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Meta-Analysis

Systematic Review of Type 1 and Type 2 Diabetes Mellitus and Risk of Fracture

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The authors conducted a systematic review of published data on the association between diabetes mellitus and fracture. The authors searched MEDLINE through June 2006 and examined the reference lists of pertinent articles (limited to studies in humans). Summary relative risks and 95% confidence intervals were calculated with a random-effects model. The 16 eligible studies (two case-control studies and 14 cohort studies) included 836,941 participants and 139,531 incident cases of fracture. Type 2 diabetes was associated with an increased risk of hip fracture in both men (summary relative risk (RR) = 2.8, 95% confidence interval (CI): 1.2, 6.6) and women (summary RR = 2.1, 95% CI: 1.6, 2.7). Results were consistent between studies of men and women and between studies conducted in the United States and Europe. The association between type of diabetes and hip fracture incidence was stronger for type 1 diabetes (summary RR = 6.3, 95% CI: 2.6, 15.1) than for type 2 diabetes (summary RR = 1.7, 95% CI: 1.3, 2.2). Type 2 diabetes was weakly associated with fractures at other sites, and most effect estimates were not statistically significant. These findings strongly support an association between both type 1 and type 2 diabetes and increased risk of hip fracture in men and women.

diabetes mellitus; fractures, bone; hip fractures; meta-analysis; review [publication type]; risk factors

Abbreviations: CI, confidence interval; RR, relative risk.

Diabetes mellitus and low-trauma fracture are major causes of morbidity and premature mortality worldwide. Although several observational studies have investigated the association between diabetes and risk of fracture, the role of diabetes as a risk factor for osteoporosis and low-trauma fracture remains unsettled.

Bone mineral density appears to be reduced in patients with type 1 diabetes in most (1–4) but not all (5, 6) studies. There have been conflicting reports about bone mineral density among patients with type 2 diabetes (3, 4, 7–18); in some studies, bone mineral density was reduced (7, 9), and in others it was increased (8, 10–12) or unchanged (13–18).

In addition, uncertainty exists about the relation between diabetes and fracture incidence. Several studies have examined the risk of fracture in persons with type 1 diabetes (9, 14–16, 19–21); the risk of hip fracture appeared to be increased in some (9, 14, 19–21), but not all (15, 16). Studies of the association between type 2 diabetes and fracture risk have demonstrated inconsistent conclusions (4, 8, 9, 11, 12, 15, 21–27): Reported associations have been positive (12, 21–27), null (4, 8, 9), or even inverse (11, 15), and in some studies an association was observed only in women (12, 14, 21, 22, 28). Type 2 diabetes is strongly associated with high bone mineral density and obesity, factors that provide protection from most fractures (11, 12, 29). Interpretation of these findings, however, has been hampered by the low frequency of occurrence of both conditions in the same person, which results in a lack of statistical power to adequately analyze this association in many studies.

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We conducted a systematic review of case-control and cohort studies to summarize the epidemiologic evidence on the association between diabetes and fracture risk and to identify possible sources of heterogeneity between studies. We also evaluated whether the association varied by sex, type of diabetes, or fracture site.

MATERIALS AND METHODS

Search strategy

We searched MEDLINE through June 2006 using the keyword ''fracture'' combined with ''diabetes mellitus,'' ''diabetes,'' ''glucose,'' or ''insulin.'' We limited the search to studies carried out in humans. We also reviewed the reference lists of the identified publications for additional pertinent studies. No language restrictions were imposed.

Eligibility criteria

The 20 epidemiologic studies considered for inclusion in this meta-analysis were six case-control studies and 14 cohort studies on the association between diabetes and the incidence of low-trauma hip, distal forearm, proximal humerus, ankle, foot, nonvertebral, or vertebral fracture (8, 9, 12, 14–16, 19–21, 23–26, 28–34). The fractures were confirmed through review of radiologic reports, radiographs, or medical records. Studies were excluded if they did not provide data that allowed calculation of standard errors for effect estimates and if the estimates had not been adjusted for age. When there were multiple publications from the same population or cohort, only data from the most recent report were included. We excluded two studies (24, 27) because of overlapping publication and two studies (16, 32) that reported only crude data that were not adjusted for age.

Data extraction

For each publication included, we extracted data on first author's surname, year of publication, country, study design, numbers of exposed and unexposed subjects, source of controls (for case-control studies), follow-up period (for cohort studies), age, sex, type of diabetes (type 1, type 2, or both), risk estimates and corresponding confidence intervals, and factors controlled for by matching or multivariable analysis. From each study, we extracted the risk estimates that reflected the greatest degree of control for potential confounding. Information on study design, participant characteristics, measurement of fractures, adjustment for potential confounders, and estimates of association was extracted independently by two reviewers (M. J. and R. M. V.). Discrepancies were resolved through discussion.

Statistical analysis

Three measures of association were reported: odds ratios (case-control studies), incidence rate ratios (cohort studies), and standardized incidence ratios (cohort studies with an external comparison group). For simplicity, we will refer to all three types of measures as relative risks. Because the frequency at which low-trauma fractures occur is relatively low, odds ratios in case-control studies and rate ratios in cohort studies yield similar estimates of relative risk (35).

We used the logarithm of the relative risk with its standard error for the meta-analysis. Summary relative risk estimates and corresponding 95 percent confidence intervals were derived by the method of DerSimonian and Laird (36) using a random-effects model, which incorporates between-study variability. Statistical heterogeneity between studies was evaluated with Cochran's Q test (37). To assess sources of heterogeneity, we conducted a meta-regression analysis with region (United States/Europe), sex (men/women and both sexes combined), fracture site, study design, duration of follow-up (in cohort studies), and type of diabetes as independent variables and log relative risk as the dependent variable. Publication bias was assessed through visual inspection of funnel plots (38). In these funnel plots, the relative risks were displayed against the inverse of the square of the standard error (a measure of the precision of the studies). Formal statistical assessment of funnel plot asymmetry was done with Egger's regression asymmetry test (39). We also used Begg's adjusted rank correlation test (39). Statistical analyses were carried out with Stata, version 9.0 (Stata Corporation, College Station, Texas). P values less than 0.05 were considered statistically significant. All statistical tests were two-sided.

RESULTS

Study characteristics

Sixteen independent studies met the predefined inclusion criteria. Of these 16 studies, two were case-control studies (20, 34) (table 1), 13 were cohort studies that used incidence rate ratios as the measure of relative risk (8, 9, 12, 14, 15, 21, 23, 25, 28–31, 33) (table 2), and one was a cohort study that used standardized hospitalization ratio as the measure of relative risk (19). Seven studies were conducted in the United States (9, 12, 15, 21, 23, 33, 34), eight in Europe (14, 19, 20, 25, 28–31), and one in Australia (8). Six studies included cases of type 1 diabetes, 12 studies included cases of type 2 diabetes, and three studies included both types of diabetes. The outcomes evaluated included incident hip fracture in 13 studies (8, 9, 12, 14, 15, 19–21, 23, 25, 28, 29, 34), all nonvertebral fractures combined in eight studies (8, 12, 20, 28–31, 33), distal forearm fracture in seven studies (8, 12, 15, 20, 29, 30, 34), proximal humerus fracture in five studies (8, 12, 15, 30, 34), foot fracture in two studies (12, 34), vertebral fracture (based on spine radiographs) in four studies (12, 15, 20, 30), and ankle fracture in three studies (8, 12, 30). In the primary meta-analysis of diabetes and fracture incidence, we included both the two case-control studies (20, 34) and the 14 cohort studies (8, 9, 12, 14, 15, 19, 21, 23, 25, 28–31, 33). These sixteen studies comprised 836,941 participants and 139,531 incident cases of fracture.

Hip fracture incidence and type 1 and type 2 diabetes

Figure 1 shows individual study results and the overall summary results for the one case-control and 11 cohort

TABLE 1. Characteristics of case-control studies of the association between diabetes mellitus and fracture risk

Study and year (ref. no.)	Country	Sex	Age (years)	No. of controls	Control selection methods	Type of diabetes	Fracture site and no. of cases	Subgroup	Odds ratio	95% confidence interval	Controlled variables
Kegan et al., 2002 (34)	United States	Both	≥45	1,913	Population controls matched by age and sex	Self-reported type 1 and type 2 diabetes combined	Forearm: 1,000		0.9	0.7, 1.2	Age, sex, and race/ethnicity
							Foot: 827		1.4	1.1, 1.8	
							Proximal humerus: 448		1.7	1.2, 2.3	
							Tibia/fibula: 168		—*	—	
							Pelvis: 172		—	—	
Vestergaard et al., 2005 (20)	Denmark	Both	All ages (mean = 43 years) (standard deviation, 27)	373,962	Population controls matched by age and sex	Type 1 and type 2 (medical records)	All: 124,655	Type 1 diabetes	1.3	1.2, 1.5	Prior fracture; use of corticosteroids, antiepileptics, diuretics, anxiolytics, sedatives, neuroleptics, antidepressants, statins, nonstatin cholesterol-lowering drugs, and antihypertensives; alcoholism; myocardial infarction; stroke; number of days spent in bed due to illness in 1999; number of contacts with a general practitioner or specialist in 1999; working; income; and living with another person
							Hip: 10,530		1.7	1.3, 2.2	
							Forearm: 20,035		1.0	0.8, 1.4	
							Spine: 3,364		2.5	1.3, 4.6	
							All: 124,655	Type 2 diabetes	1.2	1.1, 1.3	
							Hip: 10,530		1.4	1.2, 1.6	
							Forearm: 20,035		1.2	1.0, 1.5	
							Spine: 3,364		1.3	1.0, 1.9	

* Not provided in original article.

studies of type 2 diabetes and hip fracture incidence. Eight of these 12 studies found a statistically significant positive association between type 2 diabetes and hip fracture incidence. In one of the cohort studies (15), a significant inverse association between type 2 diabetes and hip fracture (relative risk (RR) = 0.8, 95 percent confidence interval (CI): 0.5, 0.9) was reported, but when we recalculated the 95 percent confidence interval based on the derived standard error, the upper limit crossed 1 (RR = 0.8, 95 percent CI: 0.6, 1.02). The range of individual relative risks was 0.6–9.2, and the summary relative risk for all 12 studies was 1.7 (95 percent CI: 1.3, 2.2). Heterogeneity among studies was found ($Q = 58.1$; p for heterogeneity (p_{het}) < 0.001). In a sensitivity analysis in which one study at a time was excluded and all other studies were included, we consistently found a statistically significant positive association between type 2 diabetes and hip fracture incidence (range of summary RRs, 1.6–1.8). The studies by Meyer et al. (25), Heath et al. (15), and Vestergaard et al. (20) contributed most to heterogeneity. In an analysis excluding these studies, the association between type 2 diabetes and hip fracture was somewhat stronger (summary RR = 1.8, 95 percent CI: 1.5, 2.2), and the test for heterogeneity was not statistically significant ($Q = 12.2$; $p_{het} = 0.14$).

Figure 2 shows individual study results and the overall summary results for the one case-control and five cohort studies of type 1 diabetes and hip fracture incidence. All six of these studies found a statistically significant positive association between type 1 diabetes and hip fracture incidence (range of individual RRs, 1.7–12.3); the summary relative risk for all six studies combined was 6.3 (95 percent CI: 2.6, 15.1). Heterogeneity among studies was significant ($Q = 89.2$; $p_{het} < 0.001$). In a sensitivity analysis excluding one study at a time, we consistently found a statistically significant positive association between type 1 diabetes and hip fracture incidence (range of summary RRs, 5.5–8.9). The case-control study by Vestergaard et al. (20) contributed most to heterogeneity. In an analysis excluding this study, the association between type 1 diabetes and hip fracture became stronger (summary RR = 8.9, 95 percent CI: 7.1, 11.2), and the test for heterogeneity was not statistically significant ($Q = 2.9$; $p_{het} = 0.57$).

We also conducted subgroup meta-analyses by study design, geographic area, sex, type of diabetes, and duration of follow-up (table 3). The association between type 2 diabetes and hip fracture incidence was somewhat stronger in cohort studies than in one case-control study and stronger in men than in women, although differences were not statistically significant. Results were consistent for studies conducted in Europe and in the United States. For type of diabetes, the summary estimate was stronger for type 1 diabetes than for type 2 diabetes; there was heterogeneity by type of diabetes ($p_{het} < 0.001$). Finally, the summary estimate was stronger for the four cohorts with 10 or more years of follow-up (summary RR = 2.7, 95 percent CI: 1.7, 4.4) than for the six cohorts with follow-up durations of less than 10 years (RR = 1.6, 95 percent CI: 1.3, 2.0); there was heterogeneity among studies by duration of follow-up (<10 years vs. ≥10 years) ($p_{het} = 0.02$).

TABLE 2. Characteristics of cohort studies of the association between diabetes mellitus and fracture risk

Study and year (ref. no.)	Country	Average follow-up period (years)	Sex	Age (years) at enrollment	Study population	Fracture site and no. of cases	Subgroup	Relative risk*	95% confidence interval	Controlled variables
Heath et al., 1980 (15)	United States	Unknown	Both	<103 (median, 61)	Rochester, Minnesota: 500 men and 486 women with medically recorded type 1 or type 2 DM†	Vertebra: 26		0.6	0.3, 0.7	Age, sex, race, residence, year, and institution
						Proximal humerus: 16		0.6	0.3, 0.9	
					Comparison group: 986 men and women without DM, matched for age, sex, race, and year	Distal forearm: 39		0.7	0.5, 0.9	
						Proximal femur: 48		0.8	0.5, 0.9	
Meyer et al., 1993 (25)	Norway	10.9	Both	35–49	Norwegian Prospective Study: 118 women and 180 men with self-reported DM (type unknown)	Hip				Age, height, BMI,† physical activity, stroke, receipt of a disability pension, marriage, and smoking
						Women: 136		9.2	3.4, 24.9	
						Men: 57		9.4	2.9, 30.5	
					Comparison group: 23,850 women and 24,333 men without DM					
Forsen et al., 1999 (14)	Norway	9	Both	≥50	Nord-Trøndelag Health Survey: 770 men and 1,080 women with self-reported type 1 or type 2 DM	Hip: 1,643	Type 1 DM			Age, BMI, and smoking
							Women	6.9	2.2, 21.6	
							Men	4.5	0.6, 31.9	
					Comparison group: 13,210 men and 13,685 women without DM		Type 2 DM			
							Women	1.8	1.1, 2.9	
							Men	1.2	0.4, 3.2	
Ivers et al., 2001 (8)	Australia	5	Both	≥49	Blue Mountains Eye Study: 216 men and women with self-reported type 2 DM	All fractures: 251		0.9	0.7, 1.2	Age, sex, and BMI
						Hip: 59		0.6	0.2, 2.2	
						Distal forearm: 53		0.7	0.2, 2.3	
					Comparison group: 3,438 men and women without DM	Proximal humerus: 26		0.5	0.08, 3.6	
						Ankle: 36		1.1	0.6, 1.9	
Nicodemus and Folsom, 2001 (9)	United States	11	Female	55–69	Iowa Women's Health Study: 47 women with self-reported type 1 DM and 1,682 women with self-reported type 2 DM	Hip: 490	Type 1 DM	12.3	5.1, 29.7	Age, BMI, smoking, estrogen use, and waist:hip ratio
							Type 2 DM	1.7	1.2, 2.4	
					Comparison group: 30,377 women without DM					

Schwartz et al., 2001 (12)	United States	9.4	Female	≥65	Study of Osteoporotic Fractures: 657 women with self-reported type 2 DM Comparison group: 8,997 women without DM	Nonvertebral: 2,624		1.3	1.1, 1.5	Age, BMI, bone density, height loss since age 25 years, contrast sensitivity, walking speed, alcohol consumption in past year, resting pulse rate, maternal hip fracture, spending <4 hours/day on feet, use of long-acting benzodiazepam, and calcium intake
						Hip: 549		1.8	1.2, 2.7	
						Proximal humerus: 355		1.9	1.2, 3.0	
						Distal forearm: 595		0.9	0.6, 1.4	
						Ankle: 282		1.1	0.7, 1.7	
						Foot: 287		1.1	0.6, 1.8	
						Vertebral: 388		1.1	0.7, 1.8	
Ottenbacher et al., 2002 (23)	United States	7	Both	>65	Hispanic portion of the Established Populations for Epidemiologic Studies of the Elderly: 291 men and 399 women with self-reported DM (type unknown) Comparison group: 922 men and 1,272 women without DM	Hip: 110	Men and women	1.5	1.0, 2.3	Age, sex, BMI, smoking, previous stroke, performance‡, and distant vision
Miao et al., 2005 (19)	Sweden	Mean = 9.9 (SD,† 5.8)	Both	Mean = 20.7 (SD, 10.9)	Population-based cohort study: 12,551 men and 12,054 women hospitalized for type 1 DM Comparison group: register of total population	Hip: 121	Sex	(SHR†,§)		Age, sex, and calendar period
							Men	7.6	5.9, 9.6	
							Women	9.8	7.3, 12.9	
Strotmeyer et al., 2005 (33)	United States	4.5	Both	70–79	Health, Aging, and Body Composition Study: 323 men and 243 women with type 2 DM defined by blood glucose and/or medication history and 106 men and 71 women with impaired fasting glucose Comparison group: 1,027 men and 1,209 women without DM	Any fracture: 161		1.6	1.1, 2.5	Age, sex, race, site, hip bone mineral density, lean mass, fat mass, and abdominal visceral fat
Gerdhem et al., 2005 (31)	Sweden	4.6	Female	75	Osteoporosis Prospective Risk Assessment: 74 women with self-reported type 2 DM Comparison group: 1,058 women without DM	Any fracture: 198		0.7	0.4, 1.4	None, but all participants were the same age and sex.

Table continues

TABLE 2. Continued

Study and year (ref. no.)	Country	Average follow-up period (years)	Sex	Age (years) at enrollment	Study population	Fracture site and no. of cases	Subgroup	Relative risk*	95% confidence interval	Controlled variables
de Liefde et al., 2005 (29)	The Netherlands	Mean = 6.8 (SD, 2.3)	Both	≥55	Rotterdam Study: 309 men and 483 women with type 2 DM defined by oral glucose tolerance testing and/or medication history	Any non-vertebral: 771	Both sexes	1.3	1.0, 1.8	Age, BMI, serum creatinine level, visual acuity, falling frequency, lower-limb disability, smoking, and bone mineral density
							Men	1.6	0.9, 2.9	
							Women	1.3	0.9, 1.8	
						Hip: 215	Both sexes	1.3	0.8, 2.3	
							Men	1.3	0.4, 4.2	
					Comparison group: 2,382 men and 3,481 women without DM		Women	1.4	0.8, 2.5	
						Wrist: 204	Both sexes	1.4	0.8, 2.4	
							Men	1.3	0.2, 10.4	
							Women	1.5	0.8, 2.6	
Holmberg et al., 2006 (30)	Sweden	Men: 19 Women: 15	Both	Men: mean = 44 Women: mean = 48	Malmö Preventive Project: 166 women and 276 men with type 2 DM (not defined)	Any fracture				Age, BMI, diastolic blood pressure, resting pulse rate, triglyceride level, γ-glutamyltransferase level, smoking, poor self-rated health, sedimentation rate for women, and cholesterol and creatinine levels for men
						Women: 1,257		1.9	1.3, 2.8	
						Men: 1,278		2.4	1.7, 3.4	
					Comparison group: 22,444 men and 10,902 women without DM	Forearm				
						Women: 600		1.5	0.7, 3.0	
						Men: 315		2.2	0.95, 4.8	
						Vertebral				
						Women: 138		2.9	1.3, 6.3	
						Men: 156		1.1	0.4, 3.5	
						Proximal humerus				
						Women: 146		2.1	0.8, 6.0	
						Men: 115		1.1	0.2, 7.9	
						Ankle				
						Women: 217		2.4	1.1, 5.4	
						Men: 250		1.4	0.5, 4.5	
						Hip				
						Women 135		4.0	1.7, 9.4	
						Men: 163		6.4	3.4, 11.8	
Ahmed et al., 2006 (28)	Norway	6	Both	25–98	Tromsø Study: 52 men and 29 women with self-reported type 1 DM and 175 men and 198 women with self-reported type 2 DM	Any nonvertebral	Type 1 DM			Age, BMI, smoking, blood pressure, high density lipoprotein cholesterol level, and triglyceride level
						Men: 446	Men	3.1	1.3, 7.4	
						Women: 803	Women	2.9	0.9, 8.9	

Comparison group: 12,639 men and 14,065 women without DM					Type 2 DM				
					Men	1.2	0.6, 2.5		
					Women	1.1	0.7, 1.7		
				Hip	Type 1 DM				
				Men: 72	Men	18.4	5.7, 59.3		
				Women: 177	Women	9.0	1.3, 65.1		
					Type 2 DM				
					Men	1.6	0.6, 4.5		
					Women	1.9	1.0, 3.5		
Janghorbani et al., 2006 (21)	United States	22	Female	34–59	Nurses' Health Study: 292 women with self-reported type 1 DM and 8,348 women with type 2 DM	Hip: 1,398	Type 1 DM	6.4	3.9, 10.3	Age, BMI, physical activity, menopausal status, estrogen use, smoking, and daily intakes of calcium, vitamin D, and protein
							Type 2 DM	2.2	1.8, 2.7	
					Comparison group: 101,343 women without DM					

* The measure of relative risk was a rate ratio in all studies, except the study by Miao et al. (19), for which the measure was a standardized hospitalization ratio.
† DM, diabetes mellitus; BMI, body mass index; SD, standard deviation; SHR, standardized hospitalization ratio.
‡ A summary performance measure of lower body function.
§ Ratio of the observed number of first hospitalizations for hip fracture to the expected number.

Age, physical activity, and body mass index are potentially the most important known confounders for the positive association between type 2 diabetes and hip fracture risk. When we restricted the meta-analysis to studies that controlled for these variables (12, 21, 25), the association between type 2 diabetes and hip fracture remained (summary RR = 2.6, 95 percent CI: 1.5, 4.5).

Other fracture sites

Of one case-control and seven cohort studies of type 2 diabetes and all nonvertebral fractures (8, 12, 20, 28–31, 33), four (12, 20, 28, 33) found a statistically significant positive association and four (8, 29–31) found no association (tables 1 and 2). When all eight studies were analyzed, a statistically significant association between type 2 diabetes and risk of any fracture was found (summary RR = 1.2, 95 percent CI: 1.01, 1.5). However, there was statistically significant heterogeneity among studies ($Q = 14.9$; $p_{het} = 0.02$). A sensitivity analysis identified the study by Ivers et al. (8) as contributing most to heterogeneity. In an analysis excluding this study, the association between type 2 diabetes and any fracture was somewhat stronger (summary RR = 1.3, 95 percent CI: 1.1, 1.5), and the test for heterogeneity was no longer statistically significant ($Q = 10.5$; $p_{het} = 0.11$). There was no significant association between type 2 diabetes and fracture of the distal forearm (summary RR = 0.98, 95 percent CI: 0.8, 1.2), ankle (RR = 1.3, 95 percent CI: 0.9, 2.0), proximal humerus (RR = 1.3, 95 percent CI: 0.8, 2.2), or vertebra (RR = 1.2, 95 percent CI: 0.7, 1.2). The association between type 2 diabetes and foot fracture (RR = 1.3, 95 percent CI: 1.1, 1.7) was statistically significant but was based on only two studies (12, 34).

Publication bias

There was no funnel plot asymmetry for the association between either type of diabetes and hip fracture risk (data not shown). *P* values for Begg's adjusted rank correlation test and Egger's regression asymmetry test were 0.41 and 0.42, respectively, indicating a low probability of publication bias.

DISCUSSION

Findings from this meta-analysis indicate that both type 1 and type 2 diabetes were associated with significantly increased risk of hip fracture; the association with type 1 diabetes was stronger than that with type 2 diabetes. The results were consistent for studies carried out in the United States and in Europe. The association was observed in both women and men.

Our analysis must be interpreted in the context of the limitations of the available data. Four of the studies (25 percent) did not distinguish between type 1 and type 2 diabetes (15, 23, 25, 34). Because type 1 diabetes (which accounts for 5–10 percent of all diagnosed cases of diabetes (40)) may be more strongly related to hip fracture (9, 14, 19,

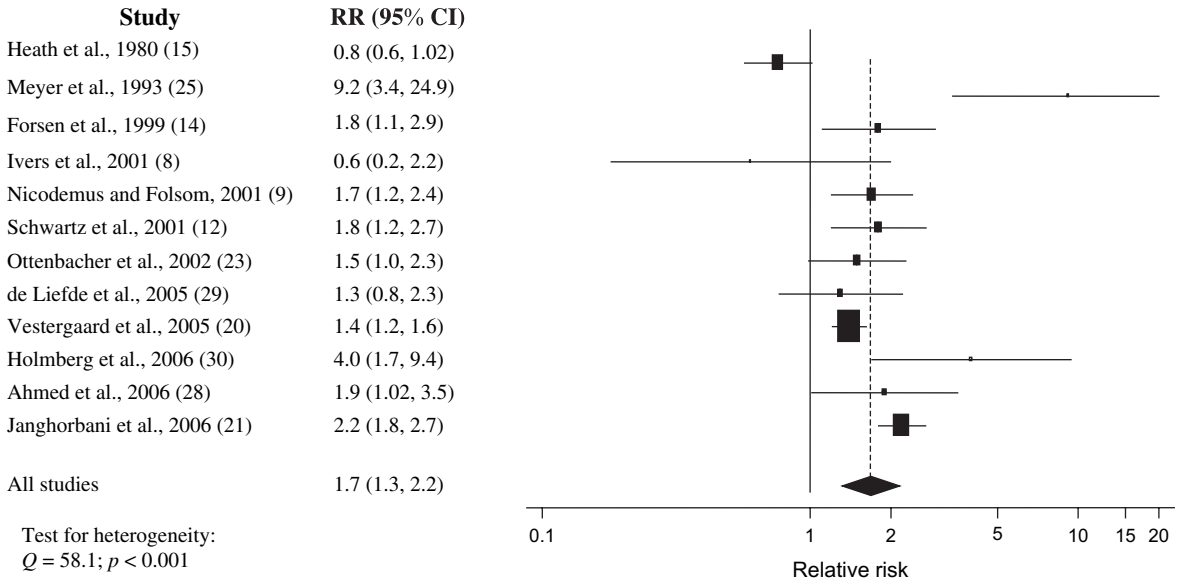

FIGURE 1. Association between type 2 diabetes mellitus and risk of hip fracture in case-control and cohort studies. Each square shows the study-specific relative risk (RR) estimate (the size of the square reflects the study-specific statistical weight, that is, the inverse of the variance), and the horizontal line shows the related 95 confidence interval (CI). The diamond shows the summary RR estimate, and its width represents the corresponding 95% CI. All statistical tests were two-sided. Statistical heterogeneity between studies was assessed with Cochran's *Q* test.

21, 28), the magnitude of the association between type 2 diabetes and hip fracture risk may have been slightly overestimated if some diagnoses of type 2 diabetes were truly cases of type 1 diabetes. In addition, because type 2 diabetes is an underdiagnosed disease, some degree of misclassification of exposure to diabetes is likely to have occurred. Such nondifferential misclassification would have tended to attenuate the true relation between type 2 diabetes and hip fracture risk. As in any meta-analysis, the possibility of publication bias is of concern. However, the results obtained from funnel plot analysis and formal statistical tests did not provide evidence for such bias.

Nearly all published studies included in this meta-analysis were conducted in Whites, and little information is available on the relation between diabetes and fracture in minority populations. Previous studies have shown that Blacks tend to have higher bone mineral density than Whites but are less likely to receive medical care for osteoporosis

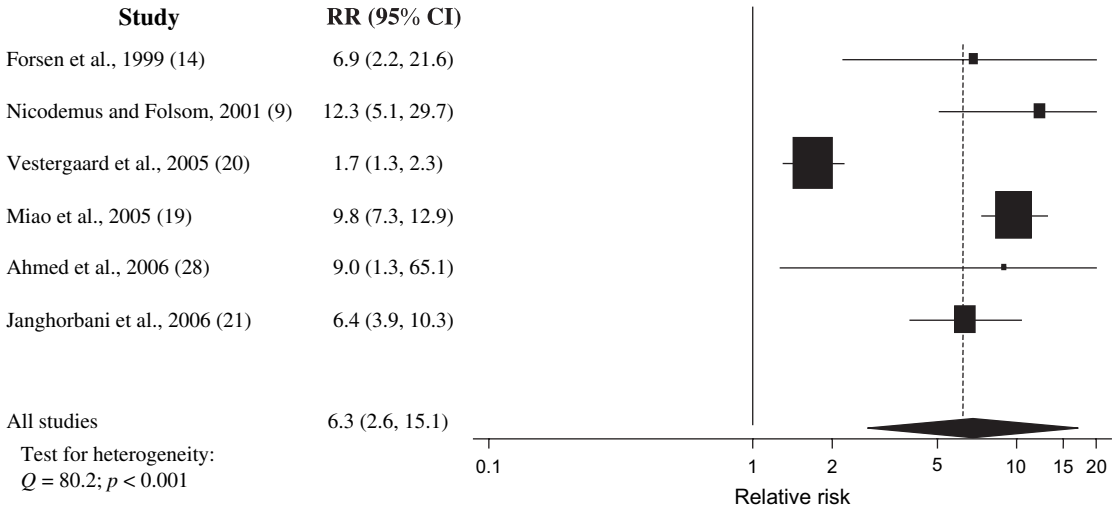

FIGURE 2. Association between type 1 diabetes mellitus and risk of hip fracture in case-control and cohort studies. Each square shows the study-specific relative risk (RR) estimate (the size of the square reflects the study-specific statistical weight, that is, the inverse of the variance), and the horizontal line shows the related 95 confidence interval (CI). The diamond shows the summary RR estimate, and its width represents the corresponding 95% CI. All statistical tests were two-sided. Statistical heterogeneity between studies was assessed with Cochran's *Q* test.

TABLE 3. Summary relative risk estimates from case-control and cohort studies of the association between type 2 diabetes mellitus and hip fracture incidence, by study design, geographic area, sex, and duration of follow-up

Subgroup	No. of studies	Summary relative risk	95% confidence interval	Between studies		Between subgroups	
				Q	*p* for heterogeneity	*Q*	*p* for heterogeneity
Study design							
Case-control	1	1.4	1.2, 1.6	00.0		−6.4	<0.001
Cohort	11	1.8	1.3, 2.4	50.8	<0.001		
Geographic area							
United States	6	1.5	1.02, 2.2	40.3	<0.001	1.09	0.27
Europe	7	1.8	1.2, 2.7	25.7	<0.001		
Sex							
Female	8	2.1	1.6, 2.7	73.0	<0.001	0.67	0.51*
Male	5	2.8	1.2, 6.6	15.4	0.004		
Both	4	1.1	0.8, 1.6	13.2	0.004	−2.58	<0.001†
Duration of follow-up (years)							
<10	6	1.6	1.3, 2.0	4.1	0.537	−2.4	0.02
≥10	4	2.7	1.7, 4.4	11.9	0.008		
Type of diabetes							
Type 2	12	1.7	1.3, 2.2	54.3	<0.001	−3.84	<0.001‡
Type 1	6	6.3	2.6, 15.1	89.2	<0.001		

* Test for heterogeneity between men and women. All statistical tests were two-sided.
† Test for heterogeneity between women and both sexes combined.
‡ Test for heterogeneity between type 1 and type 2 diabetes.

than Whites (41). In this meta-analysis, we were unable to conduct separate analyses by ethnicity. In addition, only two of 16 studies included in the meta-analysis measured and controlled for bone mineral density (29, 31). Thus, it was not possible for us to evaluate the impact of controlling for bone mineral density on the relation between diabetes and fracture risk.

Type 2 diabetes and hip fracture share similar risk factors, including age and physical inactivity, and opposing risk factors, including obesity. Thus, the observed increased risk of hip fracture associated with a history of type 2 diabetes may reflect confounding by these risk factors. However, a positive association between diabetes and hip fracture risk remained when we limited the meta-analysis to studies that controlled for age, physical activity, and body mass index.

Discrepancies among studies investigating the relation of diabetes with hip fracture risk according to sex may be attributable to small samples that produced insufficient statistical power to detect some relations in the individual studies. Because this meta-analysis included a large number of studies, we could assess the association according to sex with high precision. The association between type 2 diabetes and hip fracture was slightly stronger in men than in women, but this difference could have easily been due to chance, because the number of cases in men was relatively small.

The mechanisms whereby diabetes increases fracture risk are not entirely clear. The putative mechanisms include impaired bone quality due to the lower bone mineral density (1, 4) and long-term bone loss (42) observed among patients with type 1 diabetes. Another possible cause of the increased risk of low-trauma fracture in both type 1 and type 2 diabetes is diabetes-related comorbidity (6, 8, 43, 44), such as diabetic retinopathy, peripheral neuropathy, and cerebral stroke or hypoglycemia, which may increase risk of falling. The combination of poor bone quality and frequent falls would be expected to increase the risk of fracture independently of bone mineral density. Evidence regarding a direct relation of better glycemic control with reduced risk of fracture is very weak (8).

Our results have important clinical and public health implications. Osteoporotic fractures and diabetes mellitus continue to be important medical, social, and economic concerns to society. In the United States, approximately 8 percent of adults have diabetes (45), and it has been predicted that the number of Americans with diagnosed diabetes will increase by 165 percent in the coming half century, from 11 million in 2000 to 29 million in 2050 (46). The prevalence of diabetes has also increased rapidly in other developed countries and in many developing countries. Diabetes prevalence will continue to escalate worldwide as a result of the aging of the population and the growing obesity epidemic; thus, it will further contribute to the public health burden of low-trauma fractures.

In conclusion, the results of this meta-analysis strongly support an association between type 1 and type 2 diabetes

and increased risk of hip fracture in both women and men. With a worldwide increasing prevalence of diabetes, the contribution of diabetes to the incidence of low-trauma fracture may increase. These findings emphasize the need for fracture prevention strategies in patients with diabetes.

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