bmjmedicine

Check for updates

Effect of competing mortality risks on predictive performance of the QFracture-2012 risk prediction tool for major osteoporotic fracture and hip fracture: external validation cohort study in a UK primary care population

Shona J Livingstone,[1] Daniel R Morales,[1] Megan McMinn,[2] Chima Eke,[3] Peter Donnan,[1] Bruce Guthrie [3]

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/bmjmed-2022-000316).

For numbered affiliations see end of article.
Correspondence to: Professor Bruce Guthrie, Advanced Care Research Centre, University of Edinburgh Division of Clinical and Surgical Sciences, Edinburgh, UK; bruce.guthrie@ed.ac.uk

Cite this as: *BMJMED* 2022;1:e000316. doi:10.1136/bmjmed-2022-000316

Received: 9 July 2022
Accepted: 30 August 2022

ABSTRACT

OBJECTIVE To externally evaluate the QFracture-2012 risk prediction tool for predicting the risk of major osteoporotic fracture and hip fracture.

DESIGN External validation cohort study.

SETTING UK primary care population. Linked general practice (Clinical Practice Research Datalink (CPRD) Gold), mortality registration (Office of National Statistics), and hospital inpatient (Hospital Episode Statistics) data, from 1 January 2004 to 31 March 2016.

PARTICIPANTS 2 747 409 women and 2 684 730 men, aged 30-99 years, with up-to-standard linked data that had passed CPRD checks for at least one year.

MAIN OUTCOME MEASURES Two outcomes were modelled based on those predicted by QFracture: major osteoporotic fracture and hip fracture. Major osteoporotic fracture was defined as any hip, distal forearm, proximal humerus, or vertebral crush fracture, from general practice, hospital discharge, and mortality data. The QFracture-2012 10 year predicted risk of major osteoporotic fracture and hip fracture was calculated, and performance evaluated versus observed 10 year risk of fracture in the whole population, and in subgroups based on age and comorbidity. QFracture-2012 calibration was examined accounting for, and not accounting for, competing risk of mortality from causes other than the major osteoporotic fracture.

RESULTS 2 747 409 women with 95 598 major osteoporotic fractures and 36 400 hip fractures, and 2 684 730 men with 34 321 major osteoporotic fractures and 13 379 hip fractures were included in the analysis. The incidence of all fractures was higher than in the QFracture-2012 internal derivation. Competing risk of mortality was more common than fracture from middle age onwards. QFracture-2012 discrimination in the whole population was excellent or good for major osteoporotic fracture and hip fracture (Harrell's C statistic in women 0.813 and 0.918, and 0.738 and 0.888 in men, respectively), but was poor to moderate in age subgroups (eg, Harrell's C statistic in women and men aged 85-99 years was 0.576 and 0.624 for major osteoporotic fractures, and 0.601 and 0.637 for hip fractures, respectively). Without accounting for competing risks, QFracture-2012 systematically under-predicted the risk of fracture in all models, and more so for major osteoporotic fracture than for hip fracture, and more so in older people. Accounting for competing risks, QFracture-2012 still under-predicted the risk of fracture in the whole population, but over-prediction was considerable in older age groups and in people with high comorbidities at high risk of fracture.

CONCLUSIONS The QFracture-2012 risk prediction tool systematically under-predicted the risk of fracture (because of incomplete determination of fracture rates) and over-predicted the risk in older people and in those with more comorbidities (because of competing mortality). The current version of QFracture-2016 that is used by the UK's health service needs to be externally validated, particularly in people at high risk of death from other causes.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The QFracture risk prediction tool is recommended by the National Institute for Health and Care Excellence (NICE) to predict the risk of fracture and to guide decisions to start bisphosphonates, on the basis of previous validation studies showing good predictive performance

⇒ Previous validation studies of the original QFracture tool and QFracture-2012 have followed the derivation studies in not including fractures recorded in hospital discharge data, and in not accounting for competing risk of mortality

⇒ The QFracture-2016 prediction tool currently used by the UK's health service needs to be externally validated in the whole population

WHAT THIS STUDY ADDS

⇒ The observed incidence of fracture was higher in this study (which included hospital recorded fractures) than in the QFracture-2012 derivation and validation studies (which did not)

⇒ Despite excellent discrimination in the whole population, systematic under-prediction of the risk of fracture by QFracture-2012 was found, as was systematic over-prediction in older people and in those with more comorbidities when accounting for competing risk of mortality

⇒ Competing mortality risk is an important problem in the context of fracture prediction in older people because non-fracture death is much more common than the fracture outcomes being predicted

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY

⇒ Research is needed to examine the implications of competing mortality risk for recommended clinical prediction tools where the time-horizon for prediction is long and competing mortality is common

Introduction

Fragility or low impact fractures are a common consequence of osteoporosis and osteopenia, and a major cause of morbidity, disability and, in some cases, death. Bisphosphonates reduce the risk of hip and vertebral fractures in people with osteoporosis,[1] and international guidelines recommend drug treatment for people at high risk of fracture.[1–5] In the UK, guidelines recommend the use of a fracture risk prediction tool in middle aged and older people who have risk factors for fracture, with measurement of bone mineral density for further classification of risk in those at intermediate risk.[2 4] In the US, guidelines from the US Bone Health and Osteoporosis Foundation (previously the National Osteoporosis Foundation) recommend similar use of prediction tools for middle aged people but also recommend routine measurement of bone mineral density in older people.[5] These types of guideline recommendations based on risk are increasingly used by people who develop guidelines to target treatment to those with the greatest capacity to benefit, but the effectiveness of this strategy critically depends on the performance of the risk prediction tools used.

Many fracture risk prediction tools have been created, although only three have undergone repeated external validation: QFracture, FRAX, and Garvan.[6 7] The first version of QFracture[8] was externally validated in a UK primary care dataset, and was found to have excellent discrimination and calibration (discrimination is the ability of the prediction tool to correctly differentiate between people who have a fracture and those who have not, whereas calibration refers to how closely the predicted and observed probabilities agree).[9] Subsequently, Dagan et al externally validated the updated QFracture-2012 algorithm and the Garvan prediction tool in an Israeli dataset. QFracture-2012 had good discrimination but Garvan had moderate discrimination, and both tools systematically under-predicted the risk of fracture.[7]

The fracture risk assessment tool (FRAX) has been internally validated in several datasets, with discrimination reported as good but calibration has rarely been assessed.[6 10] FRAX cannot be externally validated, however, because the underlying FRAX algorithm has never been made public which prevents full independent evaluation.[7] Dagan et al also presented an external validation of FRAX in their analysis, but FRAX predictions were not based on full FRAX estimates of risk because the prediction equation is not published.[7] Based on the approximate FRAX risk used, considerable under-prediction of fractures for this tool was found.

In the UK, the National Institute for Health and Care Excellence (NICE) recommends the use of either QFracture or FRAX to inform decisions to start treatment with bisphosphonates, but recognises that the estimated risk of fracture for individuals can vary considerably between tools.[1 2] FRAX over-predicted the risk of fracture when the same method of determining fractures as the QFracture-2012 derivation was used.[2 8 11] Two possible reasons for these differences include how fractures are identified in the derivation of each tool, because QFracture-2012 uses codes in primary care records and mortality data[12] and FRAX uses self-report and hospital records[13] (these might be incomplete in different ways), and only FRAX takes into account competing risks of mortality. Competing risk of mortality from non-fracture causes is a known problem in risk prediction because standard modelling methods assume that patients who are censored before the intended end of follow-up have the same risk of fracture as those who are not censored. Although this assumption might be reasonable for loss to follow-up because of change in address, when someone dies the assumption is clearly false. Not accounting for competing risk of mortality over-predicts the risk of fracture, which is likely to be more of a problem in older people and those with multimorbidities.[14–16] The aim of this study therefore was to externally validate the QFracture 2012 risk prediction tool, and specifically to compare prediction in relation to better determination of fracture rates, and to examine the effect of competing risk on predictive performance. QFracture 2012 has subsequently been updated and the QFracture 2016 model is the version currently in use in the UK's health service.

Methods

Data source and population

Linked general practice (Clinical Practice Research Datalink Gold), mortality registration (Office of National Statistics), and hospital inpatient (Hospital Episode Statistics) data were used. The data are similar to the QFracture derivation dataset in terms of inclusion of linked primary care and mortality data, but we also used linked hospital admission data to determine if a fracture occurred. To be included, patients had to be permanently registered with a general practice contributing up-to-standard (ie, passing Clinical Practice Research Datalink quality checks) data for at least one year; have linkage to Hospital Episode Statistics discharge data and Office of National Statistics mortality data; and aged ≥30 years and <100 years. Cohort entry was the latest of the dates on or after 1 January 2004. Cohort exit was the date of the earliest of the first relevant fracture event, death, deregistration from the general practice, date of the last data collection from the practice, or the end of the study on 31 March 2016. All outcomes and predictors were recorded blind to the study hypothesis and recorded as part of routine clinical care. No formal power calculation was done because the study size was determined by data available in the Clinical Practice Research Datalink, which was considered sufficient.[17]

Outcomes

Two outcomes were modelled based on those predicted by the QFracture tool: major osteoporotic fracture and hip fracture.[12] Major osteoporotic fracture was defined as hip, vertebral, wrist, or proximal humeral fractures determined from codes in the general practice electronic health record (with Read codes, which have been shown to have high positive predictive value for hip fracture),[18] Hospital Episode Statistics discharge diagnoses (ICD-10 (international classification of diseases, 10th revision) codes recorded in the primary position as the reason for admission to hospital), and Office of National Statistics death registration (ICD-10 codes) (online supplemental tables S1 and S2). Major osteoporotic fracture recorded before entry into the study was used as a predictor variable. Major osteoporotic fracture or hip fracture recorded after the index date was used as the outcome variable, with the date of the event taken as the first record of fracture.

Prediction model

We used the published QFracture-2012 risk model (under GNU Lesser General Public Licence, version 3) and calculated the QFracture-2012 predicted 10 year risk of a major osteoporotic fracture and hip fracture for all patients in our cohort. Online supplemental tables S3-S5 describe the derived codelists for each morbidity predictor. The key difference from the QFracture-2012 derivation was that for QFracture-2012, body mass index, alcohol consumption, and smoking status, recorded after the date of entry into the study but before any fracture outcome, could be used in the prediction, whereas in this analysis we restricted predictor values to those recorded before entry into the study only, to avoid the use of future information in the prediction.

Comorbidity

For each patient at baseline, we calculated the Charlson comorbidity index based on primary care Read codes.[19] The Charlson comorbidity index was not used in the prediction, but was used to classify the analysis of discrimination and calibration by level of comorbidity (Charlson comorbidity index score 0, 1, 2, and ≥3 groups).

Missing data

Online supplemental table S6 details the extent and management of missing data. In common with the QFracture-2012 derivation, those with missing data for ethnic group were assumed to be white. For missing data on body mass index, smoking status, and alcohol consumption, multivariate imputation by chained equations[20] was used to generate five imputed datasets, which were combined by using Rubin's rules.[21] Morbidities and prescribing used for prediction were assumed to be absent if there were no relevant data recorded for them (the same as for the QFracture-2012 derivation), reflecting that recording of morbidity and prescribing data in the Clinical Practice Research Datalink is generally good.[22 23]

Statistical analysis

Based on the recommendations of reporting guidance,[24] the initial analysis compared the study population and fracture rates in this study with the previously published QFracture derivation and validation cohorts (although variable reporting across previously published papers means that the comparison population varies depending on the data available).[8 9 12] The performance of the QFracture-2012 risk score was assessed by examining discrimination and calibration. We used Harrell's C statistic, shortened to only include pairs where the earliest survival time is no later than 10 years after entry (a C statistic of 0.5 indicates discrimination that is no better than chance, whereas a C statistic of 1 indicates perfect discrimination). Two other measures of discrimination were calculated, the D statistic of Royston and Sauerbrei (which is based on the separation in event free survival between patients with predicted risk scores above and below the median; higher values indicate greater discrimination),[25] and a related R^2 statistic estimating explained variation for censored survival data.[26]

Calibration was assessed for 10 equally sized groups (deciles) of participants ranked by predicted risk, by plotting observed proportions versus predicted probabilities. We estimated observed risk for censored data in two ways: with the standard Kaplan-Meier estimator (which is consistent with the assumptions made in the QFracture-2012 derivation in that it does not account for competing risks); and the Aalen Johansen estimator (an extension to allow for competing events, in this case, death from causes other than fractures).[27] All models were fitted in R-4.0.0 and Stata 11.2. Plots were generated separately for sex, for all patients, and for subgroups for age and Charlson comorbidity index, based on summary statistics pooled across the imputed datasets.

Patient and public involvement

Public contributors were involved in the design and conduct of the study as members of the study steering group.

Results

We included 2 747 409 women and 2 684 730 men in the analysis, with mean ages of 50.7 and 48.5 years, respectively (table 1). The study population was similar to the previously published QFracture-2012 internal validation population in term of mean age, sex, body mass index, and ethnic group but we found a higher recorded prevalence of previous major osteoporotic

Table 1 | Baseline data in our external validation cohort and in previously published QFracture-2012 internal validation cohort[12]

Characteristics	External validation cohort		QFracture-2012 internal validation cohort[12]*
	Women (n=2 747 409, 50.6%)	Men (n=2 684 730, 49.4%)	All patients (n=1 583 373)
Mean (SD) age (years)	50.7 (17.4)	48.5 (15.6)	50 (1.6)
Mean (SD) body mass index	26.6 (6.0)	27.1 (4.8)	26.1 (4.6)
Women	2 747 409 (50.6)		804 563 (50.8)
Ethnic group:			
White or not recorded	2 614 423 (95.2)	2 556 923 (95.2)	1 493 455 (94.3)
Indian	25 420 (0.9)	27 087 (1.0)	17 670 (1.1)
Pakistani	11 121 (0.4)	12 316 (0.5)	6489 (0.4)
Bangladeshi	3473 (0.1)	4972 (0.2)	4191 (0.3)
Other Asian	18 896 (0.7)	17 758 (0.7)	10 779 (0.7)
Black Caribbean	4780 (0.2)	4030 (0.2)	10 144 (0.6)
Black African	22 736 (0.8)	20 776 (0.8)	17 367 (1.1)
Chinese	7358 (0.3)	5517 (0.2)	5206 (0.3)
Other ethnic group	39 202 (1.4)	35 351 (1.3)	18 072 (1.1)
Smoking status:			
Non-smoker	1 146 025 (41.7)	807 294 (30.1)	773 198 (48.8)
Ex-smoker	390 520 (14.2)	439 503 (16.4)	257 087 (16.2)
Light (<10 cigarettes/day)	135 272 (4.9)	125 229 (4.7)	94 400 (6.0)
Moderate (10-19 cigarettes/day)	188 078 (6.8)	190 990 (7.1)	113 757 (7.2)
Heavy (>10 cigarettes/day)	107 288 (3.9)	158 134 (5.9)	86 787 (5.5)
Current smoking amount not recorded	43 957 (1.6)	78 372 (2.9)	65 106 (4.1)
Not recorded	780 226 (26.8)	963 580 (33.0)	193 038 (12.2)
Alcohol consumption:			
None	570 900 (20.8)	317 208 (11.8)	330 695 (20.9)
<1 unit/day	854 476 (31.1)	548 761 (20.4)	402 847 (25.4)
1-2 units/day	561 603 (20.4)	669 776 (24.9)	287 441 (18.2)
3-6 units/day	52 785 (1.9)	224 507 (8.4)	84 478 (5.3)
7-9 units/day	5750 (0.2)	38 273 (1.4)	8743 (0.6)
>9 units/day	2993 (0.1)	9583 (0.7)	7429 (0.5)
Not recorded	698 902 (25.4)	866 622 (32.3)	461 740 (29.2)
Previous major osteoporotic fracture	152 417 (5.5)	113 520 (4.2)	27 907 (1.8)
Parental history of osteoporosis or hip fracture	10 561 (0.4)	1077 (0.0004)	4227 (0.3)
Nursing or care home resident	16 819 (0.6)	7455 (0.3)	1535 (0.1)
Condition or prescription:			
Type 1 diabetes	8747 (0.3)	12 008 (0.4)	4322 (0.3)
Type 2 diabetes	81 715 (3.0)	100 009 (3.7)	43 437 (2.7)
History of falls	153 841 (5.6)	74 368 (2.8)	17 382 (1.1)
Dementia	34 892 (1.3)	15 036 (0.6)	7791 (0.5)
Cancer	94 090 (3.4)	67 380 (2.5)	28 203 (1.8)
Asthma or COPD	355 014 (12.9)	303 541 (11.3)	113 175 (7.1)
Cardiovascular disease	156 577 (5.7)	195 378 (7.3)	77 824 (4.9)
Chronic liver disease	6093 (0.2)	6753 (0.3)	3216 (0.2)
Chronic renal disease	33 274 (1.2)	24 395 (0.9)	3413 (0.2)
Parkinson's disease	7585 (0.3)	8348 (0.3)	3650 (0.2)
Rheumatoid arthritis or SLE	11 970 (0.4)	32 950 (1.2)	10 091 (0.6)
Malabsorption	34 884 (1.3)	27 122 (1.0)	8026 (0.5)
Endocrine disorders	25 089 (0.9)	5866 (0.2)	7882 (0.5)
Epilepsy or prescribed anticonvulsants	66 145 (2.4)	59 214 (2.2)	26 271 (1.7)
Prescribed antidepressants	66 145 (2.4)	59 214 (2.2)	111 229 (7.0)
Prescribed corticosteroids	37 169 (1.4)	22 632 (0.8)	30 998 (2.0)
Prescribed oestrogen only HRT	33 679 (1.2)	127 (0.0)	14 988 (0.9)

Data are number (%) of participants unless stated otherwise.
SD=standard deviation; COPD=chronic obstructive pulmonary disease; HRT=hormone replacement therapy; SLE=systemic lupus erythematosus.
*Only whole population reported so could not be grouped by sex.

fracture, residence in a nursing home or care home, and many long term conditions, including type 2 diabetes, history of falls, dementia, cancer, asthma or chronic obstructive pulmonary disease, chronic renal disease, malabsorption, and epilepsy or prescribed anticonvulsant drugs. For the population evaluated for major osteoporotic fracture, median follow-up was 5.7 (interquartile range 2.2-10.5) years in women and 5.6 (2.2-10.4) years in men. For hip fracture, median follow-up was 5.9 (2.2-10.6) years in women and 5.7 (2.2-10.4) years in men.

The crude incidence of both major osteoporotic fracture and hip fracture was higher in women than in men (major osteoporotic fracture 6.12 per 1000 person years in women *v* 2.26 in men; hip fracture 2.30 *v* 0.88, respectively) (online supplemental tables S7 and S8). We found a marked increase with age for both outcomes, and differences between the sexes were larger in older ages (eg, in women aged 30-34 years, major osteoporotic fracture was 0.95 per 1000 person years, increasing to 33.53 for ages 80-99 years; in men aged 30-34 years, 1.02 per 1000 person years increasing to 15.42 for ages 80-99 years) (online supplemental tables S9 and S10). For the whole population, the incidence of major osteoporotic fracture in this study was 4.22 per 1000 person years of follow-up compared with 2.45 per 1000 person years in the previously published updated QFracture-2012 internal validation cohort,[12] and 2.89 per 1000 person years in a previously published Clinical Practice Research Datalink validation cohort.[12] For hip fracture, overall incidence was 1.60 per 1000 person years compared with 1.32 in the same previously published Clinical Practice Research Datalink validation cohort.[28] Two thirds (64 163, 67.1%) of major osteoporotic fractures in women and half (17 276, 50.3%) in men were in people aged ≥65 years. For hip fracture, 32 339 (88.8%) fractures in women and 10 167 (76.0%) in men were in people aged ≥65 years (online supplemental tables S7 and S8).

Although the incidence of major osteoporotic fracture and hip fracture increased with age in men and women, the incidence of mortality from causes other than fractures increased more steeply with age (particularly in men). The incidence of death from causes other than fractures was similar to the incidence of major osteoporotic fracture in young people, but increased greatly with age; four times as common as major osteoporotic fracture in women aged 90-99 years and almost 10 times as common in men aged 90-99 years (figure 1, online supplemental tables S15 and S16). The incidence of death from causes other than fractures was higher than for hip fracture at all ages.

In the whole population, QFracture-2012 discrimination for major osteoporotic fracture was excellent in women (C=0.813) and good in men (C=0.738), and for hip fracture was excellent in both sexes (women C=0.918, men C=0.888) (table 2). Grouped by age, however, for both outcomes discrimination was poor to moderate in older adults where prediction of fracture risk is recommended[1] (eg, for major osteoporotic fracture, ages 65-74 years, C=0.616 for women and 0.660 for men; ages 85-99 years, C=0.576 for women and C=0.624 for men) (table 2). Grouped by Charlson comorbidity index, discrimination was good for major osteoporotic fracture and good to excellent for hip fracture in all groups.

Figures 2–4 and online supplemental figures S2–S9 show the calibration plots. When observed rates for major osteoporotic fracture were estimated without accounting for competing risk (figures 2 and 3 and online supplemental figures S2–S5), in the whole population for both men and women, we found under-prediction of the risk of fracture at all levels of predicted risk. Grouped by age, under-prediction in all age groups and at all levels of predicted risk was found except in the highest predicted risk decile in people aged 80-99 years where over-prediction was evident. Similar patterns were seen when grouped by Charlson comorbidity index, with under-prediction in all groups except those with the most multimorbidities at the highest levels of predicted risk.

When observed major osteoporotic fracture rates were estimated accounting for competing risk (figures 2 and 3 and online supplemental figures S2–S5), in the whole population, we found less under-prediction with some over-prediction in women at the highest predicted risk. Grouped by age, under-prediction was found in younger age groups but to a lesser extent than without accounting for competing risk. We found considerable over-prediction in women aged 85-99 years at higher risk and in most men aged 85-99 years, and over-prediction in men and women aged 75-84 years at the highest levels of predicted risk. In these older age groups, observed risk of major osteoporotic fracture was either flat or decreased as the decile of predicted risk increased. Similar patterns were seen when grouped by Charlson comorbidity index, with over-prediction of the risk of fracture in those with the most multimorbidities (Charlson comorbidity index ≥3) and in people with a Charlson comorbidity index of 2 at the highest level of predicted risk.

For hip fracture, when observed rates of hip fracture were estimated without accounting for competing risk (figures 4 and 5 and online supplemental figures S6–S9), in the whole population, we found greater under-prediction of the risk of fracture than for major osteoporotic fracture at all levels of predicted risk for both women and men. Grouped by age, we found under-prediction in all age groups and at all levels of predicted risk except for the highest two predicted risk deciles in women aged 80-99 years where large over-prediction of risk was found. Similar over-prediction was found in the highest risk decile for men aged 80-99 years. When grouped by

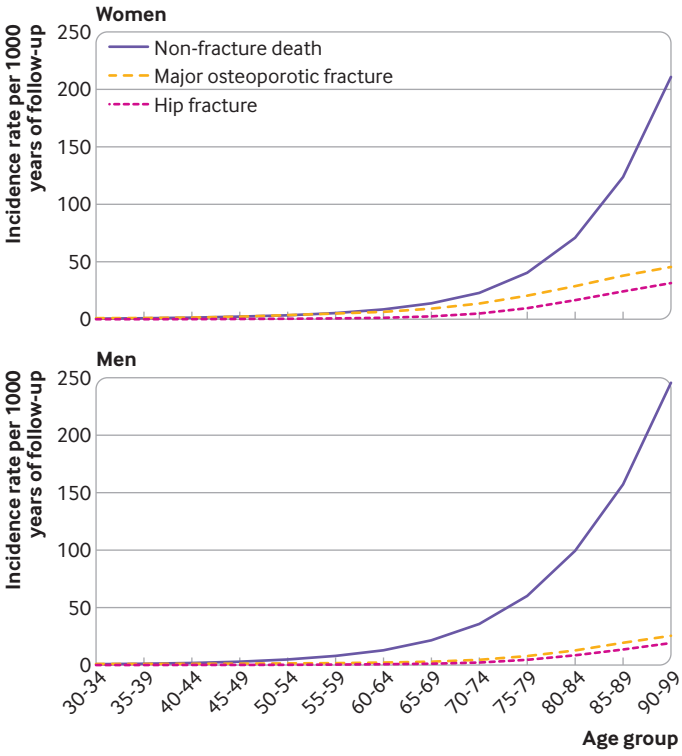


Figure 1 | Incidence of major osteoporotic fracture, hip fracture, and death from causes other than fractures (non-fracture death) in women and men

Charlson comorbidity index, similar patterns were seen, with under-prediction in all groups except for those with the most multimorbidities at the highest levels of predicted risk.

When observed hip fracture rates were estimated accounting for competing risk (figures 4 and 5 and online supplemental figures S6–S9), in the whole population, we found less under-prediction with some over-prediction in women at the highest predicted risk. Grouped by age, under-prediction was less in younger age groups, but over-prediction was considerable in both sexes aged 85-99 years at higher predicted risk, as well as in both sexes aged 75-84 years at the highest levels of predicted risk. Similar to major osteoporotic fracture, in these two older age groups, observed hip fracture rates were flat or declined across all 10 deciles of increasing predicted risk. Similar patterns were seen when grouped by Charlson comorbidity index, with over-prediction of fracture risk in those with the most multimorbidities (Charlson comorbidity index ≥3) and in people with a Charlson comorbidity index of 2 at the highest level of predicted risk.

Discussion

Summary of findings

In this external validation of the QFracture-2012 risk prediction tool, we found very good to excellent

Table 2 | Discrimination and model fit for major osteoporotic fracture and hip fracture*

	Women			Men		
	Harrell's C	D statistic	R^2	Harrell's C	D index	R^2
Major osteoporotic fracture						
All patients	0.813 (0.811 to 0.815)	2.25 (2.24 to 2.27)	54.8 (54.5 to 55.1)	0.738 (0.735 to 0.741)	1.76 (1.74 to 1.78)	42.4 (41.9 to 43.0)
Age group (years):						
30-64	0.709 (0.706 to 0.712)	1.30 (1.28 to 1.32)	28.8 (28.2 to 29.4)	0.625 (0.621 to 0.630)	0.84 (0.81 to 0.86)	14.4 (13.6 to 15.1)
65-74	0.616 (0.612 to 0.620)	0.71 (0.69 to 0.73)	10.7 (10.1 to 11.4)	0.660 (0.653 to 0.668)	1.00 (0.95 to 1.04)	19.2 (17.9 to 20.6)
75-84	0.615 (0.612 to 0.619)	0.67 (0.65 to 0.69)	9.6 (9.1 to 10.2)	0.652 (0.645 to 0.659)	0.91 (0.87 to 0.95)	16.4 (15.2 to 17.6)
85-99	0.576 (0.570 to 0.581)	0.38 (0.35 to 0.42)	3.4 (2.9 to 4.0)	0.624 (0.613 to 0.636)	0.67 (0.60 to 0.73)	9.6 (8.0 to 11.3)
Charlson comorbidity index:						
0	0.795 (0.793 to 0.798)	2.08 (2.06 to 2.10)	50.8 (50.4 to 51.2)	0.668 (0.664 to 0.673)	1.22 (1.20 to 1.25)	26.3 (25.4 to 27.1)
1	0.801 (0.797 to 0.805)	2.08 (2.05 to 2.10)	50.7 (50.1 to 51.4)	0.730 (0.723 to 0.737)	1.64 (1.59 to 1.68)	39.0 (37.7 to 40.2)
2	0.747 (0.742 to 0.753)	1.60 (1.56 to 1.63)	37.8 (36.9 to 38.8)	0.727 (0.719 to 0.736)	1.54 (1.49 to 1.60)	36.3 (34.6 to 37.9)
≥3	0.712 (0.706 to 0.718)	1.30 (1.26 to 1.33)	28.7 (27.5 to 29.8)	0.724 (0.715 to 0.733)	1.46 (1.40 to 1.51)	33.7 (32.0 to 35.4)
Hip fracture						
All patients	0.918 (0.915 to 0.921)	3.26 (3.24 to 3.28)	71.7 (71.4 to 71.9)	0.888 (0.882 to 0.893)	3.19 (3.16 to 3.23)	70.9 (70.4 to 71.3)
Age group (years):						
30-64	0.832 (0.823 to 0.841)	2.24 (2.19 to 2.30)	54.6 (53.4 to 55.8)	0.765 (0.755 to 0.776)	1.88 (1.82 to 1.94)	45.8 (44.1 to 47.4)
65-74	0.694 (0.687 to 0.701)	1.20 (1.16 to 1.24)	25.7 (24.4 to 27.0)	0.705 (0.694 to 0.716)	1.29 (1.23 to 1.36)	28.5 (26.5 to 30.5)
75-84	0.664 (0.659 to 0.669)	0.95 (0.92 to 0.98)	17.7 (16.8 to 18.5)	0.679 (0.670 to 0.687)	1.08 (1.03 to 1.13)	21.7 (20.1 to 23.3)
85-99	0.601 (0.595 to 0.608)	0.51 (0.47 to 0.55)	5.8 (5.0 to 6.7)	0.637 (0.623 to 0.651)	0.75 (0.67 to 0.82)	11.8 (9.8 to 13.9)
Charlson comorbidity index:						
0	0.924 (0.919 to 0.929)	3.36 (3.33 to 3.39)	72.9 (72.6 to 73.3)	0.852 (0.844 to 0.860)	2.84 (2.79 to 2.89)	65.8 (64.9 to 66.6)
1	0.899 (0.893 to 0.905)	2.92 (2.88 to 2.96)	67.1 (66.4 to 67.7)	0.872 (0.861 to 0.882)	2.89 (2.82 to 2.96)	66.7 (65.6 to 67.7)
2	0.839 (0.831 to 0.846)	2.24 (2.19 to 2.29)	54.5 (53.4 to 55.5)	0.808 (0.796 to 0.821)	2.17 (2.09 to 2.25)	53.0 (51.1 to 54.7)
≥3	0.783 (0.775 to 0.792)	1.75 (1.70 to 1.80)	42.2 (40.8 to 43.5)	0.782 (0.770 to 0.794)	1.90 (1.83 to 1.97)	46.4 (44.5 to 48.2)

Values are mean (95% confidence interval).

*Harrell's C has values from 0.5 (no better than chance) to 1 (perfect discrimination). For the D statistic, higher values indicate better discrimination, and a difference of >0.1 has been proposed as indicating a meaningful difference in discrimination.[25] R^2 has values from 0 (no variation in the outcome is explained by the risk model) to 100% (the risk model explains all variation in the outcome).

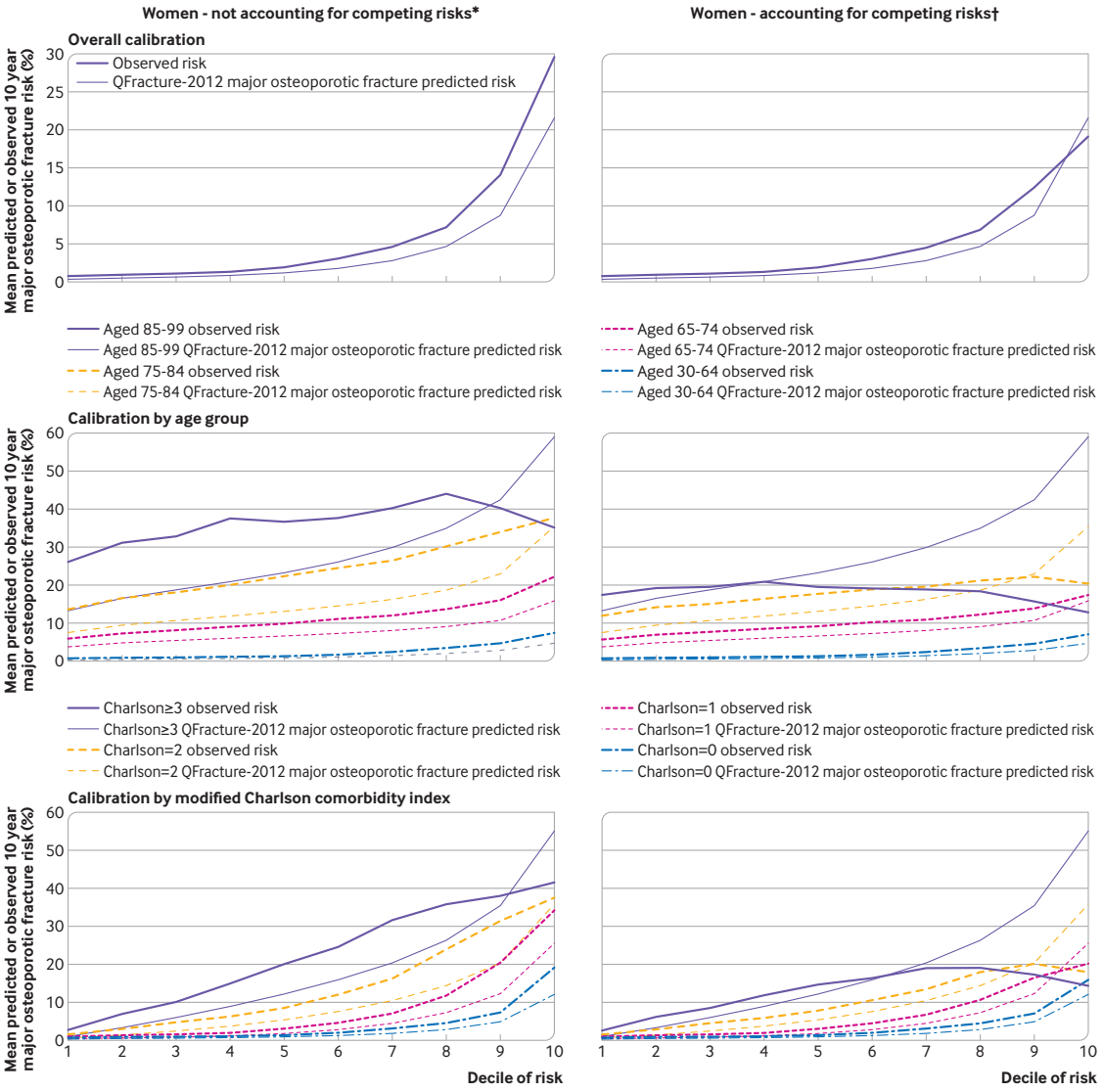


Figure 2 | Calibration for major osteoporotic fracture in women without accounting for competing risks and accounting for competing risks. For each pair, observed risk curve above predicted risk curve indicates under-prediction; observed risk curve below predicted risk curve indicates over-prediction. Separate plots for age and Charlson comorbidity index are shown in supplementary figures S2 and S4, respectively. *Observed risk based on Kaplan-Meier estimator, which does not account for competing mortality risk. †Observed risk based on Aalen-Johansen estimator, which accounts for competing mortality risk

discrimination in the whole population aged 30-99 years, but poor to good discrimination in important subgroups, including older patients and those with higher levels of multimorbidity. In contrast, calibration was poor. When evaluated without accounting for competing risk, QFracture-2012 consistently under-predicted both major osteoporotic fracture and hip fracture. The most likely explanation for this finding is that our method of determining the number of fractures in this study was more complete because fractures recorded during admission to hospital were included as well as those recorded in general practice electronic health records and death registrations. In this study, in women, only 14 802 (13.5%) major osteoporotic fractures and 6911 (19.0%) hip fractures were recorded in hospital admission data, compared with 6305 (18.4%) major osteoporotic fractures and 2515 (19.1%) hip fractures in men. Restricting determination of fractures to general practice and mortality data (to match the previously published internal[12] and external validation studies[9 28]), largely explains the higher observed incidence of hip fracture in this study, but only partially explains the observed incidence of major osteoporotic fracture (online supplemental tables S11–S14, online supplemental figure S1). Also, the earliest study entry year in our study was 2004 compared with 1998 in the QFracture-2012 derivation, and recording of fractures in general practice data is likely to have improved over time.

When evaluated against observed fractures, estimated accounting for competing risk of

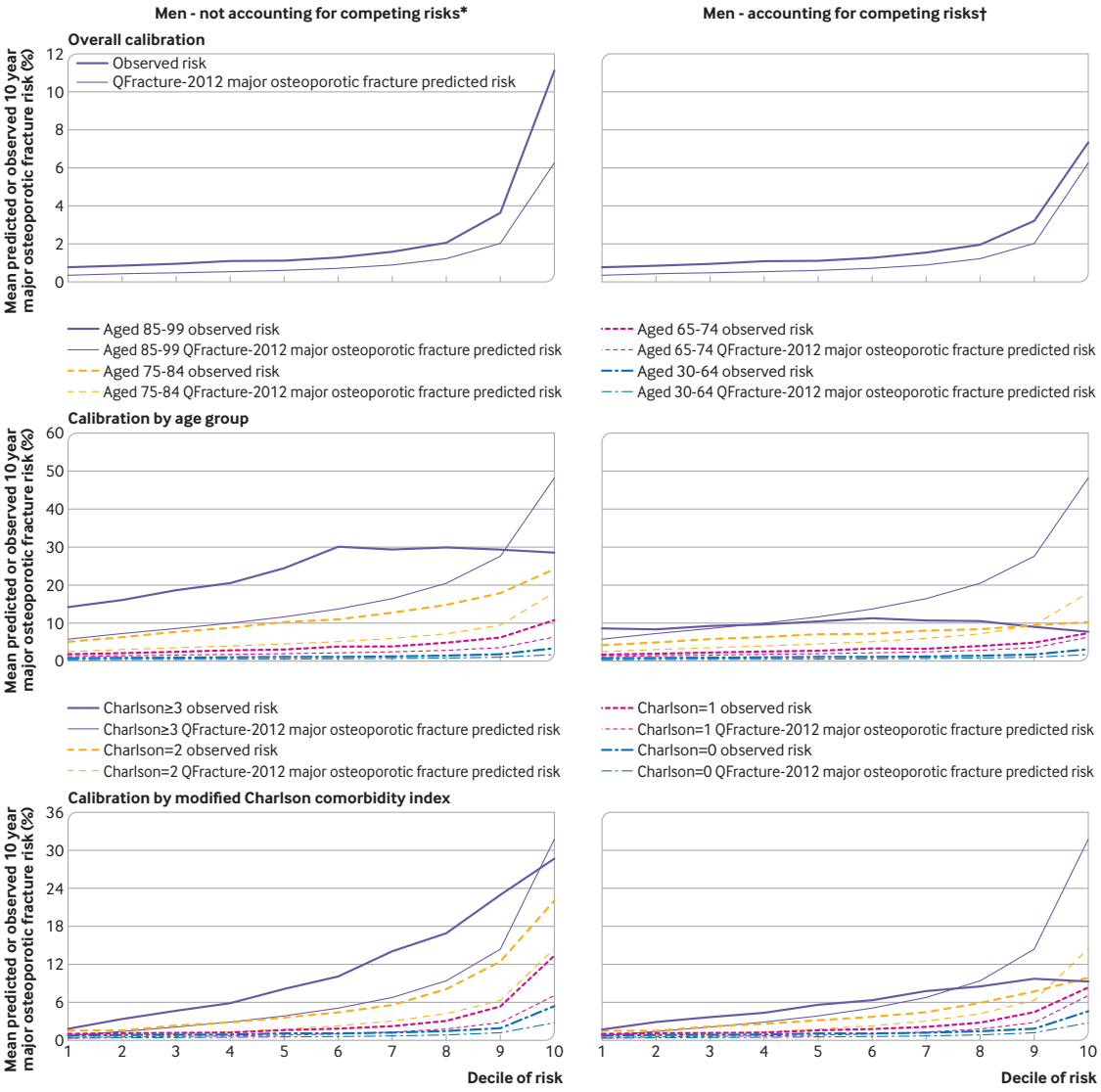


Figure 3 | Calibration for major osteoporotic fracture in men without accounting for competing risks and accounting for competing risks. For each pair, observed risk curve above predicted risk curve indicates under-prediction; observed risk curve below predicted risk curve indicates over-prediction. Separate plots for age and Charlson comorbidity index are shown in supplementary figures S3 and S5, respectively. *Observed risk based on Kaplan-Meier estimator, which does not account for competing mortality risk. †Observed risk based on Aalen-Johansen estimator, which accounts for competing mortality risk

mortality, under-prediction in general declined (because failing to account for competing risk causes over-prediction) but we found large over-prediction at higher levels of predicted risk in older people and in people with more complex multimorbidities. In people aged 85-99 years and in those with a Charlson comorbidity index of ≥3, observed risk was flat or even declining across deciles of increasing predicted risk. QFracture-2012 under-predicted in all patients because derivation was based on incomplete determination of fractures, and it over-predicted in people with a high competing risk of death (mainly elderly people and those with multiple comorbidities).

Strengths and limitations

The strengths of the study include the use of linked population data, the conduct of the study in accordance with methodology recommendations,[24 29] the codelists used all being published in the supplementary material to allow our findings to be replicated, the consideration of performance in important subgroups, and by accounting for competing risks of mortality. The high prevalence of missing data for some predictors was an important limitation, and a problem common to all studies that use routine data. Considering that QFracture used information recorded after participant study entry for some variables whereas we did not, more missing data for body mass index and smoking existed in this study

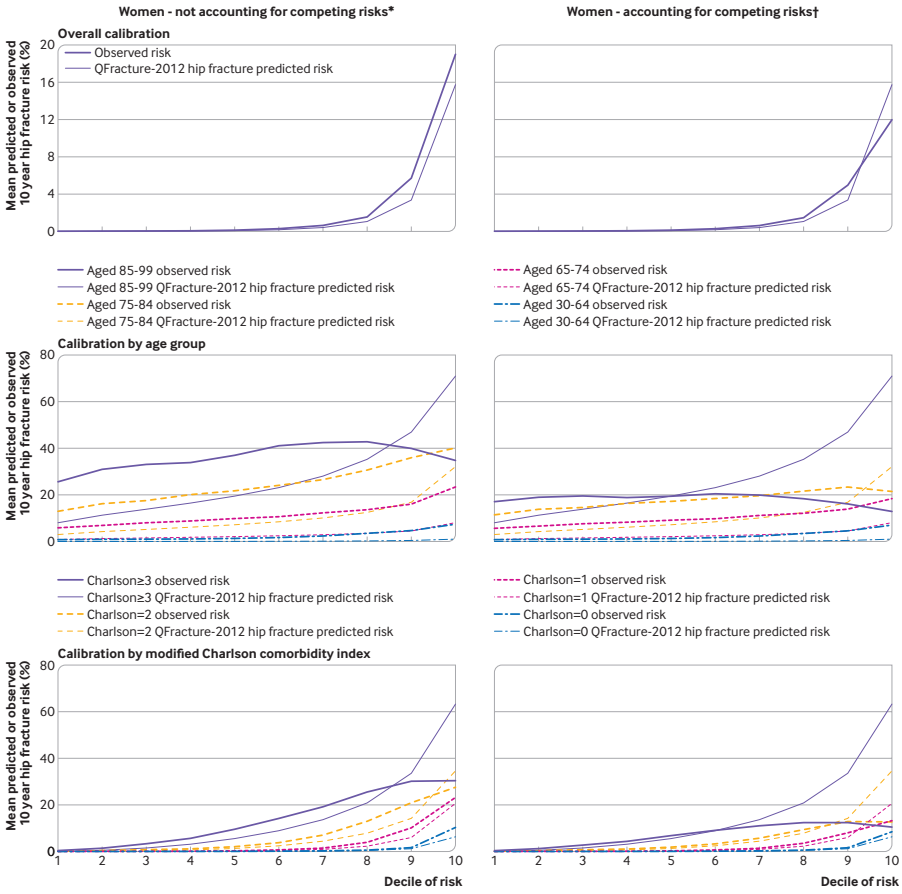


Figure 4 | Calibration for hip fracture in women without accounting for competing risks and accounting for competing risks. For each pair, observed risk curve above predicted risk curve indicates under-prediction; observed risk curve below predicted risk curve indicates over-prediction. Separate plots for age and Charlson comorbidity index are shown in supplementary figures S6 and S8, respectively. *Observed risk based on Kaplan-Meier estimator, which does not account for competing mortality risk. †Observed risk based on Aalen-Johansen estimator, which accounts for competing mortality risk

compared with the QFracture-2012 internal derivation, although missingness (ie, the extent of missing data) for alcohol status and ethnic group was similar (online supplemental table S6). We used multiple imputation based on the assumption that data are missing at random, which is likely reasonable for the imputed variables in this context. Also, censoring is common with a median follow-up of 5-6 years in this study, similar to others that have used these types of data,[9 15] including the QFracture-2012 derivation and validation studies.[8 9 12] Although we explicitly accounted for censoring because of death in this study, our analysis, similar to others that have used these types of data, still assumes that people who deregister from a Clinical Practice Research Datalink practice have the same risk of fracture as those who do not. This assumption is likely strong in older people where deregistration because they moved into care housing, or to a nursing home or care home, might be associated with a higher risk of fracture. Studies that can continue to follow up participants even if they move practice would allow this assumption to be examined, which is increasingly possible with the expansion of data linkage driven by the covid-19 pandemic.

A further limitation of our study was that humeral fractures in general practice data are often recorded without specifying whether the fracture was proximal or more distal. Therefore, we defined humeral fractures as proximal if the site was not specified, which might have caused some misclassifications (some false positives). In registry data, 80% of all humeral fractures are proximal,[30] however, and we judged that only including humeral fractures specified as proximal (as QFracture does) would have caused greater misclassification (many false negatives). We also included a wider range of wrist fractures (including distal ulnar fractures) in analysis than QFracture derivation (which only included radial fractures), because most ulnar fractures in registry data are not high-energy.[30] Some of the observed QFracture-2012 under-prediction may therefore be explained by differences in how fractures are defined. All choices of clinical codes therefore involve judgement about the likely balance of

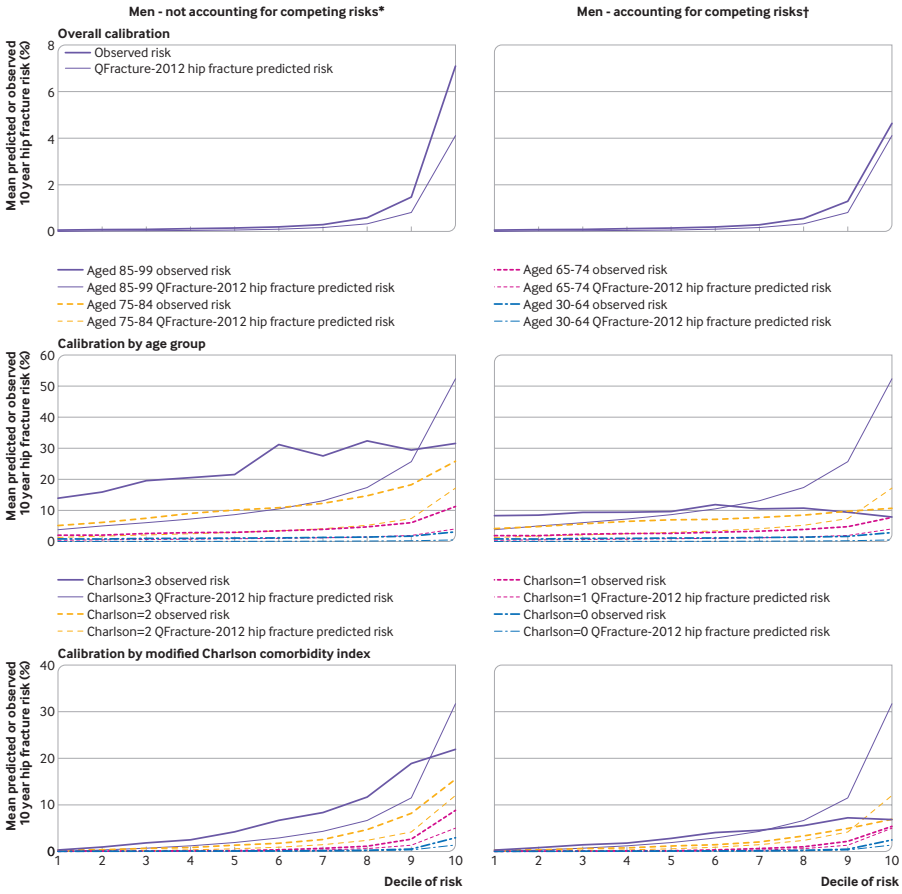


Figure 5 | Calibration for hip fracture in men without accounting for competing risks and accounting for competing risks. For each pair, observed risk curve above predicted risk curve indicates under-prediction; observed risk curve below predicted risk curve indicates over-prediction. Separate plots for age and Charlson comorbidity index are shown in supplementary figures S7 and S9, respectively. *Observed risk based on Kaplan-Meier estimator, which does not account for competing mortality risk. †Observed risk based on Aalen-Johansen estimator, which accounts for competing mortality risk

false positive and false negative, and readers can explicitly examine our choices in our codelists documented in the supplementary material). Like previous studies, we also could not validate our fractures against the gold standard of manually searching medical records, but our observed rates for hip fracture were similar to registry data.[30] Finally, the QFracture prediction tool does not include data on bone mineral density because these data are not routinely available, and also one of the guideline recommended uses of the tool is to identify those who would benefit from measurement of bone mineral density. Including bone mineral density in the prediction would be expected to improve predictive performance, but investigating this effect was outside the scope of our analysis.

Comparison with other literature

The first version of QFracture[8] was independently externally validated in a similar dataset to ours (The Health Improvement Network) and found to have excellent discrimination and calibration in the whole population.[9] The updated QFracture-2012 (evaluated in this study)[12] was externally validated in the Clinical Practice Research Datalink by the QFracture derivation team who found excellent discrimination and calibration in the whole population.[28] In this study, discrimination in the whole population for major osteoporotic fracture and hip fracture was similarly excellent. Given the large differences in the incidence of fractures across the age ranges studied, however, any prediction tool where the whole population includes people aged 30-99 years will have excellent discrimination.[31 32] When grouped by age, discrimination varied from poor to moderate (as expected when the most powerful predictor of fracture is partially removed by examining age subgroups).[31 32] Unlike these previously published validations in UK data,[8 9 12] calibration was poor.

This study differs from previously published validations of the original and QFracture-2012 models in two ways. Firstly, we also included fractures recorded during hospital admission (as well as those recorded in primary care electronic health records and in mortality data), and the primary care data were more

recent and therefore recording of fractures in the general practitioner record might also have improved. Better determination of fractures would be expected to result in under-prediction by QFracture-2012, as observed in this study. Consistent with this finding, an Israeli external validation based on community and hospital data for fractures also observed considerable under-prediction by QFracture.[7] Because the lists of Read codes used in QFracture-2012 are unpublished, however, we cannot examine the extent to which differences related to the choice of which fracture Read codes to include. Secondly, we examined calibration against observed outcomes estimated in the same way as previous external validations (with the Kaplan-Meier estimator, which does not account for competing mortality risk) and also accounting for competing risk (with the Aalen-Johansen estimator). As expected,[14 16 31] when accounting for competing risks, large changes in observed risk in older people and those with more multimorbidities were found where death from causes other than fractures is more common, consistent with over-prediction by QFracture-2012 in people with a high competing mortality risk (despite under-prediction in all patients because of incomplete determination of fracture in the QFracture-2012 derivation).

Implications for policy, practice, and research

QFracture and similar clinical prediction tools[28] including a wide age range typically have excellent discrimination, but that likely reflects that age is a powerful predictor of most outcomes.[31 32] As we found in this study, excellent discrimination in the whole population is compatible with poor discrimination and poor calibration in the subgroups most at risk of the outcome (older people and those with multiply morbidities). Examination of discrimination and calibration grouped by age (and other important predictors where applicable) provides a better indication of predictive performance from a clinical perspective. Future research could examine whether fracture prediction models that are more tailored to different age groups (including premenopausal and postmenopausal groups in women) provide better prediction (eg, osteoporosis might dominate the risk of fracture in younger people, whereas the risk of falls might be important in older people).

QFracture-2012 has two major problems. Firstly, this study and a previous external validation[7] in Israel found that it under-predicts risk in general, most likely because its derivation is based on incomplete determination of fractures. Under-prediction is likely at least partly addressed in the updated QFracture-2016 prediction model, which also ascertains fractures using both general practice and hospital admission data. QFracture-2016 is the version currently used by the UK's health service, and its algorithm was published in February 2023 (after this study was completed) on the QFracture website (https://qfracture.org/src.php). The performance of QFracture-2016 has not been externally validated in the whole population, but has been examined in people with chronic obstructive pulmonary disease where the area under the receiver operator characteristic curve was moderate to good for hip fracture (0.761) and poor for major osteoporotic fracture (0.614).[33] Hip fracture rates observed in QFracture-2016 derivation were very similar to rates in this study (for women, 2.31/1000 person years of follow-up with QFracture-2016 *v* 2.30/1000 in this study; for men, 0.86/1000 *v* 0.88/1000).[34] However, observed major osteoporotic fracture rates in QFracture-2016 derivation were still somewhat lower than in this study (for women, 5.27/1000 person years of follow-up with QFracture-2016 *v* 6.12/1000 in this study; for men, 1.92/1000 *v* 2.26/1000). This difference at least partly reflects that QFracture derivation includes fractures recorded since 1998 whereas this study only includes fractures recorded since 2004, and there is a lower incidence of non-hip fractures in 1998-2003 in QFracture derivation than in the later period (for women, 4.35/1000 person years in 1998-2003 *v* 5.69/1000 person years in 2004-15; for men, 1.40/1000 *v* 2.16/1000).[34]

Secondly, QFracture-2012 does not account for competing mortality risks that results in considerable over-prediction in people at high risk of death from other causes, notably older people and those with high level multimorbidities. Similar over-prediction has been observed in cardiovascular risk prediction models[15 35 36] but the effect is greater for prediction of the risk of fracture because death related to fractures is a smaller proportion of total mortality than cardiovascular disease. This problem could be resolved by derivation of new models that explicitly account for competing risk.

The FRAX fracture risk prediction tool is also recommended by NICE and accounts for competing risk of mortality, but systematic external validation is not possible because the prediction algorithm is not publicly available.[6 10] Dagan et al reported an external validation of FRAX from primary and secondary care Israeli data, and found similar levels of under-prediction to QFracture-2012 (although their analysis did not account for competing risk of mortality).[7] FRAX risk prediction was only approximately based on the number of clinical risk factors, however, rather than based on the actual FRAX risk equation because the FRAX prediction algorithm has never been made publicly available and therefore cannot be replicated. How FRAX accounts for competing risk of mortality and its performance in external validation is uncertain. Publication of the full algorithm would allow direct and fair comparison with other tools to identify the optimal tool for different contexts.[7]

Bisphosphonates are cost effective at relatively low thresholds of predicted risk[1] but misclassification

might occur with poor calibration. Consideration of the expected benefit for the individual is recommended in decision making, but aids to patient decision making usually rely on reasonably accurate prediction of individual risk.[37] From this perspective, determining risk with QFracture-2012 will underpredict the risk of fracture in younger people and in those with less multimorbidities (and therefore underestimate the expected benefit of treatment) and will over-predict the risk of fracture in older people and those with high levels of multimorbidities (and will therefore overestimate expected benefit of treatment). The updated QFracture-2016 tool likely corrects under-prediction of hip fracture by better ascertainment of fractures using hospital data as well as GP data (as used in this study), but could still under-predict major osteoporotic fracture because of lower recorded rates of such fractures in the late 1990s and early 2000s.

Prediction in elderly people requires specific attention, building on small existing studies of prediction in this population.[38] Updating the FRAX model, which accounts for competing mortality,[39] is planned, but publication of the prediction algorithm will be critical in establishing its external validity.[24]

Conclusion

This study found that QFracture-2012 under-predicts fracture risk in general because its derivation is based on incomplete determination of fractures, and considerably over-predicts in groups with a high risk of death from other causes because it does not account for competing mortality risk. Competing mortality risk is an important problem in the context of fracture prediction in older people because non-fracture death is much more common than the fracture outcomes being predicted. External validation of the QFracture-2016 prediction tool now used by the UK's health service is needed, including examining the impact of competing mortality.

AUTHOR AFFILIATIONS

[1]Population Health and Genomics Division, University of Dundee, Dundee, UK
[2]Centre for Population Health Sciences, University of Edinburgh, Edinburgh, UK
[3]Advanced Care Research Centre, University of Edinburgh, Edinburgh, UK

Correction notice This article has been corrected since it first published. See full Correction notice for details.

Acknowledgements This study is based in part on data from the Clinical Practice Research Datalink obtained under licence from the UK Medicines and Healthcare products Regulatory Agency. The data is provided by patients and collected by the NHS as part of their care and support. The interpretation and conclusions contained in this study are those of the authors alone. Linked data includes mortality data provided by Office for National Statistics data, but the interpretation and conclusions contained in this study are those of the authors alone. Hospital Episode Statistics and ONS data are copyright 2022, reused with the permission of The Health & Social Care Information Centre. All rights reserved.

Contributors The study was conceived of and designed by BG, DRM, and PD who obtained the funding. All authors contributed to study design and interpretation. SJL, CE, and MM led the data management and SJL led the analysis, supported in both by BG, DRM, and PD. SJL and BG drafted the paper, which all authors reviewed and edited. SJL, BG, MM, and DRM verified the underlying data. BG is the guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. Transparency: BG (the guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Funding This study and project is funded by the National Institute for Health Research (NIHR) Health Services and Delivery Research Programme (project reference 15/12/22). The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care. The study funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

Competing interests All authors have completed the ICMJE uniform disclosure form at www.icmje.org/disclosure-of-interest/ and declare: support from the National Institute for Health Research (NIHR) Health Services and Delivery Research Programme for the submitted work; BG reports funding from NIHR, Legal and General, Medical Research Council, and Chief Scientist Office unrelated to this study; CE is supported by a research grant from Legal and General (Advanced Care Research Centre) unrelated to this study; DRM is supported by a Wellcome Trust Clinical Research Development Fellowship (grant 214588/Z/18/Z) and reports funding from NIHR, Chief Scientist Office, and Tenovus, unrelated to this study; PTD reports funding from EU Health FP7 and Chief Scientist Office unrelated to this study; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethics approval The study was approved by the Clinical Practice Research Datalink Independent Scientific Advisory Committee, protocol 16_248.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available. The data controller is the Clinical Practice Research Datalink (CPRD), and under the data licence granted, the authors are not allowed to share data. Researchers can apply to CPRD directly for access to the raw data.

ORCID iD

Bruce Guthrie http://orcid.org/0000-0003-4191-4880

REFERENCES

1 National Institute for Health and Care Excellence. *Bisphosphonates for treating osteoporosis*. London, UK: National Institute for Health and Care Excellence, 2017: (accessed 17/10/22). www.nice.org.uk/guidance/ta464
2 National Institute for Health and Care Excellence. *Short clinical guideline CG146 - Osteoporosis: fragility fracture risk*. London:

National Institute for Health and Care Excellence, 2012: (accessed 17/10/22). www.nice.org.uk/Guidance/CG146
3 National Osteoporosis Guideline Group. *Osteoporosis: clinical guideline for prevention and treatment*. Sheffield: National Osteoporosis Guideline Group, 2014.
4 National Osteoporosis Guideline Group UK. *Clinical guideline for the prevention and treatment of osteoporosis*. National Osteoporosis Guideline Group UK, 2021: (accessed 17/10/22). www.nogg.org.uk/full-guideline
5 Cosman F, de Beur SJ, LeBoff MS, *et al*. Clinician's guide to prevention and treatment of osteoporosis. *Osteoporos Int* 2014;25:2359–81. doi:10.1007/s00198-014-2794-2
6 Marques A, Ferreira RJO, Santos E, *et al*. The accuracy of osteoporotic fracture risk prediction tools: a systematic review and meta-analysis. *Ann Rheum Dis* 2015;74:1958–67. doi:10.1136/annrheumdis-2015-207907
7 Dagan N, Cohen-Stavi C, Leventer-Roberts M, *et al*. External validation and comparison of three prediction tools for risk of osteoporotic fractures using data from population based electronic health records: retrospective cohort study. *BMJ* 2017;356:i6755. doi:10.1136/bmj.i6755
8 Hippisley-Cox J, Coupland C. Predicting risk of osteoporotic fracture in men and women in England and Wales: prospective derivation and validation of QFractureScores. *BMJ* 2009;339:b4229. doi:10.1136/bmj.b4229
9 Collins GS, Mallett S, Altman DG. Predicting risk of osteoporotic and hip fracture in the United Kingdom: prospective independent and external validation of QFractureScores. *BMJ* 2011;342:d3651. doi:10.1136/bmj.d3651
10 Kanis JA, Oden A, Johnell O, *et al*. The use of clinical risk factors enhances the performance of BMD in the prediction of hip and osteoporotic fractures in men and women. *Osteoporos Int* 2007;18:1033–46. doi:10.1007/s00198-007-0343-y
11 Hippisley-Cox J, Coupland C. *Validation of QFracture compared with FRAX: analysis prepared for NICE 2011*. Nottingham, UK: University of Nottingham, 2011: (accessed 17/10/22). https://qfracture.org/Validation-of-QFracture-vs-FRAX-for-NICE-2011.pdf
12 Hippisley-Cox J, Coupland C. Derivation and validation of updated QFracture algorithm to predict risk of osteoporotic fracture in primary care in the United Kingdom: prospective open cohort study. *BMJ* 2012;344:e3427. doi:10.1136/bmj.e3427
13 Kanis JA, Johnell O, Oden A, *et al*. FRAX and the assessment of fracture probability in men and women from the UK. *Osteoporos Int* 2008;19:385–97. doi:10.1007/s00198-007-0543-5
14 Andersen PK, Geskus RB, de Witte T, *et al*. Competing risks in epidemiology: possibilities and pitfalls. *Int J Epidemiol* 2012;41:861–70. doi:10.1093/ije/dyr213
15 Livingstone S, Morales DR, Donnan PT, *et al*. Effect of competing mortality risks on predictive performance of the QRISK3 cardiovascular risk prediction tool in older people and those with comorbidity: external validation population cohort study. *Lancet Healthy Longev* 2021;2:e352–61. doi:10.1016/S2666-7568(21)00088-X
16 Leslie WD, Lix LM, Wu X, *et al*. Competing mortality and fracture risk assessment. *Osteoporos Int* 2013;24:681–8. doi:10.1007/s00198-012-2051-5
17 Steyerberg E. *Clinical prediction models: a practical approach to development, validation, and updating*. New York: Springer, 2009.
18 Van Staa TP, Abenhaim L, Cooper C, *et al*. The use of a large pharmacoepidemiological database to study exposure to oral corticosteroids and risk of fractures: validation of study population and results. *Pharmacoepidemiol Drug Saf* 2000;9:359–66. doi:10.1002/1099-1557(200009/10)9:5<359::AID-PDS507>3.0.CO;2-E
19 Metcalfe D, Masters J, Delmestri A, *et al*. Coding algorithms for defining Charlson and Elixhauser co-morbidities in Read-coded databases. *BMC Med Res Methodol* 2019;19:115. doi:10.1186/s12874-019-0753-5
20 Buuren Svan, Groothuis-Oudshoorn K. mice : Multivariate Imputation by Chained Equations in *R. J Stat Softw* 2011;45:67. doi:10.18637/jss.v045.i03
21 Rubin D. *Multiple imputation for nonresponse in surveys*. New York: John Wiley and Sons, 1987.
22 Herrett E, Gallagher AM, Bhaskaran K, *et al*. Data resource profile: Clinical Practice Research Datalink (CPRD). *Int J Epidemiol* 2015;44:827–36. doi:10.1093/ije/dyv098
23 Herrett E, Thomas SL, Schoonen WM, *et al*. Validation and validity of diagnoses in the general practice research database: a systematic review. *Br J Clin Pharmacol* 2010;69:4–14. doi:10.1111/j.1365-2125.2009.03537.x
24 Collins GS, de Groot JA, Dutton S, *et al*. External validation of multivariable prediction models: a systematic review of methodological conduct and reporting. *BMC Med Res Methodol* 2014;14:40. doi:10.1186/1471-2288-14-40
25 Royston P, Sauerbrei W. A new measure of prognostic separation in survival data. *Stat Med* 2004;23:723–48. doi:10.1002/sim.1621
26 Altman DG, Vergouwe Y, Royston P, *et al*. Prognosis and prognostic research: validating a prognostic model. *BMJ* 2009;338:b605. doi:10.1136/bmj.b605
27 Putter H, Fiocco M, Geskus RB. Tutorial in biostatistics: competing risks and multi-state models. *Stat Med* 2007;26:2389–430. doi:10.1002/sim.2712
28 Hippisley-Cox J, Coupland C, Brindle P. The performance of seven QPrediction risk scores in an independent external sample of patients from general practice: a validation study. *BMJ Open* 2014;4:e005809. doi:10.1136/bmjopen-2014-005809
29 Collins GS, Reitsma JB, Altman DG, *et al*. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement. *BMJ* 2015;350:g7594. doi:10.1136/bmj.g7594
30 Bergh C, Wennergren D, Möller M, *et al*. Fracture incidence in adults in relation to age and gender: a study of 27,169 fractures in the Swedish fracture register in a well-defined catchment area. *PLoS One* 2020;15:e0244291. doi:10.1371/journal.pone.0244291
31 Kanis JA, Oden A, Johansson H, *et al*. Pitfalls in the external validation of FRAX. *Osteoporos Int* 2012;23:423–31. doi:10.1007/s00198-011-1846-0
32 Cook NR. Use and misuse of the receiver operating characteristic curve in risk prediction. *Circulation* 2007;115:928–35. doi:10.1161/CIRCULATIONAHA.106.672402
33 Akyea RK, McKeever TM, Gibson J, *et al*. Predicting fracture risk in patients with chronic obstructive pulmonary disease: a UK-based population-based cohort study. BMJ Open 2019;9:e024951. 10.1136/bmjopen-2018-024951
34 QResearch. QFracture 2016 Annual Update Information, Available: www.qresearch.org/media/qirhz3ti/qfracture-2016-annual-update-information.pdf
35 Koller MT, Leening MJG, Wolbers M, *et al*. Development and validation of a coronary risk prediction model for older U.S. and European persons in the cardiovascular health study and the Rotterdam study. *Ann Intern Med* 2012;157:389–97. doi:10.7326/0003-4819-157-6-201209180-00002
36 Wolbers M, Koller MT, Witteman JCM, *et al*. Prognostic models with competing risks: methods and application to coronary risk prediction. *Epidemiology* 2009;20:555–61. doi:10.1097/EDE.0b013e3181a39056
37 National Institute for Health and Care Excellence. *Bisphosphonates for treating osteoporosis: patient decision aid*. London, UK: National Institute for Health and Care Excellence, 2019. www.nice.org.uk/guidance/ta464/resources
38 Lam M-T, Sing C-W, Li GHY, *et al*. Development and validation of a risk score to predict the first hip fracture in the oldest old: a retrospective cohort study. *J Gerontol A Biol Sci Med Sci* 2020;75:980–6. doi:10.1093/gerona/glz178
39 Vandenput L, Johansson H, McCloskey EV, *et al*. Update of the fracture risk prediction tool FRAX: a systematic review of potential cohorts and analysis plan. *Osteoporos Int* 2022. doi:10.1007/s00198-022-06435-6. [Epub ahead of print: 31 May 2022].

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/bmjmed-2022-000316).

bmjmedicine

Check for updates

Correction: Effect of competing mortality risks on predictive performance of the QFracture risk prediction tool for major osteoporotic fracture and hip fracture: external validation cohort study in a UK primary care population

Cite this as: *BMJMED* 2023;2. doi:10.1136/bmjmed-2022-000316corr1

Linked

► http://dx.doi.org/10.1136/bmjmed-2022-000316

In the original publication by Livingstone and colleagues (*BMJMED* 2022;1:e000316. doi:10.1136/bmjmed-2022-000316, published 25 October 2022),[1] the methods stated that the QFracture model evaluated was QFracture-2016 but this is incorrect. The model evaluated in the paper was QFracture-2012, which is the model described in previous peer reviewed publications.[2 3] However, QFracture-2016 is the version available in the current online risk predictor provided by QResearch and automatically calculated in some clinical IT systems in UK general practices. The authors accessed the QFracture batch calculator via the QFracture-2016 webpage, and erroneously assumed that the calculator was for QFracture-2016. However, the batch calculator implemented QFracture-2012 not QFracture-2016 (the batch calculator instructions stated the version, so the error is the authors). The published analysis is valid as an external validation of QFracture-2012, but the implications for practice are somewhat different because QFracture-2016 has an important difference to QFracture-2012.

QFracture-2016 derivation and internal validation have not been published as peer reviewed papers but are briefly summarised on the QResearch website,[4] and QFracture-2016 has been externally validated in people with chronic obstructive pulmonary disease in the UK, finding poorer discrimination than in internal validation in the whole population.[5] The key difference is that QFracture-2016 uses both data recorded by general practitioners and those recorded at hospital discharge for fracture ascertainment, whereas QFracture-2012 only uses fractures recorded by general practitioners. Fracture ascertainment in QFracture-2016 is therefore the same as in the published external validation. The total hip fracture rates observed in QFracture-2016 derivation[4] are very similar to the observed hip fracture rates in the published article (for women, QFracture-2016 2.31/1000 person years of follow-up *v* 2.30/1000 in the external validation[1]; for men, 0.86/1000 *v* 0.88/1000). However, observed major osteoporotic fracture rates in QFracture-2016 derivation are still somewhat lower than those in the published article (for women, QFracture-2016 5.27/1000 person years of follow-up *v* 6.12/1000 in the external validation; for men, 1.92/1000 *v* 2.26/1000). This difference is likely at least partly explained by QFracture derivation using data from 1998 onwards whereas the paper's analysis used data from 2004 onwards (observed major osteoporotic fracture rates in QFracture-2016 are lower in the period 1998-2003 than in 2004–15; for women, 4.35 per 1000 person years in 1998–2003 *v* 5.69/1000 in 2004-15; for men, 1.40/1000 *v* 2.16/1000). Similar to the published external validation, the QFracture-2016 summary document also shows that QFracture-2012 under-predicts when outcomes are measured using both fractures recorded by general practitioners and at hospital. The observed under-prediction in the published article is therefore likely largely (hip fracture) or mostly (major osteoporotic fracture) corrected by the QFracture-2016 update, which is the version of the tool currently used in the UK.

There is a need to externally evaluate the QFracture-2016 model and (if possible) the FRAX (fracture risk assessment tool) model.

The main text has been changed to state the correct (QFracture-2012) version throughout, except where statements are made that refer to all three versions of the QFracture model (eg, in terms of not accounting for competing mortality). The abstract and discussion, conclusion, and what this study adds sections have been amended to reflect the implications of the differences between the 2012 and 2016 versions of QFracture.

REFERENCES

1 Livingstone SJ, Morales DR, McMinn M, *et al*. Effect of competing mortality risks on predictive performance of the qfracture risk prediction tool for major osteoporotic fracture and hip fracture: external validation cohort study in a UK primary care population. BMJMED 2022;1:e000316. 10.1136/bmjmed-2022-000316
2 Hippisley-Cox J, Coupland C. Derivation and validation of updated QFracture algorithm to predict risk of osteoporotic fracture in primary care in the United Kingdom: prospective open cohort study. BMJ 2012;344:e3427. 10.1136/bmj.e3427
3 Hippisley-Cox J, Coupland C, Brindle P. The performance of seven qprediction risk scores in an independent external sample of patients from general practice: a validation study. BMJ Open 2014;4:e005809. 10.1136/bmjopen-2014-005809
4 ClinRisk. QFracture® 2016 annual update information. Nottingham: Clin Risk, 2016. Available: https://www.qresearch.org/media/qirhz3ti/qfracture-2016-annual-update-information.pdf
5 Akyea RK, McKeever TM, Gibson J, *et al*. Predicting fracture risk in patients with chronic obstructive pulmonary disease: a UK-based population-based cohort study. BMJ Open 2019;9:e024951. 10.1136/bmjopen-2018-024951

Impact of competing mortality risks on predictive performance of the QFracture risk prediction tool for major osteoporotic fracture and hip fracture: external validation cohort study in a UK primary care population

Supplementary file

Table S1: Read codes defining major osteoporotic fracture including hip fracture

Fracture type	CPRD Medcode	Read Code	Read Code description
Hip	2225	S30..00	Fracture of neck of femur
Hip	1994	S30..11	Hip fracture
Hip	38489	S300.00	Closed fracture proximal femur, transcervical
Hip	39984	S300000	Cls # prox femur, intracapsular section, unspecified
Hip	69919	S300100	Closed fracture proximal femur, transepiphyseal
Hip	65690	S300200	Closed fracture proximal femur, midcervical section
Hip	52194	S300300	Closed fracture proximal femur, basicervical
Hip	51861	S300311	Closed fracture, base of neck of femur
Hip	36391	S300400	Closed fracture head of femur
Hip	17019	S300500	Cls # prox femur, subcapital, Garden grade unspec.
Hip	34351	S300600	Closed fracture proximal femur, subcapital, Garden grade I
Hip	33957	S300700	Closed fracture proximal femur, subcapital, Garden grade II
Hip	36599	S300800	Closed fracture proximal femur, subcapital, Garden grade III
Hip	34078	S300900	Closed fracture proximal femur, subcapital, Garden grade IV
Hip	49209	S300y00	Closed fracture proximal femur, other transcervical
Hip	68229	S300y11	Closed fracture of femur, subcapital
Hip	62966	S300z00	Closed fracture proximal femur, transcervical, NOS
Hip	5301	S302.00	Closed fracture of proximal femur, pertrochanteric
Hip	19117	S302000	Cls # proximal femur, trochanteric section, unspecified
Hip	19387	S302011	Closed fracture of femur, greater trochanter
Hip	48337	S302012	Closed fracture of femur, lesser trochanter
Hip	45141	S302100	Closed fracture proximal femur, intertrochanteric, two part
Hip	29145	S302200	Closed fracture proximal femur, subtrochanteric
Hip	51216	S302300	Cls # proximal femur, intertrochanteric, comminuted
Hip	8648	S302400	Closed fracture of femur, intertrochanteric
Hip	44735	S302z00	Cls # of proximal femur, pertrochanteric section, NOS
Hip	28965	S304.00	Pertrochanteric fracture
Hip	8243	S305.00	Subtrochanteric fracture
Hip	24276	S30w.00	Closed fracture of unspecified proximal femur
Hip	18273	S30y.00	Closed fracture of neck of femur NOS
Hip	10570	S30y.11	Hip fracture NOS
Hip	37662	S310000	Closed fracture of femur, unspecified part
Hip	520	S31z.00	Fracture of femur, NOS
Distal radius/ulna	5951	7K1LM00	Closed reduction of fracture of wrist
Distal radius/ulna	18299	S234.00	Closed fracture of radius and ulna, lower end
Distal radius/ulna	203	S234.11	Wrist fracture - closed
Distal radius/ulna	18389	S234000	Closed fracture of forearm, lower end, unspecified
Distal radius/ulna	343	S234100	Closed Colles' fracture
Distal radius/ulna	52389	S234111	Smith's fracture - closed
Distal radius/ulna	1742	S234200	Closed fracture of the distal radius, unspecified
Distal radius/ulna	28708	S234600	Closed fracture radius and ulna, distal
Distal radius/ulna	2862	S234700	Closed Smith's fracture

Distal radius/ulna	40268	S234800	Closed Galeazzi fracture
Distal radius/ulna	11066	S234900	Closed volar Barton's fracture
Distal radius/ulna	53689	S234911	Closed volar Barton's fracture-dislocation
Distal radius/ulna	65636	S234912	Closed volar Barton fracture-subluxation
Distal radius/ulna	50053	S234A00	Closd dorsal Barton's fracture
Distal radius/ulna	57736	S234A11	Closed dorsal Barton's fracture-dislocation
Distal radius/ulna	107741	S234A12	Closed dorsal Barton fracture-subluxation
Distal radius/ulna	44844	S234C00	Closed fracture distal radius, intra-articular, die-punch
Distal radius/ulna	19058	S234D00	Closed fracture distal radius, extra-articular, other type
Distal radius/ulna	28293	S234E00	Closed fracture distal radius, intra-articular, other type
Distal radius/ulna	10033	S234F00	Closed Barton's fracture
Distal radius/ulna	102302	S234G00	Greenstick fracture of distal radius
Distal radius/ulna	27591	S234z00	Closed fracture of forearm, lower end, NOS
Distal radius/ulna	199	S23B.00	Fracture of lower end of radius
Distal radius/ulna	6213	S23C.00	Fracture of lower end of both ulna and radius
Distal radius/ulna	50654	S23x000	Closed fracture of forearm, unspecified
Distal radius/ulna	17952	S23x100	Closed fracture of radius (alone), unspecified
Distal radius/ulna	137	S23x111	Fracture of radius NOS
Distal radius/ulna	17922	S4C0000	Closed fracture-dislocation distal radio-ulnar joint
Distal radius/ulna	38408	S4C0100	Closed fracture-dislocation radiocarpal joint
Distal radius/ulna	44652	S4C2000	Closed fracture-subluxation, distal radio-ulnar jt
Distal radius/ulna	50148	S4C2100	Closed fracture-subluxation radiocarpal joint
Proximal humerus	6379	7K1LF00	Closed reduction of fracture of humerus
Proximal humerus	517	S22..00	Fracture of humerus
Proximal humerus	11222	S220.00	Closed fracture of the proximal humerus
Proximal humerus	44721	S220000	Closed fracture of proximal humerus, unspecified part
Proximal humerus	11313	S220100	Closed fracture proximal humerus, neck
Proximal humerus	33489	S220200	Closed fracture of proximal humerus, anatomical neck
Proximal humerus	11044	S220300	Closed fracture proximal humerus, greater tuberosity
Proximal humerus	28739	S220400	Closed fracture proximal humerus, head
Proximal humerus	52406	S220500	Closed fracture of humerus, upper epiphysis
Proximal humerus	40330	S220600	Closed fracture proximal humerus, three part
Proximal humerus	29137	S220700	Closed fracture proximal humerus, four part
Proximal humerus	38353	S220z00	Closed fracture of proximal humerus not otherwise specified
Proximal humerus	19186	S222000	Closed fracture of humerus NOS
Proximal humerus	2101	S226.00	Fracture of upper end of humerus
Proximal humerus	10382	S22z.00	Fracture of humerus NOS
Vertebral	16895	N1y1.00	Fatigue fracture of vertebra
Vertebral	44386	N331.14	Osteoporotic vertebral collapse
Vertebral	15837	N331011	Collapse of thoracic vertebra
Vertebral	17377	N331800	Osteoporosis + pathological fracture lumbar vertebrae
Vertebral	12673	N331900	Osteoporosis + pathological fracture thoracic vertebrae
Vertebral	48772	N331A00	Osteoporosis + pathological fracture cervical vertebrae
Vertebral	9319	N331F00	Collapse of thoracic vertebra
Vertebral	45736	N331H00	Collapse of cervical vertebra due to osteoporosis
Vertebral	5841	N331J00	Collapse of lumbar vertebra due to osteoporosis

Vertebral	19048	N331K00	Collapse of thoracic vertebra due to osteoporosis
Vertebral	4013	N331L00	Collapse of vertebra due to osteoporosis NOS
Vertebral	53337	S100H00	Closed fracture cervical vertebra, wedge
Vertebral	27404	S102.00	Closed fracture thoracic vertebra
Vertebral	28524	S102100	Closed fracture thoracic vertebra, wedge
Vertebral	8266	S104100	Closed fracture lumbar vertebra, wedge
Vertebral	5381	S15..00	Fracture of thoracic vertebra

Table S2: ICD-10 codes defining major osteoporotic fractures causing hospital admission

Fracture type	**ICD10-code**	**ICD-10 Code description**
Hip	S72.0	Fracture of neck of femur
Hip	S72.1	Pertrochanteric fracture
Hip	S72.2	Subtrochanteric fracture
Distal radius/ulna	S52.5	Fracture of lower end of radius
Distal radius/ulna	S52.6	Fracture of lower end of both ulna and radius
Proximal humerus	S42.2	Fracture of upper end of humerus
Vertebral	M48.5	Collapsed vertebra, not elsewhere classified
Osteoporotic	M80.0	Postmenopausal osteoporosis with pathological fracture
Osteoporotic	M80.1	Postoophorectomy osteoporosis with pathological fracture
Osteoporotic	M80.3	Postsurgical malabsorption osteoporosis with pathological fracture
Osteoporotic	M80.5	Idiopathic osteoporosis with pathological fracture
Osteoporotic	M80.8	Other osteoporosis with pathological fracture
Osteoporotic	M80.9	Unspecified osteoporosis with pathological fracture

Table S3: Definitions of morbidity predictors for QFracture algorithm

Morbidity	**How defined**
Type 1 and type 2 diabetes	As defined for GP data in Kuan *et al* (2019)[1]
Parental history of osteoporosis/hip fracture	Bespoke codeset (table SX)
Care home resident	Bespoke codeset (table SX)
Previous fracture	As per fracture outcomes (table SX) plus bespoke codeset for 'history of' codes (table SX)
History of falls	Bespoke codeset (table SX)
Dementia	As defined for GP data in Kuan *et al* (2019)[1]
Cancer	As defined for GP data in Kuan *et al* (2019)[1]
Asthma or COPD	As defined for GP data in Kuan *et al* (2019)[1]
Heart attack, angina, stroke or TIA	CVD outcomes in GP data defined in supplementary file at Livingstone *et al* (2021)[2]
Chronic liver disease	As defined for GP data in Kuan *et al* (2019)[1]
Chronic kidney disease	As defined for GP data in Kuan *et al* (2019)[1]
Parkinson's Disease	As defined for GP data in Kuan *et al* (2019)[1]
Rheumatoid arthritis or SLE	As defined in GP data in Kuan *et al* (2019)[1]
Malabsorption[a]	Crohn's Disease, ulcerative colitis and coeliac disease as defined for GP data in Kuan *et al* (2019)[1]; malabsorption, steatorrhoea or blind loop syndrome bespoke codeset (table SX)
Endocrine problems[b]	Hyperparathyroidism as defined for GP data in Kuan *et al* (2019)[1], thyrotoxicosis and Cushing syndrome bespoke codeset (table SX)
Epilepsy	As defined for GP data in Kuan *et al* (2019)[1]

a. Crohn's disease, ulcerative colitis, coeliac disease, steatorrhoea or blind loop syndrome

b. Thyrotoxicosis, hyperparathyroidism, Cushing syndrome

Table S4: Read codes defining morbidity predictors (codesets created for this study)

Morbidity	**CPRD Medcode**	**Read Code**	**Read Code description**
Parental history of osteoporosis or hip fracture	11218	1268.00	FH: Osteoporosis
Family history of osteoporosis or hip fracture	51427	12I6.00	FH: Fragility fracture
Family history of osteoporosis or hip fracture	37204	12I4.00	FH: Maternal hip fracture
Family history of osteoporosis or hip fracture	42319	12I5.00	FH: Hip fracture in first degree relative
Family history of osteoporosis or hip fracture	43219	12I8.00	FH: maternal hip fracture before age 75
Care home resident	13359	13F6100	Lives in a nursing home
Care home resident	7653	9N1G.00	Seen in nursing home
Care home resident	24956	13FK.00	Lives in a residential home
Care home resident	13360	13F6.00	Nursing/other home
Care home resident	49681	13FX.00	Lives in care home
Care home resident	27968	13F7.00	Residential institution
Care home resident	13361	13F4.11	Lives in warden controlled accommodation
Care home resident	30807	13F4000	Resident in sheltered accommodation
Care home resident	98592	8Ce4.00	Preferred place of care - nursing home
Care home resident	6859	9N1F.00	Seen in warden sup home
Care home resident	93998	9b0i.00	Residential home visit note
Care home resident	10993	ZLG4.00	Discharge to nursing home
Care home resident	101003	9NFR.00	Home visit request by residential institution
Care home resident	28773	ZV60700	[V]Sheltered housing
Care home resident	100080	8Ce5.00	Preferred place of care - residential home
Care home resident	7101	9N1F.12	Seen in old people's home
Care home resident	59653	6991.00	Geriatric home admission exam.
Care home resident	73321	9b1P.00	Nursing home
Care home resident	102493	8Ht..00	Admission to nursing home
Care home resident	107443	9NFW000	Care home visit for initial patient assessment
Care home resident	35187	9N1D.00	Seen in warden sup house
Care home resident	35172	9N1E.00	Seen in warden sup flat
Care home resident	34794	13F9.11	Living in sheltered accomodatn
Care home resident	21280	13F5200	Resident in part III accomodation
Care home resident	107602	9NFW100	Care home visit for follow-up patient review
Care home resident	42191	ZLG3.00	Discharge to residential home
Care home resident	24828	Z177F00	Nursing home care
Care home resident	73083	9b0Y.00	Nursing home visit note
Care home resident	94070	8O24.00	Provision of continuing care in nursing home
Care home resident	107757	9NFW.00	Care home visit
Care home resident	59548	13FT.00	Lives in an old peoples home
Care home resident	102598	8Hs..00	Discharge to nursing home
Care home resident	27936	8HE6.00	Delayed discharge to nursing home
Care home resident	24816	Z177C00	Residential care
Care home resident	50792	9N1F.11	Seen in Part 3 accomodation

Care home resident	36096	13F5.11	Part 3 accomodation
Care home resident	6991	9493.00	Patient died in nursing home
Care home resident	43915	ZLG4100	Discharge to private nursing home
Care home resident	49138	ZV63212	[V]Delayed discharge - nursing home vacancy awaited
Care home resident	27360	13F5100	Part III accomodation arranged
Care home resident	98758	13Zo.00	Previously lived in care home
Care home resident	36905	ZLG5100	Discharge to warden controlled accommodation
Care home resident	35040	ZLG5.00	Discharge to sheltered housing
Care home resident	102230	M270100	Nursing home acquired pressure ulcer
Care home resident	48549	ZLG3100	Discharge to private residential home
Care home resident	95795	923O.00	FP22 - removal from residential institute
Care home resident	67903	U105100	[X]Fall involvng wheelchair occurrence residential instit'n
Care home resident	46642	9b79.00	Other residential care homes managed by local authority
Care home resident	66122	13F5111	Part 3 accommodation arranged
Care home resident	99148	9b7A.00	Other residential care home man voluntary/private agents
Care home resident	96836	ZK76.00	Temporary home care service provision
History of fracture[a]	17936	14G7.00	H/O: hip fracture
History of fracture[a]	18731	14G6.00	H/O: fragility fracture
History of fracture[a]	19235	14G8.00	H/O: vertebral fracture
History of falls	384	TC...11	Fall - accidental
History of falls	6815	TC...00	Accidental falls
History of falls	6008	16D..00	Falls
History of falls	4859	R200.12	[D] Geriatric fall
History of falls	6835	TCz..00	Accidental falls NOS
History of falls	8694	16D1.00	Recurrent falls
History of falls	8730	TCy..00	Other falls
History of falls	15112	TC5..00	Fall on same level from slipping, tripping or stumbling
History of falls	11307	TC0..00	Fall on or from stairs or steps
History of falls	11308	TCyz.00	Other accidental fall NOS
History of falls	17167	TC01.00	Fall on or from stairs
History of falls	11709	TC51.00	Fall on same level from tripping
History of falls	33887	TC4..00	Other fall from one level to another
History of falls	17728	TC01000	Fall on stairs
History of falls	108062	16D6.00	Fall
History of falls	18007	TC50.00	Fall on same level from slipping
History of falls	21081	TC01100	Fall from stairs
History of falls	26432	TC42100	Fall from bed
History of falls	7948	TC52.00	Fall on same level from stumbling
History of falls	33529	TC5z.00	Fall on same level from slipping
History of falls	98223	16D5.00	Fall onto outstretched hand
History of falls	41909	TC01z00	Fall on or from stairs NOS
History of falls	43092	TC02000	Fall on steps
History of falls	43571	TC3..00	Fall into hole or other opening in surface
History of falls	21306	TC4z.00	Fall from one level to another NOS

History of falls	53082	TC02100	Fall from steps
History of falls	44626	TC02.00	Fall on or from steps
History of falls	38818	TC42000	Fall from chair
History of falls	64696	TC0z.00	Fall on or from stairs or steps NOS
History of falls	7876	TC4yz00	Other fall from one level to another NOS
History of falls	41853	TC4y.00	Other fall from one level to another
History of falls	69020	TC4y200	Fall from stationary vehicle
History of falls	93574	8O9..00	Provision of telecare community alarm service
History of falls	53463	TC00.00	Fall on or from escalator
History of falls	56316	TC00000	Fall on escalator
History of falls	64722	TC02z00	Fall on or from steps NOS
History of falls	59404	TC42.00	Fall from chair or bed
History of falls	29568	TC3yz00	Fall into other hole
History of falls	55743	67ID.00	Falls advice - hip protectors advised
History of falls	48309	67IE.00	Falls advice - hip protectors supplied
History of falls	44119	8BIG.00	Falls caused by medication
History of falls	109088	9Nlf.00	Seen by community falls team
History of falls	16684	T04..00	Fall in
History of falls	58753	T040.00	Fall in train
History of falls	94933	T040100	Fall in train
History of falls	59911	T041.00	Fall on train
History of falls	97335	T04z.00	Fall in
History of falls	18097	T170.00	MVTA - fall down stairs of motor bus while board/alighting
History of falls	41114	T171.00	MVTA - fall from car in street while boarding/alighting
History of falls	60782	T53..00	Fall in
History of falls	110413	T53z.00	Fall in
History of falls	60003	TC42z00	Fall from chair or bed NOS
History of falls	17638	TH03.00	Late effects of accidental fall
History of falls	7970	U10..00	[X]Falls
History of falls	21903	U100.00	[X]Fall on same level involving ice and snow
History of falls	68559	U100000	[X]Fall on same level involving ice and snow occurrn home
History of falls	63515	U100200	[X]Fall sam lvl inv ice/snw occ sch oth inst/pub admin area
History of falls	43615	U100300	[X]Fall same levl involv ice/snow
History of falls	60427	U100400	[X]Fall same levl inv ice and snow
History of falls	93148	U100500	[X]Fall same levl inv ice / snow
History of falls	71613	U100z00	[X]Fall same levl inv ice / snow
History of falls	29821	U101.00	[X]Fall on same level from slipping
History of falls	49035	U101000	[X]Fall same levl frm slip trip + stumb
History of falls	49210	U101100	[X]Fall same level from slip trip + stumb occ resid instit
History of falls	60424	U101200	[X]Fall sme levl slp trp+stmb occ sch
History of falls	49100	U101300	[X]Fall sme levl frm slip trip+stumb
History of falls	52452	U101400	[X]Fall same level from slip trip+stumb
History of falls	68616	U101500	[X]Fall sme lvl frm slip trip+stumb
History of falls	68895	U101600	[X]Fall same levl

History of falls	61705	U101700	[X]Fall same level from slip trip+stumbling
History of falls	49218	U101y00	[X]Fall same level
History of falls	68579	U101z00	[X]Fall same levl frm slip trip+stumbling
History of falls	111606	U102200	[X]Fall
History of falls	66934	U103000	[X]Oth fall same levl
History of falls	109428	U103500	[X]Oth fall sme levl coll/push anth pers occ trad/serv area
History of falls	62109	U103y00	[X]Oth fall sme levl coll/push anoth per occ oth spec place
History of falls	93454	U103z00	[X]Oth fall same levl coll/push anoth pers occ unspec place
History of falls	67230	U104.00	[X]Fall while being carried or supported by other persons
History of falls	52410	U104000	[X]Fall while carried/supported by other persons
History of falls	51851	U104100	[X]Fall whle carried/supported oth persons occ resid instit
History of falls	110968	U104z00	[X]Fall whle carr'd/supportd by oth per
History of falls	21349	U105.00	[X]Fall involving wheelchair
History of falls	98315	U105000	[X]Fall involving wheelchair
History of falls	67903	U105100	[X]Fall involvng wheelchair occurrence residential instit'n
History of falls	85959	U105500	[X]Fall involvng wheelchair occurrnce at trade/service area
History of falls	98713	U105700	[X]Fall involving wheelchair
History of falls	109423	U105y00	[X]Fall involv wheelchair
History of falls	52374	U106.00	[X]Fall involving bed
History of falls	44419	U106000	[X]Fall involving bed
History of falls	69762	U106100	[X]Fall involving bed occurrence in residential institution
History of falls	50572	U107.00	[X]Fall involving chair
History of falls	68600	U107000	[X]Fall involving chair
History of falls	68617	U107z00	[X]Fall involving chair
History of falls	55553	U108.00	[X]Fall involving other furniture
History of falls	68591	U108000	[X]Fall involving other furniture
History of falls	66922	U108100	[X]Fall involv other furniture occurrn resident institut'n
History of falls	36402	U10A.00	[X]Fall on and from stairs and steps
History of falls	52432	U10A000	[X]Fall on and from stairs and steps
History of falls	52466	U10A100	[X]Fall on + from stair + step occurrnce resident instit'n
History of falls	111571	U10A200	[X]Fall on + frm stair + step occ sch oth inst/pub adm area
History of falls	99385	U10A400	[X]Fall on + from stairs + steps occurrn on street/highway
History of falls	51284	U10A500	[X]Fall on + from stair + step occurrn at trade/servce area
History of falls	41105	U10A511	[X]Fall on or from escalator
History of falls	68613	U10Ay00	[X]Fall on + from stair + step occurrn at oth specif place
History of falls	64193	U10Az00	[X]Fall on + from stair + step occurrnce at unspecif place
History of falls	50316	U10D.00	[X]Fall from
History of falls	52380	U10D000	[X]Fall from out of/through building/structur occurn home
History of falls	100710	U10D100	[X]Fall from out of/thro buildng/struct occ resid instit'n

History of falls	110898	U10D400	[X]Fall from out/thro buildng/struct occ on street/highway
History of falls	92721	U10H.00	[X]Other fall from one level to another
History of falls	51669	U10H000	[X]Other fall from one level to another
History of falls	68609	U10H200	[X]Othr fall frm one level to anothr
History of falls	68562	U10H400	[X]Othr fall from one level to anothr occurrn street/h'way
History of falls	68604	U10H500	[X]Other fall frm one level to anothr occ at trde/serv area
History of falls	95961	U10H600	[X]Other fall frm one level to anoth occ indust/constr area
History of falls	72468	U10Hy00	[X]Other fall frm one levl to anothr occ at oth specif plce
History of falls	49233	U10Hz00	[X]Othr fall frm one level to anothr occurrn at unspec plce
History of falls	48496	U10J.00	[X]Other fall on same level
History of falls	43191	U10J000	[X]Other fall on same level
History of falls	72474	U10J100	[X]Other fall on same level
History of falls	100060	U10J200	[X]Other fall on same levl occ schl oth inst/pub admin area
History of falls	101254	U10J400	[X]Other fall on same level
History of falls	68608	U10J600	[X]Other fall on same levl
History of falls	101523	U10Jy00	[X]Other fall on same level occurrn at oth specified place
History of falls	98876	U10Jz00	[X]Other fall on same level occurrence at unspecified place
History of falls	24776	U10z.00	[X]Unspecified fall
History of falls	10419	U10z000	[X]Unspecified fall
History of falls	46303	U10z100	[X]Unspecified fall
History of falls	55202	U10z300	[X]Unspecified fall
History of falls	97327	U10z400	[X]Unspecified fall
History of falls	106900	U10z700	[X]Unspecified fall
History of falls	96546	U10zy00	[X]Unspecified fall
History of falls	61170	U10zz00	[X]Unspecified fall
History of falls	6785	ZV71B00	[V]Examination and observation following a fall
Malabsorption[b]	9355	J69..00	Intestinal malabsorption
Malabsorption[b]	5088	J69yz00	Other gastrointestinal tract malabsorption NOS
Malabsorption[b]	4787	J690.15	Steatorrhea - idiopathic
Malabsorption[b]	6663	J69y.00	Other intestinal malabsorption
Malabsorption[b]	42715	J69z.00	Intestinal malabsorption NOS
Malabsorption[b]	23498	J692.00	Blind loop syndrome
Malabsorption[b]	31392	J69y600	Intestinal malabsorption of fat
Malabsorption[b]	2482	D011100	Vit B12 defic anaemia due to malabsorption with proteinuria
Malabsorption[b]	19441	C285.00	Adult osteomalacia due to malabsorption
Malabsorption[b]	37440	J693.11	Postsurgical malabsorption - other
Malabsorption[b]	49191	J69y200	Intestinal malabsorption of protein
Malabsorption[b]	55481	D012300	Folate-deficiency anaemia due to malabsorption
Malabsorption[b]	72529	Jyu9000	[X]Other intestinal malabsorption
Malabsorption[b]	57647	J693100	Post gastrointestinal tract surgery malnutrition
Malabsorption[b]	49739	J69y300	Intestinal malabsorption of carbohydrate

Malabsorption[b]	93655	N330700	Postsurgical malabsorption osteoporosis
Endocrine problems[c]	1472	C02..11	Hyperthyroidism
Endocrine problems[c]	5257	C020.12	Graves' disease
Endocrine problems[c]	6245	1431.00	H/O: hyperthyroidism
Endocrine problems[c]	3857	C052.11	Autoimmune thyroiditis
Endocrine problems[c]	17604	C150.00	Cushing's syndrome
Endocrine problems[c]	11947	L181500	Postpartum thyroiditis
Endocrine problems[c]	30799	C051.00	Subacute thyroiditis
Endocrine problems[c]	4898	C050.00	Acute thyroiditis
Endocrine problems[c]	18382	C150111	Drug-induced Cushings syndrome
Endocrine problems[c]	26362	212P.00	Hyperthyroidism resolved
Endocrine problems[c]	106640	C025.00	Subclinical hyperthyroidism
Endocrine problems[c]	21747	C051.11	De Quervain's thyroiditis
Endocrine problems[c]	20275	C150100	Iatrogenic Cushing's syndrome
Endocrine problems[c]	60534	C150z00	Cushing's syndrome NOS
Endocrine problems[c]	49508	C024.00	Thyrotoxicosis from ectopic thyroid nodule
Endocrine problems[c]	68626	FyuBD00	[X]Dysthyroid exophthalmos
Endocrine problems[c]	42323	C050z00	Acute thyroiditis NOS
Endocrine problems[c]	53682	C150200	Pituitary dependent Cushing's syndrome
Endocrine problems[c]	65444	C05y.00	Other and unspecified chronic thyroiditis
Endocrine problems[c]	61026	C054.00	Iatrogenic thyroiditis
Endocrine problems[c]	53667	C053.11	Riedel's thyroiditis
Endocrine problems[c]	65907	C05y400	Chronic thyroiditis with transient thyrotoxicosis
Endocrine problems[c]	65754	C150500	Alcohol-induced pseudo-Cushing's syndrome
Endocrine problems[c]	67972	C050000	Acute nonsuppurative thyroiditis
Endocrine problems[c]	65120	C150300	Ectopic ACTH secretion causing Cushing's syndrome
Endocrine problems[c]	60690	F395100	Myopathy due to Cushing's syndrome
Endocrine problems[c]	70967	C150000	Idiopathic Cushing's syndrome
Endocrine problems[c]	56270	C024z00	Thyrotoxicosis from ectopic thyroid nodule NOS
Endocrine problems[c]	70773	C050100	Acute suppurative thyroiditis
Endocrine problems[c]	95807	Cyu4500	[X]Other Cushing's syndrome
Endocrine problems[c]	64656	C024000	Thyrotoxicosis from ectopic thyroid nodule with no crisis

a. Used along with fracture outcomes to define baseline history of fracture

b. Malabsorption includes Crohn's Disease, ulcerative colitis and coeliac disease as defined by Kuan *et al*[1] – these codes are for malabsorption, steatorrhoea or blind loop syndrome

c. Endocrine problems includes hyperparathyroidism as defined by Kuan *et al* (2019)[1] – these codes are for thyrotoxicosis and Cushing syndrome

Table S5: CPRD Procodes defining prescribing variables (corticosteroids are only oral or injectable preparations)

QFracture variable	**CPRD drugsubstance (drug name as recorded in CPRD)**	**CPRD Prodcodes**
Antidepressants	Amitriptyline hydrochloride	34916, 45242, 83, 33090, 52867, 24141, 57972, 55491, 70991, 61835, 76839, 45233, 34731, 66578, 80135, 57107, 65879, 24152, 59161, 34401, 46801, 64000, 79826, 70300, 76298, 46818, 76927, 487, 34197, 41729, 42394, 34474, 32439, 49, 34782, 54877, 24145, 55139, 42078, 71042, 65987, 64647, 79766, 34503, 24134, 66579, 60355, 77167, 65439, 66572, 24147, 34129, 6312, 78364, 67127, 34224, 60410, 4682, 40396, 1888, 34274, 34634, 64330, 78221, 46970, 34182, 69712, 33624, 34107, 4690, 34251, 59820, 64141, 76952, 77497, 26213, 20026, 27008, 24680, 2486, 2985, 8726, 7751, 8332, 19779, 182, 22070, 3777, 2525, 48065, 8878, 8831
Antidepressants	Amitriptyline Hydrochloride/ Chlordiazepoxide	21081, 18342, 11963, 14534
Antidepressants	Amitriptyline hydrochloride/ Perphenazine	3490, 595, 1453, 1208, 38827, 16323, 6894
Antidepressants	Amoxapine	3652, 4411, 17319, 3351, 21357, 24723, 15380, 14398, 55289
Antidepressants	Butriptyline Hydrochloride	12227, 32457, 18932
Antidepressants	Clomipramine	3195
Antidepressants	Clomipramine hydrochloride	30375, 26513, 7515, 3657, 8719, 7693, 7894, 3194, 34866, 68665, 41628, 62620, 43561, 3670, 34245, 41563, 45350, 65762, 8720, 64458, 3925, 45318, 41597, 53187, 78324, 65804, 53161, 38274, 78057, 8661
Antidepressants	Desipramine	7981, 7979
Antidepressants	Dosulepin hydrochloride	43024, 77130, 70838, 84, 23426, 34745, 34643, 31824, 44853, 29875, 33164, 34641, 76317, 34223, 50722, 71023, 70593, 74, 32121, 19186, 67728, 42734, 31826, 34525, 62681, 71059, 34058, 57926, 1940, 15632, 21820, 21819, 67990, 51758, 1169, 2320, 30376, 21157, 19168, 45737, 6054, 10948
Antidepressants	Doxepin hydrochloride	5190, 9558, 15975, 3842, 3554, 5073, 73363, 7059, 35258, 35493, 10413, 12129, 12125, 14519, 40777
Antidepressants	Fluphenazine hydrochloride/ Nortriptyline hydrochloride	2936, 7780
Antidepressants	Imipramine hydrochloride	1310, 41681, 34222, 67935, 71253, 70287, 32863, 34872, 1809, 34813, 34355, 41408, 8055, 42247, 33074, 2579, 56501, 7910, 4404
Antidepressants	Iprindole	27476, 27733, 24700, 31672
Antidepressants	Lofepramine	79397
Antidepressants	Lofepramine hydrochloride	58450, 2093, 41627, 114, 34046, 34950, 71067, 74586, 66100, 34578, 68657, 67742, 56703, 34672, 60591, 56229, 43534, 4218, 77717, 25444
Antidepressants	Mianserin hydrochloride	7468, 8144, 8585, 3083, 47363, 4329, 6255, 12368, 11956, 12192

Antidepressants	Nortriptyline hydrochloride	7677
		8640, 3183, 65237, 55970, 72626, 68228, 3903, 48216, 63276, 66201, 78224, 69317, 17183, 12549, 12353, 4118, 39145, 7678
Antidepressants	Nortriptyline hydrochloride/ Fluphenazine hydrochloride	8493, 14578, 20571
Antidepressants	Protriptyline hydrochloride	60929, 7755, 7816, 11187, 7756
Antidepressants	Trazodone hydrochloride	4194, 4003, 4874, 8174, 13621, 1730, 34580, 73639, 19181, 41709, 41710, 65152, 72291, 66749, 12710, 4020, 73419, 77915, 73636, 76480, 30983, 29857, 34470, 55137, 55138, 57226, 3355, 34003, 71031, 29339, 41609, 34421, 61842, 6442, 59931, 70521, 77474, 61657, 69355
Antidepressants	Trimipramine maleate	8928, 2532, 2531, 4310, 42228, 53808, 2039, 45226, 57978, 66493, 3196, 65445, 66919, 65213
Antidepressants	Viloxazine Hydrochloride	12309, 12111
Antidepressants	Citalopram hydrobromide	3861, 79784, 63953, 1712, 2408, 34498, 476, 34586, 64423, 32848, 49165, 42660, 52100, 59650, 53787, 71005, 33720, 52408, 34436, 45286, 75697, 52824, 59193, 63441, 34499, 60888, 41528, 56355, 34413, 54827, 34722, 67, 34356, 67097, 34871, 53394, 48026, 56009, 58476, 52607, 52354, 34415, 34970, 73417, 72373, 26016, 34966, 60568, 34822, 71848, 43519, 4770, 36746, 69571, 46977, 75075, 60839, 70790, 55033, 75702, 34603, 45223, 34466, 45304, 46926, 32546, 29756, 74753, 815, 513, 57936, 56292, 72124
Antidepressants	Escitalopram oxalate	74785, 648, 74858, 26056, 6360, 41062, 785, 603, 63916, 74993, 20152, 6218, 72773, 40726, 6405
Antidepressants	Fluoxetine hydrochloride	33071, 67431, 69941, 77881, 42499, 75645, 38890, 22, 19183, 71852, 45329, 60962, 75799, 67736, 45247, 75688, 34202, 34294, 69525, 59358, 66744, 34288, 42107, 62155, 19470, 45224, 67769, 34456, 34849, 67092, 45316, 33410, 60534, 60138, 2548, 34216, 42803, 60619, 73414, 30258, 36893, 68266, 69685, 74886, 67496, 79590, 67562, 75068, 78889, 4075, 75247, 67888, 34856, 62335, 14740, 67758, 77381, 418, 48220, 61335, 69542, 57532, 252, 75943, 4907, 37256, 33779, 29786
Antidepressants	Fluvoxamine maleate	12123, 2897, 2290, 48045, 44861, 43518, 2880
Antidepressants	Nefazodone hydrochloride	3391, 4297, 63827, 4554, 4011, 67757
Antidepressants	Paroxetine hydrochloride	35021, 76946, 59288, 67259, 527, 50, 34419, 32899, 73668, 40892, 34351, 55023, 33978, 1397, 34587, 40165, 64785, 78843, 68325, 35112, 66292, 74588, 841, 73589, 77650, 3601, 1575, 55537, 76772, 79383, 79381, 75054
Antidepressants	Sertraline	65771

Antidepressants	Sertraline hydrochloride	4352, 77385, 1612, 727, 55146, 62950, 61503, 59600, 62692, 69726, 67928, 66560, 54933, 66413, 68756, 44944, 73962, 49519, 77607, 78278, 62819, 54826, 78626, 73759, 54081, 488, 32401, 58723, 42387, 45915, 62693, 69725, 63481, 58664, 67730, 69898, 55488, 75952, 62927, 75405, 7328, 77538, 77707
Antidepressants	Agomelatine	40494, 40295
Antidepressants	Duloxetine hydrochloride	74774, 7122, 13151, 62688, 63370, 65618, 65809, 66412, 70405, 70728, 73298, 74907, 79628, 6895, 14849, 51383, 63216, 63763, 64442, 65888, 65892, 66405, 68096, 69428, 69752, 69965, 72211, 73540, 73868, 74190, 78777, 76857
Antidepressants	Mirtazapine	6421, 43253, 64101, 43241, 66580, 61856, 43248, 43246, 68680, 55482, 58291, 77865, 65555, 43237, 48698, 54012, 6795, 43239, 53699, 66183, 59953, 46668, 66752, 43242, 54342, 54644, 74557, 43257, 16154, 53321, 61547, 47966, 68544, 6488, 43250, 53648, 48185, 68052, 69420, 76187, 59694, 742, 47945, 40160, 54792, 69005, 77488, 78654, 60538, 56209, 68933, 71543, 63403, 6481, 43235, 43236, 43256, 43247, 64139, 43234, 49820, 6854, 33337, 58625, 59954, 64223, 77377, 4726, 67272, 60370, 6846, 50892, 10083, 53543, 15268
Antidepressants	Nefazodone Hydrochloride	9534
Antidepressants	Reboxetine mesilate	15163, 2356
Antidepressants	Tryptophan	54747, 5611, 20504, 12221, 54686, 4422
Antidepressants	Venlafaxine hydrochloride	52516, 52074, 71806, 61236, 45664, 45959, 65738, 67271, 623, 6274, 67288, 77089, 9182, 74010, 5710, 51280, 65899, 74011, 75894, 1474, 76771, 43968, 43673, 41299, 48199, 41314, 41033, 59753, 60843, 40817, 40815, 39809, 39770, 57751, 52716, 40514, 40515, 70420, 70495, 69819, 70315, 50081, 59035, 49511, 58726, 74516, 58681, 55501, 2654, 70806, 60549, 71782, 43334, 39360, 50934, 62734, 65666, 40054, 58837, 45806, 301, 56662, 73667, 68050, 75525, 59923, 70353, 51361, 60895, 51699, 13237, 2617, 470, 71257, 59563, 68876, 43203, 39359, 1222, 60449, 73658, 66437, 56457, 63859, 53326, 63268, 40062, 40407, 45818, 40059, 44936, 44937, 71932, 70931, 40092, 67563, 40277, 76727, 75263, 40517, 42600, 40764, 40917, 40049, 78585, 40048, 75848, 55424
Antidepressants	Vortioxetine hydrobromide	67874, 69991, 69992, 65483, 66890, 65482
Antidepressants	Iproniazide	25945, 18290
Antidepressants	Isocarboxazid	41731, 12207, 12503
Antidepressants	Moclobemide	9206, 5832, 2883, 67305, 41747, 5187
Antidepressants	Phenelzine sulfate	3349, 4321
Antidepressants	Tranylcypromine sulfate	10787, 3783, 41654
Antidepressants	Trifluoperazine Hydrochloride/Tranylcypromine Sulphate	3356

Antidepressants	Trifluoperazine Hydrochloride/ Tranylcypromine Sulphate	3955, 24890
Corticosteroids	Dexamethasone Sodium Phosphate]	28215, 37500, 14906, 61316, 53173, 19259, 47598, 61958, 56940, 35453, 10657, 13972, 26299, 13952, 26454, 31948, 34083, 4233
Corticosteroids	Hydrocortisone acetate	8108, 1893
Corticosteroids	Lidocaine Hydrochloride/ Methylprednisolone Acetate	925, 20157, 50253, 49076, 50734, 7405, 35156
Corticosteroids	Methylprednisolone	18042, 8261, 10683, 15555, 14172, 10552, 76923, 10684, 2130
Corticosteroids	Methylprednisolone acetate	48800, 48748, 48746, 14982, 71106, 27413, 33132, 35349, 35040, 35688, 1133, 5493
Corticosteroids	Methylprednisolone sodium succinate	18266, 13397, 12405, 18765, 14188, 25226, 25839, 23511, 21540
Corticosteroids	Triamcinolone acetonide	14962, 35578, 14335, 14958, 50216, 22047, 50026, 33131, 16583, 48406, 9368, 11123, 4488, 30244, 4125, 4123, 8864, 13981, 768, 37737, 3703, 16582
Corticosteroids	Triamcinolone hexacetonide	50854, 50853, 57856, 66867, 15016, 7992
Corticosteroids	Betamethasone	10864, 11149, 7286, 64235, 68306, 1971, 50225
Corticosteroids	Cortisone acetate	12398, 229, 53143, 7548, 53705, 18637, 12400, 10574, 23210
Corticosteroids	Deflazacort	22555, 29112, 20577, 41335, 9375, 78839, 17410, 3992
Corticosteroids	Dexamethasone	53207, 9994, 34801, 71926, 78335, 45234, 66724, 56443, 76339, 77085, 52396, 77849, 74156, 74157, 36055, 1280, 62909, 60120, 34880, 68182, 64747, 5157, 54793, 70611, 78214, 70893, 68489, 72537, 69572, 4779, 55401, 34915, 186, 74436, 56347, 68593, 73216, 21903
Corticosteroids	Hydrocortisone	75064, 74502, 75065, 76671, 3418, 65984, 64787, 66666, 38022, 75019, 51849, 51872, 64059, 54794, 4535, 66327, 57931, 75384, 77646, 51871, 75937, 52053, 75020, 53953, 63138, 14076, 51722, 51824, 75729, 74497, 71620, 38054, 10754, 6098, 13043, 77994, 58592, 59418
Corticosteroids	Hydrocortisone sodium phosphate	35172, 35175, 71905, 37638, 43355, 77821, 9574, 2615
Corticosteroids	Hydrocortisone sodium succinate	49707, 49498, 51167, 54715, 34166, 13350, 3754, 3651

Corticosteroids	Prednisolone	78546, 27962, 28859, 25272, 23512, 20095, 34914, 5913, 5490, 59283, 34631, 66645, 66015, 80110, 59229, 69568, 78129, 64007, 64008, 64009, 69686, 64128, 63172, 58234, 65626, 34109, 9727, 33691, 64416, 74239, 66914, 72421, 80050, 578, 34452, 34404, 73553, 58384, 63549, 28376, 2368, 38407, 61132, 75001, 34660, 51753, 34748, 56891, 34978, 59338, 557, 28375, 34461, 76020, 55480, 79930, 68497, 63066, 73294, 54434, 63082, 67076, 53313, 2704, 53336, 78144, 41745, 65020, 54118, 67507, 69811, 44, 31532, 32803, 66550, 67107, 73678, 58987, 34393, 59912, 45302, 75763, 33988, 33990, 95, 21417, 29333, 58000, 58369, 34781, 60421, 41515, 55024, 63791, 67559, 61162, 32835, 64221
Corticosteroids	Prednisolone sodium phosphate	1063, 47142, 955, 61689, 74493, 63214, 19141, 78789, 70603, 77760, 24224
Corticosteroids	Prednisolone Steaglate	31327, 3345
Corticosteroids	Prednisone	21833, 54432, 44803, 44802, 44380, 3557, 46711, 58061, 44723, 62656, 43544, 2949
Corticosteroids	Triamcinolone Acetonide	24014, 15617, 19908, 23111

Table S6: Missing data

	How missingness was handled in analysis	Women external validation cohort N=2747409 No (%) missing data	Men external validation cohort N=2684730 No (%) missing data	All patients original QFracture internal validation cohort N=1583373 No (%) missing data
Age Sex Socioeconomic status	Never missing Never missing Excluded from cohort	0 0 0	0 0 0	0 0 0
Body mass index (BMI)	Imputed	932720 (34.0)	1233196 (45.9)	418478 (26.4)
Smoking status	Imputed	780226 (28.4)	963580 (35.9)	258144 (16.3)
Alcohol status	Imputed	698902 (25.4)	866622 (32.3)	461740 (29.2)
Ethnicity	Assumed to be white	1278931 (46.6)	1494450 (55.7)	855485 (54.0)
Conditions and prescribing variables	Assumed to be absent if no record	NA	NA	NA

Table S7: Crude incidence of major osteoporotic fracture (MOF) over 10 years of follow-up

	Women			Men		
Age	Incident MOF	Total follow-up Years	Rate per 1000 person-year	Incident MOF	Total follow-up Years	Rate per 1000 person years
30-34	2,603	2741657	0.95 (0.91 to 0.99)	2,828	2784175	1.02 (0.98 to 1.05)
35-39	2,025	1870595	1.08 (1.04 to 1.13)	2,121	1927589	1.10 (1.05 to 1.15)
40-44	2,698	1833507	1.47 (1.42 to 1.53)	2,222	1917796	1.16 (1.11 to 1.21)
45-49	3,633	1595805	2.28 (2.20 to 2.35)	2,239	1681808	1.33 (1.28 to 1.39)
50-54	5,292	1449369	3.65 (3.55 to 3.75)	2,248	1497499	1.50 (1.44 to 1.56)
55-59	7,422	1490080	4.98 (4.87 to 5.10)	2,644	1505675	1.76 (1.69 to 1.82)
60-64	7,762	1210157	6.41 (6.27 to 6.56)	2,743	1191801	2.30 (2.22 to 2.39)
65-69	9,455	1024227	9.23 (9.05 to 9.42)	2,859	960815	2.98 (2.87 to 3.09)
70-74	11,757	861260	13.65 (13.41 to 13.90)	3,456	748844	4.62 (4.46 to 4.77)
75-80	14,148	688855	20.54 (20.21 to 20.88)	4,068	516507	7.88 (7.64 to 8.12)
80-84	14,653	508415	28.82 (28.36 to 29.28)	3,891	304005	12.80 (12.41 to 13.20)
85-90	9,017	237728	37.93 (37.17 to 38.71)	2,080	107018	19.44 (18.63 to 20.28)
90-99	5,133	112888	45.47 (44.27 to 46.70)	922	36093	25.55 (23.97 to 27.22)
Total	95,598	15624543	6.12 (6.08 to 6.16)	34,321	15179623	2.26 (2.24 to 2.29)

Table S8: Crude incidence of hip fracture over 10 years of follow-up

	Women			Men		
Age	Incident hip fractures	Total Follow-up Years	Rate per 1000 person-year	Incident hip fractures	Total Follow-up Years	Rate per 1000 person years
30-34	93	2750441	0.03 (0.03 to 0.04)	214	2793615	0.08 (0.07 to 0.09)
35-39	109	1878222	0.06 (0.05 to 0.07)	223	1935329	0.12 (0.10 to 0.13)
40-44	183	1842965	0.10 (0.09 to 0.11)	307	1925573	0.16 (0.14 to 0.18)
45-49	374	1607632	0.23 (0.21 to 0.26)	377	1689307	0.22 (0.20 to 0.25)
50-54	599	1467062	0.41 (0.38 to 0.44)	442	1504825	0.29 (0.27 to 0.32)
55-59	1,149	1515268	0.76 (0.72 to 0.80)	701	1513119	0.46 (0.43 to 0.50)
60-64	1,554	1234523	1.26 (1.20 to 1.32)	948	1197990	0.79 (0.74 to 0.84)
65-69	2,614	1051678	2.49 (2.39 to 2.58)	1,217	966352	1.26 (1.19 to 1.33)
70-74	4,460	889669	5.01 (4.87 to 5.16)	1,709	754325	2.27 (2.16 to 2.38)
75-80	6,905	715572	9.65 (9.43 to 9.88)	2,432	521184	4.67 (4.48 to 4.86)
80-84	8,752	527816	16.58 (16.24 to 16.93)	2,640	307196	8.59 (8.27 to 8.93)
85-90	5,968	246247	24.24 (23.64 to 24.85)	1,469	108226	13.57 (12.90 to 14.28)
90-99	3,640	115681	31.47 (30.48 to 32.49)	700	36423	19.22 (17.86 to 20.68)
Total	36,400	15842775	2.30 (2.27 to 2.32)	13,379	15253462	0.88 (0.86 to 0.89)

Table S9: Comparison of major osteoporotic fracture (MOF) incidence in this study and previous external validation study[a 3]

	Women		Men	
Age	MOF rate/1000 person-years (this study)	MOF rate/1000 person-years (previous external validation)	MOF rate/1000 person-years (this study)	MOF rate/1000 person-years (previous external validation)
30-34	0.95 (0.91 to 0.99)	0.42 (0.38 to 0.46)	1.02 (0.98 to 1.05)	0.45 (0.41 to 0.50)
35-39	1.08 (1.04 to 1.13)	0.44 (0.40 to 0.49)	1.10 (1.05 to 1.15)	0.45 (0.41 to 0.49)
40-44	1.47 (1.42 to 1.53)	0.60 (0.55 to 0.66)	1.16 (1.11 to 1.21)	0.44 (0.39 to 0.49)
45-49	2.28 (2.20 to 2.35)	0.96 (0.89 to 1.04)	1.33 (1.28 to 1.39)	0.55 (0.50 to 0.61)
50-54	3.65 (3.55 to 3.75)	1.57 (1.48 to 1.66)	1.50 (1.44 to 1.56)	0.67 (0.61 to 0.73)
55-59	4.98 (4.87 to 5.10)	2.22 (2.10 to 2.34)	1.76 (1.69 to 1.82)	0.74 (0.67 to 0.81)
60-64	6.41 (6.27 to 6.56)	3.54 (3.37 to 3.70)	2.30 (2.22 to 2.39)	0.98 (0.89 to 1.07)
65-69	9.23 (9.05 to 9.42)	5.15 (4.94 to 5.36)	2.98 (2.87 to 3.09)	1.42 (1.31 to 1.54)
70-74	13.65 (13.41 to 13.90)	8.07 (7.79 to 8.36)	4.62 (4.46 to 4.77)	2.69 (2.52 to 2.88)
75-80	20.54 (20.21 to 20.88)	11.96 (11.57 to 12.35)	7.88 (7.64 to 8.12)	4.03 (3.77 to 4.31)
80-84	28.82 (28.36 to 29.28)	17.70 (17.14 to 18.28)	12.80 (12.41 to 13.20)	7.01 (6.54 to 7.51)
85-89 [b]	37.93 (37.17 to 38.71)	-	19.44 (18.63 to 20.28)	-
90-99 [b]	45.47 (44.27 to 46.70)	-	25.55 (23.97 to 27.22)	-
Total	6.12 (6.08 to 6.16)	2.93 (2.89 to 2.98)	2.26 (2.24 to 2.29)	0.98 (0.95 to 1.00)

a. QFracture derivation papers do not report incidence by age, so the external validation study data is the comparison. As with QFracture derivation and internal validation, the external validation study ascertained fractures using GP electronic health record data and mortality registration data, whereas this study also used fractures recorded at hospital discharge

b. Previous external validation study maximum age is 85; in this study maximum age is 99

Table S10: Comparison of hip fracture incidence in this study and previous external validation study[a 3]

	Women		Men	
Age	Hip fracture rate/1000 person-years (this study)	Hip fracture rate/1000 person-years (previous external validation)	Hip fracture rate/1000 person-years (this study)	Hip fracture rate/1000 person-years (previous external validation)
30-34	0.03 (0.03 to 0.04)	0.03 (0.02 to 0.05)	0.08 (0.07 to 0.09)	0.05 (0.04 to 0.06)
35-39	0.06 (0.05 to 0.07)	0.04 (0.03 to 0.06)	0.12 (0.10 to 0.13)	0.08 (0.07 to 0.10)
40-44	0.10 (0.09 to 0.11)	0.08 (0.06 to 0.10)	0.16 (0.14 to 0.18)	0.09 (0.07 to 0.12)
45-49	0.23 (0.21 to 0.26)	0.18 (0.15 to 0.21)	0.22 (0.20 to 0.25)	0.15 (0.13 to 0.18)
50-54	0.41 (0.38 to 0.44)	0.31 (0.27 to 0.35)	0.29 (0.27 to 0.32)	0.22 (0.19 to 0.26)
55-59	0.76 (0.72 to 0.80)	0.56 (0.50 to 0.62)	0.46 (0.43 to 0.50)	0.31 (0.27 to 0.36)
60-64	1.26 (1.20 to 1.32)	1.01 (0.93 to 1.10)	0.79 (0.74 to 0.84)	0.43 (0.37 to 0.49)
65-69	2.49 (2.39 to 2.58)	1.97 (1.85 to 2.10)	1.26 (1.19 to 1.33)	0.79 (0.70 to 0.87)
70-74	5.01 (4.87 to 5.16)	3.97 (3.78 to 4.17)	2.27 (2.16 to 2.38)	1.67 (1.54 to 1.82)
75-80	9.65 (9.43 to 9.88)	7.03 (6.75 to 7.32)	4.67 (4.48 to 4.86)	2.84 (2.62 to 3.08)
80-84	16.58 (16.24 to 16.93)	12.47 (12.02 to 12.94)	8.59 (8.27 to 8.93)	5.42 (5.01 to 5.86)
85-90[b]	24.24 (23.64 to 24.85)		13.57 (12.90 to 14.28)	
90-99[b]	31.47 (30.48 to 32.49)		19.22 (17.86 to 20.68)	
Total	2.30 (2.27 to 2.32)	1.37 (1.35 to 1.40)	0.88 (0.86 to 0.89)	0.47 (0.46 to 0.49)

a. QFracture derivation papers do not report incidence by age, so the external validation study data is the comparison. As with QFracture derivation and internal validation, the external validation study ascertained fractures using GP electronic health record data and mortality registration data, whereas this study also used fractures recorded at hospital discharge

b. Previous external validation study maximum age is 85; in this study maximum age is 99; reported previous external validation rate is therefore for age 80-85

Table S11: Crude incidence of major osteoporotic fracture (MOF) over 10 years of follow-up (with ascertainment restricted to GP and mortality data)

	Women			Men		
Age	Incident MOF	Total follow-up Years	Rate per 1000 person-year	Incident MOF	Total follow-up Years	Rate per 1000 person years
30-34	2,316	2742607	0.84 (0.81 to 0.88)	2,447	2785431	0.88 (0.84 to 0.91)
35-39	1,788	1871469	0.96 (0.91 to 1.00)	1,848	1928588	0.96 (0.92 to 1.00)
40-44	2,387	1834615	1.30 (1.25 to 1.35)	1,897	1918981	0.99 (0.95 to 1.03)
45-49	3,212	1597368	2.01 (1.94 to 2.08)	1,914	1682894	1.14 (1.09 to 1.19)
50-54	4,747	1451234	3.27 (3.18 to 3.37)	1,902	1498727	1.27 (1.21 to 1.33)
55-59	6,569	1493186	4.40 (4.29 to 4.51)	2,160	1507164	1.43 (1.37 to 1.49)
60-64	6,829	1213292	5.63 (5.50 to 5.76)	2,221	1193239	1.86 (1.79 to 1.94)
65-69	8,116	1028487	7.89 (7.72 to 8.06)	2,293	962282	2.38 (2.29 to 2.48)
70-74	9,965	866524	11.50 (11.28 to 11.73)	2,752	750538	3.67 (3.53 to 3.81)
75-80	11,693	695373	16.82 (16.52 to 17.12)	3,247	518140	6.27 (6.06 to 6.49)
80-84	11,873	514580	23.07 (22.67 to 23.49)	3,041	305425	9.96 (9.61 to 10.31)
85-89	7,175	241340	29.73 (29.06 to 30.41)	1,576	107622	14.64 (13.94 to 15.38)
90-99	4,126	114095	36.16 (35.09 to 37.26)	718	36261	19.80 (18.42 to 21.29)
Total	80,796	15664170	5.16 (5.12 to 5.19)	28,016	15195293	1.84 (1.82 to 1.87)

Table S12: Comparison of major osteoporotic fracture incidence in this study with complete fracture ascertainment (GP, mortality and hospital admission data), previous external validation study, and in this study using ascertainment to match previous study (GP and mortality data only) [3]

	Women			Men		
Age	MOF rate/1000 person-years (this study)[a]	MOF rate/1000 person-years (previously published external validation)[b]	MOF rate/1000 person-years (this study matched ascertainment)[b]	MOF rate/1000 person-years (this study)[a]	MOF rate/1000 person-years (previously published external validation)[b]	MOF rate/1000 person-years (this study matched ascertainment)[b]
30-34	0.95 (0.91 to 0.99)	0.03 (0.02 to 0.05)	0.84 (0.81 to 0.88)	1.02 (0.98 to 1.05)	0.05 (0.04 to 0.06)	0.88 (0.84 to 0.91)
35-39	1.08 (1.04 to 1.13)	0.04 (0.03 to 0.06)	0.96 (0.91 to 1.00)	1.10 (1.05 to 1.15)	0.08 (0.07 to 0.10)	0.96 (0.92 to 1.00)
40-44	1.47 (1.42 to 1.53)	0.08 (0.06 to 0.10)	1.30 (1.25 to 1.35)	1.16 (1.11 to 1.21)	0.09 (0.07 to 0.12)	0.99 (0.95 to 1.03)
45-49	2.28 (2.20 to 2.35)	0.18 (0.15 to 0.21)	2.01 (1.94 to 2.08)	1.33 (1.28 to 1.39)	0.15 (0.13 to 0.18)	1.14 (1.09 to 1.19)
50-54	3.65 (3.55 to 3.75)	0.31 (0.27 to 0.35)	3.27 (3.18 to 3.37)	1.50 (1.44 to 1.56)	0.22 (0.19 to 0.26)	1.27 (1.21 to 1.33)
55-59	4.98 (4.87 to 5.10)	0.56 (0.50 to 0.62)	4.40 (4.29 to 4.51)	1.76 (1.69 to 1.82)	0.31 (0.27 to 0.36)	1.43 (1.37 to 1.49)
60-64	6.41 (6.27 to 6.56)	1.01 (0.93 to 1.10)	5.63 (5.50 to 5.76)	2.30 (2.22 to 2.39)	0.43 (0.37 to 0.49)	1.86 (1.79 to 1.94)
65-69	9.23 (9.05 to 9.42)	1.97 (1.85 to 2.10)	7.89 (7.72 to 8.06)	2.98 (2.87 to 3.09)	0.79 (0.70 to 0.87)	2.38 (2.29 to 2.48)
70-74	13.65 (13.41 to 13.90)	3.97 (3.78 to 4.17)	11.50 (11.28 to 11.73)	4.62 (4.46 to 4.77)	1.67 (1.54 to 1.82)	3.67 (3.53 to 3.81)
75-80	20.54 (20.21 to 20.88)	7.03 (6.75 to 7.32)	16.82 (16.52 to 17.12)	7.88 (7.64 to 8.12)	2.84 (2.62 to 3.08)	6.27 (6.06 to 6.49)
80-84	28.82 (28.36 to 29.28)	12.47 (12.02 to 12.94)	23.07 (22.67 to 23.49)	12.80 (12.41 to 13.20)	5.42 (5.01 to 5.86	9.96 (9.61 to 10.31)
85-90[c]	37.93 (37.17 to 38.71)	-	29.73 (29.06 to 30.41)	19.44 (18.63 to 20.28)	-	14.64 (13.94 to 15.38)
90-99[c]	45.47 (44.27 to 46.70)	-	36.16 (35.09 to 37.26)	25.55 (23.97 to 27.22)	-	19.80 (18.42 to 21.29)
Total	6.12 (6.08 to 6.16)	1.37 (1.35 to 1.40)	5.16 (5.12 to 5.19)	2.26 (2.24 to 2.29)	0.47 (0.46 to 0.49)	1.84 (1.82 to 1.87)

a. Fractures ascertained using GP electronic health record data, mortality registration data, and fractures recorded at hospital discharge

b. Fractures ascertained using GP electronic health record data and mortality registration data (but NOT hospital discharge data)

c. Previous external validation study maximum age is 85; in this study maximum age is 99; reported previous external validation rate is therefore for age 80-85

Table S13: Crude incidence of hip fracture over 10 years of follow-up (with ascertainment restricted to GP and mortality data)

	Women			Men		
Age	Incident hip fracture	Total follow-up Years	Rate per 1000 person-year	Incident hip fracture	Total follow-up Years	Rate per 1000 person years
30-34	80	2750475	0.03 (0.02 to 0.04)	178	2793683	0.06 (0.06 to 0.07)
35-39	92	1878252	0.05 (0.04 to 0.06)	192	1935416	0.10 (0.09 to 0.11)
40-44	158	1843032	0.09 (0.07 to 0.10)	254	1925741	0.13 (0.12 to 0.15)
45-49	325	1607799	0.20 (0.18 to 0.23)	322	1689484	0.19 (0.17 to 0.21)
50-54	524	1467273	0.36 (0.33 to 0.39)	369	1505015	0.25 (0.22 to 0.27)
55-59	975	1515801	0.64 (0.60 to 0.68)	571	1513458	0.38 (0.35 to 0.41)
60-64	1,325	1235112	1.07 (1.02 to 1.13)	792	1198354	0.66 (0.62 to 0.71)
65-69	2,194	1052811	2.08 (2.00 to 2.17)	993	966812	1.03 (0.97 to 1.09)
70-74	3,644	891687	4.09 (3.96 to 4.22)	1,388	754978	1.84 (1.74 to 1.94)
75-80	5,570	718657	7.75 (7.55 to 7.96)	1,970	521983	3.77 (3.61 to 3.94)
80-84	6,992	531298	13.16 (12.86 to 13.47)	2,100	307978	6.82 (6.53 to 7.12)
85-90	4,700	248552	18.91 (18.38 to 19.45)	1,137	108580	10.47 (9.88 to 11.09)
90-99	2,910	116419	25.00 (24.11 to 25.91)	558	36527	15.28 (14.07 to 16.59)
Total	29,489	15857168	1.86 (1.84 to 1.88)	10,824	15258010	0.71 (0.70 to 0.72)

Table S14: Comparison of hip fracture incidence in this study with complete fracture ascertainment (GP, mortality and hospital admission data), previous external validation study, and in this study using ascertainment to match previous study (GP and mortality data only)[a 3]

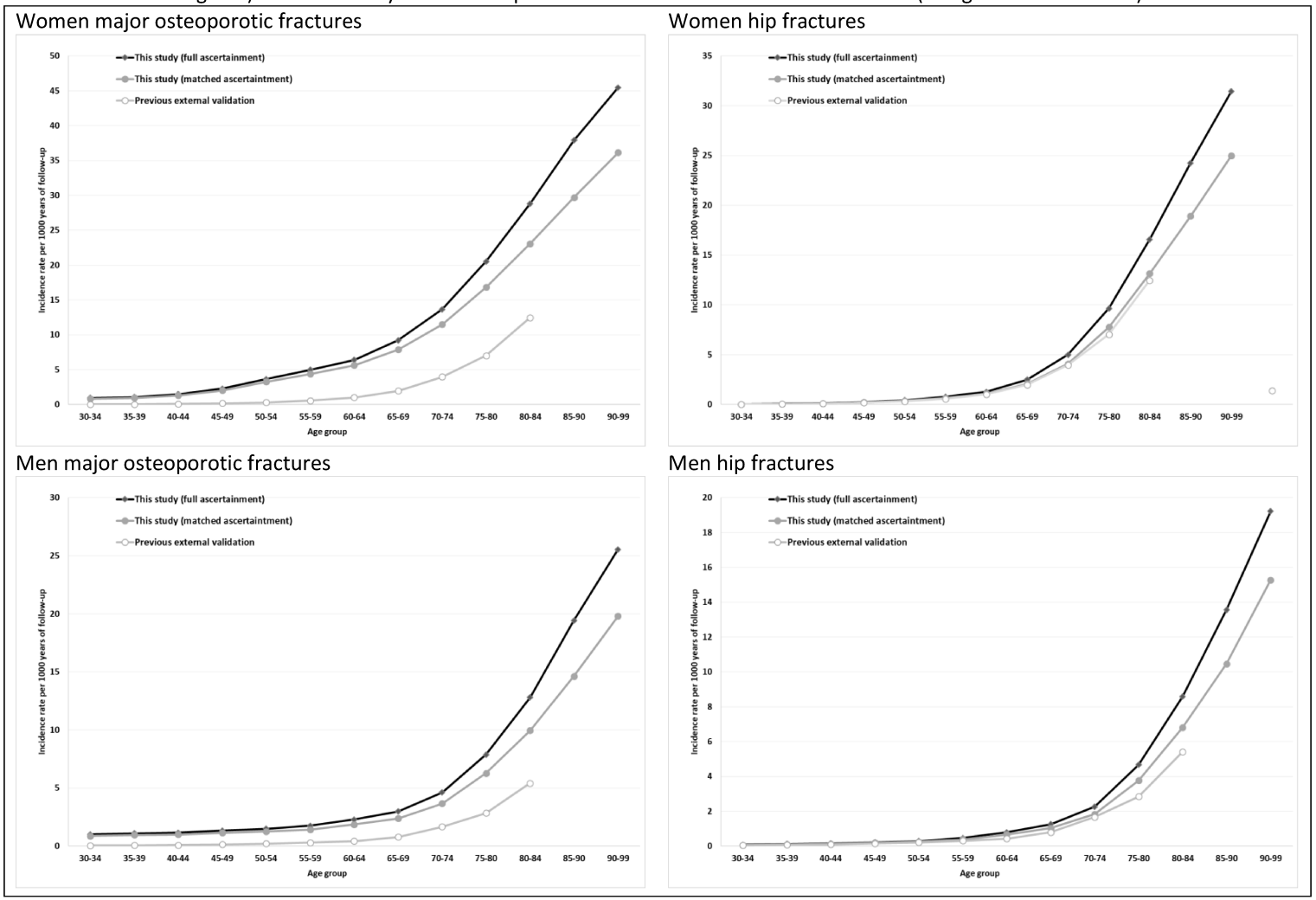
	Women			Men		
Age	Hip fracture rate/1000 person-years (this study)[a]	Hip fracture rate/1000 person-years (previously published external validation)[b]	Hip fracture rate/1000 person-years (this study matched ascertainment)[b]	Hip fracture rate/1000 person-years (this study)[a]	Hip fracture rate/1000 person-years (previously published external validation)[b]	Hip fracture rate/1000 person-years (this study matched ascertainment)[b]
30-34	0.03 (0.03 to 0.04)	0.03 (0.02 to 0.05)	0.03 (0.02 to 0.04)	0.08 (0.07 to 0.09)	0.05 (0.04 to 0.06)	0.06 (0.06 to 0.07)
35-39	0.06 (0.05 to 0.07)	0.04 (0.03 to 0.06)	0.05 (0.04 to 0.06)	0.12 (0.10 to 0.13)	0.08 (0.07 to 0.10)	0.10 (0.09 to 0.11)
40-44	0.10 (0.09 to 0.11)	0.08 (0.06 to 0.10)	0.09 (0.07 to 0.10)	0.16 (0.14 to 0.18)	0.09 (0.07 to 0.12)	0.13 (0.12 to 0.15)
45-49	0.23 (0.21 to 0.26)	0.18 (0.15 to 0.21)	0.20 (0.18 to 0.23)	0.22 (0.20 to 0.25)	0.15 (0.13 to 0.18)	0.19 (0.17 to 0.21)
50-54	0.41 (0.38 to 0.44)	0.31 (0.27 to 0.35)	0.36 (0.33 to 0.39)	0.29 (0.27 to 0.32)	0.22 (0.19 to 0.26)	0.25 (0.22 to 0.27)
55-59	0.76 (0.72 to 0.80)	0.56 (0.50 to 0.62)	0.64 (0.60 to 0.68)	0.46 (0.43 to 0.50)	0.31 (0.27 to 0.36)	0.38 (0.35 to 0.41)
60-64	1.26 (1.20 to 1.32)	1.01 (0.93 to 1.10)	1.07 (1.02 to 1.13)	0.79 (0.74 to 0.84)	0.43 (0.37 to 0.49)	0.66 (0.62 to 0.71)
65-69	2.49 (2.39 to 2.58)	1.97 (1.85 to 2.10)	2.08 (2.00 to 2.17)	1.26 (1.19 to 1.33)	0.79 (0.70 to 0.87)	1.03 (0.97 to 1.09)
70-74	5.01 (4.87 to 5.16)	3.97 (3.78 to 4.17)	4.09 (3.96 to 4.22)	2.27 (2.16 to 2.38)	1.67 (1.54 to 1.82)	1.84 (1.74 to 1.94)
75-80	9.65 (9.43 to 9.88)	7.03 (6.75 to 7.32)	7.75 (7.55 to 7.96)	4.67 (4.48 to 4.86)	2.84 (2.62 to 3.08)	3.77 (3.61 to 3.94)
80-84	16.58 (16.24 to 16.93)	12.47 (12.02 to 12.94)	13.16 (12.86 to 13.47)	8.59 (8.27 to 8.93)	5.42 (5.01 to 5.86	6.82 (6.53 to 7.12)
85-90[c]	24.24 (23.64 to 24.85)	-	18.91 (18.38 to 19.45)	13.57 (12.90 to 14.28)	-	10.47 (9.88 to 11.09)
90-99[c]	31.47 (30.48 to 32.49)	-	25.00 (24.11 to 25.91)	19.22 (17.86 to 20.68)	-	15.28 (14.07 to 16.59)
Total	2.30 (2.27 to 2.32)	1.37 (1.35 to 1.40)	1.86 (1.84 to 1.88)	0.88 (0.86 to 0.89)	0.47 (0.46 to 0.49)	0.71 (0.70 to 0.72)

a. Fractures ascertained using GP electronic health record data, mortality registration data, and fractures recorded at hospital discharge

b. Fractures ascertained using GP electronic health record data and mortality registration data (but NOT hospital discharge data)

c. Previous external validation study maximum age is 85; in this study maximum age is 99; reported previous external validation rate is therefore for age 80-85

Figure S1: Comparison of fracture incidence in this study (using GP, mortality and hospital admission data), previous external validation (using GP and ONS data but maximum age 85)[3] and this study matched to previous external validation ascertainment (using GP and ONS data)*



* The previous external validation[3] is of the first version of the QFracture tool[4] but the derivation paper for the second version[5] being evaluated in this study does not report fracture incidence by age. Key differences are that the external validation study only includes patients to age 84 years (vs to 99 years in this study), and excludes people with prior major osteoporotic fracture (who are included in this study, since prior MOF is a predictor)

Table S15: Crude incidence of non-fracture death over 10 years of follow-up

	Women			Men		
Age	Incident non-fracture death	Total follow-up Years	Rate per 1000 person-year	Incident non-fracture death	Total follow-up Years	Rate per 1000 person years
30-34	1,348	2741657	0.49 (0.47 to 0.52)	2,346	2784175	0.84 (0.81 to 0.88)
35-39	1,677	1870595	0.90 (0.85 to 0.94)	2,411	1927589	1.25 (1.20 to 1.30)
40-44	2,534	1833507	1.38 (1.33 to 1.44)	3,605	1917796	1.88 (1.82 to 1.94)
45-49	3,714	1595805	2.33 (2.25 to 2.40)	5,094	1681808	3.03 (2.95 to 3.11)
50-54	4,991	1449369	3.44 (3.35 to 3.54)	7,398	1497499	4.94 (4.83 to 5.05)
55-59	7,996	1490080	5.37 (5.25 to 5.48)	12,167	1505675	8.08 (7.94 to 8.23)
60-64	10,378	1210157	8.58 (8.41 to 8.74)	15,427	1191801	12.94 (12.74 to 13.15)
65-69	14,216	1024227	13.88 (13.65 to 14.11)	20,779	960815	21.63 (21.34 to 21.92)
70-74	19,734	861260	22.91 (22.60 to 23.23)	26,842	748844	35.84 (35.43 to 36.27)
75-80	27,874	688855	40.46 (40.00 to 40.93)	31,087	516507	60.19 (59.54 to 60.84)
80-84	36,030	508415	70.87 (70.17 to 71.58)	30,228	304005	99.43 (98.37 to 100.50)
85-89	29,415	237728	123.73 (122.42 to 125.06)	16,832	107018	157.28 (155.11 to 159.48)
90-99	23,799	112888	210.82 (208.45 to 213.21)	8,865	36093	245.62 (241.20 to 250.09)
Total	183,706	15624543	11.76 (11.70 to 11.81)	183,081	15179623	12.06 (12.01 to 12.12)

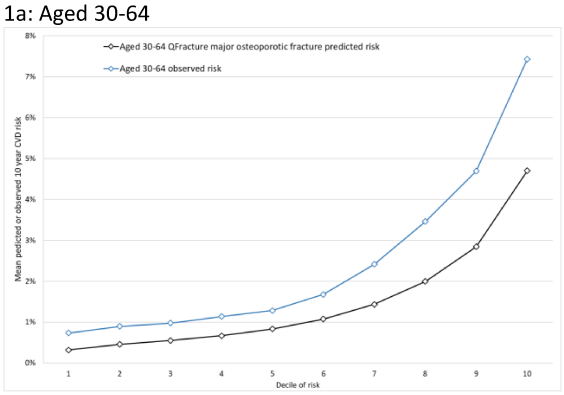
Table S16: Comparison of major osteoporotic fracture (MOF), hip fracture and non-fracture death incidence (rate per 1000 person/years [95%CI])

	Women			Men		
Age	Major osteoporotic fracture	Hip fracture	Non-fracture death	Major osteoporotic fracture	Hip fracture	Non-fracture death
30-34	0.95 (0.91 to 0.99)	0.03 (0.03 to 0.04)	0.49 (0.47 to 0.52)	1.02 (0.98 to 1.05)	0.08 (0.07 to 0.09)	0.84 (0.81 to 0.88)
35-39	1.08 (1.04 to 1.13)	0.06 (0.05 to 0.07)	0.90 (0.85 to 0.94)	1.10 (1.05 to 1.15)	0.12 (0.10 to 0.13)	1.25 (1.20 to 1.30)
40-44	1.47 (1.42 to 1.53)	0.10 (0.09 to 0.11)	1.38 (1.33 to 1.44)	1.16 (1.11 to 1.21)	0.16 (0.14 to 0.18)	1.88 (1.82 to 1.94)
45-49	2.28 (2.20 to 2.35)	0.23 (0.21 to 0.26)	2.33 (2.25 to 2.40)	1.33 (1.28 to 1.39)	0.22 (0.20 to 0.25)	3.03 (2.95 to 3.11)
50-54	3.65 (3.55 to 3.75)	0.41 (0.38 to 0.44)	3.44 (3.35 to 3.54)	1.50 (1.44 to 1.56)	0.29 (0.27 to 0.32)	4.94 (4.83 to 5.05)
55-59	4.98 (4.87 to 5.10)	0.76 (0.72 to 0.80)	5.37 (5.25 to 5.48)	1.76 (1.69 to 1.82)	0.46 (0.43 to 0.50)	8.08 (7.94 to 8.23)
60-64	6.41 (6.27 to 6.56)	1.26 (1.20 to 1.32)	8.58 (8.41 to 8.74)	2.30 (2.22 to 2.39)	0.79 (0.74 to 0.84)	12.94 (12.74 to 13.15)
65-69	9.23 (9.05 to 9.42)	2.49 (2.39 to 2.58)	13.88 (13.65 to 14.11)	2.98 (2.87 to 3.09)	1.26 (1.19 to 1.33)	21.63 (21.34 to 21.92)
70-74	13.65 (13.41 to 13.90)	5.01 (4.87 to 5.16)	22.91 (22.60 to 23.23)	4.62 (4.46 to 4.77)	2.27 (2.16 to 2.38)	35.84 (35.43 to 36.27)
75-80	20.54 (20.21 to 20.88)	9.65 (9.43 to 9.88)	40.46 (40.00 to 40.93)	7.88 (7.64 to 8.12)	4.67 (4.48 to 4.86)	60.19 (59.54 to 60.84)
80-84	28.82 (28.36 to 29.28)	16.58 (16.24 to 16.93)	70.87 (70.17 to 71.58)	12.80 (12.41 to 13.20)	8.59 (8.27 to 8.93)	99.43 (98.37 to 100.50)
85-89	37.93 (37.17 to 38.71)	24.24 (23.64 to 24.85)	123.73 (122.42 to 125.06)	19.44 (18.63 to 20.28)	13.57 (12.90 to 14.28)	157.28 (155.11 to 159.48)
90-99	45.47 (44.27 to 46.70)	31.47 (30.48 to 32.49)	210.82 (208.45 to 213.21)	25.55 (23.97 to 27.22)	19.22 (17.86 to 20.68)	245.62 (241.20 to 250.09)
Total	6.12 (6.08 to 6.16)	2.30 (2.27 to 2.32)	11.76 (11.70 to 11.81)	2.26 (2.24 to 2.29)	0.88 (0.86 to 0.89)	12.06 (12.01 to 12.12)

Figure S2: Calibration for major osteoporotic fracture in women by agegroup without accounting for competing risks (left hand) and accounting for competing risks (right hand).

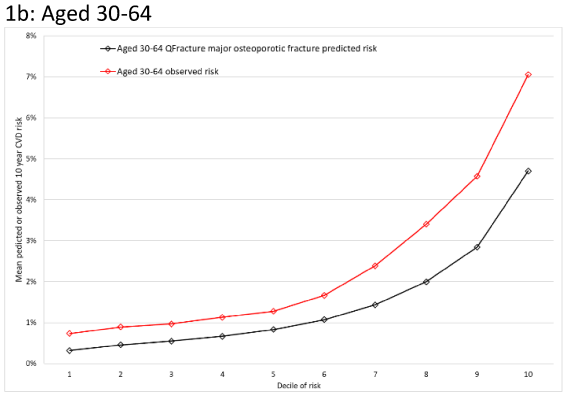
Women (not accounting for competing risks)

1a: Aged 30-64

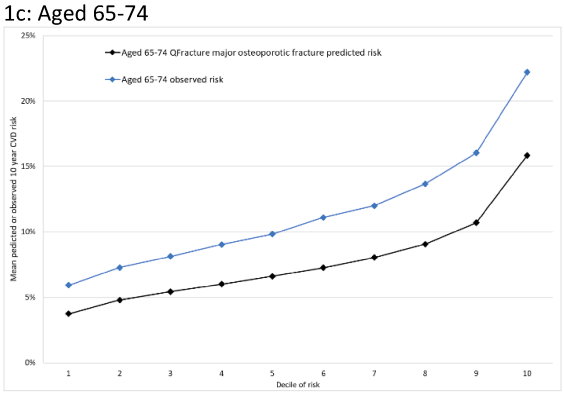


Women (accounting for competing risks)

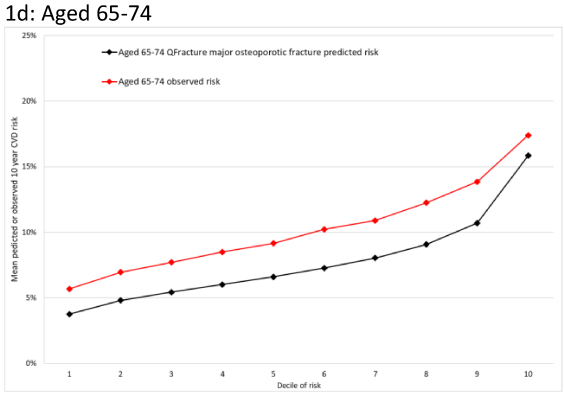
1b: Aged 30-64



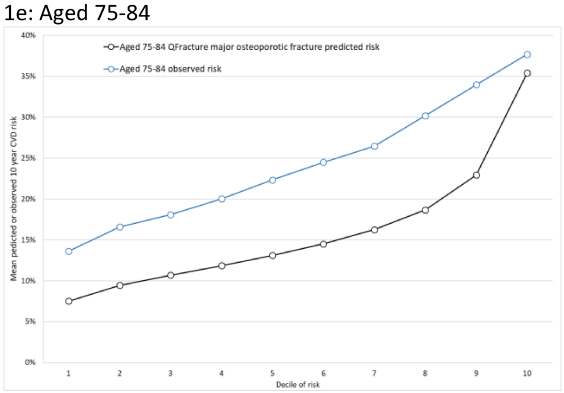
1c: Aged 65-74



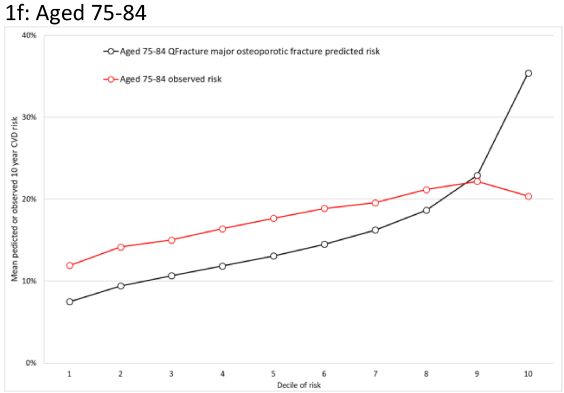
1d: Aged 65-74



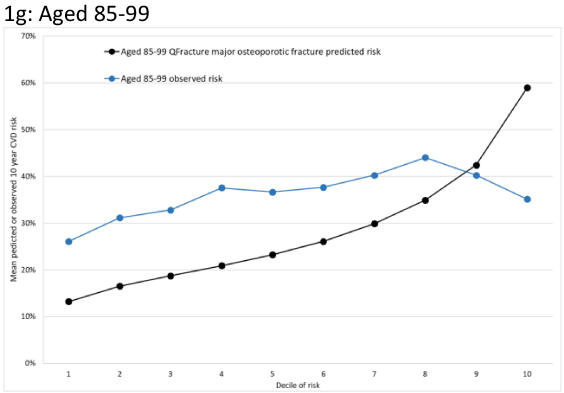
1e: Aged 75-84



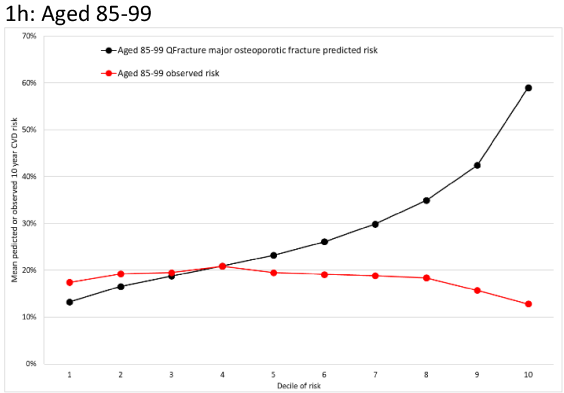
1f: Aged 75-84



1g: Aged 85-99



1h: Aged 85-99

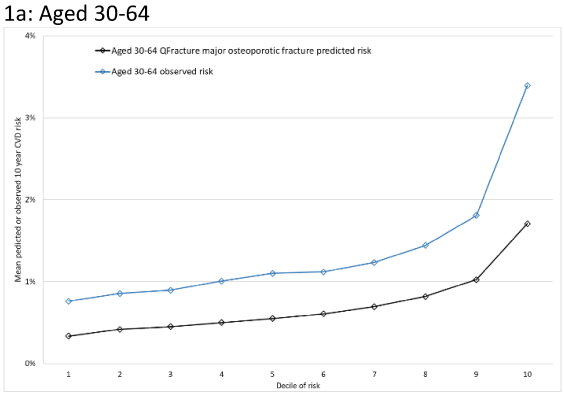


* Observed risk is based on the Kaplan-Meier estimator which does not account for competing mortality risk.
# Observed risk is based on the Aalen-Johansen estimator which accounts for competing mortality risk
Coloured line (observed risk) above matching black line (predicted risk) indicates under-prediction; below indicates over-prediction

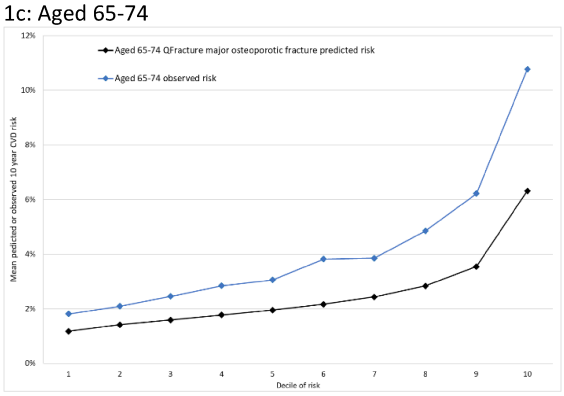
Figure S3: Calibration for major osteoporotic fracture in men by agegroup without accounting for competing risks (left hand) and accounting for competing risks (right hand)

Men (not accounting for competing risks)

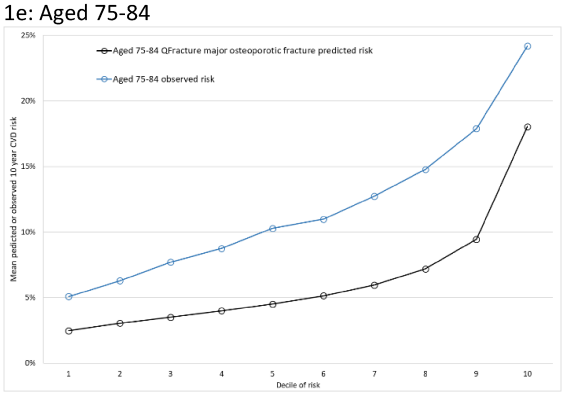
1a: Aged 30-64



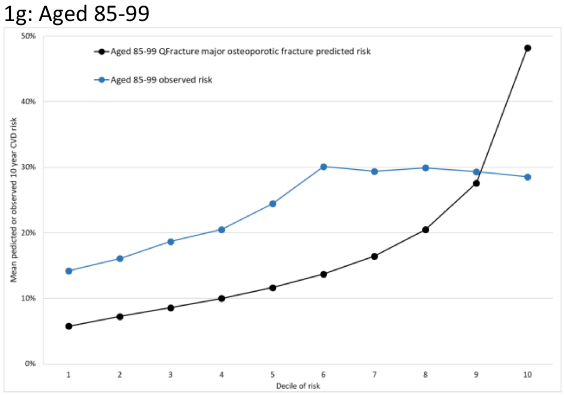
1c: Aged 65-74



1e: Aged 75-84

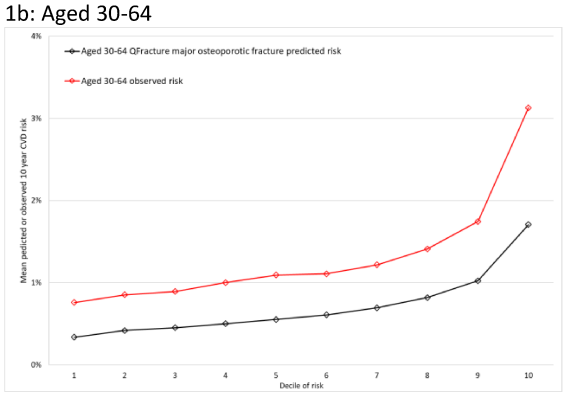


1g: Aged 85-99

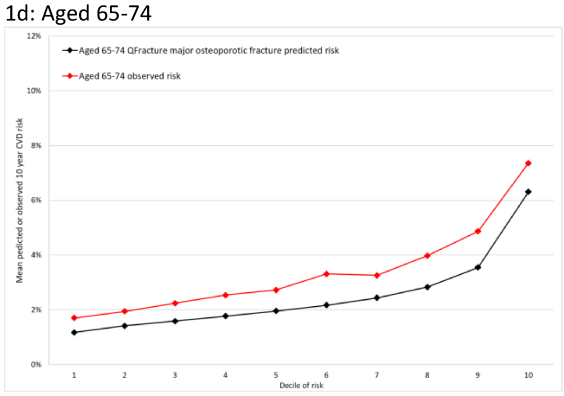


Men (accounting for competing risks)

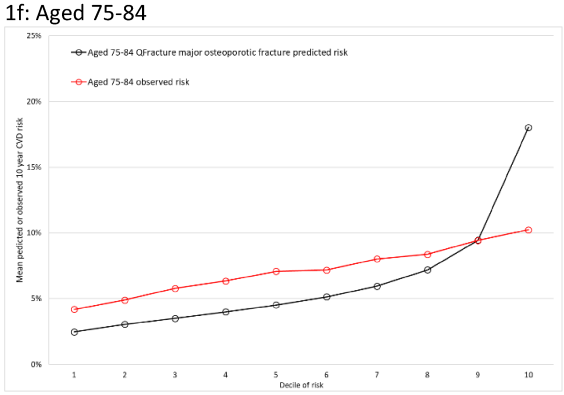
1b: Aged 30-64



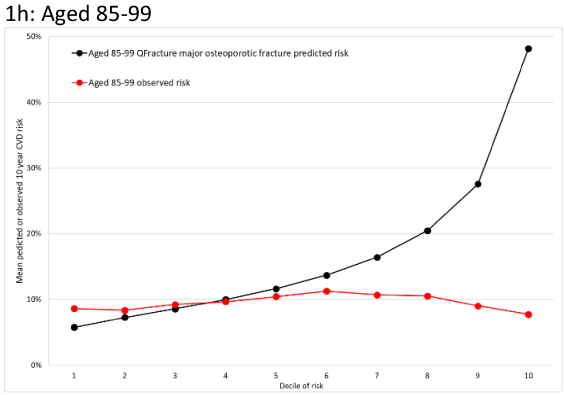
1d: Aged 65-74



1f: Aged 75-84



1h: Aged 85-99

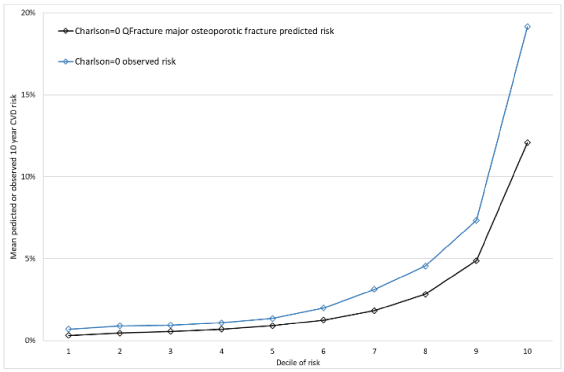


* Observed risk is based on the Kaplan-Meier estimator which does not account for competing mortality risk.
# Observed risk is based on the Aalen-Johansen estimator which accounts for competing mortality risk
Coloured line (observed risk) above matching black line (predicted risk) indicates under-prediction; below indicates over-prediction risk

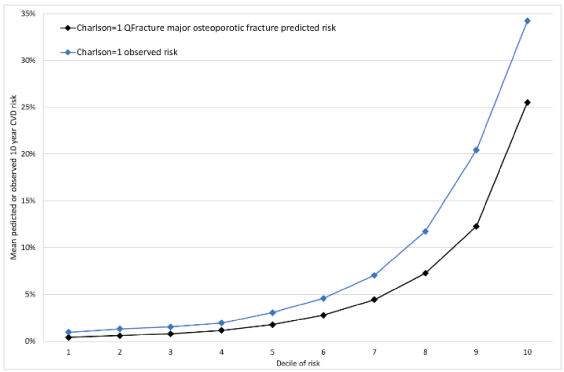
Figure S4: Calibration for major osteoporotic fracture in women by Charlson Score without accounting for competing risks (left hand) and accounting for competing risks (right hand)

Women (not accounting for competing risks)

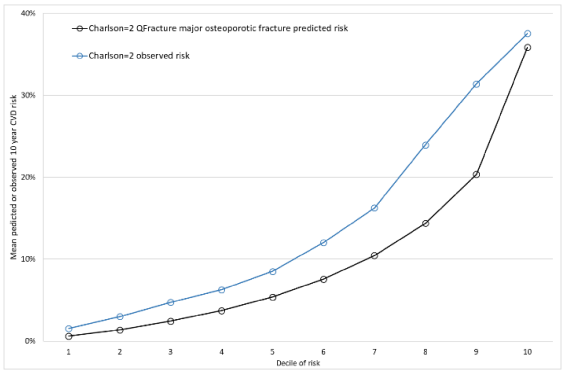
1a: mCCI=0



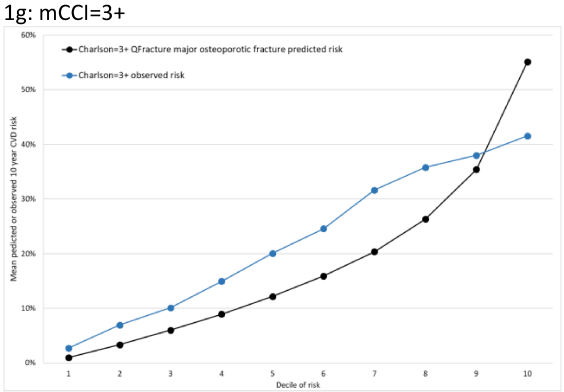
1c: mCCI=1



1e: mCCI=2

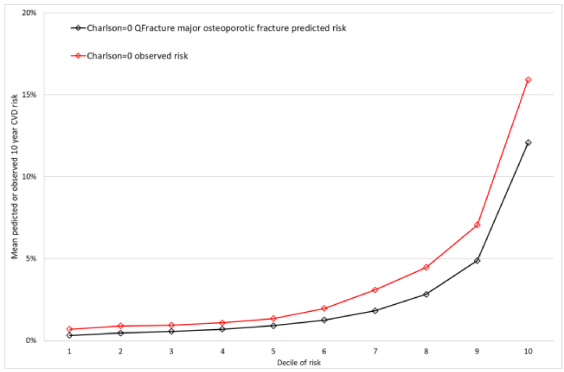


1g: mCCI=3+

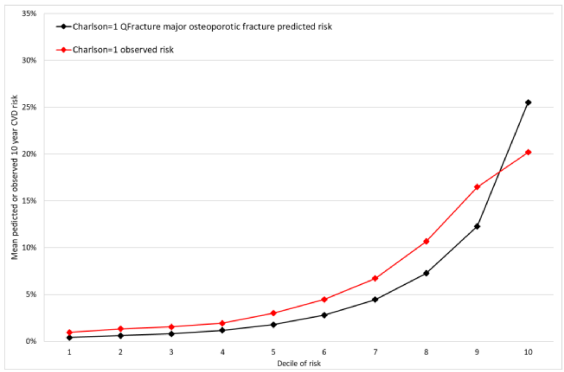


Women (accounting for competing risks)

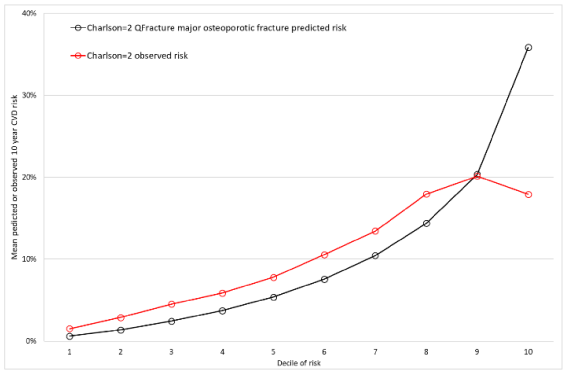
1b: mCCI=0



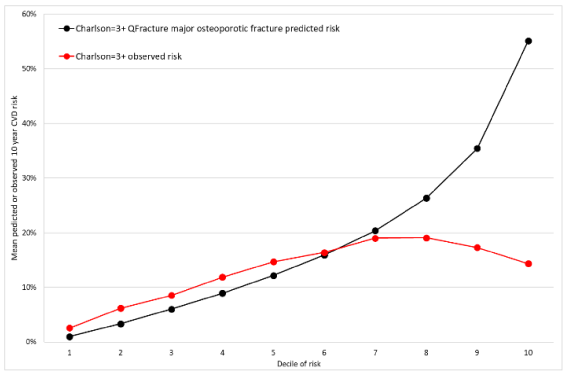
1d: mCCI=1



1f: mCCI=2



1h: mCCI=3+

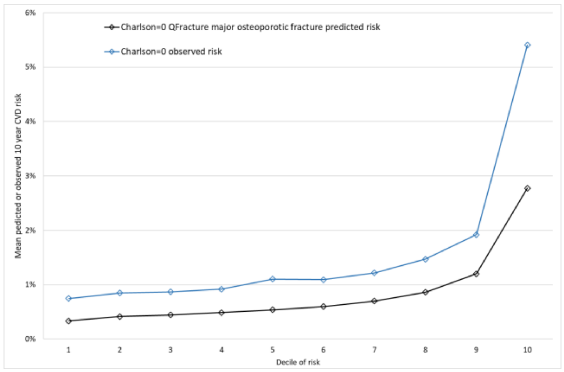


* Observed risk is based on the Kaplan-Meier estimator which does not account for competing mortality risk.
# Observed risk is based on the Aalen-Johansen estimator which accounts for competing mortality risk
Coloured line (observed risk) above matching black line (predicted risk) indicates under-prediction; below indicates over-prediction

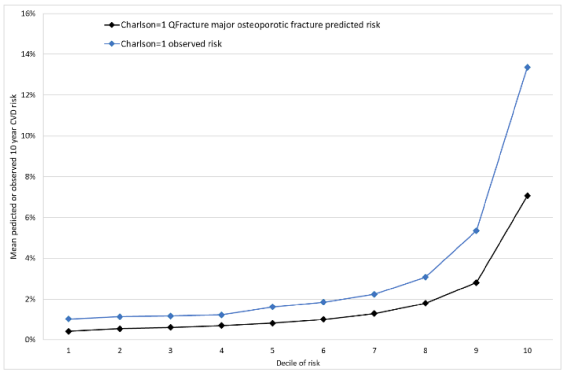
Figure S5: Calibration for major osteoporotic fracture in men by Charlson Score without accounting for competing risks (left hand) and accounting for competing risks (right hand)

Men (not accounting for competing risks)

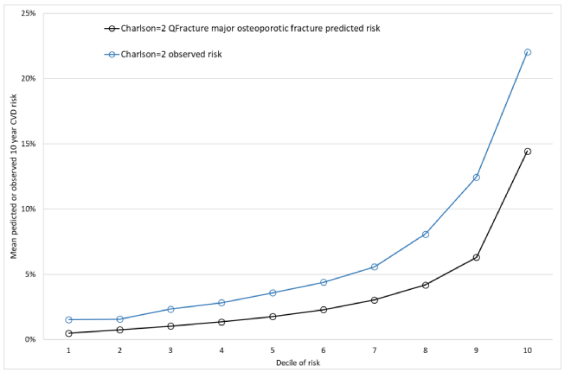
1a: mCCI=0



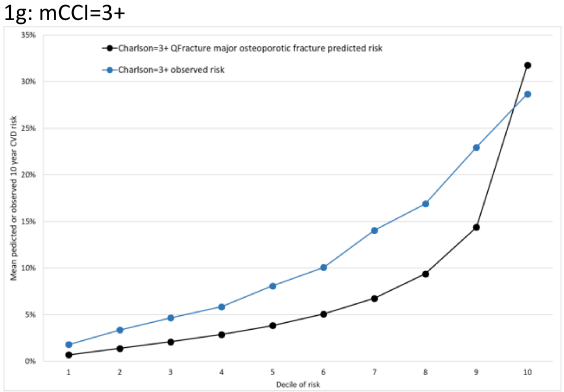
1c: mCCI=1



1e: mCCI=2

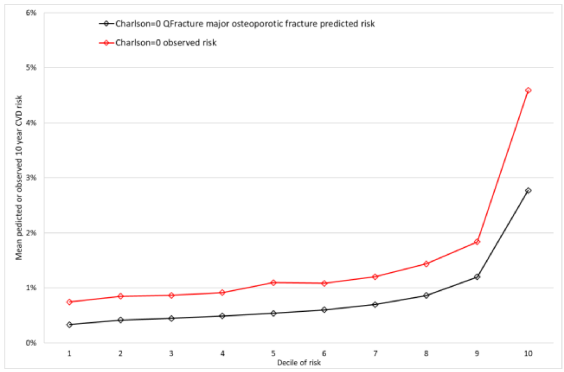


1g: mCCI=3+

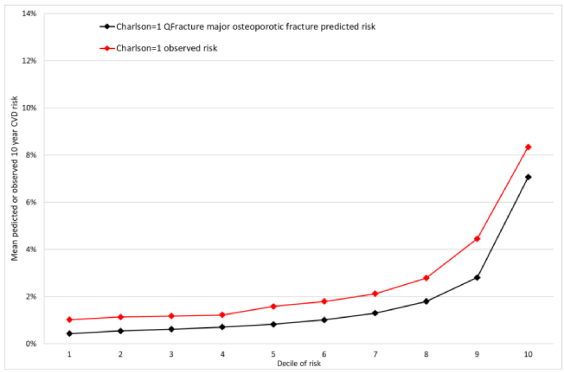


Men (accounting for competing risks)

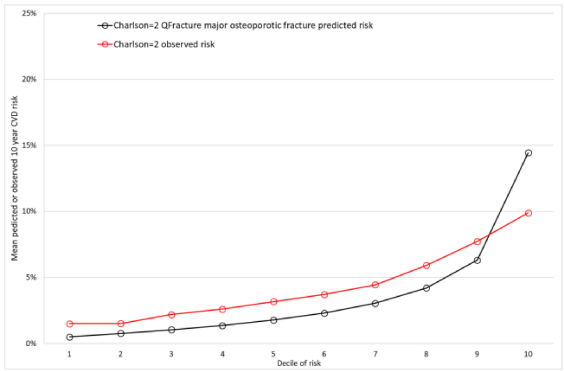
1b: mCCI=0



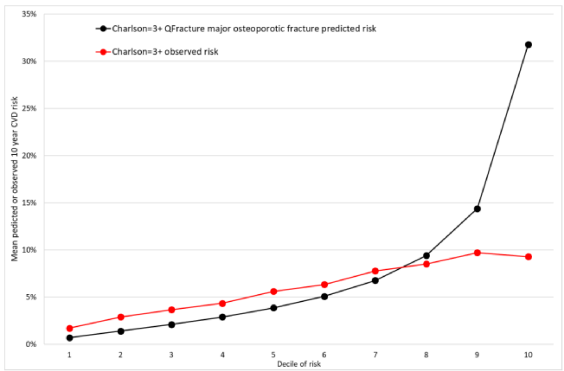
1d: mCCI=1



1f: mCCI=2



1h: mCCI=3+

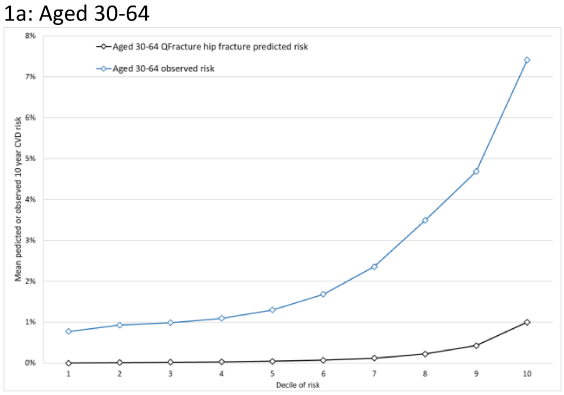


* Observed risk is based on the Kaplan-Meier estimator which does not account for competing mortality risk.
# Observed risk is based on the Aalen-Johansen estimator which accounts for competing mortality risk
Coloured line (observed risk) above matching black line (predicted risk) indicates under-prediction; below indicates over-prediction

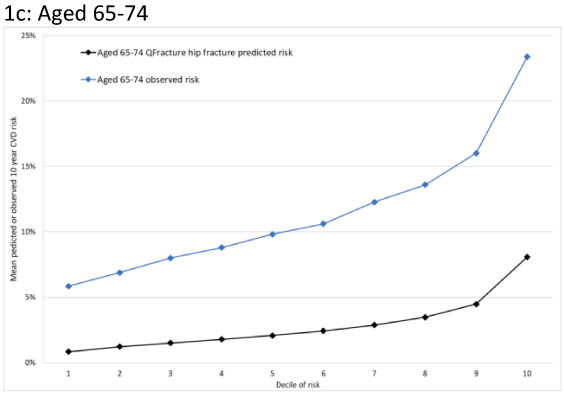
Figure S6: Calibration for hip fracture in women by agegroup without accounting for competing risks (left hand) and accounting for competing risks (right hand)

Women (not accounting for competing risks)

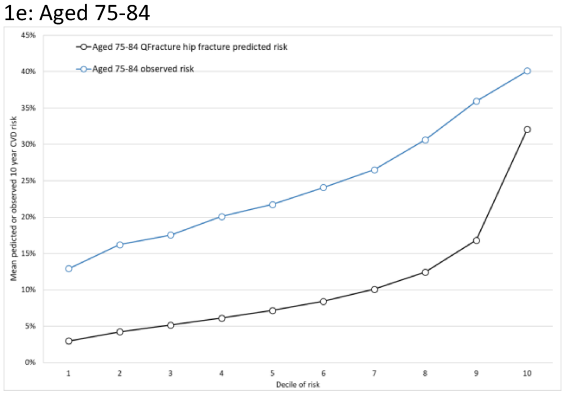
1a: Aged 30-64



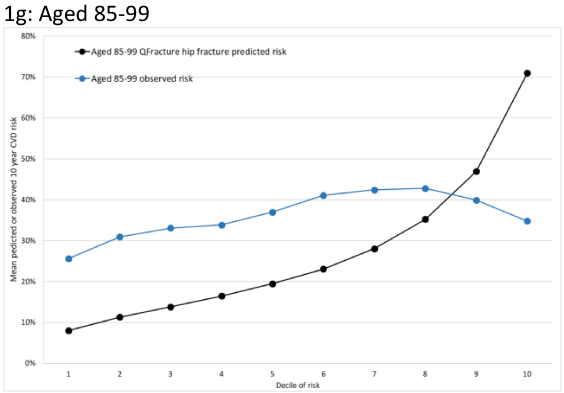
1c: Aged 65-74



1e: Aged 75-84

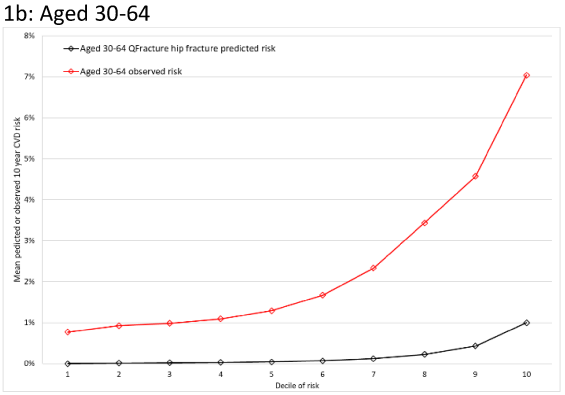


1g: Aged 85-99

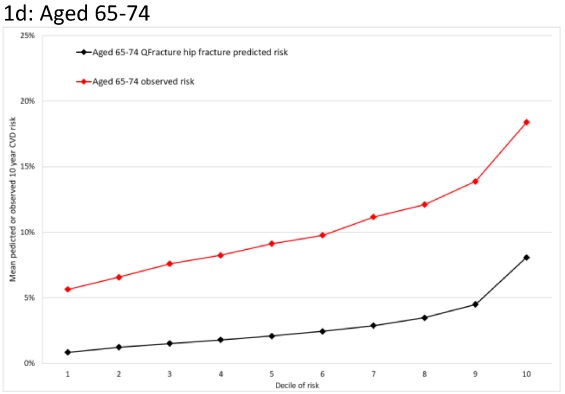


Women (accounting for competing risks)

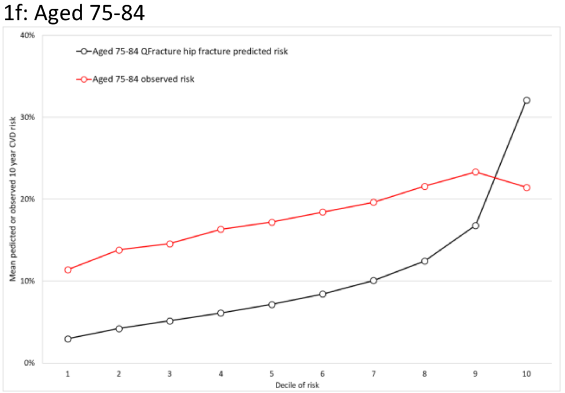
1b: Aged 30-64



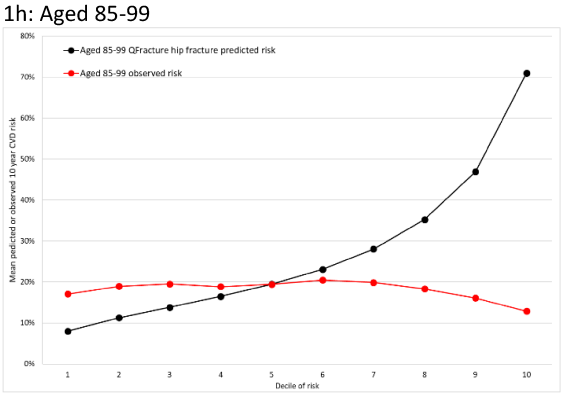
1d: Aged 65-74



1f: Aged 75-84



1h: Aged 85-99

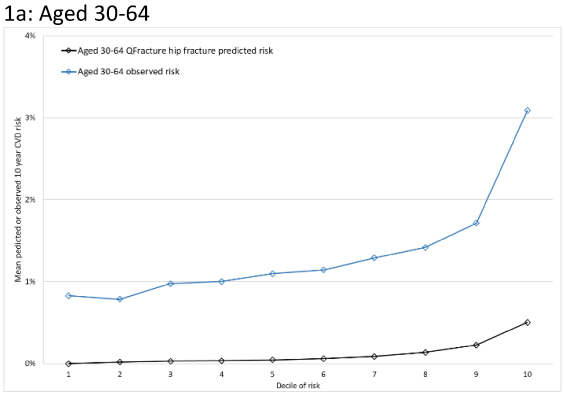


* Observed risk is based on the Kaplan-Meier estimator which does not account for competing mortality risk.
# Observed risk is based on the Aalen-Johansen estimator which accounts for competing mortality risk
Coloured line (observed risk) above matching black line (predicted risk) indicates under-prediction; below indicates over-prediction

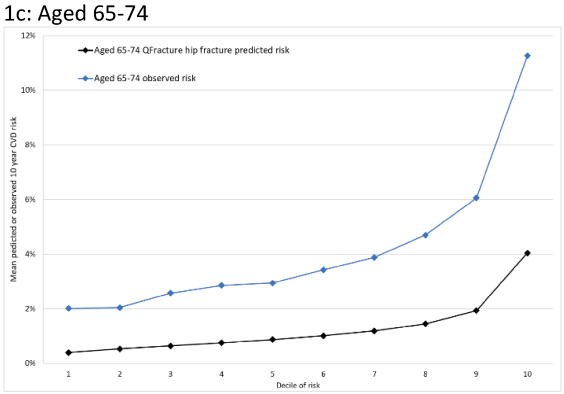
Figure S7: Calibration for hip fracture in men by agegroup without accounting for competing risks (left hand) and accounting for competing risks (right hand)

Men (not accounting for competing risks)

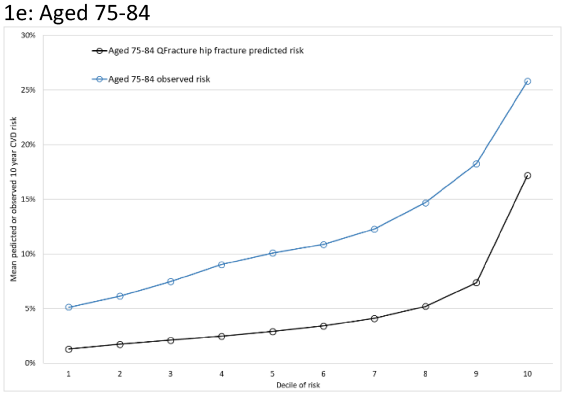
1a: Aged 30-64



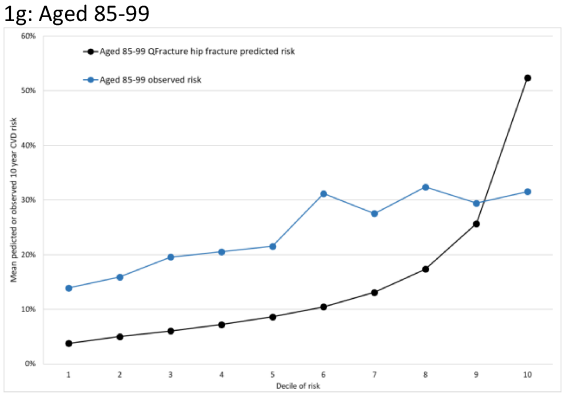
1c: Aged 65-74



1e: Aged 75-84

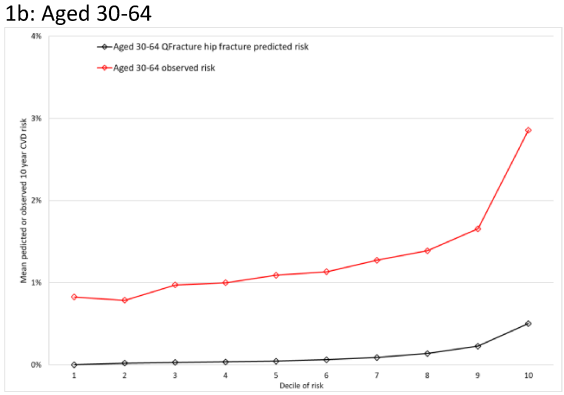


1g: Aged 85-99

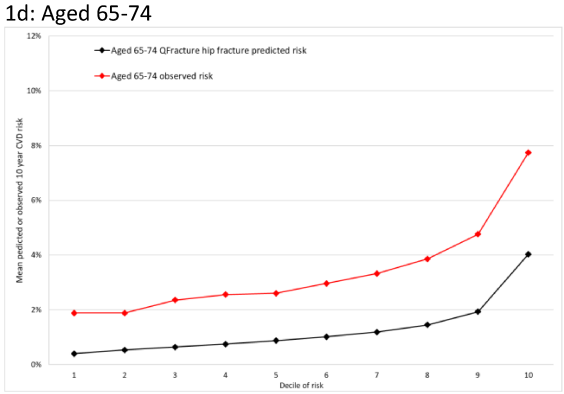


Men (accounting for competing risks)

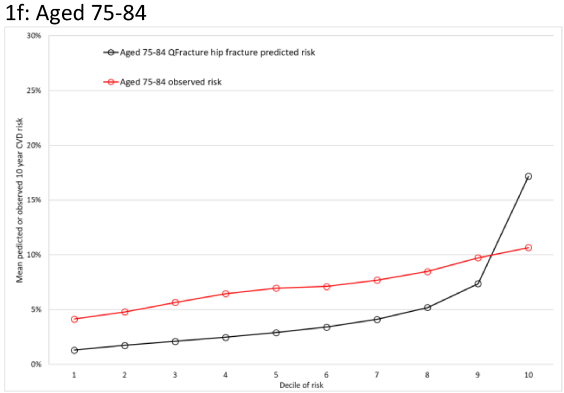
1b: Aged 30-64



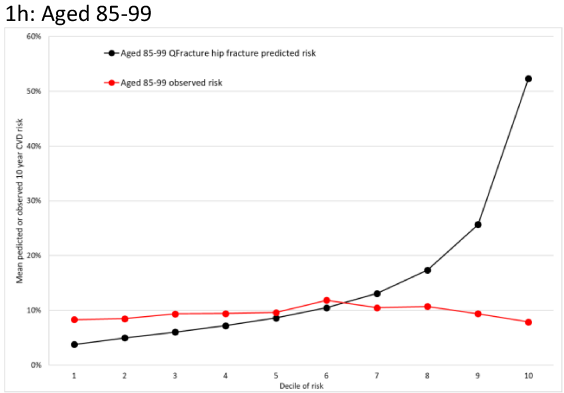
1d: Aged 65-74



1f: Aged 75-84



1h: Aged 85-99

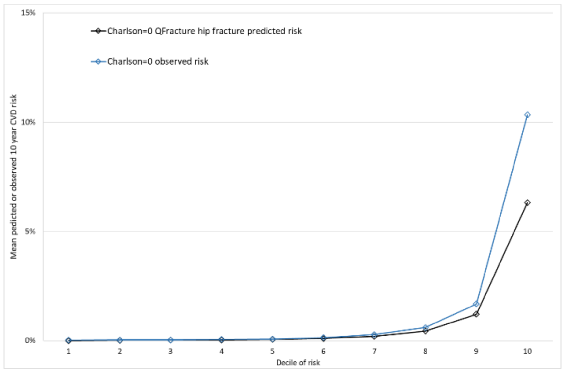


* Observed risk is based on the Kaplan-Meier estimator which does not account for competing mortality risk.
# Observed risk is based on the Aalen-Johansen estimator which accounts for competing mortality risk
Coloured line (observed risk) above matching black line (predicted risk) indicates under-prediction; below indicates over-prediction

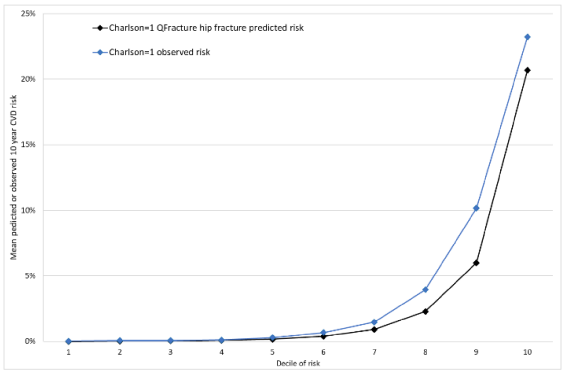
Figure S8: Calibration for hip fracture in women by Charlson Score without accounting for competing risks (left hand) and accounting for competing risks (right hand)

Women (not accounting for competing risks)

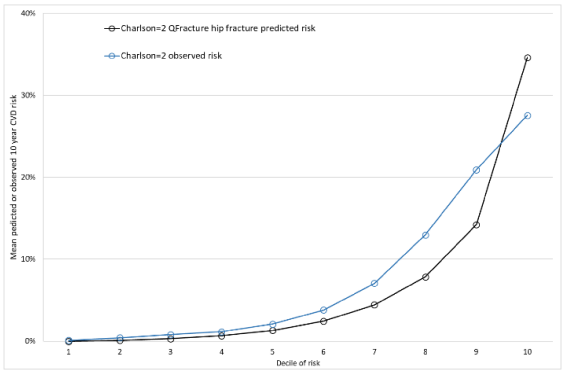
1a: mCCI=0



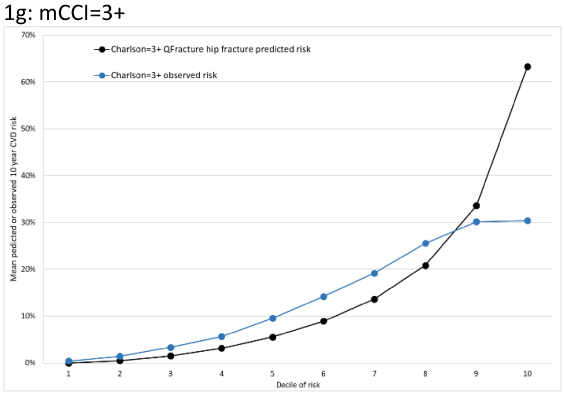
1c: mCCI=1



1e: mCCI=2

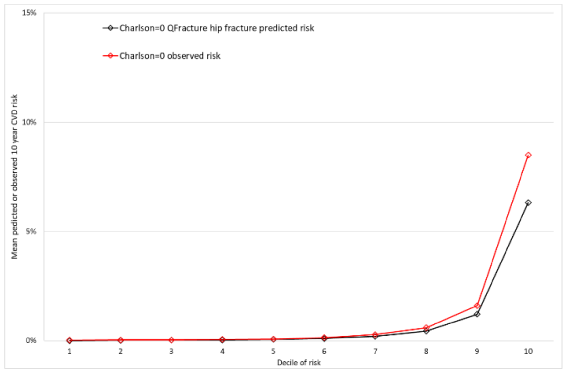


1g: mCCI=3+

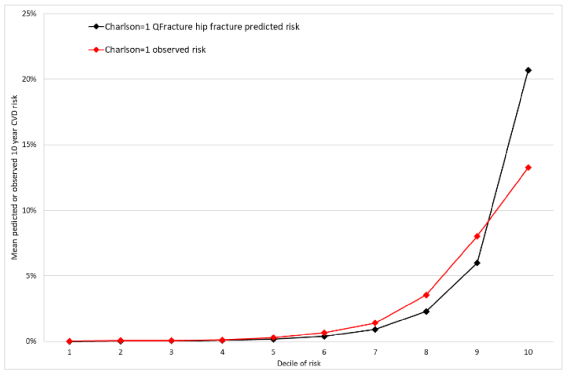


Women (accounting for competing risks)

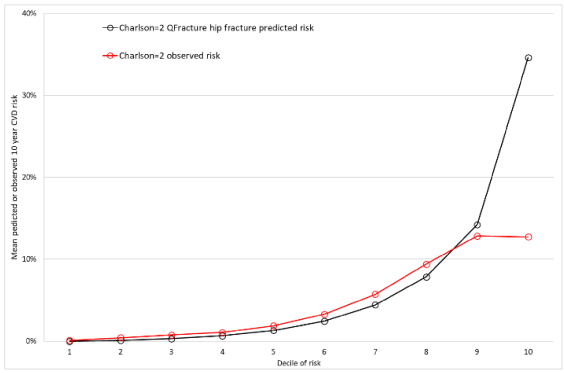
1b: mCCI=0



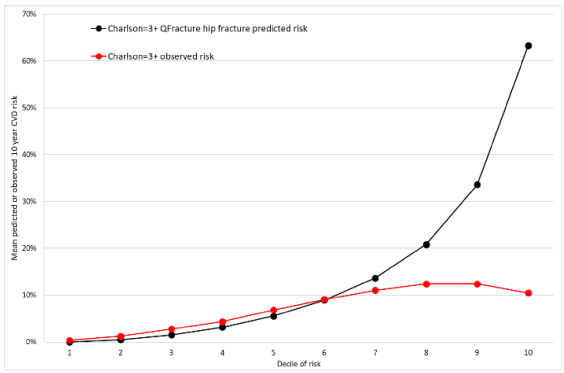
1d: mCCI=1



1f: mCCI=2



1h: mCCI=3+

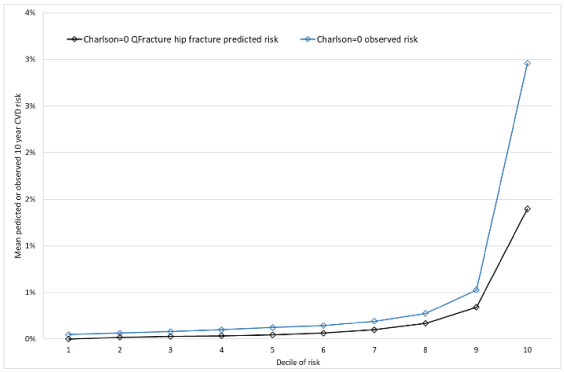


* Observed risk is based on the Kaplan-Meier estimator which does not account for competing mortality risk.
# Observed risk is based on the Aalen-Johansen estimator which accounts for competing mortality risk
Coloured line (observed risk) above matching black line (predicted risk) indicates under-prediction; below indicates over-prediction

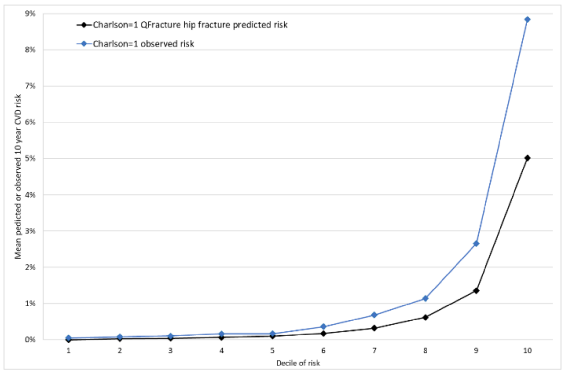
Figure S9: Calibration for hip fracture in men by Charlson Score without accounting for competing risks (left hand) and accounting for competing risks (right hand)

Men (not accounting for competing risks)

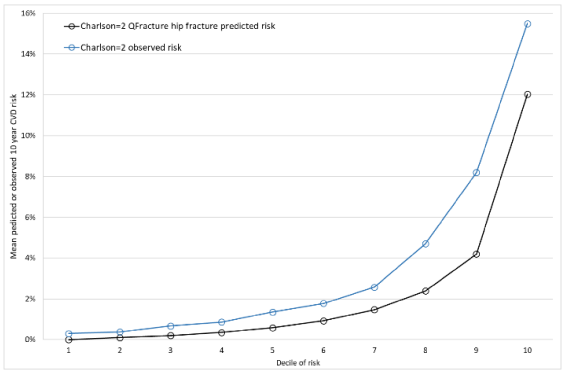
1a: mCCI=0



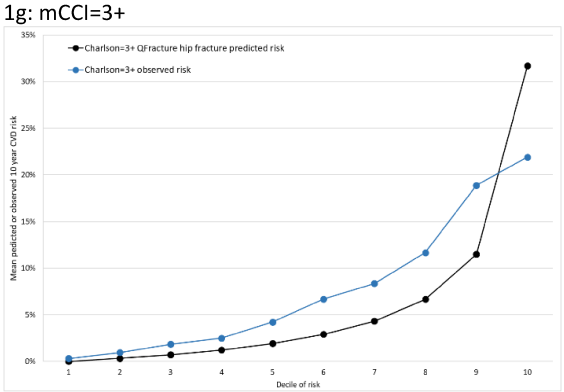
1c: mCCI=1



1e: mCCI=2

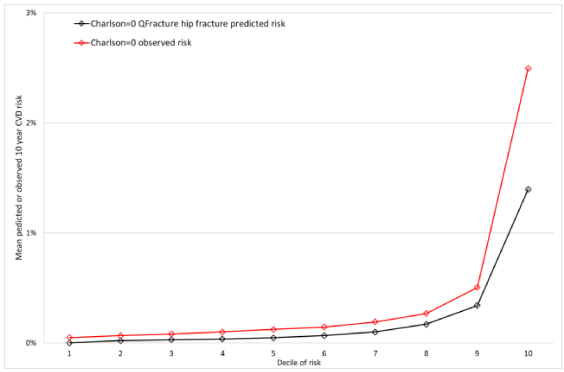


1g: mCCI=3+

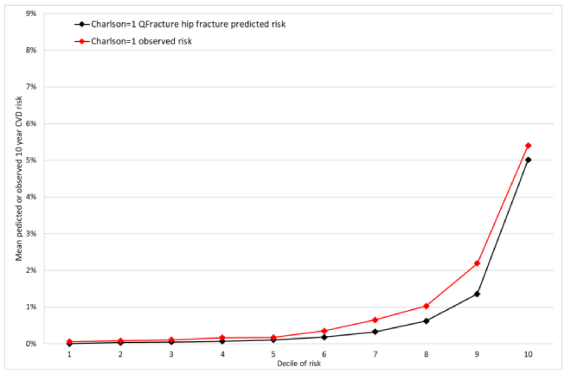


Men (accounting for competing risks)

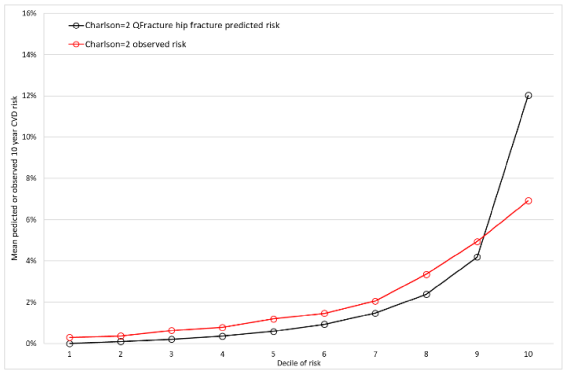
1b: mCCI=0



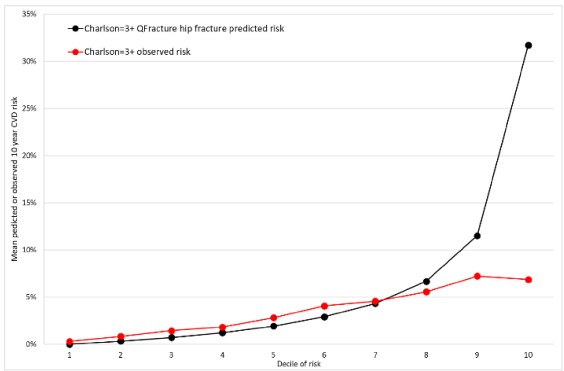
1d: mCCI=1



1f: mCCI=2



1h: mCCI=3+



* Observed risk is based on the Kaplan-Meier estimator which does not account for competing mortality risk.
# Observed risk is based on the Aalen-Johansen estimator which accounts for competing mortality risk
Coloured line (observed risk) above matching black line (predicted risk) indicates under-prediction; below indicates over-prediction

References

1. Kuan V, Denaxas S, Gonzalez-Izquierdo A, et al. A chronological map of 308 physical and mental health conditions from 4 million individuals in the English National Health Service. The Lancet Digital Health 2019;1:e63-e77.
2. Livingstone S, Morales DR, Donnan PT, et al. Effect of competing mortality risks on predictive performance of the QRISK3 cardiovascular risk prediction tool in older people and those with comorbidity: external validation population cohort study. The Lancet Healthy Longevity 2021;2:e352-e61.
3. Collins GS, Mallett S, Altman DG. Predicting risk of osteoporotic and hip fracture in the United Kingdom: prospective independent and external validation of QFractureScores2011.
4. Hippisley-Cox J, Coupland C. Predicting risk of osteoporotic fracture in men and women in England and Wales: prospective derivation and validation of QFractureScores2009.
5. Hippisley-Cox J, Coupland C. Derivation and validation of updated QFracture algorithm to predict risk of osteoporotic fracture in primary care in the United Kingdom: prospective open cohort study. BMJ 2012;344:e3427.