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A simple clinical score for estimating the long-term risk of fracture in post-menopausal women

T.P. VAN STAA[1,2], P. GEUSENS[3,4], J.A. KANIS[5], H.G.M. LEUFKENS[1], S. GEHLBACH[2] and C. COOPER[2]

From the [1]Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, Netherlands, [2]MRC Epidemiology Resource Centre, University of Southampton, Southampton, UK, [3]Department of Rheumatology, University Hospital, Maastricht, Netherlands, [4]Limburg University Center, Diepenbeek, Belgium, and [5]Centre for Metabolic Bone Disease (WHO Collaborating Centre), University of Sheffield Medical School, Sheffield, UK

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Summary

Background: Simple tools are needed to identify patients at high risk of fracture.
Aim: To develop a simple clinical tool for assessing 5-year risk of fracture.
Design: Cohort study.
Methods: The study population consisted of all women aged 50+ included in the THIN Research Database (containing computerized medical records of UK general practices). Using Cox proportional hazards models, a risk score was initially estimated from age, body mass index, and clinical risk factors. The 5-year risk of fracture (survival function) was estimated for each score.
Results: The study population included 366 104 women aged $\geqslant$ 50 years (mean follow-up 5.8 years). Of these, 6453 suffered a hip fracture. Several characteristics independently contributed to the fracture risk score (age, body mass index, fracture and fall history, previous diagnoses and use of medication). The 5-year risks for hip fracture for patients with total scores of 10, 30 and 50 were 0.3% (95%CI 0.3–0.4%), 2.2% (95%CI 2.1–2.2%), and 13.1% (95%CI 12.5–13.7%), respectively. A woman aged 65 years with low BMI and a history of both fracture and falling would have a hip fracture risk score of 37, with a corresponding 5-year risk for a hip fracture of 4.1% (4.0–4.2%). The risk score was validated and tested in another population (from GPRD), with a good concurrence between predicted and observed risks of fracture.
Discussion: This risk score predicts the long-term risk of fracture, and could be used for targeting patients for further investigation, such as bone densitometry.

Introduction

Osteoporotic fracture is a serious source of morbidity and mortality in the elderly. Prospective studies have demonstrated that bone mineral density (BMD) is a major determinant of the risk of osteoporotic fracture: the risk of hip fracture approximately doubles with a decrease in bone mineral density of 1 SD below the age-adjusted mean.[1] However, because the risk of fracture is also related to bone quality and to non-skeletal risk factors, screening the BMD of whole populations is not generally recommended. Instead, case-finding strategies are widely accepted as the way to identify

Address correspondence to Professor C. Cooper, Professor of Rheumatology and Director, MRC Epidemiology Resource Centre, Southampton General Hospital, Southampton SO16 6YD. email: cc@mrc.soton.ac.uk

individuals suitable for treatment; the targeting of high-risk populations is very important for cost-effectiveness.[2,3] In a case-finding strategy, individuals are identified by the presence of risk factors and subsequently undergo BMD examination, with intervention recommended when the BMD is below a given threshold. In a recent study, a case-finding strategy that combined the information of clinical risk factors and selective use of BMD better identified high-risk patient groups.[4]

Several studies have used information on clinical risk factors to develop scores that predict long-term risk of fractures[5–8] or low BMD.[9–11] For example, the FRACTURE Index was developed using data from the Study of Osteoporotic Fractures (SOF) and was based on age, fracture history, maternal hip fracture, weight, smoking status and use of arms to stand up from a chair. Each of these variables was then given a score, based on the relative increase in the risk of fracture in patients with this variable. The long-term risk of fracture was then calculated for the total score.[5] However, patients in the SOF study and the other prospective studies may not be representative of the general population of older women, as they relied on volunteers, who may be healthier than women of the same age in the general population.[5] The primary objective of this study was to estimate the long-term risks of fracture in a large general population of post-menopausal women.

Methods

Information for the study was obtained from The Health Improvement Network (THIN) research database of computerized medical records of UK general practitioners.[12] General practitioners (GP) play a key role in the UK health care system, as they are responsible for primary health care and specialist referrals. Patients are semi-permanently affiliated to a practice, which centralizes the medical information from the GPs, specialist referrals and hospitalizations. The data recorded in THIN include demographic information, prescription details, clinical events, preventive care provided, specialist referrals, hospital admissions and their major outcomes. A validation study of the General Practice Research Database (GPRD) reported a high validity with respect to fractures. Hip fractures were confirmed by the GP in 91.0% of fracture cases.[13]

Study population

The study population consisted of all women aged 50 years or older who were registered at one of the THIN practices. A fracture risk score and corresponding 5- and 10-year risks of fracture were calculated for each woman, using Cox proportional hazards regression models. The methodology was similar to that previously applied to an analysis of oral glucocorticoid users.[14] The study population was followed from 2 year after start of computerization of the general practice to the end of THIN data collection. Only data from 1990 onwards were used. As a specific risk score has now been developed for oral glucocorticoid users,[14] patients with recent use of oral glucocorticoids were excluded.

Cases were patients who had a clinical osteoporotic fracture during follow-up (i.e. fracture of the radius/ulna, humerus, rib, femur/hip, pelvis or vertebrae). The history of any type of fracture was determined. Also, the occurrence of osteoporotic fracture at any other site during follow-up was noted. In order to exclude fractures that occurred at the same time but were recorded at a different time in the medical record, any fractures that occurred in the prior 3-month period were not included.

The risk factors considered in the study included body mass index (BMI) and smoking history, where available. The analysis also evaluated the presence of diseases and use of drugs that have been associated with an increased risk of fracture in a previous GPRD study.[15] These included prescriptions in the previous 6 months for central nervous system medication (anticonvulsants, hypnotics/anxiolytics, antidepressants, antipsychotics and anti-Parkinsonian drugs), recorded medical history of early menopause, and of falls in the previous 6–18 months. The presence of the following diseases was also noted: chronic obstructive pulmonary disease and asthma (ICD9 492, 493, 496), cerebrovascular accident (431, 432, 433, 434, 436), heart failure (428), rheumatoid arthritis (714), and inflammatory bowel disease (555, 556). For patients with any of these diseases, presence of a record indicating a GP visit or hospitalization for these diseases in the 6 months before was also measured. Risk factors were included as categorical variables (present vs. absent). For risk factors with missing data (smoking and BMI), indicator variables for missing values were included in the regression models. The period of follow-up period was divided into 6-month intervals. As age increases over time, and clinical risk factors may vary over time (e.g. medication use), the patient's age and the presence of clinical risk factors were assessed at the start of each 6-month interval of follow-up.

Statistical methods

Cox proportional hazards models were used to estimate the long-term risks of fracture. For each set of patient characteristics, the Cox model allows calculation of an individual's probability of fracture (i.e. survivor function). We fitted regression models with age and the risk factors. Backward regression was conducted using a significance level of $p = 0.05$. We also investigated possible statistical interactions between age and the risk factors (i.e. whether risk scores differed with age). The beta-coefficients of this Cox model (the exponentials of which constitute the relative rates, RR) were converted into integer risk scores. The value of each integer is the rounded sum of the predictors of the Cox model multiplied by 10. Because age and clinical risk factors varied over time, the risk score of a patient was averaged over the total follow-up period. This score represents the probability of fracturing, conditional on patient survival. The absolute risk of fracture at the time of the mean duration of follow-up was then estimated for each risk score. The average hazard rate (log of risk) over this period was then used to calculate the 5- and 10-year risks of fracture. Various methods were used to test the fitting of the Cox models.[16] The proportional hazards assumption was evaluated by visual examination of the Schoenfeld residuals. We also compared the observed 5-year probability of fracture (based on the Kaplan-Meier estimate) to the probability predicted by the Cox model. This was done by dividing the study population into 10 groups based on the predicted probability of fracture. The observed and predicted probabilities for fracture were then compared. Receiver operator characteristic (ROC) curves and the areas under the ROC curve were estimated.

In this population, the vertebral fractures mostly concerned clinically symptomatic vertebral fractures, confirmed radiographically.[13] Systematic morphometry of vertebral fractures was not routinely done by the GP and clinically symptomatic vertebral fractures are also under-diagnosed in UK general practice.[13] In order to adjust the vertebral rates for this, we compared the rates of morphometric vertebral fracture from the European Prospective Osteoporosis Study (EPOS)[17] to the rates in the THIN cohort. The vertebral fracture rates in EPOS were about 18 times higher compared to those in THIN. We used half of this ratio, a more conservative approach, in line with estimates from a recent pharmacoeconomic analysis.[18] The log of this ratio was then added to the risk score (i.e. multiplying the hazard rates by this ratio). The underlying assumption was that the effects of risk factors are similar between the different populations, and between morphometric and clinically symptomatic vertebral fractures (i.e. RRs of exposure are identical).

Validation of predictive model

We obtained information from a random age-stratified sample of 50 000 women aged $\geqslant 50$ years from the GPRD. Patients with recent use of oral glucocorticoids were also excluded in this dataset. As some GP practices contribute data to both GPRD and THIN, patients from general practices that contribute their medical records to both THIN and GPRD were excluded. The RRs of fracture for the different risk factors were compared between the two populations. Observed fracture rates and expected rates based on risk scores as developed in THIN were also evaluated.

Results

The study population consisted of 366 104 women aged $\geqslant 50$ years. Mean duration of follow-up was 5.8 years (median 4.7 years). There were 6453 women who suffered a hip fracture (1610 clinical vertebral and 14 011 other osteoporotic fractures).

Table 1 displays the RRs of fracture for age and risk factors. Strong risk factors for fracture included age, low BMI, fall and fracture history. Patients with one of the selected chronic diseases also had increased risks of fractures, especially in those with a recent GP visit or hospitalization. Table 2 presents the risk score for various patient characteristics. For example, for a woman aged 65 years with low BMI and fracture and fall history, the total hip fracture risk score was 37 (risk score for age 13; low BMI 6; fall history 10; fracture history 8; total 37 points). The corresponding 5-year risk for a hip fracture was 4.1% (95%CI 4.0–4.2%). The 5-year risks for hip fracture for patients with total scores of 10, 30 and 50 were 0.3% (95%CI 0.3–0.4%), 2.2% (95%CI 2.1–2.2%), and 13.1% (95%CI 12.5–13.7%), respectively (Figure 1). Table 3 shows the distribution of risk scores in the study population. The median hip fracture risk score was 38 (90% percentile: 46) for women aged 80–89 years. The area under the ROC curve was 0.84 for hip fractures, 0.69 for clinical vertebral fractures and 0.60 for other clinical osteoporotic fractures.

The validation dataset (GPRD) included 32 728 women followed for a mean 5.6 years. Fracture rates in the validation dataset were higher than in THIN. There were also differences within THIN in fracture rates between practices that contributed both to

Table 1 Prevalence and the age-adjusted relative risk (95%CI) of fracture for age and clinical risk factors

Risk factor	Prevalence	Femur/hip	Clinical vertebral	Other clinical osteoporotic
Age (years)				
50–59	33.7%	Reference	Reference	Reference
60–69	27.2%	3.52 (2.98–4.15)	2.26 (1.85–2.77)	1.67 (1.59–1.76)
70–79	23.2%	12.57 (10.81–14.63)	5.46 (4.54–6.56)	2.45 (2.33–2.58)
80–89	13.0%	40.96 (35.33–47.50)	9.15 (7.60–11.01)	3.51 (3.33–3.70)
90+	2.9%	71.27 (61.03–83.24)	7.95 (6.16–10.26)	3.83 (3.53–4.15)
Fracture history	8.1%	2.00 (1.90–2.12)	2.40 (2.15–2.68)	2.05 (1.97–2.14)
Fall history	1.7%	1.96 (1.79–2.15)	1.82 (1.47–2.25)	1.74 (1.60–1.89)
*Body mass index**				
<20	6.2%	1.91 (1.74–2.09)	1.41 (1.16–1.72)	1.21 (1.13–1.31)
⩾26	44.8%	0.63 (0.58–0.69)	0.84 (0.74–0.96)	0.84 (0.80–0.88)
Smoker*	27.4%	1.44 (1.33–1.57)	1.45 (1.26–1.68)	1.13 (1.08–1.19)
Chronic disease				
Without recent GP visit/hospitalization	13.4%	1.39 (1.31–1.47)	1.63 (1.45–1.83)	1.18 (1.13–1.24)
With recent GP visit/hospitalization	2.0%	1.88 (1.68–2.11)	2.38 (1.91–2.97)	1.29 (1.17–1.43)
Recent use of central nervous system medication	18.9%	1.94 (1.85–2.04)	1.66 (1.50–1.85)	1.33 (1.28–1.38)
History of early menopause	0.1%	2.23 (1.12–4.47)	1.89 (0.47–7.58)	0.68 (0.33–1.43)

*Information missing on body mass index for 33.9% of the patients and on smoking history for 40.0%; reference group for body mass index included patients with an index between 20 and 26.

GPRD and THIN vs. those contributing to THIN only: the rate of hip fracture was 31% higher in those contributing both to GPRD and THIN. For clinical vertebral fractures, the difference was +64% and for other clinical osteoporotic fractures +35%. When stratifying within each dataset by deciles of fracture risk, a good concurrence was found between the predicted and observed risks of fracture (Table 4).

Discussion

We have developed a clinical risk score that provides an easily applicable clinical method of estimating a patient's individual risk of fracture, based on routinely available clinical information. Our data suggest that that high-risk patients can be identified based on clinical risk factors.

Several other studies have evaluated the value of clinical risk factors in the prediction of fracture risk[5–8] or low BMD.[9–11] In addition to the FRACTURE index derived from the SOF study,[5] the EPIDOS study[8] developed a score for hip fracture risk based on age, neuromuscular factors (slow gait speed, reduced visual acuity and difficulty on the tandem stand test) and history of falling. The Rotterdam study used information on age, sex, height, weight, use of a walking aid and smoking to identify patients at high risk of hip fracture.[6] There are also several risk assessment schemes for identifying women with osteoporosis.[9–11,19,20] We found that several of these risk assessments schemes performed well in identifying women at high risk of hip fracture in our study population (Figure 2). Interestingly, there were no major differences in fracture risk between the various risk assessment schemes. A simple scheme that only included age and weight (the Osteoporosis Self-Assessment Tool[10]) found fracture risks similar to our more complex scheme. This may be related to the low prevalence in the general population of some of the risk factors included in our risk assessment scheme. Simple risk assessment schemes may be useful for the screening of broad populations, but may underestimate the risks in patients with risk factors not included in the scheme.

Low body weight and BMI are important variables in the various risk classification schemes as published in literature and in the risk score scheme developed in this study. Several studies, including our own, have shown a significant protective effect of high body weight or BMI on hip

Table 2 Risk score* of fracture based on age and clinical risk factors

	Femur/hip					Clinical vertebral					Other clinical osteoporotic				
Age (years)...	50–59	60–69	70–79	80–89	90+	50–59	60–69	70–79	80–89	90+	50–59	60–69	70–79	80–89	90+
Age	0	13	24	35	40	0	9	17	22	20	0	5	9	12	12
Fracture history	12	8	8	5	5	11	9	9	7	7	8	7	7	6	6
Fall history	10	10	10	4	4	10	8	8	2	2	7	5	5	4	4
	All ages					All ages					All ages				
Body mass index															
<20	6					3					2				
⩾26	−5					−2					−2				
Smoker	2					2					1				
Chronic disease															
Without recent GP visit/hospitalization	2					4					1				
With recent GP visit/hospitalization	5					8					2				
Recent use of central nervous system medication	6					4					2				
History of early menopause	7					0					0				

*Risk score = logarithm of the adjusted RR of fracture multiplied by 10; RRs are adjusted for age and all other clinical risk factors.

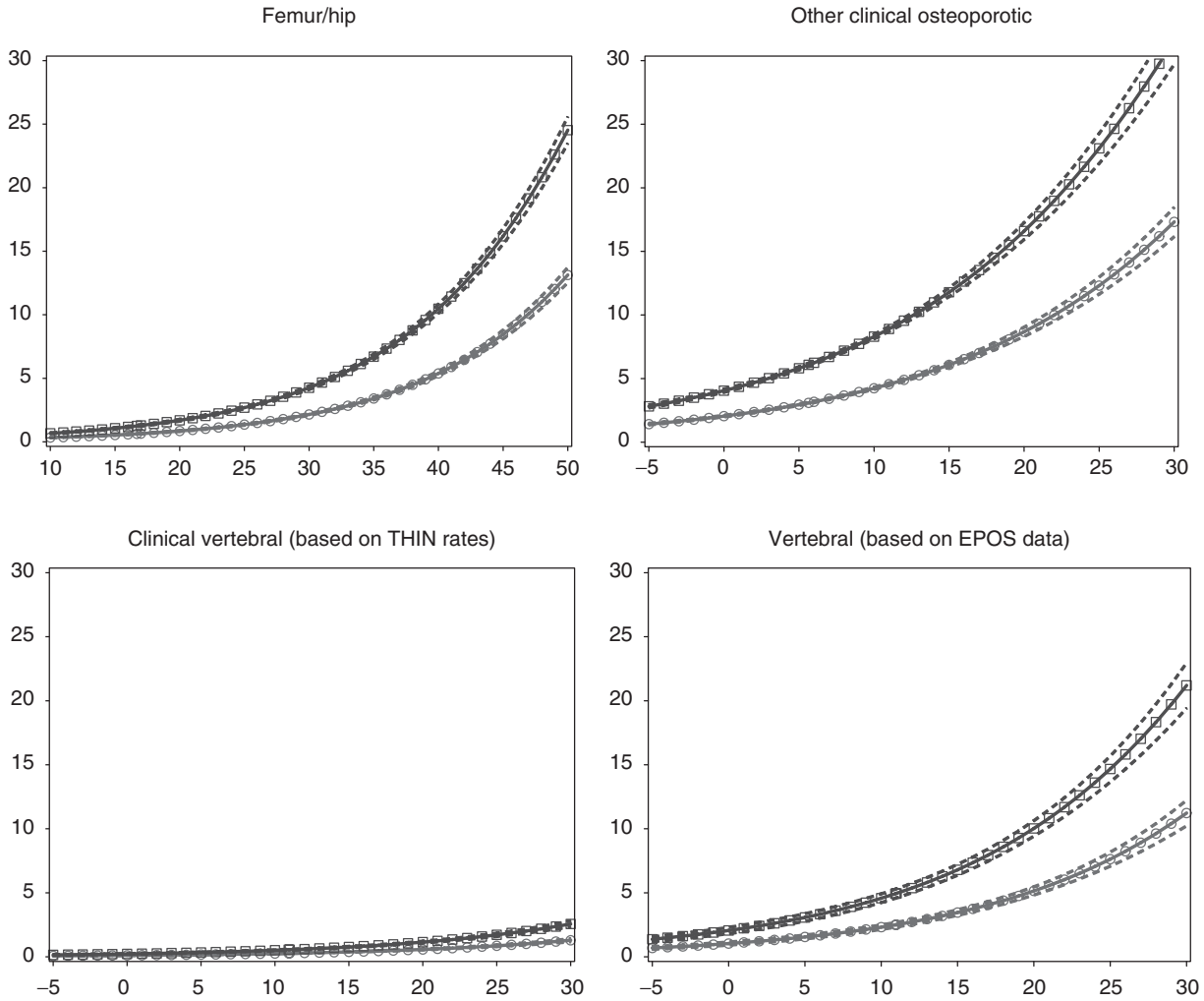

Figure 1. Relation between our risk score and risk of fracture for 5- and 10-year periods (○ = 5-year; □ = 10-year).

fracture risk.[21,22] This may be related to direct protective effect of adipose tissue around the hip, to the production of endogenous estrogens produced in adipose tissue, or to nutrient intake, including calcium and proteins. In addition, low body weight or BMI may be a marker of other conditions that increase the risk of osteoporosis or fracture. In our study population, there was a higher prevalence of other clinical risk factors in patients with low BMI. A review of clinical predictors of osteoporosis concluded that body weight <59 kg may be a simple and reasonably sensitive but non-specific measure for selecting women for further diagnostic testing.[23] These findings suggest that elderly women with low BMI should be targeted for further diagnostic testing, including bone densitometry. Furthermore, fracture history was an important predictor for fracture risk.[24]

Our results confirm that clinical risk factors can be used to identify individuals at high risk of fracture. Diagnostic examination can then be targeted to individuals with higher risks. However, the magnitude of the absolute risk of fracture does not determine the type of intervention that is required; risk of fracture can be related to both skeletal-related risk factors and fall-related risk factors.[25] An intervention that reduces the propensity for falling may be of limited value to individuals with a high risk of fracture due to low BMD or negative changes in bone micro-architecture. The same caveat may apply to giving a bisphosphonate to an individual with a high propensity of falling (e.g. due to sedative use). The efficacy of bisphosphonates in individuals with low BMD is well established, but they may be less efficacious in individuals with normal BMD.[26]

The risk estimates in this study are based on historical data. It has been argued that such data can only be an estimate for prospective prediction of fracture risk, because populations and

Table 3 Five-year fracture incidence at different percentiles of fracture risk scores

Age (years)	Percentile	Femur/hip		Other osteoporotic		Clinical vertebral		
						Based on THIN rates		Based on EPOS rates
		Score	Incidence	Score	Incidence	Score	Incidence	Incidence
50–59	10th	−5	0.1%	−2	1.8%	−3	0.1%	0.8%
	25th	0	0.1%	−1	1.9%	−2	0.1%	0.9%
	50th	1	0.1%	0	2.0%	0	0.1%	1.0%
	75th	3	0.2%	1	2.2%	2	0.1%	1.2%
	90th	8	0.3%	3	2.5%	7	0.2%	1.8%
60–69	10th	8	0.3%	3	2.5%	6	0.2%	1.7%
	25th	13	0.4%	4	2.7%	7	0.2%	1.8%
	50th	14	0.5%	5	2.9%	9	0.2%	2.1%
	75th	16	0.6%	6	3.2%	11	0.3%	2.5%
	90th	21	0.9%	9	3.9%	15	0.4%	3.5%
70–79	10th	20	0.9%	7	3.4%	14	0.4%	3.2%
	25th	24	1.2%	7	3.4%	14	0.4%	3.2%
	50th	25	1.4%	9	3.9%	17	0.5%	4.1%
	75th	30	2.2%	10	4.2%	21	0.6%	5.6%
	90th	33	2.8%	14	5.7%	25	0.9%	7.6%
80–89	10th	35	3.4%	10	4.2%	19	0.5%	4.8%
	25th	36	3.7%	10	4.2%	19	0.5%	4.8%
	50th	38	4.5%	12	4.9%	23	0.7%	6.5%
	75th	43	7.1%	14	5.7%	26	0.9%	8.2%
	90th	46	9.2%	18	7.5%	30	1.3%	11.2%
90+	10th	41	5.9%	10	4.2%	17	0.5%	4.1%
	25th	41	5.9%	10	4.2%	17	0.5%	4.1%
	50th	44	7.7%	13	5.3%	21	0.6%	5.6%
	75th	47	10.1%	15	6.1%	25	0.9%	7.6%
	90th	52	15.6%	19	8.1%	28	1.1%	9.6%

circumstances are continuously changing.[27] Also, the risk estimates in this study may not generalize to other populations, as the underlying fracture incidence and the effects of risk factors may vary. It would be more appropriate to view the risk estimates in this study as a tool to improve the prediction of fractures, rather than as definitive estimates applicable to every patient. Our findings are based on a complex mathematical model. We evaluated the key underlying assumptions and tested the predictive capacity in a different study population. However, we did not evaluate all possible interactions between the risk factors, and for certain risk factor combinations the model may therefore have over- or under-estimated fracture risks. Another limitation was that we did not have information on all risk factors for fracture (e.g. BMD, exercise, calcium intake, family history, diet), that could improve the accuracy of prediction for an individual patient. Information on BMI and smoking history was missing in about one-third of the population, as this information is not routinely measured and recorded by GPs. We can not exclude the possibility that these characteristics were only measured for selected groups of patients, but our results for the relationship to fracture are in concordance with those reported in the literature.[21,22]

In conclusion, a simple risk score based on age, BMI, fracture and fall history and history of other disease and concomitant drug use, can help to quantify the long-term absolute risk of fracture. This score can also be used to target preventative or investigative action to patients with higher long-term risks.

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Table 4 Observed[a] and predicted[b] 5-year fracture risks in the dataset used for the development of the risk score (THIN) and in the dataset used for validation (GPRD), with the population divided into 10 samples based on the fracture risk score in each dataset

Decile	Femur/hip				Clinical vertebral				Other clinical osteoporotic			
	THIN		GPRD		THIN		GPRD		THIN		GPRD	
	Observed	Predicted	Observed	Predicted	Observed	Predicted	Observed	Predicted	Observed	Predicted	Observed	Predicted
1	0.1%	0.1%	0.1%	0.2%	0.1%	0.1%	0.1%	0.2%	2.9%	2.0%	3.6%	2.8%
2	0.2%	0.2%	0.3%	0.4%	0.1%	0.1%	0.3%	0.2%	2.0%	2.1%	2.1%	3.2%
3	0.1%	0.2%	0.4%	0.5%	0.1%	0.2%	0.2%	0.3%	1.7%	2.2%	3.1%	3.6%
4	0.2%	0.3%	0.6%	1.2%	0.2%	0.2%	0.5%	0.4%	1.5%	2.5%	5.3%	4.0%
5	0.5%	0.4%	2.3%	1.9%	0.2%	0.2%	0.6%	0.4%	3.6%	2.8%	3.2%	4.4%
6	0.5%	0.7%	4.0%	3.4%	0.3%	0.3%	0.5%	0.5%	3.5%	3.1%	5.4%	4.8%
7	1.2%	1.1%	4.8%	4.8%	0.4%	0.4%	0.7%	0.5%	3.3%	3.4%	6.4%	5.0%
8	1.8%	1.8%	6.8%	5.9%	0.5%	0.4%	0.5%	0.6%	3.7%	3.7%	5.3%	5.5%
9	3.6%	3.1%	7.4%	7.4%	0.5%	0.6%	1.0%	0.8%	4.3%	4.2%	6.6%	6.4%
10	6.5%	6.4%	11.4%	12.1%	1.0%	1.0%	0.8%	1.2%	6.6%	6.7%	6.8%	8.3%

[a]Observed, based on 5-year life-table estimates; [b]Predicted, based on fracture risk scores.

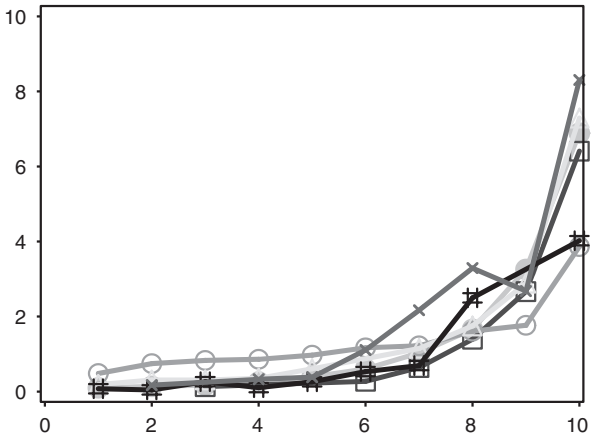

Figure 2. Five-year hip fracture incidence in deciles of the THIN population with different risk classification schemes (●, our risk score; □, Fracture Index;[5] X, Rotterdam Risk Score;[6] ○, Body weight criterion;[9] #, Osteoporosis Risk Assessment Instrument;[11] Δ, Osteoporosis Self-Assessment Tool.[10] Calculation of the risk scores was as done as follows. Fracture Index: age (years): 1 if 65–69, 2 if 70–74, 3 if 75–79, 4 if 80–84, 5 if 85+; fracture history, 1; weight (kg): 1 if <57; Smoker, 1. Rotterdam Risk Score: age (years): 7 if 60–64, 14 if 65–69, 21 if 70–74, 28 if 75–79, 35 if 80–84, 42 if 85+; height (cm): 4 if 160–164, 8 if 165–169, 12 if 170–174, 16 if 175–179, 20 if ⩾180. Weight (kg): 2 if 90–94, 4 if 85–89, 6 if 80–84, 8 if 75–79, 10 if 70–74, 12 if 65–69, 14 if 60–64, 16 if 55–59, 18 if < 55; smoker, 9. Body weight criterion: body weight in kg. Osteoporosis Risk Assessment Instrument: age (years): 5 if 55–64, 9 if 65–74, 15 if 75+; weight (kg): 9 if <60, 3 if 60–69; oestrogen use, 2. Osteoporosis Self–Assessment Tool: 0.2×(weight in kg–age in years) truncate to yield integer.

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