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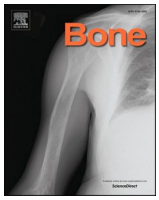

Full Length Article

Fracture patterns in adult onset type 1 diabetes and associated risk factors – A nationwide cohort study

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ABSTRACT

Objective: This study aimed to determine the hazard ratios (HR) for various fracture sites and identify associated risk factors in a cohort of relatively healthy adult people with newly diagnosed type 1 diabetes (T1D).

Methods: The study utilized data from the UK Clinical Practice Research Datalink GOLD (1987–2017). Participants included people aged 20 and above with a T1D diagnosis code (n = 3281) and a new prescription for insulin. Controls without diabetes were matched based on sex, year of birth, and practice. Cox regression analysis was conducted to estimate HRs for any fracture, major osteoporotic fractures (MOFs), and peripheral fractures (lower-arm and lower-leg) in people with T1D compared to controls. Risk factors for T1D were examined and included sex, age, diabetic complications, medication usage, Charlson comorbidity index (CCI), hypoglycemia, previous fractures, falls, and alcohol consumption. Furthermore, T1D was stratified by duration of disease and presence of microvascular complications.

Results: The proportion of any fracture was higher in T1D (10.8 %) than controls (7.3). Fully adjusted HRs for any fracture (HR: 1.43, CI95%: 1.17–1.74), MOFs (HR: 1.46, CI95%: 1.04–2.05), and lower-leg fractures (HR: 1.37, CI95%: 1.01–1.85) were statistically significantly increased in people with T1D compared to controls. The primary risk factor across all fracture sites in T1D was a previous fracture. Additional risk factors at different sites included previous falls (HR: 1.64, CI95%: 1.17–2.31), antidepressant use (HR: 1.34, CI95%: 1.02–1.76), and anxiolytic use (HR: 1.54, CI95%: 1.08–2.29) for any fracture; being female (HR: 1.65, CI95%: 1.14–2.38) for MOFs; the presence of retinopathy (HR: 1.47, CI95%: 1.02–2.11) and previous falls (HR: 2.04, CI95%: 1.16–3.59) for lower-arm and lower-leg fractures, respectively. Lipid-lowering medication use decreased the risk of MOFs (HR: 0.66, CI95%: 0.44–0.99).

Stratification of T1D by disease duration showed that the relative risk of any fracture in T1D did not increase with longer diabetes duration (0–4 years: HR: 1.52, CI95%: 1.23–1.87; 5–9 years: HR: 1.30, CI95%: 0.99–1.71; <10 years: HR: 1.07, CI95%: 0.74–1.55). Similar patterns were observed for other fracture sites. Moreover, the occurrence of microvascular complications in T1D was linked to a heightened risk of fractures in comparison to controls. However, when considering the T1D cohort independently, the association was not statistically significant.

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Conclusion: In a cohort of relatively healthy and newly diagnosed people with T1D HRs for any fracture, MOFs, and lower-leg fractures compared to controls were increased. A previous fracture was the most consistent risk factor for a subsequent fracture, whereas retinopathy was the only diabetes related one. We postulate a potential initial fracture risk, succeeded by a subsequent risk reduction, which might potentially increase in later years due to the accumulation of complications and other factors.

1. Introduction

Type 1 diabetes (T1D) is a progressive chronic autoimmune disease associated with common complications, e.g., retinopathy, nephropathy, or cardiovascular disease and thus inadequately managed T1D, increasing morbidity and mortality. Recent evidence has also indicated an augmented susceptibility to fractures among adult people with T1D (hereafter referred to as "people with T1D"), with a three to four-fold increase in fracture occurrence compared to those without the condition [1,2]. Fractures represent a significant global health concern, with an estimated annual incidence of 178 million new cases, a number that continues to rise [3]. Given the projected rise in T1D prevalence, it becomes imperative to identify risk factors and underlying mechanisms associated with fractures to enhance treatment and prevention strategies.

In general, clinical risk factors for fractures are believed to impact bone quality, fall risk, or both. It is hypothesized that these factors may vary across populations due to disparities in environmental factors, ethnicities, or lifestyle choices [4]. Furthermore, these risk factors may also differ depending on the type of fracture, as certain types, such as peripheral fractures, are primarily associated with falls [5,6]. Currently, risk factors for fractures in T1D have only been determined in a general sense or for specific fracture types, rather than for different fracture types within a single population [7,8]. Moreover, people with T1D face the necessity of insulin therapy, along with the added concerns of hyper- or hypoglycemia incidents and the increased risk of late diabetic complications. These factors could contribute to an increased susceptibility to bone health issues and fractures. E.g. T1D duration has been identified as a risk factor for fractures; however, data on this subject is limited and often restricted to specific fracture locations. Moreover, variations in T1D duration between studies complicate comparisons and may account for inconsistent findings. Some studies have also suggested that the presence of microvascular complications in T1D, such as retinopathy, neuropathy, and nephropathy, could be risk factors for fractures [9]. Previous investigations have noted a decline in bone mineral density (BMD) and microvascular complications among people with T1D [10]. Specifically, neuropathy and retinopathy have been associated with reduced BMD, while nephropathy has shown associations with both decreased BMD and increased bone markers, with BMD declining even further with greater nephropathy severity [11–13].

However, research pertaining to this topic is limited, and it remains unclear whether microvascular complications directly impact bone quality or if T1D itself, along with its duration and management, contributes to bone damage and the development of microvascular complications. Consequently, the primary objective of this study is to assess the risk of fractures at different locations and investigate potential risk factors specific to each fracture site in a cohort of relatively healthy people with T1D.

2. Methods

2.1. Source of data

Data were obtained from the UK Clinical Practice Research Datalink (CPRD) GOLD. CPRD GOLD contains primary healthcare information on approximately 7 % of the population in the UK. The recorded data include information on patient demographics, medical history, laboratory test results, prescription details, specialist referrals, lifestyle (e.g., smoking and alcohol use), hospital admissions and major outcomes since 1987, with on-going data collection [14]. Data from the CPRD have been used in >1000 published peer-reviewed observational studies and are considered high quality due to the breadth of coverage, size, long-term follow-up, transferability, and shown to be valid for a wide range of diseases, including fractures [14–16]. GP staff manually recorded data to describe a patient's condition using Read codes and contain over 96,000 codes [17]. This database has remained the largest validated and most utilized primary care database in the UK [18,19].

2.2. Study design and population

This was a nationwide population-based retrospective cohort study of people above 20 years of age identified in the CPRD between January 1, 1987, and December 31, 2017. The cohort consisted of people with newly diagnosed (incident) T1D (n = 3281) and their matched control (1:1) by sex and year of birth, and practice (Fig. 1). The study population was partly based on a previously published T1D cohort [8].

People with T1D were identified by T1D Read codes and by product codes for their first redeemed prescription of insulin and excluded if they had a prescription code for non-insulin anti-diabetic drug (NIAD). All people with T1D had at least one year of up-to-standard follow up prior to the first recorded diagnosis to accurately define the cohort. Control persons had no records for insulin or NIADs and were matched by year of birth, sex and practice to a person with T1D by incidence density sampling. The index date of people with T1D was determined by the date of their first redeemed prescription of insulin. Each control person was assigned the index date of the matched person with T1D for follow up.

2.3. Endpoints and exposures

Endpoints were Read coded fractures at different fracture sites; any fracture, major osteoporotic fractures (MOF) and peripheral fractures (lower-arm, and lower-leg fractures). Any fracture was defined as all fracture types. MOFs were defined as a fracture of the hip, vertebrae, humerus, radius, or ulna. Peripheral fractures were divided into lower arm fractures including carpal, radius, ulna or proximal humerus and lower leg fractures were tibia, fibula, ankle or foot fractures (Fig. 2). A secondary endpoint was to identify risk factors for each fracture site among people with T1D. Potential risk factors were determined at baseline and updated at the start of each interval and included demographics (sex, age, alcohol status), diabetes associated complications (Neuropathy, retinopathy, nephropathy, and hypoglycemic events and glucose levels), co-morbidities (Charlson comorbidity index (CCI)), previous falls, previous fractures, and medication within the 6 months prior to the start of an interval (glucocorticoids, anti-depressants, anxiolytics, and anti-convulsive, and bone medication (Bisphosphonates, Hormone Replacement Therapies, Calcium/D-vit, and Parathyroid Hormone Analogues)). The CCI was determined excluding Read codes for diabetes, to make it comparable to controls without T1D [20].

Follow-up was the time from the T1D diagnosis to the event of a fracture. The people were followed until end of data collection, end of study period, death, or event of interest, whichever came first. Follow-up time was divided into intervals of 90 days. Control persons were censored if they had a diagnosis of diabetes or started insulin or a NIAD during follow-up.

3. Statistics data analysis

Descriptive statistics were categorized as continuous data expressed as mean ± SD, median (interquartile range IQR), and categorical data reported as a percentage and count for each group.

A Cox-regression model was used to estimate the HRs of different fracture sites in people with T1D compared to controls (reference group). The HRs were in one model adjusted for sex and age and then also demographics, diabetic complications, comorbidities, previous falls, previous fractures, and medication. Another Cox-regression model was used to estimate specific risk factors for each fracture site exclusively in the T1D cohort with similar cause of action for adjustments.

Fracture site incidence rates (IRs) were calculated by dividing the number of fractures (per fracture site) by the total number of person years (PYs) and presented per 1000 PYs.

Two sensitivity analyses were performed regarding T1D duration and diabetic complications and whether they were potential risk factors for the different fracture sites. T1D duration was determined by subtracting the index date from the date of the start of an interval. T1D group was stratified into the following four categories: 0–4 years, 5–9 years and ≥10 years. The references were either no T1D or 0–4 years of T1D duration, respectively. Presence of microvascular complications was stratified into the following categories: 0, 1 and 2 or more complications. No T1D or 0 complications in the T1D cohort were references, respectively. The models adjusted for sex and age, demographics, comorbidities, previous falls, previous fractures, and medication.

Statistical analyses were conducted in in SAS 9.4. A two-sided p-value <0.05 was accepted as statistically significant.

4. Results

We identified 3281 people with T1D and matched them with the same number of controls. At baseline, the groups were similar on several demographic parameters like follow-up time (T1D = 7.2 years vs. controls = 7.3 years), BMI (T1D = 25.9 kg/m^2 vs. controls = 26.2 kg/m^2), current smoking status (T1D = 33.9 % vs. controls = 28.9 %), and current alcohol use (T1D = 67.4 % vs. controls = 65.1 %). In general, few diabetic complications were registered, but higher proportions of several co-morbidities like higher CCI-score, falls and fractures were seen in T1D vs. controls. In addition, the usage of medication was percentual higher for T1D than controls (Table 1).

The proportion of fractures with the corresponding IRs per 1000 PYs for people with T1D were as followed: Any fracture, n = 355 (10.8 %, IR of 16.4 PYs), MOFs, n = 124 (3.7 %, IR of 5.4 PYs), lower-arm fractures, n = 151 (4.6 %, IR of 6.6 PYs), and lower-leg fractures, n = 100 (3.0 %, IR of 4.3 PYs). Controls yielded for any fracture, n = 242 (7.3 %, IR of 10.6 PYs), MOFs, n = 89 (2.7 %, IR of 3.8 PYs), lower-arm fractures, n = 107 (3.3 %, IR of 4.5 PYs), and lower-leg fractures, n = 68. (2.1 %, IR of 2.9 PYs) (Table 2).

Age and sex adjusted results showed that people with T1D had a significantly higher risk for fractures at all sites (any fracture: HR of 1.57 (95 % CI: 1.34–1.85), MOFs: HR of 1.55 (95 % CI: 1.18–2.04), lower arm fractures: HR of 1.47 (95 % CI: 1.15–1.88), and lower leg fractures: HR of 1.52 (95 % CI: 1.12–2.07), compared with controls. Whereas the estimates for T1D compared to controls decreased in the fully adjusted analysis (any fracture: HR of 1.43 (95 % CI: 1.17–1.74), MOFs: HR of 1.46 (95 % CI: 1.04–2.05), and lower leg fractures: HR of 1.37 (95 % CI: 1.01–1.85) (Fig. 3).

Risk factors specifically in the T1D cohort for any fracture were a previous fall (HR of 1.64 (95 % CI: 1.17–2.31)), the use of anxiolytics (HR of 1.54 (95 % CI: 1.08–2.29)), anti-depressants (HR of 1.34 (95 % CI:1.02–1.76)), and a previous fracture (HR of 2.07 (95 % CI: 1.65–2.59)). A previous fracture was also significantly associated with a higher risk at other fracture sites like MOFs (HR 2.29 (95 % CI: 1.59–3.30)), lower-arm fractures (HR of 2.05 (95 % CI: 1.47–2.86)), and lower-leg fractures (HR of 1.62 (95 % CI: 1.06–2.47)). For MOFs, women were associated with an increased fracture risk compared with men (HR of 1.65, 95 % CI: 1.14–2.38) and the use of bone medication was associated with a higher risk (HR of 2.01 (95 % CI: 1.14–3.54) whereas lipid lowering medication was associated with a lower risk (HR of 0.66, 95 % CI: 0.44–0.99). Regarding lower-arm fractures, the presence of retinopathy (HR of 1.47 (95 % CI: 1.02–2.11)) was significantly associated with an increased fracture risk. For lower-leg fractures a previous fall was associated with a fracture (HR of 2.04 (95 % CI: 1.16–3.59)) (Table 3).

With longer T1D duration (reference was no T1D) the fully adjusted risk of any fracture was initially significantly associated with an increased risk during the first 0–4 years for any fracture (HR of 1.52 (95 % CI: 1.23–1.87)), MOFs (HR of 1.59 (95 % CI: 1.1–2.13)), lower-arm fractures (HR of 1.54 (95 % CI: 1.12–2.11), but not for lower-leg fractures. These results were followed by lower or non-significant HRs for the later intervals. A test-for-trends, between year-intervals did not show

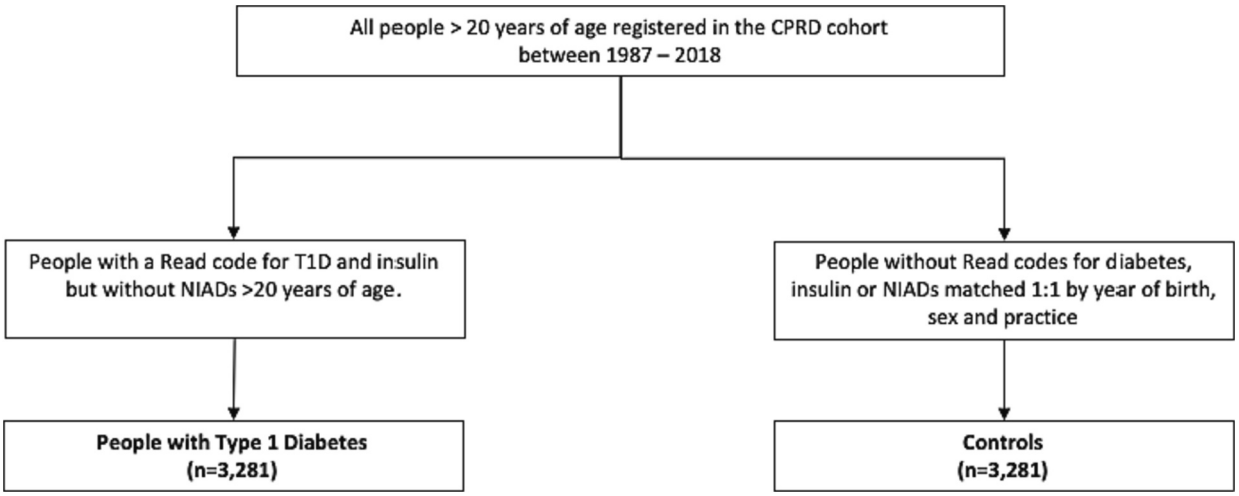

Fig. 1. Inclusion of people with T1D and their matched controls.
The cohort was extracted from the UK CPRD data cohort between January 1987 and December 31. 2017. People with a first ever prescription of insulin and one year of valid data collection were included. People with NIAD at the index date (n = 625) and people without a diabetes read code before start of treatment (n = 8495) were excluded. The final cohort comprised of 3281 people with T1D and their matched control (1:1) above 20 years of age.
Abbreviations: T1D: Type 1 diabetes, NIAD: Non-insulin anti-diabetic medications, CPRD: Clinical Practice Research Datalink.

a significant difference between a short and long T1D duration and lower fracture risk (Fig. 4). Furthermore, with 0–4 years of T1D duration as reference, the fracture risk decreased for all sites except for lower-leg fractures with longer T1D duration with significant trends between the year intervals (Test of trends: Any fracture: p = 0.02, MOFs: p = 0.003, lower-arm fractures: p = 0.002, and lower-leg fractures: p = 0.932).

For diabetic microvascular complications in T1D (reference was no T1D) the risk of any fracture was increased (0-complications: HR of 1.45 (95 % CI: 1.19–1.77), 1-complication: HR of 1.58 (95 % CI: 1.22–2.04) and ≥2-complications: HR of 1.62 (95 % CI: 1.13–2.33)). Similar significant results were seen for MOFs (0-complications: HR of 1.43 (95 % CI: 1.01–2.04), 1-complication: HR of 2.02 (95 % CI: 1.35–3.03) and ≥2-complications: HR of 1.52 (95 % CI: 0.85–2.70)) and lower-arm fractures (0-complications: HR of 1.38 (95 % CI: 1.02–1.88), 1-complication: HR of 1.69 (95 % CI: 1.16–2.48) and ≥2-complications: HR of 1.25 (95 % CI: 0.69–2.25)), whereas non-significantly increased risk were seen for lower-leg fractures (Fig. 5). Although, test-for-trends among HRs within each fracture type was non-significant. Additionally, in the T1D cohort with 0 complications as reference compared with 1 or more complications a non-significantly increased risk for all fracture sites were seen in both the crude and adjusted models (data not shown in Fig. 5).

5. Discussion

This retrospective cohort study confirmed previous studies, by finding a statistically significant association between T1D and an increased risk of fractures compared to non-diabetic controls. Specifically, the risk was shown for any fracture, MOFs and lower-leg fractures. The primary and most consistently observed risk factor across all fracture types was a previous fracture associated with a doubling of risk for a subsequent fracture. Additionally, distinct risk factors were identified for each specific fracture site (any fracture: previous falls, anxiolytics, and antidepressants; MOFs: female sex and use of bone medication, whereas lipid-lowering medications decreased the risk; lower-arm fractures: presence of retinopathy; lower-leg fractures: previous falls). Sensitivity analyses revealed a distinctive temporal pattern in fracture susceptibility. An increased risk was observed during the early stages of T1D onset, followed by a subsequent lower fracture risk as the duration of the condition approached that of the control group. However, in the T1D cohort specifically a significant decrease of fractures was seen with longer diabetes duration. Moreover, the existence of microvascular complications in T1D was linked to a higher risk of fractures compared to controls. However, there was no statistically significant difference when comparing the T1D cohort independently.

5.1. Fracture risk in T1D

With this study, we identified risk at specific fracture sites in T1D compared with controls. The findings of a higher fracture risk of any fracture in people with T1D compared with controls corresponded well with other similar studies and recent meta-analyses [6,8,21,22]. We saw a higher risk of MOFs, which also were in accordance with previous epidemiological studies of T1D for theses fracture sites [23–25]. In general, the fracture risk in our study for any fracture and MOFs were 1–2 fold increased, whereas other studies have found the risk to be 3–5-folded [6,26]. In the UK, the General Practitioners (GPs) play a crucial role in the management and coding of T1D [27,28]. They are often the first point of contact for people with diabetes, providing initial diagnosis, ongoing monitoring, and basic diabetes management. Whereas intensified treatment is allocated to the Diabetes Specialist Clinics which provides more comprehensive and specialized care for people with T1D. Therefore, this cohort of T1D people must be considered relatively healthier than people with T1D who regularly attend Diabetes Specialist Clinics. Hence, our results probably reflect a healthier proportion of people with T1D, yet still, with an increased fracture risk.

Regarding peripheral fracture sites (lower-arm and lower-leg fracture), only lower leg fractures were significantly increased in T1D compared with controls in the fully adjusted analyses. This finding is consistent with previous research conducted by Vilaca et al. who showed an increased risk of fractures at the ankle but a decreased risk at the wrist compared with controls without diabetes [22]. However, it is important to note that the aforementioned study included both T1D and T2D participants, and the diabetes group had a BMI that was 10 % higher. A meta-analysis by Wang et al. who compared people with T1D and T2D found similar results with increased fracture risk at the ankle and the upper arm, but not at the wrist [5]. A similar study by Weber et al. comparing T1D with controls found and increased risk of incident

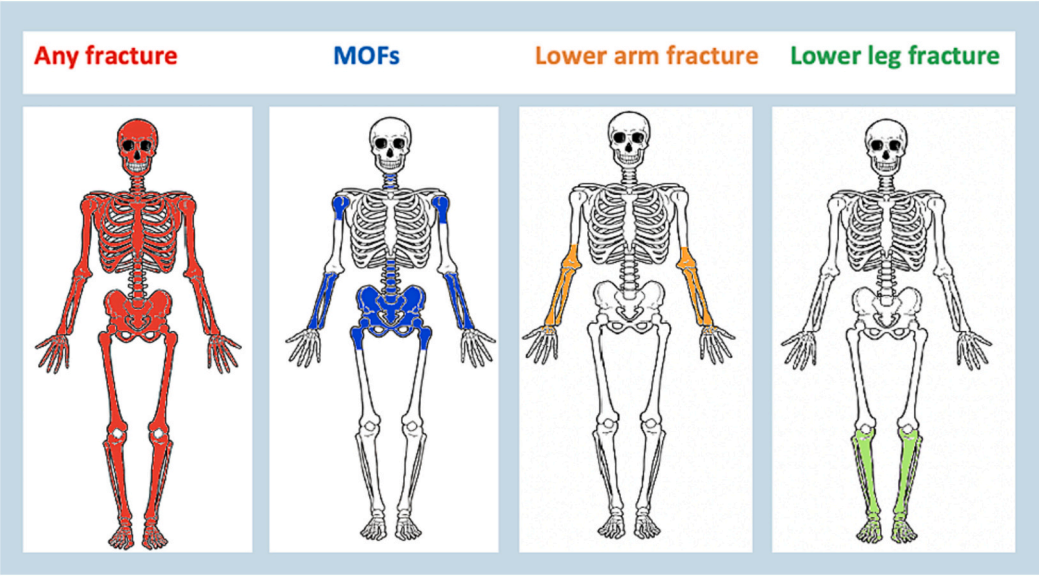

Fig. 2. Visualization of fracture sites.
Fracture sites: Any fracture was defined as all fracture types, MOFs as vertebrae, hip, humerus, ulna or radius fractures, lower arm fractures as carpal, radius, ulna or proximal humerus and lower leg fractures as tibia, fibula, ankle or foot fractures. Major osteoporotic fracture (MOF) was defined as a fracture of the hip, vertebrae, humerus, radius, or ulna.

Table 1
Person characteristics at baseline.

	T1D		Controls	
	N = 3281	(%)	N = 3281	(%)
Demographics				
Mean follow-up time (years. SD)	7.2	5.6	7.3	5.6
Women	1219	37.2	1219	37.2
Mean age (years. SD)	43.5	16.8	43.5	16.8
BMI:				
Mean BMI (kg/m2. SD)	25.9	5.4	26.2	5.4
Missing	179	5.5	682	20.8
Smoking status:				
Never	1271	38.7	1358	41.4
Past	835	25.4	720	21.9
Current	1113	33.9	948	28.9
Missing	62	1.9	726	22.1
Alcohol:				
Alcohol use (No)	701	21.4	419	12.8
Alcohol use (Yes)	2210	67.4	2136	65.1
Missing	370	11.3	370	22.1
Diabetes associated complications				
History of Microvascular complications:				
Neuropathy	45	1.4	0	0.0
Nephropathy	42	1.3	0	0.0
Retinopathy	214	6.5	0	0.0
Other:				
CVD	106	3.2	57	1.7
Hypoglycemic event	131	4.0	<5	<0.1
Hypoglycemic event with referral to hospital	8	0.2	0	0.0
Co-morbidities				
History of Charlson comorbidity index (excluding diabetes comorbidities)				
0	2159	65.8	2437	74.3
1–2	941	28.7	772	23.5
3–4	134	4.1	62	1.9
≥5	47	1.4	10	0.3
Others				
Falls - >6 months before index date	130	4.0	96	2.9
Previous fractures	749	22.8	680	20.7
Medication (6 months before index date)				
Anti-Parkinson medication	<5	0.1	6	0.2
Anti-psychotics	68	2.1	21	0.6
Anxiolytics/hypnotics	220	6.7	115	3.5
Benzodiazepines	162	4.9	89	2.7
Anti-depressants	329	10.0	239	7.3
Anti-convulsant	80	2.4	49	1.5
Oral glucocorticoids	124	3.8	54	1.6
Bone medications (6 months before index date)				
Bisphosphonates	34	1.0	21	0.6
Calcium/vit D	68	2.1	34	1.0
HRT	23	0.7	29	0.9
Strontium	0	0.0	0	0.0
PTH/calcitonin	0	0.0	0	0.0
Raloxifene	<5	0.0	<5	0.0

Abbreviations: BMI – body mass index, CVD: Cardio-vascular disease, MOFs: Major osteoporotic fracture, CCI: Charlson Comorbidity Index level 1–5. HR: Hazard Ratios. T1D: Type 1 Diabetes. CI: Confidence inter. Bone medication: Alendronates. Calcium and D-vitamin. PTH-analogues and Denosumab.

fractures in childhood that extended across a life span, including a disproportionately greater number of lower extremity fractures [29]. Additionally, the authors reported that retinopathy and neuropathy are associated with any fracture in T1D. Finally, a recent narrative review by Van Hulten et al. concurred similar results of this peripheral fracture pattern [7].

Except for lower arm fractures, the estimated fractures risks remained significantly increased despite of substantially adjustments for relevant risk factors known to increase the fracture risk, including demographics, co-morbidities, diabetic complications, and medication. However, the effect from the fully adjusted estimates decreased, which indicated that specific risk factors in T1D specifically could add to the increased fracture risk.

Table 2
Fracture site incidences.

Fracture localization	T1D (n = 3.281)		Controls (n = 3281)	
	n (%)	IR/1000 PY	N (%)	IR/1000 PY
Any fracture	355 (10.8)	16.4	242 (7.3)	10.6
MOFs	124 (3.7)	5.4	89 (2.7)	3.8
Lower-arm fracture	151 (4.6)	6.6	107 (3.3)	4.5
Lower-leg fracture	100 (3.0)	4.3	68 (2.1)	2.9

Fracture site IRs were calculated by dividing the number of fractures (per fracture site) by the total number of person years and presented per 1000 person years (PYs).
Abbreviations: T1D: Type 1 diabetes, n = numbers, MOFs = Major Osteoporotic Fractures, IR = Incidence rates and PY = Person years.

5.2. Risk factors for fractures at specific sites

In general, a previous fracture was the most predominant risk factor associated with a subsequent fracture. This is in line with other studies and considered an important risk factor, especially in T1D [5,13]. A previous fracture was also the only pervasive risk factor for all fracture sites. Furthermore, the use of bone medication was also associated with fractures for all sites (except lower-arm fractures). However, this association is most likely related to people with either diagnosed osteoporosis or who had a previous osteoporotic fracture. Hence, the effect of the bone medication reflects an ongoing treatment rather than an increased fracture risk due to the medication.

Moreover, the analysis conducted in this study revealed that previous falls, as well as the use of antidepressant and anxiolytic medications, were associated with factors that increased the risk of suffering any fracture. Given the association between these risk factors and fracture risk, it is notable that these risk factors also are more prevalent in our T1D cohort compared to controls (Table 1). Hence, the higher overall risk of fracture in T1D versus controls may be caused using this medication in a higher proportion of people with T1D vs. controls. Furthermore, falls play a significant role in the occurrence of fractures, and numerous studies examining postural control, balance, and fall occurrences have demonstrated that people with T1D are particularly affected by this issue [21,30]. The utilization of anxiolytic and antidepressant medications may increase the likelihood of falling due to the potential side effects such as drowsiness, muscle weakness, alterations in stability, dizziness, and low blood pressure [31]. However, the indication for using anxiolytic medications varies widely, ranging from treating sleep disorders, epilepsy, drug addiction, and neurological disputes, with variations in concentration, mechanism of action, and duration of use [32]. Usually, hypoglycemia is a common cause of falls [33]. However, no association was found in this study. This is probably due to the study design, as episodes of hypoglycemia were registered at the onset of T1D, and not later.

The administration of antidepressant and anxiolytic medications is commonly practiced among people with T1D, and the descriptive data obtained from this study aligns with this observation. For instance, antidepressant use has been linked to a 1.4- to 6-fold increase in the risk of experiencing falls and fractures [34]. While selective serotonin reuptake inhibitors (SSRIs) are frequently prescribed to treat depression, they are occasionally employed to alleviate neuropathic pain as well [35]. However, it is likely that most people in this study were being treated for depression, as only a small number were initially diagnosed with neuropathy. A meta-analysis demonstrated that a higher degree of depressive symptoms was associated with an increased risk of falling [relative risk (RR) 1.52, 95 % confidence interval (CI): 1.19–1.84] [36]. Medications used to address co-existing conditions in people with T1D could potentially be modified to mitigate the risk of fractures, and should be taken into account when clinically evaluating these people and their

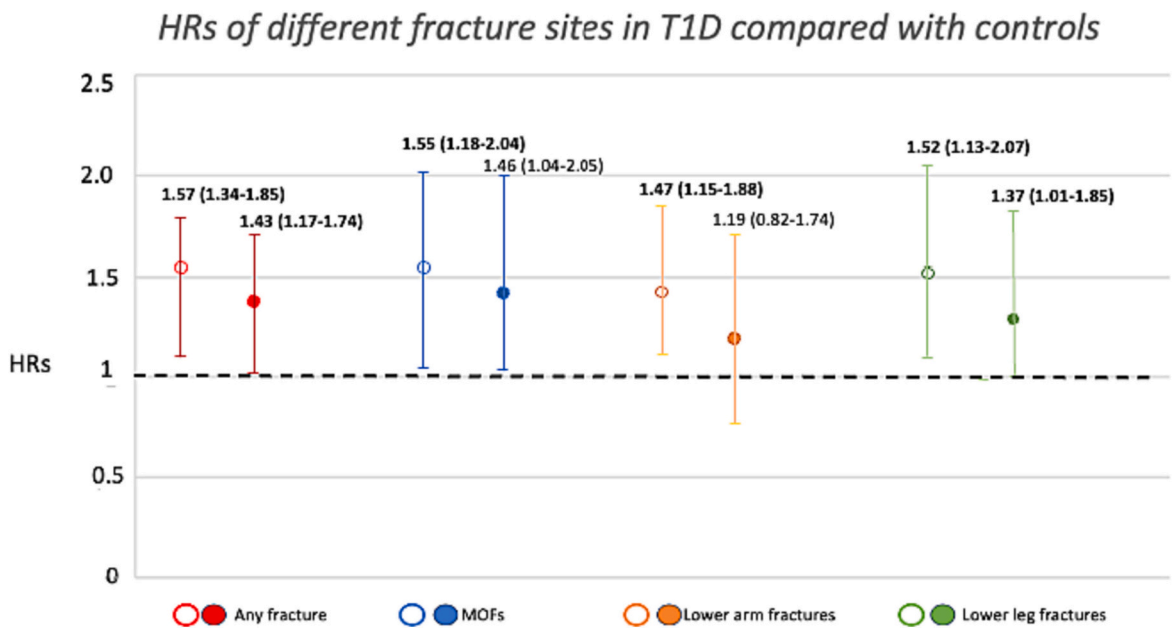

Fig. 3. [1]Half circle: adjusted for sex and age.
[2]Full circle: Fully adjusted for: Sex, age, Charlson Comorbidity index, neuropathy, retinopathy, nephropathy, hypoglycemia, previous falls, previous fractures, medication (glucocorticoids, anticonvulsive, antidepressants, anxiolytics, antipsychotics, antidepressants, bone medication and lipid lowering medications) and alcohol use in the previous 6 months.
*Bold indicates significant level ($p < 0.05$).
Abbreviations: HRs: Hazard Ratios. T1D: Type 1 Diabetes Mellitus. CI: Confidence interval. MOFs: Major osteoporotic fracture.

susceptibility to fractures [37,38].

Regarding MOFs, women were found to have a heightened risk, whereas the use of lipid-lowering drugs was associated with a decreased risk. Osteoporotic fractures are well-recognized as a risk factor for fractures, particularly in women during menopause, due to a decline in estrogen levels. The effect of lipid-lowering medications, specifically statins, on the treatment of osteoporosis has been a topic of debate in previous studies and meta-analyses. Some evidence suggests a potential positive impact on fracture risk and bone mineral density (BMD) [39,40]. Whereas others found an increased fracture risk due to circulating HDL-C levels or an associated high dose-dependent risk of osteoporosis due to statin use [41–43] Nonetheless, the findings of this study indicate that lipid-lowering medications have a positive effect on reducing the incidence of MOFs in people with T1D.

In the case of lower-arm fractures, only the presence of retinopathy was associated with an increased risk. A prospective study conducted on people with diabetes demonstrated a higher likelihood of fractures among those with retinopathy [13]. However, it is important to note that, as of our current understanding, no prior studies have specifically established a direct link between retinopathy and an elevated risk of fractures occurring specifically in the lower arms.

Lower-leg fractures, on the other hand, were found to be associated with an increased risk among people with a history of previous falls.

5.3. Sensitivity analyses

Two sensitivity analyses were conducted to explore the impact of T1D duration and diabetic microvascular complications on fracture risk. These factors are specific to T1D and can provide valuable insights into the impact of long-term diabetes management on fracture susceptibility.

The analysis of diabetes duration revealed an interesting trend in fracture risk. Initially, there was a significantly association with a higher fracture risk observed during the early years from T1D onset. This finding aligns with previous studies that have shown an increased fracture risk shortly after T1D diagnosis due to factors such as impaired bone quality and accelerated bone loss during this period [44,45]. However, as the duration of T1D increased, a subsequent decrease in fracture risk was observed among people with T1D but also when compared with controls. This reduction or normalization in fracture risk with prolonged T1D duration may be attributed to improved diabetes care, including glycemic control and the implementation of preventive measures such as lifestyle modifications and bone health interventions or a higher long term mortality risk in T1D [13,44]. In addition, the anabolic effects from insulin therapy could stimulate osteoblast function after a period with insulin deficiency [46,47]. Though, it is important to note that while our study demonstrated this temporal pattern, it is in contrast to some previous studies that have reported an increased fracture risk with longer diabetes duration [7,44]. In this study, the cohort primarily comprised people who were newly diagnosed and relatively young when they developed T1D. As a result, we hypothesize a potential initial risk, followed by a subsequent reduction in risk, which may eventually increase in later years due to the accumulation of complication etc. However, further research is warranted to better understand the underlying mechanisms contributing to this temporal variation in fracture risk among people with T1D.

The presence of diabetic microvascular complications at T1D onset revealed a significant association between a higher number of complications and fracture risk in people with T1D when compared to controls. E.g., these findings suggest that the presence of microvascular complications, like retinopathy may contribute to an increased vulnerability to fractures in people with T1D. Comparable outcomes were noted for various fracture sites; however, the associations were not statistically significant within the T1D group, which was probably due to a low number of complications at baseline.

However, developing diabetic complications at a later point in life may very well also be associated with an increased fracture risk and should be addressed in a case-control set-up.

These findings highlight the importance of considering the overall burden of microvascular complications when assessing fracture risk in people with T1D. It is crucial to note that the impact of specific complications on fracture risk may vary, and additional research is needed to elucidate the underlying mechanisms potentially linking diabetic

Table 3
Risk factors for different fractures sites in adult people with T1D.

	Any fracture	MOFs	Lower arm fracture	Lower leg fracture
	HR (CI95%)	HR (CI95%)	HR (CI95%)	HR (CI95%)
Crude analyses				
Sex (male as ref.)	1.06 (0.86–1.31)	**1.70 (1.19–2.42)**	0.95 (0.68–1.32)	1.41 (0.95–2.08)
Age	1.01 (1.00–1.01)	1.03 (1.02–1.05)	1.00 (0.99–1.01)	1.01 (0.99–1.01)
[a]Fully adjusted analyses				
Demographics				
Sex (male as ref.)	1.04 (0.83–1.29)	**1.65 (1.14–2.38)**	0.98 (0.70–1.37)	1.31 (0.87–1.99)
Age	**1.01 (1.00–1.01)**	**1.03 (1.14–1.02)**	1.00 (0.99–1.01)	1.00 (0.98–1.01)
Alcohol use, yes	1.20 (0.92–1.57)	1.27 (0.82–1.97)	1.53 (0.98–2.41)	0.75 (0.47–1.18)
Alcohol missing	1.21 (0.76–1.93)	1.30 (0.58–2.91)	1.17 (0.53–2.56)	1.08 (0.48–2.43)
Diabetes associated complications				
Neuropathy	1.22 (0.76–1.96)	0.93 (0.42–2.07)	0.53 (0.19–1.48)	1.65 (0.76–3.55)
Retinopathy	1.22 (0.95–1.56)	1.39 (0.94–2.06)	**1.47 (1.02–2.11)**	1.14 (0.72–1.80)
Nephropathy	0.99 (0.75–1.32)	0.91 (0.58–1.42)	0.85 (0.54–1.33)	1.35 (0.82–2.21)
Hypoglycemia	1.18 (0.90–1.55)	0.97 (0.61–1.53)	0.95 (0.61–1.47)	1.35 (0.83–2.20)
Glucose levels	1.25 (0.74–2.09)	0.41 (0.13–1.34)	0.34 (0.08–1.43)	1.96 (0.86–4.46)
Co-morbidities				
CCI (1–2, CCI 0 as ref)	1.08 (0.86–1.37)	1.13 (0.76–1.68)	1.09 (0.77–1.55)	1.06 (0.68–1.65)
CCI (3–5, CCI 0 as ref)	1.21 (0.75–1.98)	0.96 (0.46–2.02)	0.93 (0.38–2.25)	1.21 (0.51–2.92)
Others				
Previous Falls	**1.64 (1.17–2.31)**	1.16 (0.67–2.01)	1.41 (0.82–2.45)	**2.04 (1.16–3.59)**
Previous fractures	**2.07 (1.65–2.59)**	**2.29 (1.59–3.30)**	**2.05 (1.47–2.86)**	**1.62 (1.06–2.47)**
Medication				
Glucocorticoids	1.25 (0.74–2.09)	0.41 (0.13–1.34)	0.34 (0.08–1.43)	1.96 (0.86–4.46)
Anti-hypertensives	0.93 (0.72–1.21)	1.11 (0.73–1.71)	0.95 (0.63–1.43)	0.87 (0.53–1.42)
Anti-depressants	**1.34 (1.02–1.76)**	1.31 (0.84–2.06)	1.02 (0.64–1.60)	1.42 (0.87–2.34)
Anxiolytics	**1.54 (1.08–2.29)**	1.42 (0.80–2.51)	1.52 (0.85–2.72)	1.46 (0.76–2.80)
Anti-psychotics	1.32 (0.72–2.41)	1.67 (0.70–3.99)	1.13 (0.40–3.17)	1.71 (0.65–4.50)
Anti-convulsive	1.17 (0.77–1.78)	1.52 (0.83–2.80)	1.50 (0.80–2.83)	0.99 (0.46–2.12)
Bone medication[b]	1.43 (0.93–2.19)	**2.01 (1.14–3.54)**	1.66 (0.84–3.28)	0.79 (0.33–1.90)
Lipid lowering drugs	0.88 (0.68–1.13)	**0.66 (0.44–0.99)**	0.84 (0.57–1.24)	0.99 (0.62–1.59)

Abbreviations: HR: Hazard Ratios, T1D: Type 1 Diabetes Mellitus, CCI: Charlson Comorbidity Index, CI: Confidence inter, Bone medication: Alendronates, calcium, d-vitamin, PTH-analogues and denosumab.
Bold indicates significant level ($p < 0.05$).

[a] Multivariate analysis adjusted for demographics (sex, age, alcohol status), diabetes associated complications (Neuropathy, retinopathy, nephropathy, and hypoglycemic events and glucose levels), co-morbidities (Charlson comorbidity index (CCI)), previous falls, previous fractures, and medication within the 6 months prior to the start of an interval (glucocorticoids, anti-depressants, anxiolytics, and anti-convulsive, and bone medication (Bisphosphonates, Hormone Replacement Therapies, Calcium/D-vit, and Parathyroid Hormone Analogues)).

[b] Bone medication: Alendronates. Calcium and D-vitamin. PTH-analogues and Denosumab.

microvascular complications to fractures in T1D.

5.4. Strengths

This study possessed several strengths in determining fracture risk and identifying risk factors in people with T1D. Firstly, the utilization of a large study cohort from the CPRD GOLD database facilitated population-based HR estimations, comprehensive analysis of fracture patterns, identification of risk factors, and extensive multiple analyses. Secondly, people with T1D were included at the time of their diagnosis, allowing for the examination of fracture patterns in newly treated people with T1D, who were relatively healthy. Thirdly, the matched control group represented the general population, enabling robust risk estimations and stratifications. Lastly, the inclusion of people with T1D over a broad time window from January 1, 1987, until December 31, 2018, ensured consistency in the management of T1D with insulin, with only minor changes. This uniformity across the entire study period reduced the risk of misclassification and miscoding and made the study participants comparable.

5.5. Limitations

We enrolled adult people above 20 years of age with T1D based on their diagnosis and insulin treatment, excluding those with NIAD treatment. It is possible that misclassification of people with T2D could have occurred if they were being treated solely with insulin due to the nature of their condition. However, such cases were relatively few, and their inclusion would likely have underestimated the results since the people in the CPRD database generally have better health compared to those regularly followed in hospital clinics. Undiagnosed people with T1D are generally non-existing due the absolute need of insulin. However, a T1D diagnosis stemming from a first-time hospitalization due to ketoacidosis might not initially appear in the CPRD database but would eventually be included during subsequent GP check-ups. Also, the CRPD database did not encompass Diabetes Specialist Clinics, which could have potentially led to an underreporting of complications. This limitation might explain why we did not identify associations between these complications and various fracture types. Additionally, the CPRD data is highly valuable as it has previously demonstrated a high level of validity in capturing hip and vertebral fractures [48]. The positive predictive value for vertebral fractures in the CPRD was reported to be 88.1 % (81.3–93.0 %) [27]. However, since Read codes were used, no data was available regarding the origin of fractures (spontaneous and asymptomatic vertebral fractures were not included in this study), and there was no information on BMD or assessment of bone quality. Monitoring patients after a fracture is a fundamental skill for GPs, but it may not capture the full extent of serious complications necessitating additional hospital admissions. Lastly, a limitation of this study is the ability to generalize to the entire population with T1D. Therefore, future studies should also address the effect of younger people with T1D and fracture risk.

6. Conclusion

In this retrospective cohort study of relatively healthy people, we identified a significant association between T1D and an increased susceptibility to fractures including MOFs and lower-leg fractures. Our findings not only confirmed established risk factors but also uncovered new ones. The most consistent risk factor across all fracture types was a previous fracture, while other risk factors were more specific to each fracture site. Remarkably, the sensitivity analyses uncovered a unique temporal pattern, indicating an increased fracture risk in the initial stages of T1D onset, succeeded by a subsequent decrease (in comparison to T1D as a reference) or normalization (in comparison to controls as a reference) as the disease duration extended. Consequently, we postulate a potential initial risk, succeeded by a subsequent risk reduction, which

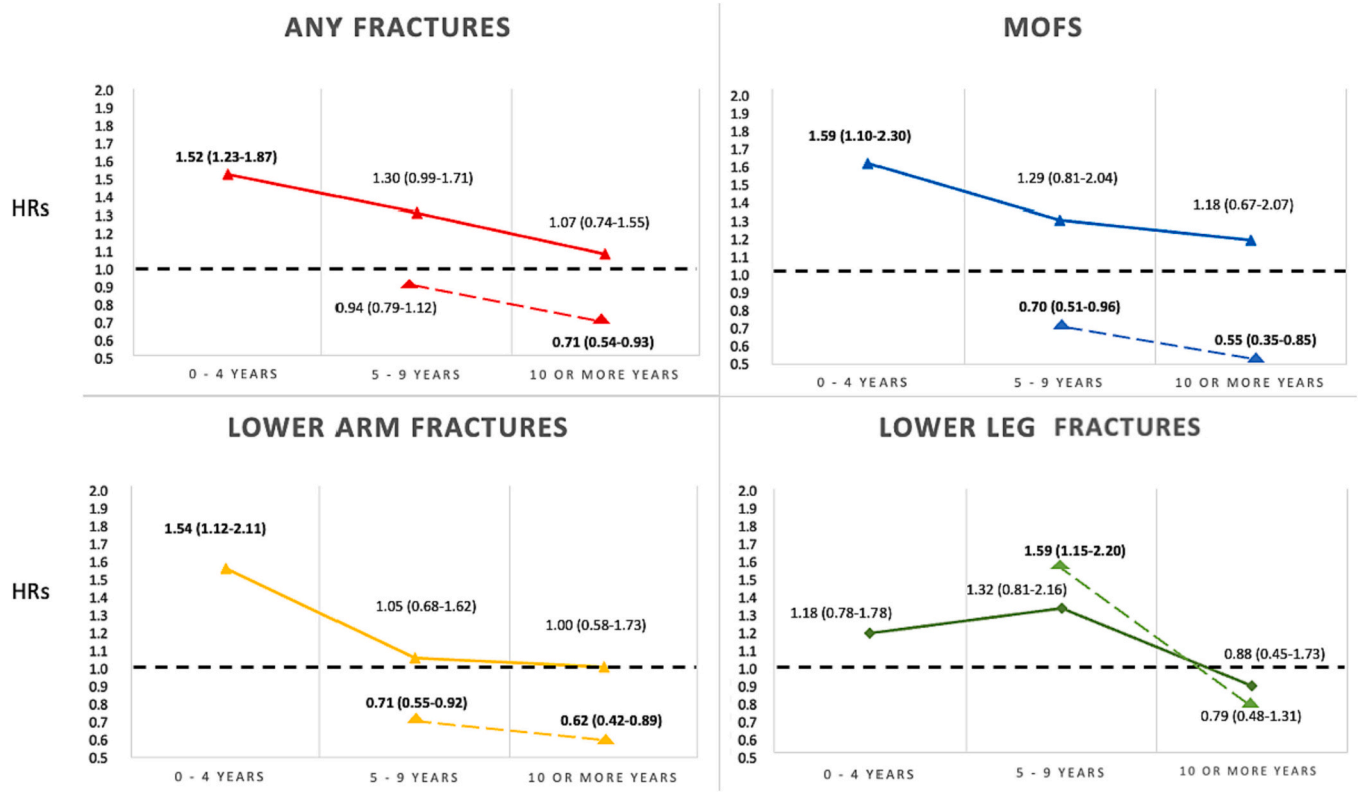

Fig. 4. Association between T1D diabetes duration and the fracture risk at different sites.
Fully adjusted[1] analyses yielding HRs of fractures sites in people with T1D by diabetes duration. Reference for full line type was no T1D. Reference for dotted line type was 0–4 years of T1D duration. The T1D group was stratified by duration in intervals from 0 to 4 years, 5–9 years, and >10 years, respectively.
[1]Adjusted for: Sex, age, Charlson Comorbidity index, neuropathy, retinopathy, nephropathy, hypoglycemia, previous falls, previous fractures, medication (glucocorticoids, anticonvulsive, antidepressants, anxiolytics, antipsychotics, antidepressants, bone medication and lipid lowering medications) and alcohol use in the previous 6 months.
[2]Bold indicates significant level ($p < 0.05$).
[3]Test of trends: $p > 0.05$ comparing T1D vs. controls for all sites (full line). Regarding the dotted line, $p = 0.02$ comparing any fractures, $p = 0.003$ for MOFs, $p = 0.002$ for lower-arm fractures and $p = 0.932$ for lower-leg fractures.
Abbreviations: HR: Hazard Ratios. T1D: Type 1 Diabetes Mellitus. CI: Confidence inter. Bone medication: Alendronates. Calcium and D-vitamin. PTH-analogues and Denosumab.

might potentially increase in later years due to the accumulation of complications and other factors.

These results contribute to the growing body of evidence linking T1D with an increased fracture risk, particularly for MOFs and lower-leg fractures. Understanding the specific fracture patterns in T1D is crucial for targeted preventive strategies and improved management of this vulnerable population. Further research is needed to explore the underlying mechanisms driving fracture susceptibility in T1D and to evaluate the effectiveness of interventions to mitigate fracture risk and improve bone health in people with T1D.

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Approval

The study protocol was approved by the Interdisciplinary Scientific Advisory Committee for Medicines and Healthcare products Regulatory Agency database research, protocol number 19_028.

Availability of data and material

The data that support the findings of this study are available from CPRD and access is subject to protocol approval via *CPRD's* Research Data Governance Process. The data were used under license for the current study, and so are not publicly available. Researchers can submit research protocols to CPRD and conduct analyses independently after obtaining research protocol approval and signing the data license.

Code availability

The code is not available.

Authors' contributions

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version.

CRediT authorship contribution statement

Nicklas H. Rasmussen: Writing – review & editing, Writing – original draft, Visualization, Validation, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Johanna H. M. Driessen:** Writing – review & editing, Supervision, Software, Investigation, Formal analysis, Data curation, Conceptualization. **Annika Vestergaard Kvist:** Writing – review & editing, Validation, Methodology, Conceptualization. **Patrick C. Souverein:** Writing – review & editing, Validation, Supervision. **Joop van den Bergh:** Writing –

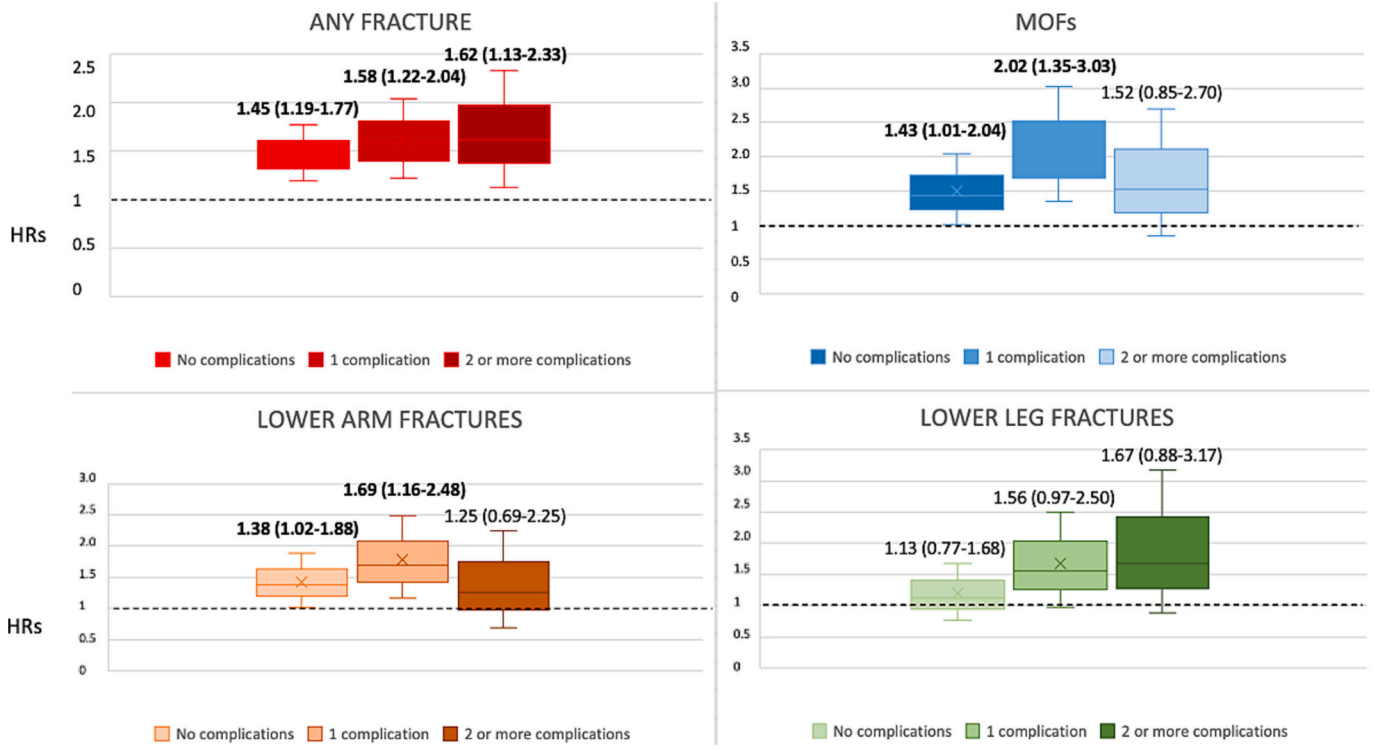

Fig. 5. Association between the number of diabetic microvascular complications in T1D and fracture risk at different fracture sites.
Fully adjusted[1] analyses yielding HRs of fractures sites in people with T1D by diabetic microvascular complications[2]. The T1D group was stratified by presence of diabetic microvascular complications. No T1D was reference.
[1]Adjusted for: Sex, age, Charlson Comorbidity index, hypoglycemia, previous falls, previous fractures, medication (glucocorticoids, anticonvulsive, antidepressants, anxiolytics, antipsychotics, antidepressants, bone medication and lipid lowering medications) and alcohol use in the previous 6 months.
[2]Retinopathy, neuropathy and nephropathy.
[3]Test of trends: $p > 0.05$ comparing T1D vs controls for all sites.
[4]Bold indicates significant level ($p < 0.05$).

review & editing, Visualization, Supervision, Methodology, Funding acquisition, Conceptualization. **Peter Vestergaard:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author(s) used ChatGPT-3,5 to improve language. After using this tool, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

Declaration of competing interest

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