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ORIGINAL ARTICLE

The use of clinical risk factors enhances the performance of BMD in the prediction of hip and osteoporotic fractures in men and women

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Abstract
Summary BMD and clinical risk factors predict hip and other osteoporotic fractures. The combination of clinical risk factors and BMD provide higher specificity and sensitivity than either alone.
Introduction and hypotheses To develop a risk assessment tool based on clinical risk factors (CRFs) with and without BMD.
Methods Nine population-based studies were studied in which BMD and CRFs were documented at baseline. Poisson regression models were developed for hip fracture and other osteoporotic fractures, with and without hip BMD. Fracture risk was expressed as gradient of risk (GR, risk ratio/SD change in risk score).
Results CRFs alone predicted hip fracture with a GR of 2.1/SD at the age of 50 years and decreased with age. The use of BMD alone provided a higher GR (3.7/SD), and was improved further with the combined use of CRFs and BMD (4.2/SD). For other osteoporotic fractures, the GRs were lower than for hip fracture. The GR with CRFs alone was 1.4/SD at the age of 50 years, similar to that provided by BMD (GR=1.4/SD) and was not markedly increased by the combination (GR=1.4/SD). The performance characteristics of clinical risk factors with and without BMD were validated in eleven independent population-based cohorts.
Conclusions The models developed provide the basis for the integrated use of validated clinical risk factors in men and women to aid in fracture risk prediction.

Keywords Bone mineral density · Hip fracture · Meta-analysis · Osteoporotic fracture · Risk assessment

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Introduction

Osteoporosis is operationally defined in terms of bone mineral density (BMD) [1]. Against this background, the clinical development of pharmaceutical agents has focussed on the selection of patients on the basis of low BMD for inclusion into trials of efficacy [2, 3]. As a consequence, guidance on therapeutic intervention has also emphasised the assessment of BMD [4–8]. In Europe, for example, women with clinical risk factors are considered for treatment where the T-score for BMD lies below the diagnostic threshold of osteoporosis, a T-score of −2.5 or less [4, 5]. Elsewhere, different T-score thresholds are used [6, 8].

The risk of fracture is, however, multi-factorial and many independent risk factors have been identified that contribute to risk over and above that reflected by BMD [9]. Their consideration along with BMD in the assessment of fracture risk increases the sensitivity of the test without sacrificing specificity [9]. In other words, the higher the gradient of risk (GR) of the test (the increase in fracture risk per standard deviation increase in risk score), the more accurately the individuals who will fracture are identified so that the overall risk in the group identified will be higher [10]. This has the effect of improving the cost-effectiveness of treatment.

Over the past several years, a series of meta-analyses has been performed to identify clinical risk factors for fracture and to determine their dependence upon age, sex and BMD [11–

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19]. These analyses were based on the individual data from prospective population-based studies carried out at different centres around the world. Access to the primary data permits the inter-dependence of each of the candidate risk factors to be examined so that they can be combined for clinical use. The aim of this study was to utilise these data to determine the impact of the addition of multiple clinical risk factors to BMD for the prediction of fractures, and to validate the findings using data from independent cohorts.

Methods

Primary cohorts

We used baseline and follow-up data from nine prospective population-based cohorts comprising the Rotterdam Study, the European Vertebral Osteoporosis Study (later the European Prospective Osteoporosis Study (EVOS/EPOS), the Canadian Multicentre Osteoporosis Study (CaMos), Rochester, Sheffield, the Dubbo Osteoporosis Epidemiology Study (DOES), a cohort from Hiroshima and two cohorts from Gothenburg. Details of each of the cohorts are published elsewhere, but are summarised briefly below and in Tables 1 and 2.

The Rotterdam Study, begun in 1990, is an ongoing prospective cohort study that aimed to examine and follow-up all residents aged 55 years and older living in Ommoord, a district of Rotterdam [20]. By 1993 7,983 residents had been included (response rate 78%). Fracture follow-up was achieved through an automatic link with general practitioner computer systems and hospital admission data [21]. Fracture data were collected and validated by two independent research physicians. For this analysis, validated fracture follow up was available for 6,851 participants (2,793 men) with an average follow-up time of 6 years. Femoral neck BMD was measured in 5,731 individuals (2,414 men) by DXA (Lunar DPX-L).

The European Vertebral Osteoporosis Study (EVOS) comprised age- and sex-stratified random samples from 36 centres in 19 European countries [22]. Equal numbers of men and women were drawn in each centre within six 5-year age bands (50–74 and 75+ years). BMD was measured in 3,461 men and women from 13 centres by DXA at the femoral neck using pencil beam machines that were cross-calibrated using the European Spine Phantom. This sample provided the framework for the European Prospective Osteoporosis Study (EPOS) where repeated assessment was undertaken in 29 of the centres [23, 24]. For this analysis, validated fracture follow up was available for

Table 1 Details of the cohorts studied

Cohort	Number	% female	Person-years	Hip fracture	Other osteoporotic fracture	Age (mean)	Age range
(a) Primary cohorts							
EVOS/EPOS	13,490	52	40,681	50	719	64	40–95
CaMos	9,101	69	25,834	40	307	62	25–103
Rochester	1,001	65	6,227	42	244	57	21–94
Rotterdam	6,851	59	39,593	220	646	69	55–106
DOES	2,089	61	15,994	103	407	71	57–96
Gothenburg II	1,970	59	15,201	271	350	78	20–89
Hiroshima	2,603	70	9,825	32	90	65	47–95
Sheffield	2,170	100	6,894	63	243	80	74–96
Gothenburg I	7,065	100	29,603	29	312	59	69–86
Totals	4,6340	68	189,852	850	3,318	65	
(b) Validation cohorts							
THIN	135,695	100	606,822	1336	4,802	60	50–116
SOF	5,251	100	57,388	523	1,313	71	65–99
York	3,409	100	5,927	35	195	77	48–99
Geelong I	1,173	100	7,315	32	143	62	35–95
Geelong II	1,865	100	-[a]	73	443	63	35–95
OPUS	2,155	100	4,161	6	100[b]	67	55–80
PERF	5,415	100	39,096	58	801	64	43–81
EPIDOS	7,435	100	26,665	302	642	81	70–100
Miyama	353	53	3,173	7	44	59	40–79
SEMOF	6,721	100	18,712	73	581[b]	75	70–91
WHI	61,014	100	439,296	915	6,250[b]	66	50–79
Totals	230,486	100	1,208,528	3360	15,183	63	

[a] Case control study; [b] Any osteoporotic fracture.

Table 2 Risk factors and their prevalence by cohort

Cohort	BMI	BMD	Family history	Glucocorticoids	Prior fracture	Smoking	Alcohol	Rheumatoid arthritis
(a) Primary cohorts								
EVOS/EPOS	27.0	+	9	5	36	20	–	–
CaMos	26.9	+	–	5	44	–	3	6
Rochester	26.1	+	–	3	18	–	–	–
Rotterdam	26.3	+	8	2	14	23	23	–
DOES	25.6	+	–	6	13	7	16	3
Gothenburg I	25.4	–	–	–	9	16	–	–
Gothenburg II	24.6	–	4	4	18	25	–	–
Hiroshima	23.0	+	–	3	26	20	–	–
Sheffield	26.7	+	5	9	51	7	–	2
Totals	26.2		7	4	29	20	11	5
(b) Validation cohorts								
THIN	26.0	–	–	2	10	40[c]	32	1
SOF	26.4	+	15	12	35	11	4	7
York	25.0[a]	–	9[b]	3	40	9	–	–
Geelong I	24.8	+	8	3	15	12	8	11
Geelong II	24.1	+	10	13	32	16	4	15
OPUS	26.6	+	11	3	44	14	3	7
PERF	25.5	+	–	–	16	–	–	–
EPIDOS	25.4	+	9	6	40	3	3	–
Miyama	22.1	+	–	0	32	27	14	–
SEMOF	28.9	+[d]	10[6]	4	51	8	<1	–
WHI	28.4	+[e]	13	1	17	7	4	5
Totals	26.7		12	2	16	27	21	3

[a] Height assumed to be 1.6 m; [b] Maternal history of hip fracture; [c] Ever smoking, [d] subset of 820 women, [e] subset of 4,193 women.

13,490 participants (6,521 men) with an average follow-up time of 3 years. Femoral neck BMD was measured in 4,746 individuals (2,141 men).

The Canadian Multicentre Osteoporosis study (CaMos) is an ongoing prospective age stratified cohort. The study is documenting the incidence of fractures and risk factors in a random sample of 9,424 men and women aged 25 years or more selected by telephone listings. The sampling frame is from nine study centres in seven provinces [25]. Characterisation of individuals was by interview. BMD was measured by DXA at the femoral neck with Hologic QDR in seven centres and the Lunar DPX Alpha in two centres in 8,297 individuals (2,589 men). Machines were cross-calibrated using the same European Spine Phantom. For this analysis, validated fracture follow-up was available for 9,101 participants (2,801 men) with an average follow-up time of 3 years.

The Rochester cohort was recruited from two random population samples stratified by decade of age, one of women who were subsequently followed for up to 20 years [26], and another sample of women and men followed for 8 years [27]. BMD of the right femoral neck was measured by dual photon absorptiometry in the first cohort (cross-calibrated to DXA) and by DXA (Hologic QDR 2000) in the second group. Fractures were ascertained by periodic interview combined with review of the in-patient and out-patient medical records of all local care providers. For this analysis, validated fracture follow up was available for 1001 participants (348 men) with an average follow-up time of 6 years. Femoral neck BMD was measured in 993 individuals (345 men).

The Sheffield cohort comprised women aged 75 years or more selected randomly from the population of Sheffield, UK and surrounding districts between 1993 and 1999. Approximately 35,000 women, identified from general practitioner listings, were contacted by letter and invited to attend for the assessment of skeletal status; 5,873 women were willing to attend. Of these, 281 women were excluded and the remainder randomly allocated to treatment with placebo or the bisphosphonate, clodronate, to study its effects on fracture risk. The material for this study comprised 2,172 women allocated to treatment with placebo only [28, 29]. All women had baseline assessment of BMD undertaken at the femoral neck using the Hologic QDR 4500. Outcomes were assessed by 6-monthly home visits. For this analysis, validated fracture follow up was

available for 2,170 participants with an average follow-up time of 6 years. Femoral neck BMD was measured in 2,150 individuals.

The Dubbo Osteoporosis Epidemiology Study (DOES) is a population-based study with multiple assessments of skeletal status in men and women aged 60 years or more from Dubbo, Australia [30]. Participation in the study was 56% of the population. Baseline measurements included BMD at the femoral neck assessed using DXA (GE-Lunar, DPX and Prodigy). Fractures are identified through radiologists' reports from the two centres servicing the region. For this analysis, validated fracture follow-up was available for 2,089 participants (819 men) with an average follow-up time of 8 years. Femoral neck BMD was measured in 2,060 individuals (801 men).

The Gothenburg I study comprised four birth cohorts of 2375 randomly sampled men and women aged 70 years or more followed for up to 20 years after a baseline BMD measurement [31]. The participants were drawn randomly from the population register in Gothenburg by the date of birth to provide cohorts aged 70, 76, 79 and 85 years at the time of investigation. The participation rate was 73%. Bone mineral density was measured at the right heel using dual photon absorptiometry. For this analysis, validated fracture follow-up was available for 1,970 participants (812 men) with an average follow-up time of 8 years. Since BMD was measured at a peripheral site, data were not used in models including BMD.

The Gothenburg II study comprised a randomly drawn population cohort of over 7,000 women aged 50–70 years followed for 4 years [32]. The participation rate was 67%. Assessment included a standardised questionnaire that recorded information on risk factors for osteoporosis. Fractures were identified prospectively through the radiology departments servicing the region. BMD was assessed at baseline at the distal forearm by using the Osteometer DTX-200. For this analysis, validated fracture follow-up was available for 7065 participants with an average follow-up time of 4 years. Since BMD was measured at a peripheral site, BMD data were not included in models adjusting for BMD.

The Adult Health Study (AHS) was established in 1958 to document the late health effects of radiation exposure among atomic bomb survivors in Hiroshima and Nagasaki. The original AHS cohort consisted of about 15,000 atomic bomb survivors and 5,000 controls selected from residents in Hiroshima and Nagasaki using the 1950 national census supplementary schedules and the Atomic Bomb Survivors Survey. AHS subjects have been followed through biennial medical examinations since 1958. The participation rate has been around 80% throughout this period. BMD was measured at the proximal femur by DXA in 1994 (Hologic QDR 2000) in 2,588 individuals (791 men). Self-reported fractures were documented at 6-monthly intervals [33, 34]. For this analysis, validated fracture follow-up was available for 2,603 participants (793 men) with an average follow-up time of 4 years.

Validation cohorts

The performance characteristics determined from the primary cohorts were evaluated in eleven independent population based cohorts that did not participate in the model synthesis. These comprise the Epidemiologie de l'osteoporose (EPIDOS) study (France), the Study of Osteoporotic Fractures (SOF) in the US, two cohorts from the Geelong osteoporosis study in Australia, the OPUS study drawn from 5 European countries, the Prospective Epidemiological Risk Factors (PERF) study from Denmark, the Health Improvement Network (THIN) data-base in the UK, the SEMOF Study from Switzerland, the Women's Health Initiative (US), a cohort from York, UK and a cohort from Miyama in Japan. The characteristics of the cohorts are shown in Tables 1 and 2, and described briefly below.

The EPIDOS study comprises a population based cohort of women aged 75 years or more from five French centres (Amiens, Lyon, Mont Pellier, Paris and Toulouse) [35]. Between April 1992 and December 1993, 7,598 women were recruited through mailings using large population-based listings such as voter registration rolls. Baseline characteristics were obtained through a structured questionnaire, as well as through clinical and functional examinations, and BMD at the femoral neck assessed by DXA (Lunar DPX). Information on fracture outcomes was obtained through direct contact with the study participants at 4-monthly intervals or from a family member or the individuals' physicians. For this analysis, validated fracture follow-up was available for 7,435 women. Femoral neck BMD was measured in 7,402 individuals.

The PERF study was a population based cohort originally comprising 8,502 postmenopausal women aged 45–70 years recruited between the years 1977–1997 [36]. The survey invited women to participate in screening for various placebo controlled clinical trials and epidemiological studies at Copenhagen. Between the years 2000–2001 individuals were recalled for a follow-up examination. Follow-up information was obtained in 6,573 women (77.3%). Of the clinical risk factors information was only available for a history of prior fracture. Incident fractures were documented from spinal radiographs and personal history. Validated follow-up information was available in 5,415 women.

The THIN research database contains computerised records of general practitioners, similar to the General Practice Research Database [37]. The study population comprised all women aged 50 years or more registered with

a general practice that contributed data to THIN (N= 366,104) with an average follow-up of 5.8 years. Information on the relevant clinical risk factors was available in 135,695 women (BMI and smoking history were not recorded in all patients). No information was available for a parental fracture history, and smoking history was for 'ever' rather than 'current smoking'. BMD tests are not ultimately undertaken in UK general practice. Fracture ascertainment was from the general practitioner records.

The OPUS study comprises five age-stratified population-based female cohorts drawn from different European centres (Sheffield and Aberdeen (UK), Berlin and Kiel (Germany), and Paris (France)). Participants completed a questionnaire at baseline and BMD was measured by DXA at the femoral neck using the Hologic QDR 4500 (Kiel, Paris and Sheffield) or the Lunar Expert (Aberdeen and Berlin). Baseline estimates for BMD were available in 2155 women [38].

The York cohort [39] was based on a study of hip protectors. The cohort comprised women aged 70 years and over drawn from general practice lists. Baseline characteristics on clinical risk factors were available in 3,409 individuals, most of whom participated in the randomised study of hip protectors. The study showed no significant effect of hip protectors on the risk of hip fracture (OR= 1.17; 95% CI=0.78–1.75). Information on alcohol intake or the presence of rheumatoid arthritis was not available. Weight but not height was available, and we assumed a height of 1.6 m for the calculation of BMI.

The SOF is a multicentre cohort study of risk factors for osteoporosis and fracture in 9,704 elderly women [40]. Participants were ambulatory, Caucasian and aged 65 years or older when recruited between September 1986 and October 1988 at four clinical centres from the USA (Baltimore, Minneapolis, Pittsburgh and Portland). Baseline characteristics were obtained through a structured questionnaire and BMD was assessed during 1990–1991 at the femoral neck using the Hologic QDR 1000. Fractures were assessed by telephone or correspondence at four monthly intervals and confirmed from X-ray reports.

The Geelong Osteoporosis study comprises two cohort studies of women drawn from Geelong and surrounding districts in south east Australia (population 222,000). Two cohorts were available for study [41]. The first (Geelong I) was an age-stratified sample of women drawn randomly from the electoral roll. Women underwent a baseline assessment between 1994 and 1997 to ascertain risk factors and BMD at the femoral neck (Lunar DPX-L). Fractures were radiographically confirmed from hospital records and deaths confirmed from the Australian Institute of Health and Welfare.

The second cohort (Geelong II) was a case-control study [41]. Cases comprised patients aged 35 years or more identified with an incident fracture by weekly database searching of the radiological practices in the region between 1994 and 1996. All women identified with incident fractures were invited to attend for assessment. Ten percent of women died during the ascertainment period and 11% were unable to give informed consent. A total of 692 cases were studied with an acceptance rate of 77%. The control group comprised the women in Geelong I who did not sustain an incident fracture between 1994 and 1996. Both cases and controls were interviewed by means of a structured questionnaire, and BMD was measured at the femoral neck by DXA (Lunar DPX-L). In cases, BMD was measured on the side contra-lateral to the fracture.

The Miyama study is a population-based cohort drawn from inhabitants born in Miyama, Japan between 1910 and 1949 as compiled in 1989 [42]. Of 1543 inhabitants, an age-stratified sample of 400 men and women was drawn by birth decade. A baseline questionnaire was administered in 1990 and BMD was measured at the femoral neck (Lunar DPX) and data available in 353 individuals. Reviews were undertaken in 1993, 1997 and 2000.

The Swiss Evaluation of the Methods of Measurement of Osteoporotic Fracture Risk (SEMOF) study is a prospective multicentre (10 centres) study, the aims of which were to compare the performance characteristics of different ultrasound technologies [43]. 60,000 women aged 70 years or more were randomly selected from an address register and 7,609 women agreed to participate in the study. Six thousand seven hundred and twenty-one women completed a questionnaire and were prospectively studied for a mean time of 2.9 years. Incident fracture was recorded by questionnaire administered at 6 monthly intervals and confirmed from medical records. BMD at the femoral neck (Hologic QDR 4500) was measured in 820 women.

The Women's Health Initiative (WHI) study comprises three overlapping randomised controlled studies and an observational study in post-menopausal women aged 50–79 years [44, 45]. The trials comprised dietary modification with low fat (n=48,836), hormone replacement therapy (HRT) in women with or without a uterus (n=27,347), and supplementation with calcium and vitamin D (n=36,282). The total sample size was 161,808. For this analysis, women less than 55 years were excluded since a history of prior fracture was not available. So too were women taking bone active medication (HRT, bisphosphonates, calcitonin), leaving a sample size of 61,014. Bone mineral density measurements at the femoral neck took place at few centres and were available in 4,193 women using the Hologic 2000. Hip fractures were documented from medical records and adjudicated at a central facility. In the clinical trials, other fractures were adjudicated locally and in the observational study by self report. In the subgroup in whom BMD was measured, non-hip fractures were locally adjudicated.

Baseline and outcome variables

Height and weight were measured using standard techniques in all cohorts. Body mass index (BMI) was calculated as weight in kg divided by height squared in metres and used as a continuous variable. BMD was assessed at the femoral neck by DXA with the exception of the two Gothenburg cohorts. Femoral neck BMD was used as a continuous variable (cohort specific Z-scores excluding the two cohorts from Gothenburg). The clinical risk factors utilised were those identified from previous meta-analyses. These comprised a parental history of hip fracture [11], exposure to systemic glucocorticoids [12], a prior history of fragility fracture [13], current smoking [18], high intake of alcohol (>2 units daily on average) [16] and the presence of rheumatoid arthritis [12]. The prevalence of the risk factors are shown in Table 2. Note that not all primary cohorts nor validation cohorts had complete information.

Fracture ascertainment in the primary cohorts was undertaken by self-report (Sheffield, EVOS/EPOS, Hiroshima) and/or verified from hospital or central databases (Gothenburg, CaMos, DOES, Sheffield, EVOS/EPOS, Rochester, Rotterdam). The EPOS and the Rotterdam study also included sequential systematic radiography to define incident morphometric vertebral fractures, but these were not used in this analysis. In the analysis, we used information on fractures considered to be osteoporotic. In addition, hip fracture alone was considered separately. An osteoporotic fracture was one considered to be due to osteoporosis by the investigator in the EVOS/EPOS study and in CaMos. For the EVOS/EPOS study, osteoporotic fractures comprised hip, forearm, humeral or spine fractures. For the CaMos Study they comprised fractures of the spine, pelvis, ribs, distal forearm, forearm and hip. In the other cohorts, fractures at sites considered to be characteristic for osteoporosis were extracted [46].

Fractures were documented in the validation cohorts by self-report (Miyama, PERF cohort details) and/or verified from hospital, general practitioner or individual imaging databases (EPIDOS, York, THIN, Geelong I and II, PERF, SEMOF) and other cohorts.

Statistical methods

The association of risk factors with the risk of hip and other osteoporotic fracture was examined using a Poisson regression model in each cohort separately. Covariates included current age and time since start of follow-up, and analyses were performed for both sexes separately with and without taking BMD information into account. BMD was expressed as sex- and cohort-specific Z-scores. BMI was analysed continuously. The β-coefficients for each covariate of each cohort and the two sexes were weighted according to the variance, and merged to determine the weighted mean of the coefficient and its standard deviation. The risk ratios at different BMI or BMD levels are then given by $e^{(\text{weighted mean coefficient})}$.

For each risk factor, all significant interactions terms that were identified by the previous meta-analyses were entered (with age, time, sex and the risk factor) with and without BMD. Interactions that were significant for hip fracture risk were also entered into the model for other osteoporotic fractures. Where interactions noted in the "mega-analyses" were no longer significant for hip fracture and other osteoporotic fractures, these were omitted in a step-wise manner by dropping the interaction with the largest p value. Take, for example, the interaction of BMD and age for hip fracture risk: hip fracture risk prediction was significantly higher with BMD at younger ages [14] and the higher predictive values persisted when entered into the model. The respective β functions for the interaction (BMD · current age) were retained in both the model for hip fracture and other osteoporotic fracture, though this fell short of significance in the model for other osteoporotic fractures ($p=0.074$). Conversely, for BMI, a significant interaction was noted with age in the meta-analysis (i.e., an increase in risk ratio of low BMI for osteoporotic fracture with age) [15], but was no longer significant in any model, and the interaction term was dropped from the hazard functions for fracture. The other interactions that were retained were age · sex, BMD · age, BMD · BMD, family history · age, prior fracture · age, BMI · BMI, and age · age.

Complete information from all cohorts used in the model were available for the continuous variables (BMI and BMD) though BMD was not used in the cohorts from Gothenburg, since BMD was not measured at the femoral neck. Not all cohorts had complete information on all the dichotomous risk factors (see Table 2). For example, a current history of smoking was not available from CaMos and Rochester. When one dichotomous variable (e.g., smoking) was deleted from the model this had a very minor effect on the β coefficients for the other variables. Since these deletions had little or no effect, the original β coefficients were used.

The performance of the original model was assessed as the gradient of risk, i.e., the increase in fracture risk per SD increase in risk score. Gradients of risk were computed for the prediction of hip fracture and other major osteoporotic fractures (clinical spine, forearm, proximal humerus) with BMD alone, the clinical risk factors alone, and the combination. The distribution of risk score was examined using the Edgeworth expansion [47].

Heterogeneity between cohorts was tested by means of the I^2 statistic [48]. Moderate heterogeneity was noted for hip fracture outcomes with and without BMD ($I^2=56\%$ and

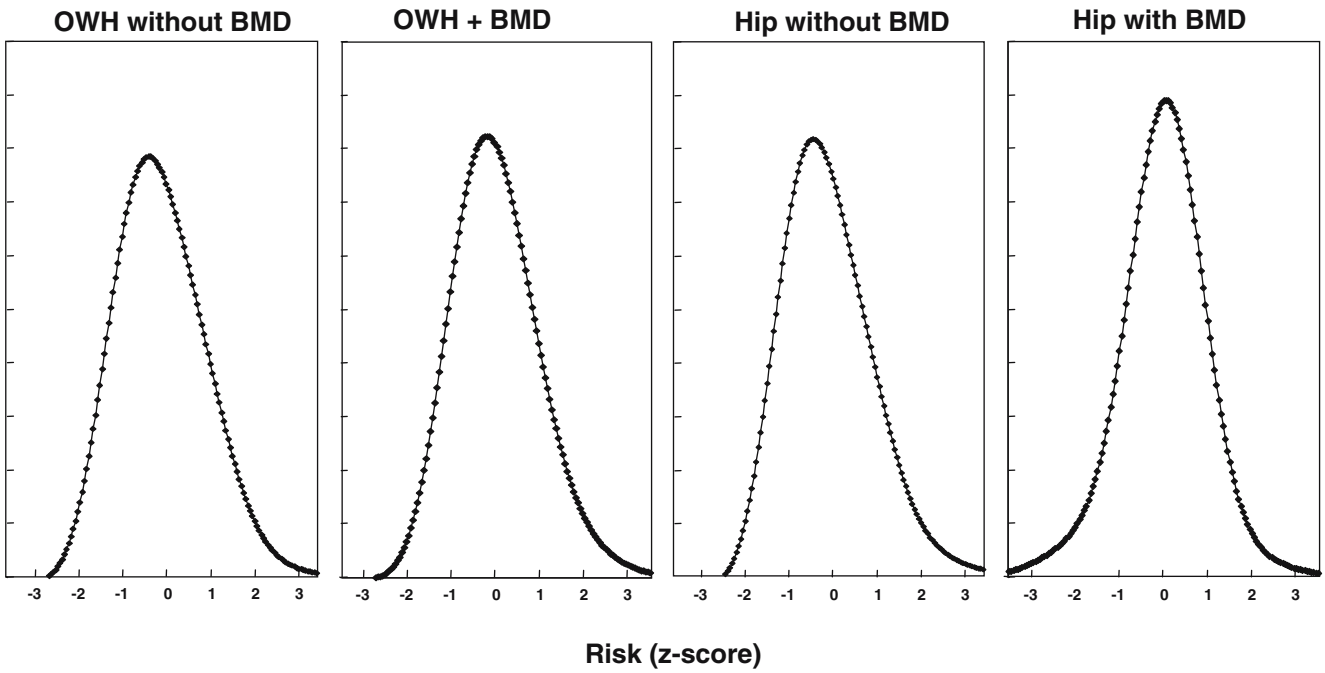

Fig. 1 Distribution of risk scores with and without BMD. OWH refers to osteoporotic fractures without hip fracture

64%, respectively; $P<0.05$) and high heterogeneity for other fracture outcomes ($I^2=83\%$ and 82%, respectively; $P<0.001$). When the interaction between risk score and current age (risk score· age) was included, there was less marked heterogeneity between cohorts for the risk score for hip fracture with or without BMD ($I^2=66\%$ and 60%, respectively) and for other osteoporotic fractures ($I^2=52\%$ and 47%, respectively).

For each validation cohort, the computed risk score was expressed as a sex-specific Z-score. The gradient of hip fracture and other osteoporotic fracture risk was examined for the use of the clinical risk factors alone and in combination with BMD. Gradients of risk were also transformed as area under the receiver operating characteristic (ROC) curve (AUC) as detailed in the Appendix.

Results

The primary cohorts comprised 46,340 men and women (68% female) followed for approximately 190,000 person-years. During follow-up, 4,168 osteoporotic fractures were documented of which 850 were at the hip. The prevalence of the risk factors is shown in Table 2 and the distribution of risk scores shown in Fig. 1. The performance characteristics of the models are given in Table 3 expressed as

Table 3 Gradients of risk per SD change in risk score (with 95% confidence intervals) with the use of BMD, clinical risk factors or the combination

Age	Gradient of risk		
	BMD only	Clinical risk factors alone	Clinical risk factors + BMD
(a) Hip fracture			
50	3.68 (2.61–5.19)	2.05 (1.58–2.65)	4.23 (3.12–5.73)
60	3.07 (2.42–3.89)	1.95 (1.63–2.33)	3.51 (2.85–4.33)
70	2.78 (2.39–3.23)	1.84 (1.65–2.05)	2.91 (2.56–3.31)
80	2.28 (2.09–2.50)	1.75 (1.62–1.90)	2.42 (2.18–2.69)
90	1.70 (1.50–1.93)	1.66 (1.47–1.87)	2.02 (1.71–2.38)
(b) Other osteoporotic fractures			
50	1.19 (1.05–1.34)	1.41 (1.28–1.56)	1.44 (1.30–1.59)
60	1.28 (1.18–1.39)	1.48 (1.39–1.58)	1.52 (1.42–1.62)
70	1.39 (1.30–1.48)	1.55 (1.48–1.62)	1.61 (1.54–1.68)
80	1.54 (1.44–1.65)	1.63 (1.54–1.72)	1.71 (1.62–1.80)
90	1.56 (1.40–1.75)	1.72 (1.58–1.88)	1.81 (1.67–1.97)

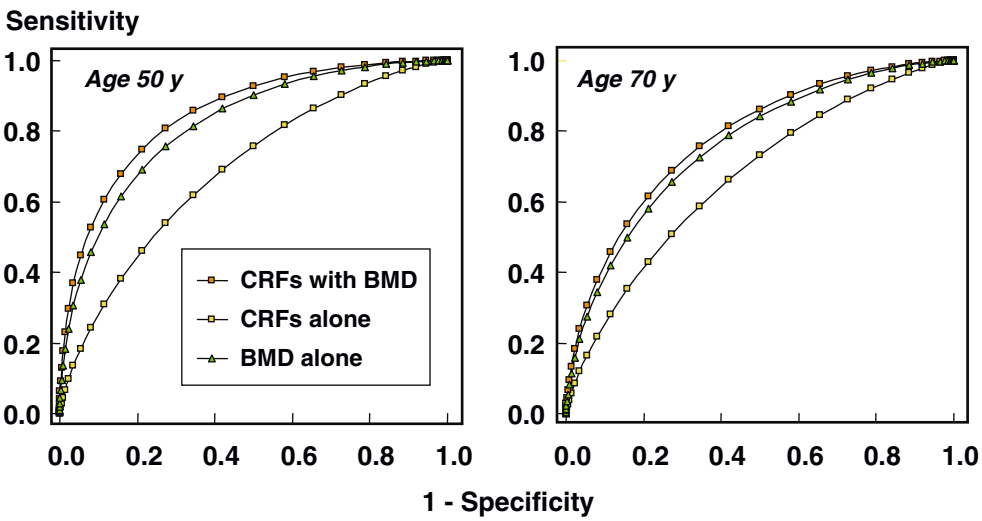

Fig. 2 Receiver operating characteristic curves for the risk score for hip fracture prediction at the ages of 50 and 70 years. CRF = clinical risk factor

gradients of risk per SD change in the risk indicator. Note that the category of other osteoporotic fracture excludes hip fracture, whereas hip fracture was included in the previously published meta-analyses under the term "any osteoporotic fracture".

For hip fracture prediction, gradients of risk decreased with age, as did the AUC of the ROC curve (Fig. 2). At all ages, BMD outperformed the clinical risk factors alone, except at the age of 90 years (Table 3). When BMD was combined with the clinical risk factors there was an increment in the GR/SD. For example, hip fracture risk increased by 3.7/SD decrease in femoral neck BMD at the age of 50 years, and by 2.1/SD with the use of clinical risk factors, but their combined use gave a GR of 4.2/SD. For the prediction of other osteoporotic fractures, GR/SD with BMD were, as expected, lower than for the prediction of hip fracture. GR varied from 1.2 to 1.6/SD depending on age and tended to increase with age, in contrast to the prediction of hip fracture. When clinical risk factors alone were used, the GR also increased with age and, unlike for hip fracture prediction, the use of clinical risk factors outperformed BMD. As in the case of hip fracture prediction, there was an increment in GR when the clinical risk factors were used in combination with BMD. The increment in GR using BMD alone and in conjunction with clinical risk factors was, however, more substantial in the case of hip fracture prediction than for the prediction of other osteoporotic fractures.

The performance characteristics of the validation cohorts are shown in Table 4. Since gradients of risk were age-

Table 4 Gradient of risk/SD change in risk score of the validation cohorts compared to the original cohorts standardised to the age of 70 years (±95% confidence estimates)

	Hip fractures		Other osteoporotic fractures	
Cohort	Without BMD	With BMD	Without BMD	With BMD
Geelong I	1.88 (1.07–3.29) [0.67]	1.71 (0.74–3.96) [0.65]	1.34 (1.12–1.61) [0.58]	1.57 (1.31–1.88) [0.63]
Geelong II	1.50 (1.05–2.13) [0.61]	3.40 (1.99–5.80) [0.81]	1.30 (1.14–1.48) [0.57]	1.54 (1.36–1.76) [0.62]
OPUS	2.48 (1.26–4.91) [0.74]	2.09 (0.98–4.47) [0.70]	1.32 (1.08–1.62) [0.58]	1.38 (1.15–1.65) [0.59]
York	2.05 (1.13–3.72) [0.69]	– [–]	1.74 (1.37–2.21) [0.65]	– [–]
PERF	1.28 (1.01–1.62) [0.57]	2.72 (1.43–5.16) [0.76]	1.14 (1.05–1.23) [0.54]	1.19 (1.05–1.35) [0.55]
SOF	1.58 (1.34–1.87) [0.63]	2.21 (1.79–2.73) [0.71]	1.24 (1.15–1.34) [0.56]	1.31 (1.20–1.42) [0.58]
THIN	1.54 (1.45–1.63) [0.62]	– [–]	1.29 (1.26–1.32) [0.57]	– [–]
EPIDOS	1.70 (1.18–2.44) [0.65]	2.89 (1.98–4.21) [0.77]	1.41 (1.11–1.78) [0.60]	1.47 (1.17–1.86) [0.61]
Miyama	2.87 (0.98–8.37) [0.77]	3.07 (0.97–9.64) [0.79]	3.50 (2.42–5.07) [0.81]	2.80 (2.06–3.80) [0.77]
SEMOF	1.76 (1.03–3.01) [0.65]	2.18 (1.27–3.74) [0.71]	1.32 (1.10–1.58) [0.58]	1.44 (1.16–1.79) [0.60]
WHI	1.54 (1.43–1.66) [0.62]	2.44 (1.85–3.21) [0.74]	1.26 (1.23–1.29) [0.56]	1.46 (1.35–1.58) [0.60]
Original cohorts	1.84 (1.65–2.05) [0.67]	2.91 (2.56–3.31) [0.78]	1.55 (1.48–1.62) [0.62]	1.61 (1.54–1.68) [0.63]

AUC's under the ROC curve are shown in square brackets.

dependent, these were standardised to the age of 70 years. Note that when one or more risk factor was unavailable from the validation cohorts, the gradient of risk was still computed from the original model, but with a β value of zero for that particular risk factor. Table 4 also shows areas under the ROC curve. Gradients of risk and AUC's were comparable in the validation cohorts compared with the original cohorts. For example, for hip fracture prediction without BMD, the mean AUC was 0.66 in the validation cohorts compared with 0.67 in the original cohorts. With the addition of BMD the mean AUC was 0.74 and 0.78, respectively. For other osteoporotic fractures the mean AUC was 0.60 in the validation cohorts and 0.62 in the original cohorts, excluding BMD. With the addition of BMD, the average AUCs were 0.62 and 0.63, respectively.

Discussion

The principal finding of this study is that the use of clinical risk factors alone provides some discriminative value in the categorisation of fracture risk. However, the addition of bone mineral density improves the GR/SD still further. For hip fracture prediction, the GR was markedly improved at younger ages, whereas little age dependency was seen for the prediction of other osteoporotic fractures.

In this analysis, we chose to provide independent models for hip fracture and for other osteoporotic fractures. The principal reason is that, although many risk factors, including those chosen here are common for both fracture types, the risk ratios differ and are generally higher for hip fracture than for other osteoporotic fractures [11–19]. It is possible that the strength of risk factors also varies between the different types of osteoporotic fracture, but much larger material than currently available would be required to incorporate this with accuracy into the model. The available evidence would suggest that, with the exception of falls, risk factors for vertebral fracture do not differ substantially from those from other osteoporotic fractures [49–52].

The use of clinical risk factors alone provided a GR/SD that lay between 1.4 and 2.1, depending upon age and the type of fracture predicted. These gradients are comparable to the use of BMD alone to predict fractures [14, 53]. For example, for the prediction of any osteoporotic fracture, the GR at the age of 70 years was 1.5 with femoral neck BMD [14]. With peripheral BMD the gradient of risk is somewhat, though not significantly lower (GR=1.4/SD; 95% CI=1.3−1.5/SD). These data suggest that clinical risk factors alone are of value and might be used, therefore, in the many countries where DXA facilities are sparse [54].

Notwithstanding the above, a further important finding is that there are substantial gains to be had in the use of the clinical risk factors in conjunction with BMD, particularly in the case of hip fracture prediction. At the age of 50 years, for example, the gradient of risk with BMD alone was 3.7/SD, but with the addition of clinical risk factors was 4.2/SD.

Although the improvement in GR with the addition of BMD was modest particularly in the case of other osteoporotic fractures, it should be recognised that gradients of risk are not multiplicative. For example, at the age of 70 years, BMD alone gave a GR of 2.8/SD for hip fracture. For the clinical risk factors the GR was 1.8/SD. If these two tests were totally independent, the combined GR would be $\sqrt{(2.8^2 + 1.8^2)} = 3.3$. The observed gradient of risk (2.9) falls short of the theoretical upper limit, since there was a significant correlation between the clinical risk factor score and BMD (r=0.25). The increment in gradient of risk for the prediction of other fractures was smaller, but there was also a significant correlation between the clinical risk factor score and BMD (r=0.10).

It is of interest that the GR for hip fracture prediction decreased with age. We have previously reported this for BMD alone [14], but in the present study, this was also evident with the use of clinical risk factors alone. It is possible that skeletal or extra-skeletal risk factors not measured, such as quality of bone or liability to falls, are captured by the risk factors included in the models that affect the GR. If so, the same cannot be said for the other osteoporotic fractures, which tended to be predicted more strongly with advancing age.

As discussed elsewhere [10, 55], increases in GR improve sensitivity without markedly affecting specificity for fracture prediction. For example, if it were appropriate to consider 10% of women aged 50 years to be at high risk, a test with a gradient of risk of 2.0/SD (i.e., the use of clinical risk factors alone) would be expected to have a sensitivity of 26% for a specificity of 91%. The same scenario, but with a test that gave a gradient of risk of 4.0 would increase greatly the sensitivity of the test to 42% without adverse effects on specificity (92%), and the positive predictive value would increase from 11% to 25%. Thus, modest improvements in GR have substantial effects on sensitivity and positive predictive value.

Several population-based studies have examined the relationship between risk factors with and without the inclusion of BMD [56–70]. With few exceptions these have not been validated in independent cohorts. An exception is a subset of the US-based SOF study which was used to produce a multivariate prediction model [57]. Twenty potential risk factors were considered in the model, both including and excluding BMD at the total hip. Age, weight and cigarette smoking appeared as independent risk factors, as did an indicator of physical condition (using the arms to stand from a chair). In addition, a history of maternal hip fracture after the age of 50 years and a history of prior

fracture in adult life were also independent risk factors. Scores derived from these models showed good discrimination for fracture risk. Women with scores in the lowest quintile had a 5-year risk of hip fracture of 0.6% compared with about a 14-fold increase risk of 8.2% for those with scores at the highest quintile without BMD. From the relationship between AUC and gradient of risk, the gradient of risk can be computed at 2.5 per SD change in risk score assuming a normal distribution of risk score (our calculations from the data of Black et al. [57]). Good separation for those at high and low risk of vertebral fracture was also demonstrated. Gradients of risk were lower for non-vertebral fractures, there being about a threefold difference in risk between the highest and lowest quintile for risk score respectively (gradient of risk=1.4 and 1.5 without, or with BMD, respectively). As with our own models, the addition of BMD values to the models derived from clinical variables alone improved performance, although not markedly. These performance characteristics were independently assessed against the EPIDOS study. For hip fracture risk there was a 5.8-fold difference in risk between the lowest and highest quintile of risk score in the absence of BMD. When BMD was included in the model the risk ratio was 24.

In the present study, there was a 5.6-fold difference in hip fracture risk comparing the highest with the lowest quintile of risk with the use of clinical risk factors. When BMD was additionally added, the risk ratio was 20.9. The risk ratios in the two studies are not directly comparable, since age is used as a risk factor in the model of Black et al. [57], whereas the risk ratios we report are all age-specific. Since age is a very important determinant of fracture risk, and the risk ratios between the two studies are broadly comparable, this suggests that the performance characteristics of the present model represent some improvement in fracture risk prediction.

There are several aspects of validity that are of relevance to the present study. The first concerns the performance of the model in independent cohorts, and a second relates to the validity of the risk factors chosen. With respect to the first, there was some variation in the GRs and AUCs of the validation cohorts, but those that performed less adequately included those with missing risk factors. This would underestimate the gradient of risk of the affected cohorts. Significant heterogeneity was noted between cohorts in the gradients of risk, but there were marked differences in age between cohorts, and the gradient of risk varied by age. When the Poisson model included the interaction between age and risk score, heterogeneity was moderate. Overall, the performance characteristics of the test in the eleven independent cohorts were comparable to that of the original cohorts, as judged by the GR/SD. These validation cohorts, however, mainly comprised women and further studies in men are required. The performance characteristics of diagnostic tests are often expressed as the areas under the ROC curves (AUC). As shown in the Appendix, there is a mathematical relationship between AUC and GR. For example, a GR of 4.2/SD is equivalent to an AUC of 84% (i.e., hip fracture prediction with risk factors plus BMD at the age of 50 years). At the other extreme, a GR of 1.4 (other osteoporotic fractures at the same age) is equivalent to an area under the ROC curve of 60%. An area equivalent to 50% indicates a predictive value no better than chance.

The choice of risk factors for the present model was made on the basis of our previous meta-analyses. Aside from the availability of sufficient data, these risk factors were chosen for their ease of use in the setting of primary care. An important further consideration is whether the risk so identified by a risk factor is amenable to a therapeutic intervention. Liability to falls, for example, is a strong risk factor for fracture, but there is some uncertainty whether patients identified on the basis of such risk factors would respond to treatment with inhibitors of bone turnover [71]. The strongest level of evidence for the validity of the use of risk factors in this way would be provided by randomised controlled trials that recruit patients on the basis of these risk factors. Responsivity to pharmacological intervention has been shown for patients selected on the basis of low BMD, prior fracture or the use of oral corticosteroids [72–75]. In the case of the other risk factors, no trials have recruited on the basis of their presence. However, analyses of randomised controlled trials indicate that the beneficial effects of treatment are not adversely (or beneficially) affected by the presence or absence of the other risk factors [30, 76–79]. Moreover, since there is a significant correlation between the risk factors and BMD, case finding on the basis of the clinical risk factors used will capture a population with low BMD [28]. These considerations suggest that the risk factors chosen are appropriate, but would need to be validated in prospective studies of intervention.

We conclude that the combined use of clinical risk factors provides an assessment of fracture risk that can be used for the prediction of osteoporotic fractures. Moreover, clinical risk factors can be used to enhance the performance characteristics of BMD. The application of these models for the assessment of fracture probability will require the incorporation of hazard functions of death and calibration to the epidemiology of specific countries. This will permit the assessment of absolute fracture probabilities of hip fracture and other osteoporotic fractures to be determined on the basis of the clinical risk factors alone or in combination with BMD.

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Appendix

Relationship between area under the ROC curve and gradient of risk for a normally distributed risk variable

Let X be a risk variable with the frequency function f_0 among the not diseased and f_1 among the diseased. Furthermore, assume that the probability of being diseased among the studied individuals is p. Then the conditional probability of belonging to the diseased group given the that X=x is

$$1/[1 + ((1-p)/p) \cdot (f_0(x)/f_1(x))]$$

We assume that f_0 and f_1 are frequency functions corresponding to normally distributed variables with the same standard deviation σ and the difference between means of diseased and not diseased equal to Δ. Then the conditional probability can be written as

$$1/[1 + \exp(-(\beta_0 + \beta_1 \cdot x))],$$

where $\beta_1 = \Delta/\sigma^2$. If individuals are followed for a short period so that the proportion of diseased are low, then the beta coefficients for a risk variable obtained by Cox regression, Poisson regression or logistic regression will be approximately the same and the standard deviation of the risk variable X in the population as a whole will be approximately as among the not diseased, σ. The gradient of risk per 1 standard deviation, GR, is $\exp(\beta_1 \cdot \sigma) = \exp(\Delta/\sigma)$, and thus

$$\ln(GR) = \Delta/\sigma \quad (1)$$

Let Y denote the value of the risk variable of a randomly chosen individual among the diseased individuals and let X be the corresponding quantity among not diseased individuals. We assume that Y tends to be larger than X. The area under the ROC curve is equal to the probability $P(Y>X) = 1-P(Y-X\leq 0)$. If Y and X have normal distributions with the same standard deviation σ and the difference Δ between the means, then the area under the curve is $1 - \Phi(-\Delta/(\sigma \cdot \sqrt{2})) = \Phi(\Delta/\sigma \cdot \sqrt{2})$, where Φ is the standardised normal distribution function. When we use the relationship (1), the area under the ROC curve can be represented as the following function of gradient of risk per 1 standard deviation, GR, *Area under the ROC curve* $= \Phi(\ln(GR)/\sqrt{2})$.

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