Development of a simple prognostic nomogram for individualising 5-year and 10-year absolute risks of fracture: a population-based prospective study among postmenopausal women

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ABSTRACT

Objectives Previous fracture prediction models have been based on the assumption of a stable risk of subsequent fractures over time. The aim of the present work was to develop a nomogram for prediction of 5-year and 10-year individualised absolute fracture risks for postmenopausal women taking into account the time relation between fractures.

Methods A population-based prospective study was performed in 23 general practice centres located in the southern part of The Netherlands. At baseline (1992–1994), 4203 postmenopausal women between 50 and 80 years participated and 2372 of them also participated 10 years later. Baseline measurements included lumbar spine bone mineral density (BMD) and clinical risk factor evaluation. The incidence of fractures was ascertained. Bayesian model averaging and Cox's proportional hazards model were used.

Results After enrolment, 382 (16.1%) women had a clinical fracture. Fracture risk was associated with advancing age (HR 1.09 per SD (5 years); 95% CI 1.01 to 1.17), lumbar spine BMD (HR 1.23 per −1 SD; 95% CI 1.10 to 1.37) and a prior fracture, with HR 3.27 (95% CI 2.50 to 4.30) for a recent prior fracture (≤5 years previously) and HR 1.97 (95% CI 1.43 to 2.71) for a non-recent prior fracture after menopause (>5 years previously). Women with a recent prior fracture had 66% higher risk of an incident fracture than those with a non-recent prior fracture (HR 1.66; 95% CI 1.15 to 2.40).

Conclusions The nomogram developed can help doctors to inform patients more effectively and thus better manage patient care by providing an individualised fracture risk taking into account the time relationship for fractures.

INTRODUCTION

Fractures are a growing problem today and an urgent public health challenge due to the increasing proportion of older people and the increasing incidence of fractures. It is estimated that one in two women aged ≥50 years will sustain a fracture during their remaining lifetime, and the resulting costs will probably double by 2025.[1 2] An osteoporotic fracture signals the start of a downward spiral with increased risk of refractures. Therefore, it is important to identify patients at high risk for fractures and refractures for whom treatment would be most effective.[3]

Previous fracture prediction models have been based on the assumption of a stable risk of subsequent fractures over time. An ideal prognostic model would be population specific, as the background risk of fracture varies between populations, and would take into account changes in risk over time.

The fracture risk assessment tool (FRAX) algorithm of the WHO can be used for calculating the 10-year fracture risk in individual patients (http://www.shef.ac.uk/FRAX/)[4] and the Garvan fracture risk calculator, (FRC) based on the Dubbo Osteoporosis Study, can be used to calculate the individualised 5-year and 10-year fracture risk (http://www.fractureriskcalculator.com).[5 6] Among others, these models include age, bone mineral density (BMD) and prior fracture. The FRC also includes the number of falls during the previous year.[5 6]

In a large meta-analysis, a history of non-vertebral fracture was found to double the risk of a subsequent fracture.[7] In addition, more recent studies have shown that the subsequent fracture risk fluctuates over time. The peak of increased risk immediately after the fracture is followed by a gradual decrease toward the population risk.[8–16] However, it has not been examined how time-dependent analysis of prior fracture could contribute to and improve the prediction of fracture risk. Therefore, the aims of this study were to examine the contribution of the time relation between fracture in the prediction of absolute fracture risk over and above age and BMD, and to develop a nomogram for predicting the individualised 5-year and 10-year absolute fracture risks for postmenopausal women.

MATERIALS AND METHODS

Participants

Between 1992 and 1994, a prospective population-based study was initiated among 4203 postmenopausal women aged 50–80 years, living in 2 cities in the southern part of The Netherlands and their surrounding suburban villages. In all, 23 general practitioners (GPs) from 12 GP centres participated in this baseline study.[17–19] Most (n=21) of these GPs continued to be involved throughout.

Approximately 10 years after the baseline study (2002–2004), the study population had been reduced to 3633 (4203–570) postmenopausal women.

Measurements

The baseline assessment included BMD, assessed by dual energy x-ray absorptiometry (Hologic

QDR-1000; Hologic Europe, Brussels, Belgium), weight and height measurements. A questionnaire enquired about possible risk factors for osteoporosis, which included their medical history (including fracture history), family history and diet.[17–19] Then, 10 years later, the women who had participated completed a questionnaire about fracture history and medical history. All subjects' fracture reports were checked in the medical files at the participating GP practices.[20]

Statistical analysis

Cox's proportional hazards regression[21 22] was used to estimate the magnitude of association between fracture risk and the risk factors, expressed by the HR and its 95% CI for each SD or unit change with ordinal risk factors.

In order to assess the incremental prognostic value attributable to fracture history, a reclassification analysis was performed.[23] Two specific models were considered: model 1 with age and BMD and model 2 with age, BMD and prior fracture. Prior fracture was categorised as either recent prior fracture (≤5 years ago) or non-recent prior fracture (>5 years ago), but still after menopause. In the analysis, the 10-year risk of fracture of individuals was estimated by each model and then classified into three risk groups: low, moderate and high tertiles, according to the estimation of model 1. The proportion of women who would be rightfully reclassified into those groups between the model with and without prior fracture was calculated, yielding the net reclassification improvement (NRI) in prediction.

Bayesian model averaging (BMA)[24] was applied to search for the most parsimonious models with consistent and maximum discriminatory power. In terms of model consistency and accuracy, it has been shown that the BMA approach performs better than traditional algorithms such as stepwise regression[25 26] because it can account for model uncertainty in predictions and parameter estimates.[24 27]

The prognostic performance of parsimonious models was assessed by the area under the receiver operating characteristic curve,[28–31] which reflects a model's ability to discriminate between those who will sustain a fracture from those who will not.

From the estimates of the model's parameters, a nomogram was constructed for predicting 5-year and 10-year risks of fracture. The nomogram was internally validated by the bootstrap method. In this method, the predicted probability of fracture was compared with the actual probability (ie, nomogram calibration) on the entire sample, again using 1000 bootstrap resample to reduce overfit bias, which would overstate the accuracy of the nomogram.

In an independent sample consisting of 204 women who entered the emergency room because of a fracture, the 10-year fracture risk of all fractures was calculated based on FRAX, Garvan FRC and the developed nomogram. All analyses were performed using the R tool (http://www.r-project.org) on the Windows XP platform (Microsoft, Redmond, Washington, USA).[32]

Ethics

The Ethical Review Committee of Maastricht University and the Maastricht University Hospital approved the study (reference number MEC 94-196.1). Written informed consent forms were obtained from all participants.

RESULTS

Characteristics of participants

Of the 3633 women, 2847 women were eligible (ie, contactable and alive) and invited to participate in the 10-year follow-up study. Of these, 474 (16.6%) declined to participate. Therefore, 2372 women were included in the analysis.[20] There were some small but significant differences between responders (n=2372) and non-responders (n=474) at study entry: age 61.6 (6.8) versus 63.9 (7.4) years (mean (SD); p<0.01), height 162 (6.1) versus 160 (6.5) (p<0.01) and fracture history after menopause 14.3% versus 18.3% (p=0.03), but not for recent fracture history (within 5 years prior to study entry) 7.4% versus 7.5% (p=0.92). In addition, the 2372 women who did participate were, compared with all 1261 women who did not participate (deceased, untraceable, opted not to participate), younger (61.6 vs 65.0 years; p<0.0001), slightly taller (162 vs 161 cm; p=0.002), had a slightly higher lumbar spine BMD (T score of −1.3 vs −1.4; p=0.047) and fracture history after menopause (14.3% vs 17.8%; p=0.004) but not within the preceding 5 years (7.4% vs 8.3%; p=0.34). The mean follow-up period was 9.1 years, yielding 21 558 person-years. During the follow-up period 382 (16.2%) women had sustained at least 1 fracture, yielding the incidence of fractures of 18 per 1000 person-years. Among these 382 women, their first fractures after study entry were 132 (34.7%) wrist; 47 (12.4%) hip and 9 (2.4%) femur; 29 (7.6%) humerus; 20 (5.3%) vertebral (clinical); 10 (2.6%) rib, as well as 44 (11.6%) other upper extremity and 91 (23.9%) other lower extremity.

In total, 338 women had a history of fractures, of whom 105 sustained more than 1 fracture after menopause. As expected, women with a history of fractures were older and had lower BMD than those without a history of fractures. There were no significant differences between those subgroups in terms of lifestyle factors including calcium intake, nor were there any differences in comorbidities, including rheumatoid arthritis (table 1).

Single Cox's proportional hazards regression showed that each SD increase in age was associated with 18% increase in fracture risk in postmenopausal women (HR 1.18; 95% CI 1.10 to 1.27). Each SD lower BMD at the lumbar spine was associated with 24% increase in fracture risk (HR 1.24; 95% CI 1.15 to 1.33). The association between risk factors and fracture risk was more pronounced in postmenopausal women with a history of fractures. The HR for postmenopausal women with a non-recent prior fracture (>5 years ago) was 2.10 (95% CI 1.51 to 2.92) and this increased to 3.81 (95% CI 2.95 to 4.94) with a recent prior fracture (≤5 years ago, table 1).

Contribution of prior fracture and its time relation in the prediction of fracture risk

Taking into account the event of a fracture and its timing altered the estimate of risk of fractures. The two models examined included age and BMD (model 1) and prior fracture (model 2). Of the 382 fracture cases, 170 (45%) women were reclassified to higher or lower risk categories. Model 2 showed less 'correct' movement toward higher risk categories (12.8%) compared to model 1 (31.7%); yielding a net decrease of 18.9% for the model with prior fracture included (table 2). In other words, model 1 (age and BMD) demonstrated better sensitivity than model 2 (age, BMD and prior fracture). However, for non-fracture participants, model 2 was superior to model 1 in terms of reclassification. Women who were considered as 'high risk' in model 1 were correctly reclassified to lower risk categories in model 2, with a net gain of 31.5% (table 2). In other words, the model with prior fracture showed a better specificity than the model without prior fracture.

Overall, the NRI of model 2 (with prior fracture) was 12.6% (p<0.0001) compared with model 1.

Table 1 Characteristics of participants and association between risk factors and fracture risk

Variable	Non-fracture (n=1990)		Fracture (n=382)		HR for risk factor Unit	HR (95% CI)	p Value
Age, years	61.3	(6.7)	63.1	(7.0)	+5	**1.18 (1.10 to 1.27)**	**<0.0001**
Weight, kg	71.2	(11.7)	71.9	(11.4)	−10	1.03 (0.95 to 1.12)	0.420
Height, cm	161.5	(6.2)	162.4	(6.0)	+5	**1.11 (1.02 to 1.20)**	**0.013**
BMI, kg/m^2	27	(4)	27	(4)	−5	1.02 (0.91 to 1.14)	0.732
LSBMD, T scores	−1.3	(1.5)	−1.7	(1.4)	−1	**1.24 (1.15 to 1.33)**	**<0.0001**
Dietary calcium intake, mg/day	876	(395)	883	(416)	+400	1.01 (0.92 to 1.12)	0.783
Age onset menopause, years	47.1	(5.7)	46.8	(5.7)	+5	1.06 (0.97 to 1.16)	0.215
Prior fracture after menopause, n (%)					vs no		
No fracture	1767	(88.8)	267	(69.9)		Reference	
Fracture >5 years	114	(5.7)	41	(10.7)		**2.10 (1.51 to 2.92)**	**<0.0001**
Fracture ≤5 years	109	(5.5)	74	(19.4)		**3.81 (2.95 to 4.94)**	**<0.0001**
Cardiovascular disease, n (%)	472	(23.7)	108	(28.3)	vs no	1.24 (0.99 to 1.55)	0.061
Family history of osteoporosis, n (%)	194	(9.7)	45	(11.8)	vs no	1.21 (0.88 to 1.65)	0.236
Current smoker, n (%)	506	(25.6)	80	(20.9)	vs no	1.27 (0.99 to 1.62)	0.057
Current sports, n (%)*	761	(38.2)	150	(39.3)	vs no	1.03 (0.84 to 1.27)	0.764
Occupational exercise in the past, n (%)*					vs high		
Mild	273	(13.7)	59	(15.4)		1.56 (0.82 to 2.98)	0.173
Moderate	1618	(81.3)	312	(81.7)		1.42 (0.78 to 2.59)	0.253
High	84	(4.2)	11	(2.9)		Reference	

Values are mean (SD), unless otherwise specified. Significant differences are shown in bold type.
The single Cox regression analysis was not performed for factors with frequency in the whole sample <10%, including corticosteroid use, rheumatoid arthritis, diabetes status, musculoskeletal disease and alcohol intake.
*Current sports: all sport-related activities with no distinction between duration, level of activity and frequency; occupation exercise in the past: participant's assessment of physical nature of employment.
BMI, body mass index; LSBMD, lumbar spine bone mineral density.

Table 2 Contribution of prior fracture in the prediction of absolute fracture risk, reclassification analysis

Model 1	Model 2 Low	Moderate	High	NRI (%)	p Value
	Fracture			−18.9	(<0.0001)
Low	**65**	3	12		
Moderate	43	**50**	34		
High	0	78	**97**		
	Non-fracture			31.5	(<0.0001)
Low	**673**	1	38		
Medium	360	**258**	54		
High	0	358	**243**		
Overall NRI				12.6	(<0.0001)

Model 1 included age and BMD; model 2, age, BMD and prior fracture. Analysis was based on 10-year risk of fracture based on each model, and individuals were classified into three risk groups: low, moderate and high tertiles, according to risk estimated from model 1.
BMD, bone mineral density; NRI, net reclassification improvement.

Development of prediction model

Based on the BMA, using the Bayesian information criterion as a metric of model selection, the model with age, BMD and prior fracture was the most parsimonious. The HR for age was 1.09 (95% CI 1.01 to 1.17); BMD, 1.16 (95% CI 1.07 to 1.25), for non-recent prior 1.97 (95% CI 1.43 to 2.71) and recent prior fracture 3.27 (95% CI 2.50 to 4.30). After adjusting for BMD and age, women with a recent prior fracture had a 66% higher risk of an incident fracture than those with a non-recent fracture (HR 1.66; 95% CI 1.15 to 2.40).

Internal validation by the bootstrap method suggested that the maximum calibration error in predicting fracture risk was about 1%. The predicted risk was slightly overestimated in the highest risk group compared to observed risk (figure 1).

Using the estimated parameters obtained from the model, we constructed a nomogram for predicting the 5-year and 10-year risk of fracture in postmenopausal women (figure 2). The nomogram has three axes representing age, BMD T scores and prior fracture. Some typical point estimates of 5-year and 10-year risks are presented for those with and without a prior fracture, according to age and BMD T scores (table 3). Clinical applications of the nomogram can be illustrated by the following test case scenarios.

Clinical case 1

This case is a 70-year-old woman with lumbar spine BMD T scores of –2.5 and a non-recent prior fracture. A vertical line from the age axis to the 'points' axis yields her age score (approximately 15); similarly for BMD score (approximately 78) and her prior fracture score (approximately 29). Therefore, the total for this woman is 15+78+29=122. From 122 on the 'total points' axis, a vertical line to the 5-year and 10-year risk axes provides the estimates of the woman's risk of fracture, about 18% and 32%, respectively.

Clinical case 2

This case concerns a similar woman to case 1, but with a recent prior fracture (approximately 51 points), yielding a total points score of 144. Accordingly, her 5-year and 10-year risks of fracture are increased to approximately 28% and 47%, respectively.

Comparison of the nomogram with FRAX and Garvan FRC

In the independent sample of patients with fractures, the overall correlation between the developed nomogram versus FRAX and FRC is 0.524 and 0.675 (p<0.001), respectively. The main difference between the nomogram and the FRAX and FRC is related to the inclusion of the time relation between fractures. FRAX had a significantly lower 10-year risk with regards to recent prior fractures (mean difference: 25.9%, p<0.0001), non-recent prior fracture (mean difference: 8.54%, p<0.0001) and no prior fractures (mean difference: 3.09%, p<0.0001, figure 3A).

The FRC had a significantly lower 10-year risk with regards to recent prior fractures (mean difference: 9.94%, p=0.002), but not with regards to a non-recent prior fracture (>5 years, mean difference: 1.16%, p=0.664). In addition, the FRC was significantly

higher for women without a prior fracture (2.10%, p=0.001, figure 3B).

DISCUSSION

In this study we constructed a nomogram based on age, BMD and a prior fracture. All these determinants are established risk factors for fracture.[6 33] Many studies have shown that a history of fracture after the age of 45–50 years is associated with a doubling of the risk of a new fracture, the risk being even higher after a vertebral fracture.[7] Several studies have reported that a recent history of fracture indicates a greater risk factor for subsequent fracture than an earlier fracture history.[8–16] For example, this is the case for morphometric vertebral fractures following a new morphometric fracture within 1 year,[8] for subsequent fractures at specific locations (vertebra, humerus and hip) after a first fracture at the same location[14] and for patients presenting with any clinical vertebral or non-vertebral fracture, regardless of BMD of the spine.[15 16] Since these studies suggested clustering of certain fractures in time, we constructed a nomogram that included prior fracture but not based on a stable fracture risk, as has been used in previous individualised fracture risk prediction models, but as recent prior and non-recent prior fracture. The nomogram indicates that women with a recent prior fracture were at much higher risk for sustaining a subsequent fracture than women with an older prior fracture, for example, a 70-year-old woman with BMD T score of

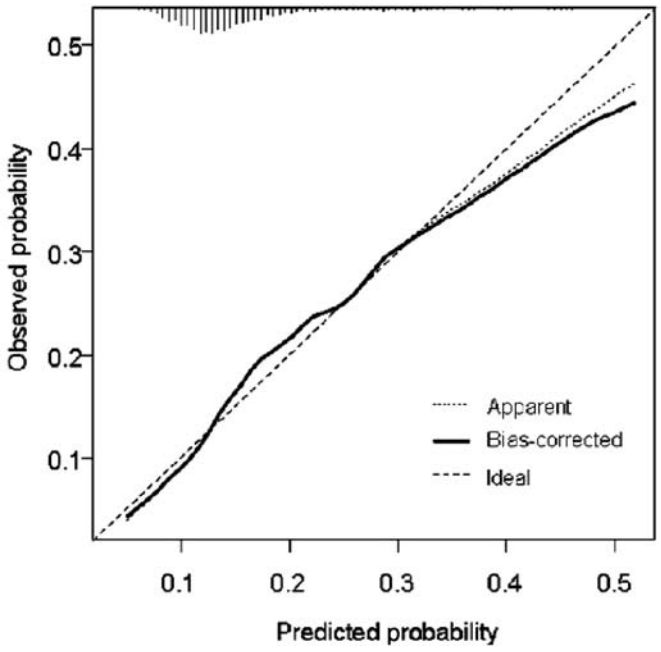

Figure 1 Comparison of the predicted and observed probabilities of fracture in the study population by using the bootstrap technique. Internal validation showed good concordance of predicted and observed probabilities, except for the overestimation at the highest level of risk.

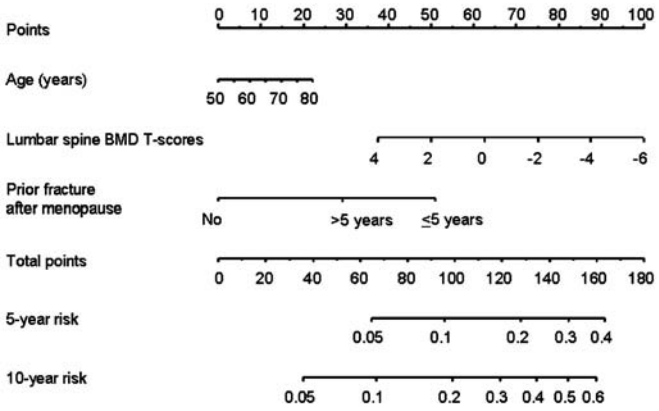

Figure 2 Nomogram for predicting 5-year and 10-year absolute risks of fracture for an individual postmenopausal woman. The points for age and other risk factors should be read on the top 'points' scale. These values should be added, and read down from the 'total points' scale to the 5-year or 10-year risk lines to ascertain the individual's probability of sustaining a fracture.

Table 3 Estimated 5-year and 10-year absolute risks of any fracture for individual women given age, BMD T scores and a history of fracture

	Prior fracture after menopause											
	Age 50			Age 60			Age 70			Age 80		
Lumbar spine BMD T score	No	>5 Years	≤5 Years	No	>5 Years	≤5 Years	No	>5 Years	≤5 Years	No	>5 Years	≤5 Years
5-Year risk												
0.0	4.8	9.2	14.8	5.6	10.8	17.3	6.6	12.6	20.1	7.8	14.8	23.4
−0.5	5.1	9.8	15.8	6.0	11.5	18.4	7.1	13.5	21.5	8.4	15.8	24.9
−1.0	5.5	10.5	16.9	6.5	12.4	19.7	7.6	14.5	22.9	9.0	16.9	26.5
−1.5	5.9	11.3	18.0	7.0	13.2	21.0	8.2	15.5	24.4	9.6	18.1	28.2
−2.0	6.3	12.1	19.2	7.5	14.2	22.4	8.8	16.6	26.0	10.3	19.3	30.0
−2.5	6.8	12.9	20.5	8.0	15.1	23.9	9.4	17.7	27.7	11.1	20.6	31.9
−3.0	7.3	13.8	21.9	8.6	16.2	25.4	10.1	18.9	29.4	11.9	22.0	33.9
−3.5	7.8	14.8	23.4	9.2	17.3	27.1	10.8	20.2	31.3	12.7	23.5	35.9
−4.0	8.4	15.8	24.9	9.9	18.5	28.8	11.6	21.5	33.2	13.6	25.0	38.0
10-Year risk												
0.0	9.1	17.1	26.9	10.7	20.0	31.0	12.6	23.3	35.6	14.7	27.0	40.7
−0.5	9.8	18.3	28.6	11.5	21.3	32.9	13.5	24.8	37.7	15.8	28.7	43.0
−1.0	10.5	19.6	30.4	12.3	22.8	34.9	14.4	26.4	39.9	16.9	30.5	45.4
−1.5	11.2	20.9	32.2	13.2	24.3	37.0	15.4	28.1	42.2	18.0	32.4	47.8
−2.0	12.0	22.3	34.2	14.1	25.8	39.2	16.5	29.9	44.5	19.2	34.3	50.3
−2.5	12.9	23.7	36.3	15.1	27.5	41.4	17.6	31.7	47.0	20.5	36.4	52.9
−3.0	13.8	25.3	38.4	16.1	29.2	43.7	18.8	33.7	49.5	21.9	38.6	55.5
−3.5	14.7	26.9	40.6	17.2	31.1	46.1	20.1	35.7	52.0	23.4	40.8	58.1
−4.0	15.8	28.6	42.9	18.4	33.0	48.6	21.4	37.8	54.6	24.9	43.1	60.8

Values are percentages.
BMD, bone mineral density.

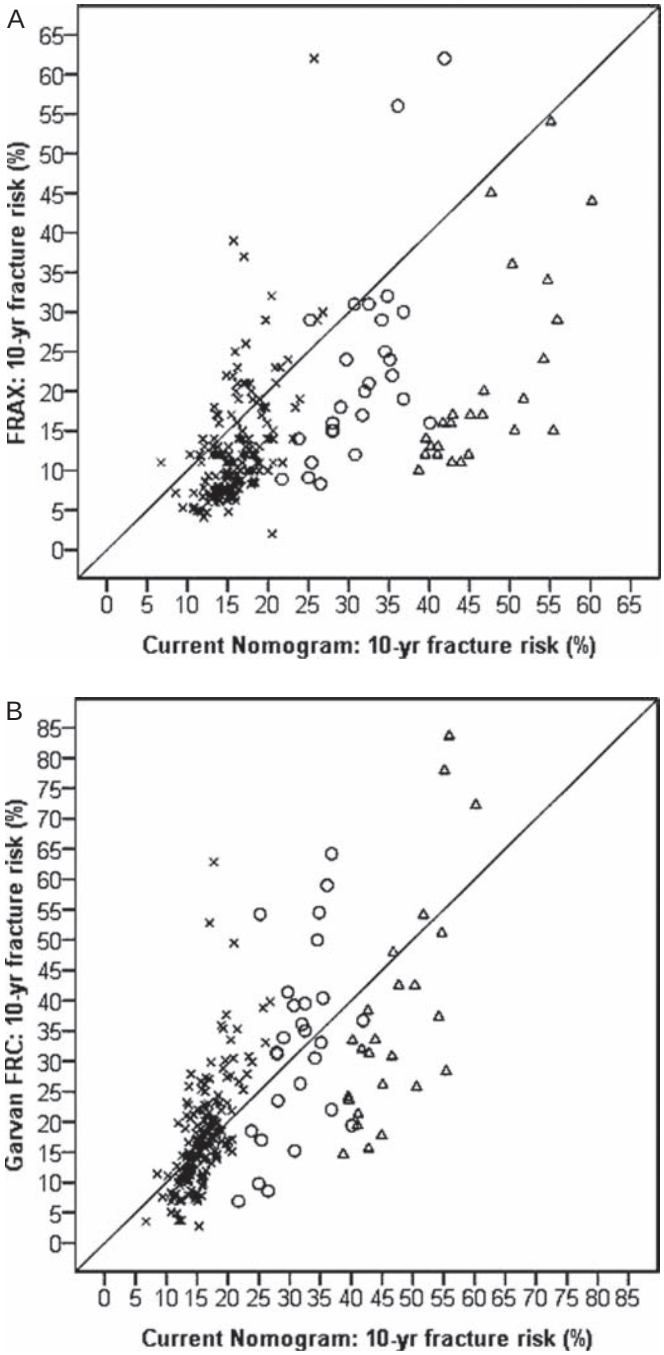

Figure 3 A. Fracture risk assessment tool (FRAX) vs current nomogram in 204 women specified for fracture history: x, no fracture history after menopause, o, fracture history >5 years ago, but still after menopause and Δ, recent fracture history ≤5 years. B. Garvan fracture risk calculator (FRC) vs current nomogram in 204 women specified for fracture history: x, no fracture history after menopause, o, fracture history >5 years ago, but still after menopause and Δ, recent fracture history ≤5 years.

–2.5 and a prior fracture longer than 5 years ago had a 10-year fracture risk of 31.7%, but if her prior fracture was within the last 5 years her risk was elevated to 47.0%. With prior fracture included simply as yes/no, the 10-year fracture risk of the women described in the above example increases to 38%, thus overestimating the 10-year fracture risk for women in whom the fracture occurred longer than 5 years ago, but underestimating the risk for women with a recent prior fracture. Therefore, the contribution of the developed nomogram compared with the FRAX and FRC is based on this time relation. Patients with a recent clinical fracture have a significantly higher 10-year fracture risk with the developed nomogram than using FRAX or Garvan FRC (figure 3). Since these women attended the emergency room with a fracture, we argue that every point to the right of or above the 45° line would be 'more correct'.

The goal of constructing this nomogram was to help GPs and clinicians to assess quickly the risk of an individual Caucasian postmenopausal woman to guide clinical decision making. Treatment is recommended for women with osteoporosis (T score less than –2.5), more than one vertebral fracture or postmenopausal women who are using a high dosage of corticosteroids (>3 months, >7.5 mg daily).[34] Treatment has been shown to reduce the fracture risk in these women.[6 34–38] However, it has also been suggested that all women with a BMD T score of –2.5 or less deserve treatment. This corresponds to a 10-year absolute fracture risk of at least 12.9%. However, a woman with a BMD T score in the osteopenic range (T score <–1.0) with a prior fracture after menopause has a 10-year absolute risk of at least 19.6% and this is even higher if her prior fracture is recent (30.4%). Even women with a BMD equal to the peak bone mass (T score=0.0) with a prior fracture had a higher 10-year absolute risk (17.1%) than women with just osteoporosis, especially if the fracture occurred recently (26.9%). These results clearly indicate that fracture risk calculation or prevention of fractures cannot be solely based on BMD. In fact, more than half of women who subsequently had a fracture had a BMD above the osteoporotic range (ie, normal or osteopenia); the comparable figure in men is more than 70%.[39] This suggests the concept that fracture prevention should be expanded beyond bone-related factors to include other risk components.[39]

Our study has several limitations. First, only clinical fractures and not morphometric vertebral fractures were assessed. In other studies two out of three morphometric vertebral fractures are clinically silent and x-rays are necessary to confirm the fracture. Arguably, spine x-rays would need to be performed every year to record the year of occurrence. Such follow-up was not available in our study. Second, only the fractures reported by the patients were confirmed in the medical files. Negative reports were not validated. However, a study by Ismail *et al*[40] assessed the validity of self-reported incidence of non-spinal fractures using a postal questionnaire and concluded that this method produced accurate information about the occurrence of most fractures. Third, 134 women (5.6%) might have improved their lifestyle. After baseline, these women received information about calcium intake and exercise. Some participants might have heeded this advice. However, the advice was almost the same as media recommendations regularly made to the general public on which women might act. In addition, these 134 women were also treated for osteoporosis (including treatment with a placebo), however, excluding these women from the analysis did not alter the results. Fourth, almost all women in the study were Caucasian, and our results cannot be extrapolated to other ethnic groups without further confirmation.

In conclusion, the assessment of fracture risk has to consider an individual's risk profile. A recent prior fracture is more important than an older prior fracture after menopause. Individualised fracture risk cannot be solely based on BMD, and therefore, a prior fracture (especially a recent one) and age should be taken into account. The developed nomogram could help primary care doctors and clinicians to effectively manage fracture risk by providing a meaningful and individualised risk level. Future studies are necessary to externally validate this nomogram, for constructing individualised nomograms for men taking into

account the time relation between fractures and to investigate why clinical fractures cluster in time.

Model availability

The model is available as a paper-based nomogram (figure 2) and will be made available on the website of Maastricht University.

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Competing interests JAE (consulting fees or other remuneration): Amgen, Decode, Eli Lilly, Ge-Lunar, Merck Sharp & Dohme, Novartis, Roche-GSK, Sanofi-Aventis, Servier and Wyeth Australia. PPG (consulting fees or other remuneration): Amgen, Eli Lilly, Ge-Lunar, Merck Sharp & Dohme, Novartis, Roche-GSK, Sanofi-Aventis, Servier, Wyeth, Schering Plough, Abbott, Pfizer. Other authors: none.

Ethics approval This study was conducted with the approval of the Ethical Review Committee of Maastricht University and the Maastricht University Hospital (reference number MEC 94-196.1). Written informed consent forms were obtained from all participants.

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