Frailty and Risk of Fractures in Patients With Type 2 Diabetes

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OBJECTIVE

We aimed to explore whether frailty was associated with fracture risk and whether frailty could modify the propensity of type 2 diabetes toward increased risk of fractures.

RESEARCH DESIGN AND METHODS

Data were from a prospective cohort study. Our primary outcome was time to the first incident clinical fragility fracture; secondary outcomes included time to hip fracture and to clinical spine fracture. Frailty status was measured by a Frailty Index (FI) of deficit accumulation. The Cox model incorporating an interaction term (frailty × diabetes) was used for analyses.

RESULTS

The analysis included 3,149 (70% women) participants; 138 (60% women) had diabetes. Higher bone mineral density and FI were observed in participants with diabetes compared with control subjects. A significant relationship between the FI and the risk of incident fragility fractures was found, with a hazard ratio (HR) of 1.02 (95% CI 1.01–1.03) and 1.19 (95% CI 1.10–1.33) for per-0.01 and per-0.10 FI increase, respectively. The interaction was also statistically significant (P = 0.018). The HR for per-0.1 increase in the FI was 1.33 for participants with diabetes and 1.19 for those without diabetes if combining the estimate for the FI itself with the estimate from the interaction term. No evidence of interaction between frailty and diabetes was found for risk of hip and clinical spine fractures.

CONCLUSIONS

Participants with type 2 diabetes were significantly frailer than individuals without diabetes. Frailty increases the risk of fragility fracture and enhances the effect of diabetes on fragility fractures. Particular attention should be paid to diabetes as a risk factor for fragility fractures in those who are frail.

Fragility fractures are a skeletal complication associated with type 2 diabetes, resulting in substantial morbidity, hospitalization, high health care costs, impaired quality of life, disability, and death (1). Type 2 diabetes itself is reported to be an independent risk factor for fractures. For instance, the risk of a hip fracture in patients with type 2 diabetes is ~70% higher than in individuals without diabetes (2). In type 2 diabetes, bone mineral density (BMD) is usually higher than in individuals without diabetes, and their BMI is often increased, both of which are typically protective factors for most fractures (3,4). Some studies suggested that even in the presence of normal or increased BMD, other factors, including poor glycemic control, abnormal bone turnover, and bone loss, may explain the increased risk of fractures in type 2 diabetes (5–8). Nevertheless, the "diabetes bone paradox" (high risk of fracture but normal or increased BMD) in type 2 diabetes remains to be further investigated (9).

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Frailty is a dynamic aging condition of increased vulnerability affecting psychological, physical, and social functioning (10,11). Emerging evidence has shown that increased frailty is significantly related to higher risks for adverse health outcomes; thus, capturing the degree of frailty could quantify an individual's risks of adverse outcomes and may predict their responses to therapeutic interventions (12–14). The concept of frailty and the risk of adverse outcome relies on the fact that the frailer an individual is, the greater the likelihood that the person will experience adverse health outcomes in the future (12). It is therefore possible that measuring frailty status may assist in the understanding of the diabetes bone paradox. Specifically, our hypotheses included *1*) patients with type 2 diabetes may be frailer than individuals without diabetes despite their greater BMD, and *2*) frailty may modify the propensity of those with type 2 diabetes toward an increased risk of fractures. In this study, we used the data from the Canadian Multicentre Osteoporosis Study (CaMos) to assess the relationship between frailty and the risk of incident fractures in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

Participants and Settings

Details on CaMos have been published elsewhere (15) and can be found at www.camos.org. Briefly, CaMos is a prospective cohort study of two-thirds women and one-third men that aims to estimate the incidence and prevalence of fractures and declining bone mass and the effect of osteoporosis in Canadians. The study enrolled 9,423 noninstitutionalized participants aged ≥25 years in nine study centers across Canada (Vancouver, British Columbia; Calgary, Alberta; Saskatoon, Saskatchewan; Kingston, Toronto, and Hamilton, Ontario; Québec City, Québec; St. John's, Newfoundland and Labrador; and Halifax, Nova Scotia) from 1995 to 1997. Participants residing in a ≤50-km radius of one of the nine study centers were contacted by telephone at random. The sample framework in CaMos represented ~40% of the Canadian population.

At baseline, year 5, and year 10, participants were scheduled to complete an extensive questionnaire by interview and receive physical examinations. Data collected from the questionnaires included demographic information, self-reported health conditions, history of family and personal fractures, medication use, dietary intake, lifestyle information, and quality of life. The physical examination included height and weight measures and DXA at the lumbar spine and hip. BMD was assessed by DXA at the lumbar spine and femoral neck regions, and BMD T-scores were calculated based on the Canadian standards (16). In addition, a short questionnaire was mailed at annual follow-up to collect data on participants' fractures, hospitalization, and use of bone health medications. Fasting blood samples were collected at baseline at one center (Québec City), at year 5 at three centers (Calgary, Hamilton, and Québec City), and at year 10 at eight centers (Vancouver, Calgary, Saskatoon, Kingston, Toronto, Québec City, St. John's, and Halifax).

Participants self-reported whether they had diabetes that was "insulin dependent" (to imply type 1 diabetes) or "insulin-independent" (to imply type 2 diabetes) at baseline, year 5, and year 10. During this study, insulin began to be used in those with type 2 diabetes; thus, more than 98% of participants likely had type 2 diabetes (subsequently called "diabetes"). In this study, the participants were included for analyses if they had *1*) a blood sample for fasting plasma glucose measurement, *2*) self-report data on whether they had diabetes, and *3*) a follow-up of 1 year or more. Therefore, the year for participants' cohort entry may be different from the year in which the participants were enrolled into the CaMos to ensure the availability of data on blood collections. Participants who had no data on fasting plasma glucose measures or had a follow-up of less than 1 year were excluded. Supplementary Fig. 1 shows the selection process of study participants.

Outcomes

Our primary outcome was time to the first incident nontraumatic clinical fragility fracture, where an incident clinical fragility fracture was defined as a fracture resulting from the force of a fall from a standing height or less, including fractures of the hip, spine, forearm, pelvis, ribs, and other sites (but excluding fractures of face, fingers, and toes) (17). Secondary outcomes included time to an incident hip fracture and to clinical spine fracture during follow-up. All incident fractures were documented on the annual mailed questionnaires by participants' self-reports. An individual who reported an incident fracture was contacted to seek consent to obtain the medical report and/or hospital discharge for verification. Medical or radiographic validation was available for 78% of all reported incident fractures in CaMos (18).

Independent Variables

Frailty status was measured by the CaMos-based algorithm for Frailty Index (FI) of deficit accumulation in this study. Details on the construction and scoring of the FI have been provided elsewhere (19). In brief, the original FI included 30 health-related deficits, with each deficit scoring from 0 to 1. Dichotomous deficits were coded as 1 (present) or 0 (absent). Deficits with multilevel responses were polychotomized to receive equal points to map the interval 0 to 1 (e.g., excellent = 0; very good = 0.25; good = 0.5; fair = 0.75; poor = 1) or combined into logical groups (e.g., same/somewhat better/better = 0, somewhat worse/worse = 1). The FI was then calculated by summing the scores of all deficits divided by the total number of deficits (n = 30). The FI ranged from 0 to 1, with higher values indicating greater frailty. However, the original FI included a deficit of diabetes that was coded as 1 (present) or 0 (absent). To align with the current study, we modified the FI slightly by removing the deficit of diabetes from the construction. The FI therefore consisted of the remaining 29 deficits, ranging from 0 to 1, and with higher scores indicating greater frailty. Supplementary Table 1 provides the deficits with their coding and counts and percentages of individual deficits with scores of 1 in groups with and without diabetes.

Other independent variables included baseline age, sex, study center, BMI, family history of fragility fracture, previous falls, use of osteoporosis medication(s) (bisphosphonates, selective estrogen-receptor modulators, calcitonin, menopausal hormone therapy, denosumab, and parathyroid hormone), use of pioglitazone or rosiglitazone (20), fasting plasma glucose, fasting insulin level, smoking, alcohol intake, and areal

BMD of the lumbar spine and femoral neck T-scores.

Statistical Analyses

Baseline variables are described as frequency and percentages for categorical data and as mean and SD for continuous variables. Crude comparisons between participants with and without diabetes were performed using χ^2 tests for categorical variables and the Student *t* test for continuous variables. Survival curves for risk of fragility fracture are presented with the Kaplan-Meier survival function.

We used multivariable linear regression analysis to further compare the difference in the FIs between participants with and without diabetes after adjusting for age, sex, and BMD femoral neck T-scores. We also compared fracture risk between groups with and without diabetes to evaluate the effect of diabetes on the risk of fractures by using Cox proportional hazards models adjusted for age, sex, and BMD femoral neck T-scores. To assess whether frailty was related to the risk of fractures and whether frailty could modify the effect of diabetes on the risk of fractures, we used the Cox proportional hazards model and incorporated an interaction term (frailty × diabetes). An interaction indicated whether and how the frailty could elevate the propensity of diabetes toward an increased risk of fractures. Results are shown in the basic models and fully adjusted models, with hazard ratios (HRs) and their corresponding 95% CIs reported. The basic models were adjusted for age, sex, and BMD femoral neck T-scores, and the fully adjusted models were adjusted for age, sex, study center, fasting insulin level, BMI, family history of fractures, previous falls, use of osteoporosis medication, use of pioglitazone or rosiglitazone, smoking, alcohol intake, and BMD femoral neck T-scores. We presented results based on both an increase of 0.01 on the FI and per-0.10 (~1 SD) increase in the FI.

Similar analyses were performed for the risk of hip and spine fractures. However, considering the small number of fracture cases that may lead to insufficient power and model instability, we only showed the results in the basic models for risk of hip and spine fractures.

A predefined subgroup analysis was performed by sex (men vs. women) for risk of fragility fractures. If more than 10% of the data were missing, we conducted a sensitivity analysis by using 10 multiple imputations to impute the missing data. We also ran a competing risk analysis as another sensitivity analysis, taking all-cause mortality as a competing event for fragility fracture if the participant died before experiencing a fracture. All tests were two-sided using the α level of 0.05. All analyses were performed with Stata 12 (StataCorp, College Station, TX) and SAS 9.3 (SAS Institute, Cary, NC) software.

RESULTS

We included 3,149 (70% women) participants for analyses (Table 1). They had a mean age of 65 (SD 12) years and a follow-up of 9.2 (SD 4.5) years. The T-scores were −0.62 for the lumbar spine and −1.40 for the femoral neck. The baseline FI was a mean of 0.17 (SD 0.10), ranging from 0 to 0.68. Supplementary Fig. 2 presents the density distribution of the FI. Comparisons of baseline characteristics between participants with and without diabetes are also reported in Table 1. There were 138 participants (4.4%) with diabetes. Participants with diabetes were significantly older, were more likely to be men and alcohol consumers, and had a higher BMI compared with participants without diabetes. Higher lumbar spine and femoral neck T-scores were observed in participants with diabetes ($P < 0.001$). Participants with diabetes had a significantly higher FI than control subjects (0.22 vs. 0.16, $P < 0.001$). Results from multivariable linear regression showed consistent findings, with a mean difference in the FIs of 0.05 (95% CI 0.03–0.06, $P < 0.001$).

During follow-up, 611 participants (19.4%) had fragility fractures, including 117 forearm or wrist fractures, 84 rib, 67 hip, 57 foot, 51 spine, 48 ankle, 40 shoulder, and 147 other nontraumatic

Table 1—Participants' baseline characteristics and comparison between individuals with and without diabetes

Baseline characteristics	Total participants (*N* = 3,149)	Without diabetes (*n* = 3,011)	With diabetes* (*n* = 138)	*P* value
Age, years	65.1 (11.8)	64.9 (11.9)	69.4 (8.2)	<0.001
Female sex, *n* (%)	2,198 (69.9)	2,115 (70.3)	83 (60.1)	0.011
BMI, kg/m^2	27.1 (4.8)	27.0 (4.8)	29.6 (5.2)	<0.001
Family history of fracture, *n* (%)	1,087 (36.0)	1,032 (35.7)	55 (41.0)	0.21
Previous falls, *n* (%)	593 (22.0)	565 (21.9)	28 (24.1)	0.57
Smoker, *n* (%)	601 (19.2)	573 (19.1)	28 (20.3)	0.73
Alcohol consumer, *n* (%)	2,026 (64.3)	1,967 (65.3)	59 (42.8)	<0.001
BMD				
Lumbar spine T-score	−0.62 (1.39)	−0.64 (1.39)	−0.14 (1.43)	<0.001
Femoral neck T-score	−1.40 (0.98)	−1.42 (0.98)	−1.10 (0.96)	<0.001
Use of osteoporosis medication, *n* (%)	884 (28.2)	857 (28.6)	27 (19.6)	0.022
Use of pioglitazone or rosiglitazone, *n* (%)	28 (0.9)	19 (0.6)	9 (6.5)	<0.001
Fasting plasma glucose, mmol/L	5.6 (1.3)	5.5 (1.1)	8.2 (2.9)	<0.001
Fasting insulin level, uIU/mL	13.9 (16.2)	13.7 (16.3)	18.7 (15.8)	0.003
FI	0.17 (0.10)	0.16 (0.10)	0.22 (0.11)	<0.001
Follow-up time, years	9.16 (4.53)	9.21 (4.54)	8.07 (4.35)	0.004

Data are presented as mean (SD) unless otherwise specified. *Including type 1 and type 2 diabetes.

clinical fragility fractures. Of all fragility fractures, 576 (19.1%) occurred in participants without diabetes and 35 (25.4%) in those with diabetes. There were 67 hip (2.1%) and 51 clinical spine (1.6%) fractures reported during follow-up. Higher incidences of fragility, hip, and clinical spine fractures in the group with diabetes are reported in Table 2. Diabetes was significantly related to an increased risk of all fragility fractures, with an HR of 1.54 (95% CI 1.07–2.20). Diabetes was also significantly associated with risk of hip fracture (HR 2.60, 95% CI 1.04–6.55) but not clinical spine fracture (P = 0.35).

Table 3 reports the results from Cox models incorporating frailty and the interaction term (frailty × diabetes). A significant relationship between the FI and the risk of incident fragility fractures was found in both basic and fully adjusted models, with an HR of 1.02 (95% CI 1.01–1.03) and 1.19 (95% CI 1.10–1.33) in the fully adjusted model reported for per-0.01 and per-0.10 FI increase, respectively. The interaction was also statistically significant: HR of 1.02 (95% CI 1.00–1.03) and 1.12 (95% CI 1.02–1.23) for per-0.01 and per-0.10 increase, respectively, in the fully adjusted model (P = 0.018). If we centered the FI on the mean (0.17), the HR for diabetes regarding fracture risk was 1.28 (95% CI 0.52–3.21) in the fully adjusted model, representing the HR for an individual with a mean value of the FI (average frailty) compared with a participant without diabetes. Figure 1 displays different HRs for diabetes regarding the fracture risk at different levels of the FI. Increased HRs for diabetes were observed when the FI rose, implying that frailty status could increase the propensity of diabetes toward fracture risk compared with nondiabetes. To further illustrate the effect modification of frailty on diabetes regarding fracture risk, we compared the cumulative fracture risk between groups with and without diabetes (Supplementary Fig. 3). We also grouped the participants as robust and frail by their frailty status based on the mean of the FI (i.e., those with an FI of <0.17 grouped as robust and ≥ 0.17 as frail) and compared diabetes with nondiabetes in the robust and frail subgroups. Higher cumulative fracture risks were consistently found in the frail group with diabetes, indicating the increased effect of combining diabetes and frailty on fracture risk.

Table 3 also indicates the relationship between frailty and fracture risk in groups with and without diabetes separately because the interaction term assigned the coding of 1 to diabetes and 0 to nondiabetes; that is, the HR for frailty can be calculated by combining the estimate for the FI itself with the estimate from the interaction term. For example, the HR for per-0.1 increase in the FI was 1.33 for diabetes using the multiplicative principle (i.e., 1.19 times 1.12), and the HR for nondiabetes remained 1.19.

Regarding secondary outcomes, the FI was significantly related to an increased risk of hip fracture (HR 1.03 for per-0.01 and 1.37 for per-0.10 FI increase, P = 0.003) but not risk of clinical spine fracture (P = 0.069) (Table 3). No evidence of interaction between frailty and diabetes was found for risk of hip and clinical spine fractures. A post hoc analysis that excluded the nonsignificant interaction term from the model (Table 3) found the FI was significantly related to risk of hip and clinical spine fracture, with an HR of 1.63 and 1.34 for per-0.1 FI increase, respectively. Diabetes was associated with increased risk of fractures (HR 2.45 for hip and 1.67 for clinical spine fracture risk); however, the relationship was not statistically significant.

When subgroup analyses were conducted by sex, the FI and interaction were significantly related to an increased risk of fragility fractures only in women (Supplementary Table 2). However, no significant subgroup differences were found regarding the relationship between fragility fracture risk and the FI (P = 0.61) or between fracture risk and the interaction (P = 0.17). Results of competing risk analyses showed findings similar to those from the main analyses (Supplementary Table 2).

Table 2—Fracture risk comparisons between groups with and without diabetes and the relationship between diabetes and fracture risk

		Without diabetes,[1]	With diabetes,[2]	Relationship between diabetes and fracture risk[3]	
	n	cases (%)	cases (%)	HR (95% CI)	*P* value
Fragility fracture[4]	611	576 (19.1)	35 (25.4)	1.54 (1.07–2.20)	0.019
Hip fracture	67	61 (2.0)	6 (4.4)	2.60 (1.04–6.55)	0.032
Clinical spine fracture	51	48 (1.6)	3 (2.2)	1.76 (0.54–5.72)	0.35

[1]Including 3,011 participants and 27,732 person-years. [2]Including 138 participants and 1,114 person-years. [3]Models adjusted for age, sex, and BMD femoral neck T-scores. [4]Including 117 forearm or wrist fractures, 84 rib fractures, 67 hip fractures, 57 foot fractures, 51 spine fractures, 48 ankle fractures, 40 shoulder fractures, and 147 others.

CONCLUSIONS

Our study revealed that despite their significantly higher BMD, those with type 2 diabetes were frailer than participants without diabetes. Frailty could increase the risk of fragility fractures and modify the propensity of those with diabetes toward fragility fracture risk; that is, the effect of diabetes on fracture risk may depend on the individual's frailty status. Such findings may help interpret the diabetes bone paradox. They may also help advance fracture risk assessment and management in diabetes, because the BMD measures and some current fracture risk estimation algorithms were found not to be sufficiently predictive in type 2 diabetes (21,22).

Consistent with other research findings (23–25), we observed that compared with the group without diabetes, participants with type 2 diabetes had significantly higher BMD values. Further research is required to explore the diabetes bone paradox (20). Despite the appearance of greater BMD (bone quantity) compared with individuals without diabetes, the reduced bone strength associated with deterioration in bone microarchitecture, inappropriate bone mass distribution, and disturbed repair and adaptation bone mechanisms may be key relevant factors for increased fracture risk in type 2 diabetes (21,22,26). Other factors, including use of insulin or some antidiabetic medications and glycemic control, were also related with a higher fracture risk in diabetes (5,23,27). Nevertheless, we did not include the data on bone strength or diabetes control for analyses in our current study. Instead, by using an FI that involved multifactorial health-related

Table 3—Results from Cox models to test whether frailty was related to risk of fractures and whether frailty could modify the effect of diabetes on risk of fractures*

	All fragility fractures (n = 611)		Hip fracture (n = 67)		Clinical spine fracture (n = 51)	
	Basic model[1]	Fully adjusted model[2]	Basic model[3]	Post hoc analysis[4]	Basic model[3]	Post hoc analysis[4]
FI						
Per-0.01 increase	1.02 (1.01–1.03) $P < 0.001$	1.02 (1.01–1.03) $P < 0.001$	1.03 (1.01–1.05) $P = 0.003$	1.05 (1.01–1.09) $P = 0.002$	1.03 (1.00–1.05) $P = 0.069$	1.03 (1.01–1.06) $P = 0.028$
Per-0.10 increase	1.20 (1.11–1.30) $P < 0.001$	1.19 (1.10–1.33) $P < 0.001$	1.37 (1.12–1.68) $P = 0.003$	1.63 (1.11–2.38) $P = 0.002$	1.29 (0.98–1.69) $P = 0.069$	1.34 (1.03–1.73) $P = 0.028$
Type 2 diabetes	0.94 (0.40–2.23) $P = 0.89$	0.92 (0.36–2.25) $P = 0.89$	0.86 (0.07–10.68) $P = 0.91$	2.45 (0.98–6.13) $P = 0.056$	0.47 (0.02–10.44) $P = 0.63$	1.67 (0.52–5.45) $P = 0.40$
Interaction term[5]						
Per-0.01 increase	1.01 (1.00–1.02) $P = 0.004$	1.02 (1.00–1.03) $P = 0.018$	1.05 (0.96–1.14) $P = 0.31$	—	1.05 (0.95–1.15) $P = 0.34$	—
Per-0.10 increase	1.14 (1.04–1.25) $P = 0.004$	1.12 (1.02–1.23) $P = 0.018$	1.57 (0.66–3.76) $P = 0.31$	—	1.58 (0.62–3.98) $P = 0.34$	—

*Results expressed as HRs (95% CIs) and P values. [1]Basic models were adjusted for age, sex, and BMD femoral neck T-scores. [2]Fully adjusted models were adjusted for age, sex, study center, fasting insulin level, BMI, family history of fractures, previous falls, use of osteoporosis medication, use of pioglitazone or rosiglitazone, smoking, alcohol intake, and BMD femoral neck T-scores. [3]Basic models were adjusted for age, sex, and BMD femoral neck T-scores; no fully adjusted models were conducted due to small number of cases. [4]Post hoc analysis was conducted by excluding interaction term from the basic model for which the interaction was not statistically significant. [5]Interaction term expressed as (frailty × diabetes) where diabetes was coded as 1 and nondiabetes was coded as 0.

deficits related to aging, our results showed that participants with diabetes had a higher FI and that frailty could modify the effect of diabetes on fracture risk after adjusting for age, previous falls, and other covariates. Interestingly, after incorporating frailty and its interaction with diabetes, diabetes was no longer a significant risk factor for fractures in those with an FI of 0 (HR 0.92) (Table 3). It may indicate that measuring frailty status could serve as an effect modifier to account for the increased fracture risk due to diabetes. More specifically, the fracture risk for diabetes could be completely modified through FI (i.e., diabetes as a nonsignificant factor in the interaction model), and there was positive synergy between diabetes and the FI (Table 3 and Fig. 1). However, such findings need to be interpreted with caution because potential bias and confounding could not be fully adjusted for when using observational data. Nevertheless, the concept of frailty for chronic noncommunicable diseases has been increasingly accepted and applied to clinical research. For instance, the literature has shown that measuring the FI can be a helpful risk prediction tool for osteoporotic fracture risk, especially in the elderly (28). In fact, it has been recommended that to improve quality of care for diabetes, quantifying the degree of frailty should be incorporated into the assessment, particularly in primary and community care settings (29).

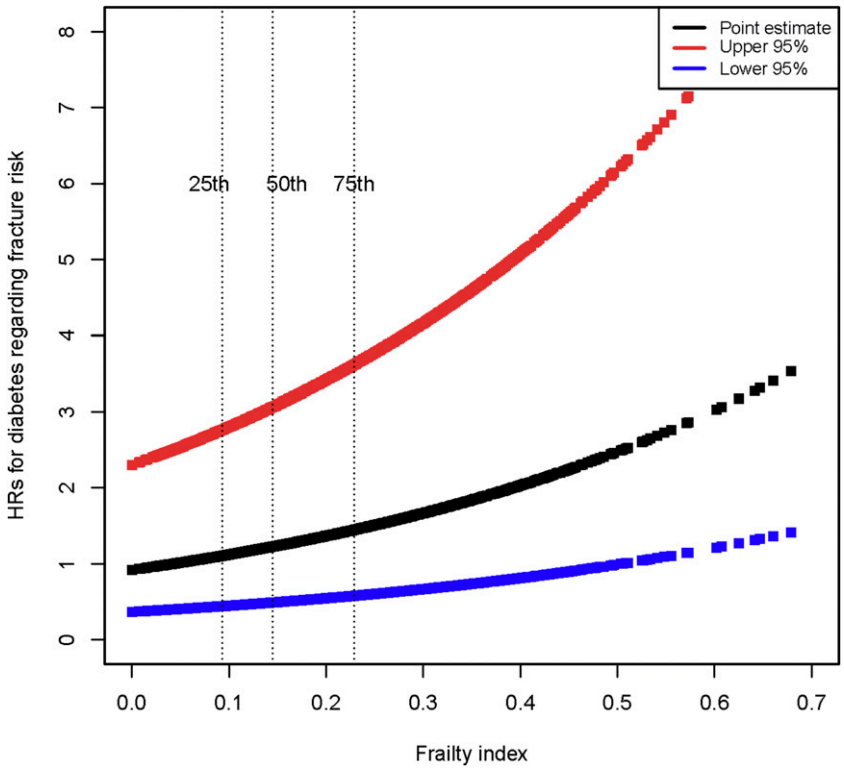

Figure 1—Different HRs for diabetes regarding the fracture risk at different levels of the FI (25th, 50th, 75th denoting quartiles of the FI). Upper 95%, upper limit of 95% CI; Lower 95%, lower limit of 95% CI.

Previous studies have reported a significant relationship between diabetes and fragility fracture risk, with a relative risk ranging from 1.3 to 2.4 (23,30,31), which was similar to our estimate among those with average frailty (HR 1.28). However, none of these studies measured frailty status or took into account the possible effect modification by frailty. Results that did not consider the interaction between diabetes and frailty may be additionally skewed by the higher prevalence of frailty among those with diabetes, because the

association between diabetes and fracture risk would be stronger with increased frailty (Fig. 1). Unfortunately, the effect modification by frailty for fracture risk among participants with diabetes in other populations remains largely unknown, given that our study was the first to explore such interaction.

However, the progression of frailty in type 2 diabetes requires more investigation. Diabetes itself tends to accelerate the aging process, which in turn increases the risk of being frail at an earlier age and results in a high risk of adverse health outcomes for participants with diabetes (32). The trajectories of the frailty status in diabetes could also vary substantially, especially when considering the short-term or long-term medication effect, lifestyle change, comorbidity development, and disease severity progression (33). Exploring frailty transition chronologically (i.e., no change, deterioration, or improvement) in diabetes would help further understand the diabetes bone paradox, better estimate the effect modification of frailty, and better assess future fracture risk in diabetes. Unfortunately, we could not assess the fluctuating frailty status in this study but could only investigate the baseline frailty degree in relation to risk of fragility fracture. Besides, after adjusting for chronological age, the frailty as an estimate of biological age (34) could help further quantify fracture risk in diabetes, especially when taking into account its effect modification. Although the FRAX (fracture risk assessment tool) has been shown to underestimate the fracture risk in type 2 diabetes (35,36), using the frailty approach may provide some insight into how to improve predictive accuracy regarding fracture risk assessment and management in diabetes.

This study has several strengths. To our knowledge, this is the first study examining the frailty and diabetes bone paradox in type 2 diabetes. We quantified the frailty degree by using the FI of deficit accumulation and measured its interaction with diabetes for fracture risk, where the FI has been widely applied as a research tool to predict risk of adverse health outcomes or to serve as an outcome measure, especially in the elderly (13,37). The frailty concept is particularly important and helpful in the endocrine system because endocrine disorders involve brain, immune system, skeletal muscle, and other complex entities (38). Another strength is the data were prospectively collected from nationwide research centers and from a long follow-up (average 9.2 years), which could improve the generalizability of our results. Outcome verifications and rigorous analyses also enhance the validity of study findings.

There are also some limitations. First, as an observational study, the nonrandomized design fails to fully adjust for potential confounding and therefore weakens the strength of evidence. No further investigations that take diabetes control into account could be performed due to lack of such data. Likewise, exploring the relationship between frailty and fracture risk after considering bone strength in diabetes would be a worthwhile endeavor. The diagnosis of diabetes was reported by the participants, without further medical record verifications. This may introduce information bias regarding the classification of diabetes, even though the levels of fasting plasma glucose and insulin were significantly higher in self-reported diabetes than in nondiabetes (Table 1). Besides, we could not distinguish type 1 from type 2 diabetes in CaMos. This may impair the strength of evidence from our current study because there was pathophysiological distinction between the two types of diabetes, even though only a very small proportion (~2%) of those with diabetes potentially had type 1 diabetes (39).

Although we tried to validate all of the reported incident fractures, ~20% of documented fractures were without medical or radiographic validation in this study (18). The relative small sample size, especially the small number of secondary outcomes, yielded insufficient power and model instability to detect potentially significant findings (Tables 2 and 3). Similarly, no further subgroup analyses could be conducted; for instance, we could not perform a subgroup analysis categorized by those aged $\geq$65 years versus $<$65 years to test whether there was an age-group difference regarding frailty and the diabetes bone paradox.

Furthermore, in general, the FI construction required multiple deficit elements (40) (n = 29 for our study); this would preclude the feasible application to busy clinical practice. However, quantifying the degree of frailty as a research aid can help with assessment, management, and decision making for fracture risk at a clinical research level as well as at a health care policy level (12,41). Besides, given no evidence of effect modification by frailty for hip or clinical spine fractures, caution was needed to interpret the effect modification by frailty for fragility fractures because such modification only applied for other nonhip, nonspine fragility fractures. Likewise, attention should be paid to increased hip or clinical spine fracture risk in participants with diabetes regardless of their frailty status.

The existence of the diabetes bone paradox remains an unsolved clinical issue in general practice for the management of fracture risk in type 2 diabetes (20,42). Our data suggest frailty status may aid in the understanding of the paradox and thus enhance the quality of assessment and care for diabetes. Further well-designed and appropriately powered studies incorporating data on diabetes control, frailty transition, and bone quality are needed to help with fracture risk management and even new pharmacological or nonpharmacological interventions in diabetes.

In conclusion, we found that regardless of BMD measures, participants with type 2 diabetes were significantly frailer than individuals without diabetes. Frailty increases the risk of fragility fracture and enhances the effect of diabetes on fragility fractures. Particular attention should be paid to diabetes as a risk factor for fragility fractures in those who are frail.

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