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RESEARCH ARTICLE

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Factors associated with fragility fractures in type 2 diabetes: An analysis of the randomised controlled Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study

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Abstract

Aims: Fracture risk is elevated in some type 2 diabetes patients. Bone fragility may be associated with more clinically severe type 2 diabetes, although prospective studies are lacking. It is unknown which diabetes-related characteristics are independently associated with fracture risk. In this post-hoc analysis of fracture data from the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial (ISRCTN#64783481), we hypothesised that diabetic microvascular complications are associated with bone fragility.

Materials and Methods: The FIELD trial randomly assigned 9795 type 2 diabetes participants (aged 50–75 years) to receive oral co-micronised fenofibrate 200 mg (n = 4895) or placebo (n = 4900) daily for a median of 5 years. We used Cox

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proportional hazards models to identify baseline sex-specific diabetes-related parameters independently associated with incident fractures.

Results: Over 49,470 person-years, 137/6138 men experienced 141 fractures and 143/3657 women experienced 145 fractures; incidence rates for the first fracture of 4·4 (95% CI 3·8–5·2) and 7·7 per 1000 person-years (95% CI 6·5–9·1), respectively. Fenofibrate had no effect on fracture outcomes. In men, baseline macrovascular disease (HR 1·52, 95% CI 1·05–2·21, $p = 0·03$), insulin use (HR 1·62, HR 1·03–2·55, $p = 0·03$), and HDL-cholesterol (HR 2·20, 95% CI 1·11–4·36, $p = 0·02$) were independently associated with fracture. In women, independent risk factors included baseline peripheral neuropathy (HR 2·04, 95% CI 1·16–3·59, $p = 0·01$) and insulin use (HR 1·55, 95% CI 1·02–2·33, $p = 0·04$).

Conclusions: Insulin use and sex-specific complications (in men, macrovascular disease; in women, neuropathy) are independently associated with fragility fractures in adults with type 2 diabetes.

KEYWORDS
bone, complications, fractures, insulin, neuropathy, osteoporosis

1 | INTRODUCTION

Type 2 diabetes (T2D) individuals have an increased risk of fragility fractures, especially of the hips and distal limbs.[1–3] Increased fracture risk occurs despite relatively preserved bone mineral density and may result from adverse bone quality and strength due to hyperglycaemia, hypogonadism, advanced glycation end-products (AGEs), and pro-inflammatory factors.[4,5] Non-bone factors, such as falls and frailty, may also contribute.[6,7]

Potential diabetes-related risk factors include microvascular complications,[8,9] higher HbA1c,[10–12] longer diabetes duration,[8,13] and insulin use.[8,9,14,15] However, many factors are closely related within an individual (e.g., those with longer diabetes duration or higher HbA1c are more likely to have complications or require exogenous insulin), and the independent contributions of each diabetes-related characteristic to fracture risk are not fully elucidated.

As post-fracture mortality is elevated in T2D,[16,17] it is critical to predict fracture risk accurately to optimise management, but most current calculators inadequately quantify fracture risk in T2D.[18] One community-based study developed a 10-year incident fracture risk calculator based on five clinical characteristics in T2D, but this is limited to hip fractures.[19] The literature is limited by the absence of robust fracture data from well-characterised T2D cohorts, being either administrative database studies with limited diabetes characteristics[10,20] or the aforementioned study on hip fractures only.[19] There are no large prospective studies of fractures at all sites with simultaneously collected detailed T2D characteristics.

We hypothesise that diabetic microvascular complications contribute to bone fragility and aim to identify potential independent contributions of diabetes-related parameters on incident fractures. In this *post hoc* analysis, we examined the fracture risk in the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial.[21,22]

2 | RESEARCH DESIGN AND METHODS

2.1 | Study design and participants

FIELD was a 63-site (Australia, New Zealand, Finland) double-blind placebo-controlled trial of T2D participants ($n = 9795$, 50–75 years) randomised (1:1) to daily 200 mg co-micronised fenofibrate or placebo for a median (IQR) 5 (4·5–5·7) years. The ethics approved protocol was conducted in accordance with the Declaration of Helsinki. All participants gave written informed consent.

Participants had baseline total plasma cholesterol 3·0–6·5 mmol/L, a total to HDL-cholesterol ratio ≥4·0, or fasting triglycerides 1·0–5·0 mmol/L. Exclusion criteria were a cardiovascular event within 3-month pre-recruitment, serum creatinine >130 μmol/L, chronic liver disease, or symptomatic gallbladder disease.

2.2 | Variables

Baseline microvascular disease was defined as a history of ≥1 of prior microvascular amputation (below-ankle amputation with palpable femoral and popliteal pulses), self-reported history of retinopathy, peripheral neuropathy (abnormal 10g monofilament test in either foot), or nephropathy (elevated urinary albumin to creatinine ratio [ACR] ≥2·5 and ≥ 3·5 mg/mmol for men and women respectively).

Baseline macrovascular disease was defined as a self-reported history of coronary artery disease (angina, myocardial infarction, coronary artery bypass, or angioplasty), stroke, or peripheral vascular disease (including peripheral revascularisation and claudication).

Baseline medications, smoking, and alcohol use were recorded. History of osteoporosis, fragility fractures, or falls were not recorded. Baseline laboratory data were an average of data from three pre-

randomisation visits (16-, 12-, and 6-week). Renal function was determined by calculating the estimated glomerular filtration rate (eGFR) using the CKD-EPI creatinine equation.[23]

Incident fracture data were prospectively collected from serious adverse event (SAE) and non-serious adverse event (nSAE) records. SAEs included any hospital presentation (emergency department or admission), and all fractures were verified radiologically. nSAEs were self-reported at each study visit (4-monthly in Year 1 then 6-monthly thereafter). Fractures were adjudicated for site and degree of trauma according to the circumstances of injury by two independent clinicians specialising in fragility fracture management.

A fracture was deemed due to minimal trauma if due to daily activities or a fall from standing height or less.[14,15] Fractures due to major trauma, malignancy, or non-osteoporosis bone diseases were excluded. Fractures of the head, fingers and toes were excluded. Fractures were classified as proximal (hip, vertebral, pelvis, femur, proximal tibia/fibula, rib, humerus, clavicle, and sternum) or distal (remaining distal upper and lower limbs). Multiple fractures on the same date were counted as one event and classified according to the most proximal site.

2.3 | Statistical analyses

All analyses (SAS version 9.4 and the R statistical environment) were on an intention-to-treat basis and sex-specific as fracture risk varies by sex. Baseline variables were compared by incident fracture using *t*-tests for normally distributed continuous variables, Wilcoxon's rank sum tests for non-normal continuous variables, and chi-squared tests for categorical variables. The primary outcome was the time to first incident fracture at any site. Pre-defined subgroup analyses were conducted for fracture site (proximal and distal). A sensitivity analysis was performed for SAE fractures only, given the potential ascertainment errors of nSAE fractures. For subgroup analyses, all subjects in the risk-set, irrespective of any on-study fractures in a different category, were included. In a second approach, subjects were censored at the time of fracture if they had a fracture from a different category. Complete-case analysis approach was predefined for the modelling as there were very few missing baseline data (9/6138 = 0.15% of men; 103/3657 = 2.82% of women) and no missing data in the outcome of interest. Two-sided p value < 0·05 were regarded as significant.

2.3.1 | Risk factors for fracture

The association of candidate variables with incident fracture was determined by Cox proportional hazards regression and repeated for age-adjusted and multivariable-adjusted regressions. Baseline variables considered were age, BMI, current smoking, alcohol excess (>10 or >14 standard drinks/week for women and men, respectively), any microvascular disease, any macrovascular disease, HbA1c, T2D duration, fenofibrate use, glucose control modality (diet, metformin only, sulphonylurea only, any combination of oral agents, insulin ± oral agents), anti-osteoporosis medication, urine ACR, serum 25OH-vitamin D, total osteocalcin, eGFR, total-, LDL-, and HDL-cholesterol, and triglycerides. Depending on the age-adjusted regression results, pre-specified exploratory analyses included grouping of non-insulin medications and separating individual macrovascular components.

Multivariable-adjusted Cox proportional hazards regression modelling identified independent associates after accounting for potential confounders. Variables were considered for the multivariable model if significant at $p < 0{\cdot}20$ on age-adjusted analyses. Interactions were tested (insulin use with lipids, microvascular complications with insulin use, diabetes duration, and HbA1c) and if negative, removed from the model. As an exploratory analysis, this multivariable model was compared to a parsimonious model containing only significant variables derived after comparing two procedures. The first was a backward elimination procedure in which candidate variables were successively removed in order of least significance until all retained variables had $p < 0{\cdot}05$. The second used an exhaustive search where all possible models of each model size were fitted and ranked according to the lowest Akaike information criterion and the best model was selected where all variables had $p < 0{\cdot}05$.

2.3.2 | Evaluation of insulin as a fracture predictor in a matched subset

Because insulin use is subject to clinical confounders, a subset of subjects matched by propensity score was created to further evaluate insulin use for fracture risk. The propensity score was derived from a logistic regression model with insulin use as an outcome and the following covariates: age, BMI, smoking status, excess alcohol use, hypertension (self-reported) and dyslipidaemia (low HDL-cholesterol [<1·03 mmol/L in men, <1·29 mmol/L in women] with triglycerides ≥1·70 mmol/L), nephropathy, peripheral neuropathy, retinopathy, macrovascular disease, HbA1c, T2D duration, fenofibrate use, and serum total-, LDL, and HDL-cholesterol, triglycerides, and eGFR. Insulin users were matched 1:1 to insulin non-users using a 5% calliper width. Men and women were matched separately. After matching, all variables that were unbalanced by insulin use/non-use were balanced with a standardised mean difference of <0·10. Paired Cox proportional hazards regression modelling was used to determine the associations of insulin with incident fractures.

3 | RESULTS

3.1 | Baseline characteristics

Between February 1998 and November 2000, 13,900 people were screened and 9795 randomly assigned to fenofibrate (n = 4895) or placebo (n = 4900; Supplementary Figure S1). Table 1 shows baseline characteristics of all participants by on-study fracture and sex. Men

TABLE 1 Baseline characteristics of all subjects according to incident fracture and sex.

	Men (n = 6138)		Women (n = 3657)	
	No fracture n = 6001	Fracture n = 137	No fracture n = 3514	Fracture n = 143
Age (y)	**62·4 ± 6·8**	**63·7 ± 7·5**	61·8 ± 6·8	62·9 ± 7·5
BMI (kg/m^2)	29·8 (26·4–32·2)	28·9 (25·8–31·4)	32·2 (27·8–36·0)	32·1 (28·0–35·4)
Weight (kg)	**88·7 (80·0–99·3)**	**83·7 (78·0–93·3)**	82·7 (71·3–94·0)	82·3 (71·7–95·7)
Current smoker, *n* (%)	622 (10·4%)	16 (11·7%)	274 (7·8%)	10 (7%)
Alcohol excess, *n* (%)	511 (8·5%)	10 (7·3%)	87 (2·5%)	5 (3.5%)
Hypertension, *n* (%)	3145 (52·4%)	71 (51·8%)	2242 (63·8%)	88 (61·5%)
Dyslipidaemia, *n* (%)	2093 (34·9%)	40 (29·2%)	1516 (43·1%)	61 (42·7%)
Microvascular disease, *n* (%)	2218 (37·0%)	55 (40·2%)	954 (27·2%)	46 (32·2%)
Nephropathy, *n* (%)	1737 (29·0%)	39 (28·5%)	703 (20·1%)	29 (20·3%)
Neuropathy, *n* (%)	387 (6·5%)	11 (8·1%)	**152 (4·3%)**	**14 (9·8%)**
Retinopathy, *n* (%)	539 (9·0%)	17 (12·4%)	244 (6·9%)	14 (9·8%)
Macrovascular disease, *n* (%)	**1403 (23·4%)**	**45 (32·9%)**	656 (18·7%)	27 (18·9%)
Diagnosis of osteoporosis, *n* (%)	28 (0·5%)	2 (1·5%)	72 (2·1%)	6 (4·2%)
Prior osteoporosis treatment, *n* (%)	26 (0·4%)	2 (1·5%)	71 (2·0%)	5 (3·5%)
HbA1c (mmol/mol)	54 (43–62)	54 (45–63)	52 (43–62)	53 (45–63)
HbA1c (%)	7·1 (6·1–7·8)	7·1 (6·3–7·9)	6·9 (6·1–7·8)	7·0 (6·3–7·9)
T2 diabetes duration (years)	**6·9 ± 6·2**	**8·1 ± 6·9**	6·4 ± 5·8	7·1 ± 6·5
T2 diabetes therapy				
None, *n* (%)	1583 (26·4%)	33 (24·1%)	960 (27·3%)	32 (22·4%)
Metformin only, *n* (%)	951 (15·9%)	16 (11·7%)	727 (20·7%)	27 (18·9%)
Sulphonylurea[a] only, *n* (%)	1081 (18·0%)	30 (21·9%)	475 (13·5%)	25 (17·5%)
Any combination of oral agents[b] *n* (%)	1570 (26·2%)	28 (20·4%)	884 (25·2%)	27 (18·9%)
Insulin (±orals), *n* (%)	**816 (13·6%)**	**30 (21·9%)**	**468 (13·3%)**	**32 (22·4%)**
Fenofibrate use, *n* (%)	2995 (50%)	76 (56%)	1750 (50%)	74 (52%)
Total cholesterol (mmol/L)	4·9 ± 0·7	4·9 ± 0·6	5·2 ± 0·7	5·1 ± 0·6
LDL-cholesterol (mmol/L)	3·0 ± 0·6	3·0 ± 0·6	3·1 ± 0·7	3·0 ± 0·6
HDL-cholesterol (mmol/L)	**1·2 (0·9–1·2)**	**1·8 (1·4–2·3)**	1·0 (0·9–1·2)	1·1 (0·9–1·2)
Triglycerides (mmol/L)	**1·9 (1·3–2·3)**	**1·8 (1·2–2·2)**	1·7 (1·3–2·3)	1·6 (1·2–2·2)
eGFR (mL/min/1.73 m^2)	89·5 ± 13·2	89·6 ± 12·2	**87·8** ± 15·2	**84·5** ± 16·8
25OHD-vitamin D (nmol/L)	52 (40–66)	53 (38–64)	52 (39–66)	53 (38–64)
Total osteocalcin (ng/ml)	9·1 (7·3–12·1)	9·3 (7·3–12·4)	**8·9 (6·8–12·3)**	**9·3 (7·3–12·4)**
Urine ACR (mg/mmol)	1·1 (0·6 ± 3·2)	1·0 (0·6 ± 3·2)	1·0 (0·6 ± 2·6)	1·2 (0·6 ± 2·9)

Note: Data displayed as mean ± SD, or median (IQR). *t*-test or Wilcoxon's rank sum tests for continuous variables, where appropriate and chi-squared test for categorical variables. Bolded variables indicate $p < 0.05$.

[a]Sulphonylureas (alone or with other medications) used were gliclazide (1392 men, 770 women), glibenclamide (838 men, 373 women) and glimepiride (100 men, 69 women).

[b]Other medications were acarbose (82 men, 40 women), repaglinide (4 men, 5 women), and guarem (54 men and 38 women).

with versus without fractures were older, more likely to have macrovascular disease, use insulin, longer diabetes duration, and higher HDL-cholesterol levels. Women with versus without fractures were more likely to have neuropathy and use insulin. Few participants had received osteoporosis treatment at baseline (28 men, 76 women). Fenofibrate had no effect on fracture outcomes.

3.2 | Fracture rates

Over 49,470 person-years (median 5 [IQR: 4·5–5·7]), 137 of 6138 men had incident fractures; 66 were proximal and 71 distal, corresponding to fracture rates (per 1000 person-years) of 4·4 (95% CI 3·8–5·2) for any, 2·1 (95% CI 1·7–2·7) for proximal, and 2·3 (95% CI 1·8–2·9) for distal fractures (Supplementary Table S1 shows fracture rates by age group). Two men experienced multiple fractures, giving a total of 141 first-event fractures. 143 of 3657 women had incident fractures. One woman had a distal fracture followed by a proximal fracture, giving 63 proximal and 81 distal first events. Fracture rates were 7·7 (95% CI 6·5–9·1) for any, 3·4 (95% CI 2·7–4·4) for proximal, and 4·4 (95% CI 3·5–5.4) for distal fractures. Two women experienced multiple fractures, giving a total of 145 first-event fractures.

The most common sites for incident fracture in men were the ankle (40, 29%) and ribs (26, 19%), followed by the hip/pelvis (18, 13%), humerus (11, 8%), wrist/forearm (9, 7%), and vertebral (8, 6%). In women, fractures at the ankle (41, 29%) were most common, followed by fractures at the humerus (21, 15%), ribs (17, 12%), wrist/forearm (14, 10%), hip/pelvis (12, 8%), and vertebral (11, 8%).

3.3 | Risk factors for any fracture

In men, baseline age-adjusted factors associated with fracture risk were HDL-cholesterol, insulin use, and macrovascular disease (Table 2). Within the medication class, only insulin use was significant for incident fracture; therefore, non-insulin users were combined, and insulin versus no insulin use was compared. Cumulative risk curves for significant variables are in Supplementary Figure S2.

In the multivariable-adjusted model (Table 2, Figure 1), macrovascular disease (HR 1·52, 95% CI 1·05–2·21, $p = 0·03$), insulin use (HR 1·62, HR 1·03–2·55, $p = 0·03$) and HDL-cholesterol (HR 2·20, 95% CI 1·11–4·36, $p = 0·02$) remained significant (Figure 2).

An exploratory analysis to identify which macrovascular components were significant found that coronary disease was significant on age-adjusted modelling and was retained with similar effect size (HR 1·68, 95% CI 1·11–2·53, $p = 0·01$) on multivariable-adjusted modelling.

In women, significant factors on age-adjusted analysis were neuropathy and insulin use (Table 2, Supplementary Figure S3). Neuropathy (HR 2·04, 95% CI 1·16–3·59, $p = 0·01$) and insulin use (HR 1·55, 95% CI 1·02–2·33, $p = 0·04$) remained significant on multivariable-adjusted modelling, with both effects attenuated compared to their age-adjusted HR (Table 2, Figures 1 and 2).

3.4 | Analysis by fracture site

Analysis of proximal fractures was similar to all fractures; however, insulin use and neuropathy (in women) were no longer statistically significant, likely related to low fracture numbers in this subgroup (Supplementary Table S2). In men, age (HR 1·64, 95% CI 1·30–2·06, $p < 0·0001$), macrovascular disease (HR 1·95, 95% CI 1·18–3·23, $p = 0·01$), and HDL-cholesterol (HR 4·19, 95% CI 1·77–9·94, $p = 0·001$) were significant in the adjusted model. In women, only age (HR 1·55, 95% CI 1·27–1·89, $p < 0·0001$) remained significant post-adjustment.

For distal fractures, insulin use and microvascular complications, but not age, were associated with fractures, supporting distinct risk profiles for proximal and distal fractures (Supplementary Table S3). In men, insulin use (HR 1·83, 95% CI 1·04–3·23, $p = 0·04$) and retinopathy (HR 1·99, 95% CI 1·04–3·83, $p = 0·04$) were significant at both age- and multivariable-adjusted analyses. In women, only neuropathy (HR 2·33, 95% CI 1·14–4·76, $p = 0·02$) remained significant on multivariable-adjusted analysis. Insulin use was significant on age-adjusted and backwards selection analysis, though not in the full multivariable-adjusted model (HR 1·70, 95% CI 1·00–2·89, $p = 0·05$).

3.5 | Risk factors for SAE fractures

The sensitivity analysis of SAE fractures showed similar results, though some variables did not reach statistical significance, likely reflecting the predominance of proximal fractures in SAE fractures within a smaller number of fractures (Supplementary Table S4).

3.6 | Evaluation of insulin as a fracture predictor in a matched subset

Insulin users had higher HbA1c levels, longer diabetes duration, and were more likely to have micro- and macro-vascular complications and cardiovascular risk factors at baseline (data not shown). Supplementary Table S5 shows baseline characteristics of the 1572 men (786/846 [93%] of insulin users) and 896 women (448/500 [90%] of insulin users) in the insulin use/non-use matched cohort. Insulin use was associated with fractures with a similar effect size as the whole cohort, though did not reach statistical significance, likely due to smaller numbers (HR 1·53, 95% CI 0·83–2·82, $p = 0·17$ for men, HR 1·12, 95% CI 0·58–2·15, $p = 0·74$ for women) (Figure 3). When analysed by the fracture site, insulin use was particularly associated with distal fractures (HR 2·00, 95% CI 0·81–4·96, $p = 0·13$ for men, HR 1·88, 95% CI 0·80–4·42, $p = 0·15$ for women), and less so for proximal fractures (HR 1·20, 95% CI 0·52–2·78, $p = 0·67$ for men, HR 0·50, 95% CI 0·15–1·66, $p = 0·26$ for women).

4 | DISCUSSION

To our knowledge, this is the first study to separate the independent effects of interrelated T2D characteristics on the risk of prospectively collected fractures (any site) in a clinically relevant younger T2D cohort. Diabetes complications (macrovascular disease in men and peripheral neuropathy in women) were associated with fracture. Insulin use was associated with fracture risk even when adjusted for

TABLE 2 Hazard ratios (95% CI) for the association between baseline variables and the risk of any incident fracture.

	Men		Women	
	n = 6001 without fracture		*n* = 3514 without fracture	
	n = 137 with fracture		*n* = 143 with fracture	
	Age-adjusted	Multivariable-adjusted[a]	Age-adjusted	Multivariable-adjusted[a]
Age (/5 years)	**1·17 (1·03–1·32)**[b]	**1·18 (1·01–1·37)**	**1·13 (1·00–1·27)**[b]	1·07 (0·93–1·22)
BMI (/5 kg/m^2)	0·86 (0·71–1·04)	0·90 (0·74–1·09)	1·02 (0·89–1·17)	
Current smoker	1·30 (0·77–2·20)		0·95 (0·50–1·81)	
Alcohol excess	0·86 (0·45–1·65)		1·37 (0·56–3·35)	
Microvascular disease	1·12 (0·80–1·58)		1·24 (0·87–1·77)	
Nephropathy	0·95 (0·66–1·38)		1·00 (0·66–1·50)	
Retinopathy	1·43 (0·86–2·37)	1·17 (0·68–2·00)	1·37 (0·79–2·38)	
Neuropathy	1·28 (0·69–2·36)		**2·39 (1·37–4·14)**	**2·04 (1·16–3·59)**
Macrovascular disease	**1·49 (1·04–2·15)**	**1·52 (1·05–2·21)**	0·92 (0·60–1·41)	
HbA1c (/%)	1·06 (0·93–1·20)		1·06 (0·94–1·19)	
Type 2 diabetes duration (/5 years)	1·12 (0·99–1·27)	1·02 (0·89–1·18)	1·07 (0·94–1·23)	
Insulin use	**1·79 (1·20–2·69)**	**1·62 (1·03–2·55)**	**1·79 (1·21–2·65)**	**1·55 (1·02–2·33)**
Fenofibrate use	1·26 (0·90–1·76)	1·28 (0·91–1·73)	1·08 (0·78–1·49)	
Prior osteoporosis treatment	3·54 (0·88–14·31)	2·88 (0·71–11·72)	1·51 (0·61–3·72)	
Total cholesterol (/mmol/L)	0·99 (0·78–1·27)		0·86 (0·68–1·09)	
LDL-cholesterol (/mmol/L)	0·99 (0·76–1·29)		0·79 (0·62–1·01)	0·81 (0·63–1·03)
HDL-cholesterol (/mmol/L)	**2·82 (1·51–5·28)**	**2·20 (1·11–4·36)**	1·46 (0·83–2·57)	1·32 (0·75–2·32)
Triglycerides (/mmol/L)	0·81 (0·65–1·01)	0·93 (0·74–1·16)	0·99 (0·80–1·23)	
eGFR (/5 ml/min/1.73 m^2)	1·06 (0·99–1·15)	1·07 (0·99–1·15)	0·95 (0·90–1·01)	0·98 (0·92–1·04)
25OHD-vitamin D (/nmol/L)	1·00 (0·99–1·01)		1·00 (0·99–1·00)	
Total osteocalcin (/5 ng/mL)	0·99 (0·83–1·19)		1·14 (0·97–1·32)	1·12 (0·96–1·31)
Urine ACR (/mg/mmol)	1·00 (0·99–1·01)		1·00 (0·99–1·01)	

[a]Adjusted for variables listed in the column and included if significant at $p < 0.20$ on age-adjusted analysis.

[b]Unadjusted analysis. Bolded variables indicate $\boldsymbol{p < 0.05}$.

correlated markers of T2D severity, including duration or glycaemia, suggesting that mechanisms for fracture may relate to insulin use itself.

Meta-analyses of T2D individuals suggest an increased risk of hip (RR 1.3–2.1)[1–3] and all fractures (RR 1.2).[1,2] Foot, ankle, humerus, and vertebral fractures may also be increased.[8,9,15] Study-related factors may contribute to discrepant results, but it is likely that only some T2D individuals have increased fracture risk. Potential diabetes-related risk factors for fracture include microvascular complications,[8,9] higher HbA1c,[10–12] longer diabetes duration,[8,13] and insulin use;[8,9,14,15] however, conclusions have been limited due to multiple clinical confounders. After adjusting for T2D duration and HbA1c, we found that complications (macrovascular disease in men and peripheral neuropathy in women), higher HDL-cholesterol (in men), and insulin use were independently associated with any fracture. Consistent with other studies, we found that T2D duration was significant in men on unadjusted analysis; however, it lost significance after adjustment. This suggests clinical overlap and confounding other characteristics, such as insulin use and chronic complications.

Three studies examined T2D-related fracture risk factors, though none have comprehensively analysed both clinical and biochemical associates with fractures at all sites, as we did. In a longitudinal community-based T2D cohort (n = 1251), neuropathy independently predicted hip fractures, but T2D duration, T2D treatment, coronary heart disease, peripheral arterial disease, HbA1c, or serum cholesterol did not.[19] In contrast, our study assessed associates of fractures at all sites in a much larger sample size, conferring greater statistical power. Similarly, peripheral neuropathy and insulin use were associated with increased risk of any fractures in older T2D subjects in both a population-based study[9] and a retrospective study of male veterans.[20] However, these studies did not account for HbA1c, T2D duration, or insulin use.

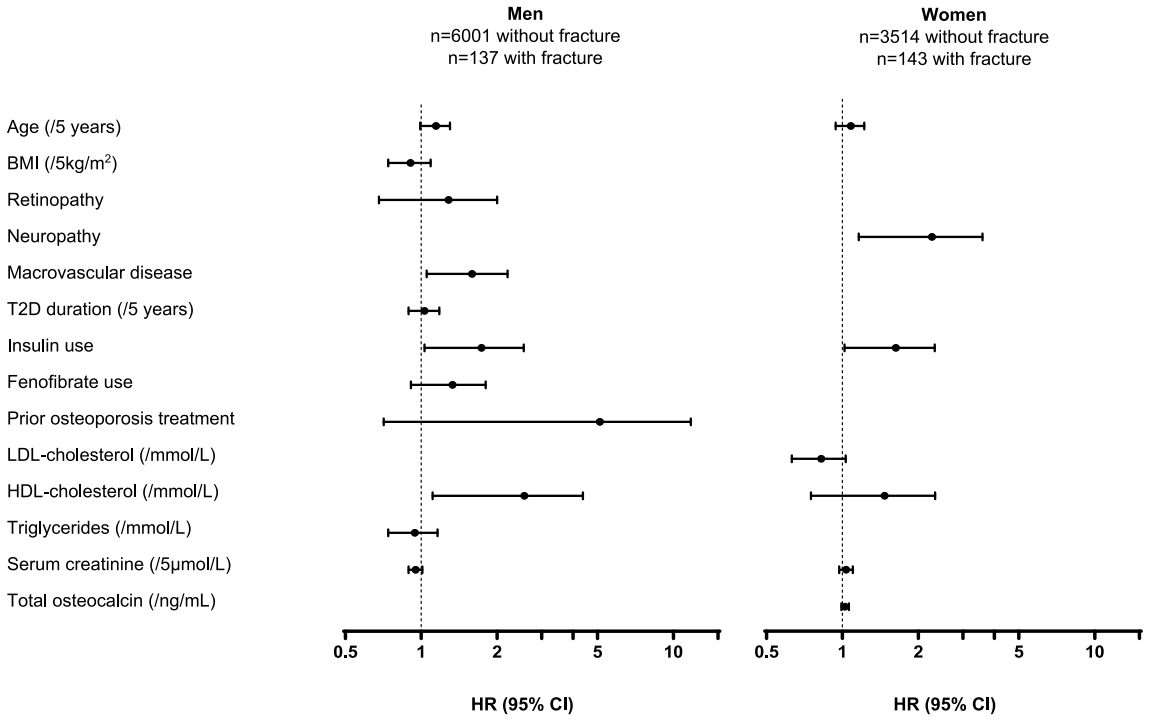

FIGURE 1 Forest plot of multivariable-adjusted hazard ratios (95% CI) for selected variables for incident fracture according to sex. Hazard ratios adjusted for candidate variables, which were significant at $p < 0.20$ on age-adjusted analysis.

In our large, detailed study, the participants were younger than in many other studies and we were able to consider more potential variables in the analyses. Baseline HbA1c was associated with a risk of fracture, but this association was no longer statistically significant once adjusted for the presence of macro- and microvascular complications (themselves likely a consequence of chronic chronically elevated HbA1c). The veterans' study found a J-curve association between HbA1c and fractures, especially for hip fractures.[10] There was a significant interaction between insulin use and HbA1c, and the authors not unreasonably concluded that hypoglycaemia contributed to fracture risk, further clouding the true independent effect of glycaemia as reflected by HbA1c. It is possible that we did not find any statistically significant association between HbA1c and fractures due to our younger study participants with good glycaemic control. Alternatively, it is possible that HbA1c is a surrogate for other markers of complicated T2D in other studies which have not been able to collect and account for as many variables as we have, and thus with inclusion of these other variables, T2D duration and HbA1c levels were no longer statistically significant, whilst existing macrovascular disease, higher HDL-cholesterol, peripheral neuropathy, and insulin use remained independently associated with fractures in our study. Further studies that replicate these findings are crucial.

The association of insulin use with increased fractures has been shown previously[8,9,14,15]; however, the mechanisms are not fully elucidated. Insulin has been postulated to be osteoanabolic, given that type 1 diabetes (T1D) is associated with osteopenia/osteoporosis, with corroborating animal and in vitro studies; thus, the increased fractures in T2D observational studies may relate to falls and hypoglycaemia secondary to insulin use. Here we show that insulin use per se is associated with increased fractures, given that it remained significant in both the matched cohort and after multiple adjustments in the whole cohort. In the subgroup analysis by the fracture site, insulin use was statistically significant only for proximal fractures in men. However, the point estimate was similar to overlapping confidence intervals compared with those for distal fractures. A similar pattern was seen for insulin use in women. Together, this evidence supports that insulin use was significant across all fracture sites. The study may have had insufficient statistical power to identify other less common risk factors (e.g. smoking) that may differ in their impact on proximal versus distal fracture. In the matched cohort, insulin use was associated most with distal fractures, which suggests that falls from hypoglycaemia and/or increased impact of falls from insulin therapy-induced weight gain may contribute. We identified 327 individuals with reported hypoglycaemic adverse events, nine of whom sustained a fracture. There was no association between hypoglycaemia and fracture, but the small numbers limit statistical power. Further studies understanding the risk of insulin use on fractures are warranted.

Established cardiovascular disease[24] and abdominal aortic calcifications[25] have been associated with an increased risk of hip and all fractures, respectively, in the general population. The underlying pathophysiology (e.g., shared genetic and environmental risk factors for vascular and skeletal disease, direct impairment of skeletal vascular supply, and circulating factors from calcified vasculature

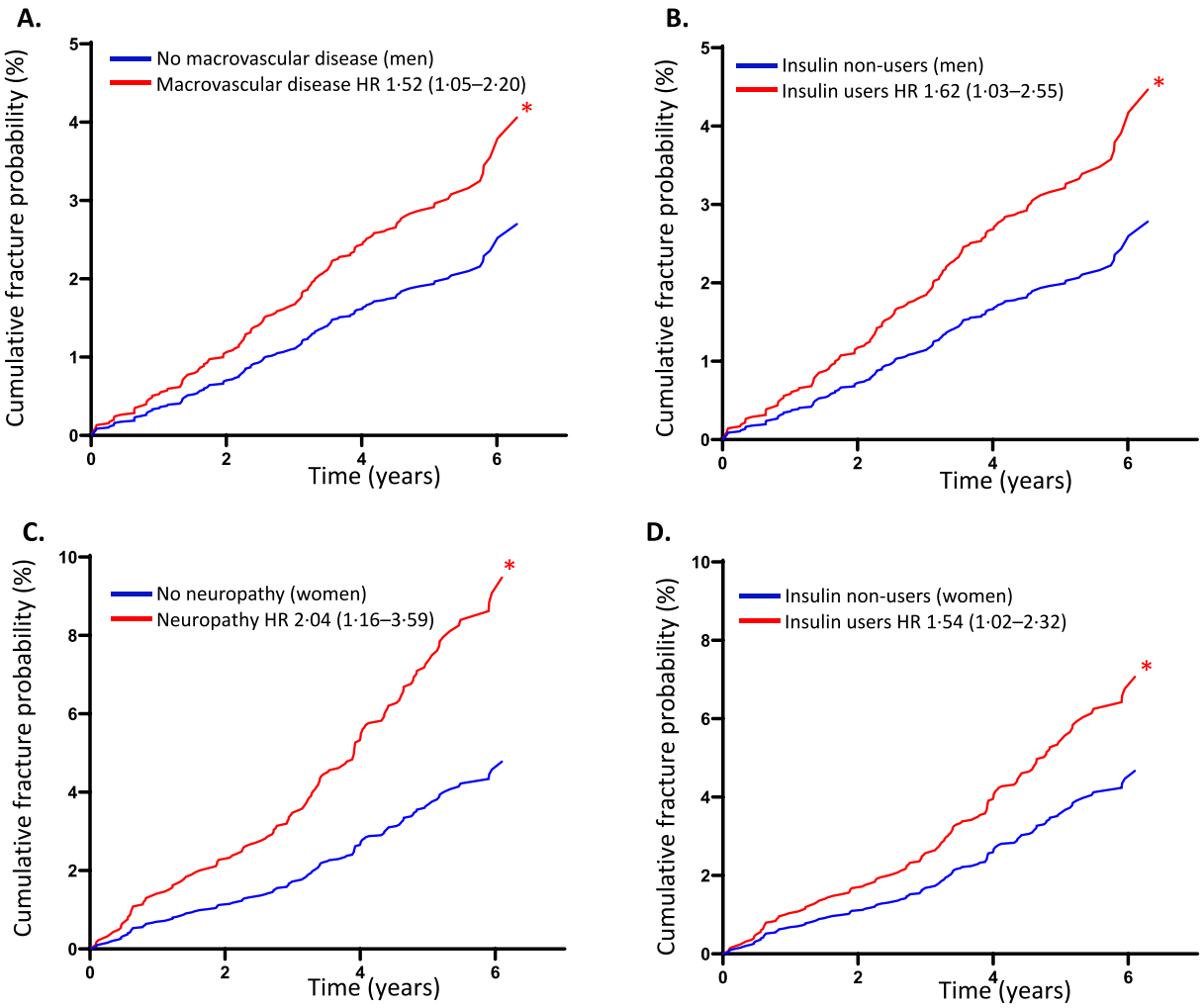

FIGURE 2 Multivariable-adjusted Cox proportional hazards regression for the first fracture according to sex. (A) Fracture risk with macrovascular disease in men. (B) Fracture risk with insulin use in men. (C) Fracture risk with neuropathy in women. (D) Fracture risk with insulin use in women. $^{*}p < 0.05$.

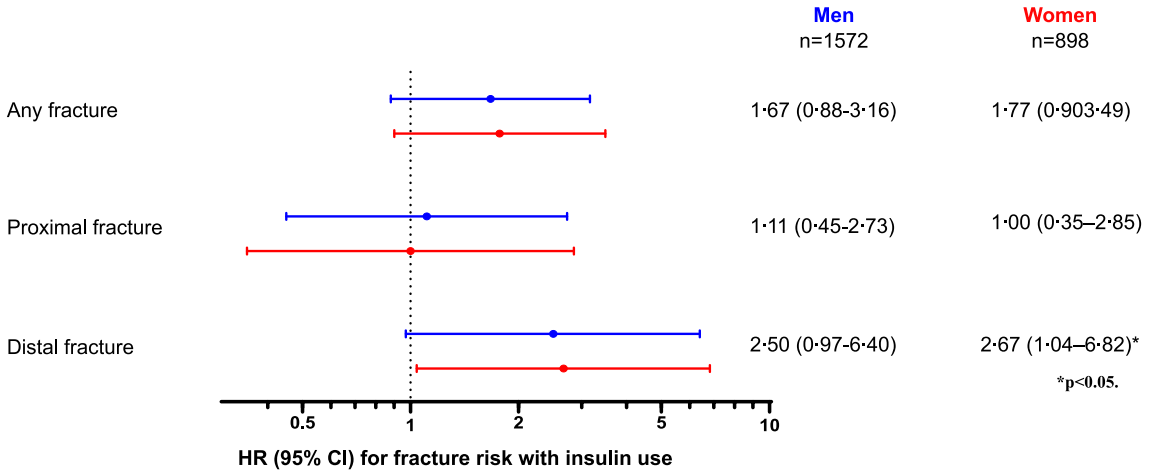

FIGURE 3 Forest plot of hazard ratios (95% CI) for the fracture type in the matched cohort according to sex and insulin use.

affecting bone calcification) may be accelerated in T2D, and thus atherosclerosis may contribute to fracture risk in T2D. Similarly, the association of HDL-cholesterol and fractures is complex.[26,27] Contributing mechanisms include the effects of insulin resistance/secretion, chronic inflammation, and direct effects on bone cells. However, studies are inconclusive on the association between HDL-cholesterol and fracture risk. Importantly, our study strengthens the independent associations of lipids and vascular disease with fractures in T2D, suggesting direct pathophysiological mechanisms leading to skeletal fragility.

This study is unique as we collected fractures at all sites in a large and relatively young T2D cohort. There are no comparative studies of fracture incidence in younger T2D cohorts, but compared with a general population-based osteoporosis study in Geelong, Australia, our fracture rates (per 1000 person-years) were higher in men (4·4, 95% CI 3·7–5·2, vs. 2·2, 95% CI 1·8–2·7) and similar in women (7·7, 95% CI 6·5–9·1, vs. 6·7, 95% CI 6·0–7·4), although they only collected hip, vertebral, wrist and humeral fractures.[28] We found similarities in fracture sites between men (ankle, ribs, hip/pelvis, and humerus) and women (ankle, humerus, ribs, and wrist/forearm). Contrarily, most common fractures differed in T2D cohorts aged ≥65 years (vertebral, ribs and hips in men,[10] vs. hip, humerus and wrist in women[15]). Studies cannot be directly compared; however, our results suggest that there are fewer phenotypic differences in fracture sites between sexes in younger T2D people (i.e., male sex is no longer osteoprotective in T2D), which could be due to the relative hypogonadism in T2D men that may parallel the female menopause. Furthermore, it appears that distal fractures may have a distinct risk profile, being more strongly driven by diabetes-related factors (possibly reflecting falls risk), while proximal fractures are associated with traditional osteoporotic fractures (including age). We acknowledge the small fracture numbers and thus these inferences are speculative.

Proposed pathophysiological drivers for increased fracture risk in T2D include obesity, hypogonadism, hyperinsulinaemia, hyperglycaemia, AGEs, and vascular disease, with obesity and hyperinsulinaemia predominating in early T2D, and accelerated ageing and vascular complications characterising later disease.[5] AGE accumulation in bone has been postulated to negatively affect bone matrix quality by increasing collagen brittleness, thereby reducing energy dissipation, and increasing microdamage.[5] Additional non-bone factors, such as falls and frailty, may also contribute.[6,7] A recent meta-analysis found no association with pre-diabetes and fracture risk,[29] suggesting diabetes-specific osteopathy.

Using high-resolution peripheral quantitative CT, women with T2D were found to have higher cortical porosity than non-diabetic women, despite improved trabecular parameters.[30] T2D may thus be associated with inefficient bone mass distribution, compromised bending strength, and increased fracture propensity. In two further studies, negative changes were seen only in the T2D subjects with fracture or microvascular complications[31], supporting the idea that bone fragility occurs in a subset of T2D people. Microarchitecture parameters did not correlate with T2D duration or glycaemia.[31]

There is similar interest in bone fragility associated with T1D, which provides further insight into T2D osteopathy. In a unique study, 11/985 (1.12%) older (age 66.0 ± 7.6 years) subjects with long T1D duration (54.7 ± 5.7 years) reported a previous hip or wrist fracture.[32] There were 65 of 985 participants who underwent BMD evaluation, with similarly low rates of osteoporosis. The risk factors for lower BMD included higher triglycerides, LDL-cholesterol, and presence of cardiovascular disease (but not microvascular complications or HbA1c). The unexpectedly low rate of fractures and osteoporosis was hypothesised to be related to the relatively few overall complications (cardiovascular disease 39.9%, proliferative retinopathy 46.4%, nephropathy 12.5%, neuropathy 69.8%) and excellent glycaemic control (HbA1c 7.2 ± 0.9%) of these unique older T1D subjects, given that a strong association with complications and fractures has also previously been described in T1D.[33] Clinical diabetes-related risk factors for non-vertebral fractures were examined in a cross-sectional study of T1D subjects (age 41.9 years ± 12.8) recruited from outpatient clinics.[34] Fracture risk (111/600, 18.5%) was associated with worse renal function and neuropathy. Multiple fractures (29/111, 26.2%) were associated with 5-year averaged HbA1c ≥ 7.9% (compared with ≤7.17%) and disease duration ≥26 years (compared with <14 years). Although there are differences between T1D- and T2D-related osteopathy, our data strengthen the associations with vascular complications and fracture risk. The effect of risk factors on other bone measures (e.g., turnover, microarchitecture, and strength) remains complicated (reviewed for T1D[35] and T2D[36]). However, diabetes-related fracture risk likely relates to reduced bone quality and strength, and further studies systemically evaluating well-characterised diabetes subjects are required.

Study strength stems from simultaneously collecting detailed T2D characteristics and incident fractures at all sites, allowing the evaluation of independent contributors to fracture risk by comprehensively accounting for confounders. Furthermore, the large sample size allows sufficient power to analyse fracture sites, providing additional insights into diabetic skeletal fragility. Finally, this is the first study to evaluate younger subjects, which is more clinically relevant, given the increasingly younger age of T2D onset and chronicity of disease.

We acknowledge the study limitations. As a T2D-focussed trial, there were limited data on bone-related characteristics, falls, or functional measures. Autonomic neuropathy was not assessed. We used a single baseline HbA1c in our analysis, which may not reflect long-term glycaemic control nor metabolic memory thereof. Our study was restricted to baseline T2D-related characteristics and are not necessarily a reflection of the T2D glycaemic status at the immediate time of the fracture. Findings from this randomised controlled trial may not be applicable to all T2D patients, though many trial participants were recruited from general practice. Although some hypoglycaemia data were collected for adverse event monitoring, mild/asymptomatic hypoglycaemia and day-to-day glucose variability were not systemically collected. Self-reported nSAE fractures were not radiologically verified; however, the sensitivity analysis of SAE fractures revealed similar findings to the whole cohort. The menopausal status of women was not recorded. However, as all participants were aged 50 years or

older (mean age of 62 years old), and the median age of menopause ranges between 50–52 years,[37] the vast majority of women in this study would have been post-menopausal. Finally, recruitment occurred during 1998–2000; thus, T2D medications were predominantly metformin, sulphonylureas, and insulin, and findings cannot be applied to all T2D medications.

In conclusion, in this *post hoc* analysis of the FIELD trial, complications (macrovascular disease in men and peripheral neuropathy in women), higher HDL-cholesterol in men, and insulin use were independently associated with incident fractures at any site. This risk was independent of T2D duration or glycaemia. Insulin use was particularly associated with distal fractures. Understanding the mechanisms for this increased fracture risk may lead to potential interventions that could reduce fracture burden in people with T2D.

AUTHOR CONTRIBUTIONS

Angela Sheu, Alicia J. Jenkins, Jacqueline R. Center, Christopher P. White and Anthony C. Keech conceived the study. Angela Sheu, Rachel L. O'Connell, Thach Tran, Alicia J. Jenkins, Jacqueline R. Center, Christopher P. White and Anthony C. Keech designed the study. Angela Sheu, Rachel L. O'Connell, Paul L. Drury, Y. Antero Kesäniemi, David R. Sullivan, Peter Colman, Richard O'Brien, Alicia J. Jenkins, Jacqueline R. Center, Christopher P. White and Anthony C. Keech acquired the data. Angela Sheu and Rachel L. O'Connell analysed the data. Angela Sheu drafted the paper. All authors interpreted the results and clinical messages, revised the draft, and approved the manuscript for submission.

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CONFLICT OF INTEREST STATEMENT

Angela Sheu, Rachel L. O'Connell, Thach Tran, Paul L. Drury, Y. Antero Kesäniemi, David R. Sullivan, Peter Colman, Richard O'Brien, and Christopher P. White have no competing interests to declare. Jacqueline R. Center has consulted and/or given educational talks for Amgen, Actavis, and Bayer. Anthony C. Keech reports grants and personal fees from Abbott and Mylan; and personal fees from Amgen, AstraZeneca, Pfizer, Sanofi, and Novartis, outside the submitted work. Outside this work, Alicia J. Jenkins has received funding from Abbott Europe, the National Health and Medical Research Council (NHMRC) of Australia, the Juvenile Diabetes Research Foundation, and the Diabetes Australia Research Programme. She is on advisory boards for Abbott Diabetes Australia, Amgen and Medtronic, and is an honorary board member of the International Diabetes Federation Western Pacific Region and the NGO Insulin For Life and is an honorary member of the Diabetes Australia research advisory panel.

ETHICS STATEMENT

The ethics approved protocol was conducted in accordance with the Declaration of Helsinki. All participants gave written informed consent.

DATA AVAILABILITY STATEMENT

The datasets analysed during the current study are not publicly available due to ethics restrictions but are available from the corresponding author on reasonable request.

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PEER REVIEW

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SUPPORTING INFORMATION

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