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Compliance with ethical standards

Conflict of interest

JA Kanis led the team that developed FRAX as director of the WHO Collaborating Centre for Metabolic Bone Diseases. EV McCloskey, WD Leslie, M Lorentzon, NC Harvey, E Liu, L Vandenput and H Johansson are members of the FRAX team. JA Kanis, NC Harvey, and EV McCloskey are members of the advisory body to the National Osteoporosis Guideline Group. JA Kanis reports no additional competing interests.

KE Åkesson has no financial interest related to FRAX; chaired the National SALAR Group for Person-Centered Care Pathway Osteoporosis.

FA Anderson led the team that developed GLOW, while director of the Center for Outcomes Research at the University of Massachusetts Medical School; he has no financial interest in FRAX.

R Azagra has received funding for research from Instituto Carlos III of Spanish Ministry of Health, IDIAP Jordi Gol of Catalan Government and from Scientific Societies SEMFYC and SEIOMM.

CL Bager is employed at Nordic Bioscience and owns stock in Nordic Bioscience. She declares no competing interests in relation to this work.

HA Bischoff-Ferrari has no financial interest in FRAX. For the DO-HEALTH trial cohort, Prof. Bischoff-Ferrari reports independent and investigator-initiated grants from European Commission Framework 7 Research Program, from the University of Zurich, from NESTEC, from Pfizer Consumer Healthcare, from Streuli Pharma, plus non-financial support from DNP. For the study cohort extension, she reports independent and investigator-initiated grants from Pfizer and from Vifor. Further, Prof. Bischoff-Ferrari reports non-financial support from Roche Diagnostics and personal fees from Wild, Sandoz, Pfizer, Vifor, Mylan, Roche, Meda Pharma, outside the submitted work with regard to speaker fees and travel fees.

JR Center has received honoraria for speaking at educational meetings and for advisory boards from Amgen and honoraria for an advisory board from Bayer.

R Chapurlat has no financial interest in FRAX. He has received grant funding from Amgen, UCB, Chugai, MSD, Mylan and Medac. He has received honoraria from Amgen, UCB, Chugai, Galapagos, Biocon, Abbvie, Haoma Medica, Pfizer, Amolyt, MSD, Lilly, BMS, Novartis, Arrow, PKMed, Kyowa-Kirin, and Sanofi.

C Christiansen owns stock in Nordic Bioscience. He declares no competing interests in relation to this work.

C Cooper reports personal fees from Alliance for Better Bone Health, Amgen, Eli Lilly, GSK, Medtronic, Merck, Novartis, Pfizer, Roche, Servier, Takeda and UCB.

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JA Eisman declares consulting and research support from Actavis, Amgen, Aspen, Lilly, Merck Sharp and Dohme, Novartis, Sanofi-Aventis, Servier and Theramex.

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MA Kotowicz has received funding from the National Health and Medical Research Council (NHMRC) Australia, and the Medical Research Future Fund (MRFF) Australia. He has served on advisory boards for Amgen Australia, Novartic and Eli Lilly – all unrelated to this work and is the Director of the Geelong Bone Densitometry Service.

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Previous fracture and subsequent fracture risk: A meta-analysis to update FRAX

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Abstract

Summary—A large international meta-analysis using primary data from 64 cohorts has quantified the increased risk of fracture associated with a previous history of fracture for future use in FRAX.

Introduction—The aim of this study was to quantify the fracture risk associated with a prior fracture on an international basis and to explore the relationship of this risk with age, sex, time since baseline and bone mineral density (BMD).

Methods—We studied 665,971 men and 1,438,535 women from 64 cohorts in 32 countries followed for a total of 19.5 million person-years. The effect of a prior history of fracture on the risk of any clinical fracture, any osteoporotic fracture, major osteoporotic fracture and hip fracture alone was examined using an extended Poisson model in each cohort. Covariates examined were age, sex, BMD and duration of follow up. The results of the different studies were merged by using the weighted β-coefficients.

Results—A previous fracture history, compared with individuals without a prior fracture, was associated with a significantly increased risk of any clinical fracture (Hazard ratio, HR = 1.88; 95% CI = 1.72-2.07). The risk ratio was similar for the outcome of osteoporotic fracture (HR = 1.87; 95% CI = 1.69-2.07), major osteoporotic fracture (HR = 1.83; 95% CI = 1.63-2.06) or for hip fracture (HR = 1.82; 95% CI = 1.62-2.06). There was no significant difference in risk ratio between men and women. Subsequent fracture risk was marginally downward adjusted when account was taken of BMD. Low BMD explained a minority of the risk for any clinical fracture (14%), osteoporotic fracture (17%), and for hip fracture (33%). The risk ratio for all fracture outcomes related to prior fracture decreased significantly with adjustment for age and time since baseline examination.

MC Zillikens has received honoraria in the past for lectures or advice from Alexion, Amgen, Eli Lilly, Kyowa Kirin, Shire and UCB, unrelated to the current work.
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Human and animal rights
This review does not contain any original studies with human participants or animals performed by any of the authors.

Ethics
All individual cohorts with candidate risk factors available have been approved by their local ethics committees and informed consent has been obtained from all study participants. General ethics approval for the use of these cohorts is also given by the University of Sheffield. Participant data will be stored in coded, de-identified form. Only summary statistics and aggregate data will be published, not allowing for identification of individual study participants.

Conclusion—A previous history of fracture confers an increased risk of fracture of substantial importance beyond that explained by BMD. The effect is similar in men and women. Its quantitation on an international basis permits the more accurate use of this risk factor in case finding strategies.

Keywords

Prior fracture; Meta-analysis; Hip fracture; Osteoporotic fracture; Major osteoporotic fracture

Introduction

A history of a prior fracture at a site characteristic for osteoporosis is an important risk factor for further fracture [1, 2, 3, 4, 5, 6]. Fracture risk is approximately doubled in the presence of a prior fracture, including morphometric vertebral fractures. The risks are in part independent of BMD [4]. However, the increase in risk is not constant with age. For example, a large meta-analysis showed that a prior fracture history was a significant risk factor for hip fracture at all ages, but the population relative risk was highest at younger ages and decreased progressively with age [4].

The identification of patients with a fracture history is a well-established goal in the clinical management of osteoporosis as outlined in most clinical guidelines worldwide [7, 8, 9, 10, 11, 12]. In many cases, individuals with a prior fracture are eligible for treatment irrespective of BMD. For example, the National Osteoporosis Guideline Group (NOGG) in the United Kingdom recommends treatment in all women with a prior fragility fracture [10]. A similar threshold is provided in the European guidance [13]. In the United States, a prior vertebral or hip fracture qualifies for a treatment recommendation irrespective of BMD [14].

Because a prior fracture provides a fracture risk that is largely independent of BMD, it has been incorporated into assessment guidelines that integrate the risks associated with a number of risk variables [15, 16, 17]. FRAX®, currently available in 78 territories, is the most widely used fracture risk assessment tool and is incorporated into a large number of assessment guidelines [7], recommended by the Committee for Medicinal Products for Human Use (CHMP) [18], and approved by the National Institute for Health and Care Excellence (NICE) [19]. The incorporation of a prior fracture as an input variable for risk prediction was based on a meta-analysis, published in 2004, of 15,259 men and 44,902 women from 11 cohorts followed for a total of 250,000 person-years [4]. Since then, many more prospectively studied cohorts have become available that have the potential to improve the accuracy of FRAX [20].

The aim of the present study was to quantify the risk for future fracture associated with a history of prior fracture in an international setting, and to explore the dependence of this risk on age, sex, time since baseline assessment and BMD.

Methods

The study population was derived from a systematic review that identified prospective cohort studies for the update of FRAX. The study was registered with the International

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prospective register of systematic reviews, PROSPERO (CRD42021227266), and followed the Preferred Reporting Items for Systematic Reviews (PRISMA) guidelines. Studies were eligible if the cohort was prospective, included at least 200 participants, assessed an adequate number of clinical risk factors and reported an adequate number of incident fracture outcomes. We studied 2,104,506 men and women from 64 prospectively studied cohorts of whom 9.7% had a prior fracture history. 58 cohorts included women (n=1,438,535) and 40 cohorts included men (n=665,971). Details of the cohorts studied have been given previously [20] and are summarized in Table 1.

Baseline and outcome variables

The construct of the question to determine a prior fracture history differed between the cohorts studied, based on time of previous fracture, fracture site, energy, validity, and inclusion of morphometric vertebral fractures (Table 2).

For outcomes Information on all clinical fractures was used for this report ‘all fractures’. In addition, fractures considered to be associated with osteoporosis were examined [21]. According to this classification, fractures of the skull, face, hands, feet, ankle and patella were excluded as well as tibial and fibular fractures in men. Hip fracture and major osteoporotic fracture were also analysed separately. No distinction was made according to trauma since both high- and low-trauma fractures show similar relationships with low BMD and future fracture risk [22]. The risk of death as function of fracture history was also assessed.

Statistical methods

The risk of fracture was estimated by an extended Poisson model applied separately to each cohort (and also separately by sex for those cohorts with both men and women) [23, 24]. Because of an embargo on transfer of primary data from Manitoba, Cox regression was used on the Manitoba cohort on site and beta-coefficients, variances and covariances forwarded to the analysis team. Covariates included current time since start of follow up, current age (derived from age at since start of follow up and current time since start of follow up), prior history of fracture, and BMD at the femoral neck. Femoral neck BMD was adjusted for manufacturer and T-scores were calculated from the NHANES III White female reference values [20]. We additionally estimated a model that excluded BMD from the covariates. A further model included the interaction term ‘prior fracture · current time since baseline’ to determine whether the strength of the association of prior fracture and fracture risk changed with time. An additional model included the interaction term ‘prior fracture · current age’ to determine whether the strength of the association of prior fracture and fracture risk changed with age. Interactions with time and with age were also explored using piece-wise linear regression to check the adequacy of the Poisson model. The hazard ratio (HR) for previous fracture was determined for each age from 40 years from the Poisson model. Results of each cohort and the two sexes were weighted according to the variance and merged to determine the weighted means and standard deviations. The HR of those with a prior fracture history versus those without a prior fracture history was equal to $e^{\text{weighted mean of } \beta}$. There was significant heterogeneity in risk between cohorts (index of heterogeneity I^2 = 82-98% depending on fracture outcome), and a random effects model was used in the meta-analysis.

The component of the risk ratio explained by BMD was computed from a meta-analysis of BMD and fracture risk in men and women combined [25]. Based on the prior evidence, the risk of any clinical fracture was assumed to increase 1.45-fold for each SD decrease in BMD at the femoral neck. For hip fracture, the gradient of risk was assumed to be 2.07 per SD and 1.55 for any osteoporotic fracture [4]. These findings permitted comparison of the calculated expected difference in mean BMD between those with, versus those without, a prior fracture, with the actual difference ascertained from the baseline data. Thus, the proportion of risk attributed to a low BMD was computed as:

$$\frac{[\log HR_a/\log GR] - [\log HR_b/\log GR]}{[\log HR_a/\log GR]}$$

where HR_a is the unadjusted hazard ratio for prior fracture, HR**b** is the hazard ratio adjusted for BMD, and GR is the gradient of risk for femoral neck BMD [4].

Individuals with missing data were excluded. No data were imputed.

Sensitivity analyses

As noted above, the effect of sex on the hazard ratio for fracture was examined in those cohorts that contributed both men and women. Similarly, differences in risk with and without BMD were additionally explored in those cohorts that contributed both scenarios. Assessment of the effects of race and ethnicity was confined to those cohorts recording more than one race or ethnic group (Asian, Black, Hispanic, White), comprising Health ABC, CAMOS, MROs USA, WHI, SOF, Manitoba and UK Biobank. Results were also computed according to study quality as previously defined [20]. Quality was based on a 0/1 score for four criteria: Population-based cohort (yes scores 1); Fracture ascertainment (self-report scores 0, others score 1); Duration of follow-up (> 2 years, scores 1); Average loss to follow-up/year (< 10%, scores 1). This gives a maximum score of 4 and a minimum of 0. A quality score of 0 or 1 was designated as poor quality (designated C), a score of 2 or 3 categorised as intermediate quality (B) and a score of 4 designated as high quality (A). Quality grades are given in Table1.

Results

Of 2,104,506 men and women studied in 32 countries, 45,059 men and 158,659 women had sustained a prior fracture. At follow up, 38,897 men and 147,897 women were identified as having a subsequent clinical fracture of any kind; 31,686 and 124,139 were characterized as osteoporotic in men and women, respectively; 26,744 men and 83,815 women sustained a MOF; 8182 and 31,176 were hip fractures. The total follow-up time was 6.8 million-person years in men and 12.7-million-person years in women. BMD measurements were available in 13.8% (289,841) of individuals. The probability of fracture history rose almost linearly with age from the age of 40 years but tended to decline in women after age 90 years (Table

3). The prevalence of recording a history of a prior fracture was higher in women than in men (OR = 1.34; 95% CI = 1.32–1.35 unadjusted).

Risk of fracture by site and sex

Previous fracture was associated with a significantly increased risk of any subsequent fracture (Table 4). In men and women, the HR ranged from 1.71 to 1.99 depending upon category of the outcome fracture. There were no significant differences in hazard ratios by site of fracture. The risk ratio was marginally but not significantly higher in men than in women by approximately 7-11%. In a sensitivity analysis using only those cohorts that contributed both men and women, there was no sex difference in hazard ratio for all sites (Appendix, Table A)

The increase in risk among those who reported a prior clinical fracture was fairly heterogeneous as shown in the Forest plots in Figure 1 for MOF and hip fracture outcomes. Forest plots for any clinical fracture and osteoporotic fracture outcomes are given in the appendix. Heterogeneity was not related to the question construct since the question construct had little effect on the outcome. In the case of an osteoporotic fracture, for example, the question construct of any prior fracture was associated with a similar increase in fracture risk (HR=1.87; 95%CI=1.58-2.22) as that when the question referred to a prior major osteoporotic fracture (HR=1.77; 95%CI=1.51-2.07) or where the site of prior fracture was unspecified (HR=1.75; 95%CI=1.61-1.89). Similarly, there was no significant difference when low or moderate trauma was specified (HR=1.77; 95%CI=1.41-2.22) or unspecified (HR=1.84; 95%CI=1.67-2.03; p>0.3).

Dependence on BMD

The impact of BMD on the fracture risk in individuals with a prior fracture is quantified in Table 5. The HR was marginally decreased by approximately 8-16% when account was taken of BMD. In the case of any clinical fracture, if it is assumed that the risk of any clinicalfracture increases 1.45-fold for each standard deviation (SD) decrease in hip BMD (gradient of risk), then the difference in risk between those with and without a prior fracture is equal to an expected difference in BMD of 1.57SD [log 1.79/log1.45]. In reality, the difference in BMD at all ages in men and women combined was approximately 0.22 SD ([log (1.79)/log(1.45)]- [log(1.65)/log(1.45)]). Thus, low BMD accounted for the minority (14%; 0.22/1.57) of the difference in risk of any clinical fracture between those with or without a prior fracture. As would be expected, the proportion of risk accounted for by BMD was greater in the case of hip fractures (see Table 5) but remained less than 50% (see Table 5).

Interaction with age

A prior fracture history was a significant risk factor for fracture at all ages. The hazard ratio was highest at younger ages and decreased progressively with age (Table 6). The interaction term was significant for all fracture outcomes in men and women combined. The decrease with age was most marked for hip fracture which decreased by approximately 16% for each decade of age (Figure 2). An almost identical relationship was observed using piece-wise linear regression (data not shown).

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Interaction with time

Fracture risk associated with a prior fracture decreased slowly with time since baseline by about 2-4% per year (Table 7). A similar relationship was observed using piece-wise linear regression (data not shown).

Race and Ethnicity

With one exception, there was no difference in the HR by race and ethnicity in those cohorts where race or ethnicity was documented (Table B of Appendix). The exception was for major osteoporotic fracture such that in Blacks, those with prior fracture history had a higher risk of subsequent fracture hazard ratio than Whites (Blacks: HR=2.43, 95% CI=1.37-3.78 vs. Whites: HR=1.57, 95% CI= 1.32-1.87). The effect was largely driven by a high HR in Blacks from Manitoba (HR=5.34, 95% CI= 1.79-15.94).

Quality scores

There was no significant difference in fracture outcomes when cohorts of high quality were compared with those of moderate quality (Appendix, Table C). For cohorts of low quality, there was a significant difference from high quality cohorts for MOF, based on a single low-quality cohort (GERICO).

Risk of death

A prior fracture was associated with a significant increase in the risk of death in both men (HR=1.11; 95%CI=1.02, 1.21) and women (HR=1.10; 95%CI=1.05-1.15). Hazard ratios remained unchanged when adjusted for femoral neck BMD.

Discussion

The present study represents the largest meta-analysis to date on the association between prior fracture and subsequent fracture risk. The effect is similar in men and women and is consistent with our previous meta-analyses [4]. It is of interest that the quantum of effect was not dependent the question construct. The size of the effect was also relatively immune to cohort quality and different race and ethnicities. Nonetheless, the true effect size relies on the accuracy of information provided which cannot be assessed in the construct of the present study. For the purposes of risk assessment, however, accuracy and causality of associations are of less concern than repeatability and that the risk identified shows reversibility of effect [17, 28].

The extensive data resource permitted the elucidation of important interactions comprising an interaction with age, and time since baseline. For all fracture outcomes, the risk ratios decreased significantly with age, consistent with our previous meta-analysis [4] and incorporated into FRAX [17]. Of Importance, we were able to examine the risk associated with prior fractures among the oldest -old. Additionally, the increased power of the present study revealed that hazard ratios also decreased significantly with time, a phenomenon not accounted for in the current FRAX model [17]. As with all risk variables used in FRAX, any interaction of effect over time is also important to incorporate in future probability models.

The present study also quantified the independent contributions of low BMD and prior fracture. For all outcomes studied, low BMD explained a minority of the total risk. The mechanism for the BMD-independent increase in risk could not be determined from this study but is likely due, in part, to coexisting morbidity that might increase the risk of falls or impair the protective responses to injury [27, 28]. In addition, changes in the structural or material properties of bone may weaken bone out of proportion to any effect on BMD [29, 30, 31, 32, 33, 34].

A particular strength of the present study is that the estimate of risk is made in an international setting largely from population-based cohorts. Calculations were based on the primary data, decreasing the risk of publication biases. The consistency of the association between cohorts additionally indicates the international validity of this risk variable.
The present study has several limitations that should be mentioned. As with nearly all population-based studies, nonresponse biases may have occurred, which we were unable to document for all cohorts. The effect is likely to exclude sicker members of society, including those in institutional care, and may underestimate the absolute risk of fracture. Thus, the probability of a prior fracture may be underestimated from a societal perspective, but this is unlikely to affect risk ratios. The greatest potential problem was the construct of the question concerning prior fractures and the methods of documenting and characterizing subsequent fracture events. These differed substantially between cohorts. The effect of this heterogeneity on fracture outcomes was, however, marginal. It should also be recognised that additional factors affect the risk associated with a prior fracture. The increase in risk is more marked the greater the number of prior fractures [35, 36, 37], particularly prior vertebral fractures for a subsequent vertebral fracture [35, 38, 39, 40, 41]. Also, the risk of a subsequent osteoporotic fracture is particularly acute immediately after an index fracture and wanes progressively with time [3, 42, 43, 44]. For example, after a fracture, the risk of subsequent fracture is highest in the immediate post fracture interval with more than one-third of subsequent fractures occurring within 1 year [45]. The waning of risk with time is also age-dependent [44]. Also, the effect of recency is site dependent [47] with higher risk ratios for hip and vertebral fracture than for humerus, forearm, or minor osteoporotic fracture. Finally, morphometric but subclinical fractures were not assessed though they do add to fracture probability independently of FRAX [48]. Data on these additional modulating factors were not available for this meta-analysis, thus residual confounding could be present in our findings. However, adjustments to FRAX probabilities for these factors is available through FRAXplus [49]. FRAXplus, which has recently been released in a beta version, brings together a number of adjustments that can illustrate the potential impact of modulating factors on FRAX fracture probabilities. These include trabecular bone score, recency of fracture (by site and time within the last two years), the number of self-reported falls in the previous year, glucocorticoid dose, and duration of type 2 diabetes mellitus. An additional limitation is that no account was taken of treatment effects.

In conclusion, this analysis has quantified the magnitude of the risk for future fractures conferred by a prior fracture in the largest meta-analysis conducted to date, and that this risk is largely independent of BMD. The effect is similar in men and women. The consistency of the association in an international setting provides the rationale for the use of these data in the next iteration of FRAX.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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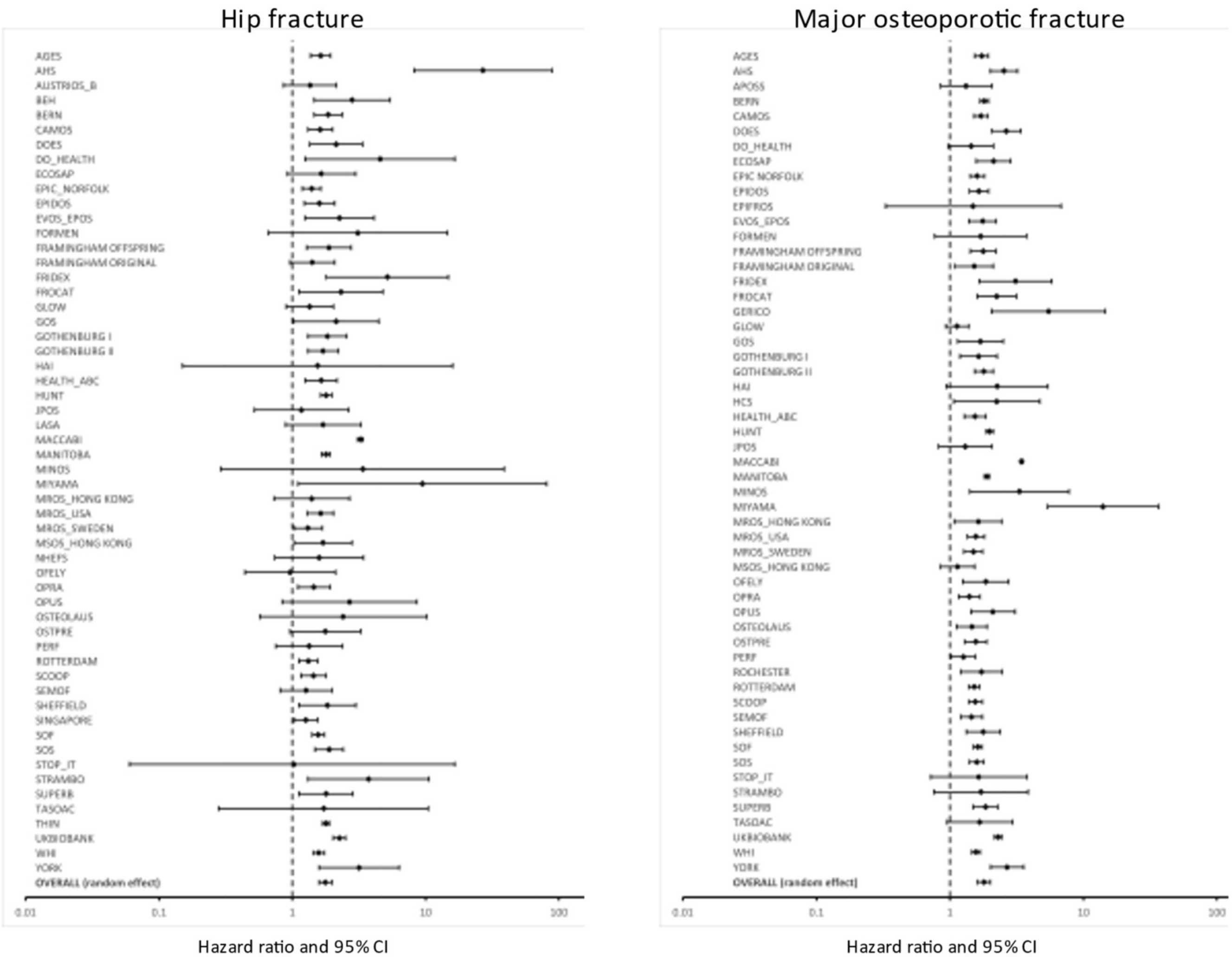

Figure 1.

Forest plot showing effect size on hip fracture risk (left panel) and major osteoporotic fracture (right panel) associated with a prior fracture in men and women combined adjusted for age and time since baseline

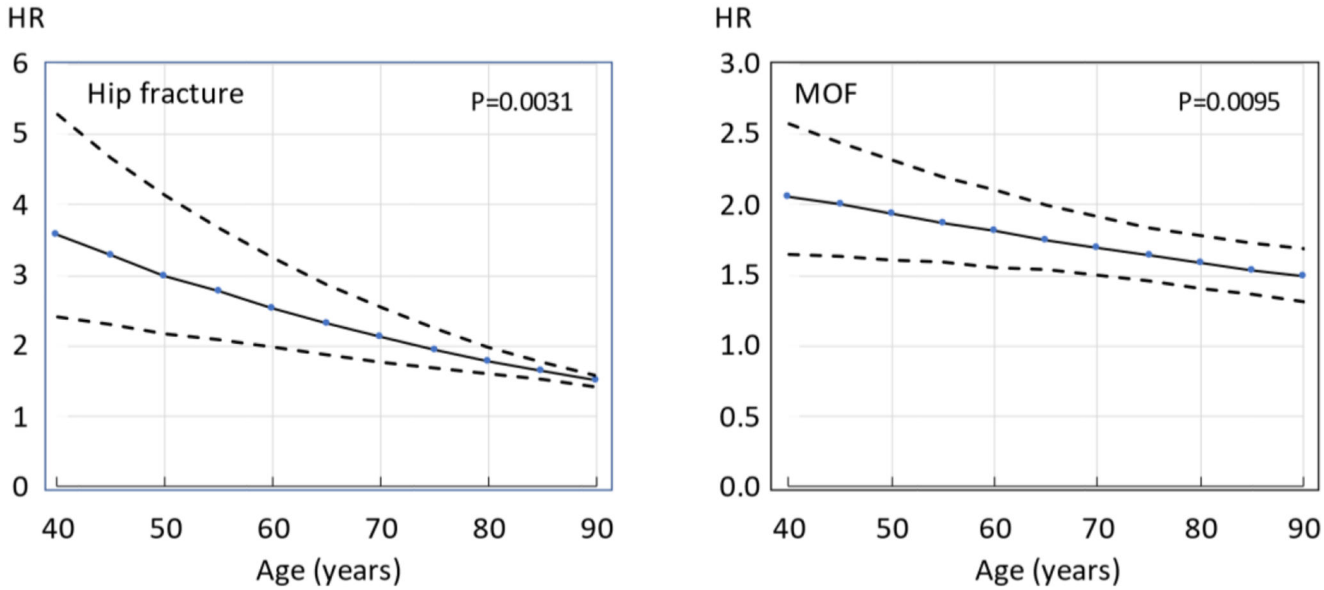

Figure 2.

Hazard ratio (HR) and 95% confidence interval of a major osteoporotic fracture (MOF) and hip fracture by age associated with a history of prior fracture in men and women combined. HRs are adjusted for time since baseline and sex.

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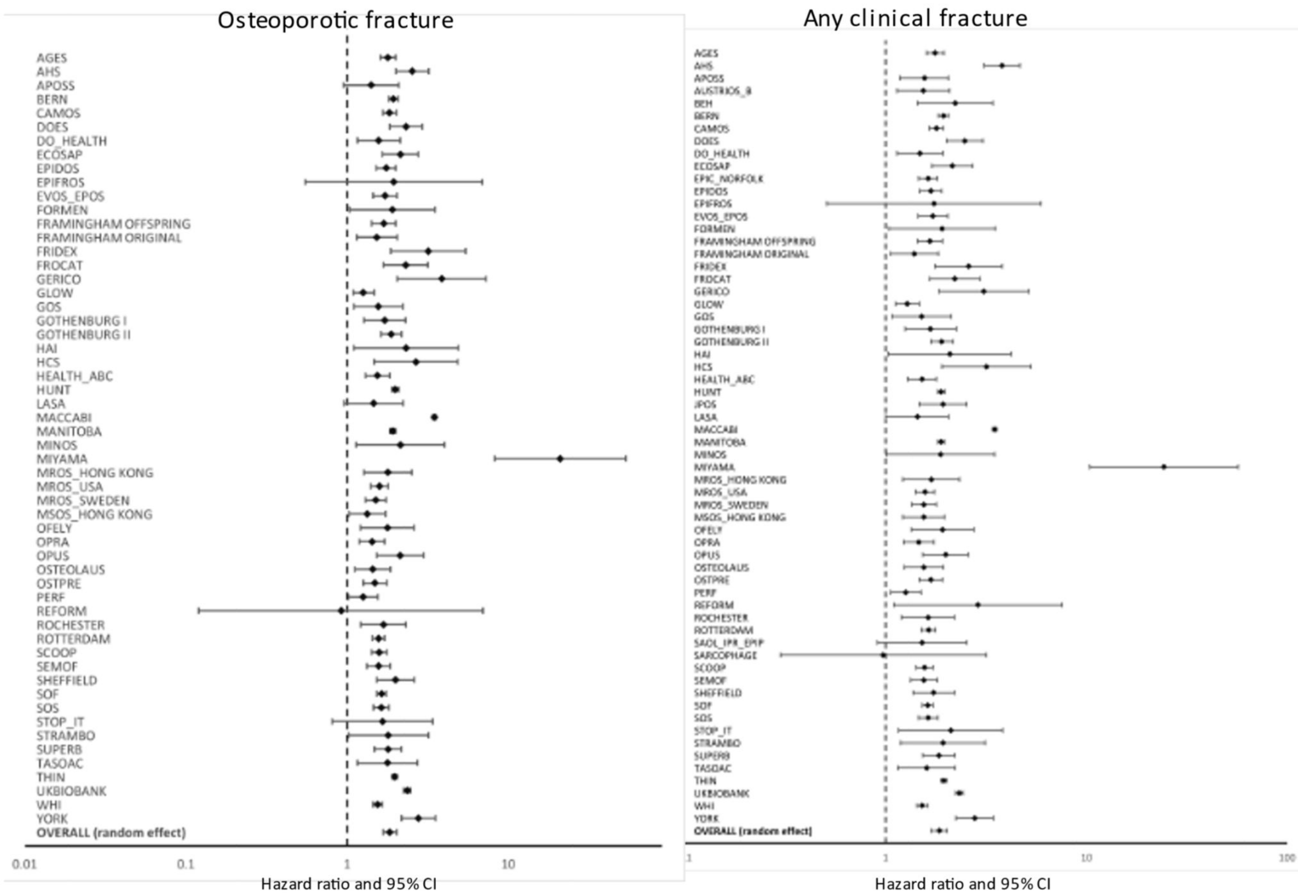

Figure 3.

Forest plot showing effect size on osteoporotic fracture risk (left panel) and any clinical fracture (right panel) associated with a prior fracture in men and women combined adjusted for age and time since baseline

Table 1

Characteristics of the cohorts studied

	Quality grade			Age (years)				Number of fractures				
Cohort		n	Person years	Mean	Range	% female	Prior fracture (%)	Hip	Any	MOF	MOF minus hip	Osteoporotic
AGES	A	5706	45508	77.0	66 -98	57.6	42.2	535	1619	1134	766	1395
AHS	B	2613	10109	65.1	47-95	69.6	25.9	32	368	281	257	281
APOSS	A	3840	33629	48.5	44-56	100	13.1	4	335	142	141	176
AUSTRIOS B	C	2046	2370	83.9	68-103	84.1	46.6	76	174	-	-	-
BEH	B	2414	10085	69.3	60-96	51.9	12.9	42	105	-	-	-
Bern	B	23104	181352	58.9	20-95	85.0	43.9	294	5033	2913	2730	3891
CaMos	A	9422	121627	62.1	25-103	69.4	44.0	340	2435	1188	935	1753
DO_HEALTH	B	2139	5914	75.0	70-95	61.9	22.5	10	264	118	111	190
DOES	A	2133	18884	70.1	47-94	60.7	15.0	110	561	363	294	465
ECOSAP	B	5146	16857	72.3	65-100	100	20.2	52	311	188	136	259
EPIC-Norfolk	A	25600	493500	59.2	39-79	54.7	7.0	1356	3040	2344	1205	-
EPIDOS	B	7595	21192	80.5	70-100	100	45.0	226	1026	568	376	837
EPIFROS	B	284	2826	61.6	40-96	54.6	4.6	3	27	16	13	20
EVOS/EPOS	B	13366	40983	63.8	41-91	52.1	36.3	44	538	286	245	538
FORMEN	A	1885	16253	72.5	65-93	0	7.9	10	90	58	49	90
Framingham offspring	A	3539	58402	61.5	33-90	54.1	33.9	105	758	316	239	533
Framingham original	A	1166	11184	79.9	72-101	65.3	20.0	136	279	187	68	242
FRIDEX	B	815	8077	56.8	40-84	100	20.4	15	112	41	28	56
FROCAT	A	1953	19404	69.2	32-111	55.7	17.1	33	229	160	135	183
GERICO	C	764	2766	67.9	65-72	79.5	46.3	2	71	26	24	51
GLOW	B	54258	216703	68.2	55-108	100	3.1	490	5690	2848	2437	4285
GOS	A	1403	9364	69.5	50-95	100	30.3	31	149	105	80	135
Gothenburg I	A	1736	9818	85.5	70-96	57.0	10.7	304	431	361	100	408
Gothenburg II	A	11371	149825	59.0	21-84	100	16.8	259	1192	739	644	856
HAI	B	2085	3303	70.5	70-72	51.1	14.1	4	42	26	22	36
HCS	A	632	5595	64.9	59-71	50.3	16.3	3	67	35	33	51
Health ABC	A	3062	36309	73.6	68-80	51.5	22.0	235	696	518	349	594
HUNT	A	50209	622020	53.2	20-100	54.6	23.4	1674	10239	4733	3601	7128
JPOS	B	1944	25812	57.5	40-82	100	15.8	29	265	99	-	-
LASA	A	1473	7575	75.7	65-89	51.6	27.9	38	131	-	-	95
Maccabi	A	659266	6297325	56.3	30-91	52.0	4.8	11293	54312	51955	42759	53907
Manitoba	B	92281	833424	63.4	20-104	89.1	21.3	3085	13506	9578	7187	12655
MINOS	B	681	6152	65.2	50-86	0	12.8	3	63	25	22	56

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	Quality grade			Age (years)				Number of fractures				
Cohort		**n**	**Person years**	**Mean**	**Range**	**% female**	**Prior fracture (%)**	**Hip**	**Any**	**MOF**	**MOF minus hip**	**Osteoporotic**
Miyama	A	400	3703	59.1	40- 79	50.0	33.5	7	61	35	30	47
MrOS Hong Kong	B	2000	19744	72.4	65-92	0	13.7	63	231	148	93	201
MrOS Sweden	A	2999	34019	74.9	69-81	0	20.9	339	968	728	482	874
MrOS USA	A	5993	74998	73.7	64-100	0	55.3	330	1394	814	490	1082
MsOS Hong Kong	B	2000	17528	72.6	65-98	100	20.8	69	338	247	189	298
NHEFS	A	12206	121623	49.4	25-74	59.6	6.7	113	-	-	-	-
OFELY	A	867	15136	58.8	40-89	100	10.3	40	245	180	159	207
OPRA	A	1044	12133	75.2	75-76	100	45.8	195	524	453	-	473
OPUS	B	1983	12167	62.0	20-80	100	42.0	14	236	113	102	148
OsteoLaus	B	1475	6726	64.5	50-82	100	36.4	8	307	226	221	245
OSTPRE	B	11200	109465	57.3	52-62	100	9.0	80	1851	918	848	1259
PERF	B	5760	37802	64.2	44-81	100	17.3	62	828	544	489	550
REFORM	C	1003	1483	77.9	65- 99	60.5	6.5	4	30	12	8	17
Rochester	A	1001	7686	56.8	21-94	65.2	18.1	37	326	243	229	283
Rotterdam	A	14619	158085	65.8	45-106	58.8	22.9	830	3317	2322	1742	2892
SAOL_IPR_EPIPorto	B	929	11284	55.9	40- 89	77.4	12.7	12	105	9	-	-
SarcoPhAge	C	228	440	75.9	68-93	57.0	25.4	1	13	5	4	8
SCHS	A	52042	462436	61.6	48- 84	57.4	8.1	1091	-	-	-	-
SCOOP	A	12368	58826	75.6	70-86	100	23.1	378	1927	1284	975	1625
SEMOF	B	7130	20624	75.2	70 -91	100	51.7	80	683	464	384	596
Sheffield	B	2148	7354	80.0	74-101	100	45.4	66	281	186	132	227
SOF	B	9619	135474	71.6	65-89	100	37.1	1404	4337	2794	1833	3455
SOS	B	16626	62119	74.2	61-92	100	30.0	260	1383	993	702	1325
STOP/IT	B	424	1840	71.1	65-87	55.0	49.1	2	50	24	22	32
STRAMBO	A	823	7582	72.1	51-88	0	11.7	17	117	42	26	86
SUPERB	B	3019	10736	77.8	75-81	100	36.8	70	463	341	-	421
TASOAC	B	1098	10955	63.0	51-81	48.9	44.2	5	146	49	46	88
THIN	A	366104	2125764	63.8	50-116	100	9.1	6942	31633	-	-	23622
UK Biobank	B	502536	5766212	56.5	37-73	54.4	3.7	3943	25190	12099	8332	20075
WHI	B	64399	868380	65.8	55-79	100	17.4	1981	5259	3712	1901	4213
York	B	4532	9044	77.1	48-99	100	44.7	42	393	223	189	310
Total		2104506	19535515		20-116			39358	186794	110559	84614	155825?
Mean				61.5		68.3	9.7					

MOF, major osteoporotic fracture; AGES, Age, Gene/Environment Susceptibility-Reykjavik Study; AHS, Adult Health Study; APOSS, Aberdeen Prospective Osteoporosis Screening Study; BEH, Bushehr Elderly Health; CaMos, Canadian Multicentre Osteoporosis Study; DOES, Dubbo Osteoporosis Epidemiology Study; DO-HEALTH, VitaminD3-Omega3-Home Exercise-Healthy Aging and Longevity Trial; ECOSAP, Ecografía Osea en Atención Primaria; EPIC-Norfolk, European Prospective Investigation of Cancer-Norfolk; EPIDOS, Epidémiologie de l'Ostéoporose; EPIFROS, EPIdemiology and Fracture Risk factors for Osteoporosis in Spain; EVOS/EPOS, European Vertebral Osteoporosis Study/European

Prospective Osteoporosis Study; FORMEN, Fujiwara-kyo Osteoporosis Risk in Men; FRIDEX, Fracture RIsk factors and bone DEnsitometry type central dual X-ray; FROCAT, Fracture Risk factors for Osteoporosis in CATalonia; GERICO, Geneva Retirees Cohort; GLOW, Global Longitudinal Study of Osteoporosis in Women; GOS, Geelong Osteoporosis Study; HAI, Healthy Ageing Initiative; HCS, Hertfordshire Cohort Study; Health ABC, Health, Aging and Body Composition; HUNT, The Trøndelag Health Study; JPOS, Japanese Population-based Osteoporosis Study; LASA, Longitudinal Aging Study Amsterdam; MINOS, Montceau les MINes OSteoporosis; MrOS, Osteoporotic Fractures in Men; MsOS, Osteoporotic Fractures in Women; NHEFS, National Health and Nutrition Examination Survey (NHANES) I Epidemiologic Follow-up Study; OFELY, Os des Femmes de Lyon; OPRA, Osteoporosis Prospective Risk Assessment; OPUS, Osteoporosis and Ultrasound Study; OSTPRE, Kuopio OSTeoporosis risk factor and PREvention study; PERF, Prospective Epidemiologic Risk Factor; REFORM, REducing Falls with ORthoses and a Multifaceted podiatry intervention; SAOL-IPR-EPIPorto, Santo António dos Olivais, Instituto Português de Reumatologia and EPIPorto; SarcoPhAge, Sarcopenia and Physical Impairment with advancing Age; SCHS, Singapore Chinese Health Study; SCOOP, screening for prevention of fractures in older women; SEMOF, Swiss Evaluation of the Methods of Measurement of Osteoporotic Fracture risk; SOF, Study of Osteoporotic Fractures; SOS, SALT Osteoporosis Study; STRAMBO, Structure of the Aging Men's Bone; SUPERB, Sahlgrenska University hospital Prospective Evaluation of Risk of Bone fractures; TASOAC, Tasmanian Older Adult Cohort; THIN, The Health Improvement Network; WHI, Women's Health Initiative.

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Table 2

Details of the construct of the questionnaire on fracture type and history in the cohorts studied.

Element	Construct
Time horizon	Ever in life, adult life, from age 18, 20, 35, 40, 45, 50, past 12 months, 5 years or10 years
Site of fracture	Any fracture, osteoporotic fracture, MOF
Energy	All trauma included, moderate trauma, low trauma
Validity	Self-reported, verified, based on GP medical record, administrative healthcare data, has a doctor/nurse/physician assistant told you?
Vertebral deformity	Vertebral fractures assessed by semiquantitative criteria included, not included

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Table 3

Prevalence of a prior fracture history in men and women by age. The Manitoba and Maccabi data are not included since primary data were not available.

Age (years)	Fracture history (%)		
	Men	Women	Combined
40-49	4.2	3.5	3.8
50-59	5.9	7.0	6.6
60-69	6.4	11.0	9.6
70-79	14.1	20.6	19.3
80-89	17.8	23.7	22.7
90+	21.4	21.8	21.8

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Table 4

Hazard ratio (HR) and 95% confidence interval (CI) of fracture at the sites indicated associated with a history of prior fracture in men and women and both sexes combined. HRs are adjusted for age and time since baseline.

	Outcome fracture	Number of cohorts	I^2(%)	HR	95% CI
Women					
	Any	56	94	1.84	1.72-1.97
	Hip	51	81	1.71	1.57-1.86
	MOF	50	94	1.77	1.63-1.93
	MOF without hip fracture	45	91	1.80	1.65-1.95
	Osteoporotic	51	94	1.82	1.70-1.96
Men					
	Any	34	97	1.92	1.56-2.34
	Hip	29	91	1.99	1.53-2.59
	MOF	31	96	1.90	1.51-2.39
	MOF without hip fracture	30	94	1.79	1.43-2.25
	Osteoporotic	31	97	1.92	1.55-2.38
Men and women					
	Any	62	98	1.85	1.69-2.02
	Hip	56	92	1.77	1.59-1.98
	MOF	55	97	1.80	1.61-2.01
	MOF without hip fracture	51	96	1.80	1.62-2.01
	Osteoporotic	56	98	1.84	1.68-2.03

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Table 5

Hazard ratio (HR) and 95% confidence interval (CI) of fracture at the sites indicated associated with a history of prior fracture in men and women combined. HRs are adjusted for age and time since baseline and additionally adjusted for BMD where indicated. The last column indicates the proportion of risk explained by BMD.

		Unadjusted		Adjusted for BMD			
Outcome fracture	**Number of cohorts**	**HR**	**95% CI**	**HR**	**(95% CI)**	**Gradient of risk (HR/SD) for BMD**	**Proportion of risk (%) from BMD**
Any	52	1.79	1.67-1.92	1.65	1.53-1.78	1.45	14
Hip	45	1.70	1.58-1.84	1.43	1.30-1.56	2.07	33
Osteoporotic	48	1.78	1.65-1.92	1.61	1.48-1.75	1.55	17

Table 6

Hazard ratio (HR) and 95% confidence interval (CI) of fracture by age at baseline at the sites indicated associated with a history of prior fracture in men and women combined. HRs are adjusted for time since baseline and sex. n refers to the number of cohorts available. P values refer to the significance of the interaction term with age

	Site of outcome fracture										
	Any (n=62)			**Hip (n=56)**			**MOF (n=55)**			**Osteoporotic (n=56)**	
Age (years)	**HR**	**95% CI**		**HR**	**95% CI**		**HR**	**95% CI**		**HR**	**95% CI**
40	2.47	1.96-3.13		3.57	2.42-5.27		2.32	1.77-3.03		2.40	1.87-3.08
45	2.38	1.93-2.94		3.27	2.30-4.67		2.22	1.74-2.84		2.31	1.84-2.89
50	2.29	1.90-2.76		3.00	2.18-4.13		2.13	1.71-2.66		2.22	1.82-2.72
55	2.20	1.87-2.59		2.76	2.08-3.66		2.05	1.68-2.49		2.14	1.79-2.55
60	2.11	1.84-2.43		2.53	1.98-3.24		1.97	1.66-2.33		2.06	1.76-2.40
65	2.03	1.81-2.28		2.32	1.88-2.86		1.89	1.63-2.19		1.98	1.73-2.25
70	1.96	1.78-2.15		2.13	1.78-2.54		1.81	1.60-2.05		1.90	1.71-2.12
75	1.88	1.75-2.02		1.95	1.70-2.25		1.74	1.57-1.92		1.83	1.68-1.99
80	1.81	1.72-1.90		1.79	1.61-1.99		1.67	1.55-1.80		1.76	1.65-1.88
85	1.74	1.68-1.80		1.64	1.52-1.77		1.60	1.52-1.69		1.69	1.62-1.77
90	1.67	1.63-1.72		1.51	1.43-1.59		1.54	1.49-1.59		1.63	1.58-1.68
		P=0.0014			**P<0.001**			**P=0.0011**			**P=0.0013**

Table 7

Hazard ratio (HR) and 95% confidence interval (CI) of fracture by time since baseline at the sites indicated associated with a history of prior fracture in men and women combined. HRs are adjusted for age and sex. N refers to the number of cohorts available. P values refer to the significance of the interaction term with time since baseline.

	Site of outcome fracture										
	Any (n=61)			**Hip (n=54)**			**MOF (n=54)**			**Osteoporotic (n=55)**	
Time (years)	**HR**	**95% CI**		**HR**	**95% CI**		**HR**	**95% CI**		**HR**	**95% CI**
0	2.12	1.78-2.52		2.12	1.73-2.69		2.06	1.65-2.57		2.13	1.76-2.58
1	2.06	1.76-2.41		2.04	1.70-2.55		2.00	1.63-2.44		2.07	1.74-2.45
2	2.00	1.73-2.30		1.97	1.68-2.42		1.93	1.61-2.32		2.00	1.71-2.33
3	1.94	1.71-2.20		1.91	1.65-2.30		1.87	1.59-2.20		1.94	1.69-2.23
4	1.88	1.68-2.11		1.84	1.63-2.19		1.81	1.56-2.10		1.88	1.66-2.13
5	1.83	1.65-2.02		1.78	1.59-2.08		1.75	1.54-2.00		1.82	1.62-2.03
6	1.77	1.61-1.95		1.72	1.56-1.99		1.70	1.50-1.92		1.76	1.58-1.95
7	1.72	1.58-1.88		1.66	1.52-1.91		1.64	1.46-1.84		1.70	1.54-1.89
8	1.67	1.53-1.83		1.60	1.48-1.84		1.59	1.41-1.78		1.65	1.49-1.83
9	1.62	1.48-1.78		1.55	1.42-1.78		1.54	1.37-1.73		1.60	1.43-1.78
10	1.58	1.43-1.74		1.49	1.37-1.73		1.49	1.31-1.69		1.55	1.38-1.74
		P=0.0035			**P=0.0031**			**P=0.0095**			**P=0.0042**

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