Differences in the roles of types 1 and 2 diabetes in the susceptibility to the risk of fracture: A systematic review and meta-analysis

Jiaqing Dou
The First Affiliated Hospital of Anhui Medical University

Jing Wang
The First Affiliated Hospital of Anhui Medical University

Qiu Zhang (✉ djqwhyy@163.com)
The First Affiliated Hospital of Anhui Medical University

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Abstract

Background: Diabetes mellitus (DM) causes excess risk of fracture at varied sites. Whereas, the difference between the roles of types 1 DM (T1DM) and 2 DM (T2DM) diabetes in the risk of fractures remains limited and inconclusive. We, therefore, conducted a meta-analysis to assess the differences for the associations of T1DM and T2DM with the risk of fractures.

Methods: We systematically searched PubMed, Embase, and the Cochrane library for eligible studies until May 2021. The odds ratios (ORs) with 95% confidence intervals (CIs) were used to calculate the pooled effect estimates for the associations of T1DM and T2DM with the risk of fractures using the random-effects model. An indirect comparison results for the ratio of OR (ROR) with 95% CI were also applied to assess the difference between T1DM and T2DM with the risk of fractures.

Results: Twenty-two cohort studies involving a total of 6,484,851 individuals were selected for meta-analysis. We noted that T1DM was associated with an increased risk of all fractures (OR: 1.72; 95% CI: 1.36–2.19; P < 0.001), and fractures at the hip (OR: 4.01; 95% CI: 2.90–5.54; P < 0.001), upper arm (OR: 2.20; 95% CI: 1.61–3.00; P < 0.001), and ankle (OR: 1.97; 95% CI: 1.24–3.14; P = 0.004), and vertebrae (OR: 2.18; 95% CI: 1.85–2.57; P < 0.001). Moreover, T2DM induced excess risk to all fractures (OR: 1.19; 95% CI: 1.09–1.31; P < 0.001), including fractures at the hip (OR: 1.25; 95% CI: 1.15–1.35; P < 0.001), upper arm (OR: 1.42; 95% CI: 1.20–1.67; P < 0.001), and ankle (OR: 1.15; 95% CI: 1.01–1.31; P = 0.029). Furthermore, we noted that T1DM versus T2DM was associated with greater risk to all fractures (ROR: 1.45; 95% CI: 1.12–1.87; P = 0.005), including fractures at the hip (ROR: 3.21; 95% CI: 2.30–4.48; P < 0.001), upper arm (ROR: 1.55; 95% CI: 1.09–2.20; P = 0.015), and ankle (ROR: 1.71; 95% CI: 1.06–2.78; P = 0.029).

Conclusions: This study found that T1DM caused an excess risk to all fractures, including fractures at the hip, upper arm, and ankle than T2DM. Further studies should therefore be conducted to directly compare the differences between T1DM and T2DM with the risk of fractures at various sites.

Background

The prevalence of diabetes has increased from 4.7%–8.5% worldwide, directly resulting in approximately 1.6 million deaths in 2016 [1]. The inadequate control of diabetes affects the patient's quality of life through diabetes-specific symptoms and microvascular complications [2, 3]. Diabetes and its complications are also considered a global burden, therefore, reducing the disease burden of diabetes is an important goal of medical care societies and health policymakers [4, 5]. Patients with diabetes are susceptible to excess risk of cardiovascular disease, neuropathy, nephropathy, retinopathy, and mortality [6]. Moreover, the rapidly increasing diabetes prevalence was also parallel with an increase in osteoporotic fractures [7].

Numerous studies have found a positive association of diabetes with the risk of fractures [8-14], and the potential reason for the association between diabetes and fractures included increased frequency of falling, cortical porosity, microvascular disease, and high levels of advanced glycation end-products [15-17]. The National Osteoporosis Foundation guidelines, therefore, suggested that screening for osteoporosis should be conducted for general women aged ≥65 years and men aged ≥70 years to prevent the morbidity and mortality related to fractures [18]. However, the strength of the association of type 1 diabetes mellitus (T1DM) and type 2 DM (T2DM) with the risk of fractures remains controversial. We, therefore, conducted a systematic review and meta-analysis of cohort studies to assess the differences between the associations of T1DM and T2DM with the risk of fracture at various sites. Moreover, whether study design and gender affected this difference was also evaluated.

Methods

Data Sources, Search Strategy, and Selection Criteria

The Meta-analysis Of Observational Studies in Epidemiology protocol was used to conduct and report this systematic review and meta-analysis [19]. On the basis of this protocol, cohort studies that investigated the role of T1DM or T2DM with the risk of fractures were eligible in our study. The databases of PubMed, Embase, and the Cochrane library were eligible studies from their inception up to May 2021. The following terms were used as medical subject headings or text words: (“diabetes” OR “diabetes mellitus” OR “glucose” OR “glycated hemoglobin”) AND (“fractures, spontaneous” OR “osteoporotic fractures” OR “fractures, compression” OR “fracture”). The reference lists of potentially relevant articles were also manually reviewed for additional new eligible studies.

The literature search and study selection were conducted independently by 2 reviewers, and face-to-face discussions were used to settle disagreements until a consensus was reached. A study was included if they fulfilled the following inclusion criteria: (1) Study design: prospective or retrospective cohort studies; (2) Participants: general population; (3) Exposure and control: T1DM, T2DM, and non-DM population; (4) Outcome: all fracture, or fractures at hip, distal forearm, upper arm, ankle, and vertebrae; and (5) all the studies should have reported the effect estimates for the role of T1DM or T2DM with the risk of fractures. This study did not contain any human or life participants, therefore, ethics approval and informed consent were not applicable.

Data Collection and Quality Assessment

Information from included studies contained the first author or study group's name, publication year, region, study design, sample size and number of DM, mean age, male proportion, smoking proportion, body mass index (BMI), DM type, follow-up duration, adjusted factors, and reported effect estimates. The quality of the individual studies were also assessed using the Newcastle–Ottawa Scale (NOS), which is widely used for assessing the quality of observational studies in a meta-analysis. The scoring system for each study ranged from 0–9 [20]. Studies having between 7 and 9 stars were regarded as high-quality. Data
Statistical Analysis

The role of T1DM and T2DM in the risk of fractures was calculated based on the effect estimates (relative risk, hazard ratio, or odds ratio [OR]) using the 95% confidence intervals (CIs) in individual studies. The pooled OR was also calculated using the random-effects models, which considered the underlying variations across included studies [21, 22]. Then, the OR ratio (ROR) with a 95% CI was estimated on the basis of specific ORs, and 95% CIs were taken for T1DM and T2DM studies having risk of fractures [23]. Heterogeneity for each investigated outcome was also assessed using the $I^2$ and Q statistic, and significant heterogeneity was defined as $I^2 > 50.0\%$ or $P < 0.10$ [24, 25]. Subgroup analyses for the differences of T1DM and T2DM with the risk of fractures were also assessed on the basis of the study design, and gender. Similarly, publication bias was evaluated as well using qualitative and quantitative methods, including funnel plots, Egger, and Begg tests [26, 27]. The 2-sided inspection level for pooled results was adopted, and statistical significance was set at $P < 0.05$. Also, all the analyses in our study were performed using the STATA (version 10.0; STATA Corporation, College Station, TX, USA) software.

Results

Literature Search

A total of 9,873 articles were identified from initial electronic searches, and 5,621 articles were retained after duplicate articles were removed. A total of 5,527 articles were further removed because these studies reported irrelevant topics. The remaining 94 studies were then retrieved for further full-text evaluations. Of these 94 remaining studies, 72 of them were excluded because they were intervention studies ($n = 34$); not cohort designs ($n = 23$); and did not differentiate DM types ($n = 15$). Reviewing the references of relevant articles found additional 14 potentially included studies, including all studies contained in electronic searches. Finally, 22 cohort studies were selected for the final meta-analysis [28-49] (Figure 1).

Study Characteristics

Of the 22 included studies, 14 studies were prospective cohort studies, whereas the remaining 8 studies were retrospective cohort studies. The characteristics of identified studies and individuals are shown in Table 1. A total of 6,484,851 individuals and 766,610 patients with DM were identified from the 22 studies. Nine studies reported the role of T1DM with the risk of fractures, and 20 studies reported the role of T2DM with the risk of fractures. The follow-up duration ranged from 1.3 to 20.0 years. Also, 9 studies contained only females. Similarly, study quality assessment using the NOS-scoring method showed that 3 studies had 9 stars, 7 studies had 8 stars, 8 studies had 7 stars, and the remaining 4 studies had 6 stars.

All Fracture

The studies assessing the role of T1DM and T2DM in the risk of all fractures were reported in studies 4 and 12 studies, respectively (Figure 2). We noted that both T1DM (OR: 1.72; 95%CI: 1.36–2.19; $P < 0.001$) and T2DM (OR: 1.19; 95% CI: 1.09–1.31; $P < 0.001$) were associated with an increased risk of all fractures. Moreover, there was a significant heterogeneity in the role of T1DM ($I^2 = 97.8\%; P < 0.001$) and T2DM ($I^2 = 94.3\%; P < 0.001$). We also noted from the selected studies that the risk of all fractures in T1DM patients was significantly higher than in T2DM patients (ROR: 1.45; 95% CI: 1.12–1.87; $P = 0.005$; Table 2). Similarly, subgroup analyses found that excess risk of fractures in T1DM patients existed during pooled prospective cohort studies (ROR: 1.21; 95% CI: 1.00–1.46; $P = 0.050$), retrospective cohort studies (ROR: 1.56; 95%CI: 1.09–2.24; $P = 0.015$), or studies that reported both male and female (ROR: 1.99; 95% CI: 1.40–2.83; $P < 0.001$) (Table 3). Also, no significant publication bias for all fractures was observed ($P$-value for Egger: 0.075; $P$-value for Begg: 0.535; Additional file 1).

Hip Fracture

The studies that reported the role of T1DM and T2DM in hip fracture risk were studies 9 and 19, respectively (Figure 3). The summarized results indicated that T1DM (OR: 4.01; 95%CI: 2.90–5.54; $P < 0.001$) and T2DM (OR: 1.25; 95% CI: 1.15–1.35; $P < 0.001$) were associated with an increased risk of hip fracture. Also, there was a significant heterogeneity in the reports for the role of T1DM ($I^2 = 95.2\%; P < 0.001$) and T2DM ($I^2 = 86.7\%; P < 0.001$) in these fractures. Patients with T1DM were associated with excessive risk of hip fracture than those with T2DM (ROR: 3.21; 95% CI: 2.30–4.48; $P < 0.001$; Table 2). Also, subgroup analyses found that a significant difference between T1DM and T2DM was associated with the risk of hip fracture in all subgroups (Table 3). In contrast, the Begg test did not find any significant publication bias for hip fracture ($P = 0.856$), while the Egger-test found significant publication bias ($P < 0.001$) (Additional file 1).

Distal Forearm Fracture

The studies that reported the role of T1DM and T2DM in distal forearm fracture risk were studies 2 and 9, respectively (Figure 4). We noted that T1DM (OR: 1.39; 95%CI: 0.70–2.77; $P = 0.344$) and T2DM (OR: 0.94; 95% CI: 0.82–1.07; $P = 0.348$) were not associated with the risk of distal forearm fracture. However, there was significant heterogeneity in the role of T1DM ($I^2 = 86.7\%; P = 0.001$) and T2DM ($I^2 = 58.8\%; P = 0.007$) in this fracture. Also, the risk of distal forearm
fracture in relation to T1DM and T2DM was not statistically significant (ROR: 1.48; 95%CI: 0.73–2.98; P = 0.274; Table 2). Similarly, no significant publication bias to distal forearm fractures was observed (P-value for Egger: 0.358; P-value for Begg: 0.584; Additional file 1).

Upper Arm Fracture

The studies that reported the role of T1DM and T2DM in upper arm fracture risk were studies 2 and 7, respectively (Figure 5). A summary of the results indicated that T1DM (OR: 2.20; 95%CI: 1.61–3.00; P < 0.001) and T2DM (OR: 1.42; 95%CI: 1.20–1.67; P < 0.001) were associated with an increased risk of upper arm fracture. Significant heterogeneity was also observed for the role of T1DM (I² = 72.6%; P = 0.026) and T2DM (I² = 81.2%; P < 0.001). From the results, T1DM patients showed an excessive risk of upper arm fracture than T2DM patients (ROR: 1.55; 95%CI: 1.09–2.20; P = 0.015, Table 2). However, there was no significant publication bias to upper arm fracture (P-value for Egger: 0.117; P-value for Begg: 0.837; Additional file 1).

Ankle Fracture

The studies that reported the role of T1DM and T2DM in ankle fracture risk were reported in studies 1 and 3, respectively (Figure 6). We noted that T1DM (OR: 1.97; 95%CI: 1.24–3.14; P = 0.004) and T2DM (OR: 1.15; 95%CI: 1.01–1.31; P = 0.029) was associated with an increased risk of ankle fracture. However, no significant heterogeneity was observed across included studies for the role of T1DM (I² = 29.3%; P = 0.234) and T2DM (I² = 0.0%; P = 0.886). Patients with T1DM were also associated with an increased risk of ankle fracture than those with T2DM (ROR: 1.71; 95%CI: 1.06–2.78; P = 0.029; Table 2). Similarly, no significant publication bias to ankle fracture was observed (P-value for Egger: 0.109; P-value for Begg: 0.060; Additional file 1).

Vertebrae Fracture

The studies that reported the role of T1DM and T2DM in vertebrae fracture risk were studies 1 and 8, respectively (Figure 7). We noted that T1DM was associated with an increased risk of vertebrae fracture (OR: 2.18; 95%CI: 1.85–2.57; P < 0.001), whereas no significant association of T2DM in vertebrae fracture risk (OR: 1.45; 95%CI: 0.82–2.56; P = 0.200) was observed. Also, no significant heterogeneity for the role of T2DM (I² = 98.5%; P < 0.001) was reported. Furthermore, the association between the risk of vertebrae fracture in T1DM and T2DM patients, respectively, was not statistically significant (ROR: 1.50; 95%CI: 0.83–2.72; P = 0.177, Table 2). Also, no significant publication bias existed in relation to vertebrae fracture (P-value for Egger: 0.267; P-value for Begg: 1.000; Additional file 1).

Discussion

This study compared the strengths of T1DM and T2DM roles in relation to the risk of fractures. A total of 6,484,851 individuals and 766,610 patients with DM from 22 cohort studies were identified in this comprehensive quantitative meta-analysis. This study found that T1DM was associated with an increased risk of all fractures, including fractures at the hip, upper arm, ankle, and vertebrae, whereas T2DM caused excess risk of all fractures, including fractures at the hip, upper arm, and ankle. Moreover, patients with T1DM were associated with an increased risk of all fractures, hip, upper arm, and ankle fractures than those with T2DM. Furthermore, significant differences in the risk of all fractures between patients having T1DM and T2DM were mainly observed in the subgroups of prospective cohort studies, retrospective cohort studies, or studies that reported both males and females. Finally, the risk of hip fracture in T1DM patients was significantly higher than in T2DM in all predefined subgroups.

A prior meta-analysis conducted by Vestergaard et al. found that T1DM and T2DM patients were associated with an increased risk of hip fracture. An increase in the relative risk of patients with T1DM was also observed to be significantly higher than those with T2DM. Moreover, bone mineral density was increased in patients with T2DM but decreased in patients with T1DM [50]. Janghorbani et al. conducted a meta-analysis based on 2 case-controls and 14 cohort studies and found similar conclusions. Previous studies have indicated that T2DM was weakly associated with fractures at other sites [51]. However, these studies focused on the risk of hip fracture between T1DM and T2DM patients, but did not compare the strength of T1DM and T2DM with the risk of fracture at various sites. Therefore, this study was conducted to update the knowledge about discrepancies in fracture risk between T1DM and T2DM patients.

From this study, it was also found both T1DM and T2DM patients were associated with an increased risk of fractures at most sites. Moreover, the risk of all fractures, including fractures at the hip, upper arm, and ankle in T1DM patients was significantly higher than in T2DM patients. This observation proposes a potential role of T1DM in skeletal fragility, including deficits in bone mineral density, bone geometry, bone microarchitecture, and biomechanical properties [52-54]. Furthermore, the role of T2DM in the risk of fracture is proposed to be because of lower levels of bone turnover markers with reduced bone formation [55, 56]. Additionally, patients with T1DM were associated with an increased risk of all fractures, hip, upper arm, and ankle fractures than those with T2DM. The potential reason for this observation is proposed to be that T2DM patients presented higher body weight and BMI than those with T1DM patients, while the fracture in T2DM patients was due to sustained higher traumatic load and soft-tissue energy absorption in obese patients [50]. Finally, the changes in body mineral density in T1DM and T2DM patients differed, which caused the observed varying fracture risk [51].

Subgroup analyses found significant differences that existed between T1DM and T2DM patients, resulting in the risk of all fractures, including hip fracture in most of the subgroups. The risk of all fractures between T1DM and T2DM patients were not also observed in the studies that focused on males and females. This observation is because of (1) the all-fracture risk between T1DM and T2DM that was balanced by fracture at other sites. Therefore, T1DM and T2DM did not affect the risk of distal forearm; (2) the imbalance characteristics between T1DM and T2DM patients, which affected the risk of fractures; and (3) the adjusted factors between T1DM and T2DM that differed, thereby affecting the risk of fracture.
The limitations of this study should be acknowledged. First, this study contained both prospective and retrospective cohort studies, and the selection or recall biases is proposed to be biases on the risk of fracture. Second, the difference between T1DM and T2DM associated with the risk of fractures at varied sites was based on indirect comparison evidence, and various adjusted factors resulted in the risk of fractures. Third, the role of T1DM in the risk of fracture was reported in a smaller number of included studies, and the power to detect potential differences affected the comparison results. Fourth, subgroup analyses were conducted based on study design and gender, but the differences based on other characteristics were not conducted. Fifth, the severity of DM was not addressed, which is proposed to play an important role in subsequent fracture risk. Finally, inherent limitations for meta-analysis of published articles, including inevitable publication bias and the restricted detailed analyses also posed a limitation to this study.

Conclusions
This study found that T1DM and T2DM induced excess risk of fractures at most sites. Moreover, T1DM patients were associated with an increased risk of all fractures, including fractures at the hip, upper arm, and ankle than T2DM patients. Further, large-scale prospective studies should thus be conducted to directly compare the differences between T1DM and T2DM patients with their risk of fracture at various sites.

Declarations

Ethics approval and consent to participate
This study did not contain any human participates, and the ethics approval and informed consent are not applicable.

Consent for publication
Not applicable

Availability of data and materials
All data generated or analysed during this study are included in this published article and its supplementary information files.

Competing interests
The authors declare that they have no competing interests.

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Authors' contributions
JQD and JW designed the study; JW and QZ did the literature collection; JQD, JW and QZ analysed the data; JQD and JW wrote the manuscript; QZ revised the manuscript. All authors read and approved the final manuscript.

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Abbreviations
DM=diabetes mellitus
T1DM=type 1 diabetes mellitus
T2DM=type 2 diabetes mellitus
OR=odds ratio
CI=confidence interval
ROR=ratio of odds ratio
NOF=National Osteoporosis Foundation
BMI=body mass index
NOS=Newcastle-Ottawa Scale

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Tables

Table 1. The characteristics of identified studies and involved participants
| Study      | Region | Study design | Sample size/DM | Mean age (years) | Male (%) | Smoker (%) | BMI (kg/m²) | DM type | Follow-up (years) | Adjusted factors                                                                 | NOS score |
|------------|--------|--------------|----------------|------------------|----------|------------|-------------|---------|------------------|--------------------------------------------------------------------------------|-----------|
| NTHS 1999  | Norway | Prospective  | 35,444/1,850   | 50.0-74.0        | 47.5     | 30.4       | NA          | I and II | 9.0              | Age, BMI and daily smoking                                                       | 8         |
| IWHS 2001  | USA    | Prospective  | 32,089/1,729   | 61.6             | 0.0       | 15.0       | 26.9        | I and II | 9.6              | Age, smoking, estrogen use, BMI, and WTHR                                       | 9         |
| BMES 2001  | Australia | Prospective | 3,654/216      | 66.2             | 43.3     | NA         | NA          | II      | 5.0              | Age, sex, and BMI                                                               | 7         |
| SOF 2001   | USA    | Prospective  | 9,754/657      | 71.0             | 0.0      | NA         | 26.2        | II      | 9.4              | Age, BMI, calcaneal BMD, height, height loss since age 25, contrast sensitivity, walking speed, consumed alcohol in past year, resting pulse, mother fractured hip, on feet < 4 h a day, use of long-acting benzodiazepines, and calcium intake | 9         |
| H-EPSE 2002| USA    | Prospective  | 2,884/690      | 71.8             | 42.1     | 42.1       | NA          | II      | 7.0              | Age, gender, BMI, ever smoked, previous stroke, lower extremity functional ability, and distance vision | 7         |
| SIR 2005   | Sweden | Retrospective | 24,605/24,605   | 20.7             | 51.0     | NA         | NA          | I       | 9.9              | Age, sex, and calendar-period-matched general population from the entire Swedish inpatient registry | 6         |
| Dobnig 2006| Australia | Prospective | 1,664/583      | > 70.0           | 0.0      | NA         | NA          | II      | 2.0              | Age and weight                                                                   | 6         |
| NHS 2006   | USA    | Prospective  | 109,983/8,640  | 56.3             | 0.0      | 17.9       | 26.0        | I and II | 20.0             | Age, BMI, physical activity, menopausal status and estrogen use, smoking and daily intake of calcium, vitamin D, and protein | 9         |
| Tromsø 2006| Norway | Prospective  | 27,159/455     | 47.0             | 47.7     | 37.0       | 25.5        | I and II | 6.0              | Age, BMI, smoking, and metabolic features                                       | 8         |
| WHI 2006   | USA    | Prospective  | 93,676/5,285   | 63.4             | 0.0      | 6.2        | NA          | II      | 7.0              | Age, ethnicity, weight, height, time-dependent history of falls, previous fracture, history of osteoporosis, trouble seeing at baseline, alcohol or tobacco use, calcium and vitamin D intake, exercise, bisphosphonate, estrogen, steroid, insulin, SERM, or thyroid hormone use | 8         |
| Melton 2008| USA    | Retrospective | 1,964/1,964     | 61.7             | 51.0     | NA         | NA          | II      | 11.8             | Age, BMI, calcaneal BMD,                                                         | 6         |
| Study | Country | Study Type | Sample Size | Age | Sex | Race | BMI | AAI | Fracture Risk Factors |
|-------|---------|------------|-------------|-----|-----|------|-----|-----|-----------------------|
| CHS 2011 | USA | Prospective | 5,641/1,456 | 72.8 | 42.0 | 12.0 | 26.7 | II | Age, sex, race, BMI, AAI<0.9 |
| Jung 2012 | Korea | Retrospective | 2,282/1,268 | 61.0 | 0.0 | NA | 25.0 | II | Age |
| Rotterdam 2013 | Netherlands | Prospective | 4,135/420 | 68.4 | 40.6 | 25.0 | 26.4 | II | Age, sex, height, weight, and femoral neck BMD |
| SIDIAP 2015 | Spain | Prospective | 171,931/58,483 | 62.6 | 56.5 | 15.6 | 29.3 | II | BMI, previous fracture, oral corticoids |
| THIN 2015 | UK | Retrospective | 334,266/30,394 | 34.0 | 56.1 | 26.7 | 25.5 | I | Exposure to steroid medication, history of prior fracture, and presence of chronic kidney disease |
| Manitoba 2016 | Canada | Retrospective | 57,938/8,840 | 64.3 | 0.0 | NA | 27.1 | II | FRAX scores, burden of comorbidity, falls, prescription osteoporosis treatments, and insulin therapy |
| FRAILCO 2017 | Sweden | Prospective | 428,305/84,702 | 80.8 | 42.4 | NA | 25.4 | I and II | Age, sex, weight, history, previous fracture, RA, glucocorticoid, alendronate use, and CCI, and self-reported known fall injury |
| Holm 2018 | Denmark | Retrospective | 6,285/229 | 61.1 | 0.0 | 28.0 | 23.4 | II | Baseline age group, BMI group, modified Charlson index, estrogen deficiency, prevalent hyperthyroidism, RA, CPD, MOF, former osteoporosis treatment, glucocorticoid use, calcium intake, family fracture history, current smoking, exercise alcohol related diagnoses and current use of ACE, ANGII, loop, thiazide, SSRI, TCA |
| DNPR 2019 | Denmark | Retrospective | 1,328,336/332,084 | 59.0 | 52.9 | NA | NA | I and II | Age, sex, previous fracture, anti-osteoporosis medication |
| PK-VF 2019 | China | Prospective | 982/186 | 62.0 | 0.0 | NA | 26.0 | II | Age, YSM, BMI, LS BMD, and any previous fractures |

or a host of other osteoporosis risk factors
Table 2. The difference for the role of T1DM and T2DM with the risk of fracture

| Fracture sites | DM type | OR and 95% CI     | P value | $\rho$ (%) / $P_{Q\text{ statistic}}$ | Ratio for OR | P value between T1DM and T2DM |
|----------------|---------|-------------------|---------|--------------------------------------|--------------|---------------------------------|
| All            | T1DM    | 1.72 (1.36-2.19)  | < 0.001 | 97.8 / <0.001                        | 1.45 (1.12-1.87) | 0.005                           |
|                | T2DM    | 1.19 (1.09-1.31)  | < 0.001 | 94.3 / <0.001                        | 1.45 (1.12-1.87) | 0.005                           |
| Hip            | T1DM    | 4.01 (2.90-5.54)  | < 0.001 | 95.2 / <0.001                        | 3.21 (2.30-4.48) | < 0.001                         |
|                | T2DM    | 1.25 (1.15-1.35)  | < 0.001 | 86.7 / <0.001                        | 1.31 (1.10-1.56) | 0.004                           |
| Distal forearm | T1DM    | 1.39 (0.70-2.77)  | 0.344   | 86.7 / 0.001                         | 1.48 (0.73-2.98) | 0.274                           |
|                | T2DM    | 0.94 (0.82-1.07)  | 0.348   | 85.8 / 0.007                         | 1.48 (0.73-2.98) | 0.274                           |
| Upper arm      | T1DM    | 2.20 (1.61-3.00)  | < 0.001 | 72.6 / 0.026                         | 1.55 (1.09-2.20) | 0.015                           |
|                | T2DM    | 1.42 (1.20-1.67)  | < 0.001 | 81.2 / <0.001                        | 1.55 (1.09-2.20) | 0.015                           |
| Ankle          | T1DM    | 1.97 (1.24-3.14)  | 0.004   | 29.3 / 0.234                         | 1.71 (1.06-2.78) | 0.029                           |
|                | T2DM    | 1.15 (1.01-1.31)  | 0.029   | 1.8 / 0.886                          | 1.71 (1.06-2.78) | 0.029                           |
| Vertebrae      | T1DM    | 2.18 (1.85-2.57)  | < 0.001 | -                                    | 1.50 (0.83-2.72) | 0.177                           |
|                | T2DM    | 1.45 (0.82-2.56)  | 0.200   | 98.5 / <0.001                        | 1.50 (0.83-2.72) | 0.177                           |

Table 3. Subgroup analyses for all fracture and hip fracture according to study design and gender
| Outcomes      | Factors          | Groups       | DM type | OR and 95% CI | P value | I² (%) / P_Q statistic | Ratio for OR | P value between T1DM and T2DM |
|---------------|------------------|--------------|---------|---------------|---------|------------------------|--------------|--------------------------------|
| All fracture  | Study design     | Prospective  | T1DM    | 1.40 (1.18-1.65) | < 0.001 | 50.6 / 0.108           | 1.21 (1.00-1.46) | 0.050                          |
|               |                  | T2DM         | 1.16 (1.07-1.27) | < 0.001 | 68.9 / 0.001           | 1.56 (1.09-2.24) | 0.015                          |
| All fracture  | Study design     | Retrospective| T1DM    | 1.86 (1.36-2.53) | < 0.001 | 99.0 / <0.001          | 1.25 (0.92-1.66) | 0.147                          |
|               |                  | T2DM         | 1.19 (0.99-1.43) | 0.060  | 96.6 / <0.001          |                |                                |
| Gender        | Male             | T1DM         | 1.50 (1.33-1.70) | < 0.001 | 51.2 / 0.129           | 1.25 (0.92-1.69) | 0.147                          |
| Gender        | Male             | T2DM         | 1.20 (0.91-1.58) | 0.200  | 93.0 / <0.001          |                |                                |
| Gender        | Female           | T1DM         | 1.52 (1.17-1.97) | 0.002  | 88.9 / <0.001          | 1.27 (0.97-1.66) | 0.085                          |
| Gender        | Female           | T2DM         | 1.20 (1.12-1.28) | < 0.001 | 54.2 / 0.026           |                |                                |
| Gender        | Both             | T1DM         | 2.47 (2.36-2.58) | < 0.001 | -                     | 1.99 (1.40-2.83) | < 0.001                        |
| Gender        | Both             | T2DM         | 1.24 (0.87-1.75) | 0.232  | 87.8 / <0.001          |                |                                |
| Hip fracture  | Study design     | Prospective  | T1DM    | 4.56 (2.49-8.34) | < 0.001 | 91.5 / <0.001          | 3.28 (1.76-6.10) | < 0.001                        |
| Hip fracture  | Study design     | T2DM         | 1.39 (1.21-1.60) | < 0.001 | 80.6 / <0.001          |                |                                |
| Hip fracture  | Study design     | Retrospective| T1DM    | 3.88 (2.68-5.61) | < 0.001 | 96.0 / <0.001          | 3.43 (2.35-5.03) | < 0.001                        |
| Hip fracture  | Study design     | T2DM         | 1.13 (1.03-1.24) | 0.010  | 89.3 / <0.001          |                |                                |
| Gender        | Male             | T1DM         | 3.95 (2.10-7.43) | < 0.001 | 95.7 / <0.001          | 3.95 (2.09-7.46) | < 0.001                        |
| Gender        | Male             | T2DM         | 1.00 (0.93-1.08) | 0.946  | 36.5 / 0.178           |                |                                |
| Gender        | Female           | T1DM         | 4.76 (2.66-8.52) | < 0.001 | 95.9 / <0.001          | 3.33 (1.83-6.05) | < 0.001                        |
| Gender        | Female           | T2DM         | 1.43 (1.25-1.64) | < 0.001 | 88.2 / <0.001          |                |                                |
| Gender        | Both             | T1DM         | 2.41 (2.20-2.65) | < 0.001 | -                     | 2.15 (1.80-2.58) | < 0.001                        |
| Gender        | Both             | T2DM         | 1.12 (0.96-1.31) | 0.136  | 41.0 / 0.132           |                |                                |

**Figures**
Figure 1
Details regarding literature search and study selection.
| Study                | OR (95% CI) | % Weight |
|---------------------|-------------|----------|
| Troms? 2006         | 3.05 (1.26, 7.38) | 2.0      |
| Troms? 2006         | 2.85 (0.92, 8.87) | 1.4      |
| THIN 2015           | 1.54 (1.45, 1.62) | 5.5      |
| THIN 2015           | 1.68 (1.58, 1.79) | 5.5      |
| FRAILCO 2017        | 1.40 (1.23, 1.60) | 5.3      |
| FRAILCO 2017        | 1.28 (1.14, 1.43) | 5.4      |
| DNPR 2019           | 2.47 (2.37, 2.59) | 5.5      |
| Subtotal            | 1.72 (1.36, 2.19); P<0.001 | 30.5    |
| (I-square: 97.8%; P<0.001) |            |          |
| BMES 2001           | 2.74 (1.44, 5.20) | 2.9      |
| SOF 2001            | 1.32 (1.13, 1.53) | 5.2      |
| Troms? 2006         | 1.21 (0.60, 2.47) | 2.6      |
| Troms? 2006         | 1.08 (0.70, 1.67) | 3.9      |
| WHF 2006            | 1.24 (0.96, 1.63) | 4.8      |
| Melton 2008         | 1.40 (1.30, 1.60) | 5.4      |
| Melton 2008         | 1.30 (1.20, 1.40) | 5.4      |
| Jung 2012           | 1.23 (0.89, 1.71) | 4.5      |
| Rotterdam 2013      | 1.19 (0.97, 1.46) | 5.0      |
| Manitoba 2016       | 1.12 (1.04, 1.21) | 5.4      |
| FRAILCO 2017        | 1.03 (0.98, 1.07) | 5.5      |
| FRAILCO 2017        | 1.12 (1.08, 1.16) | 5.5      |
| Holm 2018           | 1.29 (0.92, 1.79) | 4.4      |
| DNPR 2019           | 0.93 (0.92, 0.95) | 5.5      |
| PK-VF 2019          | 1.51 (0.90, 2.54) | 3.5      |
| Subtotal            | 1.19 (1.09, 1.31); P<0.001 | 69.5    |
| (I-square: 94.3%; P<0.001) |            |          |
| Overall             | 1.37 (1.17, 1.61); P<0.001 | 100.0   |
| (I-square: 99.0%; P<0.001) |            |          |

**Figure 2**

The role of T1DM and T2DM in the risk of all fractures.
Figure 3

The role of T1DM and T2DM in the risk of hip fracture.
Figure 4

The role of T1DM and T2DM in the risk of distal forearm fracture.
Figure 5

The role of T1DM and T2DM in the risk of upper arm fracture.
Figure 6

The role of T1DM and T2DM in the risk of ankle fracture.
Figure 7

The role of T1DM and T2DM in the risk of vertebrae fracture.

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