



# Vertebral Fractures in Individuals With Type 2 Diabetes: More Than Skeletal Complications Alone

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## OBJECTIVE

We aimed to assess whether individuals with type 2 diabetes (T2D) have increased risk of vertebral fractures (VFs) and to estimate nonvertebral fracture and mortality risk among individuals with both prevalent T2D and VFs.

## RESEARCH DESIGN AND METHODS

A systematic PubMed search was performed to identify studies that investigated the relationship between T2D and VFs. Cohorts providing individual participant data (IPD) were also included. Estimates from published summary data and IPD cohorts were pooled in a random-effects meta-analysis. Multivariate Cox regression models were used to estimate nonvertebral fracture and mortality risk among individuals with T2D and VFs.

## RESULTS

Across 15 studies comprising 852,705 men and women, individuals with T2D had lower risk of prevalent (odds ratio [OR] 0.84 [95% CI 0.74–0.95];  $I^2 = 0.0\%$ ;  $P_{\text{het}} = 0.54$ ) but increased risk of incident VFs (OR 1.35 [95% CI 1.27–1.44];  $I^2 = 0.6\%$ ;  $P_{\text{het}} = 0.43$ ). In the IPD cohorts ( $N = 19,820$ ), risk of nonvertebral fractures was higher in those with both T2D and VFs compared with those without T2D or VFs (hazard ratio [HR] 2.42 [95% CI 1.86–3.15]) or with VFs (HR 1.73 [95% CI 1.32–2.27]) or T2D (HR 1.94 [95% CI 1.46–2.59]) alone. Individuals with both T2D and VFs had increased mortality compared with individuals without T2D and VFs (HR 2.11 [95% CI 1.72–2.59]) or with VFs alone (HR 1.84 [95% CI 1.49–2.28]) and borderline increased compared with individuals with T2D alone (HR 1.23 [95% CI 0.99–1.52]).

## CONCLUSIONS

Based on our findings, individuals with T2D should be systematically assessed for presence of VFs, and, as in individuals without T2D, their presence constitutes an indication to start osteoporosis treatment for the prevention of future fractures.

Type 2 diabetes (T2D) is a chronic metabolic disease characterized by several complications such as cardiovascular disease, neuropathy, nephropathy, retinopathy, and mortality (1). Moreover, skeletal complications are also evident, as individuals with T2D present increased risk of hip and nonvertebral fractures compared with the general population, despite similar or higher levels of areal bone mineral density (BMD). This suggests that BMD underestimates risk of fracture in these individuals (2,3). Several mechanisms have been suggested to explain this increased fracture risk: increased frequency of falling, cortical porosity, and microvascular disease and

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increased levels of advanced glycation end products among others (2,4–7). Fracture risk assessment remains a low priority in clinical care, as compared with that of the extraskeletal comorbidities and complications affecting individuals with T2D, despite that fracture occurrence significantly increases disability (1). Vertebral fractures (VFs) are the most common type of osteoporotic fracture, and their identification is important not only for the diagnosis of osteoporosis but also for future fracture risk assessment and treatment decisions (8). They are very often asymptomatic, and there is evidence that they are greatly underdiagnosed worldwide (9). VFs and nonvertebral fractures differ in skeletal composition and biomechanical properties. Vertebrae are composed predominantly of trabecular bone, which is substantially more metabolically active and holds distinct biomechanical properties from cortical bone. Further, nonvertebral fractures are often preceded by a fall or some form of trauma, while this only applies to ~10–15% of VFs (10). In contrast to the well-established increase in hip and nonvertebral fracture risk among individuals with T2D consistently found across numerous studies (2,3), evidence regarding the risk of VFs in T2D remains inconclusive. Five previously published meta-analyses reporting inconsistent findings (11–15) all hold several limitations and large underlying heterogeneity of effects of undocumented source.

We aimed to assess whether individuals with T2D have increased risk of VFs by bringing together a meta-analysis, published summary data, and individual participant data from prospective cohort studies. Moreover, in cohorts with individual participant data (IPD), we aimed to investigate the influence of T2D and VFs on the risk of nonvertebral fractures and mortality.

## RESEARCH DESIGN AND METHODS

### Search Strategy and Selection Criteria

We performed a meta-analysis to ascertain the relationship between T2D and VFs in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines for reporting (16). Two systematic searches of the literature in PubMed were performed, and we included previously published studies in humans that

reported estimates and 95% CIs concerning the association between T2D and VFs (Supplementary Fig. 1). A detailed description of the search strategy can be found in Supplementary Material S2.

### IPD From Cohorts

We gathered individual-level data by contacting and inviting collaborators from seven different cohorts with participant information on prevalent T2D, prevalent or incident VFs, age, sex, BMI, BMD, corticosteroid use, and antiosteoporotic therapy. All contacted collaborators agreed to share the IPD, and all seven cohorts with IPD were available for analysis (Supplementary Figs. 1 and 3). Each study is approved by their relevant local or national ethics committees, and all participants have given informed consent to take part. Data shared was anonymized, and confidentiality agreements were signed from collaborating groups.

Prevalent T2D was defined at baseline across studies based either on general practitioner's records or according to the current World Health Organization guidelines as a fasting blood glucose  $\geq 7.0$  mmol/L, a nonfasting blood glucose  $\geq 11.1$  mmol/L, or use of blood glucose-lowering medication. Presence of VFs was assessed on lateral radiographs or lateral DXA of the spine from the fourth thoracic to the fourth lumbar vertebrae. VFs were assessed at baseline (prevalent) and, where available, at the follow-up visit (incident) at, on average, 2.5–5 years after baseline across cohorts. Incident VFs were defined as new VFs occurring in a participant free of fracture across all vertebrae at baseline. Nonvertebral fracture events and death were reported either by general practitioners in a computerized system or extracted from hospital or research records. Follow-up time was calculated as time from baseline to first nonvertebral fracture, death, end of follow-up period, or loss to follow-up, whichever occurred first. Covariates were age, sex, BMI, femoral neck BMD (FN-BMD), corticosteroid use, and antiosteoporotic treatment. In a subset of the IPD cohorts, we also tested the association between prevalent T2D and FN-BMD measured at baseline and of T2D with lumbar spine BMD (LS-BMD) and trabecular bone score (TBS) (17) measured at follow-up (Supplementary Fig. 3).

### Statistical Analysis

To address the absence of information regarding FN-BMD in 18.6% of all IPD cohorts, we imputed this information using the fully conditional specification-imputation method in SPSS. This is an iterative Markov chain Monte Carlo method that can be used to account for arbitrary missing data. Before performing the multiple imputation, FN-BMD values measured with a lunar DXA were transformed to hologic values through the formula: hologic FN-BMD =  $0.939 \times \text{lunar FN-BMD} - 0.023$  (18). To impute missing FN-BMD values, we performed 20 imputations with 10 iterations each, in which predictors were age, height, weight, BMI, sex, study center, and FN-BMD. We have shown in this study results of the pooled estimates from all 20 imputations, after comparing it with the nonimputed data and finding no differences between the imputed and nonimputed data. The imputed values of FN-BMD were used when FN-BMD was a covariate in the analyses. When FN-BMD was an outcome or exposure in the exploratory analyses, only individuals with nonmissing values were included.

The published studies reported adjusted hazard ratios (HRs), ORs, relative risk, or standardized incidence ratios with 95% CIs, and we regarded them as ORs in the meta-analysis (Supplementary Table 4). For the meta-analysis across IPD cohorts, we ran separately for each cohort, a logistic regression model stratified by sex and adjusted for age, BMI, FN-BMD, corticosteroid use, and antiosteoporotic treatment. We then analyzed both published and unpublished data combined in a random-effects meta-analysis and have provided summary statistics for the random-effects model. The heterogeneity of the study estimates was assessed using the  $I^2$  statistic. When heterogeneity was present, we performed sensitivity analyses by excluding studies one by one from the meta-analysis. We explored potential sources of heterogeneity also by testing interactions between T2D and sex, age, and BMI in the IPD cohorts. The significance threshold for interaction terms was set to  $P < 0.1$ . Further, to estimate the risk of mortality among individuals with T2D and VF, we fitted a multivariate Cox regression model. The proportionality of hazard assumption for the Cox model fit was assessed based on Schoenfeld

residuals. We found a significant relation among residuals of sex, BMI, and age with time ( $P$  value  $<0.001$ ). Therefore, to fulfill the proportionality of hazard assumption, the Cox regression model was run separately for sex and BMI categories. The model was fitted adjusted for natural age spline with 5 df, corticosteroid use, antiosteoporotic treatment, cohort, and BMD T-score. We used a similar approach to assess the risk of nonvertebral fractures based on T2D and VF comorbidity at baseline. We found a significant relationship between residuals of age with time ( $P$  value  $<0.001$ ), and the model was fitted and adjusted for natural age spline with 5 df, sex, BMI, corticosteroid use, antiosteoporotic treatment, cohort, and BMD. Based on FN-BMD T-score values, three clinical categories were created: normal (femoral neck BMD T-score  $>-1.0$ ), osteopenia (FN-BMD T-score  $\leq -1.0$  and  $>-2.5$ ), and osteoporosis (FN-BMD T-score  $\leq -2.5$ ). BMI categories were constructed based on World Health Organization guidelines into underweight ( $<18.5$  kg/m<sup>2</sup>), normal weight (18.5–24.9 kg/m<sup>2</sup>), overweight (25.0–30.0 kg/m<sup>2</sup>), and obese ( $>30.0$  kg/m<sup>2</sup>). Analyses were performed in R with packages “meta” and “survival,” as well as SPSS software (IBM SPSS Statistics 24; Armonk, NY).

## RESULTS

### Overall Characteristics of the Study Population

We identified 719 published studies through our literature search (Supplementary Material 1). Out of these, 711 were not eligible for inclusion, and 8 were included. The included studies were from the U.S. (19–21), Sweden (22), Spain (23), Germany (24), Israel (25), and Japan (26). The IPD cohorts were from Canada (27), U.K. (28), Switzerland (29), the Netherlands (30), and U.S. (31) (Supplementary Table 5). The published studies and IPD cohorts comprised 852,705 individuals, of which 58.6% were women. The prevalence of T2D and VFs, incidence of VFs, and follow-up time varied across studies (Supplementary Table 4). The association between T2D and VFs was adjusted across studies for multiple factors, including at least age and sex (Supplementary Table 4). Mean age ranged across studies from 45.6 to 79.5 years. There were

31,530 individuals in the IPD cohorts, of which 2,182 (6.9%) had a prevalent diagnosis of T2D (Table 1). Individuals with prevalent T2D were on average 1 year older (70.0 vs. 69.0;  $P < 0.001$ ); had higher BMI (28.5 vs. 26.5 kg/m<sup>2</sup>;  $P < 0.001$ ); had a higher FN-BMD T-score ( $-1.05$  vs.  $-1.33$ ;  $P < 0.001$ ) reflected in lower prevalence of osteopenia (43.6 vs. 51.3%;  $P < 0.001$ ) and osteoporosis (9.6 vs. 13.6%;  $P < 0.001$ ); and had a higher prevalence of corticosteroid use (5.3 vs. 3.8%;  $P = 0.03$ ) and antiosteoporotic treatment (10.3 vs. 8.9%;  $P = 0.03$ ). Furthermore, in the 7,819 individuals from cohorts with TBS and BMD measurements, the 472 (6.0%) with prevalent T2D had higher LS-BMD (1.21 vs. 1.14 g/cm<sup>2</sup>;  $P < 0.001$ ) and lower TBS (1.21 vs. 1.26;  $P < 0.001$ ) than individuals without T2D (Table 1).

### Type 2 Diabetes and Prevalent VFs

The meta-analysis concerning the risk of prevalent VFs among individuals with T2D included 124,631 individuals from four published studies and seven IPD cohorts. The combined meta-analysis of published studies and IPD cohorts showed no association between T2D and prevalent VFs (odds ratio [OR] 1.0

[95% CI 0.87–1.15]) but presented significant high heterogeneity ( $I^2 = 64.4\%$ ;  $P_{\text{het}} = 0.0001$ ). Sensitivity analyses of these data indicated that the main source of heterogeneity came from two published studies drawn in Japan (26) and Israel (25). Excluding those studies from the meta-analysis showed lower risk of VFs for individuals with T2D (OR 0.84 [95% CI 0.74–0.95]) without significant heterogeneity ( $I^2 = 0.0\%$ ;  $P_{\text{het}} = 0.54$ ) (Fig. 1A). In addition, sensitivity analysis (across age tertiles and BMI categories) in the cohorts with IPD showed that the lower risk of prevalent VFs in subjects with T2D was confined to individuals aged  $\geq 74.0$  years at baseline (OR 0.76 [95% CI 0.60–0.95];  $P$  for interaction = 0.09) and particularly in obese individuals (OR 0.72 [95% CI 0.54–0.94];  $P$  for interaction = 0.03) (Supplementary Table 6).

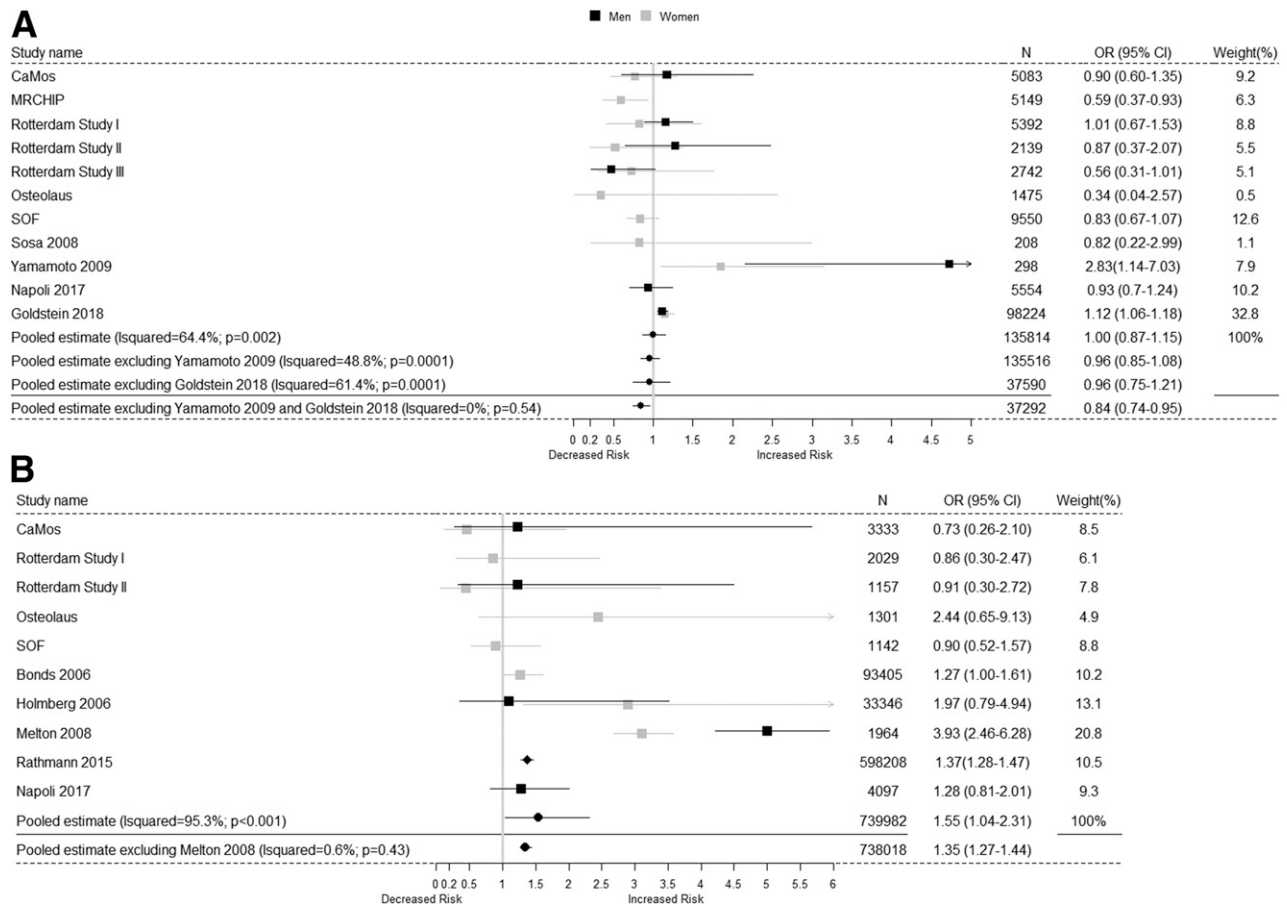
### Type 2 Diabetes and Incident VFs

In contrast to the meta-analysis of prevalent VFs, the meta-analysis of 738,018 individuals from 5 published studies and 6 IPD cohorts showed a higher risk of incident VFs among individuals with T2D (OR 1.55 [95% CI 1.04–2.31]), but displaying very high heterogeneity

**Table 1—Comparison of baseline characteristics by T2D status across cohorts with IPD**

	Without T2D ( <i>n</i> = 29,348)	With T2D ( <i>n</i> = 2,182)	<i>P</i> value
Sex (% women)	24,068 (82.0)	1,608 (73.7)	$<0.001$
Age years	69.0 (9.1)	70.0 (8.5)	$<0.001$
Weight kg	70.3 (13.2)	76.5 (15.1)	$<0.001$
Height cm	162.6 (8.9)	163.5 (9.7)	$<0.001$
BMI kg/m <sup>2</sup>	26.5 (4.2)	28.5 (4.7)	$<0.001$
Underweight	352 (1.2)	11 (0.5)	$<0.001$
Normal weight	10,817 (36.8)	478 (21.9)	
Overweight	12,560 (42.8)	919 (42.1)	
Obese	5,619 (19.2)	774 (35.5)	
FN-BMD T-score (continuous)	$-1.33$ (1.4)	$-1.05$ (1.7)	$<0.001$
FN-BMD T-score clinical categories			
Normal	10,299 (35.1)	1,021 (46.8)	$<0.001$
Osteopenia	15,067 (51.3)	952 (43.6)	
Osteoporosis	3,982 (13.6)	209 (9.6)	
Corticosteroid use	1,126 (3.8)	115 (5.3)	0.03
Antioosteoporotic treatment	2,622 (8.9)	225 (10.3)	0.03
Prevalent VFs	3,513 (11.9)	228 (10.4)	0.03
LS-TBS*	1.26 (0.12)	1.21 (0.13)	$<0.001$
LS-BMD, g/cm <sup>2</sup> *	1.14 (0.21)	1.21 (0.23)	$<0.001$

The  $P$  value corresponds to  $t$  test (continuous variables) or  $\chi^2$  test (categorical variables) for difference between individuals with and without T2D at baseline. LS-TBS, lumbar spine TBS. \*Denotes that information was available only at follow up for 7,819 individuals ( $n = 7,347$  without T2D and  $n = 472$  with T2D).



**Figure 1**—Forest plot of the meta-analysis across studies concerning the association between T2D and risk of VFs. In A, it is shown the association between T2D and prevalent VFs and, in B, the association between T2D and incident VFs. Besides the pooled overall estimates, we also show in the figures the estimates after excluding studies that were introducing heterogeneity on the estimates.

( $I^2 = 95.3\%$ ;  $P_{het} < 0.001$ ). Sensitivity analyses, established that the heterogeneity was introduced by the study from Melton et al. (21). Excluding that study showed that individuals with T2D had an increased risk of incident VFs (OR 1.35 [95% CI 1.27–1.44]) without significant evidence for heterogeneity affecting the estimates ( $I^2 = 0.6\%$ ;  $P_{het} = 0.43$ ) (Fig. 1B).

**Type 2 Diabetes and Bone Health Markers, BMD, and TBS**

In all IPD cohorts, T2D was associated at baseline with higher FN-BMD both in men ( $B = 0.029$ ; 95% CI 0.018–0.041) and women ( $B = 0.046$ ; 95% CI 0.039–0.053). After adjusting for BMI, the association was attenuated but remained significant in both men ( $B = 0.013$ ; 95% CI 0.01–0.025) and women ( $B = 0.022$ ; 95% CI 0.015–0.029). In a subsample ( $n = 7,819$ ) at follow-up, T2D was associated with higher BMD at the lumbar spine in both men ( $B = 0.040$ ; 95% CI 0.013–

0.066) and women ( $B = 0.065$ ; 95% CI 0.039–0.091), but after adjustment for BMI this association was attenuated in both men ( $B = 0.016$ ; 95% CI –0.010 to 0.043) and women ( $B = 0.020$ ; 95% CI –0.004 to 0.045). In contrast, T2D was associated with decreased TBS in the fully adjusted model in both men ( $B = -0.019$ ; 95% CI –0.035 to –0.004) and women ( $B = -0.041$ ; 95% CI –0.055 to –0.026) (Supplementary Table 7).

**Type 2 Diabetes With and Without VFs in Relation to Nonvertebral Fracture Risk and Mortality**

Individuals with both type 2 diabetes and VFs had a higher risk of nonvertebral fractures as compared with individuals without either T2D or VFs (HR 2.42 [95% CI 1.86–3.15]), compared with individuals with T2D alone (HR 1.94 [95% CI 1.46–2.59]) or compared with individuals with VFs alone (HR 1.73 [95% CI 1.32–2.27]) after multivariate adjustments (Table 2). After stratification by FN-BMD category,

we observed that individuals with both T2D and VFs had increased risk of nonvertebral fractures as compared with those without VFs and T2D, independent of BMD T-score category (HR 2.50 [95% CI 1.44–4.35] in those with normal BMD; HR 2.58 [95% CI 1.76–3.79] in those with osteopenia; and HR 2.06 [95% CI 1.25–3.38] in those with osteoporosis). When comparing individuals with both T2D and VFs to individuals with T2D alone, the increased risk of nonvertebral fractures was observed across all BMD T-score categories (being HR 2.04 [95% CI 1.14–3.65] in those with normal BMD; HR 2.0 [95% CI 1.33–3.03] in those with osteopenia; and HR 1.97 [95% CI 1.07–3.62] in those with osteoporosis). As compared with individuals with VFs alone, individuals with both T2D and VFs had a statistically nonsignificant increased risk of nonvertebral fractures independent of BMD levels (HR 1.55 [95% CI 0.86–2.78] in those with normal BMD; HR 1.82 [95% CI 1.23–2.70] in those

**Table 2—The association between T2D and/or prevalent VFs with incident nonvertebral fractures, overall and stratified by BMD category**

	Outcome: incident nonvertebral fracture, HR (95% CI)			
Without T2D or VFs (reference)	1.00	1.00	1.00	1.00
With VFs alone	1.39 (1.27–1.52)	1.61 (1.29–2.00)	1.41 (1.26–1.59)	1.32 (1.13–1.55)
With T2D alone	1.24 (1.09–1.40)	1.22 (0.98–1.52)	1.28 (1.08–1.52)	1.04 (0.71–1.51)
With both T2D and VFs	2.42 (1.86–3.15)	2.50 (1.44–4.35)	2.58 (1.76–3.79)	2.06 (1.25–3.38)
With VFs alone (reference)	1.00	1.00	1.00	1.00
With both T2D and VFs	1.73 (1.32–2.27)	1.55 (0.86–2.78)	1.82 (1.23–2.70)	1.55 (0.93–2.57)
With T2D alone (reference)	1.00	1.00	1.00	1.00
With both T2D and VFs	1.94 (1.46–2.59)	2.04 (1.14–3.65)	2.00 (1.33–3.03)	1.97 (1.07–3.62)

Data are results obtained from Cox regression model adjusted for age (natural splines with 6 df), BMI (natural splines with 5 df), sex, corticosteroid use, antiosteoporotic treatment, and study. The analysis without stratification was additionally adjusted for BMD measured at the femoral neck.

with osteopenia; and HR 1.55 [95% CI 0.93–2.57] in those with osteoporosis). The mortality analysis based on VFs and T2D status at baseline was stratified by sex and BMI to meet the proportionality of hazards assumption; we show also the overall results but will interpret them cautiously. Overall, we found increased mortality risk among individuals with both VFs and T2D compared with individuals without either T2D or VFs (HR 2.05 [95% CI 1.73–2.43]), when compared with individuals with VFs alone (HR 1.71 [95% CI 1.43–2.03]) and with a statistically nonsignificant increase when compared with individuals with T2D alone (HR 1.21 [95% CI 0.97–1.49]). After stratification by sex and BMI category, we observed an increased risk of death among overweight men with both T2D and VFs compared with overweight men without T2D or VFs (HR 2.38 [95% CI 1.15–4.96]), compared with overweight men with VFs alone (HR 2.38 [95% CI 1.15–4.96]), with a nonsignificant increase as compared with individuals with T2D alone (HR 1.61 [95% CI 0.78–3.33]). Similarly, obese men with both T2D and VFs had increased risk of death compared with obese men without T2D or VFs (HR 3.11 [95% CI 1.50–6.46]), compared with obese men with T2D alone (HR 2.54 [95% CI 1.17–5.51]), and compared with individuals with VFs alone (HR 3.10 [95% CI 1.25–7.57]). Overweight women with both T2D and VFs had increased risk of mortality compared with overweight women without T2D or VFs (HR 2.32 [95% CI 1.73–3.11]) and with VFs alone (HR 1.86 [95% CI 1.38–2.56]) but not compared with overweight women with T2D alone (HR 1.13 [95% CI 0.85–1.55]). Obese women also had increased mortality if

they had both T2D and VFs as compared with obese women without T2D or VFs (HR 1.92 [95% CI 1.37–2.68]) and with obese women with VFs alone (HR 1.65 [95% CI 1.16–2.34]), but not compared with obese women with T2D alone (HR 1.03 [95% CI 0.72–1.45]) (Table 3).

## CONCLUSIONS

This meta-analysis of 15 published studies and cohorts showed that individuals with T2D are at higher risk of sustaining an incident VF compared with individuals without T2D. Furthermore, individuals with both T2D and VFs had almost double the risk of sustaining an incident nonvertebral fracture than individuals with either VFs or T2D alone. The increased risk for incident nonvertebral fractures among individuals with T2D and VFs compared with individuals with T2D or VFs alone was increased despite clinical categories of FN-BMD T-score. We also observed a decreased prevalence of VFs among individuals with T2D, and through sensitivity analysis, we could establish that such a protective effect was mostly present among the older or among obese individuals. In addition, we found that individuals with both T2D and VFs had increased mortality risk as compared with individuals without T2D or VFs and still significantly greater than the mortality observed in individuals with T2D or VFs alone. The increased mortality among individuals with T2D and VFs was particularly increased among overweight and obese individuals of both sexes.

Our findings give clarity to the conflicting findings observed across previous meta-analyses. Five previously published meta-analyses that have reported on the association between T2D and VFs

(11–15) hold several limitations that could have influenced their findings. One meta-analysis in particular (11) had several limitations (pointed out in a letter to the editor [32]), one of which was misclassifying fracture location (major osteoporotic fracture vs. VFs) or using effect estimates that were different from those reported in the original study. Limitations of the other meta-analyses included claiming an effect on VFs when referring to nonvertebral fractures (13); not clearly explaining how point estimates were combined (14); or including studies looking at nonvertebral fractures instead of VFs (15). Moreover, none of these meta-analyses of T2D and VFs addressed the source of the heterogeneity encountered in their analyses and missed including some of the studies that were part of our present meta-analysis (11–15).

In the current meta-analysis, the studies by Yamamoto et al. (26), Goldshtein et al. (25), and Melton et al. (21) introduced heterogeneity across study estimates. The first study was in an Asian population, with a high prevalence of VFs among individuals with or without T2D. Although they mentioned that their population without T2D was chosen to be free of any skeletal disorders, an average BMD T-score of  $-2.0$  among women and  $-2.4$  among men with T2D suggests that this population likely had a high prevalence of osteoporosis and was at high risk of fracture. Further, in the Yamamoto et al. (26) study, individuals with T2D were recruited from tertiary centers, suggesting that they were severe cases of T2D. The heterogeneity introduced by the studies of Melton et al. (21) and Goldshtein et al. (25) might have been to a large extent, introduced by the type of

**Table 3—Mortality risk based on presence of T2D and VFs at baseline, stratified by sex and BMI category**

	Outcome: death during follow-up, HR (95% CI)						
	Men (N = 4,405)			Women (N = 15,417)			
	Overall (N = 19,822)	Normal weight (N = 1,413)	Overweight (N = 2,323)	Obese (N = 643)	Normal weight (N = 5,747)	Overweight (N = 6,318)	Obese (N = 3,204)
Without T2D or VFs (reference)	1.0	1.0	1.0	1.0	1.0	1.0	1.0
With VFs alone	1.20 (1.13–1.27)	1.09 (0.81–1.45)	1.03 (0.81–1.31)	1.08 (0.59–1.94)	1.26 (1.15–1.39)	1.24 (1.13–1.36)	1.15 (1.01–1.32)
With T2D alone	1.78 (1.65–1.91)	1.84 (1.44–2.36)	1.50 (1.21–1.84)	1.22 (0.83–1.78)	1.64 (1.39–1.95)	2.04 (1.79–2.32)	1.87 (1.62–2.15)
With both T2D and VFs	2.05 (1.73–2.43)	1.27 (0.46–3.48)	2.42 (1.20–4.88)	3.11 (1.50–6.46)	1.75 (1.23–2.47)	2.32 (1.73–3.11)	1.92 (1.37–2.68)
With T2D alone (reference)	1.0	1.0	1.0	1.0	1.0	1.0	1.0
With both T2D and VFs	1.21 (0.97–1.49)	0.68 (0.24–1.93)	1.61 (0.78–3.33)	2.54 (1.17–5.51)	1.06 (0.72–1.55)	1.13 (0.82–1.55)	1.03 (0.72–1.45)
With VFs alone (reference)	1.0	1.0	1.0	1.0	1.0	1.0	1.0
With both T2D and VFs	1.71 (1.43–2.03)	1.15 (0.4–3.24)	2.38 (1.15–4.96)	3.1 (1.25–7.57)	1.37 (0.97–1.95)	1.86 (1.38–2.52)	1.65 (1.16–2.34)

Individuals were assigned at baseline to four groups: without T2D or VFs, with T2D only, with VFs only, and with both T2D and VFs. A Cox regression model adjusted for age (natural splines with 5 df), corticosteroid use, antihypertensive treatment, and cohort, stratified for sex and BMI, was fitted to estimate the survival of the individuals based on their T2D and VF status at baseline.

estimation used to compare risk of fracture among individuals with T2D (i.e., standardized incidence ratio and standardized rate ratio, respectively). These types of estimations have made the assumption of expected numbers of VFs based on data from clinically diagnosed VFs, which do not include asymptomatic VFs. The latter might be more often incidentally diagnosed among individuals with T2D compared with those without, leading to an overestimation of the risk of VFs among individuals with T2D compared with those without. Although the meta-analysis regarding the incidence of VFs among individuals with T2D, after excluding the studies of Melton et al. (21) and Rathmann et al. (24), showed an increased VF incidence among individuals with T2D, it is important to note that among cohorts with IPD, we could not detect this increased incidence (Supplementary Table 8). We think this is mainly due to the fact that the IPD cohorts were population-based cohorts, all of which required participants to voluntarily visit the research centers to undergo radiographic examination in order for VFs to be diagnosed. Therefore, we may not have been able to determine when an incident VF occurred between visits among the participants who did not attend the research center the following visit. Moreover, individuals with both T2D and VFs might have not attended the following visit more often than those with VFs or T2D alone, based on our finding of increased mortality among individuals with both T2D and VFs. This finding might also explain the decreased prevalence of VFs among individuals with T2D and why the previously published meta-analyses have been inconclusive.

The increased VF risk among individuals with T2D is complicated to elucidate as multiple factors, and mechanisms might be involved directly and indirectly. Decreased bone strength might be a factor. Bone strength is a compound entity that includes bone mass, bone microarchitecture, bone turnover, and bone material properties. While BMD as assessed by DXA seems to be increased on average (33) among individuals with T2D compared with those without, lower TBS levels do suggest trabecular microarchitecture deterioration. In a recent meta-analysis, COOH-terminal cross-linked telopeptide, a bone resorption marker, was significantly

lower in individuals with T2D as well as the bone formation markers procollagen type 1 amino terminal propeptide and osteocalcin (34). These findings suggest the presence of a low bone turnover state in individuals with T2D. On cortical bone, this might predispose to increased occurrence and accumulation of microcracks, resulting in increased nonvertebral fracture risk (35), but the effect of low bone turnover on trabecular bone and a potential deleterious effect leading to increased VF risk remains to be elucidated. In contrast, trabecular bone microstructure as measured by TBS has been found in other studies to be decreased in individuals with T2D (36,37), as well as in the subsample of our current study with TBS measurements. Individuals with T2D have been reported to have decreased muscle mass, increased immobility, and increased frailty compared with healthy subjects (38,39). The increased frailty among individuals with T2D could increase the risk of fragility fractures in this group (39). Similarly to our findings, a previous study found a 20% excess in all-cause mortality after a VF among individuals with T2D compared with individuals without T2D who acquired a VF (40).

Currently, clinical fracture risk estimation tools, such as the Fracture Risk Assessment Tool, underestimate the risk of fracture among individuals with T2D, due to the tendency of this group to fracture at a higher BMD T-score (33,41). This highlights the need for other bone strength markers that can increase accuracy in fracture risk prediction among individuals with T2D. VFs are often asymptomatic, and as such, they very often go undetected but even if asymptomatic, they are strongly associated with increased incidence of fractures not only in the spine but also elsewhere in the skeleton (42). Screening for VFs is recommended in high-risk groups such as postmenopausal women and older men with a height loss  $\geq 4$  cm, kyphosis, or long-term use of glucocorticoids (43). In the current study, the presence of prevalent VFs was associated with a 50% increased hazard of nonvertebral fractures, but individuals with T2D and VFs had almost twice the risk for incident nonvertebral fractures compared with individuals with T2D alone or VFs alone. The increased risk for nonvertebral fractures was similar across all FN-BMD T-score categories (normal, osteopenia, or osteoporosis). This, together

with the elevated mortality risk observed, suggests that individuals with T2D might also be good candidates for systematic VF screening without the need of BMD assessment.

This study had several limitations. Although most of the studies included in the meta-analysis had their analyses adjusted for multiple confounders, including BMI, given the U-shaped association between BMI and fracture risk, it would have been appropriate stratifying the analysis for BMI categories. Furthermore, we did not have information on other comorbidities and cause-specific mortality; this information would have helped to better understand the mechanism by which T2D and VF comorbidity is associated with increased nonvertebral fractures and mortality. We did not have information regarding the type of treatment that individuals with T2D were receiving across studies and therefore could not explore potential mechanistic influences of antidiabetes medication in our findings. Moreover, in the cohorts with IPD, we found evidence of bias due to loss to follow-up that may have resulted in underestimation of the association between T2D and VF.

Currently, there are no specific guidelines for the assessment of fracture risk or treatment of osteoporosis in individuals with T2D. On average, individuals with T2D tend to fracture at a higher BMD T-score compared with healthy individuals without diabetes (33), and traditional clinical risk assessment tools underestimate their fracture risk (41). Based on our findings, we suggest that individuals with T2D should be systematically assessed for the presence of VF, measurement currently facilitated by the lateral VF assessment readily implemented in modern DXA devices. Similar to the management of individuals without T2D, presence of VFs among individuals with T2D should be an indication for starting osteoporosis treatment (independent of any given BMD T-score) in order to prevent future fracture. Notoriously, presence of VFs in patients with T2D also constitutes a call for attention to potentially frail individuals at higher risk of mortality than that expected from T2D alone.

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O.L., D.H., E.H.O., and F.R. contributed to data collection, study design, and data interpretation and critically reviewed the report. F.K. and F.R. are the guarantors of this work and, as such, had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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