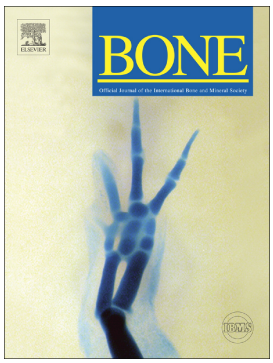


Impact of diabetes on the risk of subsequent fractures in 92,600 patients with an incident hip fracture: A Danish nationwide cohort study 2004–2018

Dennis Vinther, Reimar W. Thomsen, Ove Furnes, Jan-Erik Gjertsen, Alma B. Pedersen

PII: S8756-3282(24)00093-0

DOI: https://doi.org/10.1016/j.bone.2024.117104

Reference: BON 117104

To appear in: *Bone*

Received date: 19 September 2023

Revised date: 5 April 2024

Accepted date: 14 April 2024

Please cite this article as: D. Vinther, R.W. Thomsen, O. Furnes, et al., Impact of diabetes on the risk of subsequent fractures in 92,600 patients with an incident hip fracture: A Danish nationwide cohort study 2004–2018, *Bone* (2023), https://doi.org/10.1016/j.bone.2024.117104

Impact of diabetes on the risk of subsequent fractures in 92,600 patients with an incident hip fracture: A Danish nationwide cohort study 2004-2018

Dennis Vinther[1], Reimar W. Thomsen[1], Ove Furnes[2,3], Jan-Erik Gjertsen[2,3], Alma B. Pedersen[1]

Affiliations:

[1]Department of Clinical Epidemiology, Department of Clinical Medicine, Aarhus University and Aarhus University Hospital, Aarhus, Denmark

[2]The Norwegian Arthroplasty Register, Department of Orthopaedic Surgery, Haukeland University Hospital, Bergen, Norway.

[3]Department of Clinical Medicine, University of Bergen, Bergen, Norway.

Declaration of interest: None

Corresponding author:

Alma B. Pedersen

E-mail: abp@clin.au.dk

Department of Clinical Epidemiology, Aarhus University Hospital,

Olof Palmes Alle 43-45, DK-8200 Aarhus N, Denmark

Word count: 4,324

Ethics Approval

This study was reported to the Danish Data Protection Agency through registration at Aarhus University (record number: AU-2016-051-000001, sequential number: 880). This is an observational registry-based study without patient contact, clinical intervention, or involvement of biological material and as such does not require approval from the Danish Scientific Ethics Committee according to Danish law.

Data availability

The data used in this study cannot be made publicly available due to Danish law on personal data protection. The statistical code can be made available upon reasonable request. The data for this project can be applied for at Statistics Denmark after approval by the Danish Data Protection Agency (https://www.datatilsynet.dk)

Disclosure

None of the authors have any disclosures to declare regarding this study.

Authors contributions

All authors have contributed substantially to the design of the study, interpretation of data, statistics, critical revision of the manuscript, and final approval of the submitted version. DV and ABP drafted the manuscript and accept full responsibility for the work, the conduct of the study, and access to the data.

Funding

This study was supported by a grant from Aarhus University Research Foundation.

Acknowledgments

The authors wish to thank the surgeons, physicians, and other healthcare professionals for their cooperation in submitting high-quality clinical data to the national registries. We thank Aarhus University Research Foundation for funding this research.

Abstract

Purpose:

We investigated the incidence rates of a subsequent hip fracture (HF) and other subsequent fractures than HF after first incident HF, comparing patients with and without diabetes.

Methods:

Using Danish medical databases, we identified 92,600 incident HF patients in the period 2004-2018. Diabetes exposure was examined overall, by type of diabetes (T2D and T1D), and by presence of diabetes complications. We estimated cumulative incidence of subsequent HFs and fractures other than HF within two years of the incident HF. Using Cox regression, adjusted hazard ratios (aHRs) with 95% confidence interval (CI) were calculated.

Results:

Among incident HF patients, 11,469 (12%) had diabetes, of whom 10,253 (89%) had T2D and 1,216 (11%) had T1D. The 2-year incidence rates for a new subsequent HF were 4.8% (95% CI: 4.6-4.9) for patients without diabetes (reference group), 4.1% (95% CI: 3.8-4.6) for T2D, and 4.3% (95% CI: 3.3-5.6) for T1D. Corresponding aHRs were 1.01 (95% CI 0.90-1.14) for T2D and 1.17 (95% CI 0.87-1.58) for T1D. There was effect modification by sex, as women with T1D had an aHR of 1.52 (95% CI: 1.09-2.11) for subsequent HF, and by specific diabetes complications (for example, patients with T2D and prior hypoglycemia had an aHR of 1.75 (95% CI: 1.24-2.42) for subsequent HF, while patients with T1D and neuropathy had an aHR of 1.73 (1.09-2.75), when compared with patients without diabetes).

For fractures other than HF, the 2-year incidence rates were 7.3% (95% CI: 7.2-7.5) for patients without diabetes, 6.6% (95% CI: 6.1-7.1) for T2D, and 8.5% (95% CI: 7.0-10.1) for T1D, with corresponding aHRs of 1.01 (95% CI 0.92-1.11) for T2D and 1.43 (95% CI: 1.16-1.78) for T1D. T2D was only a risk factor for other subsequent fractures among HF patients of high age (age 86-89 years: aHR 1.22 (95% CI 0.99-1.55), age 90+ years: aHR 1.37 (95% CI 1.08-1.74)), whereas T1D was robustly associated with increased risk of fractures other than HF in all subgroups.

Conclusion: Among HF patients, we found no strong overall association of T2D or T1D with increased risk of subsequent HF, but diabetes patients with prior hypoglycemic events or neuropathy were at increased risk. In contrast, patients with T1D had a clearly increased risk of subsequent fractures other than HF.

Keywords:

Diabetes, epidemiology hip fracture, other fractures, osteoporosis, subsequent fracture

1. Introduction

Osteoporosis is the most common metabolic skeletal disease worldwide, affecting 200 million persons and is thus a global public health concern (1). A hip fracture (HF) is the most serious complication of osteoporosis with over 10 million fractures per year globally, estimated to double by the year of 2050 (1-3) and is associated with high mortality (4). HF patients are at increased risk of sustaining subsequent fracture, including both subsequent HF and fractures other than HF such as vertebral fractures and fractures of upper limb, ribs and lower limb (5). The risk of death is further increased after a subsequent fracture (6). Risk factors for subsequent fractures after incident HF are rather similar to risk factors for a first incident HF, including high age, female gender, and comorbidity (7-9).

Diabetes is a complex and costly metabolic disease that has now reached pandemic proportions; the estimated global diabetes prevalence in 2019 was 9.3% rising to 10.2% (578 million) by 2030 (10, 11). Diabetes affects all organs with macro- and microvascular disease, including progression of skeletal fragility (12). Moreover, diabetes may accelerate potential risk factors for falls that may lead to fracture, e.g., through poor vision

(retinopathy), lower extremity poor balance (obesity, neuropathy), dizziness (cerebro-/cardiovascular disease), or use of hypoglycemic drugs and other medications (13-15). Patients with diabetes have a 50% increased risk of incident fracture, compared to patients without diabetes (16), and fracture risk is higher for patients with type 1 diabetes (T1D) than type 2 diabetes (T2D) (17). Previous studies on the impact of diabetes on the risk of subsequent fractures in incident HF patients are sparse (8, 9).

In this study, we aim to investigate the cumulative incidence rates of subsequent HF and fractures other than HF in incident HF patients with diabetes. In addition, we investigate if specific characteristics of diabetes patients are association with increased risk of subsequent HF and fractures other than HF in patients with incident HF. We hypothesized that diabetes type, severity, and diabetes-related characteristics, in particular use of insulin therapy (T1D) and previous hypoglycemic episodes, might impact the risk of subsequent fractures in this elderly and frail population with incident HF.

2. Material and methods

2.1 Setting and data sources

This nationwide cohort study was conducted using five Danish population-based health registries. The Danish healthcare system is tax-supported for all Danish residents, and registrations in the health registries are mandatory for all public hospital treatment (18). Since 1968 all Danish residents are assigned a unique 10-digit identifier at birth or upon immigration which is registered in the Civil Registration System (CRS). The identifier is used in all registries allowing unambiguous and individual-level linkage of data across multiple registries (19).

The Danish Multidisciplinary Hip Fracture Registry (DMHFR) contains data on all incident HF patients aged 65 or older undergoing surgery for HF since 2004 (20). Registration has been mandatory since 2006 and includes data on fracture and surgery type, residence, body mass index (BMI), and assessment of several in-hospital quality indicators.

The Danish National Patient Registry (DNPR) contains discharge dates and diagnoses from all hospital contacts since 1977, i.e., both inpatient admission, hospital outpatient clinics, and emergency room contacts, which were all included in this study (21). From 1993 all primary and secondary diagnoses were registered using the International Classification of Diseases, 10th revision (ICD-10) codes.

The Danish National Prescription Registry contains information on all redeemed prescriptions, including those among nursing home residents, at pharmaceuticals stores since 1995 based on the Anatomical Therapeutic Chemical (ATC) classification system, and dispensing dates (22). Drugs used during hospital admissions or supplied directly from the hospitals are not captured in the register.

The Population Education Register contains information on the highest completed education for each individual from 1974 by the length of education until 2007, whereas after registration is based on educations identifier and length (23).

The CRS contains information on death, immigration, and emigration status since 1968 (19).

2.2 Study population

The study population consisted of all patients aged 65 and over who had a first surgery for incident HF in Denmark from 2004-2018, identified through the DMHFR.

2.3 Exposure: Diabetes

We used a combination of ICD-10 codes from the DNPR and ATC codes from the Danish National Prescription Registry to identify patients with diabetes. Diabetes was present if a patient had a hospital contact with a primary or secondary diagnosis of diabetes (ICD-10: E10-E14) within 10 years before HF admission or had redeemed at least one prescription of any glucose-lowering drug (ATC: A10A, A10BA, A10BB, A10BG, A10B, A10BH, A10BJ, A10BK) within one year before HF admission.

T2D vs T1D is often misclassified when relying on ICD-10 codes in the DNPR, and exact age of onset of diabetes (e.g. <30 or 40 years) is a difficult criterion to assess historically in our population with a median age of more than 80 years. Therefore, we defined T1D as insulin mono-therapy in the year before HF admission and no use of any other glucose-lowering drugs than insulin at least 10 years before HF admission. The remaining patients were assigned as having T2D. The duration of diabetes was defined based on the date of first prescription of any glucose-lowering medications or date of first ICD-10 diagnosis of diabetes before HF admission.

The presence of microvascular disease (including neuropathy, eye complications, nephropathy, angiopathy, and diabetic arthropathy) and macrovascular disease (including angina pectoris, acute coronary syndrome, ischemic heart disease, intracerebral hemorrhage, atherosclerotic cerebral- and peripheral vascular disease, claudicatio intermittens, and atherosclerosis), was identified from each patient's complete hospital contact history in the DNPR with a 10-year lookback period (13). The history of a recent hypoglycemic event was identified through ICD-10 codes from the DNPR with a one-year lookback period.

2.4 Outcome: Subsequent fractures

The outcome of subsequent fractures after incident HF was identified through the DNPR. Outcomes included fractures at any site, excluding fractures of skull, face, and digits (Supplementary 1) in line with previous studies (24-26). For the outcome of subsequent HF, ICD-codes for HF were combined with a new surgical procedure code for HF (internal fixation, hemiarthroplasty, or total hip replacement), to avoid counting possible hospital contacts related to the incident HF. We analyzed separately the two outcomes of subsequent HF and subsequent fractures other than HF after incident HF (other subsequent fracture). The length of the follow-up was 24 months.

2.5 Covariates

We ascertained data on a range of covariates related to diabetes and HF. A modified version of the Charlson comorbidity index (CCI) excluding the index condition of diabetes and diabetic complications was used as a measure for patient comorbidity (27). Patients were categorized into comorbidity score levels of 0, 1, 2, and 3+ based on the CCI-score, where 0 corresponded to no previous hospital-diagnosed comorbidities included in the CCI. All CCI diagnoses were identified from primary or secondary ICD-10 codes registered at discharge from any public hospital contact in Denmark, including both hospital inpatient and hospital outpatient contacts, in the DNPR within 10 years before HF.

Data on individual-level BMI was obtained through the DMHFR. Patients were categorized into one of the following groups: underweight (<19 kg/m^2), normal (20-25 kg/m^2), overweight (26-29 kg/m^2), and obese (30+ kg/m^2). From the DMHFR we also included data on HF type, pre-

fracture mobility and mobility at discharge, and residence of stay (nursing home or living with another adult/alone in own house/other institution or missing) before HF.

Fall-related medications were defined as dispensing of diuretics (loop and thiazide), alfa-receptor blockers, nitrates, beta-blockers, calcium-channel blockers, antidepressants, benzodiazepines, antipsychotics, opioids, or anticholinergics in the year before HF (28).

Bone mineral density-lowering medications were defined as dispensing of glucocorticoids, thyroid hormone, aromatase inhibitors, gonadotropin-releasing hormones, medroxyprogesterone acetate, anti-androgens, selective serotonin reuptake inhibitors, antiepileptics, heparin, vitamin-K-antagonists, loop-diuretics, calcineurin inhibitors, antiretroviral therapy, and proton-pump-inhibitors in the 10 years before HF. The same method was used to define bone-protective medications (bisphosphonates, denosumab, and raloxifene).

Highest achieved education was categorized as low (elementary school or less), medium (higher than elementary, but less than university degree), and high (university degree).

All ICD- and ATC-codes, as well as surgery procedure codes (Nordic NOMESCO Classification of surgical Procedures (NCSP)) used to identify HF patients, diabetes, outcome, and covariates are listed in the supplementary table 1.

2.6 Statistical analysis

Patient characteristics were presented as numbers and percentages for patients without diabetes, for those with any diabetes, and for those with T2D and T1D separately. The follow-up period started at the date of HF surgery and ended at the first subsequent fracture, death, emigration, or end of the 2-year follow-up, whichever came first. The absolute risk of subsequent fractures was computed using cumulative incidence function with death as a competing risk. We estimated 95% confidence intervals (CIs) using log-normal approximation. Adjusted Hazard Ratios (aHRs) with 95% CI were computed using a cause-specific Cox regression model, comparing patients with diabetes, T2D and T1D, respectively, with those without diabetes as a reference group, while adjusting for age, sex, and BMI as potential confounders (29). Each risk factor was analysed in the separate Cox regression model censoring patients at the time of death. Confounders were decided a priory and discussed for each risk factor.

We further performed analyses stratifying on patient characteristics including subgroups of age, gender, CCI score, BMI, pre-fracture mobility, fall-related medication, bone mineral density-lowering medications, bone protective medications, residence of stay, and education. In these analyses we compared the impact of any diabetes, T2D and T1D, respectively, on the risk of subsequent fractures to that of no diabetes as reference group in each subgroup (Supplementary 1).

Finally, we conducted sub-exposure category analyses, further classifying diabetes, T2D and T1D according to the presence or absence of microvascular disease, macrovascular disease, duration of diabetes, and hypoglycemic events using no diabetes as reference group (Supplementary 2).

Cox proportional hazards models were inspected with Schoenfeld residuals and found reasonable to use regarding the assumption of proportionality.

All statistical analyses were done using R software.

3. Results

3.1 Patient characteristics

We identified 92,600 patients who underwent surgery for incident HF. Of these, 11,469 (12.3%) had diabetes, including 10,253 (89%) patients with T2D and 1,216 (11%) patients with T1D. Patient characteristics are presented in Table 1. Among HF patients without diabetes 72% were female, whereas both T2D patients (65%) and T1D patients (57.6%) had a lower proportion of women. Both T2D and T1D patients were younger (mean: 81 and 78 years, respectively) compared to patients without diabetes (mean: 83 years). The highest proportion of overweight or obesity was observed among T2D patients (39.1%) compared to patients without diabetes (23.1%) and T1D patients (24.9%). Presurgical comorbidities were higher among diabetes patients, where around 24% among T2D- and T1D patients had a CCI of ≥3 compared to only 15% among patients without diabetes. Higher prevalence of fall related medications (without diabetes: 76.8%, T2D: 87.3%, T1D: 85.7%) and bone mineral lowering medications (without diabetes: 78.8%, T2D: 87.1%, T1D: 85.7%) were observed among patients with diabetes. In contrast, the proportions with bone protective medications were lower among patients with diabetes (without diabetes: 17.3%, T2D: 11.7%, T1D: 14.7. Both T2D and T1D patients had increased proportions of macrovascular diseases, including cardiac disease (without diabetes: 18.2%, T2D: 29.7%, T1D: 31.0%),

cerebrovascular disease (without diabetes: 17.5%, T2D: 26.5%, T1D: 31.4%), and peripheral vascular disease (without diabetes: 5.9%, T2D: 16.6%, T1D: 31.2%) compared to those without diabetes. The patient proportions having microvascular disease was highest among T2D (48.7%) and, in particular T1D (72.9%) compared to patients without diabetes (27.4%).

Previous hypoglycemic events were substantially more frequent in T1D patients (34.5%) than in T2D patients (7.1%), and rarely present among patients without diabetes (0.1%) as expected. Among T2D patients with HF, 23.4% were insulin users, of which half were on insulin monotherapy (11.1%), and 73.6% used other glucose-lowering drugs.

Table 1: Baseline characteristics of the incident hip fracture patients by diabetes history.

	None	Diabetes	T2D[1]	T1D[2]	Overall
Total	81,131	11,469	10,253	1,216	92,600
Men	22,680 (28.0%)	4,107 (35.8%)	3,591 (35.0%)	516 (42.4%)	26,787 (28.9%)
Women	58,451 (72.0%)	7,362 (64.2%)	6,662 (65.0%)	700 (57.6%)	65,813 (71.1%)
Age, mean (SD[3])	82.8 (8.03)	80.9 (7.65)	81.3 (7.60)	78.1 (7.52)	82.6 (8.01)
Age group					
65-74	15,400 (19.0%)	2,791 (24.3%)	2,328 (22.7%)	463 (38.1%)	18,191 (19.6%)
75-80	16,087 (19.8%)	2,801 (24.4%)	2,498 (24.4%)	303 (24.9%)	18,888 (20.4%)
81-85	18,673 (23.0%)	2,657 (23.2%)	2,415 (23.6%)	242 (19.9%)	21,330 (23.0%)
86-89	14,918 (18.4%)	1,797 (15.7%)	1,662 (16.2%)	135 (11.1%)	16,715 (18.1%)
90+	16,053 (19.8%)	1,423 (12.4%)	1,350 (13.2%)	73 (6.0%)	17,476 (18.9%)
Body mass index categories					
Underweight	12,344 (15.2%)	840 (7.3%)	711 (6.9%)	129 (10.6%)	13,184 (14.2%)
Normal	31,670 (39.0%)	3,679 (32.1%)	3,224 (31.4%)	455 (37.4%)	35,349 (38.2%)
Overweight	14,973 (18.5%)	3,018 (26.3%)	2,743 (26.8%)	275 (22.6%)	17,991 (19.4%)
Obese	3,769 (4.6%)	1,360 (11.9%)	1,261 (12.3%)	99 (8.1%)	5,129 (5.5%)
Missing	18,375 (22.6%)	2,572 (22.4%)	2,314 (22.6%)	258 (21.2%)	20,947 (22.6%)
Charlson Comorbidity Index (CCI)					
CCI 0	35,927 (44.3%)	3,617 (31.5%)	3,237 (31.6%)	380 (31.3%)	39,544 (42.7%)
CCI 1	19,650 (24.2%)	2,804 (24.4%)	2,524 (24.6%)	280 (23.0%)	22,454 (24.2%)
CCI 2	13,419 (16.5%)	2,281 (19.9%)	2,017 (19.7%)	264 (21.7%)	15,700 (17.0%)
CCI 3 or over	12,135 (15.0%)	2,767 (24.1%)	2,475 (24.1%)	292 (24.0%)	14,902 (16.1%)
Diabetes-related characteristics					
Diabetes ≥ 5 years	0 (0%)	8,005 (69.8%)	6,909 (67.4%)	1,096 (90.1%)	8,005 (8.6%)
Insulin users	0 (0%)	3,611 (31.5%)	2,395 (23.4%)	1,216 (100%)	3,611 (3.9%)
Insulin monotherapy	0 (0%)	2,351 (20.5%)	1,135 (11.1%)	1,216 (100%)	2,351 (2.5%)
Hypoglycemic events	75 (0.1%)	1,150 (10.0%)	731 (7.1%)	419 (34.5%)	1,225 (1.3%)
Microvascular disease					

Microvascular, any	22,233 (27.4%)	5,879 (51.3%)	4,992 (48.7%)	887 (72.9%)	28,112 (30.4%)
Neuropathy	3,070 (3.8%)	1,587 (13.8%)	1,243 (12.1%)	344 (28.3%)	4,657 (5.0%)
Eye complications	18,298 (22.6%)	4,193 (36.6%)	3,478 (33.9%)	715 (58.8%)	22,491 (24.3%)
Nephropathy	2,345 (2.9%)	1,482 (12.9%)	1,219 (11.9%)	263 (21.6%)	3,827 (4.1%)
Angiopathy (Diabetic)	0 (0%)	780 (6.8%)	669 (6.5%)	111 (9.1%)	780 (0.8%)
Macrovascular disease					
Cardiac disease	14,742 (18.2%)	3,427 (29.9%)	3,050 (29.7%)	377 (31.0%)	18,169 (19.6%)
Cerebrovascular disease	14,219 (17.5%)	3,104 (27.1%)	2,722 (26.5%)	382 (31.4%)	17,323 (18.7%)
Peripheral vascular disease	4,778 (5.9%)	2,077 (18.1%)	1,698 (16.6%)	379 (31.2%)	6,855 (7.4%)
Medications					
Fall related medications	62,303 (76.8%)	9,988 (87.1%)	8,946 (87.3%)	1,042 (85.7%)	72,291 (78.1%)
BMD[4]-lowering medications	63,957 (78.8%)	9,985 (87.1%)	8,929 (87.1%)	1,056 (86.8%)	73,942 (79.9%)
Bone protective medications	14,048 (17.3%)	1,378 (12.0%)	1,199 (11.7%)	179 (14.7%)	15,426 (16.7%)
Osteoporosis diagnosis	9,642 (11.9%)	1,070 (9.3%)	934 (9.1%)	136 (11.2%)	10,712 (11.6%)
Pre-fracture mobility					
CAS[5] ≥ 5	32,218 (39.7%)	5,023 (43.8%)	4,528 (44.2%)	495 (40.7%)	37,241 (40.2%)
CAS < 5	4,080 (5.0%)	733 (6.4%)	662 (6.5%)	71 (5.8%)	4,813 (5.2%)
Missing	44,833 (55.3%)	5,713 (49.8%)	5,063 (49.4%)	650 (53.5%)	50,546 (54.6%)
Mobility at discharge					
CAS ≥ 5	17,154 (21.1%)	2,342 (20.4%)	2,085 (20.3%)	257 (21.1%)	19,496 (21.1%)
CAS < 5	20,392 (25.1%)	3,552 (31.0%)	3,223 (31.4%)	329 (27.1%)	23,944 (25.9%)
Missing	43,585 (53.7%)	5,575 (48.6%)	4,945 (48.2%)	630 (51.8%)	49,160 (53.1%)
Nursing home before HF[6]					
No	31,962 (39.4%)	5,035 (43.9%)	4,510 (44.0%)	525 (43.2%)	36,997 (40.0%)
Yes	10,285 (12.7%)	1,643 (14.3%)	1,495 (14.6%)	148 (12.2%)	11,928 (12.9%)
Missing	38,884 (47.9%)	4,791 (41.8%)	4,248 (41.4%)	543 (44.7%)	43,675 (47.2%)
Education					
Low	37,149 (45.8%)	6,087 (53.1%)	5,502 (53.7%)	585 (48.1%)	43,236 (46.7%)
Medium	19,248 (23.7%)	2,902 (25.3%)	2,517 (24.5%)	385 (31.7%)	22,150 (23.9%)
High	7,185 (8.9%)	831 (7.2%)	697 (6.8%)	134 (11.0%)	8,016 (8.7%)
Missing	17,549 (21.6%)	1,649 (14.4%)	1,537 (15.0%)	112 (9.2%)	19,198 (20.7%)
HF type					
Femoral neck	42,977 (53.0%)	6,143 (53.6%)	5,529 (53.9%)	614 (50.5%)	49,120 (53.0%)
Pertrochanteric	32,427 (40.0%)	4,484 (39.1%)	3,986 (38.9%)	498 (41.0%)	36,911 (39.9%)
Subtrochanteric	5,727 (7.1%)	842 (7.3%)	738 (7.2%)	104 (8.6%)	6,569 (7.1%)
HF operation year					
2004-2008	28,375 (35.0%)	3,300 (28.8%)	2,914 (28.4%)	386 (31.7%)	31,675 (34.2%)
2009-2013	22,276 (27.5%)	3,172 (27.7%)	2,814 (27.4%)	358 (29.4%)	25,448 (27.5%)
2014-2018	30,480 (37.6%)	4,997 (43.6%)	4,525 (44.1%)	472 (38.8%)	35,477 (38.3%)

[1]T2D- Type 2 diabetes; [2]T1D- Type 1 diabetes; [3]SD- Standard Deviation; [4]BMD- Bone mineral density [5]CAS- Cumulative Ambulation Score, [6]HF- Hip fracture.

Table 2: 2-year cumulative incidences rate and hazard ratio (HR) with 95% confidence intervals (CIs) for subsequent hip fracture and other subsequent fractures than hip fracture.

.

Exposure	At risk	Events	Cum. Incidence (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)
Subsequent hip fracture					
None	81,131	3,694	4.8 (4.6-4.9)	Ref	Ref
Diabetes	11,469	451	4.2 (3.8-4.5)	0.90 (0.82-0.99)	1.03 (0.92-1.15)
T2D[1]	10,253	400	4.1 (3.8-4.6)	0.90 (0.81-0.99)	1.01 (0.90-1.14)
T1D[2]	1,216	51	4.3 (3.3-5.6)	0.92 (0.70-1.21)	1.17 (0.87-1.58)
Other subsequent fracture					
None	81,131	5,697	7.3 (7.2-7.5)	Ref	Ref
Diabetes	11,469	740	6.8 (6.3-7.3)	0.96 (0.89-1.04)	1.06 (0.97-1.16)
T2D[1]	10,253	640	6.6 (6.1-7.1)	0.93 (0.86-1.01)	1.01 (0.92-1.11)
T1D[2]	1,216	100	8.5 (7.0-10.1)	1.19 (0.97-1.45)	1.43 (1.16-1.78)

Adjusted for age, sex, and body mass index; [1]T2D- Type 2 diabetes; [2]T1D- Type 1 diabetes;

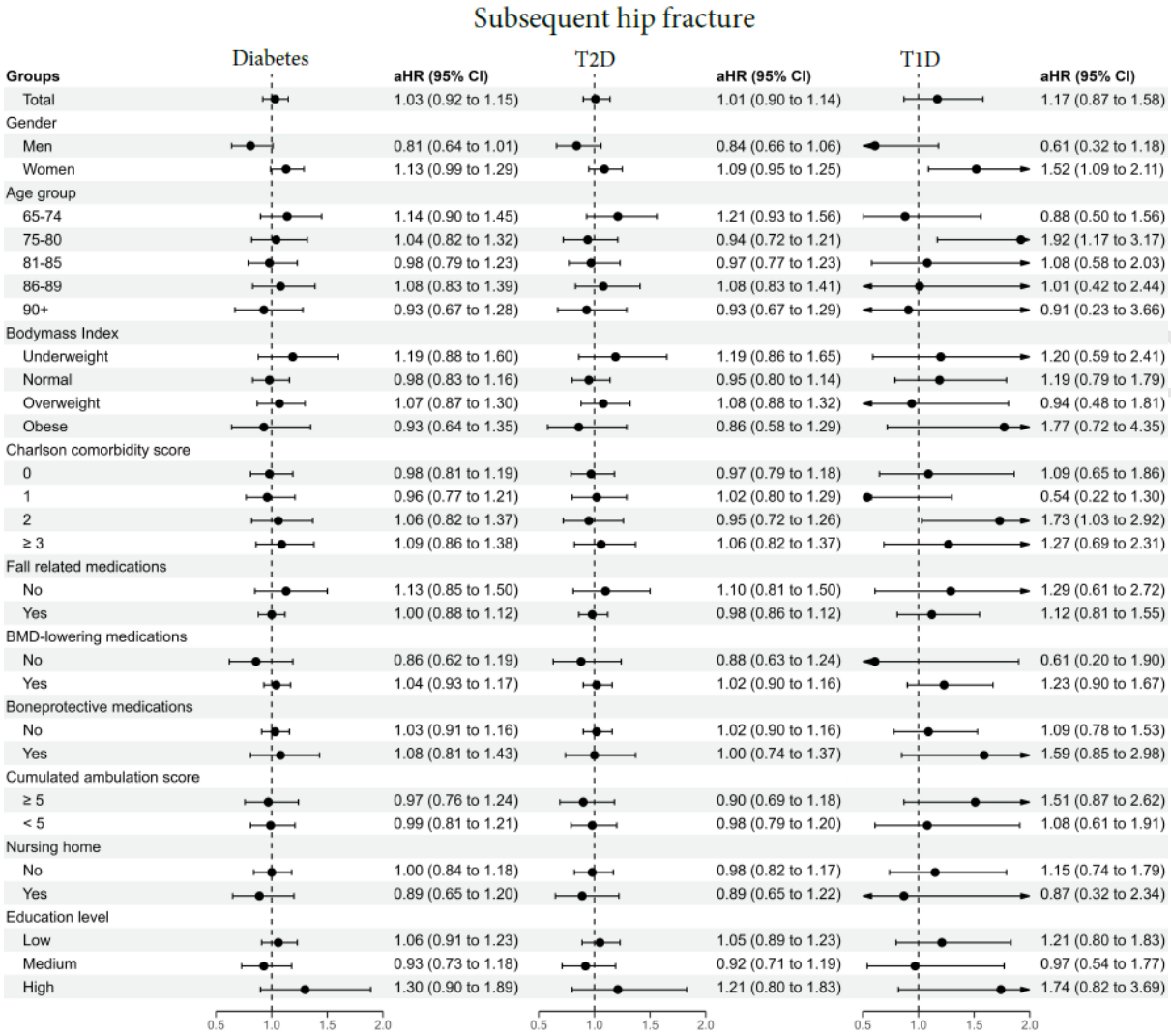
3.2 Subsequent HF

The 2-year cumulative incidence rates for subsequent HF were 4.8% (95% CI: 4.6-4.9) for patients without diabetes, 4.1% (95% CI: 3.8-4.6) for T2D and 4.3% (95% CI: 3.3-5.6) for T1D. After confounder adjustment, aHRs were 1.01 (95% CI: 0.90-1.14) for T2D and 1.17 (95% CI: 0.87-1.58) for T1D.

The analyses stratified on different HF patient characteristics revealed that there was no major association of T2D with subsequent HF in any subgroup examined compared to patients without diabetes. Among T1D patients, female T1D patients had a notably higher risk of subsequent HF (aHR 1.52 (95% CI: 1.09-2.11) compared to females without diabetes (Figure 1).

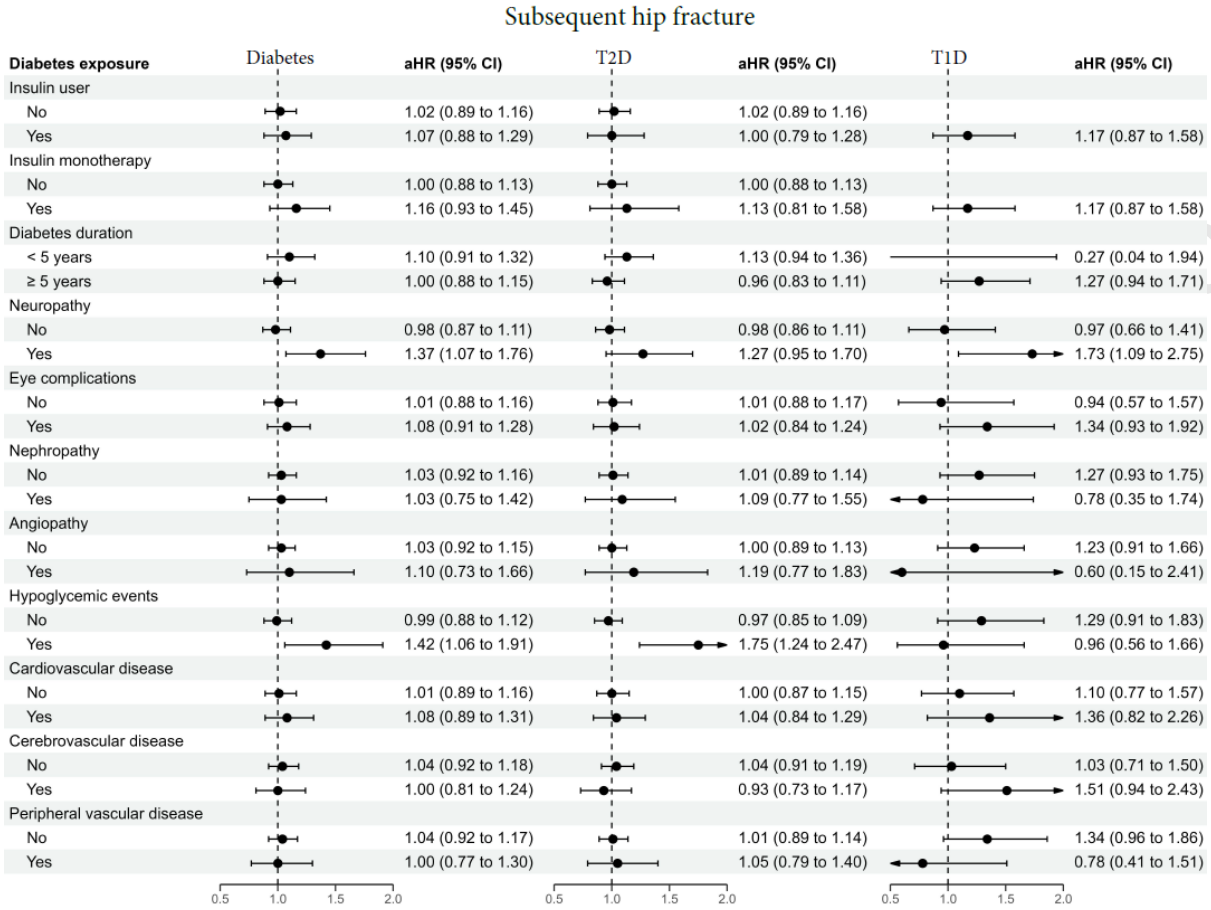
The sub-exposure analyses by different diabetes-related characteristics showed that HF patients with T2D and history of hypoglycemia had a markedly increased aHR of 1.75 (95% CI: 1.24-2.47) for subsequent HF compared to HF patients without diabetes. T1D patients with a history of neuropathy had an aHR of 1.73 (95% CI: 1.09-2.75) of subsequent HF compared to patients without diabetes (Figure 2).

Figure 1: 2-year adjusted hazard ratios (aHRs) for subsequent hip fracture in patients with incident hip fracture and any diabetes, type 2 diabetes, and type 1 diabetes, respectively, as compared with patients without diabetes (reference group) *. Impact of diabetes was examined within different hip fracture patient subgroups.



T1D- Type 1 diabetes; T2D- Type 2 diabetes; aHR- Adjusted hazard ratio; CI- Confidence interval; CCI- Charlson Comorbidity Index. HR adjusted for age, sex, and body mass index.
*Example: Women with HF and T2D compared to women with HF without diabetes.

Figure 2: 2-year adjusted hazard ratios (aHRs) for subsequent hip fracture in patients with incident hip fracture associated with diabetes, further categorizing diabetes exposure by treatment, duration, and complications compared with patient without diabetes*.



T1D- Type 1 diabetes; T2D- Type 2 diabetes; aHR- Adjusted hazard ratio; CI- Confidence interval. HR adjusted for age, sex, and body mass index. *Example: HF patients with T2D and neuropathy compared to HF patients without diabetes.

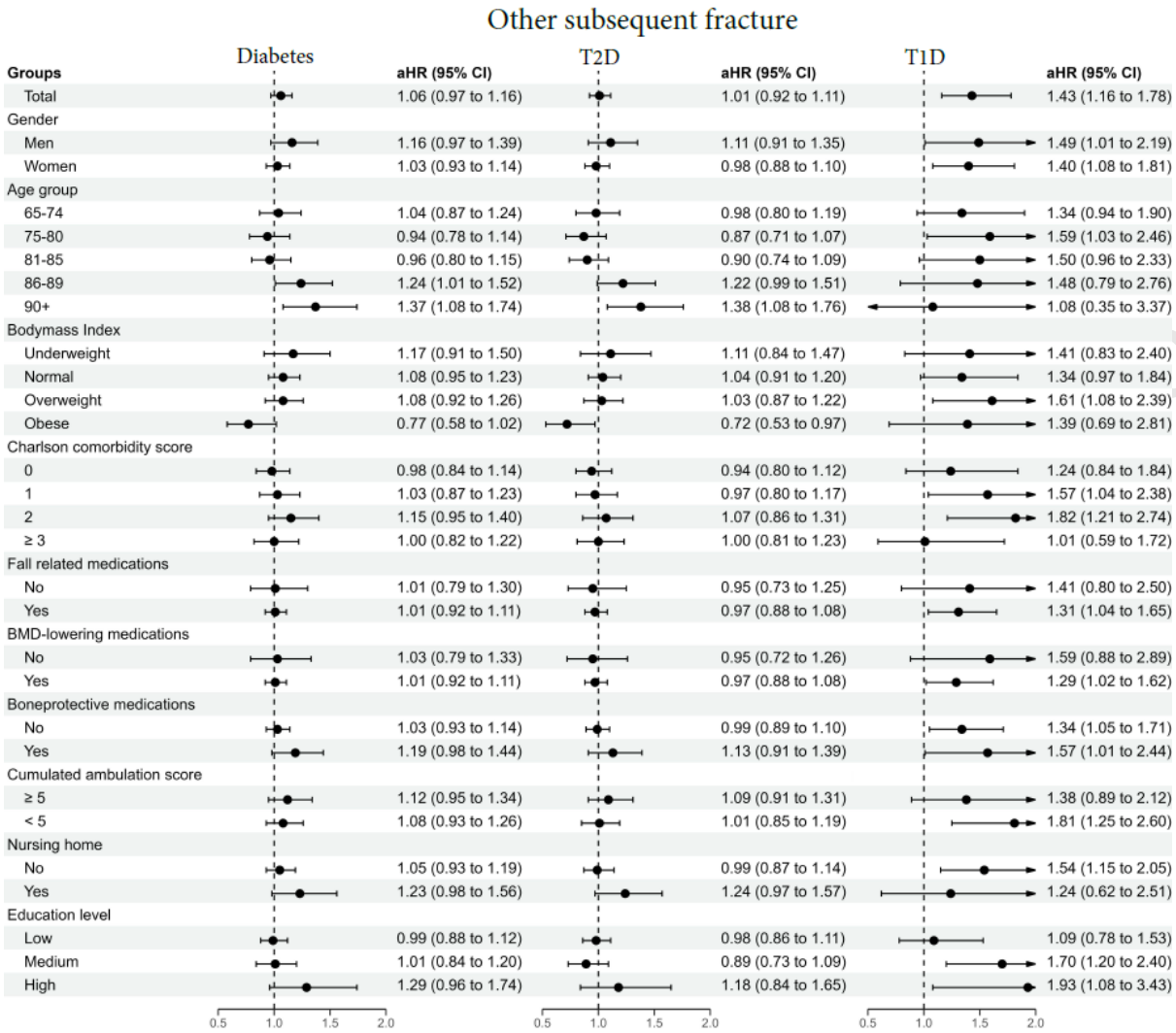
3.3 Other subsequent fracture

The 2-year cumulative incidence rates for fractures other than HF were 7.3% (95% CI: 7.2-7.5) for patients without diabetes, 6.6% (95% CI: 6.1-7.1) for T2D, and 8.5% (95% CI: 7.0-10.1) for T1D. Compared to the HF patients without diabetes, aHR for other subsequent fractures was 1.06 (95% CI. 0.97-1.16) among diabetes patients with HF. The association depended on diabetes type, with aHR of 1.01 (95% CI: 0.92-1.11) for HF patients with T2D and 1.43 (95% CI: 1.16-1.78) among HF patients with T1D (Table 2).

The analyses stratified on different HF patient characteristics among T2D patients revealed that older age modified the association of T2D with other subsequent fractures (86-89 years: aHR 1.22 (95% CI: 0.99-1.51), 90+ years: aHR 1.38 (95% CI: 1.08-1.76)). T1D was robustly associated with increased risk of other subsequent fractures in most subgroups examined, compared to patients without diabetes with the same characteristics, however, the statistical precision of many aHRs was low due to limited sample size (Figure 3).

The sub-exposure analyses showed that patients with T1D in general had an increased risk of other subsequent fractures irrespective of severity and complications of T1D, but again, the statistical precision of many aHRs was low (Figure 4).

Figure 3: 2-year adjusted hazard ratios (aHRs) for other subsequent fracture than hip fracture in patients with incident hip fracture and any diabetes, type 2 diabetes, and type 1 diabetes, respectively, as compared with patients without diabetes as reference group*. Impact of diabetes was examined within different hip fracture patient subgroups.



T1D- Type 1 diabetes; T2D- Type 2 diabetes; CCI- Charlson Comorbidity Index. HR adjusted for age, sex, and body mass index. *Example: *Example: Women with HF and T2D compared to women with HF without diabetes.

Figure 4: 2-year adjusted hazard ratios (aHRs) for other subsequent fracture than hip fracture in patients with incident hip fracture associated with diabetes, further categorizing diabetes exposure by treatment, duration, and complications compared with patient without diabetes.

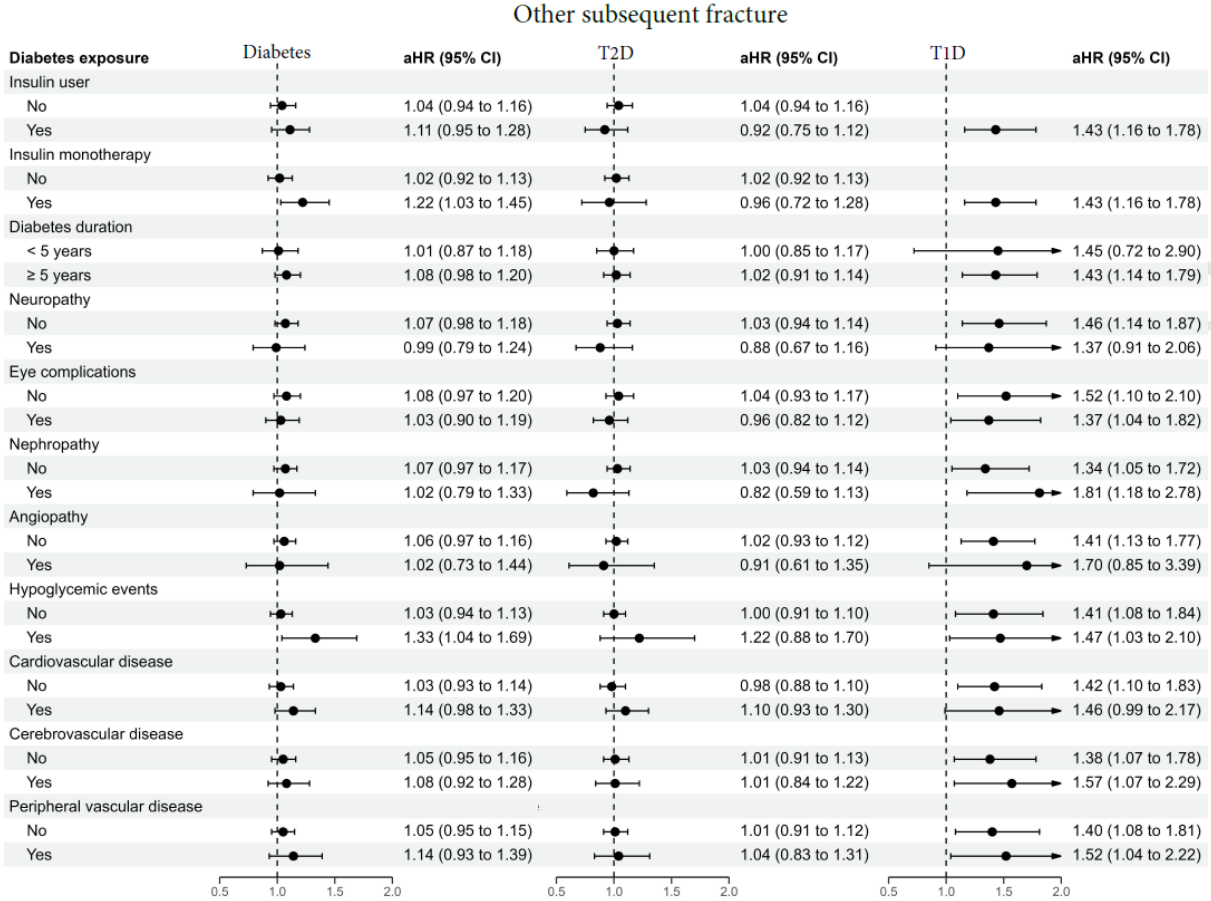


Figure 1: T1D- Type 1 diabetes; T2D- Type 2 diabetes. HR adjusted for age, sex, and body mass index. *Example: HF patients with T2D and neuropathy compared to HF patients without diabetes.

4. Discussion

Among incident HF patients, we found no strong overall association of T2D or T1D with increased risk of subsequent HF, but diabetes patients with previous hypoglycemic events and those with a history of neuropathy were at clearly increased risk. In contrast, patients with T1D had a clearly increased risk of subsequent fractures other than HF.

4.1 Comparison with other studies

The 2-year risk of subsequent HF has been reported to range between 5-11% in previous studies (26, 30-32) which is higher compared to our rates of less than 5%. The discrepancy could be due to different methodical approaches used to identifying subsequent HFs. A subsequent HF in most previous studies was defined based on the ICD-10 codes alone. Since a HF diagnosis is likely to be registered in the DNRP due to readmission for other reasons or reoperation shortly after incident HF surgery, use of ICD-codes alone will by capturing these registrations falsely increase the risk of subsequent HF. To counteract this, we combined ICD-10 code for HF with a surgical procedure for first-time HF. Other Danish register-based studies have counteracted this by excluding registration in the DNPR with same-site HF within the first 6 months of the incident HF, arguing that these registrations are complications related to incident HF rather than subsequent new HF (24-26). It is worth mentioning, that there is no published and validated method of identification of subsequent fractures, and each method is biased to some extent. A Danish study by Ryg et al. (30), based on 1977-2001 data found a higher incidence of subsequent HF than we did, despite including surgical procedure codes. Several factors could explain the reduction in incidence of subsequent HF such as more focus on major risk factors and osteoporosis treatment, change from internal fixation to total hip replacement as treatment for HF, and improvement in pre- and postoperative in-hospital quality of

treatment (20, 33). For comparison, the incidence rate of HF in Denmark is reported as 316 per 100,000 persons in those aged 50 or above during 2005-2018 (34).

The association between diabetes and the risk of subsequent fractures after an incident HF is not well established. Our results of no association between diabetes in general and subsequent HF agrees with results of some earlier published studies (9, 35). However, a study by Shen et al (8) found increased risk of subsequent hip fracture among patients with diabetes. Shen et al (8) study was based on HF patients age ≥ 45, whereas our and two other studies (9, 35) are based on HF patients ≥ 65 years. In addition, demographic differences between an Asian population (8) and a Caucasian population (9) could explain differences in the results. The study by Yamasashi et al (35) was only based on 714 HF patients and the follow up was only 3-6 months, rather different from our study.

To our knowledge, this study is the first to investigate multiple general HF patient characteristics and detailed diabetes-related characteristics or complications such as medicine, hypoglycemic events, neuropathy and retinopathy, as a proxy for increased fall risk leading to increased risk of subsequent fractures after incident HF. Therefore, we can only compare our results with the results of several studies that have investigated the risk of incident fractures in patients with diabetes (36-38). These studies (36-38) observed that patients with insulin-treated T2D have an increased risk of both incident HF and fractures other than HF due to insulin-induced hypoglycemic events. This is partly in agreement with our finding of history of hypoglycemic events being a risk factor for subsequent HF in T2D, but we did not find an association between the use of

insulin and the risk of subsequent HF, neither as monotherapy nor in combination with other novel-glucose-lowering drugs. Further, hypoglycemic events did not increase the risk of subsequent HFs in T1D, despite that these patients have a high prevalence of history of hypoglycemic events and everyone using insulin, questioning the insulin-induced hypoglycemic events theory in T2D patients.

The proportion of patients with neuropathy was almost four-fold higher in those with diabetes compared to those without diabetes. Diabetic neuropathies have been shown to increase the risk of incident fractures in patients with diabetes, which most likely is due to loss in proprioception and increase risk of falling (39). Further, poorly regulated diabetes and neuropathy increases the likelihood of diabetic foot disease such as foot ulcers, which further have shown to increase the risk of falls (40, 41).

Higher proportion of low education in T2D patients than in T1D or patients without diabetes could indirectly contribute to subsequent HFs.

Our finding of increased risk of other subsequent fractures in T1D, irrespective of diabetes-related characteristics, is in line with findings by Wallander et al. who observed an increased risk of incident other fractures in T1D patients (36). Further, Miao et al. (42) observed an increased risk of incident HF in T1D with neurological complications, while Hamilton et al (43) did not. Both studies are based on very few fracture outcomes resulting in uncertainty of their results.

Fracture type distribution was rather similar in T2D and T1D which is accordance with previous findings from Denmark (44), although T1D patients are younger. The ratio between femoral neck / trochanteric fractures is rather similar in Danish population irrespective of age (44).

Even with diabetes being a risk factor for incident fracture and T1D being a risk factor for other subsequent fracture, the proportion of HF patients with diabetes receiving bone-protective osteoporosis medication was very low in our study (less than 15%) and similar to HF patients without diabetes patients (17%). HF in elderly population is a diagnostic criteria for osteoporosis and according to Danish guidelines almost all patients with a low-energy HF are candidates for bone-protective osteoporosis treatment, regardless the T-score (45). Despite guidelines, only 20% of patients receive osteoporosis treatment one year after HF surgery (34).

Our patients with diabetes (both T2D and T1D) had a high prevalence of micro- and macrovascular disease which is comparable to elderly diabetes patients in general (46, 47)

A high proportion of T2D used insulin, but this prescription pattern is similar to studies from the US (48). Newer novel-glucose lowering drugs such as Sodium-Glucose cotransporter-2 inhibitors and Glucagon Like Peptide-1 Receptor Agonists are associated with a lower risk of hypoglycemic events (49). These drugs were rarely prescribed in our population, despite being on the market from 2009 and 2014. Updated analyses including the patients sustaining HF after 2018 could elucidate time-trend changes in use of newer glucose lowering drugs.

4.2 Strength and weaknesses

This study was based on Danish population-based health registries. Since access to health care in Denmark is tax-funded, and all patients admitted for a HF are treated at a public hospital, the risk of selection bias is low. Due to linkage to CRS, the risk of loss to follow-up is minimal, and only <0.1% were lost due to emigration.

The positive predictive value of diagnosis codes for HF in the DMHFR and the DNPR is above 90% (50). Positive predictive value of diabetes based on ICD-10 codes has been reported to be 97% with a sensitivity of 65%, while positive predictive value of diabetes captured through ATC codes is 95% with a sensitivity of 72% (51).

Most patients with T2D are treated by a general practitioner, and public hospitals only account for 20% of the treatment, mostly due to diabetic complications (52). Including ATC codes from the National Prescription Registry, the patients treated at the general practitioners will also be included. In addition, any misclassification of diabetes is not related to later registration of subsequent fractures. T1D is normally identified as the first diabetes diagnosis code in a younger population (age < 30-40) or lifelong monotherapy with insulin (53). We were not able to apply this method due to the age of our population, thus, T1D in our population might include some cases of long-term severe T2D, who switched to insulin.

CCI diagnosis through DNPR have shown overall positive predictive value 98% in previous studies (54). However, we lacked diagnoses from the general practitioner as well as data on the severity of some CCI diagnoses. Thus, we may have residual confounding to some extent.

Our study results could be bias by unmeasured confounding. We did not have information on physical activity, only a pre-fracture mobility and mobility at discharge. It is possible that patients with less physical activity, in a wheelchair or bed most of the day have lower risk of getting a

fracture. Patients with T2D could be more likely in this situation due to less activity than patients without diabetes (55). Further, we did not have information on smoking, which is both associated with a higher risk of HF and diabetes with complications, and therefore a potential confounder to be adjusted for (56, 57).

We had missing data on CAS and BMI. However, a previous study from our research group showed that BMI was missing at random. Regarding CAS, missing is also at random since registration of CAS in the DMHFR was not mandatory from the DMHFR initiation.

4.3 Conclusion

In this real-world nationwide cohort of incident HF patients, we found no strong overall association between T2D or T1D with increased 2-year risk of subsequent HF. However, diabetes patients with a history of hypoglycemia and those with a history of neuropathy were at increased risk. In contrast, patients with T1D have a higher risk of other subsequent fractures irrespective of HF and diabetes-related characteristics.

This HF diabetes cohort had a high prevalence of insulin users and micro- and macrovascular diseases. More focus should be put toward osteoporosis treatment among diabetes patients in general to prevent both incident and subsequent fractures, and patients with T2D could potentially benefit from newer glucose-lowering medications with a lower rate of hypoglycemic events.

References

1. Hernlund E, Svedbom A, Ivergård M, Compston J, Cooper C, Stenmark J, McCloskey EV, Jönsson B, Kanis JA. Osteoporosis in the European Union: medical management, epidemiology and economic burden. A report prepared in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA). Arch Osteoporos. 2013;8(1):136.doi:10.1007/s11657-013-0136-1.

2. Global, regional, and national burden of bone fractures in 204 countries and territories, 1990-2019: a systematic analysis from the Global Burden of Disease Study 2019. Lancet Healthy Longev. 2021;2(9):e580-e92.doi:10.1016/s2666-7568(21)00172-0.
3. Cheung C-l. Hip fractures will nearly double worldwide by 2050; researchers cite urgent need for better prevention and care, especially for men and the very old. American Society of Bone and Mineral Research; Austin, Texas2022.
4. Carpintero P, Caeiro JR, Carpintero R, Morales A, Silva S, Mesa M. Complications of hip fractures: A review. World J Orthop. 2014;5(4):402-11.doi:10.5312/wjo.v5.i4.402.
5. van der Velde RY, Wyers CE, Geusens P, van den Bergh JPW, de Vries F, Cooper C, van de Staa TP, Harvey NC. Incidence of subsequent fractures in the UK between 1990 and 2012 among individuals 50 years or older. Osteoporos Int. 2018;29(11):2469-75.doi:10.1007/s00198-018-4636-0.
6. Llopis-Cardona F, Armero C, Hurtado I, García-Sempere A, Peiró S, Rodríguez-Bernal CL, Sanfélix-Gimeno G. Incidence of Subsequent Hip Fracture and Mortality in Elderly Patients: A Multistate Population-Based Cohort Study in Eastern Spain. J Bone Miner Res. 2022;37(6):1200-8.doi:10.1002/jbmr.4562.
7. Marks R. Hip fracture epidemiological trends, outcomes, and risk factors, 1970-2009. Int J Gen Med. 2010;3:1-17.
8. Shen S-H, Huang K-C, Tsai Y-H, Yang T-Y, Lee MS, Ueng SWN, Hsu RWW. Risk Analysis for Second Hip Fracture in Patients After Hip Fracture Surgery: A Nationwide Population-Based Study. Journal of the American Medical Directors Association. 2014;15(10):725-31.doi:https://doi.org/10.1016/j.jamda.2014.05.010.
9. Harvey L, Toson B, Mitchell R, Brodaty H, Draper B, Close J. Incidence, timing and impact of comorbidity on second hip fracture: a population-based study. ANZ J Surg. 2018;88(6):577-81.doi:10.1111/ans.14507.
10. Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, Colagiuri S, Guariguata L, Motala AA, Ogurtsova K, Shaw JE, Bright D, Williams R, Committee IDFDA. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9(th) edition. Diabetes Res Clin Pract. 2019;157:107843.doi:10.1016/j.diabres.2019.107843.
11. Institut SS. Faglige anbefalinger om diabetes - Tal og fakta https://www.sst.dk/da/Viden/Diabetes/Faglige-anbefalinger-om-diabetes/Tal-og-fakta2020 [
12. Rasmussen NH, Vestergaard P. Diabetes and osteoporosis - Treating two entities: A challenge or cause for concern? Best Pract Res Clin Rheumatol. 2022;36(3):101779.doi:10.1016/j.berh.2022.101779.
13. Hofbauer LC, Busse B, Eastell R, Ferrari S, Frost M, Müller R, Burden AM, Rivadeneira F, Napoli N, Rauner M. Bone fragility in diabetes: novel concepts and clinical implications. Lancet Diabetes Endocrinol. 2022;10(3):207-20.doi:10.1016/s2213-8587(21)00347-8.
14. Hidayat K, Fang QL, Shi BM, Qin LQ. Influence of glycemic control and hypoglycemia on the risk of fracture in patients with diabetes mellitus: a systematic review and meta-analysis of observational studies. Osteoporos Int. 2021;32(9):1693-704.doi:10.1007/s00198-021-05934-2.

15. Khan KS, Christensen DH, Nicolaisen SK, Gylfadottir SS, Jensen TS, Nielsen JS, Thomsen RW, Andersen H. Falls and fractures associated with type 2 diabetic polyneuropathy: A cross-sectional nationwide questionnaire study. J Diabetes Investig. 2021;12(10):1827-34.doi:10.1111/jdi.13542.
16. Bai J, Gao Q, Wang C, Dai J. Diabetes mellitus and risk of low-energy fracture: a meta-analysis. Aging Clin Exp Res. 2020;32(11):2173-86.doi:10.1007/s40520-019-01417-x.
17. Vilaca T, Schini M, Harnan S, Sutton A, Poku E, Allen IE, Cummings SR, Eastell R. The risk of hip and non-vertebral fractures in type 1 and type 2 diabetes: A systematic review and meta-analysis update. Bone. 2020;137:115457.doi:https://doi.org/10.1016/j.bone.2020.115457.
18. Schmidt M, Schmidt SAJ, Adelborg K, Sundbøll J, Laugesen K, Ehrenstein V, Sørensen HT. The Danish health care system and epidemiological research: from health care contacts to database records. Clin Epidemiol. 2019;11:563-91.doi:10.2147/clep.S179083.
19. Schmidt M, Pedersen L, Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. Eur J Epidemiol. 2014;29(8):541-9.doi:10.1007/s10654-014-9930-3.
20. Kristensen PK, Röck ND, Christensen HC, Pedersen AB. The Danish Multidisciplinary Hip Fracture Registry 13-Year Results from a Population-Based Cohort of Hip Fracture Patients. Clin Epidemiol. 2020;12:9-21.doi:10.2147/clep.S231578.
21. Schmidt M, Schmidt SA, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. Clin Epidemiol. 2015;7:449-90.doi:10.2147/clep.S91125.
22. Pottegård A, Schmidt SAJ, Wallach-Kildemoes H, Sørensen HT, Hallas J, Schmidt M. Data Resource Profile: The Danish National Prescription Registry. Int J Epidemiol. 2017;46(3):798-f.doi:10.1093/ije/dyw213.
23. Jensen VM, Rasmussen AW. Danish Education Registers. Scand J Public Health. 2011;39(7 Suppl):91-4.doi:10.1177/1403494810394715.
24. Khalid S, Pineda-Moncusí M, El-Hussein L, Delmestri A, Ernst M, Smith C, Libanati C, Toth E, Javaid MK, Cooper C, Abrahamsen B, Prieto-Alhambra D. Predicting Imminent Fractures in Patients With a Recent Fracture or Starting Oral Bisphosphonate Therapy: Development and International Validation of Prognostic Models. J Bone Miner Res. 2021;36(11):2162-76.doi:10.1002/jbmr.4414.
25. Khalid S, Reyes C, Ernst M, Delmestri A, Toth E, Libanati C, Abrahamsen B, Prieto-Alhambra D. One- and 2-year incidence of osteoporotic fracture: a multi-cohort observational study using routinely collected real-world data. Osteoporos Int. 2022;33(1):123-37.doi:10.1007/s00198-021-06077-0.
26. Hjelholt TJ, Johnsen SP, Brynningsen PK, Andersen G, Pedersen AB. Impact of Stroke History on the Risk of Recurrent Hip Fracture or Major Osteoporotic Fractures among Patients with Incident Hip Fracture: A Nationwide Cohort Study. J Bone Miner Res. 2022.doi:10.1002/jbmr.4760.
27. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373-83.doi:10.1016/0021-9681(87)90171-8.

28. Birkmose ALL, Kristensen PK, Madsen M, Pedersen AB, Hjelholt TJ. Association of anticholinergic drug use with postoperative mortality among patients with hip fracture. A nationwide cohort study. Arch Gerontol Geriatr. 2023;113:105017.doi:10.1016/j.archger.2023.105017.
29. Gray N, Picone G, Sloan F, Yashkin A. Relation between BMI and diabetes mellitus and its complications among US older adults. South Med J. 2015;108(1):29-36.doi:10.14423/smj.0000000000000214.
30. Ryg J, Rejnmark L, Overgaard S, Brixen K, Vestergaard P. Hip fracture patients at risk of second hip fracture: a nationwide population-based cohort study of 169,145 cases during 1977-2001. J Bone Miner Res. 2009;24(7):1299-307.doi:10.1359/jbmr.090207.
31. Sheikh HQ, Hossain FS, Khan S, Usman M, Kapoor H, Aqil A. Short-term risk factors for a second hip fracture in a UK population. Eur J Orthop Surg Traumatol. 2019;29(5):1055-60.doi:10.1007/s00590-019-02412-8.
32. Lönnroos E, Kautiainen H, Karppi P, Hartikainen S, Kiviranta I, Sulkava R. Incidence of second hip fractures. A population-based study. Osteoporos Int. 2007;18(9):1279-85.doi:10.1007/s00198-007-0375-3.
33. Kjeldgaard HK, Holvik K, Abrahamsen B, Tell GS, Meyer HE, O'Flaherty M. Explaining declining hip fracture rates in Norway: a population-based modelling study. Lancet Reg Health Eur. 2023;30:100643.doi:10.1016/j.lanepe.2023.100643.
34. Sing CW, Lin TC, Bartholomew S, Bell JS, Bennett C, Beyene K, Bosco-Levy P, Bradbury BD, Chan AHY, Chandran M, Cooper C, de Ridder M, Doyon CY, Droz-Perroteau C, Ganesan G, Hartikainen S, Ilomaki J, Jeong HE, Kiel DP, Kubota K, Lai EC, Lange JL, Lewiecki EM, Lin J, Liu J, Maskell J, de Abreu MM, O'Kelly J, Ooba N, Pedersen AB, Prats-Uribe A, Prieto-Alhambra D, Qin SX, Shin JY, Sørensen HT, Tan KB, Thomas T, Tolppanen AM, Verhamme KMC, Wang GH, Watcharathanakij S, Wood SJ, Cheung CL, Wong ICK. Global Epidemiology of Hip Fractures: Secular Trends in Incidence Rate, Post-Fracture Treatment, and All-Cause Mortality. J Bone Miner Res. 2023;38(8):1064-75.doi:10.1002/jbmr.4821.
35. Yamanashi A, Yamazaki K, Kanamori M, Mochizuki K, Okamoto S, Koide Y, Kin K, Nagano A. Assessment of risk factors for second hip fractures in Japanese elderly. Osteoporos Int. 2005;16(10):1239-46.doi:10.1007/s00198-005-1835-2.
36. Wallander M, Axelsson KF, Nilsson AG, Lundh D, Lorentzon M. Type 2 Diabetes and Risk of Hip Fractures and Non-Skeletal Fall Injuries in the Elderly: A Study From the Fractures and Fall Injuries in the Elderly Cohort (FRAILCO). J Bone Miner Res. 2017;32(3):449-60.doi:10.1002/jbmr.3002.
37. Mattishent K, Loke YK. Meta-Analysis: Association Between Hypoglycemia and Serious Adverse Events in Older Patients Treated With Glucose-Lowering Agents. Front Endocrinol (Lausanne). 2021;12:571568.doi:10.3389/fendo.2021.571568.
38. Hidayat K, Du X, Wu MJ, Shi BM. The use of metformin, insulin, sulphonylureas, and thiazolidinediones and the risk of fracture: Systematic review and meta-analysis of observational studies. Obes Rev. 2019;20(10):1494-503.doi:10.1111/obr.12885.
39. Schwartz AV, Vittinghoff E, Sellmeyer DE, Feingold KR, de Rekeneire N, Strotmeyer ES, Shorr RI, Vinik AI, Odden MC, Park SW, Faulkner KA, Harris TB. Diabetes-related complications, glycemic control, and falls in older adults. Diabetes Care. 2008;31(3):391-6.doi:10.2337/dc07-1152.
40. Oliver TI, Mutluoglu M. Diabetic Foot Ulcer. StatPearls. Treasure Island (FL) ineligible companies. Disclosure: Mesut Mutluoglu declares no relevant financial relationships with ineligible companies.: StatPearls Publishing

41. Fang M, Hu J, Jeon Y, Matsushita K, Selvin E, Hicks CW. Diabetic foot disease and the risk of major clinical outcomes. Diabetes Res Clin Pract. 2023;202:110778.doi:10.1016/j.diabres.2023.110778.
42. Miao J, Brismar K, Nyrén O, Ugarph-Morawski A, Ye W. Elevated hip fracture risk in type 1 diabetic patients: a population-based cohort study in Sweden. Diabetes Care. 2005;28(12):2850-5.doi:10.2337/diacare.28.12.2850.
43. Hamilton EJ, Davis WA, Bruce DG, Davis TME. Risk and associates of incident hip fracture in type 1 diabetes: The Fremantle Diabetes Study. Diabetes Res Clin Pract. 2017;134:153-60.doi:10.1016/j.diabres.2017.10.011.
44. Abrahamsen B, Laursen HVB, Skjødt MK, Jensen MH, Vestergaard P. Age at hip fracture and life expectancy in Denmark – Secular trends over two decades. Bone. 2020;130:115083.doi:https://doi.org/10.1016/j.bone.2019.115083.
45. Kamilla Grønborg Laut JR, Lars Rejnmark. Behandling af primær osteoporose i almen praksis. Sundhedsstyrelsen, Rationel Farmakoterapi. 2019.
46. Chawla A, Chawla R, Jaggi S. Microvasular and macrovascular complications in diabetes mellitus: Distinct or continuum? Indian J Endocrinol Metab. 2016;20(4):546-51.doi:10.4103/2230-8210.183480.
47. Huang D, Refaat M, Mohammedi K, Jayyousi A, Al Suwaidi J, Abi Khalil C. Macrovascular Complications in Patients with Diabetes and Prediabetes. Biomed Res Int. 2017;2017:7839101.doi:10.1155/2017/7839101.
48. Pilla SJ, Segal JB, Alexander GC, Boyd CM, Maruthur NM. Differences in National Diabetes Treatment Patterns and Trends between Older and Younger Adults. J Am Geriatr Soc. 2019;67(5):1066-73.doi:10.1111/jgs.15790.
49. Anderson M, Powell J, Campbell KM, Taylor JR. Optimal management of type 2 diabetes in patients with increased risk of hypoglycemia. Diabetes Metab Syndr Obes. 2014;7:85-94.doi:10.2147/dmso.S48896.
50. Hjelholt TJ, Edwards NM, Vesterager JD, Kristensen PK, Pedersen AB. The Positive Predictive Value of Hip Fracture Diagnoses and Surgical Procedure Codes in the Danish Multidisciplinary Hip Fracture Registry and the Danish National Patient Registry. Clin Epidemiol. 2020;12:123-31.doi:10.2147/clep.S238722.
51. Carstensen B, Kristensen JK, Marcussen MM, Borch-Johnsen K. The National Diabetes Register. Scand J Public Health. 2011;39(7 Suppl):58-61.doi:10.1177/1403494811404278.
52. Carstensen B, Rønn PF, Jørgensen ME. Prevalence, incidence and mortality of type 1 and type 2 diabetes in Denmark 1996-2016. BMJ Open Diabetes Res Care. 2020;8(1).doi:10.1136/bmjdrc-2019-001071.
53. Thomsen RW, Sørensen HT. Using registries to identify type 2 diabetes patients. Clin Epidemiol. 2015;7:1-3.doi:10.2147/clep.S75572.
54. Thygesen SK, Christiansen CF, Christensen S, Lash TL, Sørensen HT. The predictive value of ICD-10 diagnostic coding used to assess Charlson comorbidity index conditions in the population-based Danish National Registry of Patients. BMC Med Res Methodol. 2011;11:83.doi:10.1186/1471-2288-11-83.

55. Thomas N, Alder E, Leese GP. Barriers to physical activity in patients with diabetes. Postgraduate Medical Journal. 2004;80(943):287.doi:10.1136/pgmj.2003.010553.
56. Ampelas DG. Current and former smokers and hip fractures. J Frailty Sarcopenia Falls. 2018;3(3):148-54.doi:10.22540/jfsf-03-148.
57. Brath H, Kaser S, Tatschl C, Fasching P. [Smoking, alcohol and diabetes (Update 2019)]. Wien Klin Wochenschr. 2019;131(Suppl 1):67-70.doi:10.1007/s00508-019-1455-z.

Highlights

- Among 92,600 patients with incident hip fracture 11,469 (12%) had diabetes.
- No overall association of T2D or T1D with increased risk of subsequent hip fracture.
- Diabetes with prior hypoglycemic events had increased risk of subsequent hip fracture.
- Diabetes with neuropathy had increased risk of subsequent hip fracture.
- Patients with T1D had clearly increased risk of other fractures than hip fracture.