Development and Validation of a Simple Hip Fracture Risk Prediction Tool for Type 2 Diabetes: The Fremantle Diabetes Study Phase I

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OBJECTIVE

To develop a type 2 diabetes hip fracture risk tool in community-based patients, to validate it in an independent cohort, and to compare its performance against the only published prediction equation to include type 2 diabetes as a risk factor (QFracture).

RESEARCH DESIGN AND METHODS

Hip fracture hospitalizations in 1,251 participants with type 2 diabetes aged 40–89 years from the longitudinal Fremantle Diabetes Study Phase I (FDS1) were ascertained between entry (1993–1996) and end-2012. Competing risk regression modeling determined independent predictors of time to first fracture over 10 years and the coefficients incorporated in a risk model. The model was validated in 286 participants with type 2 diabetes from the Busselton Health Study (BHS).

RESULTS

Fifty FDS1 participants (4.0%) experienced a first hip fracture during 10,306 person-years of follow-up. Independent predictors of fracture were older age, female sex, lower BMI, peripheral sensory neuropathy, and estimated glomerular filtration rate <45 mL/min/1.73 m^2. The model-predicted mean 10-year incident fracture risk was 3.3% with good discrimination, calibration, and accuracy. For a 3% cutoff, sensitivity was 76.0%, specificity 71.9%, positive predictive value (PPV) 10.1%, and negative predictive value (NPV) 98.6%. Model performance in the small BHS sample was also good (sensitivity 66.7%, specificity 79.8%, PPV 6.2%, and NPV 99.2%). QFracture performed well in FDS1 but required availability of 25 variables.

CONCLUSIONS

The FDS1 hip fracture risk equation is a simple validated adjunct to type 2 diabetes management that uses variables that are readily available in routine care.

The use of risk calculators that facilitate management of chronic diseases has increased considerably since the first cardiovascular risk assessment equations were developed in the 1970s (1). Osteoporosis has been no exception, with ~50 fracture risk prediction tools now available that could be used to guide investigation and treatment (2). Most of these tools have, however, not been externally validated in a population-based setting (2), with a few exceptions, including the relatively

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well-evaluated Fracture Risk Assessment calculator (FRAX) and QFracture (3). The need for validation across different populations is exemplified by the observation that fracture rates are higher in Northern and Eastern Europe compared with Anglo-Celt and Southern European countries, paralleling regional differences in osteoporosis risk factors such as calcium intake, sunlight exposure, smoking, alcohol use, and physical activity (4).

Type 2 diabetes is associated with an increased fracture risk (5–7). However, it is incorporated as a binary variable in only QFracture among available risk prediction tools (8). The QFracture algorithm has been criticized for its reliance on a U.K. primary care database with incomplete ascertainment of risk factors and inappropriate risk factor weighting in comparison with FRAX, which may lead to underestimation of major fracture risk (3). The need for differentiation by diabetes status is, nevertheless, illustrated by a number of studies that have consistently found FRAX to underestimate fracture risk in type 2 diabetes (9–11). This limitation can only be partially addressed by modifying individual input variables to simulate the effects of diabetes (12). In the case of QFracture, no study to date has assessed its validity in a population with diabetes.

Hip fracture is the most serious osteoporotic fracture because of the increased associated morbidity and mortality, including in diabetes (13). It is also the most reliably ascertained because it is almost always treated in hospital. This is in contrast to vertebral fractures, the majority of which do not come to medical attention (14). In people with diabetes, a significant proportion of the increased risk of hip fracture is explained by diabetes-related comorbidities such as neuropathy and retinopathy that may not be considered as variables, or accorded appropriate weighting, in available fracture risk equations (15,16).

Given that type 2 diabetes is associated with an increased incidence of hip fracture and a distinct fracture risk factor profile, and in view of the fact that no risk estimation tool derived from general population data has demonstrated validity in type 2 diabetes, there is a clear need for diabetes-specific fracture risk estimation. The aim of the current study was, therefore, to: *1*) develop a hip fracture risk assessment tool for use in type 2 diabetes based on variables that should be available as part of usual clinical care, *2*) validate the tool in an independent cohort of people with type 2 diabetes, and *3*) compare its performance against QFracture and FRAX.

RESEARCH DESIGN AND METHODS

Participants, Epidemiologic Setting, and Approvals

The Fremantle Diabetes Study Phase I (FDS1) is a longitudinal observational cohort study of known diabetes (requiring a clinician-verified diagnosis) conducted in a zip code–defined urban community of 120,097 people in the state of Western Australia (WA). Descriptions of recruitment, sample characteristics including classification of diabetes type, and details of nonrecruited people with diabetes living in the catchment area have been published (17). Of 2,258 residents with diabetes identified between 1993 and 1996, 1,426 (63%) were recruited to the FDS1, and 1,296 had type 2 diabetes. Eligible residents who declined participation were a mean 1.4 years older than participants, but their sex distribution, the proportion with type 2 diabetes, and their use of blood glucose–lowering therapies were similar (17). The 44 FDS1 participants with type 2 diabetes aged $<$40 years and 1 aged $\geq$90 years were excluded, as done for conventional fracture risk calculators such as FRAX, leaving a final sample of 1,251. The FDS1 protocol was approved by the Human Rights Committee at Fremantle Hospital, and all subjects gave informed consent before participation. Data linkage was approved by the WA Department of Health Human Research Ethics Committee.

Clinical Methods

Participants had comprehensive face-to-face assessments at baseline and annually for up to 8 years (17). At each visit, demographic and clinical information including details of diabetes and other illnesses was documented. Race/ethnicity categorization (Anglo-Celt, Southern European, Other European, Asian, Indigenous Australian, or mixed/other) was based on self-identification, country of birth, country of father's and/or mother's birth, and language spoken at home. A physical examination and relevant investigations were performed, and fasting blood and first-morning urine samples were taken for biochemical analysis.

Complications of diabetes were identified using standard criteria (17), including peripheral sensory neuropathy (PSN; a score $>$2 out of 8 on the clinical portion of the Michigan Neuropathy Screening Instrument [18]); retinopathy (any grade detected by direct/indirect ophthalmoscopy and/or ophthalmologist assessment); nephropathy (urinary albumin-to-creatinine ratio $>$3.0 mg/mmol); renal impairment by estimated glomerular filtration rate (eGFR) determined using the Chronic Kidney Disease Epidemiology Collaboration equation with stages 1–5 defined as $>$90, 60–89, 30–59, 15–29, and $<$15 mL/min/1.73 m^2, respectively (19); coronary heart disease (CHD; self-reported history of myocardial infarction, angina, and/or revascularization, or prior hospitalizations for these events); cerebrovascular disease (self-reported stroke/transient ischemic attack or prior hospitalizations for these events); and peripheral arterial disease (PAD; ankle/brachial index $\leq$0.90 on either leg or diabetes-related amputation).

Hip Fracture Cases and Comorbidity Ascertainment

Annual assessments continued until 2001, but collection of morbidity and mortality data continues with health service linkages through the WA Data Linkage System (20). All hospitalizations (public and private) in WA are recorded in the Hospital Morbidity Data Collection (HMDC) that was established in 1970. The HMDC was used to determine prior hip fracture history at FDS1 study entry from ICD coding after 1982 and incident hip fracture to end of December 2012. Hip fracture was identified in the HMDC using the following ICD-9-CM and ICD-10-AM codes: 733.14, 820, and S72.0–S72.2. The presence or recent history of hip fracture at death was also identified from the Registry for Births, Deaths and Marriages.

Biochemical Assays

All biochemical tests were performed in a single nationally accredited laboratory. Serum creatinine, glucose, cholesterol, triglycerides, and HDL cholesterol, as well as urine albumin and creatinine,

were measured by standard methods on a Hitachi 911 analyzer (Roche Diagnostics Australia, Castle Hill, New South Wales, Australia). Glycated hemoglobin was estimated by cation-exchange high-performance liquid chromatography using a Mono S HR 5/5 column (Amersham Biosciences, Castle Hill, New South Wales, Australia).

Validation Cohort

The Busselton Health Study (BHS) comprises serial population-based cross-sectional surveys in the regional WA town of Busselton starting in 1966 (21). From assessments in 1994 to 1995, 292 participants aged 40–89 years were identified who had: *1*) been told by their doctor that they had diabetes/high blood glucose, *2*) been treated for diabetes, *3*) a prior hospitalization for/with diabetes, and/or *4*) a fasting plasma glucose $\geq$7.0 mmol/L. From the HMDC and Death Registrations, time to first hip fracture over the next 10 years was determined using the same methodology as for the FDS1 cohort. Because PSN was not ascertained in the validation cohort, two models were used in which it was assumed: *1*) no participant had PSN, and *2*) a random sample of 32% of the BHS cohort had PSN (the FDS1 cohort had a PSN prevalence of 31.6%). BMI was missing for 6 cases (2.1%), and validation was, therefore, performed on a final sample of 286 participants.

Data Analysis, Model Development, and Validation

The computer packages IBM SPSS Statistics 22 (IBM Corporation, Armonk, NY) and Stata/IC 13 (StataCorp LP, College Station, TX) were used for statistical analysis. Data are presented as percentages, mean $\pm$ SD, geometric mean (SD range), or, in the case of variables that did not conform to a normal or log-normal distribution, median (interquartile range). For independent samples, two-way comparisons for proportions were by Fisher exact test, for normally distributed variables by Student *t* test, and for nonnormally distributed variables by Mann-Whitney *U* test.

Fine and Gray competing risk regression modeling was used to determine independent predictors of time to first hip fracture (22). Variables were included if they were clinically plausible and likely to be routinely available with a bivariate $P < 0.20$ and removed one at a time, those with least statistical significance first, until all variables in the model were significant at $P < 0.05$. Due to the expected nonlinear association of age with incident hip fracture, the square of age (age^2) was considered for inclusion. Excluded variables were added again to the final model to confirm their lack of significance, clinical importance, or confounding. Because the baseline cumulative subdistribution hazard refers to a state in which all variables are zero, and zero age and BMI, for example, do not make sense in this context, such continuous variables were centered at the respective mean values for the cohort (e.g., 65.0 years for age and 29.4 kg/m^2 for BMI). The proportional subdistribution hazards assumption was checked using the log-minus-log curves.

Some variables of interest were missing for up to 5.8% of participants, mainly measures of PSN due to equipment necessary for assessment not being available at the start of FDS1. Missing covariates were multiply imputed (times 20), defining imputation models that included the outcomes of hip fracture and competing risk of death (from reasons other than hip fracture). With the exception of the baseline characteristics (Tables 1 and 3), results are reported for imputed data (see Supplementary Table 1 for full details).

Regression coefficients from the final model were used to compute a linear risk function, L, that uses a participant with average values of each risk factor as the reference point (23). The subsequent result was exponentiated to calculate a 10-year hip fracture probability, *P*, after insertion into a survival function:

$$P = 1 - \exp(-c \times \exp(L))$$

where c is the 10-year cumulative baseline subdistribution hazard. Model discrimination was assessed from the area under the receiver operating characteristic curve (AUC), calibration (goodness-of-fit) by the Hosmer-Lemeshow $\hat{C}$-test ($P > 0.05$ implying no significant discrepancy between observed and predicted events), and accuracy by the Brier score (mean squared error; range 0 to 1, the lower the better).

The variables required for estimation of hip fracture risk using QFracture in FDS1 participants were supplied to the QFracture investigators and a 10-year risk calculated (8). The FRAX equation was obtained from the FRAX website with Australia specified as the country of origin among input data required for calculation of the 10-year probability of hip fracture (24).

RESULTS

Participant Characteristics and Outcome

The 1,251 eligible participants (96.5%) had a mean $\pm$ SD age of 65.0 $\pm$ 10.0 years, and 48.8% were males. Their median (interquartile range) diabetes duration and HbA_{1c} were 4.0 (1.0–9.0) years and 7.4% (6.4–8.8%) (57 [46–73] mmol/mol), respectively. Nineteen (1.5%) had a prior history of hip fracture. During follow-up to first incident hip fracture, death, or census (at 10.0 years), whichever came first (a total follow-up time of 10,306 person-years or a mean $\pm$ SD of 8.2 $\pm$ 2.9 years), 50 participants (4.0%) experienced at least one hip fracture, and 415 (33.2%) died (37 following incident hip fracture and 7 of these with hip fracture recorded on the death certificate).

Those who had an incident hip fracture during follow-up were older at study entry and at diabetes diagnosis, had longer diabetes duration, were more likely to be female, had more difficulties with activities of daily living and mobility problems, were less likely to be married, to have ever smoked, or to have exercised in the past fortnight, consumed less alcohol, had lower BMI, and had a higher systolic blood pressure than those who did not have a fracture (Table 1). They were less likely to be taking lipid-modifying medication, but serum lipid profiles were similar in those with and without incident hip fracture. History of hip fracture, microvascular complications (nephropathy, retinopathy, and PSN), atrial fibrillation, digoxin use, cerebrovascular disease, and PAD, but not CHD, were more prevalent in those with incident hip fracture. Gastrointestinal disease, osteoporosis or use of antiosteoporosis medications, and use of glucocorticoids or proton pump inhibitors were not associated with incident hip fracture.

Table 1—Baseline characteristics of people with type 2 diabetes in FDS1 aged 40–89 years by 10-year incident hip fracture status

	No hip fracture	Hip fracture	*P* value
Number (%)	1,201 (96.0)	50 (4.0)	
Age (years)	64.7 ± 9.9	73.6 ± 7.3	<0.001
Sex (% male)	50.0	20.0	<0.001
Ethnic background (%)			0.29
Anglo-Celt	61.3	62.0	
Southern European	17.7	22.0	
Other European	8.4	14.0	
Asian	3.5	0	
Indigenous Australian	1.3	0	
Mixed/other	7.8	2.0	
Not fluent in English (%)	15.3	24.0	0.11
Education higher than primary school level (%)	73.6	63.3	0.14
Married/de facto relationship (%)	66.0	52.0	0.046
Age at diagnosis of diabetes (years)	58.6 ± 10.6	63.7 ± 11.3	0.001
Diabetes duration (years)	4 [1–9]	5 [2–19]	0.010
Any exercise (% past 2 weeks)	73.3	49.0	<0.001
Any difficulty with activities of daily living (%)	8.5	20.8	0.008
Any mobility problem (%)	21.1	45.8	<0.001
Alcohol (standard drinks/day)	0 [0–0.8]	0 [0–0.1]	0.004
Smoking status (%)			0.010
Never	43.7	64.0	
Former	41.7	22.0	
Current	14.6	14.0	
BMI (kg/m^2)	29.5 ± 5.3	27.3 ± 4.1	0.005
HbA_{1c} (%)	7.4 [6.4–8.8]	7.4 [6.5–8.8]	0.88
HbA_{1c} (mmol/mol)	57 [46–73]	57 [48–73]	0.88
Diabetes treatment (%)			0.08
Diet	32.3	20.0	
Oral agents	55.7	60.0	
Insulin with or without oral agents	12.0	20.0	
Hypoglycemia (% ever)	29.6	34.7	0.43
Systolic blood pressure (mmHg)	151 ± 23	160 ± 25	0.007
Diastolic blood pressure (mmHg)	81 ± 11	78 ± 12	0.12
Postural hypotension (%)	29.2	32.7	0.63
Antihypertensive medication (%)	52.0	62.0	0.19
Diuretic use (%)	21.1	32.0	0.08
Serum total cholesterol (mmol/L)	5.5 ± 1.1	5.4 ± 1.3	0.48
Serum HDL cholesterol (mmol/L)	1.06 ± 0.32	1.12 ± 0.42	0.39
Serum triglycerides (mmol/L)	1.89 (1.10–3.27)	1.78 (1.06–2.96)	0.43
Lipid-modifying medication (%)	11.2	2.0	0.036
Aspirin use (%)	22.7	18.0	0.49
Urinary albumin-to-creatinine ratio (mg/mmol)	3.0 (0.7–12.9)	6.6 (1.3–33.9)	<0.001
eGFR category (%) (mL/min/1.73 m^2)			<0.001
≥90	21.4	6.1	
60–89	54.8	40.8	
45–59	16.8	24.5	
30–44	5.3	22.4	
<30	1.8	6.1	
Any retinopathy (%)	16.1	28.9	0.038
PSN (%)	30.5	59.6	<0.001
PAD (%)	29.1	48.9	0.007
Digoxin treatment (%)	6.0	14.0	0.034
Atrial fibrillation (%)	4.7	12.0	0.036
Cerebrovascular disease (%)	9.8	20.0	0.030

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Independent Associates of First Incident Hip Fracture

In Fine and Gray competing risk regression modeling, independent risk factors for incident hip fracture were older age, male sex (protective), BMI (higher BMI protective), PSN, and eGFR <45 mL/min/1.73 m^2 (Table 2). Variables considered for entry but excluded due to statistical nonsignificance included history of hip fracture, mobility problems, exercise status, smoking status, educational attainment, English fluency, diabetes duration, diabetes treatment, systolic blood pressure, diuretic use, serum HDL cholesterol, digoxin use, atrial fibrillation, CHD, PAD, retinopathy, and urinary albumin-to-creatinine ratio. Age^2 was also in this category. Inspection of the log-minus-log curves for each independent risk factor (with continuous variables dichotomized at the mean) showed no violation of the proportional hazards assumption.

The final model for 10-year incident hip fracture risk, *P*, was $1 - \exp(-0.024 \times \exp(L))$. From the final Fine and Gray competing risk model for prediction of 10-year incident hip fracture risk (Table 2):

$$\begin{aligned} L = {} & 0.0629 \times (\text{age (years)} - 65.0) \\ & - 1.3854\ (\text{if male}) \\ & - 0.0574 \times (\text{BMI } (\text{kg/m}^2) - 29.4) \\ & + 0.8059\ (\text{if PSN present}) \\ & + 0.7153 (\text{if eGFR} < 45\ \text{mL/min/1.73 m}^2). \end{aligned}$$

As an example of the risk calculation, consider a 61.0-year-old man with a BMI of 26.4 kg/m^2, no PSN, and eGFR of ≥45 mL/min/1.73 m^2:

$$\begin{aligned} L = {} & 0.0629 \times (61.0 - 65.0) \\ & - 1.3854 - 0.0574 \times (26.4 - 29.4) = \\ & - 1.4648. \end{aligned}$$

His probability of an incident hip fracture during the next 10 years is then given by

$$1 - \exp(-0.0240 \times \exp(-1.4648)) = 0.0055\ (\text{or } 0.6\%).$$

In comparison, consider a 79.6-year-old woman with a BMI of 30.0 kg/m^2, PSN present, and eGFR of <45 mL/min/1.73 m^2:

$$\begin{aligned} L = {} & 0.0629 \times (79.6 - 65.0) \\ & - 0.0574 \times (30.0 - 29.4) \\ & + 0.8059 + 0.7153 = 2.4051 \end{aligned}$$

Table 1—Continued

	No hip fracture	Hip fracture	*P* value
CHD (%)	30.0	40.0	0.16
Gastrointestinal disease (%)	2.1	4.0	0.29
Self-reported osteoporosis (%)	0.9	2.9	0.39
Antiosteoporosis medications (%)	3.0	4.0	0.66
Glucocorticoid treatment (%)	1.4	2.0	0.52
Proton pump inhibitor treatment (%)	0.7	0	>0.99
Antidepressant medications (%)	6.3	14.0	0.043
Antianxiety medications (%)	2.8	0	0.40
Prior hip fracture (%)	1.2	8.0	0.006

Data are mean ± SD, geometric mean (SD range), or median [interquartile range] unless otherwise indicated.

and her probability of an incident hip fracture during the next 10 years is

$$1 - \exp(-0.0240 \times \exp(2.4051)) = 0.2335 \text{ (or 23.4\%)}.$$

Model Performance

The model predicted a mean 10-year incident hip fracture risk of 3.3% compared with the observed risk of 4.0% (95% CI 3.0–5.3%). The discrimination (AUC 0.82 [95% CI 0.76–0.88]; $P < 0.001$), calibration (Ĉ-test, $P = 0.69$), and accuracy (Brier score 0.035 [range 0–0.991]) of the algorithm were good. The observed versus predicted numbers of participants with an incident hip fracture by deciles of risk were closely aligned (Fig. 1). For a 10-year predicted incident hip fracture cutoff of 3%, the sensitivity was 76.0%, the specificity 71.9%, the positive predictive value (PPV) 10.1%, and the negative predictive value (NPV) 98.6%.

A minimal model including only age, sex, and BMI was constructed. There was good discrimination (AUC 0.81 [0.75–0.86]; $P < 0.001$) and accuracy (Brier score 0.044 [0–0.986]), but calibration (Ĉ-test, $P < 0.001$) was poor, and the model substantially overestimated the percentage of people who would have a hip fracture during 10 years of follow-up (8.3% predicted vs. 4.0% observed).

Model Validation

The baseline characteristics of the FDS1 and validation cohorts are compared in Table 3. Age and sex distribution were similar, but the validation cohort had significantly lower BMI, fasting serum glucose, and eGFR ($P \leq 0.003$), although the proportions with eGFR <45 mL/min/1.73 m^2 were similar. Three-quarters of the BHS cohort were Australian-born compared with half of the FDS1 cohort, but the majority of both were of European ancestry. PSN was not measured in the BHS cohort.

During 10 years of follow-up, the proportion of participants with an incident hip fracture in the BHS and FDS1 cohorts did not differ significantly. Six (2.1% [95% CI 0.9–4.7%]) of the 286 members of the validation cohort had an incident hip fracture compared with a mean risk of 2.4% (7 cases) predicted by the FDS1 risk equation, assuming no PSN was present. There was good discrimination (AUC 0.84 [0.74–0.93]; $P = 0.005$), calibration (Ĉ-test, $P = 0.98$) (Fig. 1), and accuracy (Brier score 0.020 [0–0.970]). At a risk cutoff of 3%, the sensitivity was 66.7%, specificity 80.0%, PPV 6.7%, and NPV 99.1%. Observed versus predicted numbers of hip fractures by deciles of risk were similar, albeit with small numbers in each category (Fig. 1).

The model generated from the sensitivity analysis in which a random sample of 32% of the BHS cohort was assumed to have PSN also showed good calibration (AUC = 0.89 [0.82–0.97]; $P = 0.001$), discrimination (Ĉ-test, $P = 0.92$), and accuracy (Brier score 0.019 [0–0.930]). This model predicted a mean 10-year incident hip fracture risk of 3.3% (9 cases).

Table 2—Subdistribution hazard ratios (sdHRs) and 95% CI in a Fine and Gray competing risk model of 10-year first incident hip fracture in FDS1 participants with type 2 diabetes aged 40–89 years at study entry

	Regression coefficient, β	sdHR (95% CI)	*P* value
(Age − 65.0) years (increase of 1 year)	0.0629	1.06 (1.03–1.10)	<0.001
Male	−1.3854	0.25 (0.12–0.50)	<0.001
(BMI − 29.4) (increase of 1 kg/m^2)	−0.0574	0.94 (0.90–0.996)	0.034
PSN	0.8059	2.24 (1.23–4.08)	0.008
eGFR <45 mL/min/1.73 m^2	0.7153	2.04 (1.04–4.04)	0.039

QFracture Performance

During 10 years of follow-up, 48 (3.94%) out of the 1,219 (of 1,251 [97.4%]) members of the FDS1 cohort with type 2 diabetes with all required data had an incident hip fracture compared with a mean risk of 4.06% (49.5 cases) predicted by the QFracture hip fracture risk equation. There was good discrimination (AUC 0.82 [0.77–0.87]; $P < 0.001$), calibration (Ĉ-test, $P = 0.57$) (Fig. 1), and accuracy (Brier score 0.035 [0–0.99]). At a risk cutoff of 3%, the sensitivity was 83.3%, specificity 65.4%, PPV 9.0%, and NPV 99.0%. The observed versus predicted numbers of participants by deciles of fracture risk were similar but not as good as for the FDS1 risk equation (Fig. 1).

FRAX Performance

There were 1,245 out of 1,251 (99.5%) FDS1 participants with type 2 diabetes with all required data for the FRAX hip fracture risk equation excluding bone mineral density (BMD). Although FRAX showed good discrimination (AUC 0.80 [0.74–0.85]; $P < 0.001$) and accuracy (Brier score 0.038 [0–0.998]), its calibration was poor (Ĉ-test, $P < 0.001$) (Fig. 1), and it substantially underestimated the percentage of people who had a hip fracture during 10 years of follow-up (1.6% [19.3 cases] predicted vs. 4.0% [50 cases] observed) (Fig. 1).

CONCLUSIONS

Fracture risk equations developed using general population data may not adequately capture disease-specific effects (25,26). This includes type 2 diabetes (9–11), a disease in which the influence of its distinctive chronic complications can be substantial (15,16). Using longitudinal data from a large representative community-based FDS1 cohort (17), we

Table 3—Comparison of baseline characteristics of the BHS external validation cohort and FDS1 cohort

	BHS	FDS1	*P* value
Number (%)	286	1,251	
Age (years)	64.9 ± 11.7	65.0 ± 10.0	0.83
Sex (% male)	51.7	48.8	0.39
Region of birth (%)			<0.001
Australia/New Zealand	74.5	52.5	
Europe	17.5	39.8	
Asia	0.7	4.8	
Unknown/other	7.3	2.9	
BMI (kg/m^2)	28.4 ± 4.7	29.4 ± 5.3	0.003
Fasting serum glucose (mmol/L)	6.7 (5.3–8.6)	8.5 (6.9–10.7)	<0.001
eGFR (mL/min/1.73 m^2)	66.6 ± 16.6	72.7 ± 19.5	<0.001
eGFR <45 mL/min/1.73 m^2 (%)	9.1	7.9	0.55
PSN (%)	—	31.6	—
Prior hip fracture (%)	2.1	4.0	0.16

Data are mean ± SD or median (interquartile range) unless otherwise indicated.

have developed a type 2 diabetes hip fracture risk assessment tool based on five readily accessible clinical variables (age, sex, BMI, PSN, and renal function) that performed well in predicting incident events. The equation also had good performance characteristics when applied to a smaller independent cohort of people with type 2 diabetes from another WA population center. We assessed the QFracture hip fracture risk equation based on 25 variables (8) using FDS1 data and found that it also performed well, suggesting that issues with its potential underestimation of fracture risk observed in general population studies (3) do not apply in the specific case of type 2 diabetes. As observed in other studies (9–11), FRAX substantially underestimated fracture risk in FDS1 participants with type 2 diabetes, a condition that, unlike QFracture, is not among the input variables.

In general population fracture risk assessment tools, measurement of BMD adds predictive value, with a lower BMD associated with a higher risk of skeletal failure (3). However, the increased fracture risk in type 2 diabetes is in the presence of a higher rather than a lower BMD (5), which is considered to reflect the skeletal effects of obesity and adipokines (27). In light of this situation,

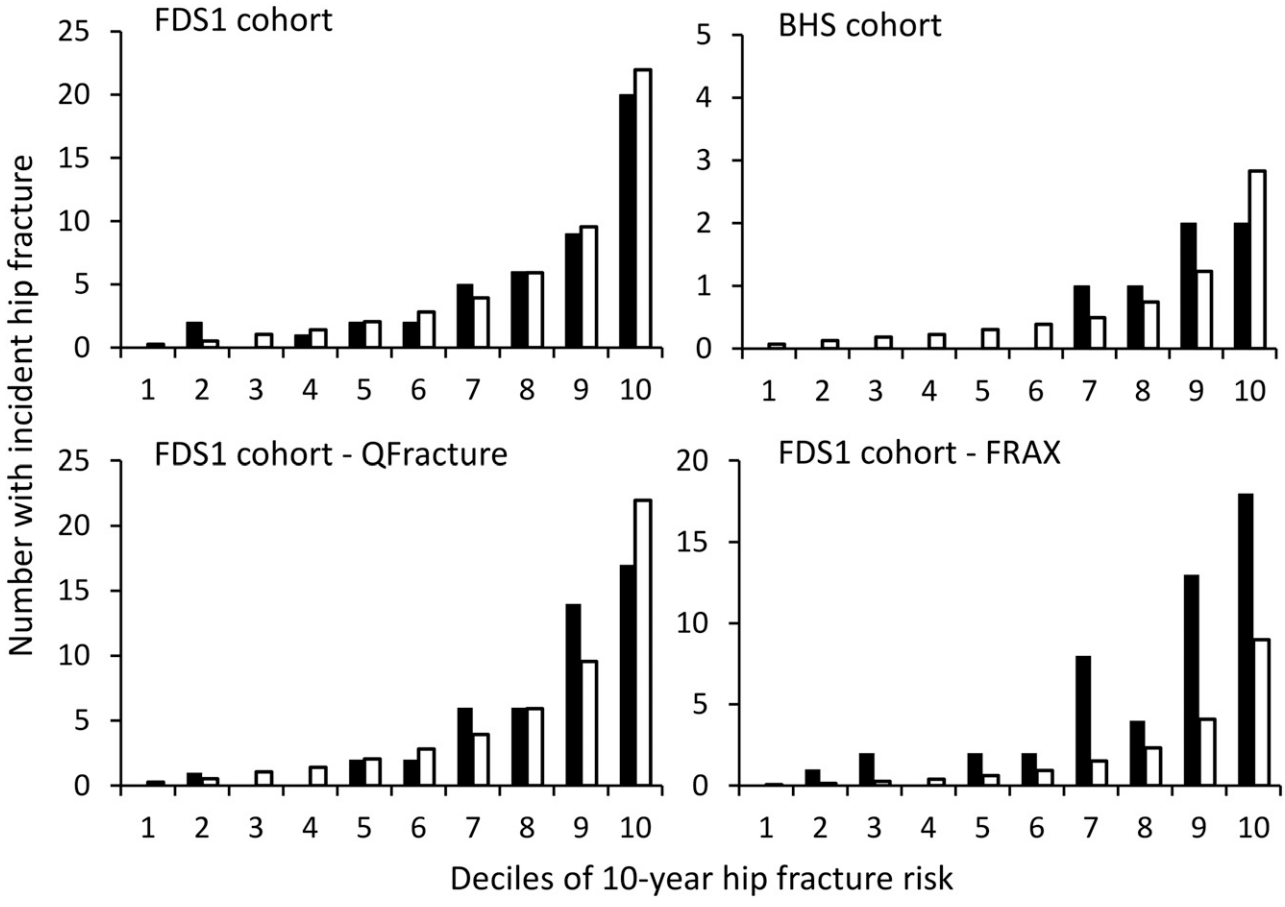

Figure 1—Observed (black bars) vs. predicted (white bars) numbers of incident hip fractures by decile of risk in *1*) FDS1 participants with type 2 diabetes and aged 40–89 years at study entry using the FDS1 risk equation (top left panel), *2*) BHS participants with type 2 diabetes (top right panel), *3*) FDS1 participants with type 2 diabetes using QFracture (bottom left panel), and *4*) FDS1 participants with type 2 diabetes using FRAX (bottom right panel).

and given the high AUC (0.82) and NPV (98.6%) of our simple clinical model, it is doubtful whether the availability of BMD would further enhance risk prediction in type 2 diabetes. QFracture has been criticized for not incorporating BMD in its algorithm, unlike the Garvan and FRAX calculators (3), but its similarly high AUC (0.82) and NPV (99.0%) in the FDS1 cohort suggest that this is not a deficiency in the specific case of type 2 diabetes.

Although there are differences in dietary and lifestyle risk factors for osteoporosis and thus fracture among racial/ethnic groups and geographical areas (4), the QFracture calculator (developed using a large U.K. primary care database) performed well in an Australian urban setting. It could be argued that QFracture is based on data from largely Anglo-Celt U.K. residents (8), a group that was also the majority in FDS1 (62% of participants). However, QFracture has also performed well in an Israeli validation study (28), other risk tools such as the Garvan and FRAX calculators have been validated across a range of different populations (2), and we did not find that race/ethnicity was a significant variable in our own risk equation. We assume that effects of race/ethnicity on hip fractures are manifest via differences in clinical features such as BMI, PSN, and eGFR in our cohort (29,30).

Although the performance of the FDS1 hip fracture risk assessment tool and that of the QFracture hip fracture equation were essentially equivalent in our FDS1 cohort, the range of data required by QFracture is much more extensive than that for the FDS1 equation. The FDS1 database is comprehensive, and so the requisite QFracture data were available for incorporation, but this may not be the case for individuals with diabetes in a usual care setting. All of the variables in the FDS1 equation are part of routine regular assessment of people with type 2 diabetes. The FDS1 equation and QFracture share major risk factors such as age, sex, and chronic kidney disease. Others present in QFracture but not in our equation such as malabsorption and glucocorticoid use are likely to be infrequent, well managed, and/or have relatively small effect sizes. It is also likely that the effects of BMI and PSN that are included in the FDS1 tool but not QFracture are covered by highly correlated covariates in QFracture such as a history of falls (31).

The current study had limitations. Missing data may have biased results even though this was a relatively small proportion of some variables, and multiple imputation was used in analysis. We had no PSN data for the relatively small BHS validation cohort but attempted to allow for this with appropriate sensitivity analyses. We used hip fracture as the end point of interest, and it may be that other osteoporotic fractures (such as vertebral compression) have a different set of predictive variables. We did not perform BMD on all FDS1 participants at baseline but have shown previously that BMD in a subset was at least that in matched control subjects without diabetes (32), consistent with other studies showing that type 2 diabetes is associated with a higher rather than a lower BMD despite an increased fracture risk (5). The inclusion of BMD in the FRAX calculator may, therefore, have led to an even lower estimated 10-year fracture risk than found in the current study, consistent with other studies of type 2 diabetes (9–11). The effect of BMD on fracture risk in FRAX is difficult to ascertain because its details and source code are not publicly available (33). Although our equation was developed and validated using participant samples that were relatively small compared with those used to develop general population risk calculators, the FDS1 is one of the largest diabetes-specific natural history studies yet conducted, involving well-characterized participants and, together with the BHS, an appropriately long duration of follow-up. In addition, the use of competing risk analysis in model development addresses the issue of premature mortality, which is an important consideration in type 2 diabetes (34).

The FDS1 hip fracture risk calculator is a useful addition to the suite of similar tools (2) because it is the only one that has been developed and validated in people with type 2 diabetes. Despite its limited range of simple clinical variables, it has good performance characteristics. It can be readily implemented as part of the routine assessment of the person with type 2 diabetes. It could be easily incorporated in future studies of fractures complicating type 2 diabetes with a view to potentially wider validation and implementation.

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