

## Full Length Article

# Fracture patterns and associated risk factors in pediatric and early adulthood type 1 diabetes: Findings from a nationwide retrospective cohort study

Nicklas H. Rasmussen<sup>a,\*</sup>, Johanna H.M. Driessen<sup>b,c,d,e</sup>, Annika Vestergaard Kvist<sup>f,g,h,i</sup>, Patrick C. Souverein<sup>c</sup>, Joop P. van den Bergh<sup>j,k,l</sup>, Peter Vestergaard<sup>a,m</sup>

<sup>a</sup> Steno Diabetes Center North Denmark, Aalborg University Hospital, Denmark

<sup>b</sup> NUTRIM Research School, Maastricht University, Maastricht, the Netherlands

<sup>c</sup> Division of Pharmacoepidemiology & Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, the Netherlands

<sup>d</sup> Department of Clinical Pharmacy and Toxicology, Maastricht University Medical Centre+, Maastricht, the Netherlands

<sup>e</sup> Cardiovascular Research Institute Maastricht (CARIM), Maastricht University, Maastricht, the Netherlands

<sup>f</sup> Department of Endocrinology and Metabolism, Molecular Endocrinology & Stem Cell Research Unit (KMEB), Odense University Hospital, Odense, Denmark

<sup>g</sup> University of Southern Denmark, Odense, Denmark

<sup>h</sup> Steno Diabetes Center North Denmark, Aalborg University Hospital, Aalborg, Denmark

<sup>i</sup> Institute of Pharmaceutical Sciences, Department of Chemistry and Applied Biosciences, ETH-Zurich, Zurich, Switzerland

<sup>j</sup> School for Nutrition and Translational Research in Metabolism (NUTRIM), Maastricht University, Maastricht, the Netherlands

<sup>k</sup> Department of Internal Medicine, Division of Rheumatology, Maastricht University Medical Center+, Maastricht, the Netherlands

<sup>l</sup> Department of Internal Medicine, VieCuri Medical Center, Venlo, the Netherlands

<sup>m</sup> Department of Clinical Medicine and Endocrinology, Aalborg University Hospital, Aalborg, Denmark

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## ABSTRACT

**Purpose:** People with pediatric and early adulthood type 1 diabetes (T1D) might have a higher fracture risk at several sites compared to the general population. Therefore, we assessed the hazard ratios (HR) of various fracture sites and determined the risk factors associated with fractures among people with newly diagnosed childhood and adolescence T1D.

**Methods:** All people from the UK Clinical Practice Research Datalink GOLD (1987–2017), below 20 years of age with a T1D diagnosis code ( $n = 3100$ ) and a new insulin prescription, were included and matched 1:1 by sex, age, and practice to a control without diabetes. Cox regression was used to estimate HRs of any, major osteoporotic fractures (MOFs) and peripheral fractures (lower-arm and lower-legs) for people with T1D compared to controls. The analyses were adjusted for sex, age, diabetic complications, medication (glucocorticoids, anti-depressants, anxiolytics, bone medication, anti-convulsive), Charlson-comorbidity-index (CCI), hypoglycemia, falls and alcohol. T1D was further stratified by diabetes duration, presence of diabetic microvascular complications (retinopathy, nephropathy, and neuropathy) and boys versus girls.

**Results:** The crude HRs for any fracture (HR: 1.30, CI95%: 1.11–1.51), lower-arm (HR: 1.22, CI95%: 1.00–1.48), and lower-leg fractures (HR: 1.54, CI95%: 1.11–2.13) were statistically significant increase in T1D compared to controls, but the effect disappeared in the adjusted analyses. For MOFs, no significant differences were seen. Risk factors in the T1D cohort were few, but the most predominantly one was a previous fracture (any fracture: HR: 2.00, CI95%: 1.70–2.36; MOFs: HR: 1.89, CI95%: 1.44–2.48, lower-arm fractures: HR: 2.08, CI95%: 1.53–2.82 and lower-leg fractures: HR: 2.08, CI95%: 1.34–3.25). Others were a previous fall (any fracture: HR: 1.54, CI95%: 1.20–1.97), hypoglycemia (Any fracture: HR: 1.46, CI95%: 1.21–1.77 and lower-leg fractures: HR: 2.34, CI95%: 1.47–3.75), and anxiolytic medication (Any fracture: HR: 1.52, CI95%: 1.10–2.11). Whereas girls had a lower risk compared to boys (Any fracture: HR: 0.78, CI95%: 0.67–0.90 and lower-arm fractures: HR: 0.51, CI95%: 0.38–0.68). The risk of any fracture in T1D did not increase with longer diabetes duration compared to controls (0–4 years: HR: 1.20, CI95%: 1.00–1.44; 5–9 years: HR: 1.17, CI95%: 0.91–1.50; <10 years: HR: 0.83, CI95%: 0.54–1.27). Similar patterns were observed for other fracture sites. Furthermore, one complication compared to none in T1D correlated with a higher fracture risk (1 complication: HR: 1.42, CI95%: 1.04–1.95).

\* Corresponding author.

E-mail address: [nicklas.rasmussen@rn.dk](mailto:nicklas.rasmussen@rn.dk) (N.H. Rasmussen).

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**Conclusion:** The overall fracture risk was not increased in pediatric and early adulthood T1D; instead, it was associated with familiar risk factors and specific diabetes-related ones.

## 1. Introduction

Type 1 diabetes (T1D) is a chronic autoimmune disease that primarily affects children and adolescents, characterized by the destruction of pancreatic beta cells, leading to insulin deficiency [1]. T1D is the major type of diabetes in youth, accounting for  $\geq 85\%$  of all diabetes cases in youth  $<20$  years of age worldwide [2]. Inadequate management of pediatric T1D can result in long-term health consequences and increased morbidity and mortality [3]. T1D is associated with various complications, including retinopathy, nephropathy, and cardiovascular disease but also other co-morbidities like fractures. The extensive body of literature has consistently reported an elevated risk of fractures among adults with T1D, highlighting various contributing risk factors [4–6]. E.g., hyperglycemia, increased falls risk, lower body mass index (BMI), several types of medication usage and micro-vascular complications. Fractures, which represent a significant global health concern, can have a profound impact on a child's physical and psychosocial well-being [7].

Recently, evidence also suggests an elevated risk of fractures in pediatric people with T1D, compared to those without T1D [8]. However, data is scarce, and most have focused on bone mass, bone architecture, and bone markers as pseudo risk of fractures. A recent meta-analysis on BMD and bone architecture found that children and youth with T1D have lower bone mineral content (BMC), areal bone mineral density (aBMD) and deficits in trabecular density and micro-architecture. Deficits in BMC and aBMD appeared to increase with age and disease duration [9]. Although, spine BMD seems to be similar in T1D and those without across a lifespan [10]. Additionally, the onset of T1D can be associated with early bone loss, even during childhood, leading to a reduced peak bone mass and consequently an increased susceptibility to osteoporosis and fractures in later stages of life [11]. Finally, markers of bone turnover, measured by CTX Z-score and P1NP Z-score, in childhood and adolescences T1D have shown to be decreased [12].

However, there is a limited number of studies examining hard endpoints such as fracture risk, patterns, and potential long-term risk increase. Understanding fracture risk in pediatric T1D is abundant for developing effective preventive strategies and improving patient outcomes. Comprehensive studies addressing fracture risk and associated factors in children and adolescents with T1D are needed. Therefore, we aimed at assessing the fracture risk, identify fracture patterns and associated risk factors in pediatric and early adulthood T1D.

## 2. Methods

### 2.1. Source of data

The data was comprised from the UK Clinical Practice Research Datalink (CPRD) GOLD. The 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 [13]. 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 [13–15]. GP staff manually recorded data to describe a patient's condition using Read codes and contain over 96,000 codes [16]. This database has remained the largest validated and most utilized primary care database in the UK [17,18].

### 2.2. Study design and population

This retrospective cohort study utilized a nationally representative sample of people below 20 years of age, identified within CPRD GOLD database between January 1, 1987, and December 31, 2017. The cohort comprised people with newly diagnosed (incident) pediatric and early adulthood T1D ( $n = 3100$ ) and their corresponding matched controls in a 1:1 ratio, selected based on sex, year of birth and practice (refer to Fig. 1).

The identification of people with T1D was based on the presence of T1D-specific Read codes and by product codes for their first redeemed prescription of insulin. Conversely, people with a Read code for non-insulin antidiabetic drugs (NIADs) were excluded from the T1D group. To accurately define the cohort, all people with T1D were required to have at least one year of up-to-standard follow-up preceding the first recorded insulin prescription.

Controls were defined as people without any Read code for insulin or NIADs and were matched to the T1D group based on year of birth, sex and practice, employing incidence density sampling techniques. The index date for people with T1D was established as the date of their initial redeemed insulin prescription. Each control person was assigned the same index date as their matched individual with T1D for follow-up.

The follow-up period encompassed the duration from the index date to the occurrence of death, completion of data collection, conclusion of the study period, or the manifestation of the outcome of interest, whichever event came first, for both people with T1D and controls. Control people were censored if they had a Read code for insulin, NIADs, or a diabetes diagnosis during the study period. The follow-up time was split into intervals of 90 days.

### 2.3. Endpoints and exposures

Endpoints were Read coded fractures at different fracture sites; any fracture, MOFs, lower arm fractures, and lower leg fractures (Fig. 2). 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. Potential risk factors were determined at baseline and updated at the start of each interval and included demographics (sex, age, and alcohol status [19]), diabetes associated complications (Neuropathy, retinopathy, nephropathy, CVD, and hypoglycemia events), co-morbidities ((Charlson comorbidity index (CCI), previous falls, and previous fractures), and medication within the 6 months the start of an interval (glucocorticoids, anti-depressants, anxiolytics, and anti-convulsive, and bone medication (BPs, Calcium/D-vit, and PTH analogues)). The CCI-index was determined excluding Read codes for diabetes, to make it comparable to controls without T1D [20].

### 2.4. Data analysis

Descriptive statistics were employed to summarize the data. Continuous variables were presented as mean  $\pm$  standard deviation (SD), median (interquartile range IQR) for non-normally distributed data, and categorical variables were reported as percentages and counts for each respective group.

Fracture site incidence rates (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).

To estimate the hazard ratios (HRs) of various fracture sites in people

with T1D compared to the control group (reference group), a Cox regression model was utilized. The HRs were adjusted for several covariates, including demographic factors, diabetes-associated complications, co-morbidities, and medication usage. Furthermore, another Cox regression model was employed to identify specific risk factors for each fracture site within the T1D group alone.

Three sensitivity analyses were conducted to further explore the relationships between different fracture sites and the duration of diabetes, the presence of diabetic complications or boys versus girls as potential risk factors. The duration of T1D was calculated by subtracting the index date from the start date of each interval and was stratified into three categories: 0–4 years, 5–9 years, and  $\geq 10$  years, with the reference group being people with the shortest duration (0–4 years). Presence of complications was stratified into the following categories: 0, 1 and 2 or more complications. The T1D group was stratified into boys and girls.

All statistical analyses were performed using SAS 9.4 software. A two-sided *p*-value below 0.05 was considered statistically significant, indicating a significant association or difference.

### 3. Results

We identified 3100 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 = 6.6 years vs. controls = 6.3 years), BMI (T1D = 20.9 kg/m<sup>2</sup> vs. controls = 22.7 kg/m<sup>2</sup>), current smoking status (T1D = 7.8 % vs. controls = 7.8 %) except for current alcohol use (T1D = 18.6 % vs. controls = 9.9 %). In general, almost zero diabetic complications were registered, but slightly higher proportions of co-morbidities, falls and fractures were seen in T1D vs. controls. Any types of medication use were low in both groups (refer to Table 1).

The IRs per 1000 PYs for T1D were: Any fracture; 20.6 (12.3 %), MOFs; 6.0 (3.8 %), lower-arm fractures; 11.8 (7.3 %) and lower-leg fractures; 4.6 (3.0 %). Divided into girls and boys, the corresponding IRs per 1000 PY were: Any fracture; 14.4 (3.9 %) and 25.8 (8.5 %), MOFs; 4.8 (1.3 %) and 7.0 (2.5 %), lower-arm fractures; 7.7 (2.1 %) and 15.1 (5.1 %), and lower-leg fractures; 4.2 (1.1 %) and 5.1 (1.8 %) respectively. Whereas for controls (all) site specific IRs for any fracture were 16.0 (9.2 %), 5.4 (3.2 %) for MOFs, 3.0 (5.8 %) for lower-arm fractures and 9.8 (1.8 %) for lower-leg fractures. Additionally, IRs are also shown for T1D duration and complications (refer to Table 2).

The age and sex adjusted results showed that people with T1D had a

statistically and significant higher risk for fractures at all sites except for MOFs (any fracture (HR of 1.30 (95 % CI: 1.11–1.51)), lower arm fractures (HR of 1.22 (95 % CI: 1.00–1.48)), and lower leg fractures (HR of 1.54 (95 % CI: 1.11–2.13)), compared with controls. However, in the fully adjusted analysis, the estimates for T1D versus controls attenuated and were not significant anymore (refer to Fig. 3).

In general, there was an association between a prior fracture and an increased risk of fractures across all fracture sites in T1D (any fracture: HR of 2.00 (95 % CI: 1.70–2.36), MOFs (HR of 1.89 (95 % CI: 1.44–2.48), lower-arm fractures (HR of 2.08 (95 % CI: 1.53–2.82), and lower-leg fractures (HR of 2.08 (95 % CI: 1.34–3.25)). Other factors associated with an increased risk of any fracture included hypoglycemia (HR of 1.46, 95 % CI: 1.21–1.77), previous falls (HR of 1.54, 95 % CI: 1.20–1.97), use of anxiolytics (HR of 1.52 (95 % CI: 1.10–2.21), and bone medication (HR of 1.50 (95 % CI: 1.00–2.25)). However, being a girl was associated with a decreased risk (HR of 0.78 (95 % CI: 0.67–0.90)) for any fracture. Specifically, for lower-arm fractures, girls had a decreased risk compared to boys (HR of 0.51 (95 % CI: 0.38–0.68)). In the case of lower-leg fractures, hypoglycemia was significantly associated with an increased risk (HR of 2.34 (95 % CI: 1.47–3.75)). Apart from a previous fracture, no other risk factors for MOFs were found to be significantly associated with fracture risk in T1D (refer to Table 3).

In the first sensitivity analysis, the risk of any fracture was assessed based on the onset of diabetes, with people without T1D serving as the reference group. Stratification by T1D duration revealed that the highest fracture risk was observed within the 0–4-year duration group (HR of 1.20 (95 % CI: 1.00–1.44)), followed by the 5–9-year duration group (HR of 1.17 (95 % CI: 0.91–1.50)), and the  $>10$ -year duration group (HR of 0.83 (95 % CI: 0.54–1.27)). Notably, statistical significance was only reached for the 0–4-year duration group. Test of trends were insignificant for all sites (refer to Table 4). In the second analysis, the relationship between the number of microvascular complications in T1D and fracture risk was examined. It was found that as the number of microvascular complications increased, the risk of any fracture increased (0 complications: HR of 1.17 (CI95%: 0.99–1.39), 1 complication: HR of 1.42 (CI95%: 1.04–1.95);  $\geq 2$  complications: HR of 1.56 (CI95%: 0.76–3.22)). Importantly, statistical significance was observed solely within the 1-complication group, but test of trend was significantly with increased complications for any fracture (other fracture sites were not) (refer to Table 4). In the third analysis, no differences were observed between boys and girls in regard of risk factors for fractures (data not

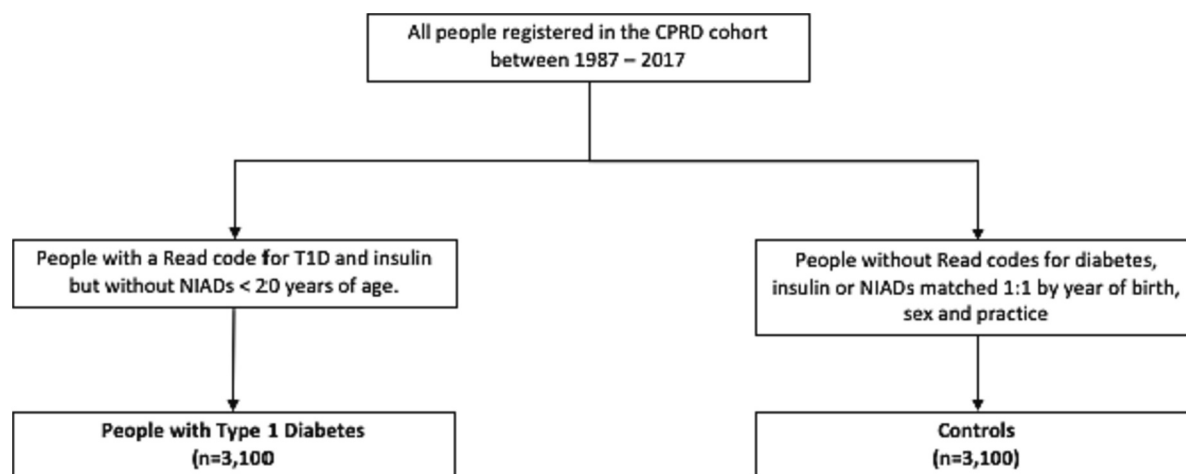


Fig. 1. Flow of inclusion.

The cohort was extracted from the UK CPRD data cohort between January 1987 until 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 3100 people with T1D and their matched control (1:1) under 20 years of age.

Abbreviations: T1D: Type 1 diabetes, NIAD: Non-insulin anti-diabetic medications, CPRD: Clinical Practice Research Datalink.

shown).

4. Discussion

In this study, we scrutinized a cohort of 3100 people with pediatric and early adulthood T1D alongside their matched controls to assess fracture risk and its associated factors. Initially, both groups exhibited similarity in demographic parameters, with marginally higher proportions of comorbidities, such as falls and fractures, noted in the T1D cohort. While people with T1D displayed a significantly elevated risk of fractures across all sites, except for MOFs in unadjusted analyses, this effect diminished upon adjustment. Consequently, the overarching conclusion suggests that the overall fracture risk in T1D was not heightened. Subsequent identification of traditional fracture risk factors highlighted previous fractures as the predominant and consistent factor across sites. Additionally, prior falls, anxiolytic use, and bone medication emerged as supplementary risk factors in T1D, whereas female sex exhibited a reduced risk compared to males. Notably, hypoglycemia stood out as the sole diabetes-specific risk factor. Sensitivity analyses disclosed the highest fracture risk within the first 0–4 years of T1D duration, and the presence of a single microvascular complication correlated with an increased fracture risk.

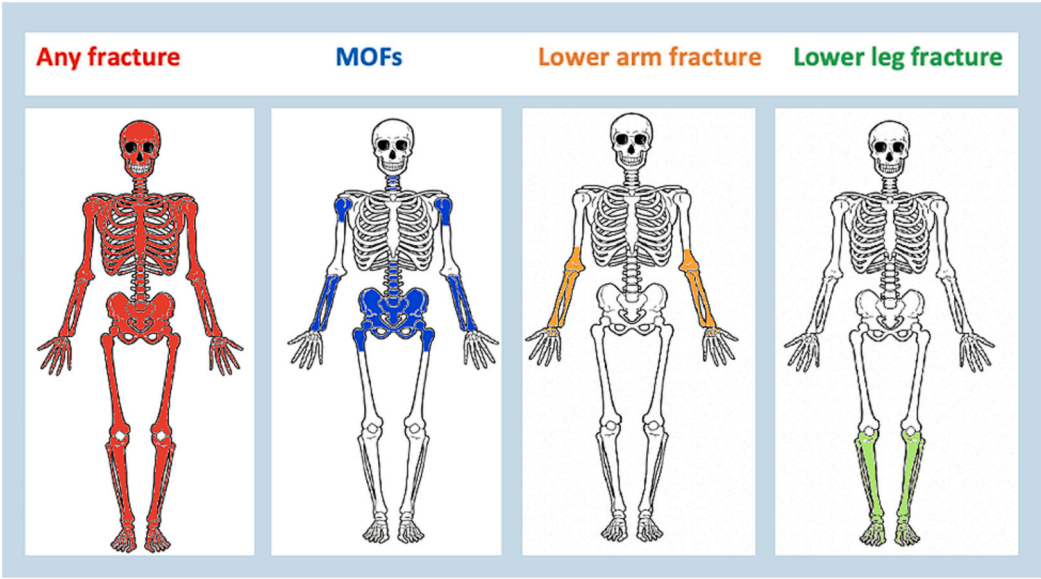
4.1. Fracture risk in pediatric and early adulthood T1D

People with T1D exhibited a higher absolute risk of fractures compared to those without T1D. Additionally, there were higher sex-adjusted fracture risks for all sites except for MOFs, where the risk showed a non-significant increase in the fully adjusted analysis. In comparison, there are numerous studies on adult T1D, but only a few focus on fracture risk in pediatric and early adulthood T1D. A study by Weber et al. also revealed an increased risk of fracture in the 0–19 years age group, with hazard ratios of 1.14 (1.01–1.29) for boys and 1.35 (1.12–1.62) for girls, compared to controls [21]. These findings align with ours, suggesting an early occurrence of fracture incidence in people with pediatric and early adulthood T1D.

Weber et al. also examined fracture risk across all age groups and identified a peak at 10 years of age in T1D [21]. A similar study by Eckert et al., comparing people with T1D under 25 years who had experienced fractures to those without fractures, found the peak age for

fractures in T1D to be 7 to <15 years for boys and 9 to <11 years for girls [8]. These findings align with our study, showing a mean age of 10 years in T1D. Interestingly, in the general population, the fracture incidence rate increases from birth, peaking between the ages of 10–14 years during puberty [22]. Therefore, the highest fracture risk in this age-groups of T1D appears to occur at a younger age than in the general population. However, this fracture peak also correlates with the time when most people are diagnosed with T1D in childhood. Thus, the higher fracture risk at a younger age is more likely associated with an imminent risk at the time of T1D diagnosis due to factors like more episodes of hypoglycemia and ketoacidosis. This is supported by our results, indicating that the years 0–4 have the highest HRs of fractures for all sites, followed by a decline or normalization for some years. However, we cannot determine if being diagnosed with T1D in childhood is associated with an even higher risk of fractures later in adulthood compared to a later-life diagnosis. Nonetheless, other studies on pediatric and early adulthood T1D have found that BMD is associated with abnormal bone development, decreased peak bone mass, and decreased bone markers [23,24], suggesting a potential increased fracture risk later in life. Despite this, a higher fracture risk close to the time of diagnosis is observed across all age groups with T1D and is linked to the initiation of insulin treatment and more frequent episodes of hypoglycemia and ketoacidosis [25,26]. Therefore, we hypothesize an initial risk imminent risk of fractures followed by a subsequent reduction, with the possibility of an increase in later years due to the accumulation of complications and other factors.

Moreover, the two previously mentioned studies revealed that people with fractures exhibited higher HbA1c levels and encountered more severe hypoglycemia episodes. Consistent with our study results, episodes of hypoglycemia were linked to any fracture and lower-leg fractures, although HbA1c levels were not obtainable. In our cohort, people with T1D had a lower baseline BMI compared to the control group. This observation is likely linked to the weight loss typically observed leading up to the diagnosis of T1D. However, it's crucial to note that caution is necessary in interpreting these findings due to the high prevalence of missing BMI values in both groups.



**Fig. 2.** Fracture localizations  
Fracture localizations: Any fracture was defined as all fracture types. Major osteoporotic fractures (MOF) were vertebrae, hip, humerus, ulna or radius fractures. Lower arm fractures included carpal, radius, ulna, or proximal humerus. Lower leg fractures were tibia, fibula, ankle or foot fractures.



**Table 1**

Person characteristics at baseline.

	T1D (n = 3100)	Controls (n = 3100)
<b>Demographics</b>		
Mean follow-up time (years, SD)	6.6 (5.0)	6.3 (4.8)
Girls (%)	1370 (44.2)	1370 (44.2)
Mean age (years, SD)	10.7 (4.4)	10.7 (4.4)
Mean BMI (kg/m <sup>2</sup> ,SD)	20.9 (5.0)	22.7 (6.9)
Missing (%)	664 (21.4)	2064 (66.6)
<b>Smoking status</b>		
Never (n, %)	1724 (55.6)	1215 (39.2)
Past (n, %)	50 (1.6)	56 (1.8)
Current (n, %)	241 (7.8)	243 (7.8)
Missing (n, %)	1085 (35.0)	1586 (51.2)
<b>Current Alcohol use within 6 months</b>		
Alcohol use, NO (n, %)	465 (15.0)	208 (6.7)
Alcohol use, YES (n, %)	576 (18.6)	308 (9.9)
Missing (n, %)	2059 (66.4)	2584 (83.4)
<b>Diabetes associated complications</b>		
<b>Microvascular complications</b>		
Neuropathy (n, %)	0 (0.0)	0 (0.0)
Nephropathy (n, %)	<6 (0.1)	0 (0.0)
Retinopathy (n, %)	7 (0.2)	0 (0.0)
<b>Other:</b>		
CVD (n, %)	<6 (0.1)	<6 (0.1)
Hypoglycemic event (n, %)	31 (1.0)	<6 (0.0)
Hypoglycemic event referral to hospital (n, %)	<6 (0.1)	<6 (0.0)
<b>Co-morbidities</b>		
Charlson comorbidity index (excluding diabetes co-complications) (n, %)		
0	2504 (80.8)	2502 (80.7)
1–2	590 (19.0)	591 (19.1)
3–4	<6 (0.1)	7 (0.2)
≥ 5	<6 (0.1)	0 (0.0)
Falls - >6 months before index date (n, %)	138 (4.5)	115 (3.7)
Previous fractures (n, %)	430 (13.9)	375 (12.1)
<b>Medication (last 6 months)</b>		
Anti-psychotics (n, %)	<6 (0.1)	<6 (0.1)
Anxiolytics/hypnotics (n, %)	13 (0.4)	10 (0.3)
Anti-depressants (n, %)	9 (0.3)	17 (0.5)
Anti-convulsant (n, %)	19 (0.6)	11 (0.4)
Oral glucocorticoids (n, %)	35 (1.1)	38 (1.2)
<b>Bone medications (6 months before index date)</b>		
Bisphosphonates (n, %)	0 (0.0)	0 (0.0)
Calcium / vit D (n, %)	14 (0.5)	<6 (0.1)
Strontium (n, %)	0 (0.0)	0 (0.0)
PTH/calcitonin (n, %)	0 (0.0)	0 (0.0)
Raloxifene (n, %)	0 (0.0)	0 (0.0)

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

N < 6: Anonymized data when observations are below 6.

#### 4.2. Associated risk factors for fractures at different sites in pediatric and early adulthood T1D

The fracture risk in T1D showed a statistically significant increase for all sites except MOFs in the sex and age-adjusted analyses, but these associations disappeared in the fully adjusted models. These findings suggest a higher risk, likely associated with specific risk factors for fractures in T1D. The most prevalent and consistent factors were a previous fracture, followed by a previous fall more than six months ago. It is well-established in the general population that there is a high imminent fracture risk following a previous incident [27]. Falls have also been previously associated with fractures in diabetes [28]. Childhood osteoporosis is rare and often linked to other diseases, and osteoporotic fractures were not expected to be increased in T1D or controls. Alcohol use at the index date was registered as twice as high in the T1D group. Although alcohol use is typically associated with an increased fall risk, this study did not find a significant association, considering missing

values.

Other risk factors included being a boy (associated with any and lower-arm fractures), hypoglycemia (associated with any and lower-leg fractures), and anxiolytics (associated with any fracture). Notably, no factors were found to be fracture protective (except being a girl). In general, around 33 % of children experience a bone fracture before reaching 17 years of age. The risk of fractures varies between sexes, with girls having a range of 27 % to 40 % and boys having a range of 42 % to 64 % [29,30]. Most childhood fractures occur during play and sports activities and are typically caused by mild to moderate trauma, rather than severe incidents, usually associated with lower-arm fractures. Episodes of hypoglycemia and initiating treatment with insulin are likely correlated with falls and fractures due to lipotomies, confirming the aforementioned statement. Anxiolytic medication increased the risk of any fractures [6]. Explanations for this lie within CNS-affectations and derivative effects like falls and lipotomies [31].

#### 4.3. Sensitivity analyses

The sensitivity analysis uncovered a heightened risk of any fractures at T1D onset, followed by a subsequent decrease in the overall fracture risk compared to the control group. This contrasts with findings from other studies that have reported a continuous increase over time [32]. However, given the relatively short mean follow-up time in our cohort at just 6.6 years, we cannot rule out the possibility of an elevated risk later in adulthood. Therefore, further extensive investigations are necessary to evaluate the risk beyond the initial years of diagnosis. Diabetic complications were infrequent at the time of diagnosis but escalated the fracture risk with the presence of one complication. Tests of trend revealed a significant association with complications and T1D but no associations with duration.

#### 4.4. Strengths

This study showcased several notable strengths in evaluating fracture risk and identifying associated factors in pediatric and early adulthood T1D. Firstly, the utilization of a large study cohort from the CPRD GOLD database allowed for population-based hazard ratio estimations, thorough analysis of fracture patterns, and the identification of various risk factors through multiple analyses. Secondly, the inclusion of younger people with T1D at the time of their diagnosis enabled the examination of fracture patterns in newly treated and healthy T1D cases. Thirdly, the matched control group represented the general population, providing a robust foundation for risk estimations and categorizations. Lastly, the study encompassed people with T1D diagnosed over an extensive period, from January 1, 1987, until December 31, 2017, ensuring consistency in insulin treatment and minimizing potential misclassification or miscoding. This consistency throughout the study duration enhanced comparability among the study participants.

#### 4.5. Limitations

This study has certain limitations that warrant consideration. Although the CPRD data has demonstrated high validity in capturing hip and vertebral fractures, it is important to recognize specific constraints. The data relies on Read codes, thus lacking information regarding biochemistry as HbA1c and the specific origin of fracture like trauma, accidental, osteoporotic etc. Furthermore, this study did not include data on spontaneous or asymptomatic vertebral fractures and there was no information available on BMD or the assessment of bone quality. Moreover, the study's follow-up duration was limited, and the small number of people with T1D for >4 years, especially beyond 10 years, restricts the ability to establish correlations between fractures and the duration of diabetes. Missing data was more noticeable in the control group, likely due to incomplete data collection. This disparity may arise because demographic measures, standard in T1D disease evaluation, are

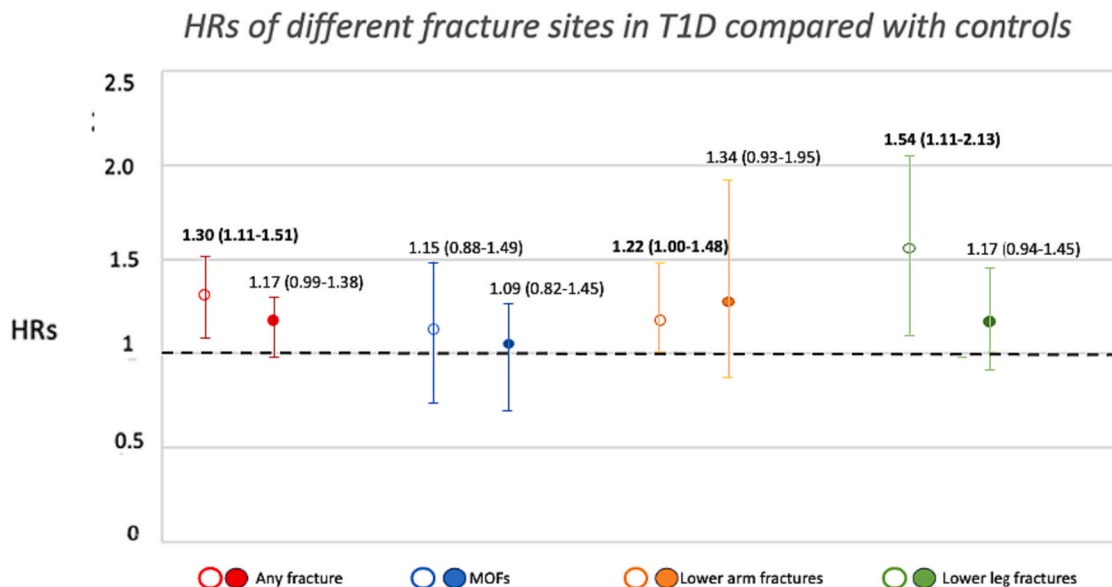
**Table 2**  
Fracture incidences and percent.

	Any fracture		MOFs		Lower arm fracture		Lower leg fracture	
Groups:	n (%)	IR / 1000 PY	n (%)	IR / 1000 PY	n (%)	IR / 1000 PY	n (%)	IR / 1000 PY
All								
T1D	383 (12.3)	20.6	120 (3.8)	6.0	228 (7.3)	11.8	94 (3.0)	4.6
Controls	286 (9.2)	16.0	101 (3.2)	5.4	180 (5.8)	3.0	58 (1.8)	9.8
T1D by girls and boys								
Girls	121 (3.9)	14.4	42 (1.3)	4.8	67 (2.1)	7.7	37 (1.1)	4.2
Boys	262 (8.5)	25.9	78 (2.5)	7.0	161 (5.1)	15.1	57 (1.8)	5.1
T1D by complications								
0	322 (10.4)	20.4	108 (3.4)	6.5	180 (5.8)	12.2	73 (2.3)	4.3
1	53 (1.7)	22.8	11 (0.3)	4.1	26 (0.8)	10.1	19 (0.6)	7.0
2	8 (0.2)	20.5	<6 (0.1)	2.0	<6 (0.1)	6.3	<6 (0.1)	4.2
T1D by duration								
0-4 years	244 (7.8)	21.4	88 (2.8)	7.5	158 (5.8)	13.6	38 (1.2)	3.2
5-9 years	106 (3.4)	21.4	26 (0.8)	4.8	51 (1.6)	9.7	45 (1.4)	8.1
<10 years	33 (1.0)	15.3	6 (0.1)	2.3	19 (0.6)	7.6	11 (0.3)	4.2

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.

N < 6: Anonymized data when observations are below 6.



**Fig. 3.** <sup>1</sup>Empty circle: Adjusted for sex and age.

<sup>2</sup>Full circle: Fully adjusted for: Sex, age, most recent Charlson Comorbidity index, history of neuropathy, retinopathy, nephropathy, hypoglycemia, falls, fractures, medication (glucocorticoids, anticonvulsive, anti-hypertensives, antidepressants, anxiolytics, antipsychotics, antidepressants, bone medication and lipid lowering medications) in the previous 6 months and alcohol use.

\*Bold indicates significant level ( $p < 0.05$ ).

Abbreviations: HRs: Hazard Ratios. T1D: Type 1 Diabetes Mellitus. CI: Confidence interval. MOFs: Major osteoporotic fracture.

not necessarily as comprehensively documented in control subjects. Nevertheless, this only underestimate the study results. Despite these limitations, the data suggests that risk factors largely contribute to the occurrence of fractures. It is important to interpret the findings while keeping these limitations in mind, as they may impact the generalizability and comprehensiveness of the results. Future research should address study limitations, incorporating additional data sources, biochemistry like HbA1c, and assessments of BMD and evaluations of bone quality.

## 5. Conclusion

This study is one of the first to delve into fracture risks and associated factors in pediatric and early adulthood T1D, providing valuable insights. Unlike in adult T1D, findings suggest no overall increase in fracture risk in pediatric and early adulthood T1D. Identified risk factors in the diabetes cohort include previous fractures, falls, medication, sex (boys), and diabetes-related factors like hypoglycemia and complications, associated with varying risks at different sites. Given the generally high fracture risk in children, early consideration and identification of risk factors in T1D are crucial for risk reduction. A focused approach could highlight insulin administration, specific medications like

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

Co-variables:	Any fracture	MOFs	Lower arm fracture	Lower leg fracture
	HR (CI95%)	HR (CI95%)	HR (CI95%)	HR (CI95%)
Demographics				
Sex (boy as ref.)	<b>0.78 (0.67 – 0.90)</b>	1.15 (0.89 – 1.49)	<b>0.51 (0.38 – 0.68)</b>	0.87 (0.57 – 1.33)
Age	1.00 (0.99 – 1.00)	<b>1.01 (1.00 – 1.02)</b>	<b>0.97 (0.94 – 0.99)</b>	1.01 (0.97 – 1.06)
Alcohol yes	1.11 (0.91 – 1.36)	1.04 (0.73 – 1.47)	1.18 (0.78 – 1.80)	1.10 (0.60 – 2.01)
Alcohol missing	<b>1.39 (1.11 – 1.75)</b>	<b>2.10 (1.41 – 3.14)</b>	1.26 (0.85 – 1.85)	1.28 (0.70 – 2.33)
Diabetes associated complications				
Neuropathy	1.17 (0.73 – 1.86)	1.03 (0.47 – 2.26)	0.00 (0.00 – 0.00)	0.00 (0.00 – 0.00)
Retinopathy	1.19 (0.98 – 1.45)	1.07 (0.77 – 1.49)	0.72 (0.42 – 1.24)	0.90 (0.48 – 1.68)
Nephropathy	0.96 (0.76 – 1.21)	0.87 (0.59 – 1.27)	1.17 (0.69 – 1.99)	0.97 (0.47 – 2.01)
Hypoglycemia	<b>1.46 (1.21 – 1.77)</b>	1.14 (0.82 – 1.60)	1.29 (0.90 – 1.86)	<b>2.34 (1.47 – 3.75)</b>
Co-morbidities				
CCI (1-2, CCI 0 as ref)	1.13 (0.96 – 1.33)	1.13 (0.85 – 1.50)	1.14 (0.84 – 1.56)	1.26 (0.79 – 2.00)
CCI (3-5, CCI 0 as ref)	1.42 (0.90 – 2.25)	1.17 (0.58 – 2.38)	2.93 (0.36 – 23.59)	0.00 (0.00 – 0.00)
Others				
Previous falls more than 6 months ago	<b>1.54 (1.20 – 1.97)</b>	1.45 (0.97 – 2.18)	1.39 (0.88 – 2.20)	0.50 (0.18 – 1.38)
Previous fractures	<b>2.00 (1.70 – 2.36)</b>	<b>1.89 (1.44 – 2.48)</b>	<b>2.08 (1.53 – 2.82)</b>	<b>2.08 (1.34 – 3.23)</b>
Medication				
Antipsychotics	1.31 (0.74 – 2.32)	1.62 (0.68 – 3.84)	2.70 (0.60 – 12.19)	0.00 (0.00 – 0.00)
Antihypertensives	0.95 (0.74 – 1.21)	1.26 (0.86 – 1.87)	0.50 (0.12 – 2.14)	0.33 (0.04 – 2.62)
Anticonvulsive	1.16 (0.80 – 1.67)	1.31 (0.74 – 2.33)	1.15 (0.39 – 3.36)	0.00 (0.00 – 0.00)
Antidepressants	1.26 (0.99 – 1.62)	1.08 (0.71 – 1.63)	1.23 (0.52 – 2.88)	2.28 (0.98 – 5.30)
Anxiolytics	<b>1.52 (1.10 – 2.11)</b>	1.35 (0.78 – 2.33)	0.71 (0.17 – 3.00)	0.64 (0.08 – 4.82)
Bone medication <sup>1</sup>	<b>1.50 (1.00 – 2.25)</b>	<b>2.54 (1.50 – 4.30)</b>	1.32 (0.31 – 5.57)	0.00 (0.00 – 0.00)
Lipid lowering drugs	0.85 (0.67 – 1.07)	0.72 (0.49 – 1.07)	0.00 (0.00 – 0.00)	1.64 (0.37 – 7.24)

Multivariate analysis adjusted for sex, age, diabetic complications, Co-morbidities, and medication showing HRs for each fracture site in the T1D cohort.

\*Bold indicates significant level ( $p < 0.05$ ).

Abbreviations: CCI: Charlson Comorbidity Index level. HR: Hazard Ratios. T1D: Type 1 Diabetes. CI: Confidence Interval.

<sup>1</sup>Bone medication: Alendronates. Calcium and D-vitamin. PTH-analogues and Denosumab.

anxiolytics, and their absolute necessity. Treating T1D at the highest standard is emphasized to prevent complications, and awareness of fracture risk due to insulin administration may prompt reconsideration of overly strict treatment regimens. Finally, sensitivity analyses hint at a decline in fracture risk over time, necessitating further long-term investigations beyond initial diagnosis years. Overall, this study contributes to the existing literature on fracture risk in T1D, underscoring the need for preventive measures and interventions in this vulnerable population.

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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.

## Code availability

The code is not available.

## CRediT authorship contribution statement

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

## 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.

**Table 4**

Sensitivity analyses of pediatric T1D by diabetes duration and presence of diabetic complications.

Fracture sites	Any fracture	MOFs	Lower-arm fracture	Lower-leg fracture
	HR (CI95%)	HR (CI95%)	HR (CI95%)	HR (CI95%)
No T1D	Reference	Reference	Reference	Reference
<b>T1D by diabetes duration<sup>1</sup></b>				
0–4 years	<b>1.20 (1.00–1.44)</b>	1.13 (0.83–1.53)	1.23 (0.98–1.55)	1.09 (0.71–1.69)
5–9 years	1.17 (0.91–1.50)	0.99 (0.61–1.59)	1.00 (0.71–1.41)	<b>2.08 (1.32–3.26)</b>
10 or more years	0.83 (0.54–1.27)	0.76 (0.30–1.93)	0.98 (0.56–1.72)	0.79 (0.35–1.76)
<b>T1D by presence of complications<sup>2</sup></b>				
0 complications	1.17 (0.99–1.39)*	1.09 (0.81–1.45)	1.17 (0.94–1.45)	1.34 (0.92–1.94)
1 complication	<b>1.42 (1.04–1.95)*</b>	1.04 (0.54–2.02)	1.16 (0.75–1.80)	1.53 (0.86–2.74)
2 ≥ complications	1.56 (0.76–3.22)*	0.80 (0.11–5.93)	1.04 (0.32–3.35)	0.93 (0.21–4.02)

Multivariate analyses yielding HRs of fractures sites in people with T1DM by diabetes duration<sup>1</sup> or diabetic complications<sup>2</sup>, reference was no T1D and the T1D group was stratified by duration / presence of complications respectively.

<sup>1</sup>Adjusted for: Sex, age, Charlson Comorbidity index, neuropathy, retinopathy, nephropathy, hypoglycemia, previous falls, previous fractures, medication (glucocorticoids, anticonvulsive, antidepressants, anti-hypertensives, anxiolytics, antipsychotics, antidepressants, bone medication and lipid lowering medications) and alcohol use.

<sup>1,2</sup>Adjusted for: Sex, age, Charlson Comorbidity index, hypoglycemia, previous falls, previous fractures, medication (glucocorticoids, anticonvulsive, antidepressants, anxiolytics, antipsychotics, anti-hypertensives, antidepressants, bone medication and lipid lowering medications) and alcohol use.

\*Significant P-value ( $p < 0.05$ ) for test of trends between groups.

Bold indicates significant HRs ( $p < 0.05$ ).

Abbreviations: Hazard Ratios, T1D: Type 1 Diabetes Meletus, CI: Confidence inter, Bone medication: Alendronates, Calcium and D-vitamin, PTH-analogues and Denosumab, IR: Incidence rates, PY: Person years.

## Declaration of competing interest

Peter Vestergaard is head of research in the Steno Diabetes Center North Denmark sponsored by the Novo Nordisk Foundation. Joop van den Bergh: unrestricted research grant and lecture fee from Amgen and UCB, is consultant for PoroUS. Nicklas H. Rasmussen holds shares in Novo Nordisk, has lecture fees from Boehringer Ingelheim and travel expenses from UCB. The other authors Johanna Driessen, Patrick Souverein and Annika Kvist declare that they have no conflict of interest.

## Data availability

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.

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