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The Risk of Hip and Non-vertebral Fractures in Type 1 and Type 2 Diabetes: A Systematic Review and Meta-Analysis update

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Abstract

Background

Diabetes is associated with increased fracture risk but we do not know what affects this risk. We investigated the risk of hip and non-vertebral fractures in diabetes and whether

this risk was affected by age, gender, body mass index, diabetes type and duration, insulin use and diabetic complications.

Methods

We selected a previously published review to be updated. MEDLINE, Embase and Cochrane databases were searched up to March 2020. We included observational studies with age and gender-adjusted risk of fractures in adults with diabetes compared to adults without diabetes. We extracted data from published reports that we summarised using random effects model.

Findings

From the 3140 records identified, 49 were included, 42 in the hip fracture analysis, reporting data from 17,571,738 participants with 319,652 fractures and 17 in the non-vertebral fracture review, reporting data from 2,978,487 participants with 181,228 fractures. We found an increase in the risk of fracture in diabetes both for hip (RR 4.93, 3.06-7.95, in type 1 diabetes and RR1.33, 1.19-1.49, in type 2 diabetes) and for non-vertebral fractures (RR 1.92, 0.92-3.99, in type 1 and RR 1.19, 1,11-1.28 in type 2). At the hip, the risk was higher in the younger population in both type 1 and type 2 diabetes. In those with type 2 diabetes, longer diabetes duration and insulin use was associated with an increased risk. We did not investigate the effect of bone density, falls, anti-diabetic drugs and hypoglycemia.

Conclusion

Diabetes is associated with an increase in both hip and non-vertebral fracture risk.

Highlights

The risk of hip fractures was greater in T1D than T2D

Hip fracture risk is higher in in people younger than 65 years for both type 1 and type 2 diabetes

In type 2 diabetes, insulin use and longer diabetes duration is associated with greater risk of hip fractures

Introduction

Diabetes is a public health concern. The global prevalence has recently increased from 4.7% to 8.5%. In 2016, 1.6 million deaths were directly caused by diabetes (1). Fractures are also a public health concern. Notably, up to 20% of patients die in the first year after a hip fracture, and less than half regain the previous level of function (2). People

with diabetes have higher mortality after a hip fracture as compared to people without diabetes (3).

Fractures at the spine, hip, wrist and humerus are considered major osteoporotic fractures. Whilst hip, wrist and humerus fractures are usually captured by hospital records, vertebral fractures are often asymptomatic. They are largely underdiagnosed and their identification requires spinal imaging. A recent review on the risk of vertebral fractures was based on individual participant data from cohorts, since registry data would not be reliable (4). Hip fractures are associated with the greatest morbidity and mortality. The analysis of non-vertebral fractures allows a comprehensive approach not affected by the complexity of assessing vertebral fractures, enabling the use of registry data. A number of reviews have assessed the risk of fractures in diabetes but they have not explored the risk of non-vertebral fractures as a group nor the effect of important features such as age, body mass index (BMI), diabetes duration, insulin use and the presence of complications (4-10). The aim of this systematic review and meta-analysis was to update the risk of hip fracture and to assess the risk of non-vertebral fractures in adults with diabetes compared to adults without diabetes in observational studies. We also assessed if gender, age, BMI and diabetes-related features such as diabetes type, duration, insulin use and the presence of complications affect this risk.

Methods

Search strategy and selection criteria

This review complies with key principles from the Cochrane Handbook and the Centre for Reviews Dissemination Handbook (11, 12). This report followed the Preferred

Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and MOOSE guidelines (13, 14). The protocol was registered in PROSPERO (CRD42018090378).

The search strategy was to identify a published systematic review that we could then update. Searches were conducted on 9th March 2018 (MEDLINE, Embase and Cochrane databases) and updated (primary study) up to 25th March 2020 (MEDLINE). The full search strategies are described in appendix 1. In summary, we combined terms for fractures and diabetes mellitus and related synonyms including free and thesaurus terms. The most comprehensive review with inclusion and exclusion criteria similar to this review was selected. The primary study research was conducted from the date of the selected review search, June 2006. The reference lists of key existing reviews were searched for additional primary studies (5, 7-9, 15) and experts in the field were consulted for additional relevant studies.

We included systematic reviews of observational studies (review of systematic reviews) or summary estimates of observational studies that reported age and gender adjusted risk of hip and/or non-vertebral fractures in adults (>18 years) with diabetes compared to participants without diabetes. Studies were excluded if: the diabetes definition/diagnosis or the comparator group was unclear; the diabetes diagnosis was made after the fracture or where the sequence was unclear; only data including spine/vertebral fractures were reported; fracture risk was based on an algorithm or risk tool; outcome data was unclear, missing or incomplete; the study was not in English; or was a narrative review, letter, editorial, commentary, conference abstract, animal or biological study.

For both the previous reviews and primary studies searches, one reviewer excluded clearly irrelevant records on the basis of their title and abstracts. A second reviewer independently sifted a 10% sample and the kappa statistic for the agreement was calculated. The full text sift was conducted by one reviewer in the reviews search and independently by two reviewers in the primary study search. Disagreements at any step were resolved through discussion or involvement of a third reviewer.

Data analysis

Search results were uploaded to Endnote and the duplicates were removed. Two reviewers independently conducted the data extraction, the quality assessment and the data checking using standardized and piloted forms (appendix 2 and 3). The full text of studies included in the existing systematic review were revisited for data extraction and quality assessment. For each study, we extracted the author, date, country, diabetes type, age, follow-up, population (total/ DM), number of fractures, ethnicity, gender, fracture site and risk estimate.

We used the Newcastle Ottawa Scales (NOS) to assess study quality (appendix 3). The tool assesses the selection and comparability of the study groups, and the ascertainment of exposure (for case-control studies) or outcome of interest (for cohort studies). Stars are awarded to a maximum of nine. We considered studies scoring equal or greater than seven to be high quality. We conducted a narrative synthesis, including tabulation of study characteristics, and a description of the available data.

Some studies reported the risk estimates in several categories, such as gender, age groups and diabetes type. Studies that reported more than two risk estimate for a given group in the subgroup analyses were summarised using the random-effects model, before the main analysis. For the non-vertebral fracture analyses, studies that reported the risk of fractures for two or more sites were summarised using the random effects model.

Subgroup analyses anticipated in the protocol (gender, age, BMI, DM type and duration, insulin use and the presence of complications) and an exploratory analysis for the same features for each diabetes type were performed when enough data was available. The ratio of relative risk (RRR) and the 95% CI was applied to compare the risk (16). Studies that described the same population but reported the risk for different subgroups were included in different subgroup analysis, but a given population/cohort was not included twice in the same analysis. For the overall analysis the most comprehensive data was included. We used the random-effects model (DerSimonian & Laird method) to pool the studies.

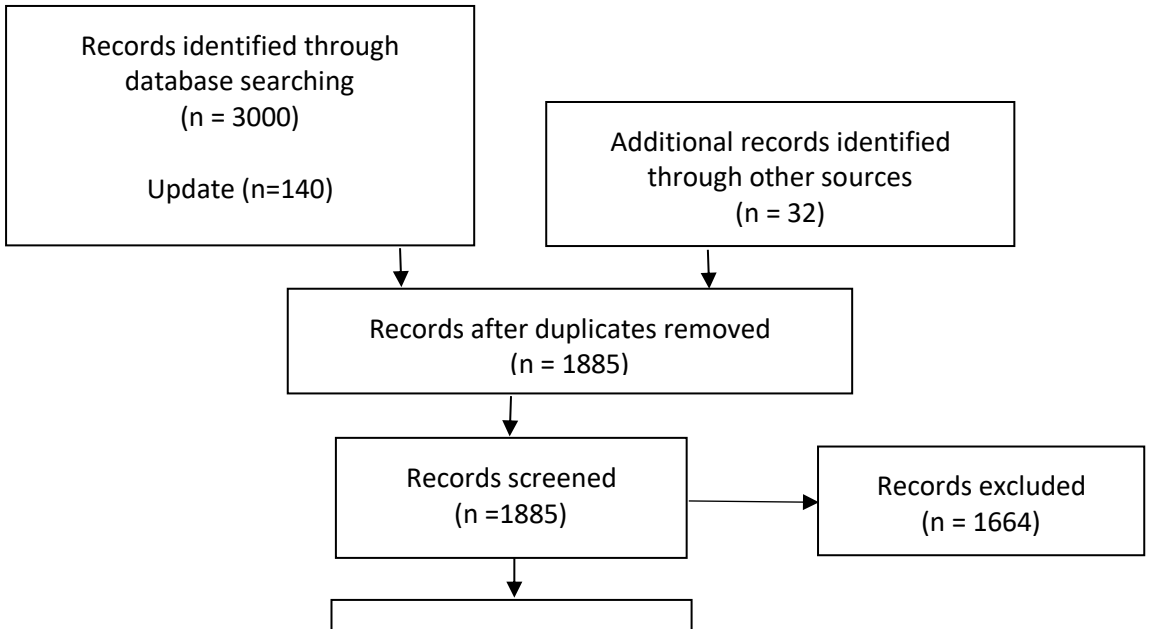
Heterogeneity, when high, was explored by subgroup analysis, sensitivity analysis and meta-regression. Subgroup analyses were performed when enough data was available. We performed a sensitivity analysis excluding one study at a time, the case-control studies, the studies that scored less than seven in the quality assessment and each kind of risk estimate included (e.g. hazard ratio). In the hip fracture analysis, meta-regression was performed to assess how much of the variation observed was due to diabetes type

or age group (< 65 years vs > 65 years). We used STATA/IC 16.0 software (StataCorp, USA).

Results

The search for systematic reviews identified 452 unique records, 388 excluded on the assessment of the title and abstract. From the remaining 64 records, eight reviews reported the risk of fractures in diabetes and one was selected (6). The kappa statistic for the agreement between reviewers about studies selection was perfect (1.00 95%CI 1.0, 1.0).

The search process of primary studies is described in the PRISMA diagram (fig 1). From the 3140 records identified, 221 underwent full-text assessment and 49 studies met the inclusion criteria. Of these, 48 were included in the meta-analyses, 42 in the hip fractures analysis (17-58) and 17 in the analysis of non-vertebral fractures (17, 21, 28, 30, 32, 34, 36, 50, 52, 53, 56, 57, 59-63). Studies that included some or all of the same patients as another study (overlapping studies) were included if they reported different aspects of that population that could be used in our subgroup analyses. Potential small overlaps were considered non-relevant.



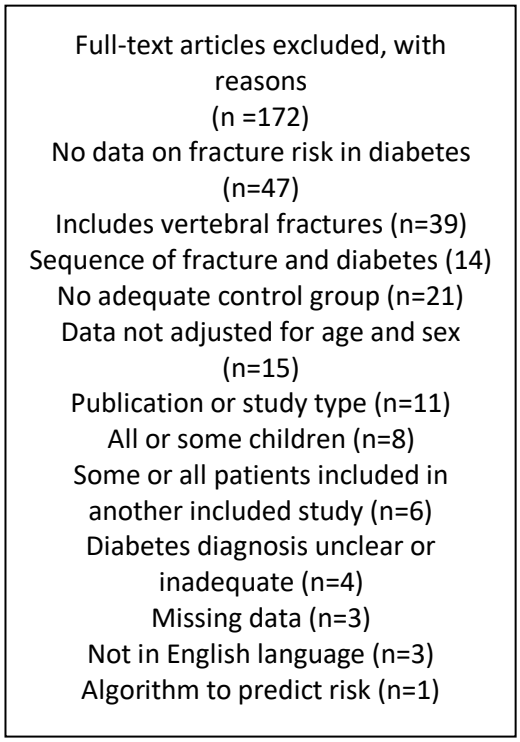


Fig 1 Prisma Flowchart (List of papers excluded at full text in appendix 4)

Hip fractures

Hip fracture study characteristics

Table 1 summarises the study characteristics. Forty-three studies reported data on hip fracture risk in people with diabetes compared to people without diabetes (17-58, 64). Six analysed overlapping populations but reported subgroup data relevant to our subgroup analyses (19-21, 28, 29, 38-40, 44, 45, 64). One study with overlapping

247 population was the only study to report the RR according to metabolic control and was
248 not included in the meta-analysis (64). Forty studies were cohorts (17-23, 25-48, 50-
249 53, 55-58, 64) and three studies were case-control studies (24, 49, 54). The study size
250 varied from 238 (54) to 3,861,874 participants (31). Nineteen studies were from North
251 America; five from Canada (38-42) and others from the USA (18, 24, 33, 36, 37, 43, 47-
252 49, 51-53, 55, 56). Sixteen studies were from Europe; three from Norway (17, 23, 46),
253 two from the Netherlands (21, 64), one from Austria (22), three from the United
254 Kingdom (27, 31, 58), two from Denmark (28, 29), two from Sweden (30, 57), two from
255 Spain (44, 45), and one from Germany (50). Five studies were from Asia (Taiwan (19,
256 20), Korea (34), Singapore (35) and Israel (54) and three from Australia (25, 26, 32). Two
257 studies reported data only from T1D participants (26, 58), ten studies reported data
258 only from T2D participants (21, 22, 25, 34, 44, 45, 49, 50, 53, 64) and the others reported
259 data from participants of both DM types (17, 23, 27, 31, 33, 37-39, 41-43, 47, 57) or did
260 not specify the participant's DM type (18-20, 24, 28-30, 32, 35, 36, 40, 46, 48, 51, 52,
261 54-56). Ages varied from 20 to 100 years. Six studies reported data just from women
262 (22, 33, 36, 40, 47, 53) and three just from men (37, 45, 49). The other studies reported
263 data from both. Not all studies reported the population ethnicity. Studies from Asia
264 were included (19, 20, 34, 35, 54) and some studies from North America included blacks
265 and Hispanics (18, 36, 37, 43, 48, 51, 52, 55, 56) , but the majority of data reported
266 addressed white populations. The studies reported relative risk, odds ratio, hazard ratio
267 and incidence rate ratio. For simplicity they will be called relative risk. Overall the quality
268 of the studies was good as most scored higher than seven, which is considered high

quality. The full description of the criteria and the author's judgement with reason is described in appendix 5.

Table 1 Study characteristics (hip and non-vertebral)

Author, year (cohort name)	Country	DM type	Age (y)	Fol-up y (SD)	Pop total / DM	Fracture (n)	Ethnicity (%)	Sex (% f)	Fracture site included	Risk estimate group	Risk
Hip fracture											
Ahmed, 2006[1] (The Tromsø study)	Norway	Both	25-98	6	27,159/ 455	249	NR	52	Hip	Calculated overall	3.9 (1.19-12.8)[4]
Berry, 2017[2] (FRAiL)	USA	NS	65-113	1.8	419,668/ 119,490	14,553	White 83% Black 13% Hispanic 2% Asian 1% Native American 0.4%, Others/ Unknown 0.8%	71	Hip	Overall	1.09 (1.05-1.13)[5]
Chen, 2008[2]	Taiwan	NS	> 35	6	969,821/ 484787	20220	NR	53	Hip	Male	1.28 (1.21–1.34)[6]
										Female	1.72 (1.66–1.78)[5]
Lai, 2015[2]	Taiwan	NS	≥65	5	81,245/ 16249	4005	NR	48	Hip	DM < 5y	1.20(1.14, 1.26)[7]
										DM ≥ 5y	1.37(1.28, 1.46)[7]

de Liefde, 2005[1] (Rotterdam Study)	Nether-lands	T2D	≥65	5.2 (3.6)	6,655/ 792	771	NR	59	Hip	Overall	1.18 (0.76–1.83)[8]
Oei, 2013[1] (Rotterdam Study)	Nether-lands	T2D	≥55	12.2 (4.2)	4,135/ 420	1068	NR	59	Hip	ACD	1.15 (0.68-1.94)[9]
								59		ICD	0.96 (0.52-1.75)[9]
Dobnig, 2006[1]	Austria	T2D	>70	2	1,664/ 583	110	White	100	Hip	Overall	0.90 (0.60 –1.34)[11]
Forsen, 1999	Norway	Both	≥50	9	35,444/ 1850	1643	NR (Norwegian)	52	Hip	Calculated overall	1.23 (0.95-1.59)[11]
Gerber, 2013[3]	USA	NS	>50	1985-2006	3,808/ 559	1904	White	76	Hip	By period 1985-1999	1.03 (0.83-1.31)[12]
										2000-2006	1.77 (1.33-2.35)[12]
Hamilton, 2017b[1] (Fremantle Diabetes Study I)	Australia	T1D	NR	14.5 (5.8)	605/ 121	14	NR	40	Hip	Overall	7.11 (2.45–20.64)[5]
Hamilton, 2017a[1]	Australia	T2D	NR	12.9 (6.1)	6,450/ 1291	424	White 77.5% Non-European 12.5%	51	Hip	Overall	1.34 (1.06–1.69)[5]

(Fremantle Diabetes Study I)											
Hippisley-Cox, 2012[1]	UK	Both	30-100	NR	3,142,673/ 97,537	23810	White or not recorded 95.3%. Indian 0.9% Pakistani 0.5% Bangladeshi 0.3% Other Asian 0.5% Caribbean 0.5% Black African 0.8% Chinese 0.2% Other 0.9%	51	Hip	Calculated overall	2.48 (1.65-3.72)[13]
Holm, 2018[2]	Denmark	NS	NR	NR	6,285/ 229	NR	NR	NR	Hip	T2D female	1.31 (1.02-3.31)[14]
Jorgensen, 2014[2]	Denmark	NS	≥65	NR	1,276,891/ NR	89150	NR	58	Hip	Overall	1.12 (1.09-1.14)[15]
Holmberg, 2006[1]	Sweden	NS	NR	F 11 M 16	33,346/ NR	3915	NR	32	Hip	Female	4.07 (1.79-9.26)[4]

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										Male	7.75 (4.37- 13.7)[4]
Hothersall, 2014[2]	Scotland	Both	≥20	NR	3,861,874/ 201,874	13,259	NR	NR	Hip	Calculated overall	1.76 (1.3-2.39)[16]
Ivers, 2001[1] (The Blue Montains Eye Study)	Australia	NS	≥ 49	5	3,654/ 216	251	NR	57	Hip		0.6 (0.2–2.2)[4]
Janghorbani, 2006[1] (NHS)	USA	Both	30-55	18 T1D - 20 Non-DM	109,983/ 8,640	1398	White 98%	100	Hip	T1D	7.1 (4.4–11.4)[17]
										T2D	1.7 (1.4–2.0)[17]
Kim, 2017[2]	Korea	T2D	≥50	6	51,330/ 17,110	1,816	NR (Korean)	54	Hip	Female	2.11 (1.71–2.60)[17]
										Male	1.81 (1.30–2.52)[17]
Koh, 2010[1]	Singapore	NS	45–74	12.2 (3.3)	63,154/ 5,668	1213	NR (Chinese)	DM 57 Non-DM 56	Hip	Overall	2.00 (1.73–2.31)[18]

Lee, 2015[1] (EPESE)	USA	NS	≥ 65	6.5	2,704/ 566	173	Blacks 54.5% White 45% Others 0.5%	100	Hip	Overall	1.27 (0.80–2.02)[19]
Lee, 2018	USA	Both (98% T2D)	65-99	NR	2,798,309/ 900,402	11,176	White 71.5% Black 8.4% Other 3.9% Unknown 16.1%	0		Overall	1.21 (1.19–1.23)[20]
Leslie, 2007[2]	Canada Manitoba	Both	≥20	NR	318,776/ 82,094	17,342	NR (Aborigines 7.2% controls, 10.7 % DM)	50	Hip	Calculated overall	1.1 (0.59-1.51)[21]
Leslie, 2014[2]	Canada Manitoba	Both	≥40	6	62,413/ 6,455	1,108	White 97.8%	Controls 92 DM 86	Hip	<60	4.67 (2.76–7.89)[22]
										60-69	2.68 (1.77–4.04)[22]
										70-79	1.57 (1.20–2.04)[22]
										≥80	1.42 (1.01– 1.99)[22]
Majumdar, 2016[2]	Canada Manitoba	NS	≥40	7	57,938/ 8,840	1,388	NR	100	Hip	Female	1.32 (1.03–1.69)[23]
Li, 2019[1] (CaMos)	Canada	Both (98% T2D)	≥ 25	9.2 (4.5)	3,149/ 138	67	NR	70	Hip	Overall	2.60 (1.04–6.55)[24]

Lipscombe, 2007[2]	Canada	Both (90% T2D)	≥66	6.1	598,812/ 197,412	22,267	NR	49	Hip	Female	1.11 (1.08–1.15)[25]
										Male	1.18 (1.12–1.24)[25]
Looker, 2016[2] (NHANESIII NHANES 1999-2004)	USA	Both (3% T1D)	≥ 65	6.7	5,032/ 897	298	NHW 61% NHB 17% MA 17.5% Other 3.3%	49	Hip	Overall	1.35(0.82-2.22)[26]
Martinez-Laguna, 2015[2]	Spain	T2D	NR	Md 2.63	171,931/ 58,483	1,220	NR	43	Hip	Overall	1.11 (0.99-1.24)[27]
Reyes, 2014[2]	Spain	T2D	≥65	Md 2.99 (2.37, 2.99)	186,171/ 36,865	1,718	NR	0	Hip	Male	1.45 (1.25–1.69)[28]
Meyer, 1993[1]	Norway	NS	35-49	10.9	52,313/ 298	212	NR	48	Hip	Female	5.81 (2.15-15.71)[5]
										Male	7.67 (2.40-24.53)[5]
Nicodemus 2001[1] (The Iowa Women's Health Study)	USA	Both	55-69	9.5	32,089/ 1,729	490	NR	100	Hip	T1D	14.1 (5.85, 34.2)[17]

										T2D	1.75 (1.25, 2.43)[17]
Ottenbacher 2002[1] H-EPESE	USA	NS	≥ 65	NR	2,884/ 690	134	100% Mexican Americans	58	Hip	Overall	1.57 (1.03–2.39)[29]
Poor, 1995[3]	USA	T2D	>35	1965-1989	464/ 42	232	White	0	Hip	Overall	0.9 (0.5-1.7)[17]
Rathmann, 2015[2]	Germany	T2D	NR	2.9 (3.3)	598,208/ 299,104	NR	NR	49	Hip	Overall	1.56 (1.45–1.67)[30]
Robbins, 2007[1] (WHI-OS)	USA	NS	50-79	7.6 (1.7)	93,676/ 38,502	1,132	White 83.3% Black 8.2% Hispanic 3.9 % American Indian 0.5% Asian/Pacific Islander 2.9%	100	Hip	Overall	1.74 (1.17-2.60)[31]
Schneider, 2013[1] (ARIC)	USA	NS	45-64	md 20	15,140/ 1,800	1,078	White 74% Black 26%	55	Hip	Prevalent DM	1.76 (0.68, 4.60)[32]
										Newly diagnosed	2.99 (1.24, 7.21)[32]
Schwartz, 2001[1] (SOF)	USA	T2D	≥ 65 years	9.4 (2.4)	9,654/ 657	2,624	"mainly white" (black women were excluded	100	Hip	Non-insulin user	1.49 (1.09–2.05)[17]
										Insulin user	1.26 (0.56–2.81)[17]

Segal, 2009[3]	Israel	NS	'Elderly'	1	238/ 41	142	NR (Israel)	Cases 76 Controls 94	Hip	Overall	3.9 (1.50–10.4)[33]
Strotmeyer 2011[1] (CHS)	USA	NS	≥ 65	10.9 (4.6)	3,506/ 918	334	15.5% black	58	Hip	Overall	1.05 (0.80–1.39)[34]
Taylor, 2011[2]	USA	NS	≥ 65	4.2 p-y	1,694,051/ NR	124,241	White 88% Asian 1.3% African 7.8% Hispanic 1.5% Other 1.5%	58	Hip	Overall	1.01 (0.99, 1.02)[35]
Wallander, 2017[1] (FRAILCO)	Sweden	Both	≥65	md 1.3 (0.6–2.3)	428,305/ 84,702	36,132	NR	58	Hip	Calculated overall	1.12 (0.99-1.27)[9]
Weber, 2015[2] (THIN)	UK	T1D	NR	md 4.7 (2–8.8)	334,266/ 30,394	21,239	NR	44	Hip	Calculated overall	3.51 (2.7-4.55)[36]
Non-vertebral fracture											
Ahmed, 2006[1]	Norway	Both	25-98	6	27,159/ 455	1,249	NR	52	Non-vertebral	Calculated overall	1.56 (0.84-2.90)[4]

(The Tromsø study)											
Bonds, 2006[1] (WHI-OS)	USA	T2D	50-79	7	93,405/ 5285	NR	NHW 83.2% Black 8.1% Hispanic 3.8% American Indian 0.4% Asian/Pacific Islander 3.1% Unknown 1.4%	100	Hip/pelvis/ upper leg, Lower leg/ankle/ knee, Foot, Upper arm/ shoulder/ elbow, Lower arm/wrist/ hand	Calculated overall	1.28 (1.11-1.47)[5]
de Liefde, 2005[1] (The Rotterdam Study)	Nether-lands	T2D	≥55	6.8 (2.3)	6,655/ 792	771	NR	60	Non-vertebral	Overall	1.18 (0.92–1.52)[6]
Oei, 2013[1] (The Rotterdam Study)	Nether-lands	T2D	≥55	12 (4.2)	4,135/ 420	1,068	NR	60	Hip, wrist	Calculated overall	1.12 (0.83-1.53)[9]
Holm, 2018[2]	Denmark	T2D	NR	5.8 (NR)	6,285/ 229	NR	NR	100	Hip, lower arm, upper arm	Calculated overall	1.45 (1.03-2.03)[6]
Holmberg 2006[1]	Sweden	NS	NR	F 11(NR)	33,346/ NR	3,915	NR	32	Hip, Forearm, Proximal Humerus, Ankle	Calculated overall	1.29 (0.54-3.13)[4]

Malmö Preventive Project				M 16 (NR)							
Ivers, 2001[1] The Blue Montains Eye Study	Australia	NS	≥ 49	5	3,654/ 216	251	NR	57	Non-vertebral (exclude ribs)	Overall	0.90 (0.70-1.20)[5]
Jung, 2012[2]	Korea	NS	>20	5.7 (2.0)	2,282/ 1,268	81	Korean	100	Non-vertebral (hip, distal radius, elsewhere)	Overall	1.62 (1.02-2.56)[4]
Keegan, 2002[3]	USA	NS	≥45	Oct 1996 -May 2001	4,528/ 472	2,615	WHite 61% Asian 14.9%, Black 12.7%, Hispanic 11.6%	75	Foot, distal forearm, proximal humerus	Calculated overall	1.26 (0.87-1.83)[37]
Kim, 2017[2] NHIS-KNHIS	Korea	T2D	≥50	6	51,330/ 17,110	3,855	NR (Korean)	54	Non-vertebral	Female	1.14 (1.02–1.25)[4]
										Male	1.14 (0.93–1.39)[4]
Lee, 2015 (EPESE)[1]	USA	NS	≥ 65	6.5	2,704/ 566	572	Blacks 54.5% White 45% Others 0.5%	100	Hip and non-hip, non-vertebral	Hip fracture	1.27 (0.80–2.02)[19]
										Non-hip, non-	1.23 (0.97–1.56)[19]

										vertebral fracture	
Napoli, 2014[1] (MrOS)	USA	NS	≥ 65	9.1 (2.7)	3,967/ 881	871	White 90% Black 4.07% Asian 3.19% Hispanic 2.10% Other 1.18%	0	Non-vertebral	Overall	1.12 (0.94-1.34)[38]
Rathmann 2015[2]	Germany	T2D	NR	2.9 (3.3)	598,208/ 299,104	11,535	NR	49	Hip, forearm, upper arm and shoulder	Calculated overall	1.41 (1.12-1.78)[30]
Schafer, 2010[1] (Health ABC)	USA	NS	70-79	8.2 (2.3)	1,949/ 658	NR	White 58% Black 42%	50	Non-vertebral	Overall	1.42 (1.07–1.89)[39]
Schneider 2013[1] (ARIC)	USA	NS	45-64	md 20	15,140/ 1,800	1,078	White 74% Black 26%	5	Hip, upper limb, lower limb	Calculated overall	1.78 (1.21-2.61)[32]
Schwartz, 2001[1] (SOF)	USA	T2D	≥ 65	9.4 (2.4)	9,654/ 657	2,624	"mainly white" (black women were excluded	100	Non-vertebral	Insulin user	1.58 (1.14–2.20)[5]
										Non-insulin user	1.16 (0.99–1.37)[5]
Taylor, 2011[2]	USA	NS	≥ 65	4.2 p-y	1,694,051/ NR	124,241	White 88% Asian 1.3% African 7.8%	58	Hip, distal radius/ulna,	Calculated overall	1.13 (1.00-1.27)[35]

							Hispanic 1.5% Other 1.5%		humerus, tibia/fibula		
Wallander 2017[1] (FRAILCO)	Sweden	Both	≥65	md 1.3	428,305/ 84,702	36,132	NR	58	Hip, wrist, upper arm, ankle	Calculated overall	1.13 (0.98-1.30)[7]

Fol up Follow-up;; F female; M male; NHS Nurses' Health Study; KNHIS Korean National Health Insurance Service; EPESE North Carolina Established Populations for Epidemiologic Studies of the Elderly; NHW non-Hispanic white; NHB non-Hispanic black; MA Mexican American; ARIC The Atherosclerosis Risk in Communities Study; SOF Study of Osteoporotic Fractures; CHS Cardiovascular Health Study; FRAILCO Fractures and Fall Injuries in the Elderly Cohort; THIN The Health Improvement Network; WHI-OS Women's Health Initiative- Observational Cohort; NHW - NHIS Non-Hispanic white; F female; NHIS- NSC National Health Insurance Service National Sample Cohort of the Korean National Health Insurance Service; Md median; p-y person-years;;

[1]Prospective Cohort; [2]Retrospective Cohort; [3]Case-control

Adjustments:

[3] Age adjusted, reported by sex

[4] Age and sex

[5] Age as a continuous variable, geographic area, and urbanization status

[6] Groups were matched for sex, age and the year of diagnosis of DM

[7] Age, gender, BMI, smoking, serum creatinine, visual acuity, falling frequency, lower limb disability

[8] Age, sex, height, weight

[9] Age and weight

[10] Age, BMI and daily smoking

[11] Age and sex matched controls

[12] Ethnic origin, alcohol intake, smoking, age, BMI, medical or social factors (Asthma or chronic obstructive airways disease, any cancer, cardiovascular disease, dementia, epilepsy diagnosis or prescribed anticonvulsants , history of falls, chronic liver disease, Parkinson's disease, rheumatoid arthritis or systemic lupus

erythematosus Chronic renal disease, Type 1 diabetes, Type 2 diabetes, previous fracture, endocrine disorders, gastrointestinal malabsorption, parental history of osteoporosis, any antidepressants, corticosteroids, unopposed hormone replacement therapy

[13] Adjusted for baseline age, BMI group (<20, 20–30, >30), modified Charlson index, estrogen deficiency, MOF, prevalent rheumatoid arthritis, former osteoporosis treatment, glucocorticoid use >450 prednisone eq., family fracture history, current smoking, exercise level, prevalent alcohol related diagnoses

[14] Age, gender, income, calendar year and comorbidity (ischemic heart disease, COPD, dementia, depression, diabetes, osteoporosis and stroke)

[15] Age, calendar year, SIMD, and for the overall estimate, an SIMD-age interaction

[16] Age

[17] Age at recruitment, sex (for all), year of recruitment, dialect group (Hokkien, Cantonese), level of education (no formal education, primary, secondary or higher)

[18] Age, race, BMI

[19] Adjusted for age, race/ethnicity, tobacco use, alcohol use, glucocorticoid use, rheumatoid arthritis, and BMI.

[20] Age, sex, income quintile, are of residence and ethnicity

[21] Age, sex, BMI, glucocorticoid use, rheumatoid arthritis, high alcohol use, any prior fracture, and femoral neck T-score

[22] Frax adjusted

[23] Adjusted for age, sex, and BMD femoral neck T-scores

[24] Age group chronic unstable disease; prior stroke; visual impairment; neuropathy; amputation; treatment with nitrates, statins, anticonvulsants, inhaled corticosteroids, thiazides, estrogen, and medications that increase risk of falling; and history of BMD test

[25] Age, sex and survey

[26] Age and sex matched

[27] Age, body mass index, smoking, alcohol consumption, use of oral corticosteroids, and co-morbid conditions (COPD Heart failure Chronic kidney disease, severe liver disease MLDa malignant tumour (without metastasis), metastasis, connective tissue disease, AIDS, paraplegia, dementia, peptic ulcer disease, myocardial infarction, cerebrovascular disease, peripheral vascular disease

[28] Age, gender, smoking status, BMI, and history of stroke.

[29] Age, sex, diabetologist care, depression, chronic kidney disease, peripheral vascular disease, heart failure, hyperlipidemia, obesity.

[30]Age, self-reported health, height, change in height since the age of 18 years, change in weight since the age of 35 years, history of fracture after the age of 55 years, race/ethnicity, physical activity, smoking, history of parental fracture after the age of 40 years, diabetes treated with medications, and corticosteroid use

[31] Age, sex and race/study center, body mass index, sports-activity tertile, alcohol consumption, cigarette smoking, and medication use.

[32] Plasma PTH serum 25(OH)D3 concentration, concomitant diseases (hypertension, ischemic heart disease and diabetes mellitus), smoking status, age, gender and season.

[33] Age-sex-race adjusted

[34] Gender, race-ethnicity, age, calendar year, urban/rural, geographic location, median income, previous fracture, other predisposing conditions (glucocorticoid related, fall-related, renal disease, depressive illness, AMI, other heart disease, bone disease, cancer)

[35] Matched by age, sex, and GP practice.

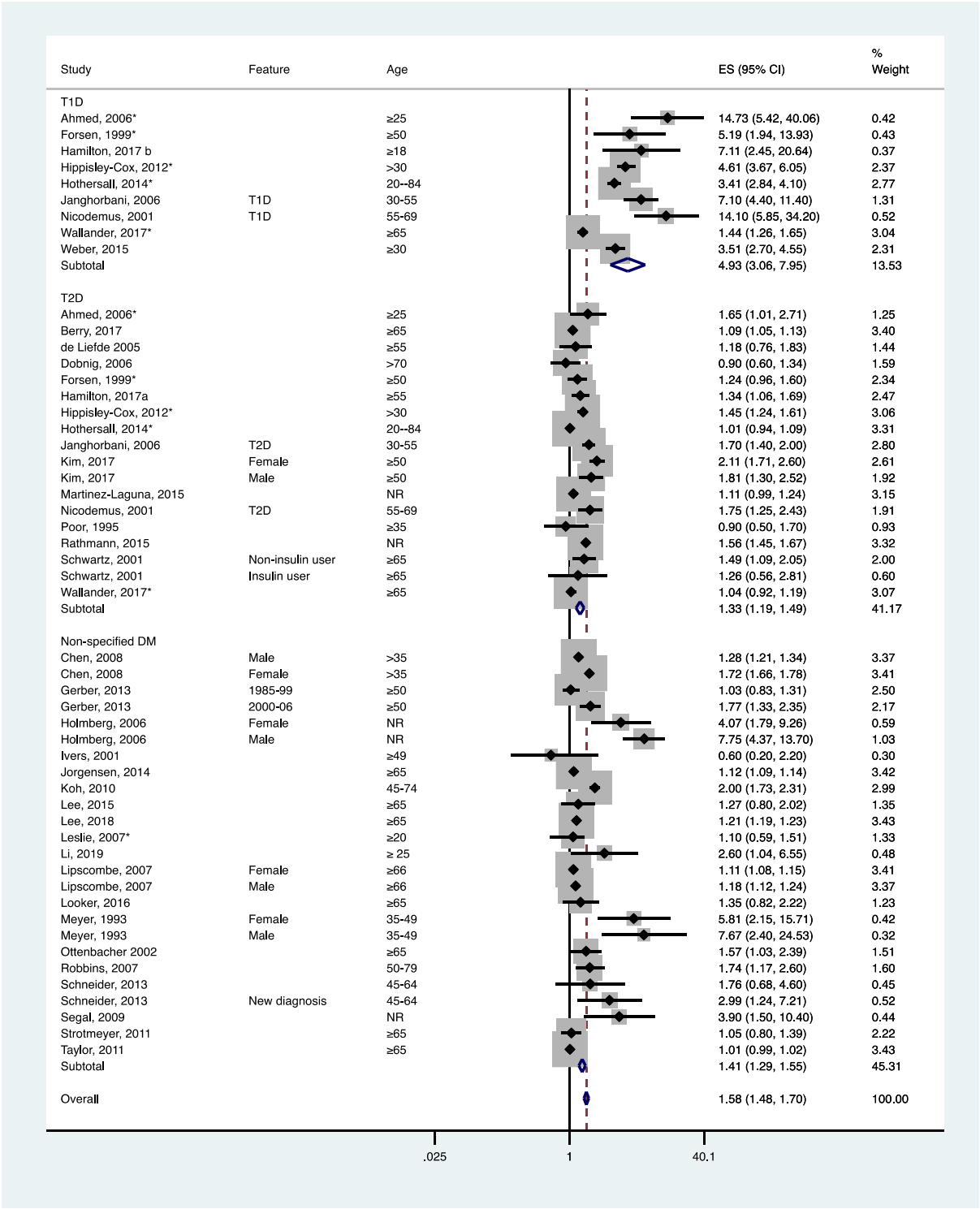
[36] Five-year age, gender, and race/ethnicity, as indicated by inpatient medical files (White, non-White, and unknown), and the following: age in years, self-reported race/ethnicity, and type of interview (in person vs. over the telephone).

[37] Adjusted for age, race, clinic

[38] Age, race, sex, clinic site, and total hip BMD

Hip fractures – meta-analysis results

The summary of the 37 (out of 42) non-overlapping studies resulted in a RR of 1.58, 95%CI 1.48-1.70 and high heterogeneity (I^2 96.9% p<0.001) (Fig 2). We explored the heterogeneity using subgroup and sensitivity analyses and meta-regression.



* Summarised using random-effects model DM diabetes mellitus

Fig 2 Forest plot overall hip fracture risk in diabetes

We performed subgroup analysis by gender, age (younger and older than 65 years old), diabetes type, insulin use, diabetes duration (using a 5- and 10-years cut-off) and BMI. When enough data was available the same analysis was performed in each diabetes type subgroup. Table 2 reports the results. The risk of hip fractures was higher in T1D compared to T2D and in the younger population compared to the elderly in both T1D and T2D. In T2D, the risk of hip fractures was higher in females than in males, in those using insulin compared to non-insulin users and in those with longer disease duration (>10 years). Finally, the analysis by BMI including both T1D and T2D did not detect difference between the groups. There was not enough data to perform this analysis in each diabetes type.

Table 2 Subgroup analyses hip and non-vertebral risk of fracture in diabetes combined analysis (T1D and T2D) and by diabetes type

Feature	Subset	RR (95% CI)	n	Het	RR (95% CI)	n	Het	RR (95% CI)	n	Het
		Overall DM analysis (T1D + T2D)			T1D			T2D		
Hip fracture analysis										
Overall risk		1.58 (1.48-1.70)		96.9% p<0.001	4.93 (3.06,7.95)*	9	94.9% p<0.001	1.37 (1.22, 2.21)	19	87.8% p<0.001
Gender	Female	1.77 (1.54, 2.04)*	25	94.8% p<0.001	4.54 (2.59, 7.94)	8	91.6% p<0.001	1.34 (1.17, 1.54)*	12	91.0% p<0.001
	Male	1.35 (1.22, 1.49)			3.66 (2.16, 6.18)			1.13 (0.99, 1.29)		
Age (65 y cut-off)	< 65 years old	3.21 (2.38, 4.32)*	22	94.9% p<0.001	5.21 (3.75, 7.22)*	3	86.1% p<0.001	1.74 (1.24, 2.43)*	6	85.9% p<0.001
	> 65 years old	1.21 (1.14, 1.28)			2.48 (2.13, 2.89)			1.20 (1.07, 1.34)		
Insulin use	Insulin user	†			†			1.79 (1.19, 2.69)*	5	82.7% p<0.001
	Non-insulin user	†			†			1.18 (1.02, 1.36)		
DM dur (5y)	< 5 years	1.22 (1.03, 1.45)*	11	88.2% p<0.001	‡			1.34 (1.09, 1.65)	5	60.8% p=0.003
	> 5 years	1.55 (1.39, 1.73)			‡			1.59 (1.33, 1.90)		
DM dur (10y)	< 10 years	1.30 (1.10, 1.54)*	10	92.2% p<0.001	‡			1.34 (1.09, 1.65)*	5	69.0% p=0.004
	> 10 years	2.42 (2.08, 2.81)			‡			2.40 (1.89, 3.04)		
BMI	BMI< 25kg/m2	1.69 (1.08, 2.63)	4	98.3% p<0.001	‡			‡		
	BMI 25-30 kg/m2	1.18 (0.98, 1.42)			‡			‡		
	BMI > 30 kg/m2	0.96 (0.58, 1.59)			‡			‡		

Non-vertebral fracture analysis										
Overall risk		1.24 (1.15, 1.32)*	17	53.4%, p=0.02	1.92 (0.92, 3.99)	2	78.1% p=0.033	1.19 (1.11, 1.28)	8	25.2% p=0.212
Gender	Female	1.19 (1.13-1.26)	11	0.0%, p=0.75	1.65 (0.82, 3.29)	2	60.0% p=0.05	1.17 (1.08, 1.27)	7	21.1% p=0.236
	Male	1.14 (1.03, 1.27)			1.89 (1.04, 3.42)			1.08 (0.96, 1.20)		
Insulin use	Insulin users	†			†			1.25 (1.02, 1.53)	3	76.6% p=0.001
	Non-insulin users	†			†			1.04 (0.93, 1.16)		
DM dur	Prevalent	2.14 (1.72, 2.65)*	4	81.3%, p<0.001	‡			‡		
	Incident	1.09 (0.69, 1.73)			‡			‡		

n number of studies included; het heterogeneity; DM dur diabetes mellitus duration

*significantly higher; †only T2D included in this analysis, since all T1D patients are treated with insulin; ‡ insufficient data for this subgroup analysis;

Few studies addressed the effect of diabetes control (n=1) or microvascular complications (n=1) on the risk of fractures, therefore, it was not possible to perform subgroup analyses. Oie et al reported that, in patients with inadequate control, there was an increase in the risk of all fractures and wrist fractures, but not for hip fractures (64). Lee et al reported that neuropathy explained around 20% of the risk of hip and any fractures (37). These meta-analyses report the data of 17,571,738 participants, 2,387,479 with DM and 319,652 fractures.

We ran the analyses excluding one study at a time and no important variation was observed in the RR or heterogeneity. We also excluded the case-control studies, and each kind of risk estimate (e.g. OR, HR) and found similar results in the RR and heterogeneity. Meta-regression analysis showed that age (65 years old cut-off) and DM type accounted for 83% of the RR of hip fractures in diabetes.

Non-vertebral fractures

Table 1 summarises the study characteristics. Eighteen studies reported the risk of fractures in two or more sites and 17 were included in the non-vertebral fractures risk analysis (17, 21, 28, 30, 32, 34, 36, 50, 52, 53, 56, 57, 59-64). One overlapping study was the unique to report the risk of fractures (wrist and hip) for metabolic control and could not be included in the meta-analysis calculations. All but one study (61) were cohorts, (17, 21, 28, 30, 32, 34, 36, 50, 52, 53, 56, 57, 59, 60, 62-64). Eight studies were from the USA (36, 52, 53, 56, 59, 61-63), seven from Europe (one from Norway (17); two from the Netherlands (21, 64); one from Denmark (28); two from Sweden (30, 57) and one from

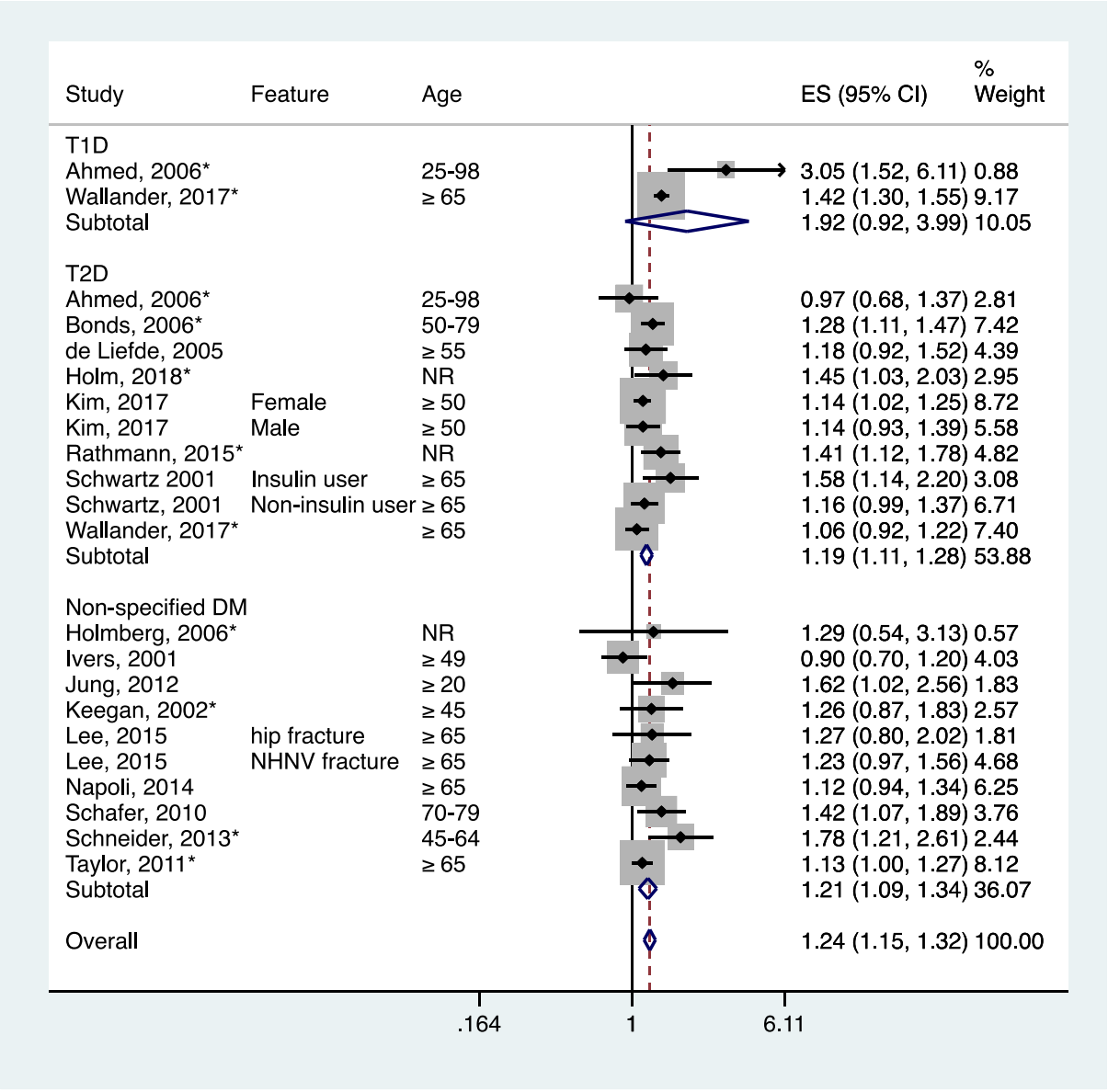
Germany (50)); the two Asian studies were from Korea (34, 60) and one study from Australia (32). Nine studies did not specify diabetes type (30, 32, 36, 52, 56, 60-63), while seven reported data just from T2D (21, 28, 34, 50, 53, 59, 64) and two from both types (17, 57). Five studies reported data just from women (28, 36, 53, 59, 60), one just from men (62) and the others from both genders (17, 21, 30, 32, 34, 50, 52, 56, 57, 61, 63, 64). The age range varied from 20 to 98 years. The study size varied from 1,949 (63) to 1,694,051 participants (56). Although other ethnicities were included, such as Asian, blacks, Hispanics and others (34, 36, 52, 59, 60, 62, 63, 65), the majority of the data addressed white populations. Nine studies reported the risk of non-vertebral fractures as a category (17, 21, 32, 34, 53, 57, 60, 62, 63) and the others reported several combinations of sites including axial and peripheral sites. Only one study did not include hip fracture (61). Overall the quality of the studies was good as most scored higher than seven, which is considered high quality (full description in appendix 5).

Non-vertebral fractures meta-analysis results

The risk of non-vertebral fractures was increased in diabetes (RR1.24 95%CI 1.15-1.32) and heterogeneity was moderate (I^2 53.4%, p=0.02) (Fig 3). The risk in T1D was 1.92 95% CI 0.92-3.99 while in T2D was 1.19 95%CI 1.11-1.28.

Subgroup analyses are reported in Table 2. The risk was not significantly different between T1D and T2D, but only two studies reported the risk on T1D. No difference was found between female and male (both for T1D and T2D) or between insulin users and non-insulin users in T2D. Due to a lack of enough data, age and BMI subgroup analyses were not performed. Sensitivity analyses did not affect the results. Seventeen studies

were included in this analysis, reporting data from 2,978,487 participants, 413,775 with diabetes and 181,228 fractures.



* Summarised using random-effects model

DM diabetes mellitus; NHNV non-hip non-vertebral fracture

Fig 3 Forest plot non-vertebral fractures risk in diabetes

Discussion

There was an increase in the risk of hip and non-vertebral fractures in diabetes compared to those without diabetes. At the hip, the risk was higher in T1D than T2D. In

390 both T1D and T2D, the risk of hip fractures was higher in the younger population. In
391 T2D, the risk of hip fractures was higher in females, insulin users and those with longer
392 disease duration.
393 The mechanism for the increase in the risk of fractures in diabetes is not understood
394 and might be associated with several features. Some of them are common to both
395 diabetes types. Diabetes is associated with an increased risk of falls (57, 66, 67),
396 especially in those using insulin, those with microvascular complications and those with
397 hypoglycaemic episodes (68-70). Chronic hyperglycaemia favours non-enzymatic
398 reactions between proteins and glucose producing advanced glycation end products
399 (AGEs) what might affect bone material properties (71).
400 Conversely, bone mineral density (BMD) is discordant in T1D and T2D. In T1D, BMD is
401 decreased, but the small decrease in BMD does not explain the huge increase in the
402 risk of fractures (5). In T2D, BMD is increased and the risk of fractures is paradoxically
403 increased as well, suggesting that bone fragility in diabetes is not explained by
404 decreased BMD. Microarchitecture studies have reported favourable, neutral and
405 unfavourable patterns in T2D (72-74). In T1D, unfavourable microarchitecture was
406 reported in patients with microvascular disease (75). Therefore, the bone structure
407 seems not to fully explain the bone fragility in diabetes (76).
408 In T2D , antidiabetic drugs might also be involved. Increased risk of fractures has been
409 associated with sulfonylureas, thiazolidenediones (TZD), glucagon like peptide 1 (GLP1
410 analogues) and sodium/glucose co-transporter2 inhibitors (SGLT2 inhibitors) (77). Data
411 from cohorts on metformin showed a neutral or positive effect on the risk of fractures

412 (77-79). Sulfonylureas have no direct effect on bone but they were associated with an
413 increase in the risk of fractures, possibly due to hypoglycaemic episodes and falls (80).
414 Conversely, data on incretin mimetics are inconsistent, with both decrease and increase
415 in the risk described with GLP-1 (81) and a decreased risk associated with DPP-4
416 inhibitors (82). TZD increase adipogenesis and impair osteoblastogenesis and were
417 associated with an increase in the risk of fractures (80, 83). More recently, SGLT2
418 inhibitor canaglifozin, but not empaglifozin or dapaglifozin, was also associated with
419 an increase in the risk of fractures (80, 84). Therefore, several factors could affect the
420 risk of fractures in diabetes.
421 Several meta-analyses have reported an increase of hip fractures (5, 8, 9, 85-87) both
422 in T1D and T2D and any fractures in T1D (8, 88) but none of them has investigated the
423 risk of non-vertebral fractures nor the effect of several features in the risk of fractures
424 in this population. The results of this meta-analysis are consistent with previous studies
425 as we reported an overall 58% increase in the risk of hip fractures, with a significant
426 33% increase in the risk in T2D (26-70% previously reported) and a substantial 4 -fold
427 increase in T1D (3-7 fold previously reported)(5, 6, 8, 9, 85, 89). This greater increase in
428 T1D is probably associated with the lower BMD observed in T1D and the higher risk of
429 hypoglycaemia and falls associated with insulin use (90). We speculate that the early
430 onset of the disease, often before the peak of bone mass accrual might play a role (91).
431 We are the first to report a greater increase in the risk of hip fractures in women (34%)
432 than in men (13%) in T2D. We speculate that an interaction between female gender and
433 diabetes might result in a greater increase in the risk in women.

This is the first meta-analysis to assess the effect of age, insulin use, diabetes duration and BMI on the risk of fractures in diabetes. In the hip fractures analysis, we found a greater increase in the RR of fractures in people with diabetes younger than 65 years old, than in the population older than 65 years old, for both T1D and T2D. The incidence of hip fractures in the younger than 65 years old is low (92) and the impact of an increase in the incidence of fractures associated with diabetes in the relative risk will be greater at this age range (93). As the population gets older and the background risk of fractures increases, the additional risk associated with diabetes play a less important role. In addition, diabetes is associated with premature mortality, which also impact the fracture risk (94).

The subgroup analysis by BMI included few studies reporting mainly data from T2D and showed no difference between the groups. Obesity is associated with a lower risk of hip fractures, due to mechanical and endocrine mechanisms (95, 96). In the USA, estimates suggested that 85% of people with T2D are overweight or obese (97). Despite the high prevalence of obesity in T2D, overall the risk of fractures is still increased in this population and the mechanisms are unknown.

In T2D, insulin use was associated with higher fracture risk. Since insulin is used in advanced T2D, this increased risk probably does not reflect an effect of insulin at the skeleton but its indication and adverse effects, such as hypoglycaemia and falls. Patients with longer diabetes duration also showed a greater increase in the risk for both hip (overall analysis and T2D) and non-vertebral fractures (overall analysis). These patients

455 are more likely to have diabetes complications and to be exposed to potentially harmful
456 antidiabetic treatments.
457 In the hip fractures analysis, we found high heterogeneity. Heterogeneity reflects the
458 differences between studies (98). We included data from men and women, from 18 to
459 100 years old, with both diabetes types so high clinical diversity is expected. In addition,
460 data came from prospective and retrospective cohorts and case-control studies, from
461 recruited participants and registry data, adding substantial methodological diversity.
462 These features should be considered while interpreting the results. Although we found
463 a 58% increase in the risk of hip fracture in diabetes, this is an overall estimate. The risk
464 will vary according to gender, age, diabetes type, diabetes duration and treatment.
465 This study has several strengths. This is the most comprehensive review on the risk of
466 hip fractures, with the greater number of studies included in the meta-analysis (n=42
467 compared with a maximum n=28 studies in previous reviews) (10) and most
468 comprehensive subgroup analysis pooled so far. This is the first systematic review and
469 meta-analysis on the risk of non-vertebral fractures in diabetes. The high heterogeneity
470 found in the hip fracture analysis was extensively explored by subgroup and sensitivity
471 analysis and meta-regression.
472 However, this study also has limitations. This is a systematic review update, so we relied
473 on the search done by the previous systematic review (6). However, reference lists of
474 several previous reviews also were included as a source of papers. In addition, we used
475 the original full text of these studies for data extraction and quality assessment. The
476 initial study sifting was done by one reviewer but the random 10% double sifting kapa

477 statistic for agreement was good. Many studies do not report the risk by diabetes type
478 (non-specified diabetes). However, the risk of fractures in these studies showed a
479 pattern very similar to the T2D analysis (fig 2 and 3). In addition, T2D is estimated to
480 account for 90% of the cases of diabetes (2). Therefore, it is likely that the majority of
481 data from the non-specified diabetes study is related to T2D. We could not investigate
482 the effect of BMD, falls, the competing risk of death, metabolic control, the presence of
483 microvascular complications, the effect of anti-diabetic drugs and hypoglycemia on the
484 risk of fractures.
485 The criteria to establish osteoporosis diagnosis in diabetes is based on the presence of
486 fragility fractures and/or low BMD (as in general population). However, since BMD and
487 fracture prediction tools, such as FRAX, underestimate this risk (99, 100), the IOF Bone
488 and Diabetes Working group suggested that patients with diabetes should be
489 considered for treatment at more favourable BMD and FRAX values than patients
490 without diabetes (77).
491 There is no specific treatment for bone fragility in diabetes. As for all complications
492 associated with diabetes, adequate metabolic control is advisable. However, the risk of
493 hypoglycaemia should be considered, especially in the elderly (90, 101, 102). In addition,
494 antidiabetic medications with unfavourable effect on bone metabolism should be
495 avoided in patients with diabetes and bone fragility (77). Most previous studies with
496 anti-osteoporotic medications showed similar effects on BMD and fracture risk in
497 people with and without diabetes (103, 104). However, most of the data available

assessed postmenopausal women with T2D and additional data about anti-fracture efficacy in other groups such as males, T1D and younger populations is required.

In summary, this meta-analysis highlights the complexity of assessing the risk of fractures in diabetes. Evidence suggest a different mechanism from osteoporosis, since bone fragility in diabetes is not directly associated with reduced BMD. The increase in the risk of fractures is observed in both T1D and T2D, suggesting that features common to both types such as hyperglycemia and the development of microvascular complications might be involved. Conversely, the substantially higher risk observed in T1D suggest that mechanisms associated with the different pathophysiology (early onset, lack of endogenous insulin) might have an important impact in the risk in T1D. Despite growing evidence on the increased risk of fractures in diabetes, the skeleton is not widely recognised as a site for diabetic complications. In addition, there is limited data on the assessment of fracture risk, the impact of the increased risk of fractures in diabetes management and the efficacy and safety of anti-osteoporotic treatments in diabetes. The population with diabetes is heterogeneous and identifying groups with higher risk of fractures is a key factor. This could allow policies and practices to target specific groups. In addition, this is a first step to guide future research in order to understand the underlying mechanisms.

Contributions

Authors' contribution: Study design: TV, EP, SC, RE. Data collection: TV, MS, SH, AS, EP. Data analysis and interpretations: TV, MS, SH, IA, SC, RE. Manuscript drafting: TV, RE. All authors have revised and approved the manuscript.

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