or subjects alive 1 year after the first MOF (Sensitivity analysis 3). Moreover, we evaluated the proportions and incidence rates (IR) of treatment initiation within the first year after the MOF among anti-osteoporotic treatment naïve subjects without a history of MOF before the index date. The corresponding incidence rate ratios (IRR) and HRs between T2D and controls subjects were calculated (Sensitivity analysis 4). Lastly, we examined the effect of unmeasured confounding using the E-value estimate, i.e., minimum strength of association, that an unmeasured confounder would need to have to be associated with the exposure (type 2 diabetes) and outcome (treatment after MOF) for the association to be explained away to the null [41].

To eliminate and evaluate immortal time bias, we made sensitivity analyses on the mortality estimate by only including subjects with MOF or the index date after 2010.

All analyses were conducted in STATA 17.0 (StataCorp, College Station, Texas, US).

2.9. Resource availability

Data were available and anonymized by Statistics Denmark. All authorized Danish research organizations can apply for access. Approval by ethics committee is not required for epidemiological studies in Denmark. We had no access to personally identifiable information and the registries are subject to control by the Danish Data Protection Agency.

3. Results

3.1. Baseline characteristics

For detailed inclusion of study population and baseline characteristics see Supplemental Figs. S1 and S2 and Table 1. In short, the total population consisted of 124,570 subjects ≥50 years with a MOF after the index date and a mean index age of 69.74 (±10.22) years. Subjects with T2D (n = 26,588 subjects) were younger compared to control subjects (n = 97,982), mean age 69.33 (±10.34) and 69.85 (±10.19), respectively ($p < 0.001$). Subjects with T2D had a lower proportion of female subjects (65.14 % versus 67.28 %, RR 0.97 [0.96–0.98]), and were more comorbid (mean CCI 0.82 [±1.34] versus 0.46 [±1.01], $p < 0.001$) compared to subjects without diabetes. Subjects with T2D had a higher prevalence of previous other fractures (12.78 % versus 11.59 %, RR 1.10 [1.06; 1.14]) and previous MOFs (16.80 % versus 15.00 %, RR 1.12 [1.09; 1.16]). The proportion of redeemed anti-osteoporotic therapy before the index date was lower among T2D subjects (6.16 % versus 7.99 %, RR 0.77 [0.73; 0.81]). However, the proportion of a previous osteoporosis diagnosis did not differ between T2D and control subjects (4.86 % versus 4.94 %, RR 0.98 [0.93; 1.05]) before the index date. Mean follow up time from the index date to first MOF was 6.22 years (±4.61) and longer among control (6.33 years [±4.62]) than T2D subjects (5.82 years [±4.52], $p < 0.001$).

Table 1
Baseline characteristics of study population with MOF after the index date.

At index characteristic	All subjects	Type 2 diabetes	Control subjects
	n = 124,570	n = 26,588	n = 97,982
Age (years), mean ± SD	69.74 (10.22)	69.33 (10.34)	69.85 (10.19)
Age category (years), n (%)			
50–59	26,638 (21.38)	6052 (22.76)	20,586 (21.01)
60–69	38,220 (30.68)	8372 (31.49)	29,848 (30.46)
70–79	39,494 (31.70)	7960 (29.94)	31,534 (32.18)
≥80	20,218 (16.23)	4204 (15.81)	16,014 (16.34)
Sex, n (%)			
Male	41.330 (33.18)	9268 (34.86)	32,062 (32.72)
Female	83,240 (66.82)	17,320 (65.14)	65,920 (67.28)
History of other fracture, n (%)	14,757 (11.85)	3397 (12.78)	11,360 (11.59)
History of MOF, n (%)	19,160 (15.38)	4467 (16.80)	14,693 (15.00)
Humerus	4870 (3.91)	1204 (4.53)	3666 (3.74)
Forearm	9309 (7.47)	1945 (7.32)	7364 (7.52)
Spine	1399 (1.12)	359 (1.35)	1040 (1.06)
Hip	3582 (2.88)	959 (3.61)	2623 (2.68)
Osteoporosis diagnosis, n (%)	6136 (4.93)	1293 (4.86)	4843 (4.94)
Anti-osteoporotic drug use, n (%)	9471 (7.60)	1638 (6.16)	7833 (7.99)
Heavy smoking, n (%)	27,832 (22.34)	7631 (28.70)	20,201 (20.62)
Alcohol abuse, n (%)	6079 (4.88)	1881 (7.07)	4198 (4.28)
Obesity, n (%)	11,131 (8.94)	4673 (17.58)	6458 (6.59)
Pancreatitis, n (%)	1047 (0.84)	521 (1.96)	526 (0.54)
Hyperthyroidism, n (%)	3511 (2.82)	885 (3.33)	2626 (2.68)
Hypothyroidism, n (%)	6451 (5.18)	1720 (6.47)	4731 (4.83)
Glucocorticoid use, n (%)	29,244 (23.48)	7615 (28.64)	21,629 (22.07)
Dyslipidemia, n (%)	24,527 (19.69)	8748 (32.90)	15,779 (16.10)
Hypertension, n (%)	67,254 (53.99)	19,592 (73.69)	47,662 (48.64)
Anxiolytics incl. opioids, n (%)	76,272 (61.23)	18,035 (67.83)	58,237 (59.44)
CCI, mean ± SD	0.54 (1.10)	0.82 (1.34)	0.46 (1.01)
CCI categories, n (%)			
0	88,776 (71.27)	15,824 (59.52)	72,952 (74.45)
1	17,823 (14.31)	4885 (18.37)	12,938 (13.20)
≥2	17,971 (14.43)	5879 (22.11)	12,092 (12.34)
Income, € in thousands, median (IQR)	24.89 (18.72–36.16)	24.50 (18.73–33.78)	25.03 (18.72–36.82)
Marital status, n (%)			
Married	60,93 (48.88)	12,297 (46.25)	48.596 (49.60)
Divorced	16,609 (13.33)	4176 (15.71)	12,433 (12.69)
Unmarried	9097 (7.30)	2174 (8.18)	6923 (7.07)
Widowed	37,971 (30.48)	7941 (29.87)	30,030 (30.65)
Index year, n (%)			
1998–2002	32,290 (25.92)	6616 (24.88)	25,674 (26.20)
2003–2007	40,209 (32.28)	8595 (32.33)	31,614 (32.27)
2008–2012	38,510 (30.91)	8305 (31.24)	30,205 (30.83)
2013–2018	13,561 (10.89)	3072 (11.55)	10,489 (10.71)

All characteristics were evaluated at the index date. Data are presented as numbers (n, %), mean with ±SD or median with IQR.

3.2. Type of first MOF

The types of first MOFs are presented in Table 2. Overall, the most frequent type of first MOF was fractures of the forearm, yet lower among T2D compared to control subjects. Subjects with T2D had a relatively more frequent first MOF of humerus and hip compared to controls.

The crude predicted probability differences from control to T2D subjects for humerus, forearm, spine, or hip as first MOF were 3.48 % (2.90; 4.07), −6.79 % (−7.42; −6.16), 0.95 % (0.51; 1.39) and 2.36 % (1.73; 6.16), respectively. The multiple adjusted predicted discrete probability difference from control to T2D was 2.82 % (2.17; 3.46) for humerus, −6.77 % (−7.46; −6.08) for forearm, −0.03 % (−0.48; 0.42) for spine and 3.98 % (3.29; 4.67) for hip (Table 2 and Fig. 1). As sex and age were effect modifiers, we further stratified the analysis as presented in Table 2 and visualized in Figs. 1 and 2, respectively.

Results from the sensitivity analyses are presented in Table 3. After excluding all subjects with a follow-up below 2 years, spine fractures as first MOF moved toward a lower probability for subjects with T2D (−0.42 % [−0.94; 0.09]).

3.3. First anti-osteoporotic treatment after MOF

We identified the first redeemed anti-osteoporotic treatment after the first MOF after the index date in the entire study cohort (Table 4). In general, subjects with T2D were less frequently treated with anti-osteoporotic therapy after the first MOF compared to control subjects (18.78 % [18.31; 19.26] versus 24.26 % [23.99; 24.53], RR 0.77 [0.75;

Table 2
First type of MOF and multiple adjusted predicted probability differences of the first MOF type stratified by sex and age categories.

N (%)	Any MOF	Type of MOF, Numbers, n (%) and predicted probability difference, % (95 % CI)			
		Humerus	Forearm	Spine	Hip
All	124,570 (100)	28,845 (23.16)	44,113 (35.41)	14,256 (11.44)	37,356 (29.99)
Control	97,982 (100)	21,960 (22.41)	36,118 (36.86)	11,014 (11.24)	28,890 (29.49)
T2D	26,588 (100)	6885 (25.90)	7995 (30.07)	3242 (12.19)	8466 (31.84)
Difference*	–	2.82 (2.17; 3.46)	−6.77 (−7.46; −6.08)	−0.03 (−0.48; 0.42)	3.98 (3.29; 4.67)
Female					
Control	65,920 (67.28)	13,636 (20.69)	28,292 (42.92)	5939 (9.01)	18.053 (27.39)
T2D	17,320 (65.14)	4426 (25.55)	5883 (33.97)	1735 (10.02)	5276 (30.46)
Difference*	–	4.12 (3.33; 4.91)	−9.13 (−10.01; −8.25)	−0.17 (−0.33; 0.66)	4.85 (4.02; 5.67)
Male					
Control	32,062 (32.72)	8324 (25.96)	7826 (24.41)	5075 (15.83)	10,837 (33.80)
T2D	9268 (34.86)	2459 (26.53)	2112 (22.79)	1507 (16.26)	3190 (34.42)
Difference*	–	0.42 (−0.69; 1.53)	−1.99 (−3.03; −0.94)	−0.49 (−1.41; 0.43)	2.06 (0.86; 3.26)
Age 50–59					
Control	20,586 (7.80)	5782 (28.09)	9966 (48.41)	2161 (10.50)	2677 (13.00)
T2D	6052 (7.37)	2034 (33.61)	2348 (38.80)	673 (11.12)	997 (16.47)
Difference*	–	5.54 (4.05; 7.03)	−7.57 (−9.16; −5.98)	−0.23 (−1.14; 0.68)	2.26 (1.21; 3.20)
Age 60–69					
Control	29,848 (10.82)	7234 (24.24)	12,361 (41.41)	3503 (11.74)	6750 (22.61)
T2D	8372 (9.63)	2426 (28.98)	2761 (32.98)	1038 (12.40)	2147 (25.65)
Difference*	–	4.56 (3.37; 5.74)	−7.46 (−8.72; −6.19)	−0.34 (−1.12; 0.44)	3.24 (2.12; 4.36)
Age 70–79					
Control	31,534 (17.49)	6193 (19.64)	9932 (31.50)	3763 (11.93)	11,646 (36.93)
T2D	7960 (13.93)	1684 (21.16)	2044 (25.68)	1046 (13.14)	3186 (40.03)
Difference*	–	1.04 (0.02; 2.10)	−5.63 (−6.778; −4.50)	0.31 (−0.50; 1.11)	4.29 (3.01; 5.57)
Age ≥ 80					
Control	16,014 (25.26)	2751 (17.18)	3859 (24.10)	1587 (9.91)	7817 (48.81)
T2D	4204 (18.00)	741 (17.63)	842 (20.03)	485 (11.54)	2136 (51.81)
Difference*	–	0.02 (−1.32; 1.37)	−3.80 (−5.21; −2.39)	0.55 (−0.46; 1.56)	3.22 (1.46; 4.99)

* Multiple adjusted predicted probability differences between type 2 diabetes and control subjects by type of MOF, % (95 % CI) with control subjects as comparator. T2D; Type 2 Diabetes. Multiple adjustment for sex, age, follow up time, history of any MOF, history of other fractures, history of osteoporosis diagnosis, history of anti-osteoporotic treatment, use of anxiolytics/opioids, dyslipidemia, smoking, alcohol, obesity, glucocorticoid use, hypertension, rheumatoid arthritis, CCI category, income and marital status. Both main and interaction effects were included in the analysis (sex * age). Sex and age were omitted from the model in the stratified analyses for each variable.

0.80]). This was present during all years of first MOF after the index date, and independent of MOF type and age (Table 4).

3.4. Mortality after MOF

In the evaluation of any current explanation on the lower anti-osteoporotic treatment in subjects with T2D with a MOF, we first evaluated mortality after the first MOF and found that a higher proportion of subjects with T2D were dead before end of follow-up (December 31, 2018) compared to control subjects (45.80 % versus 39.11 %). By Cox proportional hazards we identified mortality risk after first MOF after the index date with control subjects as comparator. The crude HR was 1.27 (1.24; 1.30) for subjects with T2D and remained significant after multiple adjustment with HR 1.18 (1.15; 1.20). The 1-Kaplan-Meier incidence curve is presented in Fig. 3A. In addition, the proportion of deaths among subjects without any anti-osteoporotic treatment after MOF was also higher among T2D subjects (46.11 % [45.45; 46.78] versus 39.86 [39.50; 40.21]).

We performed 2 sensitivity analyses to eliminate the possibility of immortal time bias between index and 2010. Firstly, we only included subjects with a MOF after 2010 and found a multiple adjusted HR for death of 1.23 (1.20; 1.26). Secondly, we only included subjects with an index date after 2010 and the HR did not chance markedly (HR 1.23 [1.18; 1.29]).

3.5. Osteoporosis diagnosis after MOF

We then identified the proportion of subjects with an osteoporosis diagnosis after the first MOF after the index date. We found that subjects with T2D were less likely to receive a diagnosis of osteoporosis after the first MOF compared to control subjects (14.54 % versus 17.67 %, RR 0.82 [0.80; 0.85]). Though this proportion was higher among subjects with hip fractures as the first MOF (a MOF type with direct affiliation to the osteoporotic diagnosis and treatment in Denmark), it was still significantly lower among T2D subjects compared to control subjects (19.64 % versus 23.00 %, RR 0.85 [0.81; 0.90]). Even among those with an osteoporosis diagnosis after the first MOF, redemption of anti-osteoporotic drugs was lower among subjects with T2D than control subjects (46.86 % versus 49.19 %, RR 0.95 [0.92; 0.98]).

3.6. Evaluation of treatment-naïve subjects

Lastly, we evaluated the characteristics and chance of anti-osteoporotic treatment from the first MOF in treatment naïve subjects (n = 109,911), i.e., we only included those without any kind of anti-osteoporotic treatment before the first MOF event after the index date in the analysis.

There was a lower chance of redemption of anti-osteoporotic therapy after the first MOF among T2D subjects compared to control subjects. The crude and multiple adjusted HRs were 0.82 (95 % CI 0.79; 0.86) and 0.80 (95 % CI 0.77; 0.88), respectively (Table 5). The hazard risk ratios were visualized by 1-Kaplan-Meier cumulative incidence curves and presented in Fig. 3B. The results did not change in the competing risk analysis (data not shown). We performed 4 sensitivity analyses. The results did not change after evaluation of the treatment only including female subjects, subjects with a hip and spine fractures as the first MOF after the index date or excluding those who died within the first year after the MOF (Table 5). We evaluated those who initiated anti-osteoporotic treatment (among treatment-naïve subjects without a MOF before the index date) within 1 year after the first MOF. The proportion of subjects receiving anti-osteoporotic treatment within the first year after the first MOF was lower among T2D (7.14 %) compared to controls (8.42 %), RR 0.85 (95 % CI 0.80; 0.90). The crude IRs of treatment within the first year after the first MOF (among treatment naïve subjects without a history of MOF before the index date) were 149.39 (95 % CI 143.75; 155.24) for T2D and 188.17 (95 % CI 184.85;

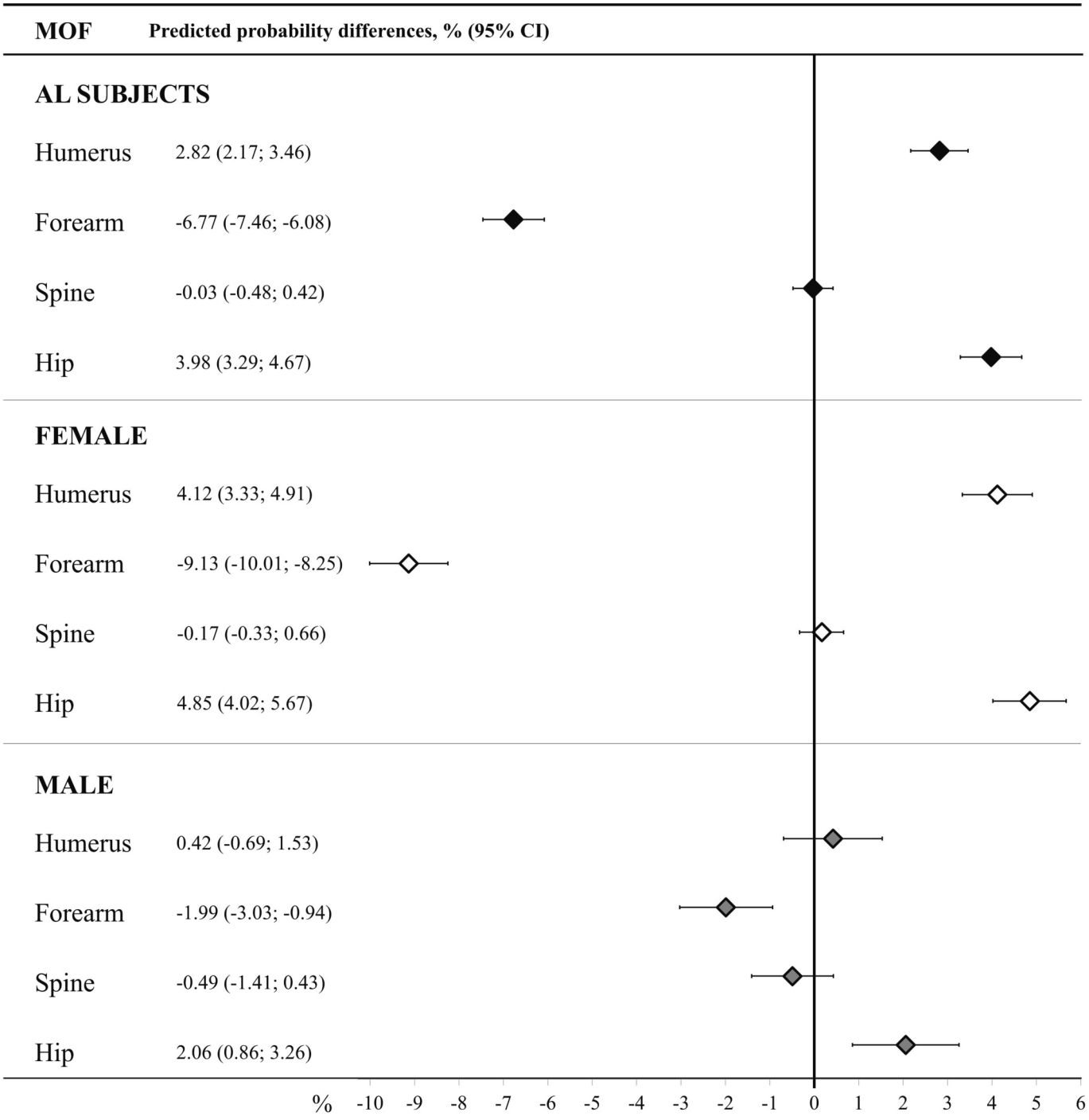

Fig. 1. Multiple adjusted predicted probability differences (%) for type of first MOF between Type 2 diabetes and control subjects, stratified by gender.

191.56) for control subjects per 1000 person-years with an IRR of 0.79 (95 % CI 0.76; 0.83). The crude and multiple adjusted HR for time to treatment within the first year was 0.79 (95 % CI 0.76; 0.83) and 0.80 (95 % CI 0.76; 0.84), respectively.

Finally, the E-value was 1.61 for the primary point outcome (HR 0.80) and 1.53 for the confidence interval (0.77; 0.88). Thus, unmeasured confounders would need to be associated with both the exposure and the outcome by HR 1.61 each, above and beyond the measured confounders, for the observed HR to be explained away to the null.

The fraction of treatment-naïve subjects with a diagnosis of osteoporosis or anti-osteoporotic treatment after the first MOF after the index date was 17.28 % and 16.58 %, respectively (Table 6). Of those subjects diagnosed with osteoporosis after the first MOF only 60.45 % received anti-osteoporotic treatment with a lower fraction among T2D (55.41 %) compared to control subjects (61.66 %).

Lastly, we evaluated any differences in covariates at MOF date between subjects with and without anti-osteoporotic treatment after the first MOF after the index date (Table 6). Subjects with anti-osteoporotic treatment after the first MOF after the index date were slightly younger at the time of MOF compared to subjects without treatment after MOF (74.98 (±9.04) versus 75.63 (±10.68) years, $p < 0.001$). Treated subjects were more often females compared to non-treated subjects (78.32 % [77.72; 78.92] versus 61.57 % [61.25; 61.89]). The proportion of treated subjects was highest after a spine fracture as the first MOF

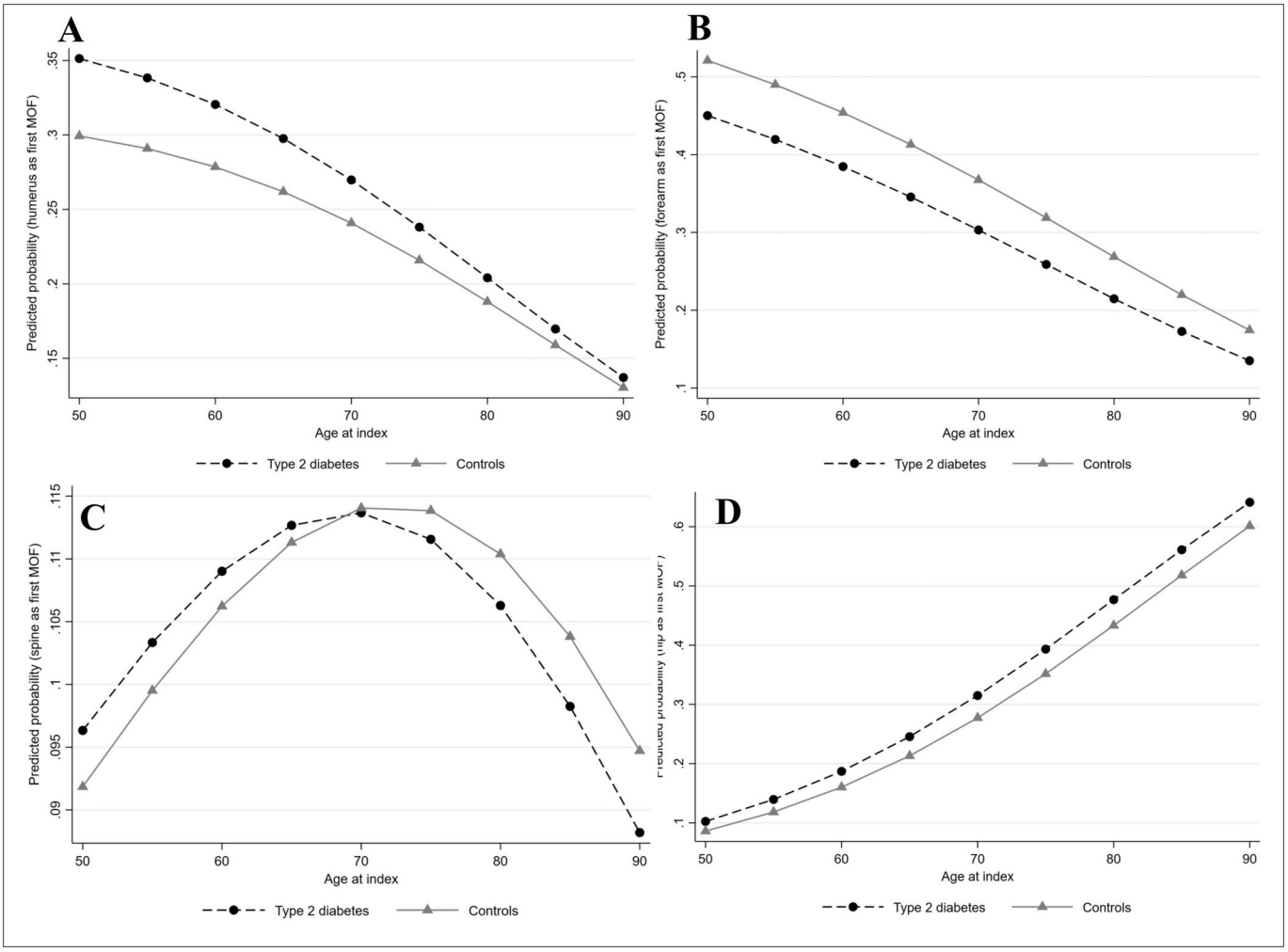

Fig. 2. Multiple adjusted predicted probability (%) for type of first MOF in Type 2 diabetes and control subjects by age at the index date. A, Humerus; B, Forearm; C, Spine; D, Hip.

(28.00 % [27.17; 28.84]), followed by hip (17.87 % [17.46; 18.28]), forearm (15.10 % [14.75; 15.45]) and humerus (12.29 % [11.89; 12.69]) fractures. Subjects treated with anti-osteoporotic drugs after the MOF were more likely to have a history of glucocorticoid use, anxiolytic use and smoking but less likely to have a history of alcohol abuse, dyslipidemia, hypertension, and obesity ($p \leq 0.001$ for all). Moreover, treated persons were less comorbid (mean CCI 1.04 [1.02; 1.06] versus 1.25 [1.24; 1.26]) and had a lower income compared to subjects without treatment after MOF (see Table 6). Finally, we evaluated differences in comorbidities defined by the diagnosis and categories within CCI (Table 6). We found that the treated subjects were less likely to have late diabetic complications (CCI nr. 13) compared to untreated subjects (3.87 % versus 5.17 %, RR 0.75 [0.69; 0.81]). Likewise, treated subjects were less likely to suffer from nephrological- (2.02 % versus 3.89 %, RR 0.52 [0.47; 0.58]), cardiovascular- (22.08 % versus 25.35 %, RR 0.87 [0.85; 0.90]) and cancer-related diseases (14.77 % versus 17.32 %, RR 0.85 [0.82; 0.89]). These findings of higher levels of comorbidity among untreated compared to treated subjects was present in both type 2 diabetes and control subjects in a subgroup analysis (data not shown).

4. Discussion

The primary result of the present study was the findings of the most frequent first MOF types after T2D diagnosis. The most frequent MOF type in both subjects with T2D and control subjects was forearm fractures. However, the chance of a forearm fracture as first MOF was significantly lower among T2D subjects compared to control subjects. Contrarily, the probability of a humerus or hip fracture as first MOF where significantly higher among subjects with T2D. Only the chance of spine fractures as the first MOF did not differ between T2D and control subjects.

Type 2 diabetes is a disorder with high prevalence among men [42], whereas women are at higher risk of developing osteoporosis and a related fracture after menopause [43]. Consequently, the presented results reflect the effects of the female gender, and a significant probability difference from control subjects was observed in T2D women compared to men. Yet, the higher likelihood of a hip fracture and lower likelihood of a forearm fracture as the first MOF in subjects with T2D were significantly different from subjects without diabetes in both genders. The presented results also demonstrate an association with age. Both humerus and forearm fractures decrease with increasing age in both groups whereas the probability of a hip fracture as the first MOF increased with increasing age. The likelihood of a spine fracture as the first MOF demonstrated an inverted U-shaped curve in both subjects with T2D and without diabetes. The latter may indicate a probability switch after the age of 70 from higher to lower where age of 70 may act as a threshold on the probability to have sustained the first MOF. However, the deflection also demonstrated a shift between subjects with T2D and subjects without diabetes at an age of 70. It may indicate that subjects with T2D are more likely to obtain a spine fracture as the first MOF before the age of 70 but less likely after age 70, compared to subjects without diabetes.

Table 3
Sensitivity analyses of predicted probability differences of the first MOF type.

Sensitivity analysis		Multiple adjusted predicted probability difference, % (95 % CI)			
		Humerus	Forearm	Spine	Hip
1, Follow-up time ≥ 2 years	Controls, n (%)	17,226 (22.04)	27,863 (35.64)	9112 (11.66)	23,973 (30.67)
	T2D, n (%)	5287 (26.27)	5902 (29.33)	2467 (12.26)	6468 (32.14)
	Prob. diff*	3.52 (2.78: 4.25)	−6.57 (−7.34; −5.80)	−0.42 (−0.94; 0.09)	3.47 (2.68; 4.27)
2, No history of MOF before index	Controls, n (%)	18,587 (22.32)	31,097 (37.34)	9318 (11.19)	24,287 (29.16)
	T2D, n (%)	5844 (26.42)	6720 (30.38)	2696 (12.19)	6861 (31.02)
	Prob. diff*	3.51 (2.80; 4.23)	−6.84 (−7.60; −6.08)	−0.05 (−0.45; 0.54)	3.27 (2.53; 4.02)
3, No history of treatment before index	Controls, n (%)	20,394 (22.62)	33,562 (37,23)	9583 (10.63)	26,610 (29.52)
	T2D, n (%)	6550 (26.25)	7582 (30.39)	2878 (11.54)	7940 (31.82)
	Prob. diff*	2.95 (2.28; 3.63)	−6.86 (−7.58; −6.14)	−0.08 (−0.53; 0.38)	3.99 (3.28; 4.70)
4, No history of MOF/ treatment/ diagnosis before index	Controls, n (%)	17,711 (22.50)	29,529 (37.52)	8448 (10.73)	23,013 (29.24)
	T2D, n (%)	5648 (26.64)	6478 (30.56)	2469 (11.65)	6605 (31.16)
	Prob. diff*	3.53 (2.79; 4.26)	−6.91 (−7.69; −6.13)	−0.06 (−0.55; 0.44)	3.44 (2.67; 4.20)

Sensitivity analysis 1, follow-up (=diabetes duration) min. 2 years; Sensitivity analysis 2, no history of MOF; Sensitivity analysis 3, no history of anti-osteoporotic treatment; Sensitivity analysis 4, no history of MOF or anti-osteoporotic treatment or osteoporosis diagnosis. Sensitivity analysis 5, exclusion of subjects with death 1 year after the first MOF after the index date. T2D; Type 2 Diabetes.

* Multiple adjusted predicted probability differences between type 2 diabetes and control subjects by type of MOF, % (95 % CI) analysis by multinomial logistic regression modeling with control subjects as comparator. T2D; Type 2 Diabetes. Multiple adjustment for sex, age, follow-up time (omitted in 1), history of any MOF (omitted in 2 and 4), history of other fractures, history of osteoporosis diagnosis (omitted in 4), history of anti-osteoporotic treatment (omitted in 3 and 4), use of anxiolytics/opiods, dyslipidemia, smoking, alcohol, obesity, glucocorticoid use, hypertension, rheumatoid arthritis, CCI category, income and marital status. Both main and interaction effects were included in the analysis (sex * age).

To our knowledge, previous studies have mainly been focusing on incidence rates of fractures rather than the type of first fracture in subjects with diabetes. A study by Bonds et al. followed 5285 women with T2D by annual questionnaires for 5 years [12]. They found that the most frequent type of fractures in women with T2D were lower leg and lower arm followed by foot, upper arm, hip, and spine [12]. Furthermore, the fracture risk rates were all different from subjects without diabetes except from lower arm fractures [12]. A Danish historical follow-up study on 6285 women (229 with T2D) found a 56 % increased risk of sustaining a MOF during 6 years of follow-up among subjects with T2D compared to subjects without diabetes [13]. However, the estimated higher risk of MOFs differed according to site (hip, upper arm, lower arm, spine) and only hip fracture risk was significantly higher after multiple adjustment [13]. Additionally, a recent study by Sarodnik et al. investigated the incidence rates of fractures in naïve T2D subjects [14]. They found that the incidence rates of MOF in general were lower among newly treated T2D subjects compared to control subjects and suggested a protective effect of BMI. In addition, they found that the incidence risk ratio of forearm fractures was lower (IRR 0.81 [95 % CI 0.75; 0.86]) and that hip and humerus fracture risk rates were higher (IRR 1.44 [95 % CI 1.33; 1.55] and 1.11 [95 % CI 1.03; 1.20], respectively). This is in accordance with the present findings that the probability of a hip or humerus fracture as the first MOF was higher among subjects with type 2 diabetes. So, we wondered if these differences could be an expression of early site-specific alterations in bone structure among subjects with T2D. A previous meta-analysis found that subjects with T2D had elevated bone mineral density (BMD) at the femoral neck, hip, and spine with no major differences in BMD at the forearm [44]. Accordingly, and frequently reported, the higher risk of fractures in T2D subjects is not sufficiently explained by BMD measured by dual-energy X-ray absorptiometry (DXA) and consequently, subjects with T2D are more likely to have a normal T-score compared to subjects without diabetes despite a 20–30 % higher risk of fractures [45–47]. Thus, early detection of bone deterioration and diagnosis of osteoporosis in subjects with T2D may require restricted criteria such as an altered threshold for T-scores as in corticosteroid induced osteoporosis. It is likely that more advanced diagnostic tools are necessary to enable early anti-osteoporotic treatment and prevention of osteoporotic fractures, e.g., high-resolution peripheral quantitative computed tomography (HRpQCT), micro-indentation and/or biochemical markers. HRpQCT provides quantitative evaluation of bone microarchitecture and a higher cortical porosity have been suggested in subjects with T2D as presented in a recent meta-analysis, however only located to the radius and not the tibia [48]. Moreover, results from microindentation have suggested a reduced cortical bone material strength in subjects with T2D [49]. However, results from these techniques are in general inconsistent and suggest heterogeneous findings on trabecular bone volume, estimated bone strength and cortical microstructure [50]. Furthermore, there is evidence of decreased turnover markers in subjects with T2D compared to people without diabetes [51]. However, the variation does not necessarily correspond to a change in actual bone turnover or BMD [51]. Consequently, none of these methods are currently sufficient for early detection of poor bone quality in subjects with T2D. Larger studies are needed to determine if these techniques have any predictive value in the assessment of fracture risk in subjects with T2D.

We found that the chance of treatment with anti-osteoporotic drug therapy after the MOF was lower among subjects with T2D. Currently, the main treatment strategies of osteoporosis are either by denosumab or bisphosphonates and both treatments are successfully in prevention of a new MOF in T2D subjects [20]. We found that subjects with T2D had a higher proportion of previous fractures and MOFs compared to subjects without diabetes. Yet, they were equally given an osteoporosis diagnosis before the index date, nonetheless, subjects with T2D were less likely to have received anti-osteoporotic treatment before the diabetes diagnosis. Moreover, subjects with T2D were not provided an osteoporosis diagnosis in the same level as subjects without diabetes after the first MOF after the index date. This matter became even more troublesome as subjects with T2D had a higher chance of hip fracture as first MOF compared to control subjects – a fracture type with direct indication for treatment of osteoporosis in Denmark without need of DXA examination. However, they were still 20 % less likely to be treated with anti-osteoporotic therapy after the first MOF after the index date compared to subjects without diabetes. It is possible that this issue is related to pour compliance among T2D subjects resulting in lower redemption of drug prescriptions and no-show to hospital evaluations, both of which we cannot distinguish in this study. Likewise, subjects who redeemed a prescription of anti-osteoporotic therapy after the first MOF were less comorbid and had a lower income compared to subjects without any anti-osteoporotic treatment after MOF, and this was present in both type 2 diabetes and control subjects. The mortality after the first MOF was 20 % higher among subjects with T2D, as confirmed in previous studies as well [18,52,53], that demonstrate the importance of early detection and treatment of osteoporosis in subjects with diabetes.

As reflected in the presented results, the post-fracture treatment rates were overall higher in females, decreased after the age of 70, were greatest after a spine fracture, and decreased over time. The aforementioned Danish cohort study reported decreasing hip and humerus

Table 4
First type of anti-osteoporotic therapy after MOF.

Numbers and %		Any treatment	Type of anti-osteoporotic treatment, n (row %)			
			Alendronate	Other bisphosphonates	Denosumab	Others[a]
Overall	All	28,763 (23.09)	25,593 (88.98)	1738 (6.04)	1091 (3.79)	341 (1.19)
	Control	23,769 (24.26)	21,089 (88.72)	1499 (6.31)	886 (3.73)	295 (1.24)
	T2D	4994 (18.78)	4504 (90.19)	239 (4.79)	205 (4.10)	46 (0.92)
By gender						
Female	Control	19,443 (29.49)	17,074 (87.82)	1347 (6.93)	758 (3.90)	264 (1.36)
	T2D	3941 (22.75)	3531 (89.60)	199 (5.05)	172 (4.36)	39 (0.99)
Male	Control	4326 (13.49)	4015 (92.81)	152 (3.15)	128 (2.96)	31 (0.72)
	T2D	1053 (11.36)	973 (92.73)	40 (3.80)	33 (3.13)	7 (0.66)
By age at MOF						
50–59	Control	1045 (15.06)	939 (89.86)	68 (6.51)	28 (2.68)	10 (0.96)
	T2D	267 (12.44)	239 (89.51)	21 (7.81)	6 (2.25)	1 (0.37)
60–69	Control	4800 (22.33)	4351 (90.65)	279 (5.81)	127 (2.65)	43 (0.90)
	T2D	1072 (16.84)	974 (90.86)	53 (4.94)	36 (3.36)	9 (0.84)
70–79	Control	8977 (28.65)	7923 (88.26)	605 (6.74)	535 (3.93)	96 (1.07)
	T2D	1951 (22.11)	1772 (90.83)	85 (4.36)	81 (4.15)	13 (0.67)
≥80	Control	8947 (23.42)	7876 (88.03)	547 (6.11)	378 (4.22)	146 (1.63)
	T2D	1704 (18.42)	1519 (89.14)	80 (4.69)	82 (4.81)	23 (1.35)
By MOF type						
Humerus	Control	4208 (19.16)	3728 (88.59)	290 (6.89)	133 (3.16)	58 (1.35)
	T2D	945 (13.73)	835 (88.36)	61 (6.46)	44 (4.66)	5 (0.53)
Forearm	Control	8234 (22.80)	7309 (88.77)	596 (7.12)	254 (3.08)	13 (1.02)
	T2D	1273 (15.92)	1151 (90.42)	71 (5.58)	38 (2.99)	13 (1.02)
Spine	Control	4281 (38.87)	3745 (87.48)	230 (5.37)	263 (6.14)	43 (1.00)
	T2D	1074 (33.13)	956 (89.01)	48 (4.47)	60 (5.59)	10 (0.93)
Hip	Control	7046 (24.39)	6307 (89.71)	393 (5.58)	236 (3.35)	110 (3.35)
	T2D	1702 (20.10)	1562 (91.77)	59 (3.47)	63 (3.70)	18 (1.06)
By year of MOF						
1998–2002	Control	982 (31.55)	747 (76.07)	220 (22.40)	7 (0.71)	8 (0.81)
	T2D	155 (22.56)	118(76.13)	31 (20.00)	3 (1.94)	3 (1.94)
2003–2007	Control	3861 (30.74)	3269 (84.67)	432 (11.19)	36 (0.93)	124 (3.21)
	T2D	786 (23.55)	690 (87.79)	68 (8.65)	8 (1.02)	20 (2.54)
2008–2012	Control	8221 (25.99)	7362 (89.55)	494 (6.01)	239 (2.91)	126 (1.53)
	T2D	1770 (20.62)	1613 (91.13)	88 (4.97)	50 (2.82)	19 (1.97)
2013–2018	Control	10,705 (21.13)	9711 (90.71)	353 (3.30)	604 (5.64)	37 (0.35)
	T2D	2283 (16.33)	2083 (91.24)	52 (2.28)	144 (6.31)	4 (0.18)

T2D; Type 2 Diabetes.
[a] Others: Ipriflavon, strontium, teriparatide.

fracture incidence rates between 1997 and 2017 in subjects with and without T2D [54]. Though the incidence of humerus and hip fractures was higher among subjects with T2D, the decreasing rates were significantly different from subjects without diabetes. However, the incidence of clinical vertebral fractures increased in the same period in both subjects with and without T2D and significantly more in T2D [54].

One notable strength of the current study is the utility of the Danish National Registers based on the unique personal identification number assigned to all Danish citizens with high quality and validity [23,26,55,56]. Furthermore, the identification of subjects with diabetes and MOF in Denmark was nationwide without any selection bias. Another strength was the ability to include a high number of potential confounders in the adjusted analysis as well as using a competing risk regression analysis when estimating the chance of treatment after the first MOF.

We were marginally limited in the diagnostic criteria for T2D. Glucose-lowering drugs besides insulin were not approved as treatment in subjects with T1D in Denmark until 2019. In addition, newer anti-diabetic drugs, e.g., sodium-glucose cotransporter-2 inhibitors and glucagon-like peptide-1 receptor agonists, where not indicated as treatment for other diseases than T2D before 2019. Consequently, we find it unlikely that this will impact on the T2D classification in the current study with a follow-up period. All Danish citizens with T1D will eventually be in contact with the hospital and thereby be given an ICD-10 DE10 code. Contrarily, general practitioners outside the hospital will most often be responsible for treatment of subjects with T2D. Thus, only complicated cases of subjects with T2D will be in contact with the hospital and receive an ICD-10 DE11 (T2D mellitus) code. In addition, we did not have access to laboratory results and thus, we were unable to differentiate if a subject identified by ATC-codes, were treated with glucose-lowering drugs due to diabetes or other conditions such as prediabetes or polycystic ovary syndrome. However, according to international guidelines at the time of study period, treatment of prediabetes or other conditions with glucose-lowering drugs was not recommended [57], and consequently we only expect subjects with prediabetes to present a minor proportion of the included subjects. And lastly, we were able to exclude subjects with polycystic ovary syndrome based on drug redemption.

We did not have access to glycemic control, BMI, or BMD measurements, all of which may influence on bone microarchitecture and fracture type as well as treatment choice. The pre-diabetic state may impact bone health and be present before the time of diabetes treatment, which are also suggested in our results, i.e., higher levels of fractures and MOFs before diabetes diagnosis. It was previously reported that approximately half of the elderly population with prediabetes have a T-score below −1 and a higher risk of hip fractures (despite higher hip BMD) compared to subjects without diabetes [3]. Likewise, there was no difference in osteoporosis diagnoses before the index date that may be a result of the above-mentioned bone-related diagnostic difficulties in subjects with pre-diabetes as well as in subjects with T2D. Furthermore, some fractures, especially vertebral fractures, may go undetected and undiagnosed that may have led to an underreporting of spine fractures in our analysis. Indeed, subjects with T2D are suggested to have a higher risk of vertebral fractures that may induce a skewed distribution and underestimation of spine fractures in our analysis. However, findings are inconsistent. A recent study from the Danish registers reported similar rates of clinical vertebral fractures among subjects with T2D compared to control subjects [54]. A recent meta-analysis suggests lower risk of

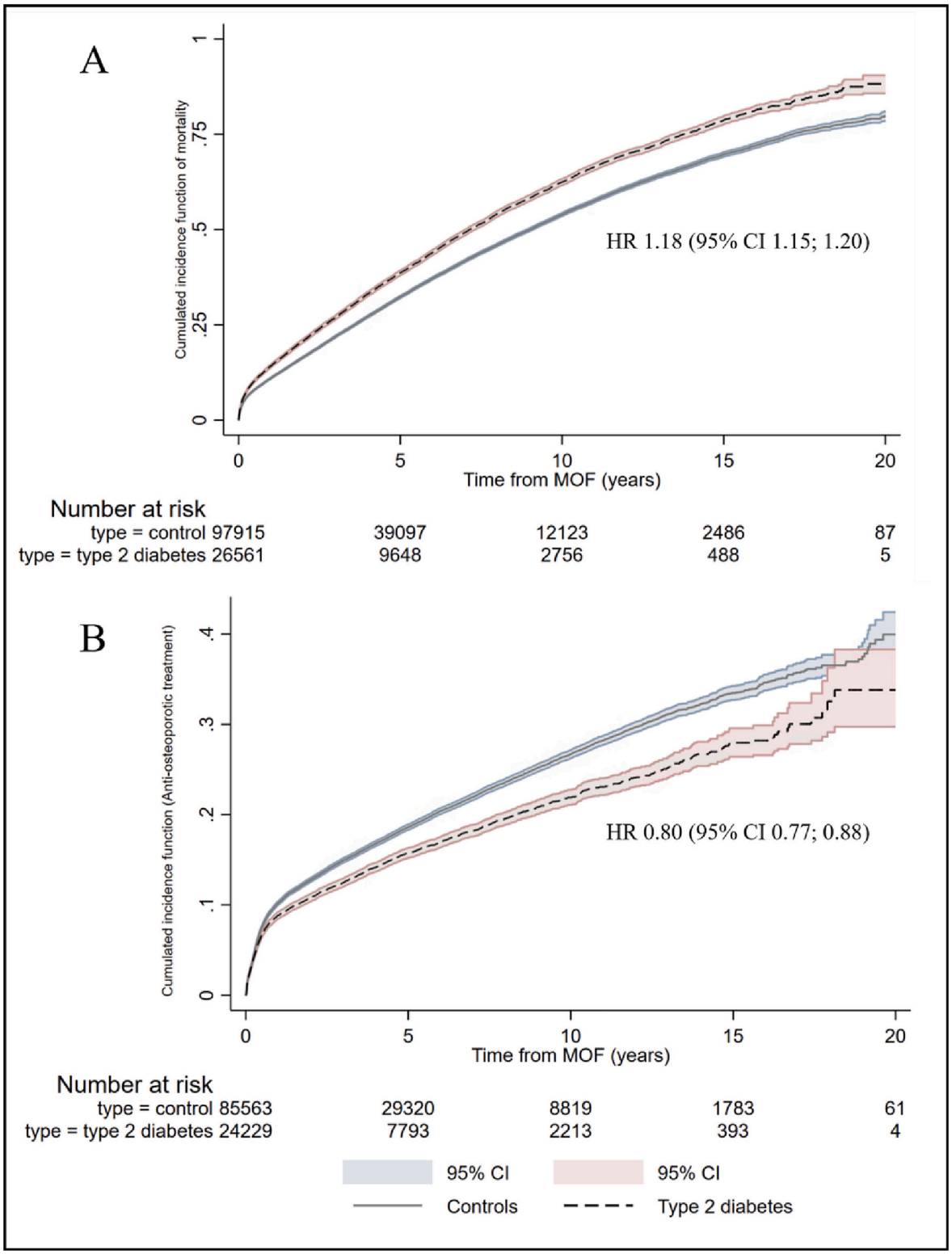

Fig. 3. 1-Kaplan-Meier cumulative incidence curves. Mortality risk (A) and time to first treatment after the first MOF (B).

prevalent vertebral fractures (OR 0.84 [95 % CI 0.74; 0.95]) but higher risk of incident vertebral fractures (OR 1.35 [95 % CI 1.27; 1.44]) among subjects with T2D [58]. Moreover, adjustment for BMD is reported to increase the association between T2D and vertebral fractures [59] indicating an insufficient prediction of fracture risk by BMD.

Though the Danish registry contains a wide range of validated information, we did not have access to over-the-counter-medicine, e.g., vitamin D supplementation, or information on lifestyle factors, e.g., diet and exercise, and so, we cannot dismiss the possibility of residual confounding. However, the E-value indicates that substantial unmeasured confounding is needed to explain away the results. In addition, the registries did not include data on smoking habits and alcohol consumptions; however, we estimated some of these baseline characteristics using ICD-10 and ATC codes as proxies. Consequently, we only obtained

Table 5
Hazard risk ratios of anti-osteoporotic treatment after first MOF after the index date among treatment-naïve subjects and sensitivity analyses.

Numbers and %	Any treatment	Hazard risk ratios (HR) and 95 % CI		
		Crude	Adjusted 1[a]	Adjusted 2[b]
All treatment-naïve subjects, n = 109,911				
Control, *n* = 85,650	14,874 (17.37)	Reference	Reference	Reference
T2D, *n* = 24,261	3345 (13.79)	0.82 (0.79; 0.86)	0.84 (0.81; 0.97)	0.80 (0.77; 0.88)
Sensitivity analysis 1: Female subjects, *n* = 70,725				
Control, *n* = 55,342 (64.61)	11,715 (21.17)	Reference	Reference	Reference
T2D, *n* = 15,383 (63.41)	2555 (16.61)	0.81 (0.78; 0.85)	0.81 (0.78; 0.85)	0.82 (0.78; 0.85)
Sensitivity analysis 2: Hip and Spine as first MOF, *n* = 44,244				
Control, *n* = 33,780 (39,44)	7123 (21.09)	Reference	Reference	Reference
T2D, n = 10,464 (43.13)	1916 (18.31)	0.88 (0.84; 0.93)	0.86 (0.82; 0.90)	0.84 (0.80; 0.89)
Sensitivity analysis 3: Subjects alive after 1 year, n = 97,592				
Control, *n* = 76,658 (89.50)	14,540 (18.97)	Reference	Reference	Reference
T2D, *n* = 20,934 (86.29)	3209 (15.33)	0.82 (0.79; 0.86)	0.83 (0.81; 0.87)	0.80 (0.77; 0.83)

Any anti-osteoporotic treatment after the first MOF after the index date in treatment-naïve subjects. Adjusted HRs (95 % CIs) with control subjects as comparator (reference). Sensitivity analysis 1, only including female subjects. Sensitivity analysis 2, only including subject with hip and spine as first MOF. Sensitivity analysis 3, only including subjects alive 1 year after the first MFO.

[a] Adjusted for sex (omitted in 1) and age.

[b] Multiple adjustment for sex (omitted in 1), age at MOF, type of MOF (omitted in no. 2), history of any MOF, history of other fractures, history of osteoporosis diagnosis, use of anxiolytics/opiods, dyslipidemia, smoking, alcohol, obesity, glucocorticoid use, hypertension, rheumatoid arthritis, CCI category, income and marital status. T2D; Type 2 Diabetes.

these covariates from subjects with already developed concomitant disease at the index date. Though few adverse events have been reported after initiation of alendronate [60], these events are rarely reported after initiation of denosumab for example [61]. Though we were able to adjust for comorbidities, it is likely that these are incompletely measured by ICD-10 codes, allowing confounding by indication in choice or withdraw of anti-osteoporotic treatment.

To our knowledge, this is the first study to evaluate the differences in type of first MOF and the following treatment after diabetes diagnosis in subjects with T2D compared to control subjects. In conclusion, the probability of forearm fractures as the first MOF was lower among T2D subjects, however the probability of both humerus and hip fractures as the first MOF were higher. Furthermore, subjects with T2D were less likely to receive a diagnosis or treatment of osteoporosis after the first MOF compared to subjects without diabetes. Indeed, further research is needed and in particularly clinical trials. We encourage health care providers to be aware of an increased risk of hip and humerus fractures as the first osteoporotic fracture in subjects with T2D. Moreover, examination and treatment of osteoporosis are paramount and need more attention in subjects with T2D.

CRediT authorship contribution statement

All authors contributed to the article according to the ICJME requirements for co-authorship. All authors had full access to all data used in the study, critically revised the paper for intellectual content and approved submitted versions and the final version of the paper. PV and JSL ensured funding acquisition. RV and PV designed the study and

Table 6
Characteristics of treatment-naïve subjects.

Subjects, n (%)	All treatment naïve subjects	Treatment after MOF	No treatment after MOF
	n = 109,911 (100)	*n* = 18,219 (16.58)	*n* = 91,692 (83.42)
Age at MOF (years), mean (±SD)	75.52 (10.42)	74.98 (9.04)	75.63 (10.68)
Age category (years), n (%)			
50–59	8824 (8.03)	1094 (6.00)	7730 (8.43)
60–69	25,867 (23.53)	4294 (23.57)	21,573 (23.53)
70–79	35,032 (31.87)	7047 (38.68)	27,985 (30.52)
≥80	40,188 (36.56)	5784 (31.75)	34,404 (37.52)
Sex, n (%)			
Male	39,186 (35.65)	3949 (21.68)	35,237 (38.43)
Female	70,725 (64.35)	14,270 (78.32)	56,455 (61.57)
History of any fracture, n (%)	25,479 (23.18)	4328 (23.76)	21,151 (23.07)
History of MOF, n (%)	15,987 (14.55)	3510 (19.27)	12,477 (13.61)
MOF type after index, n (%)			
Humerus	26,135 (23.78)	3212 (17.63)	22,923 (25.00)
Forearm	39,532 (35.97)	5968 (32.76)	33,564 (36.61)
Spine	11,194 (10.18)	3134 (17.20)	8060 (8.79)
Hip	33,050 (30.07)	5905 (32.41)	27.145 (29.60)
Osteoporosis diagnosis (after MOF), n (%)	18,990 (17.28)	11,027 (60.52)	7963 (8.68)
Heavy smoking, n (%)	33,512 (30.49)	5929 (32.54)	27,583 (30.08)
Alcohol abuse, n (%)	8356 (7.60)	1103 (6.05)	7253 (7.91)
Obesity, n (%)	12,147 (11.05)	1677 (9.20)	10,470 (11.42)
Glucocorticoid use, n (%)	36,570 (33.27)	6615 (36.31)	29,955 (32.67)
Dyslipidemia, n (%)	43,576 (39.65)	6769 (37.15)	36,807 (40.14)
Hypertension, n (%)	79,840 (72.64)	12,881 (70.70)	66,959 (73.03)
Anxiolytics incl. opioids, n (%)	85,020 (77.35)	14,262 (78.28)	70,758 (77.17)
CCI, mean (±SD)	1.21 (1.74)	1.04 (1.52)	1.25 (1.78)
Late diabetic complications (CCI 13)	5444 (4.95)	705 (3.87)	4739 (5.17)
Nephrological disease (CCI 12)	3937 (3.58)	368 (2.02)	3569 (3.89)
Cardiovascular disease (CCI 1, 2, 3, 4)	27,267 (24.81)	4022 (22.08)	23,245 (25.35)
Cancer (CCI 14, 15, 16, 18)	18,571 (16.90)	2691 (14.77)	15,880 (17.32)
Income, € in thousands, median (IQR)	25.97 (20.13; 34.66)	24.64 (18.84; 32.33)	26.24 (20.39; 35.11)
Marital status, n (%)			
Married	48,482 (44.11)	8131 (44.63)	40,351 (44.01)
Unmarried	8232 (7.49)	1053 (5.78)	7179 (7.83)
Divorced	15,088 (13.73)	2286 (12.55)	12,802 (13.96)
Widowed	38,109 (34.67)	6749 (37.04)	31,360 (34.20)

All characteristics were evaluated at/before MOF except the osteoporosis diagnosis (after MOF). Data are presented as numbers (n, %), mean with ±SD or median with IQR. CCI, Charlson Comorbidity Index.

methodology. RV performed data curation and statistical analyses with assistance from PV and JSL. RV, PV and JSL interpreted the data. RV wrote the original draft. PV and JSL made critical revisions of data management, design, data interpretation and editing the manuscript.

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Guarantor's statement

Peter Vestergaard and Rikke Viggers are guarantors of this work and, as such, have full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data

analysis.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The authors do not have permission to share data.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bone.2023.116745.

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