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Diabetes mellitus and risk of fractures at specific sites: a meta-analysis

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Running title: DM and fractures

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Abstract

Objective: Studies have shown diabetes mellitus (DM) is associated with an increased fracture risk; however, whether this relationship differs according to different DM types, gender, and study design remains controversial.

Design: Meta-analysis.

Methods: Three electronic databases—PubMed, EMBASE, and the Cochrane Library—were searched to identify potential cohort studies from inception to March 2018. The relative risks (RRs) with 95% CIs were calculated by using a random-effects model.

Results: Overall, DM was associated with an increased risk of total (RR: 1.32; P<0.001), hip (RR: 1.77; P<0.001), upper arm (RR: 1.47; P=0.037), and ankle fractures (RR: 1.24; P<0.001) whereas it had no significant impact on the incidence of distal forearm and vertebrae fractures. The RR ratios suggested that compared to type 2 DM (T2DM) patients, type 1 DM (T1DM) patients had a greater risk of total (RR ratio: 1.24; P=0.002), hip (RR ratio: 3.43; P<0.001), and ankle fractures (RR ratio: 1.71; P=0.029). Although no other significant differences between subgroups were observed, the relationship between DM and fracture risk at different sites was different in specific populations.

Conclusions: DM patients had greater risks of total, hip, upper arm, and ankle fractures. Further, T1DM seems to have a more harmful effect than T2DM.

Keywords: diabetes mellitus; fracture; meta-analysis

Article Summary:

Strengths and limitations of this study:

(1) The current study based on cohort studies, which could eliminate various confounding factors that could bias the results.

(2) This relationship differs according to different DM types, gender, and study design were also conducted.

(3) The large sample size of patients were included, and thus our findings are potentially more robust than are those of any individual study.

(4) The DM ascertainment in individual studies was not consistent, which may have introduced confounders into the representative DM cohort.

(5) The adjusted models were different across the included studies, and these factors might have played an important role in the development of fractures.

Introduction

Diabetes mellitus (DM) is regarded as a major global public health problem, and is likely to be among the five leading causes of disease burden, with an estimated global prevalence of 4.4% by 2030 [1]. Age is an important factor and the age of a majority of DM patients is greater than 65 years [2]. Previous studies have already confirmed the harmful impact of DM on the risk of vascular outcomes [3,4], cancer at different sites [5], and renal dysfunction [6]. Due to DM, patients might have affected calcium metabolism [7], increased bone turnover [8], and reduced bone mineral density level (BMD) [9], which in turn may influence the risk of fractures in patients with DM. However, previous meta-analyses reported different strengths of association of DM with the risk of fractures in type 1 and type 2 DM [10,11], which pointed to a need to verify and evaluate the relationship between DM and fracture at other sites.

Previous studies have already illustrated the relationship between several clinical factors and the risk of fractures at different sites, in turn clinicians and patients could benefit from assessing fracture risk [12,13]. However, due to limited sample sizes, these associations in specific populations were not determined and need further verification. It is of critical importance that clinicians be able to identify DM patients and the risk of fracture at different sites in specific populations, and the preventive strategies that should be implemented in each such subset. Vestergaard conducted a meta-analysis based on 16 observational studies and found that patients with both T1DM and T2DM were associated with an increased risk of hip fracture, and BMD increased in T2DM but decreased in T1DM. However, fracture at other sites and differences among gender and study design were not separately studied [10]. Fan et al. indicated that DM patients had a greater risk of hip fractures than did those without DM, and this association was more pronounced in patients with T1DM [11]. Two problems should be highlighted in this study: (1) although random-effect models were used due to higher heterogeneity, the summary results of the subsets in individual studies should be pooled first based on heterogeneity; and (2) the relationship between DM and the risk of fracture at other sites,

including total, distal forearm, upper arm, ankle, and vertebrae fractures, should be calculated. Therefore, we conducted this study to determine whether the relationship between DM and fracture at different sites is different in specific populations.

Material and methods

Search strategy and inclusion criteria

The meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement (Checklist S1) [14]. PubMed, EMBASE, and the Cochrane Library were searched for studies since their inceptions to March 2018, and the following core search terms were used: (“diabetes” OR “diabetes mellitus” OR “glucose”) AND (“fractures, spontaneous” OR “hip fractures” OR “osteoporotic fractures” OR “fractures, compression” OR “spinal fractures” OR “fracture”) AND ("epidemiologic study" OR "cohort"). We restricted the search to include only studies published in English. Further, we performed manual searches of reference lists from potentially relevant studies to identify additional eligible studies. Article, study design, exposure, and fractures at different sites were used to identify potential studies.

The literature search and study selection process was conducted by 2 authors independently using a standardized approach. Any inconsistency was resolved by group discussion until a consensus was reached. Study inclusion criteria are listed as follows: (1) the study had to have a cohort design, whether prospective or retrospective; (2) participants with DM, whether T1DM or T2DM; and (3) the studies should report effect estimates for comparisons of DM and non-DM and the risk of fracture at different sites. We excluded all case-control studies due to various confounding factors that could bias the results.

Data Collection and Quality Assessment

Data extraction and quality assessment were conducted independently by 2 authors. Information was examined and adjudicated independently by an additional author by referring to the original studies. The data abstracted included the first author or study

group's name, publication year, country, study design, sample size, mean age, percentage of male, number of DM patients, percentage of current smoker, mean body mass index (BMI), follow-up duration, and adjusted factors. The outcome variable was abstracted using the effect estimate with corresponding 95% confidence intervals (CIs). If the study reported several multivariable adjusted effect estimates, the effect estimate was maximally adjusted to account for potential confounders. The Newcastle-Ottawa Scale (NOS) was used to evaluate methodological quality, which has been validated by evaluating the quality of observational studies in meta-analyses [15]. The NOS was based on selection (4 items with a total of 4 stars), comparability (1 item with a total of 2 stars), and outcome (3 items with a total of 3 stars) with a total of 9 stars that were developed for assessment.

Statistical Analysis

The relationship between DM and the subsequent risk of fractures at different sites was based on effect estimates and corresponding 95% CIs in each study. We first used the fixed-effect model to calculate the summary RR and 95% CI for the relationship between DM and fractures in individual studies [16]. We then combined the RRs of fracture risk in DM versus non-DM patients by using a random-effects model [17]. Heterogeneity among the included studies was investigated using I-square and Q statistic, and a P value less than 0.10 was considered to indicate significant heterogeneity [18,19]. Sensitivity analyses were conducted by removing each individual study from the overall analysis [20]. Stratified analyses were conducted for total, hip, distal forearm, upper arm, ankle, and vertebrae fractures based on DM types, gender, and study design. The ratio of RR and its 95% CI was estimated by using specific RR and 95% CI according to the DM types, gender, and study design [21,22]. Funnel plot, Egger [23], and Begg [24] tests were used to evaluate publication bias for total fractures. P values were 2-sided, and if they were less than 0.05, they were considered statistically significant across included studies. Statistical analyses were conducted using STATA software (version 12.0; Stata Corporation, College Station, TX, USA).

Results

Search of the Published Literature

A total of 684 articles were identified from our electronic search, of which 602 studies were excluded due to duplication, irrelevance, and other design issues. We retrieved the full text for the remaining 59 studies and 25 cohort studies were selected for the final analysis after detailed evaluations [25-49]. The manual search of the reference lists of relevant reviews did not yield new eligible studies. The results of the study selection process are shown in Fig 1, and the general characteristics of the included studies are presented in Table 1.

Table 1. Baseline characteristic of studies included

Study	Publication year	Country	Study design	Sample size	Mean age (yr)	Per male (%)	Number of DM	Current smoker (%)	BMI (kg/m²)	Follow-up (yr)	Adjusted factors
CHS [25]	2011	US	Pro	5641	72.8	42.0	1456	12.0	26.7	10.9	Age, sex, race, BMI, AAI<0.9
Jung [26]	2012	Korea	Retro	2282	61.0	0.0	1268	NA	<25.0	7.0	Age
FRAILCO [27]	2016	Sweden	Pro	428305	80.8	42.4	84702	NA	25.4	1.3	Age, sex, weight, height, previous fracture, RA, glucocorticoid, alendronate use, and CCI, and self-reported known fall injury
Dobnig [28]	2006	Australia	Pro	1664	>70.0	0.0	583	NA	NA	2.0	Age and weight
H-EPESE [29]	2002	US	Pro	2884	71.8	42.1	690	42.1	NA	7.0	Age, gender, BMI, ever smoked, previous stroke, lower extremity functional ability, and distance vision
WHS [30]	2001	US	Pro	32089	61.6	0.0	1729	15.0	26.9	9.6	Age, smoking, estrogen use, BMI, and WTHR
SCI-DC [31]	2014	UK	Retro	3801874	20.0-84.0	NA	201874	NA	NA	NA	Age, calendar year, SIMD, and for the overall estimate, an SIMD-age interaction
SIDIAP [32]	2015	Spain	Pro	171931	62.6	56.5	58483	15.6	29.3	2.6	BMI, previous fracture, oral corticoids
THIN [33]	2015	UK	Retro	334266	34.0	56.1	30394	26.7	25.5	5.7	Exposure to steroid medication, history of prior fracture, and presence of chronic kidney disease
NHS [34]	2006	US	Pro	109983	56.3	0.0	8640	17.9	26.0	20.0	Age, BMI, physical activity, menopausal status and estrogen use, smoking and daily intake of calcium, vitamin D, and protein

The Rotterdam Study [35]	2013	Netherland	Pro	4135	68.4	40.6	420	25.0	26.4	12.2	Age, sex, height, weight, and femoral neck BMD
The Tromsø study [36]	2006	Norway	Pro	27159	47.0	47.7	455	37.0	25.5	6.0	Age, BMI, smoking, and metabolic features
Swedish Inpatient Register [37]	2005	Sweden	Retro	24605	20.7	51.0	24605	NA	NA	9.9	Age, sex, and calendar-period- matched general population from the entire Swedish inpatient registry
The Blue Mountains Eye Study [38]	2001	Australia	Pro	3654	66.2	43.3	216	NA	NA	5.0	Age, sex, and BMI
Singapore Chinese Health Study [39]	2010	Singapore	Pro	63257	56.4	44.3	5668	19.4	NA	12.0	Age at recruitment, sex, year of recruitment, dialect group, level of education, weekly vigorous work or strenuous sports, BMI, smoking status, total calcium intake from food and supplement, total soy isoflavone intake, and self-reported stroke.
Meyer [40]	1993	Norway	Pro	52313	35.0-49.0	51.6	288	16.9	NA	10.9	Age, height, BMI, physical activity, stroke, receipt of a disability pension, marriage, and smoking
Lipscombe [41]	2007	Canada	Retro	598812	>66.0	50.6	197412	NA	NA	6.1	Age, chronic unstable disease, prior stroke, visual impairment, neuropathy, amputation, treatment with nitrates,

											statins, thiazides, estrogen, anticonvulsants, inhaled corticosteroids, and medications increasing falling risk, and history of BMD test
Melton [42]	2008	US	Retro	1964	61.7	51.0	1964	NA	NA	11.8	Age, BMI, calcaneal BMD, or a host of other osteoporosis risk factors
Nord-Trùndelag Health Survey [43]	1999	Norway	Pro	35444	50.0-74.0	47.5	1850	30.4	NA	9.0	Age, BMI and daily smoking
Malmö Preventive Project [44]	2006	Sweden	Pro	33346	27.0-61.0	67.3	166	NA	NA	16.0 for men and 11.0 for women	Age, BMI, DBP, resting pulse rate, triglyceride level, gamma-glutamyltransferase, smoking, poor self-rated health, sedimentation rate for women, and cholesterol or creatinine for men
WHI [45]	2006	US	Pro	93676	63.4	0.0	5285	6.2	NA	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
Leslie [46]	2007	Canada	Retro	318776	58.0	50.0	82094	NA	NA	10.0	Age, sex, income quintile, area of residence and ethnicity

Majumdar [47]	2016	Canada	Retro	57938	64.3	0.0	8840	NA	27.1	7.2	FRAX scores, burden of comorbidity, falls, prescription osteoporosis treatments, and insulin therapy
SOF [48]	2001	US	Pro	9754	71.0	0.0	657	NA	26.2	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
Chen [49]	2008	China	Retro	969820	60.0	47.0	484787	NA	NA	6.0	Age as a continuous variable, geographic area, and urbanization status

*DM: diabetes mellitus; Yr: year; Per: percentage; Pro: prospective; Retro: retrospective; BMI: body mass index; AAI: ankle-armindex; NA: not available; RA: rheumatoid arthritis; CCI: Charlson comorbidity index; WTHR: waist-to-hip ratio; SIMD: Scottish Index of Multiple Deprivation;

Study Characteristics

Of the 25 included studies, 16 had a prospective cohort design [25,27-30,32,34-36,38-40,43-45,48], and the remaining 9 studies had a retrospective cohort design [26,31,33,37,41,42,46,47]. The sample size ranged from 1,664 to 3,801,874, while the number of DM patients ranged from 166 to 484,787. Twelve studies were conducted in the US, Australia, or Canada [25,28-30,34,38,41,42,45-48]; 10 in Europe [27,31-33,35-37,40,43,44]; and the remaining 3 in Asia [26,39,49]. The results of total fractures were available in 12 studies, hip fracture in all studies, distal forearm fracture in 8 studies, upper arm fracture in 6 studies, ankle fracture in 4 studies, and vertebrae fractures in 6 studies. Study quality was evaluated by NOS, and a study with 7 or more stars was regarded as a high-quality study. Overall, 7 studies had a score of 9, 8 studies had a score of 8, 6 studies had a score of 7, and the remaining 4 studies had a score of 6 (S1 Table).

Total fractures

A total of 12 studies reported an association between DM and the risk of total fractures. The summary RR indicated that compared with non-DM individuals, DM patients were associated with an increased risk of total fractures (RR: 1.32; 95% CI: 1.17-1.48; P<0.001; Fig 2), and substantial heterogeneity was detected (I^2=97.1%; P<0.001). A sensitivity analysis was conducted and the conclusion was not affected by the sequential exclusion of individual studies from the overall analysis (S2 Table). A subgroup analysis for total fractures based on DM types, gender, and study design was performed. Results showed that patients with DM had increased risk of total fractures in all of subsets (Table 2). Further, the ratio of RR of the comparison between T1DM and T2DM for the risk of total fractures significantly increased and the association was statistically significant (ratio of RR: 1.24; 95% CI: 1.08-1.41; P=0.002; Table 2).

Table 2. Subgroup analyses based on DM types, gender, and study design

Fracture sites	Factors	Subsets	RR and 95%CI	P value	I^2 (%)	P value for heterogeneity	Ratio of RR between subgroups	P value for ratios of RR
All	DM types	I	1.51 (1.35-1.68)	<0.001	78.3	<0.001	1.24 (1.08-1.41)	0.002
		II	1.22 (1.13-1.31)	<0.001	83.0	<0.001		
	Gender	Men	1.49 (1.20-1.85)	<0.001	96.1	<0.001	1.14 (0.89-1.46)	0.313
		Women	1.31 (1.16-1.49)	<0.001	92.8	<0.001		
	Study design	Prospective	1.32 (1.20-1.46)	<0.001	83.4	<0.001	1.01 (0.84-1.21)	0.936
		Retrospective	1.31 (1.12-1.54)	0.001	97.6	<0.001		
Hip	DM types	I	4.35 (2.91-6.49)	<0.001	95.4	<0.001	3.43 (2.27-5.17)	<0.001
		II	1.27 (1.16-1.39)	<0.001	85.5	<0.001		
	Gender	Men	2.05 (1.68-2.51)	<0.001	97.0	<0.001	1.00 (0.78-1.29)	0.969
		Women	2.04 (1.76-2.37)	<0.001	97.5	<0.001		
	Study design	Prospective	2.02 (1.71-2.39)	<0.001	91.4	<0.001	1.09 (0.87-1.36)	0.472
		Retrospective	1.86 (1.60-2.16)	<0.001	98.7	<0.001		
Distal forearm	DM types	I	1.09 (0.43-2.75)	0.861	78.3	0.032	1.12 (0.43-2.94)	0.812
		II	0.97 (0.66-1.09)	0.573	13.1	0.323		
	Gender	Men	1.04 (0.66-1.65)	0.863	58.5	0.090	1.12 (0.70-1.80)	0.644

		Women	0.93 (0.82-1.05)	0.257	6.3	0.380		
	Study design	Prospective	1.00 (0.83-1.19)	0.982	41.0	0.094	0.93 (0.69-01.27)	0.662
		Retrospective	1.07 (0.84-1.37)	0.565	0.0	0.944		
Upper arm	DM types	I	1.83 (1.41-2.39)	<0.001	0.0	0.487	1.19 (0.82-1.72)	0.359
		II	1.54 (1.19-1.99)	0.001	79.6	<0.001		
	Gender	Men	1.21 (0.80-1.83)	0.368	73.2	0.011	0.82 (0.50-1.36)	0.450
		Women	1.47 (1.10-1.96)	0.009	79.1	<0.001		
	Study design	Prospective	1.38 (1.07-1.76)	0.011	76.0	<0.001	0.80 (0.47-1.36)	0.412
		Retrospective	1.72 (1.08-2.73)	0.022	68.5	0.075		
Ankle	DM types	I	1.97 (1.24-3.14)	0.004	29.3	0.234	1.71 (1.06-2.78)	0.029
		II	1.15 (1.01-1.31)	0.029	0.0	0.886		
	Gender	Men	1.35 (0.68-2.65)	0.390	74.1	0.021	0.96 (0.46-2.01)	0.922
		Women	1.40 (1.07-1.84)	0.014	51.6	0.083		
	Study design	Prospective	1.24 (1.10-1.40)	<0.001	0.0	0.400	-	-
		Retrospective	-	-	-	-		
Vertebrae	DM types	I	-	-	-	-	-	-
		II	1.74 (0.96-3.16)	0.070	96.7	<0.001		

Gender	Men	2.26 (0.40-12.73)	0.354	88.9	0.003	1.42 (0.23-8.85)	0.706
	Women	1.59 (0.88-2.87)	0.125	84.1	<0.001		
Study design	Prospective	1.36 (0.88-2.11)	0.167	66.4	0.018	0.54 (0.25-1.14)	0.105
	Retrospective	2.54 (1.37-4.70)	0.003	96.1	<0.001		

Hip fracture

A total of 25 studies reported an association between DM and the risk of hip fracture. In the pooled analysis, the comparison of DM and non-DM participants showed a harmful effect on hip fracture (RR: 1.77; 95% CI: 1.56-2.02; P<0.001; Fig 3). Although substantial heterogeneity was detected across the included studies (I^2=98.0%; p<0.001), the conclusion did not change after sequential exclusion of individual studies (S3 Table). The results of the subgroup analysis for hip fracture are listed in Table 2, and all of results indicated DM had a harmful effect on hip fracture. Furthermore, the ratio of RR showed a statistically significant association between DM and the risk of hip fracture in T1DM when compared with T2DM (ratio of RR: 3.43; 95% CI: 2.27-5.17; P<0.001).

Distal forearm fracture

A total of 8 studies reported an association between DM and the risk of distal forearm fracture. The summary RR showed that patients with DM were not associated with the risk of distal forearm fracture (RR: 1.02; 95% CI: 0.88-1.19; P=0.809; Fig 4), and non-significant heterogeneity was observed (I^2=27.5%; p=0.209). The sensitivity analysis suggested that the conclusion was not affected by the exclusion of any specific study (S4 Table). The subgroup analysis indicated the conclusions in each subset continued to be non-significant and no significant differences were observed between subgroups based on DM types, gender, and study design (Table 2).

Upper arm fracture

A total of 6 studies reported an association between DM and the risk of upper arm fracture. We noted DM patients were associated with higher risk of upper arm fracture as compared with non-DM individuals (RR: 1.47; 95% CI: 1.02-2.10; P=0.037; Fig 5), and evidence of significant heterogeneity was seen (I^2=84.9%; p<0.001). The sensitivity analysis indicated the results varied possibly due to the smaller number of studies on fractures occurring in the upper arm (S5 Table). The subgroup analysis indicated DM had no significant impact on upper arm fracture in men, whereas this risk increased in other subsets (Table 2).

Ankle fracture

A total of 4 studies reported an association between DM and the risk of ankle fracture. The risk of ankle fracture significantly increased in DM patients (RR: 1.24; 95% CI: 1.10-1.40; P<0.001; Fig 6), and no evidence of heterogeneity existed (I^2=0.0%; p=0.400). The results of the sensitivity analysis were consistent with those of the overall analysis and are shown in S6 Table. The subgroup analysis showed no association between DM and ankle fracture risk in men, whereas in other subsets, the risk increased and was statistically significant (Table 2). Further, T1DM patients were at a greater ankle fracture risk than were T2DM patients (ratio of RR: 1.71; 95% CI: 1.06-1.78; P=0.029; Table 2).

Vertebrae fracture

A total of 6 studies reported an association between DM and the risk of vertebrae fracture. The results of pooled analysis indicated that there was no significant association between DM and vertebrae fracture risk (RR: 1.56; 95% CI: 0.78-3.12; P=0.209; Fig 7), and potential evidence of significant heterogeneity was seen (I^2=96.3%; P<0.001). As a result, a sensitivity analysis was conducted and although each study was sequentially excluded from the pooled analysis, the conclusion was not affected by the exclusion of any specific study (S7 Table). The subgroup analysis indicated DM was associated with an increased risk of vertebrae fracture in retrospective cohort studies, whereas no significant effect in other subsets and no difference between subgroups were observed (Table 2).

Publication bias

Review of the funnel plots could not rule out the publication bias for total fractures (Fig 8). Further, the Egger and Begg test results showed no evidence of a publication bias (P value for Egger: 0.311; P value for Begg: 0.537).

Discussion

Because the characteristics of DM patients might have affected the incidence of fracture at different sites, we considered cohort studies to evaluate the correlations between DM and fractures according to DM types, gender, and study design. The meta-analysis

included 7,185,572 participants from 16 prospective cohort studies and 9 retrospective cohort studies with a broad range of individual characteristics. The findings of this study indicated DM was associated with an elevated risk of total, hip, upper arm, and ankle fractures, but had no effect on distal forearm and vertebrae fractures. Mostly, the findings of subgroup analyses were consistent with those of the overall analysis except for those of upper arm and ankle fractures in men. Finally, T1DM was associated with a greater risk of total fractures, hip fracture, and ankle fracture risk than T2DM was.

A previous study based on 14 observational studies evaluated the relationship between T1DM and the risk of fractures [50]. It indicated T1DM was associated with a higher risk of total fractures (RR, 3.16; P=0.002), hip fractures (RR, 3.78; P<0.001), and spinal fractures (RR, 2.88; P<0.001). Further, different study designs might bias this relationship and the role of T2DM was not evaluated in this study. Similar limitations of two other meta-analyses have already been mentioned [10,11]. The major strengths of this study included the comprehensive inclusion of cohort studies with a large sample size and broad characteristics of DM patients. The large sample size ensured the stability of our conclusions, and the broad characteristics ensured the applicability of the summary results.

The pooled results showed a significantly increased risk of total, hip, upper arm, and ankle fractures for DM patients compared with that in non-DM individuals; this result is consistent with those of previous studies [10,11,50]. However, several studies reported inconsistent results. Strotmeyer et al. [25] indicated after adjusting for BMI, sex, race, and age, T2DM had no significant effect on the risk of hip fracture. Jung et al [26] showed the RR in the T2DM cohort increased the risk of total and hip fractures, though these increases were not statistically significant. One possible explanation for this could be the percentage of patients newly diagnosed with DM that might be higher than that in other studies and the increase in insulin level might affect bone metabolism [51]. Further, a smaller sample size and a lower incidence of fracture events were associated with lower statistical power and acquired broad 95% CI. Finally, the summary results for upper arm

and ankle fractures might have varied due to the few studies included and potential confounding factors that could be explored.

There were no significant differences between DM patients and non-DM individuals with regard to distal forearm fracture. Most individual studies reported similar results, whereas the FRAILCO study indicated DM patients were associated with a lower risk of distal forearm fracture [27]. The reason could be the main role of this decrease in patients with oral antidiabetics compared with non-DM individuals. Further, the incidence of distal forearm fracture might be underestimated in register based data. Finally, distal forearm fractures usually develop earlier in life, and the age of the participants in the individual studies might play a confounding role. Similar results were found for vertebrae fractures. Two of the included studies indicated T2DM was associated with a higher risk of vertebrae fractures [42,44]. We could speculate that higher levels of serum γ-glutamyl transferase in women and heavy alcohol consumption in men might affect the risk of vertebral fracture.

Mostly, results of the stratified analysis were consistent with those of the overall analysis. However, two breakthroughs should be highlighted: (1) T1DM was associated with a higher risk for total, hip, and ankle fractures than T2DM. The possible reasons for this could be the different reasons for the incidence of fracture, such as the BMI in T1DM was different from that in T2DM, which played a protective role in fractures [52]. Further, while BMI is a major determinant of BMD and fracture risk, not all studies adjusted for the impact of BMI, which could have affected the intrinsic correlation of DM and fractures. (2) Although there was no significant effect on upper arm and ankle fractures in men with T2DM, these result might be unreliable due to the small number of studies included. This finding should be verified in future large-scale cohort studies.

This meta-analysis has several limitations. The DM ascertainment in individual studies was not consistent, which may have introduced confounders into the representative DM cohort. Further, there were inherent recall and selection biases associated with retrospective cohort studies. In addition, the adjusted models were different across the

included studies, and these factors might have played an important role in the development of fractures. Additionally, substantial heterogeneity could not be explored fully due to the unavailability of several important factors. Finally, the inherent limitation in any meta-analysis, including publication bias, and individual data were be available.

In conclusion, DM was associated with total, hip, upper arm, and ankle fractures. Further, T1DM patients were associated with a higher risk of total, hip, and ankle fractures than were T2DM patients. There was no gender difference in fractures at different sites. Future studies are warranted to clarify the effect of anti-diabetic therapies and to investigate effective prevention strategies for fractures at different sites.

Authors' Contributions

Jian-Ling Du and Hao Wang contributed to conception and design; Hao Wang, Ying Ba, Qian Xing contributed to acquisition, analysis and interpretation of data; Hao Wang and Jian-Ling Du were involved in drafting or critical revision of the manuscript. All the authors approved the final version.

Conflict of interests: All authors declare no conflict of interest.

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Data sharing statement: No additional data available.

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Figure legends:

Fig 1. Study selection process.

Fig 2. Association between DM and the risk of total fractures.

Fig 3. Association between DM and the risk of hip fracture.

Fig 4. Association between DM and the risk of distal forearm fracture.

Fig 5. Association between DM and the risk of upper arm fracture.

Fig 6. Association between DM and the risk of ankle fracture.

Fig 7. Association between DM and the risk of vertebrae fracture.

Fig 8. Publish bias for total fractures.

Supporting information

S1 Table. Quality scores of prospective cohort studies using Newcastle-Ottawa Scale.

S2 Table. Sensitivity analysis for total fractures.

S3 Table. Sensitivity analysis for hip fracture.

S4 Table. Sensitivity analysis for distal forearm fracture.

S5 Table. Sensitivity analysis for upper arm fracture.

S6 Table. Sensitivity analysis for ankle fracture.

S7 Table. Sensitivity analysis for vertebrae fracture.

Checklist S1. PRISMA Checklist

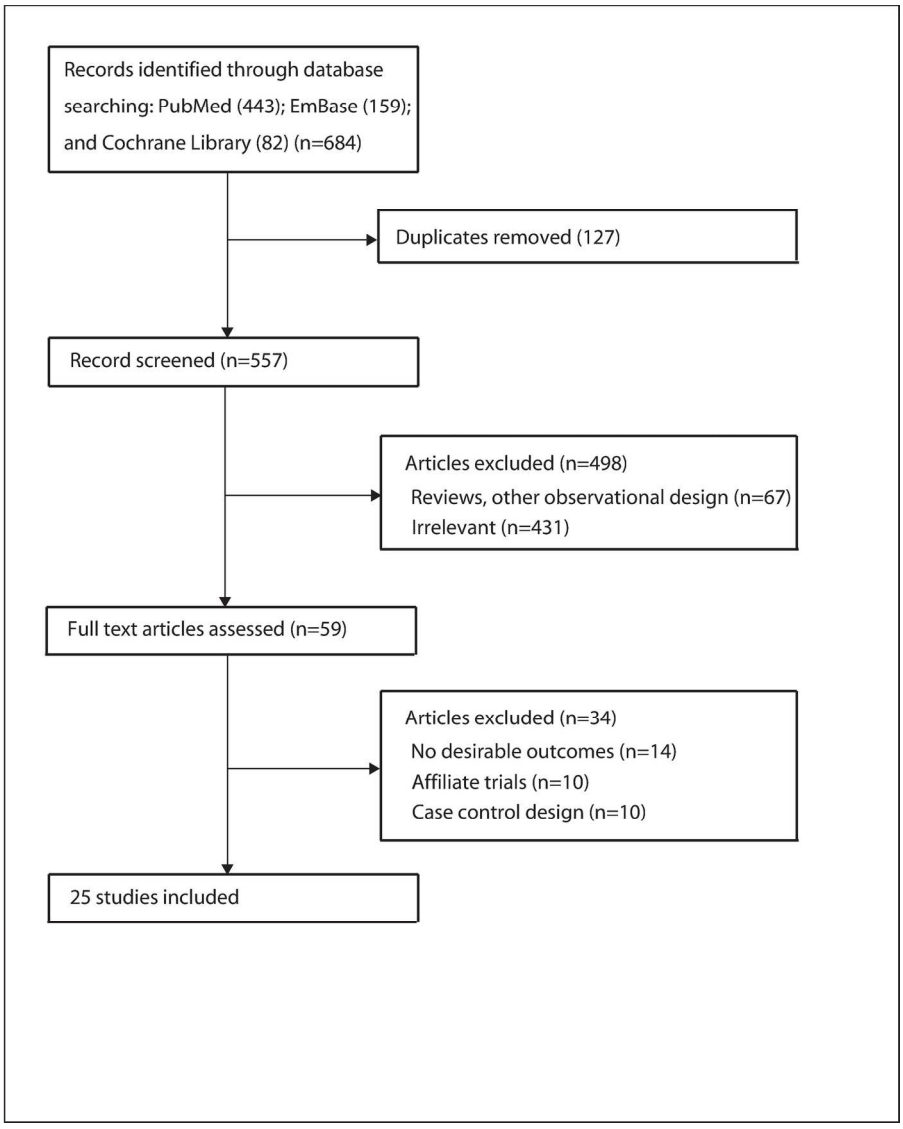

Fig 1. Study selection process.

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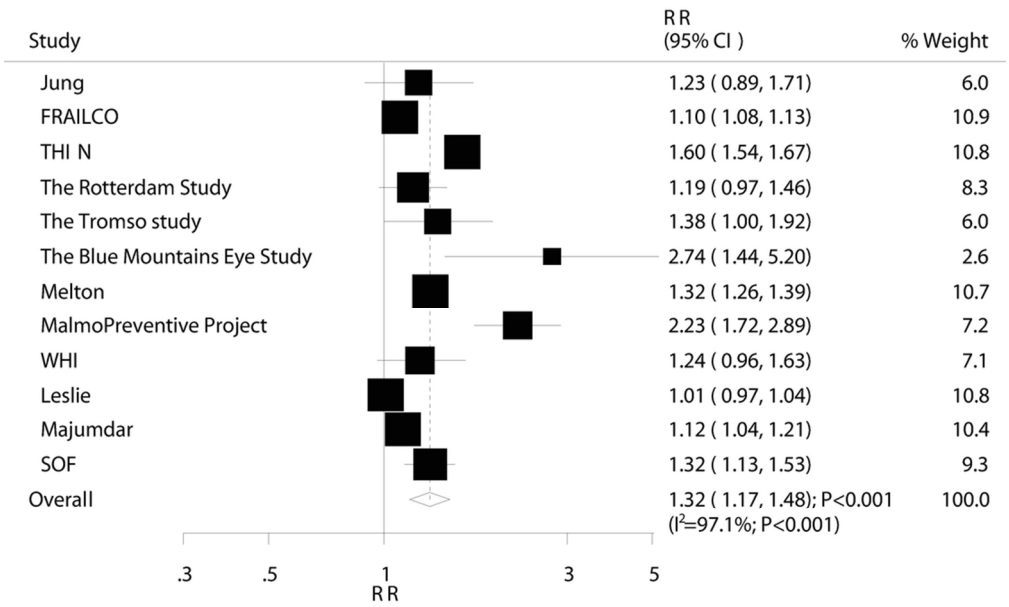

Fig 2. Association between DM and the risk of total fractures.

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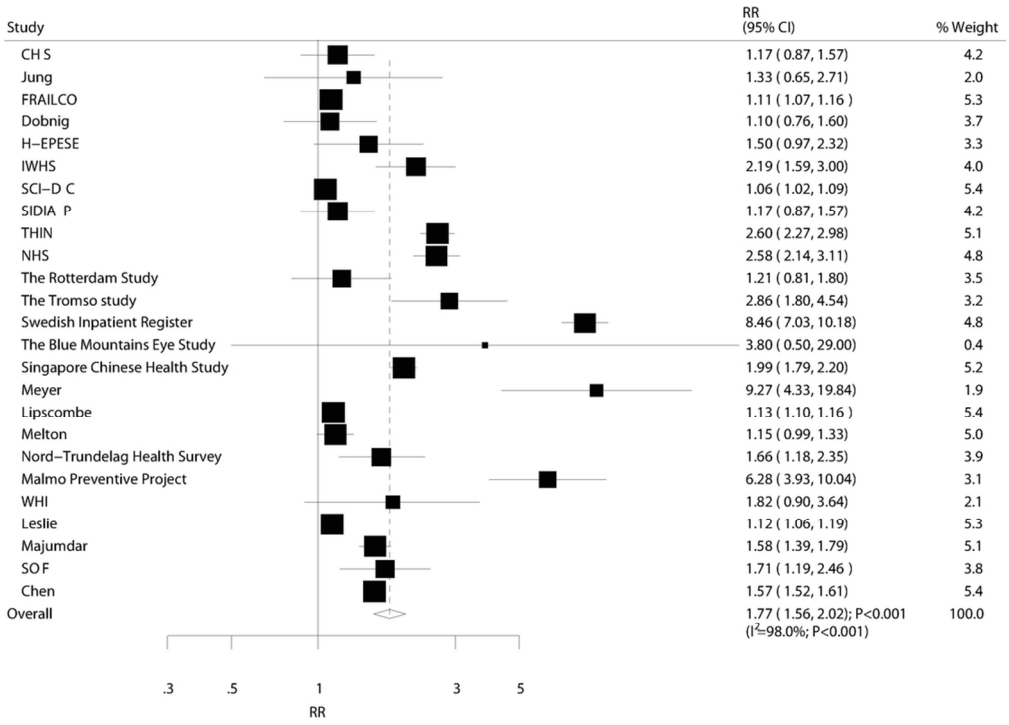

Fig 3. Association between DM and the risk of hip fracture.

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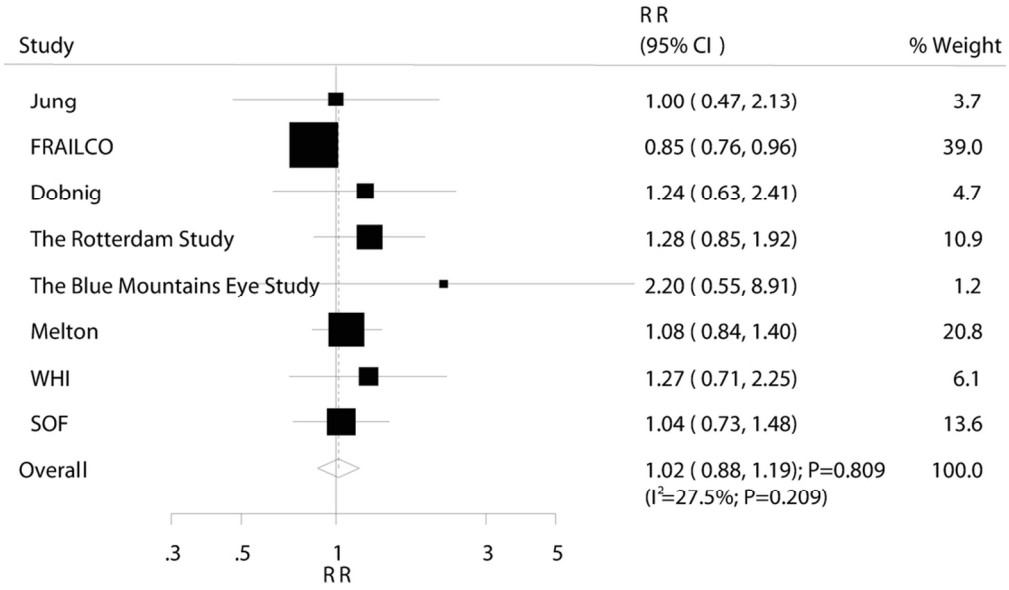

Fig 4. Association between DM and the risk of distal forearm fracture.

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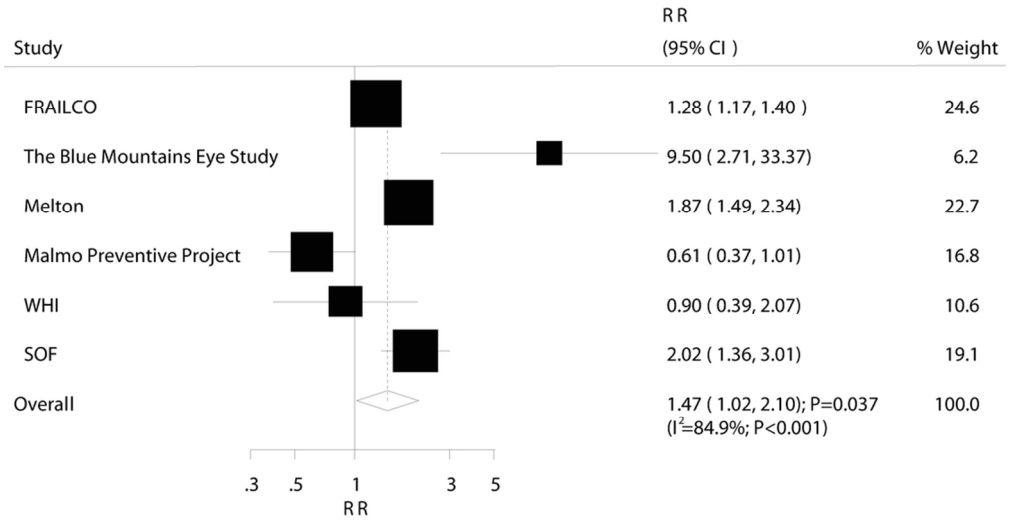

Fig 5. Association between DM and the risk of upper arm fracture.

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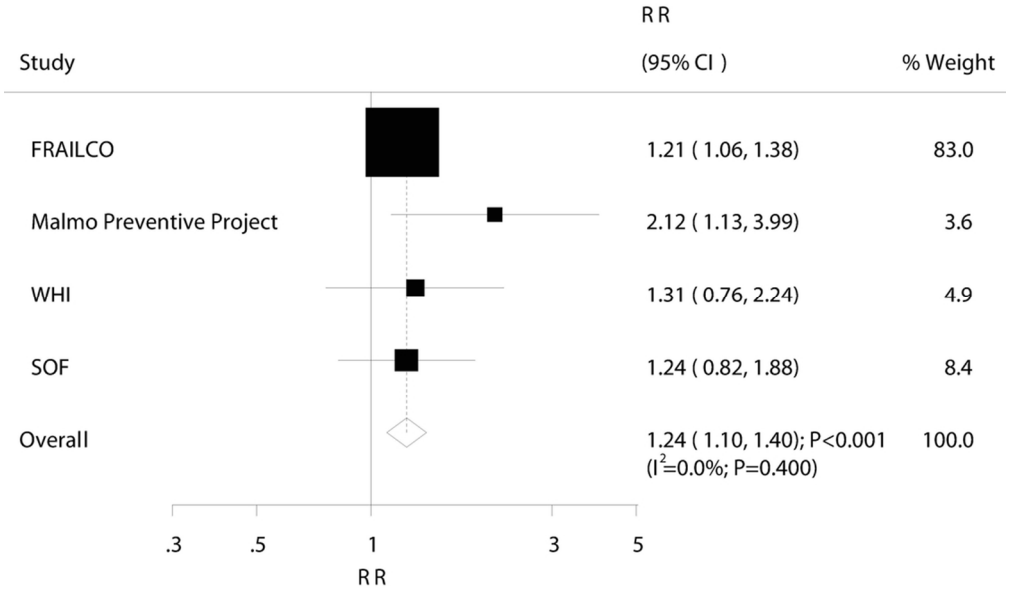

Fig 6. Association between DM and the risk of ankle fracture.

94x55mm (300 x 300 DPI)

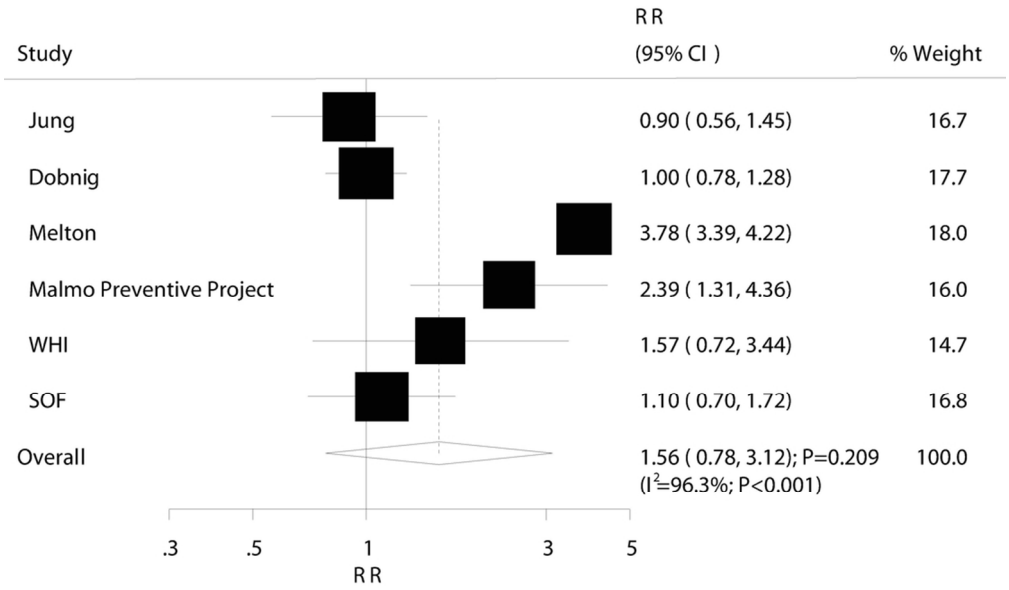

Fig 7. Association between DM and the risk of vertebrae fracture.

94x54mm (300 x 300 DPI)

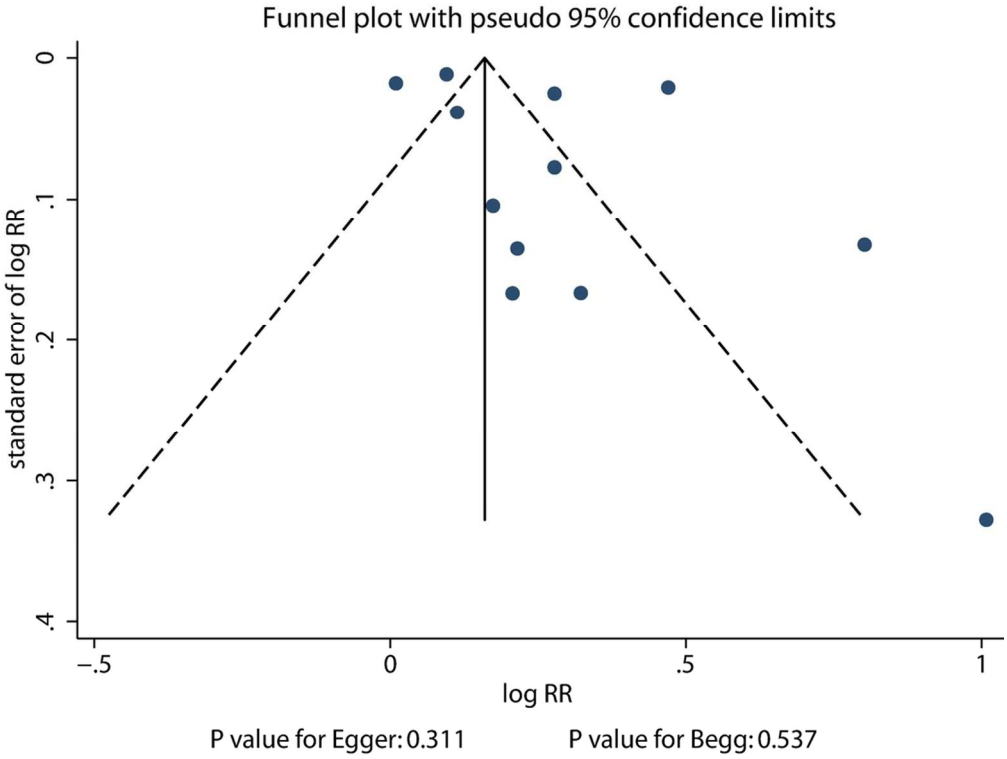

Fig 8. Publish bias for total fractures.

99x74mm (300 x 300 DPI)

S1 Table. Quality scores of prospective cohort studies using Newcastle-Ottawa Scale.

Study	Selection				Comparability	Outcome			NOS
	Representativeness of the exposed cohort	Selection of the non exposed cohort	Ascertainment of DM disease	Demonstration that outcomes was not present at start of study	Comparability on the basis of the design or analysis	Assessment of outcome	Adequate follow-up duration	Adequate follow-up rate	Overall score
CHS [25]	0	1	1	1	2	1	1	1	8
Jung [26]	0	1	1	1	2	1	0	1	7
FRAILCO [27]	1	1	1	1	2	1	0	1	8
Dobnig [28]	0	1	1	1	1	1	0	1	6
H-EPESE [29]	0	1	1	1	2	1	0	1	7
IWHS [30]	1	1	1	1	2	1	1	1	9
SCI-DC [31]	1	1	1	1	2	1	0	0	7
SIDIAP [32]	1	1	1	1	2	1	0	1	8
THIN [33]	1	1	1	1	1	1	0	0	6
NHS [34]	1	1	1	1	2	1	1	1	9
The Rotterdam Study [35]	0	1	1	1	2	1	1	1	8
The Tromsø study [36]	1	1	1	1	2	1	0	1	8
Swedish Inpatient Register [37]	0	1	1	1	1	1	1	0	6
The Blue Mountains Eye Study [38]	0	1	1	1	2	1	0	1	7
Singapore Chinese	1	1	1	1	2	1	1	1	9

Health Study [39]									
Meyer [40]	1	1	1	1	2	1	1	1	9
Lipscombe [41]	1	1	1	1	1	1	0	1	7
Melton [42]	0	1	1	1	1	1	0	1	6
Nord-Trùndelag Health Survey [43]	1	1	1	1	2	1	1	1	9
Malmö Preventive Project [44]	1	1	1	1	2	1	0	0	7
WHI [45]	1	1	1	1	2	1	0	1	8
Leslie [46]	1	1	1	1	2	1	1	1	9
Majumdar [47]	1	1	1	1	2	1	0	1	8
SOF [48]	1	1	1	1	2	1	1	1	9
Chen [49]	1	1	1	1	2	1	0	1	8

S2 Table. Sensitivity analysis for total fractures

Excluding study	RR and 95% CI	P value	Heterogeneity (%)	P value for heterogeneity
Jung	1.32 (1.17-1.50)	<0.001	97.4	<0.001
FRAILCO	1.36 (1.17-1.58)	<0.001	96.9	<0.001
THIN	1.25 (1.14-1.36)	<0.001	91.7	<0.001
The Rotterdam Study	1.33 (1.17-1.51)	<0.001	97.4	<0.001
The Tromsø study	1.31 (1.16-1.46)	<0.001	97.4	<0.001
The Blue Mountains Eye Study	1.29 (1.14-1.46)	<0.001	97.4	<0.001
Melton	1.32 (1.16-1.51)	<0.001	97.2	<0.001
Malmö Preventive Project	1.26 (1.12-1.42)	<0.001	97.2	<0.001
WHI	1.32 (1.17-1.50)	<0.001	97.4	<0.001
Leslie	1.36 (1.19-1.56)	<0.001	96.6	<0.001
Majumdar	1.34 (1.18-1.53)	<0.001	97.4	<0.001
SOF	1.32 (1.16-1.49)	<0.001	97.4	<0.001

S3 Table. Sensitivity analysis for hip fracture

Excluding study	RR and 95% CI	P value	Heterogeneity (%)	P value for heterogeneity
CHS	1.81 (1.58-2.06)	<0.001	98.1	<0.001
Jung	1.78 (1.57-2.03)	<0.001	98.1	<0.001
FRAILCO	1.83 (1.59-2.10)	<0.001	98.0	<0.001
Dobnig	1.81 (1.58-2.06)	<0.001	98.1	<0.001
H-EPESE	1.78 (1.56-2.03)	<0.001	98.1	<0.001
IWHS	1.76 (1.54-2.00)	<0.001	98.1	<0.001
SCI-DC	1.83 (1.59-2.11)	<0.001	97.9	<0.001
SIDIAP	1.81 (1.58-2.06)	<0.001	98.1	<0.001
THIN	1.73 (1.52-1.97)	<0.001	97.9	<0.001
NHS	1.74 (1.53-1.98)	<0.001	98.0	<0.001
The Rotterdam Study	1.80 (1.58-2.05)	<0.001	98.1	<0.001
The Tromsø study	1.75 (1.53-1.99)	<0.001	98.1	<0.001
Swedish Inpatient Register	1.61 (1.44-1.80)	<0.001	97.1	<0.001
The Blue Mountains Eye Study	1.77 (1.55-2.01)	<0.001	98.1	<0.001
Singapore Chinese Health Study	1.76 (1.54-2.00)	<0.001	98.0	<0.001
Meyer	1.72 (1.51-1.95)	<0.001	98.1	<0.001
Lipscombe	1.83 (1.58-2.13)	<0.001	97.9	<0.001
Melton	1.81 (1.59-2.07)	<0.001	98.1	<0.001
Nord-Trùndelag Health Survey	1.78 (1.56-2.03)	<0.001	98.1	<0.001
Malmö Preventive Project	1.70 (1.50-1.93)	<0.001	98.0	<0.001
WHI	1.77 (1.56-2.02)	<0.001	98.1	<0.001
Leslie	1.82 (1.59-2.09)	<0.001	98.1	<0.001
Majumdar	1.78 (1.56-2.04)	<0.001	98.1	<0.001
SOF	1.78 (1.56-2.02)	<0.001	98.1	<0.001
Chen	1.79 (1.56-2.05)	<0.001	97.5	<0.001

S4 Table. Sensitivity analysis for distal forearm fracture.

Excluding study	RR and 95% CI	P value	Heterogeneity (%)	P value for heterogeneity
Jung	1.04 (0.87-1.23)	0.687	37.7	0.141
FRAILCO	1.13 (0.96-1.34)	0.139	0.0	0.928
Dobnig	1.02 (0.86-1.19)	0.849	33.1	0.176
The Rotterdam Study	0.97 (0.84-1.12)	0.671	17.3	0.298
The Blue Mountains Eye Study	1.00 (0.87-1.16)	0.965	26.8	0.224
Melton	1.02 (0.85-1.22)	0.846	27.3	0.220
WHI	1.01 (0.86-1.18)	0.942	29.8	0.201
SOF	1.04 (0.86-1.24)	0.700	35.4	0.158

S5 Table. Sensitivity analysis for upper arm fracture

Excluding study	RR and 95% CI	P value	Heterogeneity (%)	P value for heterogeneity
FRAILCO	1.59 (0.89-2.83)	0.116	85.1	<0.001
The Blue Mountains Eye Study	1.31 (0.95-1.82)	0.100	83.2	<0.001
Melton	1.40 (0.86-2.30)	0.178	83.3	<0.001
Malmö Preventive Project	1.73 (1.21-2.46)	0.003	82.8	<0.001
WHI	1.56 (1.06-2.29)	0.025	87.6	<0.001
SOF	1.36 (0.90-2.06)	0.142	86.2	<0.001

S6 Table. Sensitivity analysis for ankle fracture

Excluding study	RR and 95% CI	P value	Heterogeneity (%)	P value for heterogeneity
FRAILCO	1.42 (1.05-1.90)	0.021	2.2	0.360
Malmö Preventive Project	1.22 (1.08-1.38)	0.002	0.0	0.958
WHI	1.30 (1.03-1.63)	0.026	31.2	0.234
SOF	1.33 (1.02-1.73)	0.034	32.2	0.229

S7 Table. Sensitivity analysis for vertebrae fracture

Excluding study	RR and 95% CI	P value	Heterogeneity (%)	P value for heterogeneity
Jung	1.74 (0.82-3.69)	0.148	96.5	<0.001
Dobnig	1.72 (0.84-3.52)	0.140	93.5	<0.001
Melton	1.20 (0.89-1.63)	0.233	52.6	0.077
Malmö Preventive Project	1.44 (0.65-3.17)	0.370	97.1	<0.001
WHI	1.56 (0.72-3.35)	0.258	97.0	<0.001
SOF	1.67 (0.77-3.63)	0.194	96.6	<0.001

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4-5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	None
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5-6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	12
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	12
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	12-18
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	12-18
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	12-18
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	12-18
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	18-20
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	20
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	20
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	21

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Diabetes mellitus and the risk of fractures at specific sites: a meta-analysis

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Diabetes mellitus and the risk of fractures at specific sites: a meta-analysis

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Running title: DM and fractures

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Abstract

Objective: Diabetes mellitus (DM) is associated with an increased fracture risk; however, the impact of DM and subsequent fracture at different sites and the associations according to patient characteristics remain unknown.

Design: Meta-analysis

Data Sources: The PubMed, EMBASE, and Cochrane Library databases were searched from inception to March 2018.

Eligibility Criteria: We included prospective and retrospective cohort studies on the associations of DM and subsequent fracture risk at different sites.

Data extraction and synthesis: Two authors independently extracted data and assessed the study quality. Relative risks (RRs) with 95% confidence intervals (CIs) were calculated using a random-effects model, and the heterogeneity across the included studies was evaluated using I^2 and Q statistics.

Results: Overall, DM was associated with an increased risk of total (RR: 1.32; 95% CI: 1.17–1.48; P<0.001), hip (RR: 1.77; 95% CI: 1.56–2.02; P<0.001), upper arm (RR: 1.47; 95% CI: 1.02–2.10; P=0.037), and ankle fractures (RR: 1.24; 95% CI: 1.10–1.40; P<0.001), whereas DM had no significant impact on the incidence of distal forearm (RR: 1.02; 95% CI: 0.88–1.19; P=0.809) and vertebral fractures (RR: 1.56; 95% CI: 0.78–3.12; P=0.209). RR ratios suggested that compared with type 2 DM (T2DM) patients, type 1 DM (T1DM) patients had greater risk of total (RR ratio: 1.24; 95% CI: 1.08–1.41; P=0.002), hip (RR ratio: 3.43; 95% CI: 2.27–5.17; P<0.001), and

ankle fractures (RR ratio: 1.71; 95% CI: 1.06–2.78; P=0.029). Although no other significant differences were observed between subgroups, the association of DM with upper arm or ankle, vertebrae, and total fracture differed according to sex, study design, and country, respectively.

Conclusions: DM patients had greater risks of total, hip, upper arm, and ankle fractures, with T1DM having a more harmful effect than T2DM.

Keywords: diabetes mellitus; fracture; meta-analysis

Article Summary:

Strengths and limitations of this study:

(1) The current study was based on cohort studies, which could eliminate various confounding factors.

(2) A large sample size of patients was included; thus, our findings are potentially more robust than those of any individual study.

(3) DM diagnosis in individual studies was not consistent, which may have introduced confounders in the representative DM cohort.

(4) The adjusted models differed across the included studies, and these factors might have played an important role in the development of fractures.

INTRODUCTION

Diabetes mellitus (DM) is considered a major global public health problem and is likely to be among the five leading causes of disease burden, with an estimated global prevalence of 4.4% by 2030[1]. Age is an important factor, with the majority of DM patients aged >65 years[2]. Previous studies have confirmed the harmful impact of DM on the risk of vascular outcomes[3,4], cancer at different sites[5], and renal dysfunction[6]. Due to DM, patients might have altered calcium metabolism[7], increased bone turnover[8], and reduced bone mineral density (BMD)[9], which in turn may influence the risk of fractures in DM patients. However, previous meta-analyses reported different strengths of association between DM and the risk of fractures in type 1 and type 2 DM (T1DM and T2DM, respectively)[10,11], which highlights the need to verify and evaluate the association between DM and fracture at other sites.

Previous studies have illustrated the association between clinical factors and the risk of fractures at different sites; in turn, clinicians and patients could benefit from assessing fracture risk[12,13]. However, due to limited sample sizes, the associations in patients with specific characteristics were not determined, and thus, there is a need for further verification. It is of critical importance that clinicians are able to identify DM patients and the risk of fracture at different sites in patients with specific characteristics to implement preventive strategies in each such subset. Vestergaard conducted a meta-analysis based on 16 observational studies and found that both

T1DM and T2DM were associated with an increased risk of hip fracture and that BMD was increased in T2DM but decreased in T1DM. However, fracture at other sites and differences according to country, sex, and study design were not separately assessed[10]. Fan et al. indicated that DM patients had a greater risk of hip fractures compared with non-DM individuals and that this association was more pronounced in T1DM patients[11]. However, the stratified results of individual studies should be first pooled using fixed-effect models, and the summary results of the included studies should be calculated using random-effects models. Furthermore, the associations between DM and the risk of fracture at other sites, including total, distal forearm, upper arm, ankle, and vertebra, were not assessed. Therefore, this study was conducted to determine whether the association between DM and fracture at different sites differed according to patient characteristics.

MATERIAL AND METHODS

Search strategy and inclusion criteria

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement (Checklist S1)[14]. The PubMed, EMBASE, and Cochrane Library databases were searched for studies from their inception to March 2018 using the following core search terms: (“diabetes” OR “diabetes mellitus” OR “glycuresis”) AND (“fractures, spontaneous” OR “hip fractures” OR “osteoporotic fractures” OR “fractures, compression” OR “spinal

fractures" OR "fracture") AND ("epidemiologic study" OR "cohort"). The details of the search strategy for PubMed are shown in Supplemental 1. We restricted the search to include only studies published in English. Furthermore, manual searches of reference lists of relevant studies were performed to identify additional eligible studies. The study topic, design, exposure, and fractures at different sites were used to identify relevant studies.

The literature search and study selection process were independently conducted by two authors using a standardized approach. Any inconsistency was resolved by group discussion until a consensus was reached. The study inclusion criteria are as follows: (1) a prospective or retrospective cohort design; (2) participants with T1DM or T2DM; and (3) report of the effect estimates for comparisons of DM and non-DM and the risk of fracture at different sites. We excluded case-control studies due to various confounding factors that could bias the results.

Data collection and quality assessment

Data extraction and quality assessment were conducted independently by two authors. The information was examined and adjudicated independently by an additional author by referring to the original studies. The abstracted data included the first author or study group's name, publication year, country, study design, sample size, mean patient age, percentage of men, number of DM patients, percentage of current smokers, mean body mass index (BMI), follow-up duration, DM diagnosis, and

adjusted factors. The outcome variable was abstracted using the effect estimate with corresponding 95% confidence intervals (CIs). If the study reported several multivariable adjusted effect estimates, the effect estimate was maximally adjusted to account for potential confounders. The Newcastle-Ottawa Scale (NOS) was used to evaluate the methodological quality, which has been validated by evaluating the quality of observational studies in meta-analyses[15]. The NOS was based on selection (four items with a total of four stars), comparability (one item with a total of two stars), and outcome (three items with a total of three stars) with a total of nine stars for assessment.

Statistical Analysis

The association between DM and the subsequent risk of fractures at different sites was based on effect estimates and corresponding 95% CIs in each study. We first used the fixed-effect model to calculate the summary relative risk (RR) and 95% CI for the association between DM and fractures in individual studies[16]. We then combined the RRs of fracture risk in DM versus non-DM individuals using a random-effects model[17]. Heterogeneity among the included studies was assessed using I^2 and Q statistics, and P values <0.10 were considered to indicate significant heterogeneity[18,19]. Sensitivity analyses were conducted by removing each individual study from the overall analysis[20]. Stratified analyses were conducted for total, hip, distal forearm, upper arm, ankle, and vertebral fractures based on country,

DM type, sex, and study design. The RR ratio and its 95% CI was estimated using specific RR and 95% CI according to country, DM types, sex, and study design[21,22]. Funnel plot, Egger[23], and Begg[24] tests were used to evaluate publication bias for total fractures. P-values were 2-sided, and those <0.05 were considered statistically significant across the included studies. The statistical analyses were conducted using STATA (version 12.0; Stata Corporation, College Station, TX, USA).

Patient and public involvement

No patients were involved in the development of the research question, outcome measures, design, study implementation, dissemination of the results of the research to the study participants, or interpretation of the results.

RESULTS

Search of published literature

A total of 684 articles were identified from our electronic search, of which 602 were excluded due to duplication, irrelevance, and other design issues. We retrieved the full text for the remaining 59 studies and selected 25 cohort studies for the final analysis after detailed evaluations[25-49]. The manual search of the reference lists of relevant reviews did not yield any new eligible studies. The results of the study selection

process are shown in Fig 1, and the general characteristics of the included studies are presented in Table 1 and S1 Table.

Table 1. Baseline characteristic of studies included

Study	Publication year	Country	Study design	Sample size	Mean age (yr)	Per men (%)	Number of DM	Follow-up (yr)
CHS [25]	2011	US	Pro	5641	72.8	42.0	1456	10.9
Jung [26]	2012	Korea	Retro	2282	61.0	0.0	1268	7.0
FRAILCO [27]	2016	Sweden	Pro	428305	80.8	42.4	84702	1.3
Dobnig [28]	2006	Australia	Pro	1664	>70.0	0.0	583	2.0
H-EPESE [29]	2002	US	Pro	2884	71.8	42.1	690	7.0
IWHS [30]	2001	US	Pro	32089	61.6	0.0	1729	9.6
SCI-DC [31]	2014	UK	Retro	3801874	20.0-84.0	NA	201874	NA
SIDIAP [32]	2015	Spain	Pro	171931	62.6	56.5	58483	2.6
THIN [33]	2015	UK	Retro	334266	34.0	56.1	30394	5.7
NHS [34]	2006	US	Pro	109983	56.3	0.0	8640	20.0
The Rotterdam Study [35]	2013	Netherland	Pro	4135	68.4	40.6	420	12.2
The Tromsø study [36]	2006	Norway	Pro	27159	47.0	47.7	455	6.0
Swedish Inpatient Register [37]	2005	Sweden	Retro	24605	20.7	51.0	24605	9.9
The Blue Mountains Eye Study [38]	2001	Australia	Pro	3654	66.2	43.3	216	5.0
Singapore Chinese Health Study [39]	2010	Singapore	Pro	63257	56.4	44.3	5668	12.0
Meyer [40]	1993	Norway	Pro	52313	35.0-49.0	51.6	288	10.9
Lipscombe [41]	2007	Canada	Retro	598812	>66.0	50.6	197412	6.1
Melton [42]	2008	US	Retro	1964	61.7	51.0	1964	11.8
Nord-Trùndelag Health Survey [43]	1999	Norway	Pro	35444	50.0-74.0	47.5	1850	9.0
Malmö Preventive Project [44]	2006	Sweden	Pro	33346	27.0-61.0	67.3	166	16.0 for men and 11.0 for women
WHI [45]	2006	US	Pro	93676	63.4	0.0	5285	7.0
Leslie [46]	2007	Canada	Retro	318776	58.0	50.0	82094	10.0
Majumdar [47]	2016	Canada	Retro	57938	64.3	0.0	8840	7.2
SOF [48]	2001	US	Pro	9754	71.0	0.0	657	9.4

Chen [49]	2008	China	Retro	969820	60.0	47.0	484787	6.0

*Yr: year; Per: percentage; Pro: prospective; Retro: retrospective

Study characteristics

Of the 25 included studies, 16 had a prospective cohort design[25,27-30,32,34-36,38-40,43-45,48] and the remaining nine studies had a retrospective cohort design[26,31,33,37,41,42,46,47]. The sample sizes ranged from 1,664 to 3,801,874, while the number of DM patients ranged from 166 to 484,787. Twelve studies were conducted in the US, Australia, or Canada[25,28-30,34,38,41,42,45-48]; 10 in Europe[27,31-33,35-37,40,43,44]; and the remaining three in Asia[26,39,49]. The results of total fractures were available in 12 studies, hip fracture in all studies, distal forearm fracture in eight studies, upper arm fracture in six studies, ankle fracture in four studies, and vertebral fractures in six studies. Study quality was evaluated by NOS, and a study with seven or more stars was regarded as a high-quality study. Overall, seven studies had a score of 9, eight studies had a score of 8, six studies had a score of 7, and the remaining four studies had a score of 6 (S2 Table).

Total fractures

A total of 12 studies reported an association between DM and the risk of total fractures. The summary RR indicated that compared with non-DM individuals, DM patients were associated with an increased risk of total fractures (RR: 1.32; 95% CI:

1.17–1.48; P<0.001; Fig 2), and substantial heterogeneity was detected (I^2=97.1%; P<0.001). A sensitivity analysis revealed that the conclusion was not affected by the sequential exclusion of individual studies from the overall analysis (S3 Table). A subgroup analysis of total fractures based on country, DM type, sex, and study design was performed. The results showed that DM patients had an increased risk of total fractures in nearly all subsets except for studies conducted in Eastern countries (Table 2). Furthermore, the RR ratio for the comparison between T1DM and T2DM of the risk of total fractures was significantly increased, and the association was also statistically significant (ratio of RR: 1.24; 95% CI: 1.08–1.41; P=0.002; Table 2).

Table 2. Subgroup analysis for total fracture based on country, DM types, sex, and study design

Factors	Subsets	RR and 95%CI	P value	I^2 (%)	P value for heterogeneity	Ratio of RR between subgroups	P value for ratios of RR
Country	Western	1.32 (1.17-1.50)	<0.001	97.4	<0.001	1.07 (0.76-1.52)	0.690
	Eastern	1.23 (0.89-1.70)	0.214	-	-		
DM types	I	1.51 (1.35-1.68)	<0.001	78.3	<0.001	1.24 (1.08-1.41)	0.002
	II	1.22 (1.13-1.31)	<0.001	83.0	<0.001		
Sex	Men	1.49 (1.20-1.85)	<0.001	96.1	<0.001	1.14 (0.89-1.46)	0.313
	Women	1.31 (1.16-1.49)	<0.001	92.8	<0.001		
Study design	Prospective	1.32 (1.20-1.46)	<0.001	83.4	<0.001	1.01 (0.84-1.21)	0.936
	Retrospective	1.31 (1.12-1.54)	0.001	97.6	<0.001		

*CI: confidence interval; DM: diabetes mellitus; RR: relative risk

Hip fracture

A total of 25 studies reported an association between DM and the risk of hip fracture. In the pooled analysis, the comparison of DM and non-DM individuals showed a harmful effect on hip fracture (RR: 1.77; 95% CI: 1.56–2.02; P<0.001; Fig 3). Although substantial heterogeneity was detected across the included studies (I^2=98.0%; P<0.001), the conclusion did not change after sequential exclusion of individual studies (S4 Table). The results of subgroup analysis for hip fracture are listed in Table 3, and all results indicated that DM had a harmful effect on hip fracture. Furthermore, the RR ratio showed a statistically significant association between DM and the risk of hip fracture in T1DM when compared with that of T2DM (ratio of RR: 3.43; 95% CI: 2.27–5.17; P<0.001).

Table 3. Subgroup analysis for hip fracture based on country, DM types, sex, and study design

Factors	Subsets	RR and 95%CI	P value	I^2 (%)	P value for heterogeneity	Ratio of RR between subgroups	P value for ratios of RR
Country	Western	1.79 (1.56-2.05)	<0.001	97.5	<0.001	1.04 (0.81-1.34)	0.759
	Eastern	1.72 (1.39-2.14)	<0.001	89.5	<0.001		
DM types	I	4.35 (2.91-6.49)	<0.001	95.4	<0.001	3.43 (2.27-5.17)	<0.001
	II	1.27 (1.16-1.39)	<0.001	85.5	<0.001		
Sex	Men	2.05 (1.68-2.51)	<0.001	97.0	<0.001	1.00 (0.78-1.29)	0.969
	Women	2.04 (1.76-2.37)	<0.001	97.5	<0.001		
Study design	Prospective	2.02 (1.71-2.39)	<0.001	91.4	<0.001	1.09 (0.87-1.36)	0.472
	Retrospective	1.86 (1.60-2.16)	<0.001	98.7	<0.001		

*CI: confidence interval; DM: diabetes mellitus; RR: relative risk

Distal forearm fracture

A total of eight studies reported an association between DM and the risk of distal forearm fracture. The summary RR showed that DM was not associated with the risk of distal forearm fracture (RR: 1.02; 95% CI: 0.88–1.19; P=0.809; Fig 4) and non-significant heterogeneity was observed (I^2=27.5%; P=0.209). The sensitivity analysis suggested that the conclusion was not affected by the exclusion of any specific study (S5 Table). The subgroup analysis indicated the conclusions in each subset continued to be non-significant and no significant differences were observed between subgroups based on country, DM type, sex, or study design (Table 4).

Table 4. Subgroup analysis for distal forearm fracture based on country, DM types, sex, and study design

Factors	Subsets	RR and 95%CI	P value	I^2 (%)	P value for heterogeneity	Ratio of RR between subgroups	P value for ratios of RR
Country	Western	1.04 (0.87-1.23)	0.687	37.7	0.141	1.04 (0.48-2.26)	0.921
	Eastern	1.00 (0.47-2.13)	1.000	-	-		
DM types	I	1.09 (0.43-2.75)	0.861	78.3	0.032	1.12 (0.43-2.94)	0.812
	II	0.97 (0.66-1.09)	0.573	13.1	0.323		
Sex	Men	1.04 (0.66-1.65)	0.863	58.5	0.090	1.12 (0.70-1.80)	0.644
	Women	0.93 (0.82-1.05)	0.257	6.3	0.380		
Study design	Prospective	1.00 (0.83-1.19)	0.982	41.0	0.094	0.93 (0.69-01.27)	0.662
	Retrospective	1.07 (0.84-1.37)	0.565	0.0	0.944		

*CI: confidence interval; DM: diabetes mellitus; RR: relative risk

Upper arm fracture

A total of six studies reported an association between DM and the risk of upper arm fracture. Compared with non-DM individuals, DM patients had a higher risk of upper arm fracture (RR: 1.47; 95% CI: 1.02–2.10; P=0.037; Fig 5), and evidence of significant heterogeneity was observed (I^2=84.9%; P<0.001). The sensitivity analysis indicated the results varied possibly due to the smaller number of studies on fractures occurring in the upper arm (S6 Table). The subgroup analysis indicated that DM had no significant impact on upper arm fracture in men, whereas this risk increased in other subsets (Table 5).

Table 5. Subgroup analysis for upper arm fracture based on country, DM types, sex, and study design.

Factors	Subsets	RR and 95%CI	P value	I^2 (%)	P value for heterogeneity	Ratio of RR between subgroups	P value for ratios of RR
Country	Western	1.47 (1.02-2.10)	0.037	84.9	<0.001	-	-
	Eastern	-	-	-	-		
DM types	I	1.83 (1.41-2.39)	<0.001	0.0	0.487	1.19 (0.82-1.72)	0.359
	II	1.54 (1.19-1.99)	0.001	79.6	<0.001		
Sex	Men	1.21 (0.80-1.83)	0.368	73.2	0.011	0.82 (0.50-1.36)	0.450
	Women	1.47 (1.10-1.96)	0.009	79.1	<0.001		
Study design	Prospective	1.38 (1.07-1.76)	0.011	76.0	<0.001	0.80 (0.47-1.36)	0.412
	Retrospective	1.72 (1.08-2.73)	0.022	68.5	0.075		

*CI: confidence interval; DM: diabetes mellitus; RR: relative risk

Ankle fracture

A total of four studies reported an association between DM and the risk of ankle

fracture. The risk of ankle fracture significantly increased in DM patients (RR: 1.24; 95% CI: 1.10–1.40; P<0.001; Fig 6), with no evidence of heterogeneity (I^2=0.0%; P=0.400). The results of the sensitivity analysis were consistent with those of the overall analysis and are shown in S7 Table. The subgroup analysis showed no association between DM and ankle fracture risk in men, whereas in other subsets, the risk was significantly increased (Table 6). Furthermore, T1DM patients were at a greater risk of ankle fracture than were T2DM patients (ratio of RR: 1.71; 95% CI: 1.06–1.78; P=0.029; Table 6).

Table 6. Subgroup analysis for ankle fracture based on country, DM types, sex, and study design.

Factors	Subsets	RR and 95%CI	P value	I^2 (%)	P value for heterogeneity	Ratio of RR between subgroups	P value for ratios of RR
Country	Western	1.24 (1.10-1.40)	<0.001	0.0	0.400	-	-
	Eastern	-	-	-	-		
DM types	I	1.97 (1.24-3.14)	0.004	29.3	0.234	1.71 (1.06-2.78)	0.029
	II	1.15 (1.01-1.31)	0.029	0.0	0.886		
Sex	Men	1.35 (0.68-2.65)	0.390	74.1	0.021	0.96 (0.46-2.01)	0.922
	Women	1.40 (1.07-1.84)	0.014	51.6	0.083		
Study design	Prospective	1.24 (1.10-1.40)	<0.001	0.0	0.400	-	-
	Retrospective	-	-	-	-		

*CI: confidence interval; DM: diabetes mellitus; RR: relative risk

Vertebrae fracture

A total of six studies reported an association between DM and the risk of vertebrae

fracture. The results of pooled analysis indicated no significant association between DM and vertebrae fracture risk (RR: 1.56; 95% CI: 0.78–3.12; P=0.209; Fig 7) and evidence of significant heterogeneity (I^2=96.3%; P<0.001). As a result, a sensitivity analysis was conducted and, although each study was sequentially excluded from the pooled analysis, the conclusion was not affected by the exclusion of any specific study (S8 Table). The subgroup analysis indicated that DM was associated with an increased risk of vertebrae fracture in retrospective cohort studies, whereas no significant effect in other subsets and no difference between subgroups were observed (Table 7).

Table 7. Subgroup analysis for vertebrae fracture based on country, DM types, sex, and study design.

Factors	Subsets	RR and 95%CI	P value	I^2 (%)	P value for heterogeneity	Ratio of RR between subgroups	P value for ratios of RR
Country	Western	1.74 (0.82-3.69)	0.148	96.5	<0.001	1.93 (0.79-4.71)	0.146
	Eastern	0.90 (0.56-1.45)	0.664	-	-		
DM types	I	-	-	-	-	-	-
	II	1.74 (0.96-3.16)	0.070	96.7	<0.001		
Sex	Men	2.26 (0.40-12.73)	0.354	88.9	0.003	1.42 (0.23-8.85)	0.706
	Women	1.59 (0.88-2.87)	0.125	84.1	<0.001		
Study design	Prospective	1.36 (0.88-2.11)	0.167	66.4	0.018	0.54 (0.25-1.14)	0.105
	Retrospective	2.54 (1.37-4.70)	0.003	96.1	<0.001		

*CI: confidence interval; DM: diabetes mellitus; RR: relative risk

Publication bias

Review of the funnel plots could not rule out a publication bias for total fractures (Fig 8). Furthermore, the Egger and Begg test results showed no evidence of a publication bias (P value for Egger: 0.311; P value for Begg: 0.537).

DISCUSSION

Because the characteristics of DM patients might have affected the incidence of fracture at different sites, we considered cohort studies to evaluate the correlations between DM and fractures according to country, DM type, sex, and study design. The meta-analysis included 7,185,572 participants from 16 prospective cohort studies and nine retrospective cohort studies with a broad range of individual characteristics. The findings of this study indicated that DM was associated with an elevated risk of total, hip, upper arm, and ankle fractures but had no effect on distal forearm and vertebral fractures. The findings of the subgroup analyses were mostly consistent with those of the overall analysis except for those of total fracture in Eastern countries and upper arm and ankle fractures in men. Finally, compared with T2DM, T1DM was associated with a greater risk of total, hip, and ankle fracture.

A previous study based on 14 observational studies evaluated the association between T1DM and the risk of fractures[50]. The results indicated T1DM was associated with a higher risk of total (RR, 3.16; P=0.002), hip (RR, 3.78; P<0.001), and spinal fractures (RR, 2.88; P<0.001). Moayeri et al. conducted a meta-analysis to evaluate the association between T2DM and fracture risk and possible risk factors, suggesting

an increased risk of hip, vertebral, and foot fractures in T2DM patients and no significant association between T2DM and wrist, proximal humerus, and ankle fractures. They also reported patients with T2DM had an increased risk of total fracture that increased with age, duration of diabetes, and insulin therapy[51]. However, different study designs might bias this association and the role of DM type was not evaluated in previous studies. Similar limitations of two other meta-analyses have already been described[10,11]. Therefore, the present meta-analysis of available cohort studies was performed to address these limitations.

The pooled results showed a significantly increased risk of total, hip, upper arm, and ankle fractures in DM patients compared with those in non-DM individuals; this result is consistent with those of previous studies[10,11,50]. However, several studies reported inconsistent results. After adjusting for BMI, sex, race, and age, Strotmeyer et al.[25] indicated that T2DM had no significant effect on the risk of hip fracture. Jung et al.[26] showed that the RR in the T2DM cohort increased the risk of total and hip fractures, although these increases were not statistically significant. One possible explanation for this could be the percentage of patients newly diagnosed with DM that might be higher than that in other studies and the increase in insulin level might affect bone metabolism[52]. Furthermore, a smaller sample size and a lower incidence of fracture events were associated with lower statistical power and broad 95% CI. Finally, the summary results for upper arm and ankle fractures might have varied due to the limited number of studies included; the interaction of these associations with

age, severity of DM, and antidiabetic drugs should be explored[51].

There were no significant differences between DM patients and non-DM individuals with respect to distal forearm fracture. Most individual studies reported similar results, whereas the FRAILCO study indicated that DM was associated with a lower risk of distal forearm fracture[27]. The reason for this difference could be the main role of this decrease in patients taking oral antidiabetics compared with non-DM individuals. Furthermore, the incidence of distal forearm fracture might be underestimated in register-based data. Finally, distal forearm fractures usually develop earlier in life, and the age of the participants in the individual studies might play a confounding role. Similar results were found for vertebral fractures. Two of the included studies indicated that T2DM was associated with a higher risk of vertebral fractures[42,44]. The reason for this finding could be the baseline levels of serum γ-glutamyl transferase and metabolic syndrome in women and alcohol overconsumption, which are associated with higher serum γ-glutamyl transferase levels in men and may play an important role in the risk of vertebral and ankle fractures [53-55].

The results of the stratified analysis were generally consistent with those of the overall analysis. However, two breakthroughs should be highlighted: (1) T1DM was associated with a higher risk for total, hip, and ankle fractures compared with that in T2DM. The possible reasons for this include the different reasons for the incidence of fracture, such as differences in BMI between T1DM and T2DM, which played a protective role in fractures[56]. Furthermore, while BMI is a major determinant of

BMD and fracture risk, not all studies adjusted for the impact of BMI, which could have affected the intrinsic correlation of DM and fractures. (2) Although there was no significant effect on upper arm and ankle fractures in men with T2DM, these results might be unreliable due to the small number of studies included. This finding should be verified in future large-scale cohort studies.

This meta-analysis had several limitations. The DM diagnosis in individual studies was not consistent, which may have introduced confounders in the representative DM cohort. Furthermore, retrospective cohort studies might introduce recall and selection biases, which could affect the evidence levels and representativeness of the cohorts. In addition, the adjusted models differed across the included studies; these factors might have played an important role in the development of fractures. Additionally, the substantial heterogeneity could not be explored completely due to the unavailability of several important factors, including metabolic and lifestyle. Finally, there were limitations inherent to any meta-analysis, including a publication bias and the lack of availability of individual data.

In conclusion, DM was associated with total, hip, upper arm, and ankle fractures. Furthermore, patients with T1DM had a higher risk of total, hip, and ankle fractures compared with those with T2DM. There was no sex difference in fractures at different sites. Future studies are warranted to clarify the effect of anti-diabetic therapies and investigate effective prevention strategies for fractures at different sites.

Authors' Contributions

Jian-Ling Du and Hao Wang contributed to conception and design; Hao Wang, Ying Ba, Qian Xing contributed to acquisition, analysis and interpretation of data; Hao Wang and Jian-Ling Du were involved in drafting or critical revision of the manuscript. All the authors approved the final version.

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Data sharing statement: No additional data available.

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Figure legends:

Fig 1. Study selection process.

Fig 2. Association between DM and the risk of total fractures.

Fig 3. Association between DM and the risk of hip fracture.

Fig 4. Association between DM and the risk of distal forearm fracture.

Fig 5. Association between DM and the risk of upper arm fracture.

Fig 6. Association between DM and the risk of ankle fracture.

Fig 7. Association between DM and the risk of vertebrae fracture.

Fig 8. Publish bias for total fractures.

Supporting information

S1 Table. Additional characteristic of studies included

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S3 Table. Sensitivity analysis for total fractures.

S4 Table. Sensitivity analysis for hip fracture.

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S6 Table. Sensitivity analysis for upper arm fracture.

S7 Table. Sensitivity analysis for ankle fracture.

S8 Table. Sensitivity analysis for vertebrae fracture.

Checklist S1. PRISMA Checklist

Supplemental 1. Searching strategy in PubMed

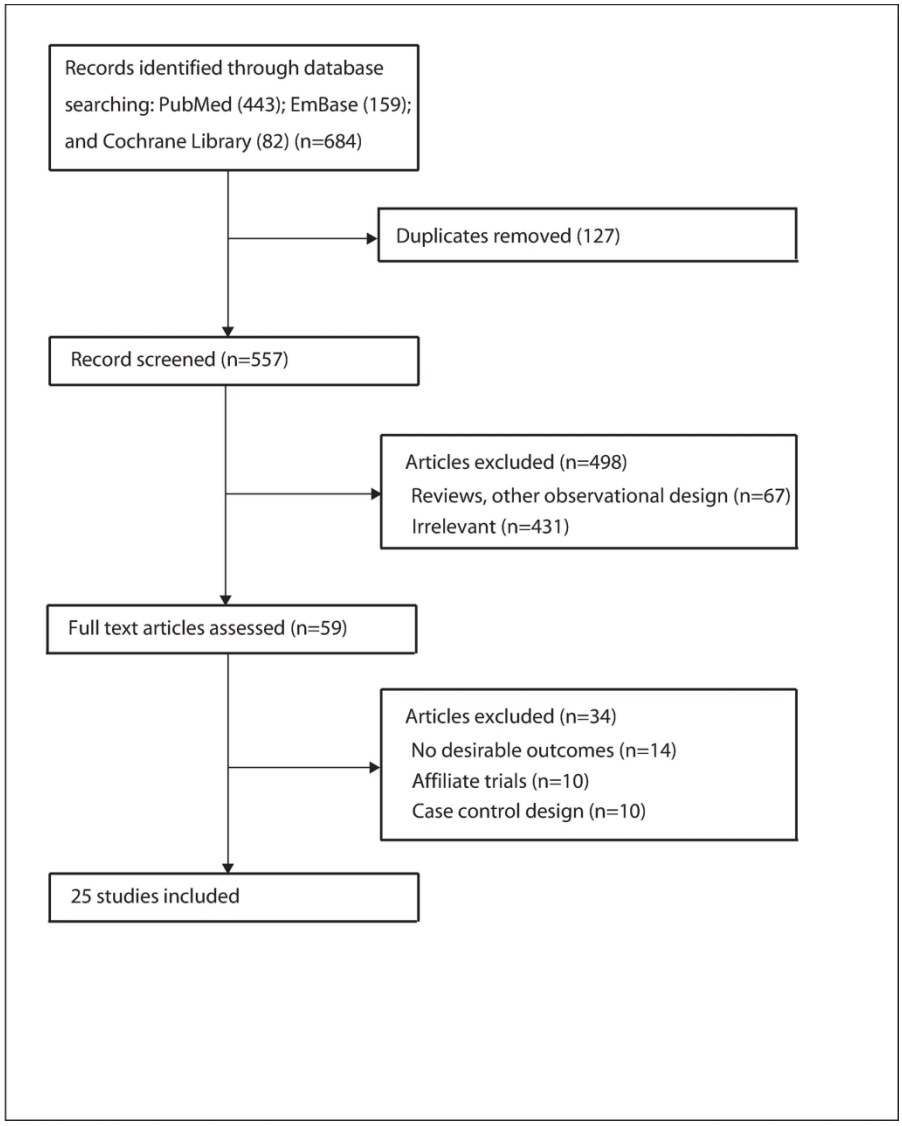

Fig 1. Study selection process.

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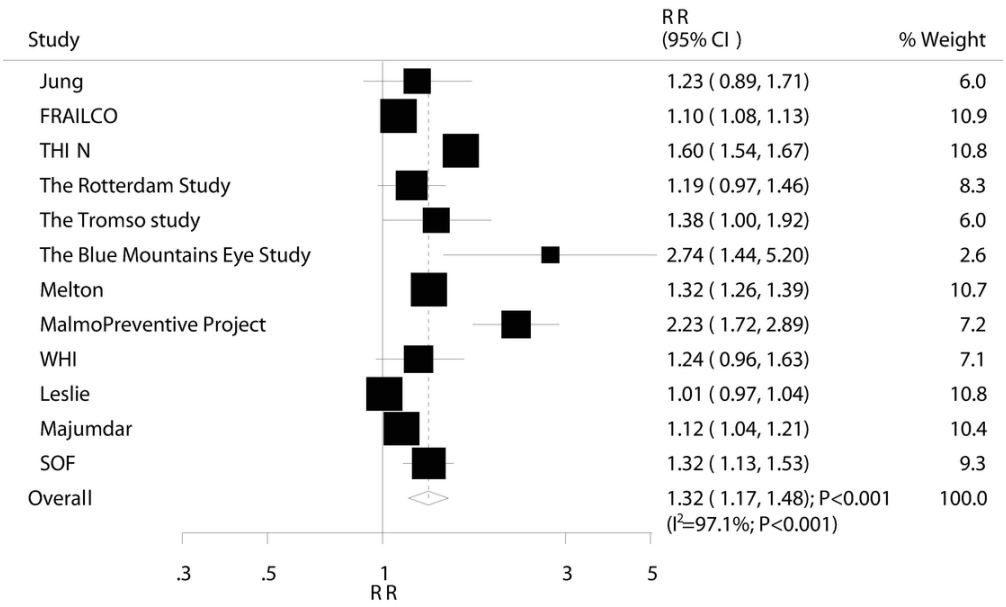

Fig 2. Association between DM and the risk of total fractures.

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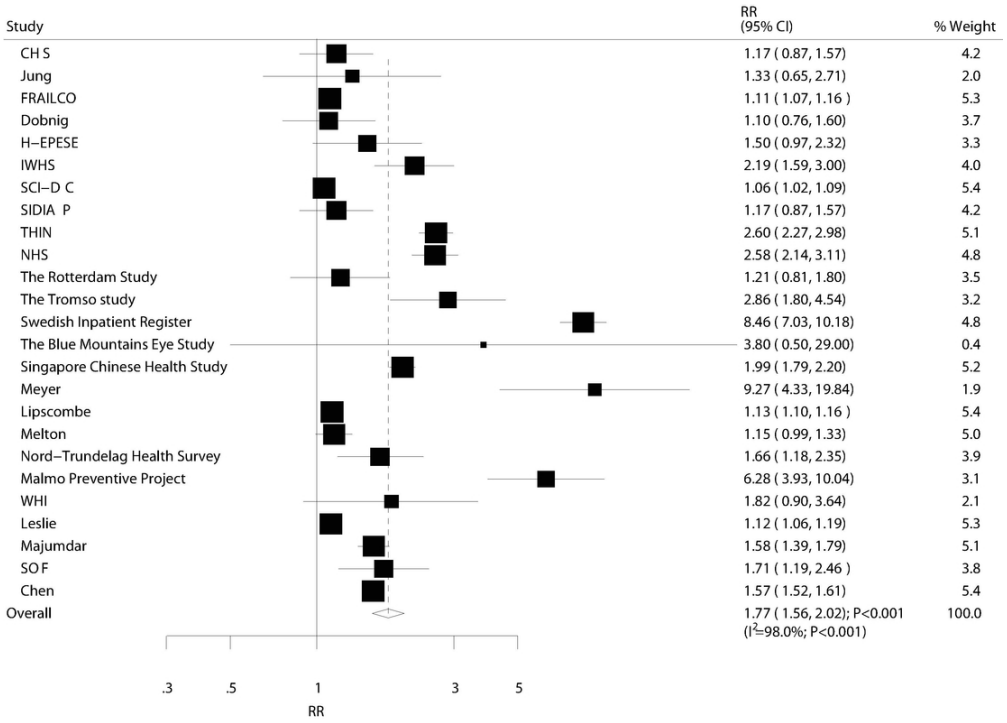

Fig 3. Association between DM and the risk of hip fracture.

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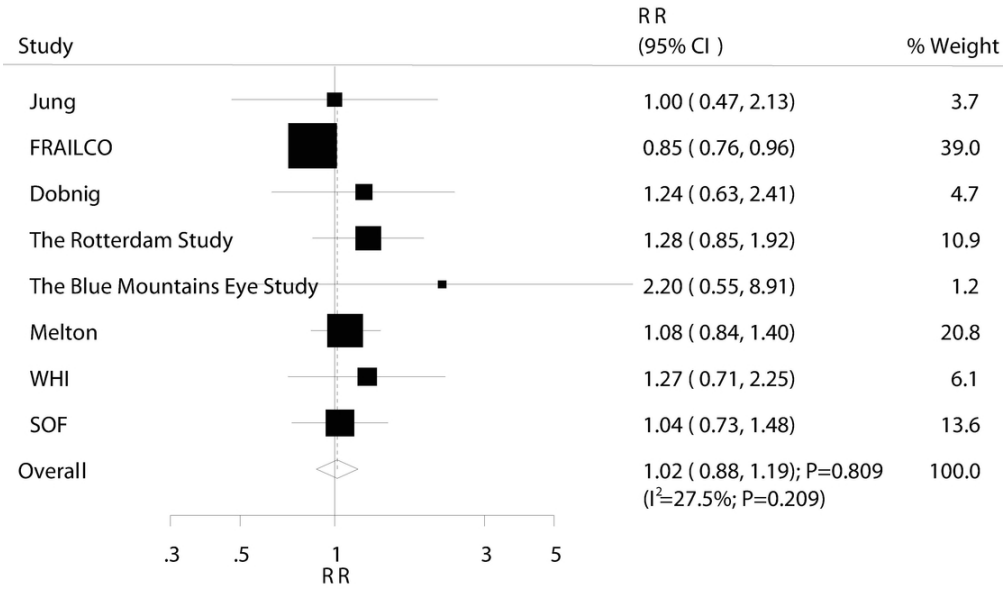

Fig 4. Association between DM and the risk of distal forearm fracture.

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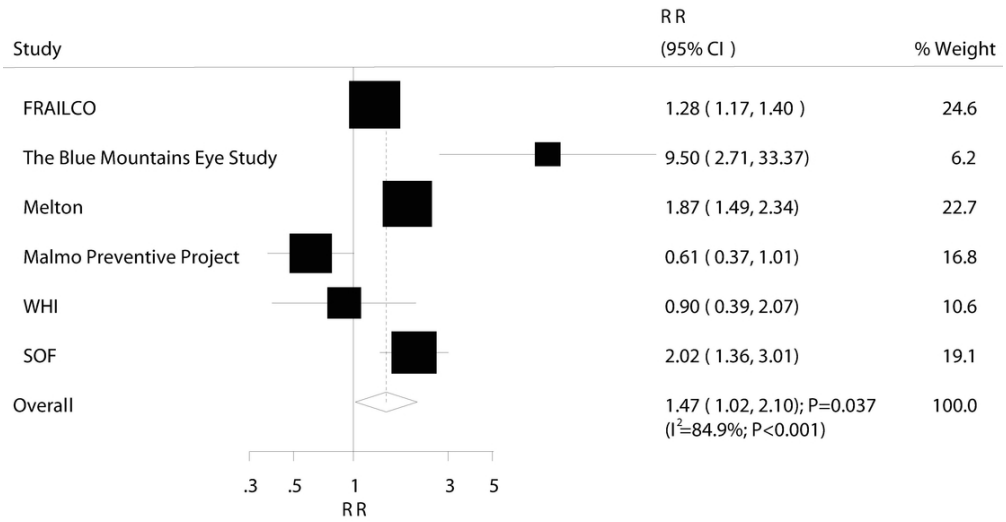

Fig 5. Association between DM and the risk of upper arm fracture.

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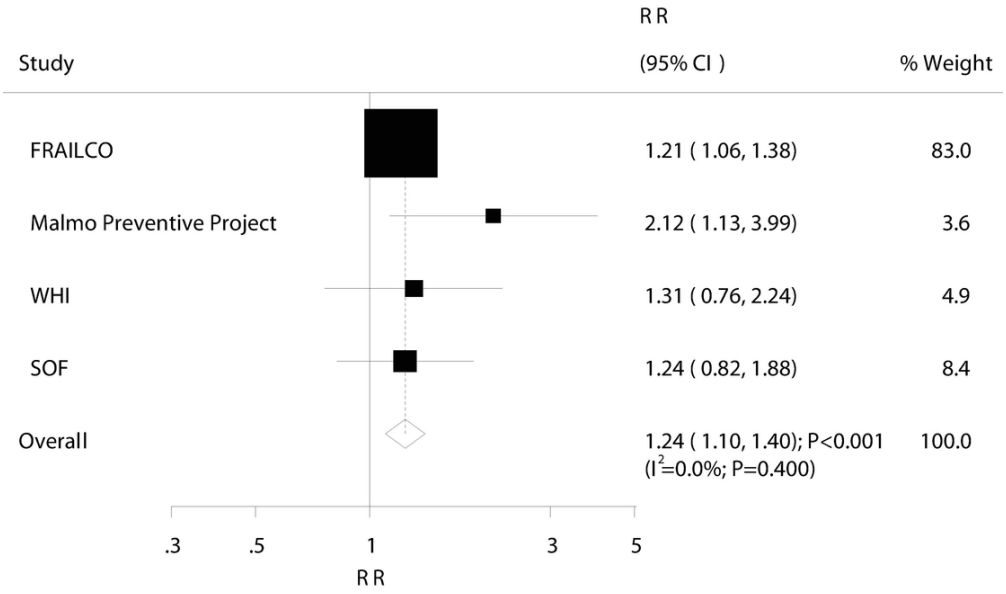

Fig 6. Association between DM and the risk of ankle fracture.

94x55mm (300 x 300 DPI)

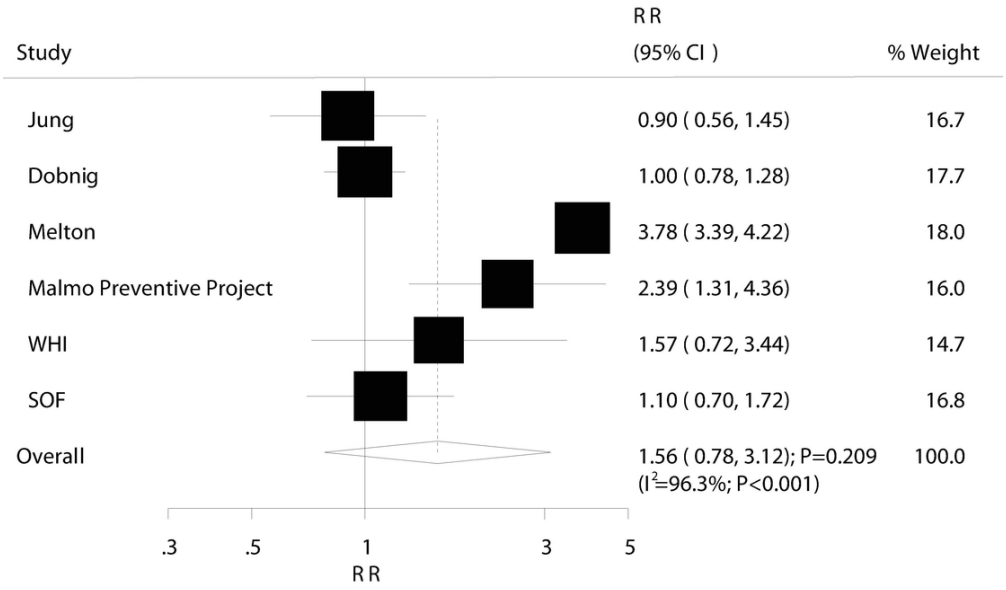

Fig 7. Association between DM and the risk of vertebrae fracture.

94x54mm (300 x 300 DPI)

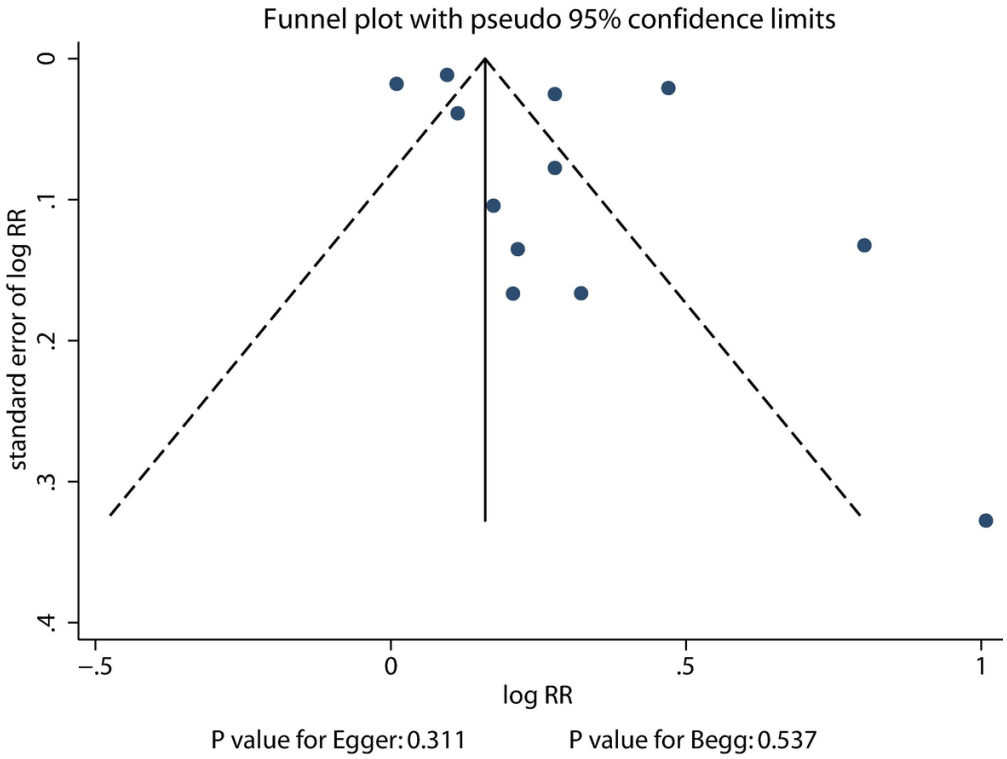

Fig 8. Publish bias for total fractures.

99x74mm (300 x 300 DPI)

Table S1. Additional characteristic of studies included

Study	Current smoker (%)	BMI (kg/m2)	DM ascertainment	Adjusted factors
CHS [25]	12.0	26.7	hypoglycemic medication use or a fasting glucose ≥126 mg/dL	Age, sex, race, BMI, AAI<0.9
Jung [26]	NA	<25.0	oral hypoglycemic agents or received insulin treatment	Age
FRAILCO [27]	NA	25.4	"treatment with insulin"as any known prescriptions of insulin and"treatment with oral antidiabetics"as any prescription of non-insulin antidiabetics (including injectable GLP-1 analogues) in the Drug Dispensation Register. Because many patients receive their diagnosis of type 2 diabetes in primary-care units and thus not included in the Patient Register and because of possible misclassifications between ICD E10 to E11, patients were classified as type 1 diabetes if they were diagnosed with E10 and had received prescriptions of insulin but no other non-insulin antidiabetic medications. We subsequently defined type 2 diabetes as all other patients with diabetes, based on either a diagnosis of E10 with oral antidiabetics, E11, or without any diagnosis but with known prescriptions of antidiabetic medications.	Age, sex, weight, height, previous fracture, RA, glucocorticoid, alendronate use, and CCI, and self-reported known fall injury
Dobnig [28]	NA	NA	antidiabetic drugs prescribed, or were found to have glycosylated HbA1c levels of more than 5.9%	Age and weight
H-EPESE [29]	42.1	NA	Physician diagnosis	Age, gender, BMI, ever smoked, previous stroke, lower extremity functional ability, and distance vision
IWHS [30]	15.0	26.9	Self-reported	Age, smoking, estrogen use, BMI, and WTHR

SCI-DC [31]	NA	NA	We defined type 1 diabetes on the basis of the type of diabetes assigned in the database with the additional requirement that the prescription history did not contradict this (ie, no evidence of lengthy period of diabete before insulin and no coprescribing of nonmetformin oral diabetes drugs). Type 2 diabetes was defined as either a recorded diagnosis of type 2 diabetes or a diagnosis of type 1 diabetes that was contradicted by clinical history and prescription data.	Age, calendar year, SIMD, and for the overall estimate, an SIMD-age interaction
SIDIAP [32]	15.6	29.3	T2DM diagnosis (ICD-10 codes E11.0, E11.1, E11.2, E11.3, E11.4, E11.5, E11.6, E11.7, E11.8, and E11.9)	BMI, previous fracture, oral corticoids
THIN [33]	26.7	25.5	Exposure to type 1 diabetes was defined by the presence of one or more Read codes specific for type 1 diabetes and the absence of a code specific for type 2 diabetes	Exposure to steroid medication, history of prior fracture, and presence of chronic kidney disease
NHS [34]	17.9	26.0	When women reported that diabetes had been diagnosed by a physician, confirmation was based on responses to a supplementary questionnaire about complications, diagnostic tests, and treatments	Age, BMI, physical activity, menopausal status and estrogen use, smoking and daily intake of calcium, vitamin D, and protein
The Rotterdam Study [35]	25.0	26.4	Diabetes was defined as antidiabetic medication use or a preload or postload serum glucose level>11.1 mmol/L	Age, sex, height, weight, and femoral neck BMD
The Tromsø study [36]	37.0	25.5	Medical records	Age, BMI, smoking, and metabolic features
Swedish Inpatient Register [37]	NA	NA	We used age<30 years at first hospitalization for diabetes (even if it preceded the start of cohort accrual) as an obligatory criterion	Age, sex, and calendar-period-matched general population from the entire Swedish inpatient registry
The Blue Mountains Eye Study [38]	NA	NA	Diabetes was diagnosed from a self-reported positive physician-diagnosis	Age, sex, and BMI
Singapore Chinese	19.4	NA	Physician diagnosed	Age at recruitment, sex, year of

Health Study [39]				recruitment, dialect group, level of education, weekly vigorous work or strenuous sports, BMI, smoking status, total calcium intake from food and supplement, total soy isoflavone intake, and self-reported stroke
Meyer [40]	16.9	NA	Nonfasting blood sample	Age, height, BMI, physical activity, stroke, receipt of a disability pension, marriage, and smoking
Lipscombe [41]	NA	NA	Ontario Diabetes Database	Age, chronic unstable disease, prior stroke, visual impairment, neuropathy, amputation, treatment with nitrates, statins, thiazides, estrogen, anticonvulsants, inhaled corticosteroids, and medications increasing falling risk, and history of BMD test
Melton [42]	NA	NA	Community medical records	Age, BMI, calcaneal BMD, or a host of other osteoporosis risk factors
Nord-Trùndelag Health Survey [43]	30.4	NA	blood sample drawn for analysis of HbA1	Age, BMI and daily smoking
Malmö Preventive Project [44]	NA	NA	Fasting blood glucose	Age, BMI, DBP, resting pulse rate, triglyceride level, gammaglutamyltransferase, smoking, poor self-rated health, sedimentation rate for women, and cholesterol or creatinine for men
WHI [45]	6.2	NA	Participants with type 1 diabetes, defined as those diagnosed before age 20 yr or who were ever hospitalized for a diabetic coma	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
Leslie [46]	NA	NA	two physician office visits or a single hospitalization with a diagnosis of diabetes (ICD-9-CM code 250)	Age, sex, income quintile, area of residence and ethnicity

Majumdar [47]	NA	27.1	coded using the ICD-9-CM prior to 2004 and International Classification of Diseases, 10th revision, Canada thereafter	FRAX scores, burden of comorbidity, falls, prescription osteoporosis treatments, and insulin therapy
SOF [48]	NA	26.2	Interview	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
Chen [49]	NA	NA	diabetes-related diagnosis (ICD-9 250 or A code 181)	Age as a continuous variable, geographic area, and urbanization status

*BMI: body mass index; AAI: ankle-armindex; NA: not available; RA: rheumatoid arthritis; CCI: Charlson comorbidity index; WTHR: waist-to-hip ratio; SIMD: Scottish Index of Multiple Deprivation

S1 Table. Quality scores of prospective cohort studies using Newcastle-Ottawa Scale.

Study	Selection				Comparability	Outcome			NOS
	Representativeness of the exposed cohort	Selection of the non exposed cohort	Ascertainment of DM disease	Demonstration that outcomes was not present at start of study	Comparability on the basis of the design or analysis	Assessment of outcome	Adequate follow-up duration	Adequate follow-up rate	Overall score
CHS [25]	0	1	1	1	2	1	1	1	8
Jung [26]	0	1	1	1	2	1	0	1	7
FRAILCO [27]	1	1	1	1	2	1	0	1	8
Dobnig [28]	0	1	1	1	1	1	0	1	6
H-EPESE [29]	0	1	1	1	2	1	0	1	7
IWHS [30]	1	1	1	1	2	1	1	1	9
SCI-DC [31]	1	1	1	1	2	1	0	0	7
SIDIAP [32]	1	1	1	1	2	1	0	1	8
THIN [33]	1	1	1	1	1	1	0	0	6
NHS [34]	1	1	1	1	2	1	1	1	9
The Rotterdam Study [35]	0	1	1	1	2	1	1	1	8
The Tromsø study [36]	1	1	1	1	2	1	0	1	8
Swedish Inpatient Register [37]	0	1	1	1	1	1	1	0	6
The Blue Mountains Eye Study [38]	0	1	1	1	2	1	0	1	7
Singapore Chinese	1	1	1	1	2	1	1	1	9

Health Study [39]									
Meyer [40]	1	1	1	1	2	1	1	1	9
Lipscombe [41]	1	1	1	1	1	1	0	1	7
Melton [42]	0	1	1	1	1	1	0	1	6
Nord-Trùndelag Health Survey [43]	1	1	1	1	2	1	1	1	9
Malmö Preventive Project [44]	1	1	1	1	2	1	0	0	7
WHI [45]	1	1	1	1	2	1	0	1	8
Leslie [46]	1	1	1	1	2	1	1	1	9
Majumdar [47]	1	1	1	1	2	1	0	1	8
SOF [48]	1	1	1	1	2	1	1	1	9
Chen [49]	1	1	1	1	2	1	0	1	8

S2 Table. Sensitivity analysis for total fractures

Excluding study	RR and 95% CI	P value	Heterogeneity (%)	P value for heterogeneity
Jung	1.32 (1.17-1.50)	<0.001	97.4	<0.001
FRAILCO	1.36 (1.17-1.58)	<0.001	96.9	<0.001
THIN	1.25 (1.14-1.36)	<0.001	91.7	<0.001
The Rotterdam Study	1.33 (1.17-1.51)	<0.001	97.4	<0.001
The Tromsø study	1.31 (1.16-1.46)	<0.001	97.4	<0.001
The Blue Mountains Eye Study	1.29 (1.14-1.46)	<0.001	97.4	<0.001
Melton	1.32 (1.16-1.51)	<0.001	97.2	<0.001
Malmö Preventive Project	1.26 (1.12-1.42)	<0.001	97.2	<0.001
WHI	1.32 (1.17-1.50)	<0.001	97.4	<0.001
Leslie	1.36 (1.19-1.56)	<0.001	96.6	<0.001
Majumdar	1.34 (1.18-1.53)	<0.001	97.4	<0.001
SOF	1.32 (1.16-1.49)	<0.001	97.4	<0.001

S3 Table. Sensitivity analysis for hip fracture

Excluding study	RR and 95% CI	P value	Heterogeneity (%)	P value for heterogeneity
CHS	1.81 (1.58-2.06)	<0.001	98.1	<0.001
Jung	1.78 (1.57-2.03)	<0.001	98.1	<0.001
FRAILCO	1.83 (1.59-2.10)	<0.001	98.0	<0.001
Dobnig	1.81 (1.58-2.06)	<0.001	98.1	<0.001
H-EPESE	1.78 (1.56-2.03)	<0.001	98.1	<0.001
IWHS	1.76 (1.54-2.00)	<0.001	98.1	<0.001
SCI-DC	1.83 (1.59-2.11)	<0.001	97.9	<0.001
SIDIAP	1.81 (1.58-2.06)	<0.001	98.1	<0.001
THIN	1.73 (1.52-1.97)	<0.001	97.9	<0.001
NHS	1.74 (1.53-1.98)	<0.001	98.0	<0.001
The Rotterdam Study	1.80 (1.58-2.05)	<0.001	98.1	<0.001
The Tromsø study	1.75 (1.53-1.99)	<0.001	98.1	<0.001
Swedish Inpatient Register	1.61 (1.44-1.80)	<0.001	97.1	<0.001
The Blue Mountains Eye Study	1.77 (1.55-2.01)	<0.001	98.1	<0.001
Singapore Chinese Health Study	1.76 (1.54-2.00)	<0.001	98.0	<0.001
Meyer	1.72 (1.51-1.95)	<0.001	98.1	<0.001
Lipscombe	1.83 (1.58-2.13)	<0.001	97.9	<0.001
Melton	1.81 (1.59-2.07)	<0.001	98.1	<0.001
Nord-Trùndelag Health Survey	1.78 (1.56-2.03)	<0.001	98.1	<0.001
Malmö Preventive Project	1.70 (1.50-1.93)	<0.001	98.0	<0.001
WHI	1.77 (1.56-2.02)	<0.001	98.1	<0.001
Leslie	1.82 (1.59-2.09)	<0.001	98.1	<0.001
Majumdar	1.78 (1.56-2.04)	<0.001	98.1	<0.001
SOF	1.78 (1.56-2.02)	<0.001	98.1	<0.001
Chen	1.79 (1.56-2.05)	<0.001	97.5	<0.001

S4 Table. Sensitivity analysis for distal forearm fracture.

Excluding study	RR and 95% CI	P value	Heterogeneity (%)	P value for heterogeneity
Jung	1.04 (0.87-1.23)	0.687	37.7	0.141
FRAILCO	1.13 (0.96-1.34)	0.139	0.0	0.928
Dobnig	1.02 (0.86-1.19)	0.849	33.1	0.176
The Rotterdam Study	0.97 (0.84-1.12)	0.671	17.3	0.298
The Blue Mountains Eye Study	1.00 (0.87-1.16)	0.965	26.8	0.224
Melton	1.02 (0.85-1.22)	0.846	27.3	0.220
WHI	1.01 (0.86-1.18)	0.942	29.8	0.201
SOF	1.04 (0.86-1.24)	0.700	35.4	0.158

S5 Table. Sensitivity analysis for upper arm fracture

Excluding study	RR and 95% CI	P value	Heterogeneity (%)	P value for heterogeneity
FRAILCO	1.59 (0.89-2.83)	0.116	85.1	<0.001
The Blue Mountains Eye Study	1.31 (0.95-1.82)	0.100	83.2	<0.001
Melton	1.40 (0.86-2.30)	0.178	83.3	<0.001
Malmö Preventive Project	1.73 (1.21-2.46)	0.003	82.8	<0.001
WHI	1.56 (1.06-2.29)	0.025	87.6	<0.001
SOF	1.36 (0.90-2.06)	0.142	86.2	<0.001

S6 Table. Sensitivity analysis for ankle fracture

Excluding study	RR and 95% CI	P value	Heterogeneity (%)	P value for heterogeneity
FRAILCO	1.42 (1.05-1.90)	0.021	2.2	0.360
Malmö Preventive Project	1.22 (1.08-1.38)	0.002	0.0	0.958
WHI	1.30 (1.03-1.63)	0.026	31.2	0.234
SOF	1.33 (1.02-1.73)	0.034	32.2	0.229

S7 Table. Sensitivity analysis for vertebrae fracture

Excluding study	RR and 95% CI	P value	Heterogeneity (%)	P value for heterogeneity
Jung	1.74 (0.82-3.69)	0.148	96.5	<0.001
Dobnig	1.72 (0.84-3.52)	0.140	93.5	<0.001
Melton	1.20 (0.89-1.63)	0.233	52.6	0.077
Malmö Preventive Project	1.44 (0.65-3.17)	0.370	97.1	<0.001
WHI	1.56 (0.72-3.35)	0.258	97.0	<0.001
SOF	1.67 (0.77-3.63)	0.194	96.6	<0.001

Searching strategy in PubMed:

PubMed	Search strategy
#1	"Diabetes Mellitus"[Mesh]
#2	diabetes OR diabetes mellitus OR type 2 diabetes mellitus OR type 1 diabetes mellitus OR glycuresis
#3	DM OR T2DM OR T1DM
#4	#1 OR #2 OR #3
#5	"fracture"[Mesh]
#6	fractures, spontaneous OR hip fractures OR osteoporotic fractures OR fractures, compression OR spinal fractures
#7	#5 OR #6
#8	epidemiologic study OR cohort
#9	#4 AND #7 AND #8

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4-5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	None
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5-6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	12
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	12
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	12-18
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	12-18
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	12-18
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	12-18
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	18-20
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	20
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	20
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	21

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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Diabetes mellitus and the risk of fractures at specific sites: a meta-analysis

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Diabetes mellitus and the risk of fractures at specific sites: a meta-analysis

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Abstract

Objective: Diabetes mellitus (DM) is associated with an increased fracture risk; however, the impact of DM and subsequent fracture at different sites and the associations according to patient characteristics remain unknown.

Design: Meta-analysis

Data Sources: The PubMed, EMBASE, and Cochrane Library databases were searched from inception to March 2018.

Eligibility Criteria: We included prospective and retrospective cohort studies on the associations of DM and subsequent fracture risk at different sites.

Data extraction and synthesis: Two authors independently extracted data and assessed the study quality. Relative risks (RRs) with 95% confidence intervals (CIs) were calculated using a random-effects model, and the heterogeneity across the included studies was evaluated using I^2 and Q statistics.

Results: Overall, DM was associated with an increased risk of total (RR: 1.32; 95% CI: 1.17–1.48; P<0.001), hip (RR: 1.77; 95% CI: 1.56–2.02; P<0.001), upper arm (RR: 1.47; 95% CI: 1.02–2.10; P=0.037), and ankle fractures (RR: 1.24; 95% CI: 1.10–1.40; P<0.001), whereas DM had no significant impact on the incidence of distal forearm (RR: 1.02; 95% CI: 0.88–1.19; P=0.809) and vertebral fractures (RR: 1.56; 95% CI: 0.78–3.12; P=0.209). RR ratios suggested that compared with type 2 DM (T2DM)

patients, type 1 DM (T1DM) patients had greater risk of total (RR ratio: 1.24; 95% CI: 1.08–1.41; P=0.002), hip (RR ratio: 3.43; 95% CI: 2.27–5.17; P<0.001), and ankle fractures (RR ratio: 1.71; 95% CI: 1.06–2.78; P=0.029). Although no other significant differences were observed between subgroups, the association of DM with upper arm or ankle, vertebrae, and total fracture differed according to sex, study design, and country, respectively.

Conclusions: DM patients had greater risks of total, hip, upper arm, and ankle fractures, with T1DM having a more harmful effect than T2DM.

Keywords: diabetes mellitus; fracture; meta-analysis

Article Summary:

Strengths and limitations of this study:

(1) The current study included articles that were based on cohort study designs, which could eliminate various confounding factors.

(2) A large sample size of patients was included; thus, our findings are potentially more robust than those of any individual study.

(3) DM diagnosis in individual studies was not consistent, which might have introduced confounding to the representative DM cohort.

(4) The adjusted models differed across the included studies, and the factors in these models might have played an important role in the development of fractures.

INTRODUCTION

Diabetes mellitus (DM) is considered a major global public health problem that is likely to be among the five leading causes of disease burden, with an estimated global prevalence of 4.4%, by 2030.[1] Age is an important factor, with the majority of DM patients aged >65 years.[2] Previous studies have confirmed the harmful impact of DM on the risk of vascular outcomes,[3,4] cancer at different sites,[5] and renal dysfunction.[6] Due to DM, patients might have altered calcium metabolism,[7] increased bone turnover,[8] and reduced bone mineral density (BMD);[9] which in turn may influence the risk of fractures in DM patients. However, previous meta-analyses reported different strengths of association between DM and the risk of fractures in type 1 and type 2 DM (T1DM and T2DM, respectively),[10,11] which highlights the need to verify and evaluate the association between DM and fracture at other sites.

Previous studies have illustrated the association between clinical factors and the risk of fractures at different sites.[12,13] However, due to limited sample sizes, the associations in patients with specific characteristics were not determined, and thus, there is a need for further verification. Furthermore, clinicians and patients could benefit from the assessment of fracture risk in patients. Therefore, it is of critical importance that clinicians are able to identify DM patients and the risk of fracture at different sites in patients with specific characteristics, to implement preventive strategies in each of such subsets. Vestergaard conducted a meta-analysis based on 16

observational studies and found that both T1DM and T2DM are associated with an increased risk of hip fracture, and that BMD is increased in T2DM but decreased in T1DM. However, fractures at other sites and differences according to country, sex, and study design were not separately assessed.[10] Fan et al. indicated that DM patients have a greater risk of hip fractures compared with non-DM individuals and that this association was more pronounced in T1DM patients.[11] However, the stratified results of individual studies should first be pooled using fixed-effect models, and the summary results of the included studies should be calculated using random-effects models. Furthermore, the associations between DM and the risk of fracture at other sites, including total, distal forearm, upper arm, ankle, and vertebra, were not assessed. Therefore, this study was conducted to determine whether the association between DM and fracture at different sites differed according to patient characteristics.

MATERIAL AND METHODS

Search strategy and inclusion criteria

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement (Checklist S1).[14] The PubMed, EMBASE, and Cochrane Library databases were searched for studies from their inception to March 2018 using the following core search terms: (“diabetes” OR “diabetes mellitus” OR “glycuresis”) AND (“fractures, spontaneous” OR “hip fractures”

OR “osteoporotic fractures” OR “fractures, compression” OR “spinal fractures” OR “fracture”) AND ("epidemiologic study" OR "cohort"). The details of the search strategy for PubMed are shown in Supplemental 1. We restricted the search to include only studies published in English. Furthermore, manual searches of reference lists of relevant studies were performed to identify additional eligible studies. The study topic, design, exposure, and fractures at different sites were used to identify relevant studies.

The literature search and study selection process were independently conducted by two authors using a standardized approach. Any inconsistency was resolved by group discussion until a consensus was reached. The study inclusion criteria are as follows: (1) a prospective or retrospective cohort design; (2) participants with T1DM or T2DM; and (3) report of the effect estimates of comparisons between DM and non-DM and the risk of fracture at different sites. We excluded case-control studies due to various confounding factors that could bias the results.

Data collection and quality assessment

Data extraction and quality assessment were conducted independently by two authors. The information was examined and adjudicated independently by an additional author by referring to the original studies. The abstracted data included the first author or study group’s name, publication year, country, study design, sample size, mean patient age, percentage of men, number of DM patients, percentage of current smokers, mean body

mass index (BMI), follow-up duration, DM diagnosis, and adjusted factors. The outcome variable was abstracted using the effect estimate with corresponding 95% confidence intervals (CIs). If the study reported several multivariable adjusted effect estimates, the effect estimate was maximally adjusted to account for potential confounders. The Newcastle-Ottawa Scale (NOS), which has been validated by evaluating the quality of observational studies in meta-analyses, was used to evaluate the methodological quality.[15] The NOS was based on selection (four items with a total of four stars), comparability (one item with a total of two stars), and outcome (three items with a total of three stars), with a total of nine stars for assessment.

Statistical analysis

The association between DM and the subsequent risk of fractures at different sites was based on effect estimates and corresponding 95% CIs in each study. We first used the fixed-effect model to calculate the summary relative risk (RR) and 95% CI for the association between DM and fractures in individual studies.[16] We then combined the RRs of fracture risk in DM versus non-DM individuals using a random-effects model.[17] Heterogeneity among the included studies was assessed using I^2 and Q statistics; and P values <0.10 were considered to indicate significant heterogeneity.[18,19] Sensitivity analyses were conducted by removing each individual study from the overall analysis.[20] Stratified analyses were conducted for total, hip,

distal forearm, upper arm, ankle, and vertebral fractures based on country, DM type, sex, and study design. The RR ratio and its 95% CI was estimated using specific RR and 95% CI according to country, DM types, sex, and study design.[21,22] Funnel plot, Egger,[23] and Begg[24] tests were used to evaluate publication bias for total fractures. P-values were 2-sided, and those <0.05 were considered statistically significant across the included studies. The statistical analyses were conducted using STATA (version 12.0; Stata Corporation, College Station, TX, USA).

Patient and public involvement

No patients were involved in the development of the research question, outcome measures, design, study implementation, dissemination of the results of the research to the study participants, or interpretation of the results.

RESULTS

Search of published literature

A total of 684 articles were identified from our electronic search, of which 602 were excluded due to duplication, irrelevance, and other design issues. We retrieved the full text for the remaining 59 studies and selected 25 cohort studies for the final analysis after detailed evaluations.[25-49] The manual search of the reference lists of relevant

reviews did not yield any new eligible studies. The results of the study selection process are shown in Fig 1, and the general characteristics of the included studies are presented in Table 1 and S1 Table.

Table 1. Baseline characteristic of studies included

Study	Publication year	Country	Study design	Sample size	Mean age (yr)	Per men (%)	Number of DM	Follow-up (yr)
CHS [25]	2011	US	Pro	5641	72.8	42.0	1456	10.9
Jung [26]	2012	Korea	Retro	2282	61.0	0.0	1268	7.0
FRAILCO [27]	2016	Sweden	Pro	428305	80.8	42.4	84702	1.3
Dobnig [28]	2006	Australia	Pro	1664	>70.0	0.0	583	2.0
H-EPESE [29]	2002	US	Pro	2884	71.8	42.1	690	7.0
IWHS [30]	2001	US	Pro	32089	61.6	0.0	1729	9.6
SCI-DC [31]	2014	UK	Retro	3801874	20.0-84.0	NA	201874	NA
SIDIAP [32]	2015	Spain	Pro	171931	62.6	56.5	58483	2.6
THIN [33]	2015	UK	Retro	334266	34.0	56.1	30394	5.7
NHS [34]	2006	US	Pro	109983	56.3	0.0	8640	20.0
The Rotterdam Study [35]	2013	Netherland	Pro	4135	68.4	40.6	420	12.2
The Tromsø study [36]	2006	Norway	Pro	27159	47.0	47.7	455	6.0

Swedish Inpatient Register [37]	2005	Sweden	Retro	24605	20.7	51.0	24605	9.9
The Blue Mountains Eye Study [38]	2001	Australia	Pro	3654	66.2	43.3	216	5.0
Singapore Chinese Health Study [39]	2010	Singapore	Pro	63257	56.4	44.3	5668	12.0
Meyer [40]	1993	Norway	Pro	52313	35.0-49.0	51.6	288	10.9
Lipscombe [41]	2007	Canada	Retro	598812	>66.0	50.6	197412	6.1
Melton [42]	2008	US	Retro	1964	61.7	51.0	1964	11.8
Nord-Trùndelag Health Survey [43]	1999	Norway	Pro	35444	50.0-74.0	47.5	1850	9.0
Malmö Preventive Project [44]	2006	Sweden	Pro	33346	27.0-61.0	67.3	166	16.0 for men and 11.0 for women
WHI [45]	2006	US	Pro	93676	63.4	0.0	5285	7.0
Leslie [46]	2007	Canada	Retro	318776	58.0	50.0	82094	10.0
Majumdar [47]	2016	Canada	Retro	57938	64.3	0.0	8840	7.2
SOF [48]	2001	US	Pro	9754	71.0	0.0	657	9.4
Chen [49]	2008	China	Retro	969820	60.0	47.0	484787	6.0

*Yr: year; Per: percentage; Pro: prospective; Retro: retrospective

Study characteristics

Of the 25 included studies, 16 used a prospective cohort design[25,27-30,32,34-36,38-40,43-45,48] while the remaining 9 studies used a retrospective cohort design.[26,31,33,37,41,42,46,47] The sample sizes ranged from 1,664 to 3,801,874; while the number of DM patients ranged from 166 to 484,787. Twelve studies were conducted in the US, Australia, or Canada;[25,28-30,34,38,41,42,45-48] 10 in Europe;[27,31-33,35-37,40,43,44] and the remaining 3 in Asia.[26,39,49] The results of total fractures were available in 12 studies, hip fractures in all studies, distal forearm fractures in 8 studies, upper arm fractures in 6 studies, ankle fractures in 4 studies, and vertebral fractures in 6 studies. Study quality was evaluated by NOS, and a study with seven or more stars was regarded as a high-quality study. Overall, 7, 8, 6, and the remaining 4 studies had scores of 9, 8, 7, and 6, respectively (S2 Table).

Total fractures

Overall, 12 studies reported an association between DM and the risk of total fractures. The summary RR indicated that compared with non-DM, having DM was associated with an increased risk of total fractures (RR: 1.32; 95% CI: 1.17–1.48; P<0.001; Fig 2) and substantial heterogeneity was detected (I^2=97.1%; P<0.001). The sensitivity analysis revealed that the conclusion was not affected by the sequential exclusion of individual studies from the overall analysis (S3 Table). A subgroup analysis of total fractures based on country, DM type, sex, and study design was performed. The results

showed that DM patients had an increased risk of total fractures in nearly all subsets except for studies conducted in Eastern countries (Table 2). Furthermore, the RR ratio for the comparison between T1DM and T2DM of the risk of total fractures was significantly increased, and the association was also statistically significant (ratio of RR: 1.24; 95% CI: 1.08–1.41; P=0.002; Table 2).

Table 2. Subgroup analysis for total fracture based on country, DM types, sex, and study design

Factors	Subsets	RR and 95%CI	P value	I^2(%)	P value for heterogeneity	Ratio of RR between subgroups	P value for ratios of RR
Country	Western	1.32 (1.17-1.50)	<0.001	97.4	<0.001	1.07 (0.76-1.52)	0.690
	Eastern	1.23 (0.89-1.70)	0.214	-	-		
DM types	I	1.51 (1.35-1.68)	<0.001	78.3	<0.001	1.24 (1.08-1.41)	0.002
	II	1.22 (1.13-1.31)	<0.001	83.0	<0.001		
Sex	Men	1.49 (1.20-1.85)	<0.001	96.1	<0.001	1.14 (0.89-1.46)	0.313
	Women	1.31 (1.16-1.49)	<0.001	92.8	<0.001		
Study design	Prospective	1.32 (1.20-1.46)	<0.001	83.4	<0.001	1.01 (0.84-1.21)	0.936
	Retrospective	1.31 (1.12-1.54)	0.001	97.6	<0.001		

*CI: confidence interval; DM: diabetes mellitus; RR: relative risk

Hip fracture

In total, 25 studies reported an association between DM and the risk of hip fracture. In

the pooled analysis, the comparison of DM and non-DM showed a harmful effect on hip fracture (RR: 1.77; 95% CI: 1.56–2.02; P<0.001; Fig 3). Although substantial heterogeneity was detected across the included studies (I^2=98.0%; P<0.001), the conclusion did not change after sequential exclusion of individual studies (S4 Table). The results of subgroup analysis for hip fracture are listed in Table 3, and all results indicated that DM had a harmful effect on hip fracture. Furthermore, the RR ratio showed a statistically significant association between DM and the risk of hip fracture in T1DM when compared with that of T2DM (ratio of RR: 3.43; 95% CI: 2.27–5.17; P<0.001).

Table 3. Subgroup analysis for hip fracture based on country, DM types, sex, and study design

Factors	Subsets	RR and 95%CI	P value	I^2(%)	P value for heterogeneity	Ratio of RR between subgroups	P value for ratios of RR
Country	Western	1.79 (1.56-2.05)	<0.001	97.5	<0.001	1.04 (0.81-1.34)	0.759
	Eastern	1.72 (1.39-2.14)	<0.001	89.5	<0.001		
DM types	I	4.35 (2.91-6.49)	<0.001	95.4	<0.001	3.43 (2.27-5.17)	<0.001
	II	1.27 (1.16-1.39)	<0.001	85.5	<0.001		
Sex	Men	2.05 (1.68-2.51)	<0.001	97.0	<0.001	1.00 (0.78-1.29)	0.969
	Women	2.04 (1.76-2.37)	<0.001	97.5	<0.001		
Study design	Prospective	2.02 (1.71-2.39)	<0.001	91.4	<0.001	1.09 (0.87-1.36)	0.472
	Retrospective	1.86 (1.60-2.16)	<0.001	98.7	<0.001		

*CI: confidence interval; DM: diabetes mellitus; RR: relative risk

Distal forearm fracture

Overall, eight studies reported an association between DM and the risk of distal forearm fracture. The summary RR showed that DM was not associated with the risk of distal forearm fracture (RR: 1.02; 95% CI: 0.88–1.19; P=0.809; Fig 4) and non-significant heterogeneity was observed (I^2=27.5%; P=0.209). The sensitivity analysis suggested that the conclusion was not affected by the exclusion of any specific study (S5 Table). The subgroup analysis indicated that the conclusions in each subset continued to be non-significant and no significant differences were observed between subgroups based on country, DM type, sex, or study design (Table 4).

Table 4. Subgroup analysis for distal forearm fracture based on country, DM types, sex, and study design

Factors	Subsets	RR and 95%CI	P value	I^2(%)	P value for heterogeneity	Ratio of RR between subgroups	P value for ratios of RR
Country	Western	1.04 (0.87-1.23)	0.687	37.7	0.141	1.04 (0.48-2.26)	0.921
	Eastern	1.00 (0.47-2.13)	1.000	-	-		
DM types	I	1.09 (0.43-2.75)	0.861	78.3	0.032	1.12 (0.43-2.94)	0.812
	II	0.97 (0.66-1.09)	0.573	13.1	0.323		
Sex	Men	1.04 (0.66-1.65)	0.863	58.5	0.090	1.12 (0.70-1.80)	0.644
	Women	0.93 (0.82-1.05)	0.257	6.3	0.380		
Study	Prospective	1.00 (0.83-1.19)	0.982	41.0	0.094	0.93 (0.69-01.27)	0.662

design	Retrospective	1.07 (0.84-1.37)	0.565	0.0	0.944

*CI: confidence interval; DM: diabetes mellitus; RR: relative risk

Upper arm fracture

In total, six studies reported an association between DM and the risk of upper arm fracture. Compared with non-DM, DM had a higher risk of upper arm fracture (RR: 1.47; 95% CI: 1.02–2.10; P=0.037; Fig 5) and evidence of significant heterogeneity was observed (I^2=84.9%; P<0.001). The sensitivity analysis indicated that the results varied possibly due to the smaller number of studies on fractures occurring in the upper arm (S6 Table). The subgroup analysis indicated that DM had no significant impact on upper arm fracture in men, whereas this risk increased in other subsets (Table 5).

Table 5. Subgroup analysis for upper arm fracture based on country, DM types, sex, and study design.

Factors	Subsets	RR and 95%CI	P value	I^2(%)	P value for heterogeneity	Ratio of RR between subgroups	P value for ratios of RR
Country	Western	1.47 (1.02-2.10)	0.037	84.9	<0.001	-	-
	Eastern	-	-	-	-		
DM types	I	1.83 (1.41-2.39)	<0.001	0.0	0.487	1.19 (0.82-1.72)	0.359
	II	1.54 (1.19-1.99)	0.001	79.6	<0.001		
Sex	Men	1.21 (0.80-1.83)	0.368	73.2	0.011	0.82 (0.50-1.36)	0.450
	Women	1.47 (1.10-1.96)	0.009	79.1	<0.001		

Study design	Prospective	1.38 (1.07-1.76)	0.011	76.0	<0.001	0.80 (0.47-1.36)	0.412
	Retrospective	1.72 (1.08-2.73)	0.022	68.5	0.075		

*CI: confidence interval; DM: diabetes mellitus; RR: relative risk

Ankle fracture

In all, four studies reported an association between DM and the risk of ankle fracture. The risk of ankle fracture significantly increased in DM patients (RR: 1.24; 95% CI: 1.10–1.40; P<0.001; Fig 6) with no evidence of heterogeneity (I^2=0.0%; P=0.400). The results of the sensitivity analysis were consistent with those of the overall analysis and are shown in S7 Table. The subgroup analysis showed no association between DM and ankle fracture risk in men, whereas in other subsets, the risk was significantly increased (Table 6). Furthermore, T1DM patients were at a greater risk of ankle fracture than were T2DM patients (ratio of RR: 1.71; 95% CI: 1.06–1.78; P=0.029; Table 6).

Table 6. Subgroup analysis for ankle fracture based on country, DM types, sex, and study design.

Factors	Subsets	RR and 95%CI	P value	I^2(%)	P value for heterogeneity	Ratio of RR between subgroups	P value for ratios of RR
Country	Western	1.24 (1.10-1.40)	<0.001	0.0	0.400	-	-
	Eastern	-	-	-	-		
DM types	I	1.97 (1.24-3.14)	0.004	29.3	0.234	1.71 (1.06-2.78)	0.029
	II	1.15 (1.01-1.31)	0.029	0.0	0.886		

Sex	Men	1.35 (0.68-2.65)	0.390	74.1	0.021	0.96 (0.46-2.01)	0.922
	Women	1.40 (1.07-1.84)	0.014	51.6	0.083		
Study design	Prospective	1.24 (1.10-1.40)	<0.001	0.0	0.400	-	-
	Retrospective	-	-	-	-		

*CI: confidence interval; DM: diabetes mellitus; RR: relative risk

Vertebrae fracture

Overall, six studies reported an association between DM and the risk of vertebrae fracture. The results of pooled analysis indicated no significant association between DM and vertebrae fracture risk (RR: 1.56; 95% CI: 0.78–3.12; P=0.209; Fig 7); and there was evidence of significant heterogeneity (I^2=96.3%; P<0.001). As a result, a sensitivity analysis was conducted and, although each study was sequentially excluded from the pooled analysis, the conclusion was not affected by the exclusion of any specific study (S8 Table). The subgroup analysis indicated that DM was associated with an increased risk of vertebrae fracture in retrospective cohort studies, whereas no significant effect in other subsets and no difference between subgroups were observed (Table 7).

Table 7. Subgroup analysis for vertebrae fracture based on country, DM types, sex, and study design.

Factors	Subsets	RR and 95%CI	P value	I^2(%)	P value for heterogeneity	Ratio of RR between subgroups	P value for ratios of RR

Country	Western	1.74 (0.82-3.69)	0.148	96.5	<0.001	1.93 (0.79-4.71)	0.146
	Eastern	0.90 (0.56-1.45)	0.664	-	-		
DM types	I	-	-	-	-	-	-
	II	1.74 (0.96-3.16)	0.070	96.7	<0.001		
Sex	Men	2.26 (0.40-12.73)	0.354	88.9	0.003	1.42 (0.23-8.85)	0.706
	Women	1.59 (0.88-2.87)	0.125	84.1	<0.001		
Study design	Prospective	1.36 (0.88-2.11)	0.167	66.4	0.018	0.54 (0.25-1.14)	0.105
	Retrospective	2.54 (1.37-4.70)	0.003	96.1	<0.001		

*CI: confidence interval; DM: diabetes mellitus; RR: relative risk

Publication bias

From the review of the funnel plots, publication bias for total fractures could not be ruled out (Fig 8). However, the Egger and Begg test results showed no evidence of publication bias (P value for Egger: 0.311; P value for Begg: 0.537).

DISCUSSION

Due to the consideration that the characteristics of DM patients might have affected the incidence of fractures at different sites, we used cohort studies to evaluate the correlations between DM and fractures according to country, DM type, sex, and study design. The meta-analysis included 7,185,572 participants from 16 prospective and 9 retrospective cohort studies with a broad range of individual characteristics. The

findings of this study indicated that DM was associated with an elevated risk of total, hip, upper arm, and ankle fractures but had no effect on distal forearm and vertebral fractures. The findings of the subgroup analyses were mostly consistent with those of the overall analysis except for those of total fracture in Eastern countries and upper arm and ankle fractures in men. Finally, compared with T2DM, T1DM was associated with a greater risk of total, hip, and ankle fracture.

A previous study based on 14 observational studies evaluated the association between T1DM and the risk of fractures [50]. The results indicated that T1DM was associated with a higher risk of total (RR, 3.16; P=0.002), hip (RR, 3.78; P<0.001) and spinal fractures (RR, 2.88; P<0.001). However, different study designs might bias this association and the role of the T2DM type was not evaluated in previous studies. Similar limitations of two other meta-analyses have already been described.[10,11] Therefore, the present meta-analysis of available cohort studies was performed to address these limitations.

The pooled results showed a significantly increased risk of total, hip, upper arm, and ankle fractures in DM patients compared with those in non-DM individuals; this result is consistent with those of previous studies.[10,11,50] However, several studies reported inconsistent results. After adjusting for BMI, sex, race, and age, Strotmeyer et al.[25] indicated that T2DM had no significant effect on the risk of hip fracture. Jung et al.[26] showed by the RR that in the T2DM cohort, increased risk of total and hip

fractures occurred, although these increases were not statistically significant. One possible explanation for this could be the number of patients newly diagnosed with DM that might be higher than that reported in other studies; and the increase in insulin level might affect bone metabolism. Furthermore, a smaller sample size and a lower incidence of fracture events were associated with lower statistical power and broad 95% CI in the previous study. Finally, the summary results for upper arm and ankle fractures might have varied due to the limited number of studies included; the interaction of these associations with age, severity of DM, and antidiabetic drugs should be explored.

There were no significant differences between DM patients and non-DM individuals with respect to distal forearm fracture. Most individual studies reported similar results, whereas the FRAILCO study indicated that DM was associated with a lower risk of distal forearm fracture.[27] The reason for this difference could be the study compared patients taking oral antidiabetics with non-DM individuals. Furthermore, the incidence of distal forearm fracture might be underestimated in register-based data. Finally, distal forearm fractures usually develop earlier in life, and the age of the participants in the individual studies might play a confounding role. Similar results were found for vertebral fractures. Two of the included studies indicated that T2DM was associated with a higher risk of vertebral fractures.[42,44] The reason for this finding could be the baseline levels of serum γ-glutamyl transferase and metabolic syndrome in women; as well as alcohol overconsumption, which are associated with higher serum γ-glutamyl transferase levels in men, and may play an important role in the risk of vertebral and

ankle fractures.[51-53]

The results of the stratified analysis were generally consistent with those of the overall analysis. However, two breakthroughs should be highlighted: (1) T1DM was associated with a higher risk of total, hip, and ankle fractures compared with that in T2DM. The possible reasons for this include the different reasons for the incidence of fracture, such as differences in BMI between T1DM and T2DM, which might have played a protective role in fractures.[54] Furthermore, while BMI is a major determinant of BMD and fracture risk, not all studies adjusted for the impact of BMI, which could have affected the intrinsic correlation of DM and fractures. (2) Although there was no significant effect on upper arm and ankle fractures in men with T2DM, these results might be unreliable due to the small number of studies included. This finding should be verified in future large-scale cohort studies.

This meta-analysis had several limitations. The DM diagnosis in individual studies was not consistent; this may have introduced confounders in the representative DM cohort. Furthermore, retrospective cohort studies might have introduced recall and selection biases, which could affect the evidence levels and representativeness of the cohorts. In addition, the adjusted models differed across the included studies; these factors might have played important roles in the development of fractures. Additionally, the substantial heterogeneity could not be explored completely due to the unavailability of several important factors, including metabolic syndrome and lifestyle. Finally, there

were limitations inherent to any meta-analysis, including publication bias and the lack of availability of individual data.

In conclusion, DM was associated with total, hip, upper arm, and ankle fractures. Furthermore, patients with T1DM had a higher risk of total, hip, and ankle fractures compared with those with T2DM. There was no sex difference in fractures at different sites. Future studies are warranted to clarify the effect of anti-diabetic therapies and investigate effective prevention strategies for fractures at different sites.

Authors' contributions

Jian-Ling Du and Hao Wang contributed to the conception and design; Hao Wang, Ying Ba, and Qian Xing contributed to acquisition, analysis, and interpretation of data; Hao Wang and Jian-Ling Du were involved in drafting or critical revision of the manuscript. All the authors approved the final version.

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Figure legends:

Fig 1. Study selection process.

Fig 2. Association between DM and the risk of total fractures.

Fig 3. Association between DM and the risk of hip fracture.

Fig 4. Association between DM and the risk of distal forearm fracture.

Fig 5. Association between DM and the risk of upper arm fracture.

Fig 6. Association between DM and the risk of ankle fracture.

Fig 7. Association between DM and the risk of vertebrae fracture.

Fig 8. Publish bias for total fractures.

Supporting information

S1 Table. Additional characteristics of studies included

S2 Table. Quality scores of prospective cohort studies using Newcastle-Ottawa Scale.

S3 Table. Sensitivity analysis for total fractures.

S4 Table. Sensitivity analysis for hip fracture.

S5 Table. Sensitivity analysis for distal forearm fracture.

S6 Table. Sensitivity analysis for upper arm fracture.

S7 Table. Sensitivity analysis for ankle fracture.

S8 Table. Sensitivity analysis for vertebrae fracture.

Checklist S1. PRISMA Checklist

Supplemental 1. Search strategy in PubMed

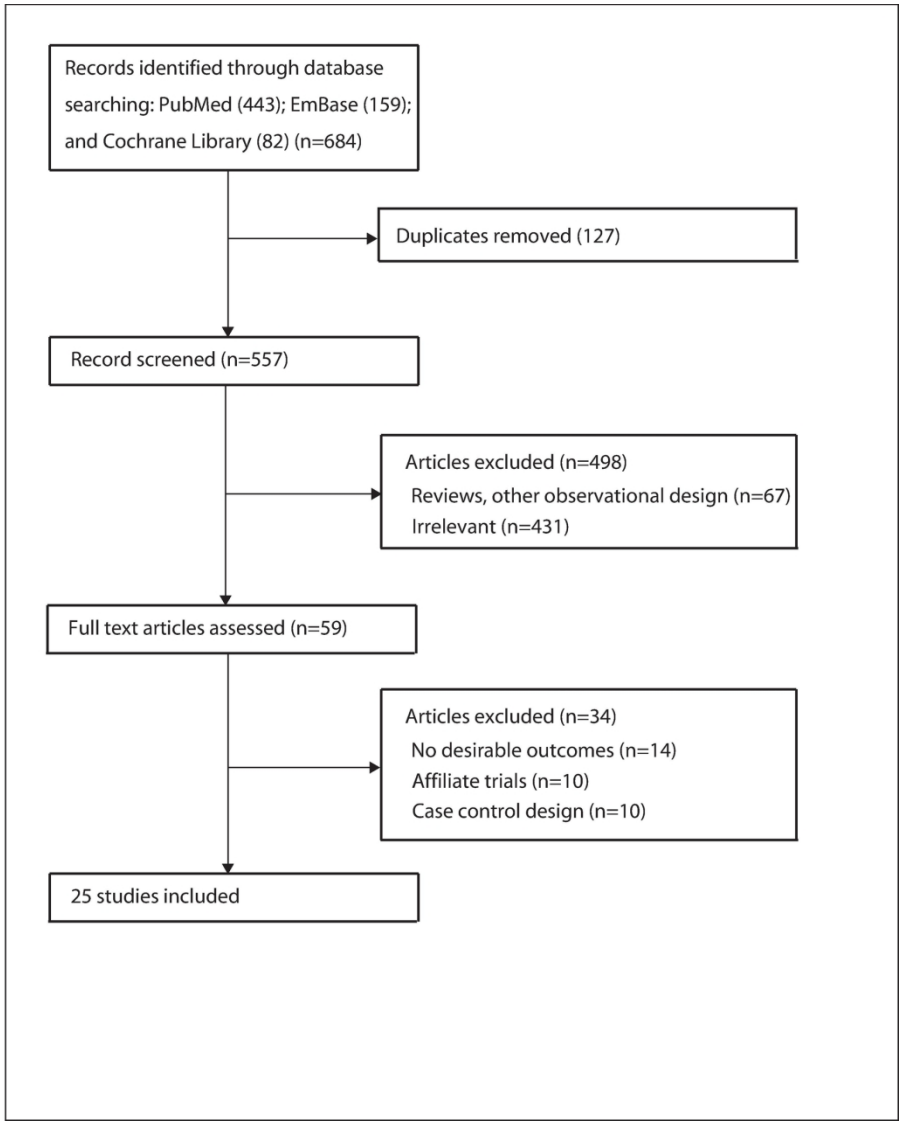

Fig 1. Study selection process.

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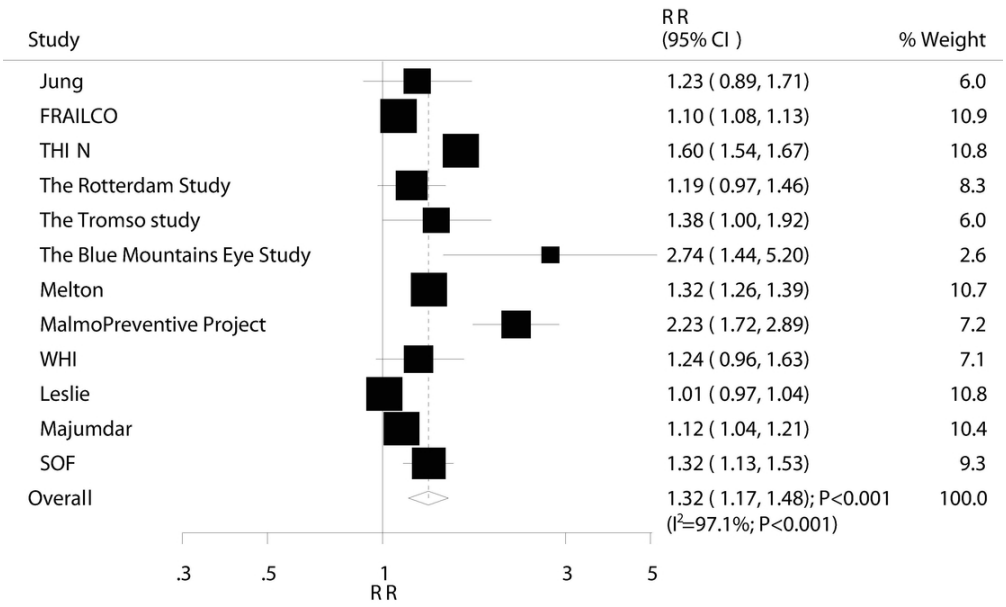

Fig 2. Association between DM and the risk of total fractures.

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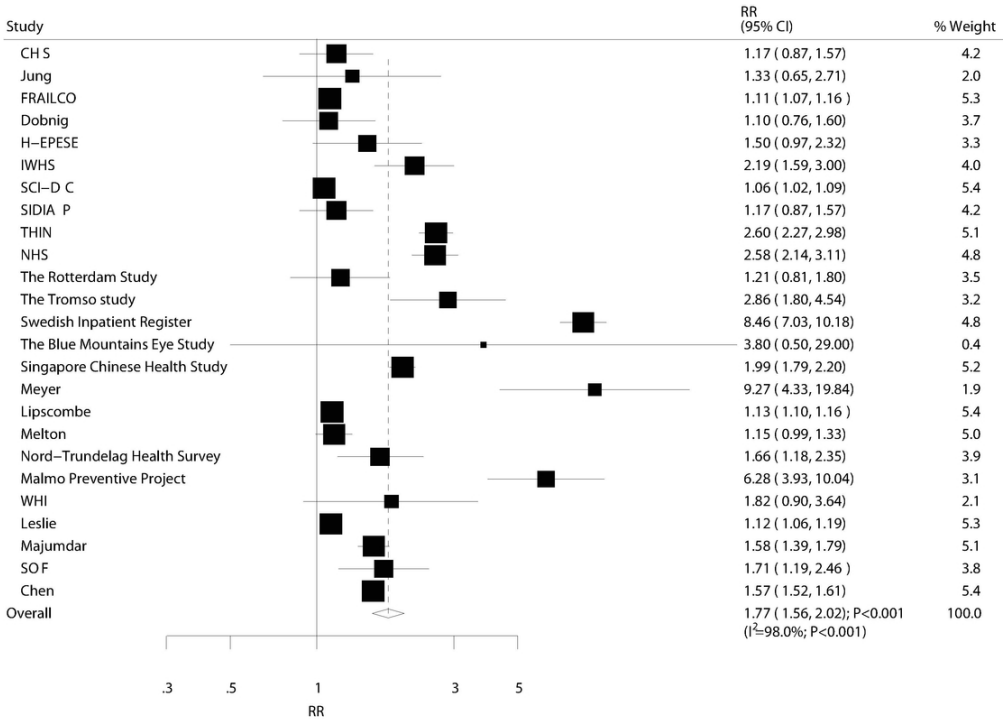

Fig 3. Association between DM and the risk of hip fracture.

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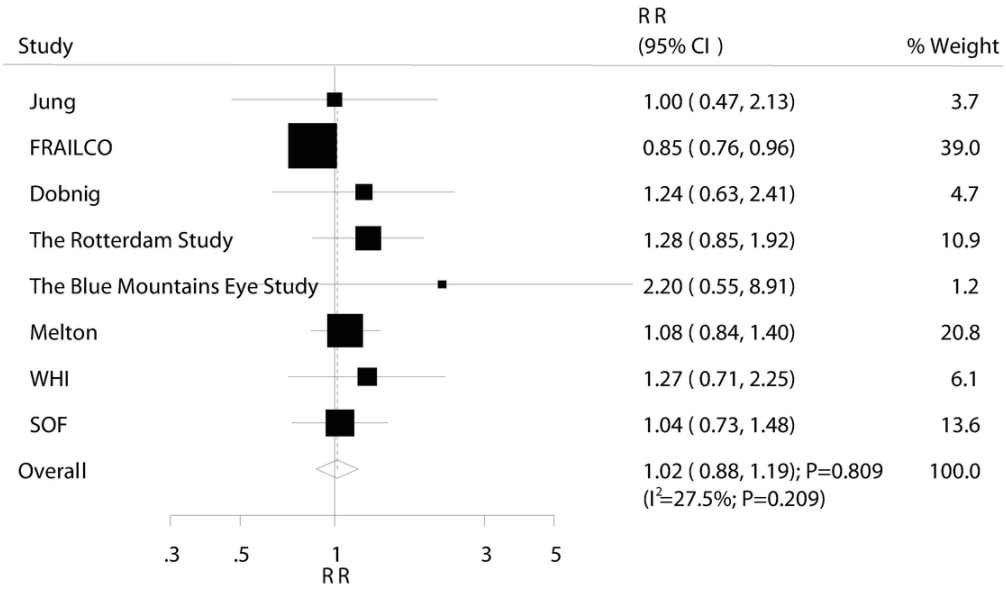

Fig 4. Association between DM and the risk of distal forearm fracture.

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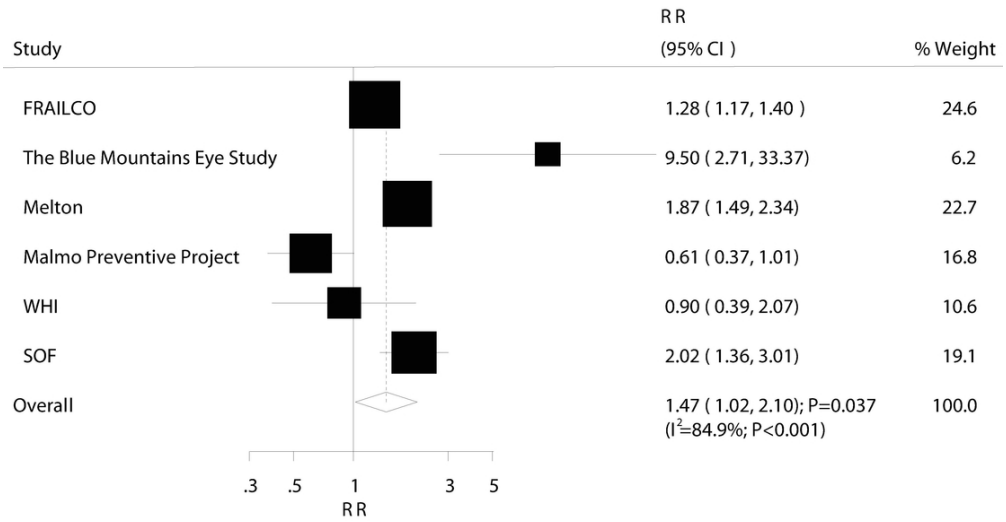

Fig 5. Association between DM and the risk of upper arm fracture.

94x48mm (300 x 300 DPI)

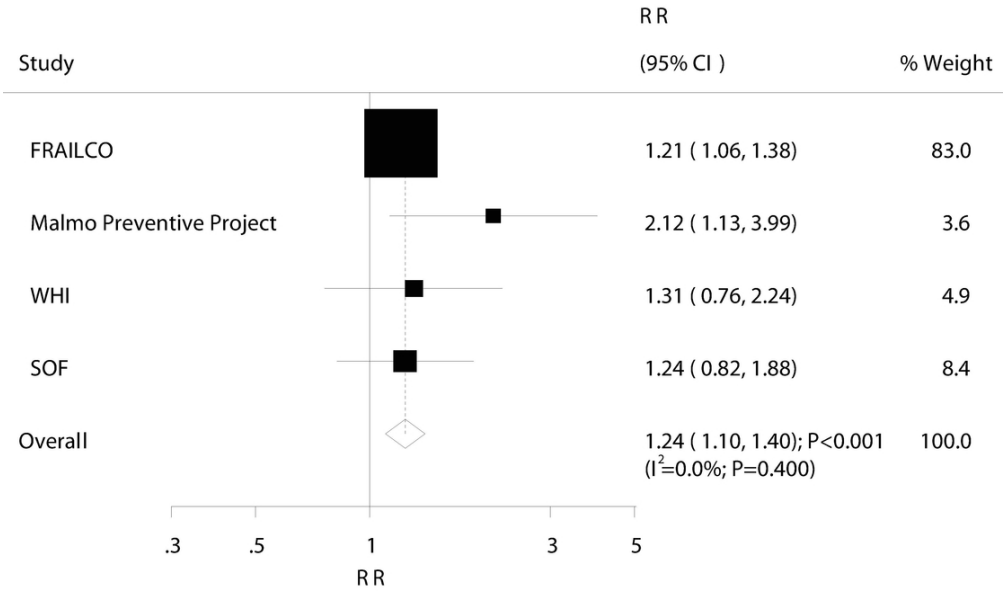

Fig 6. Association between DM and the risk of ankle fracture.

94x55mm (300 x 300 DPI)

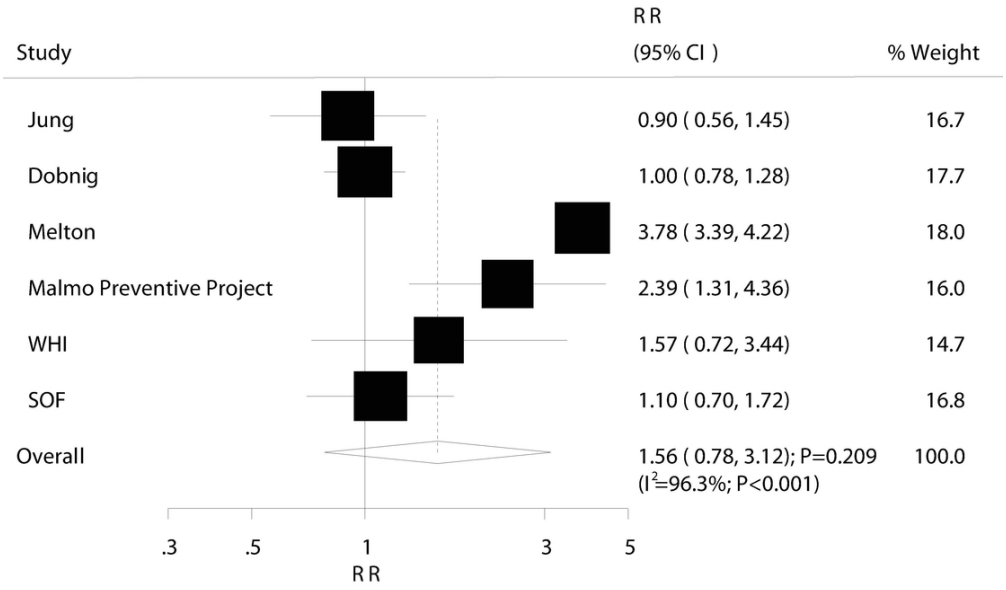

Fig 7. Association between DM and the risk of vertebrae fracture.

94x54mm (300 x 300 DPI)

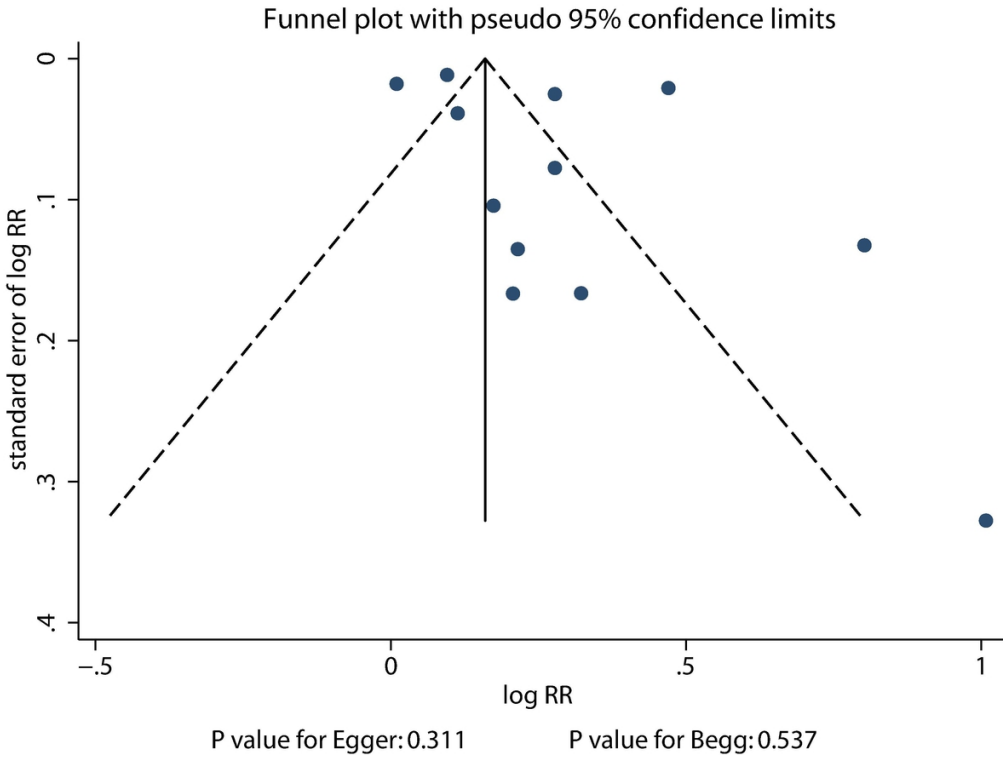

Fig 8. Publish bias for total fractures.

99x74mm (300 x 300 DPI)

S1 Table. Additional characteristics of studies included

Study	Current smoker (%)	BMI (kg/m^2)	DM ascertainment	Adjusted factors
CHS [25]	12.0	26.7	Hypoglycemic medication use or a fasting glucose ≥126 mg/dL	Age, sex, race, BMI, AAI<0.9
Jung [26]	NA	<25.0	Oral hypoglycemic agents or received insulin treatment	Age
ERAILCO [27]	NA	25.4	"treatment with insulin"as any known prescriptions of insulin and"treatment with oral antidiabetics"as any prescription of non-insulin antidiabetics (including injectable GLP-1 analogues) in the Drug Dispensation Register. Because many patients receive their diagnosis of type 2 diabetes in primary-care units and thus not included in the Patient Register and because of possible misclassifications between ICD E10 to E11, patients were classified as type 1 diabetes if they were diagnosed with E10 and had received prescriptions of insulin but no other non-insulin antidiabetic medications. We subsequently defined type 2 diabetes as all other patients with diabetes, based on either a diagnosis of E10 with oral antidiabetics, E11, or without any diagnosis but with known prescriptions of antidiabetic medications	Age, sex, weight, height, previous fracture, RA, glucocorticoid, alendronate use, and CCI, and self-reported known fall injury
Dobnig [28]	NA	NA	Antidiabetic drugs prescribed, or were found to have glycosylated HbA1c levels of more than 5.9%	Age and weight
H-EPESE [29]	42.1	NA	Physician diagnosis	Age, gender, BMI, ever smoked, previous stroke, lower extremity functional ability, and distance vision
WHS [30]	15.0	26.9	Self-reported	Age, smoking, estrogen use, BMI, and WTHR
SCI-DC [31]	NA	NA	We defined type 1 diabetes on the basis of the type of diabetes assigned in the database with the additional requirement that the prescription history did not contradict this (ie, no evidence of lengthy period of diabete before insulin and no coprescribing of nonmetformin oral diabetes drugs). Type 2 diabetes was defined as either a recorded diagnosis of type 2 diabetes or a diagnosis of type 1 diabetes that was contradicted by clinical history and prescription data	Age, calendar year, SIMD, and for the overall estimate, an SIMD-age interaction
SIDIAP	15.6	29.3	T2DM diagnosis (ICD-10 codes E11.0, E11.1,	BMI, previous fracture, oral corticoids

[32]			E11.2, E11.3, E11.4, E11.5, E11.6, E11.7, E11.8, and E11.9)	
THIN [33]	26.7	25.5	Exposure to type 1 diabetes was defined by the presence of one or more Read codes specific for type 1 diabetes and the absence of a code specific for type 2 diabetes	Exposure to steroid medication, history of prior fracture, and presence of chronic kidney disease
NHS [34]	17.9	26.0	When women reported that diabetes had been diagnosed by a physician, confirmation was based on responses to a supplementary questionnaire about complications, diagnostic tests, and treatments	Age, BMI, physical activity, menopausal status and estrogen use, smoking and daily intake of calcium, vitamin D, and protein
The Rotterdam Study [35]	25.0	26.4	Diabetes was defined as antidiabetic medication use or a preload or postload serum glucose level>11.1 mmol/L	Age, sex, height, weight, and femoral neck BMD
The Tromsø study [36]	37.0	25.5	Medical records	Age, BMI, smoking, and metabolic features
Swedish Inpatient Register [37]	NA	NA	We used age<30 years at first hospitalization for diabetes (even if it preceded the start of cohort accrual) as an obligatory criterion	Age, sex, and calendar-period- matched general population from the entire Swedish inpatient registry
The Blue Mountains Eye Study [38]	NA	NA	Diabetes was diagnosed from a self-reported positive physiciandiagnosis	Age, sex, and BMI
Singapore Chinese Health Study [39]	19.4	NA	Physician diagnosed	Age at recruitment, sex, year of recruitment, dialect group, level of education, weekly vigorous work or strenuous sports, BMI, smoking status, total calcium intake from food and supplement, total soy isoflavone intake, and self-reported stroke.
Meyer [40]	16.9	NA	Nonfasting blood sample	Age, height, BMI, physical activity, stroke, receipt of a disability pension, marriage, and smoking
Lipscombe [41]	NA	NA	Ontario Diabetes Database	Age, chronic unstable disease, prior stroke, visual impairment, neuropathy, amputation, treatment with nitrates, statins, thiazides, estrogen, anticonvulsants, inhaled corticosteroids, and medications increasing falling risk, and history of BMD test
Melton [42]	NA	NA	Community medical records	Age, BMI, calcaneal BMD, or a host of other osteoporosis risk factors
Nord-Trùnd clag Health	30.4	NA	Blood sample drawn for analysis of HbA1	Age, BMI and daily smoking

Survey [43]				
Malmö Preventive Project [44]	NA	NA	Fasting blood glucose	Age, BMI, DBP, resting pulse rate, triglyceride level, gamma-glutamyltransferase, smoking, poor self-rated health, sedimentation rate for women, and cholesterol or creatinine for men
WHI [45]	6.2	NA	Participants with type 1 diabetes, defined as those diagnosed before age 20 yr or who were ever Hospitalized for a diabetic coma	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
Leslie [46]	NA	NA	Two physician office visits or a single hospitalization with a diagnosis of diabetes (ICD-9-CM code 250)	Age, sex, income quintile, area of residence and ethnicity
Majumdar [47]	NA	27.1	Coded using the ICD-9-CM prior to 2004 and International Classification of Diseases, 10th revision, Canada thereafter	FRAX scores, burden of comorbidity, falls, prescription osteoporosis treatments, and insulin therapy
SOF [48]	NA	26.2	Interview	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
Chen [49]	NA	NA	Diabetes-related diagnosis (ICD-9 250 or A code 181)	Age as a continuous variable, geographic area, and urbanization status

*BMI: body mass index; AAI: ankle-armindex; NA: not available; RA: rheumatoid arthritis; CCI: Charlson comorbidity index; WTHR: waist-to-hip ratio; SIMD: Scottish Index of Multiple Deprivation

S2 Table. Quality scores of prospective cohort studies using Newcastle-Ottawa Scale.

Study	Selection				Comparability	Outcome			NOS
	Representativeness of the exposed cohort	Selection of the non exposed cohort	Ascertainment of DM disease	Demonstration that outcomes was not present at start of study	Comparability on the basis of the design or analysis	Assessment of outcome	Adequate follow-up duration	Adequate follow-up rate	Overall score
CHS [25]	0	1	1	1	2	1	1	1	8
Jung [26]	0	1	1	1	2	1	0	1	7
FRAILCO [27]	1	1	1	1	2	1	0	1	8
Dobnig [28]	0	1	1	1	1	1	0	1	6
H-EPESE [29]	0	1	1	1	2	1	0	1	7
IWHS [30]	1	1	1	1	2	1	1	1	9
SCI-DC [31]	1	1	1	1	2	1	0	0	7
SIDIAP [32]	1	1	1	1	2	1	0	1	8
THIN [33]	1	1	1	1	1	1	0	0	6
NHS [34]	1	1	1	1	2	1	1	1	9
The Rotterdam Study [35]	0	1	1	1	2	1	1	1	8
The Tromsø study [36]	1	1	1	1	2	1	0	1	8
Swedish Inpatient Register [37]	0	1	1	1	1	1	1	0	6
The Blue Mountains Eye Study [38]	0	1	1	1	2	1	0	1	7
Singapore Chinese	1	1	1	1	2	1	1	1	9

Health Study [39]									
Meyer [40]	1	1	1	1	2	1	1	1	9
Lipscombe [41]	1	1	1	1	1	1	0	1	7
Melton [42]	0	1	1	1	1	1	0	1	6
Nord-Trùndelag Health Survey [43]	1	1	1	1	2	1	1	1	9
Malmö Preventive Project [44]	1	1	1	1	2	1	0	0	7
WHI [45]	1	1	1	1	2	1	0	1	8
Leslie [46]	1	1	1	1	2	1	1	1	9
Majumdar [47]	1	1	1	1	2	1	0	1	8
SOF [48]	1	1	1	1	2	1	1	1	9
Chen [49]	1	1	1	1	2	1	0	1	8

S3 Table. Sensitivity analysis for total fractures

Excluding study	RR and 95% CI	P value	Heterogeneity (%)	P value for heterogeneity
Jung	1.32 (1.17-1.50)	<0.001	97.4	<0.001
FRAILCO	1.36 (1.17-1.58)	<0.001	96.9	<0.001
THIN	1.25 (1.14-1.36)	<0.001	91.7	<0.001
The Rotterdam Study	1.33 (1.17-1.51)	<0.001	97.4	<0.001
The Tromsø study	1.31 (1.16-1.46)	<0.001	97.4	<0.001
The Blue Mountains Eye Study	1.29 (1.14-1.46)	<0.001	97.4	<0.001
Melton	1.32 (1.16-1.51)	<0.001	97.2	<0.001
Malmö Preventive Project	1.26 (1.12-1.42)	<0.001	97.2	<0.001
WHI	1.32 (1.17-1.50)	<0.001	97.4	<0.001
Leslie	1.36 (1.19-1.56)	<0.001	96.6	<0.001
Majumdar	1.34 (1.18-1.53)	<0.001	97.4	<0.001
SOF	1.32 (1.16-1.49)	<0.001	97.4	<0.001

S4 Table. Sensitivity analysis for hip fracture

Excluding study	RR and 95% CI	P value	Heterogeneity (%)	P value for heterogeneity
CHS	1.81 (1.58-2.06)	<0.001	98.1	<0.001
Jung	1.78 (1.57-2.03)	<0.001	98.1	<0.001
FRAILCO	1.83 (1.59-2.10)	<0.001	98.0	<0.001
Dobnig	1.81 (1.58-2.06)	<0.001	98.1	<0.001
H-EPESE	1.78 (1.56-2.03)	<0.001	98.1	<0.001
IWHS	1.76 (1.54-2.00)	<0.001	98.1	<0.001
SCI-DC	1.83 (1.59-2.11)	<0.001	97.9	<0.001
SIDIAP	1.81 (1.58-2.06)	<0.001	98.1	<0.001
THIN	1.73 (1.52-1.97)	<0.001	97.9	<0.001
NHS	1.74 (1.53-1.98)	<0.001	98.0	<0.001
The Rotterdam Study	1.80 (1.58-2.05)	<0.001	98.1	<0.001
The Tromsø study	1.75 (1.53-1.99)	<0.001	98.1	<0.001
Swedish Inpatient Register	1.61 (1.44-1.80)	<0.001	97.1	<0.001
The Blue Mountains Eye Study	1.77 (1.55-2.01)	<0.001	98.1	<0.001
Singapore Chinese Health Study	1.76 (1.54-2.00)	<0.001	98.0	<0.001
Meyer	1.72 (1.51-1.95)	<0.001	98.1	<0.001
Lipscombe	1.83 (1.58-2.13)	<0.001	97.9	<0.001
Melton	1.81 (1.59-2.07)	<0.001	98.1	<0.001
Nord-Trùndelag Health Survey	1.78 (1.56-2.03)	<0.001	98.1	<0.001
Malmö Preventive Project	1.70 (1.50-1.93)	<0.001	98.0	<0.001
WHI	1.77 (1.56-2.02)	<0.001	98.1	<0.001
Leslie	1.82 (1.59-2.09)	<0.001	98.1	<0.001
Majumdar	1.78 (1.56-2.04)	<0.001	98.1	<0.001
SOF	1.78 (1.56-2.02)	<0.001	98.1	<0.001
Chen	1.79 (1.56-2.05)	<0.001	97.5	<0.001

S5 Table. Sensitivity analysis for distal forearm fracture.

Excluding study	RR and 95% CI	P value	Heterogeneity (%)	P value for heterogeneity
Jung	1.04 (0.87-1.23)	0.687	37.7	0.141
FRAILCO	1.13 (0.96-1.34)	0.139	0.0	0.928
Dobnig	1.02 (0.86-1.19)	0.849	33.1	0.176
The Rotterdam Study	0.97 (0.84-1.12)	0.671	17.3	0.298
The Blue Mountains Eye Study	1.00 (0.87-1.16)	0.965	26.8	0.224
Melton	1.02 (0.85-1.22)	0.846	27.3	0.220
WHI	1.01 (0.86-1.18)	0.942	29.8	0.201
SOF	1.04 (0.86-1.24)	0.700	35.4	0.158

S6 Table. Sensitivity analysis for upper arm fracture

Excluding study	RR and 95% CI	P value	Heterogeneity (%)	P value for heterogeneity
FRAILCO	1.59 (0.89-2.83)	0.116	85.1	<0.001
The Blue Mountains Eye Study	1.31 (0.95-1.82)	0.100	83.2	<0.001
Melton	1.40 (0.86-2.30)	0.178	83.3	<0.001
Malmö Preventive Project	1.73 (1.21-2.46)	0.003	82.8	<0.001
WHI	1.56 (1.06-2.29)	0.025	87.6	<0.001
SOF	1.36 (0.90-2.06)	0.142	86.2	<0.001

S7 Table. Sensitivity analysis for ankle fracture

Excluding study	RR and 95% CI	P value	Heterogeneity (%)	P value for heterogeneity
FRAILCO	1.42 (1.05-1.90)	0.021	2.2	0.360
Malmö Preventive Project	1.22 (1.08-1.38)	0.002	0.0	0.958
WHI	1.30 (1.03-1.63)	0.026	31.2	0.234
SOF	1.33 (1.02-1.73)	0.034	32.2	0.229

S8 Table. Sensitivity analysis for vertebrae fracture

Excluding study	RR and 95% CI	P value	Heterogeneity (%)	P value for heterogeneity
Jung	1.74 (0.82-3.69)	0.148	96.5	<0.001
Dobnig	1.72 (0.84-3.52)	0.140	93.5	<0.001
Melton	1.20 (0.89-1.63)	0.233	52.6	0.077
Malmö Preventive Project	1.44 (0.65-3.17)	0.370	97.1	<0.001
WHI	1.56 (0.72-3.35)	0.258	97.0	<0.001
SOF	1.67 (0.77-3.63)	0.194	96.6	<0.001

Search strategy in PubMed:

PubMed	Search strategy
#1	"Diabetes Mellitus"[Mesh]
#2	diabetes OR diabetes mellitus OR type 2 diabetes mellitus OR type 1 diabetes mellitus OR glycuresis
#3	DM OR T2DM OR T1DM
#4	#1 OR #2 OR #3
#5	"fracture"[Mesh]
#6	fractures, spontaneous OR hip fractures OR osteoporotic fractures OR fractures, compression OR spinal fractures
#7	#5 OR #6
#8	epidemiologic study OR cohort
#9	#4 AND #7 AND #8

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4-5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	None
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5-6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	12
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	12
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	12-18
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	12-18
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	12-18
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	12-18
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	18-20
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	20
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	20
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	21

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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