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ORIGINAL ARTICLE

A meta-analysis of previous falls and subsequent fracture risk in cohort studies

Liesbeth Vandenput · Helena Johansson · Eugene V. McCloskey · Enwu Liu · Marian Schini · Kristina E. Åkesson, et al. ***[full author details at the end of the article]***

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Abstract

Summary The relationship between self-reported falls and fracture risk was estimated in an international meta-analysis of individual-level data from 46 prospective cohorts. Previous falls were associated with an increased fracture risk in women and men and should be considered as an additional risk factor in the FRAX® algorithm.

Introduction Previous falls are a well-documented risk factor for subsequent fracture but have not yet been incorporated into the FRAX algorithm. The aim of this study was to evaluate, in an international meta-analysis, the association between previous falls and subsequent fracture risk and its relation to sex, age, duration of follow-up, and bone mineral density (BMD).

Methods The resource comprised 906,359 women and men (66.9% female) from 46 prospective cohorts. Previous falls were uniformly defined as any fall occurring during the previous year in 43 cohorts; the remaining three cohorts had a different question construct. The association between previous falls and fracture risk (any clinical fracture, osteoporotic fracture, major osteoporotic fracture, and hip fracture) was examined using an extension of the Poisson regression model in each cohort and each sex, followed by random-effects meta-analyses of the weighted beta coefficients.

Results Falls in the past year were reported in 21.4% of individuals. During a follow-up of 9,102,207 person-years, 87,352 fractures occurred of which 19,509 were hip fractures. A previous fall was associated with a significantly increased risk of any clinical fracture both in women (hazard ratio (HR) 1.42, 95% confidence interval (CI) 1.33–1.51) and men (HR 1.53, 95% CI 1.41–1.67). The HRs were of similar magnitude for osteoporotic, major osteoporotic fracture, and hip fracture. Sex significantly modified the association between previous fall and fracture risk, with predictive values being higher in men than in women (e.g., for major osteoporotic fracture, HR 1.53 (95% CI 1.27–1.84) in men vs. HR 1.32 (95% CI 1.20–1.45) in women, P for interaction = 0.013). The HRs associated with previous falls decreased with age in women and with duration of follow-up in men and women for most fracture outcomes. There was no evidence of an interaction between falls and BMD for fracture risk. Subsequent risk for a major osteoporotic fracture increased with each additional previous fall in women and men.

Conclusions A previous self-reported fall confers an increased risk of fracture that is largely independent of BMD. Previous falls should be considered as an additional risk factor in future iterations of FRAX to improve fracture risk prediction.

Keywords fracture risk · hip fracture · major osteoporotic fracture · meta-analysis · previous falls · risk factors

Introduction

Falls are common in the aging population, with more than one-third of community-dwelling adults above the age of 75 years experiencing a fall every year [1]. Falls are a leading cause of injury, disability, and death with around 10–15% of falls in older adults resulting in a fracture [2, 3]. Indeed, many epidemiological studies have shown that falls history is associated with an increase in fracture risk [4–19]. In addition, a fall within the past 4 months appears to confer a similarly high fracture risk as a recent fracture [20].

The FRAX® tool, released in 2008 by the then World Health Organization (WHO) Collaborating Centre at

Sheffield, UK, is a fracture risk assessment tool for estimating individualized 10-year probability of hip and major osteoporotic fracture (MOF: hip, clinical spine, distal forearm or proximal humerus) [21]. The algorithm integrates seven dichotomous clinical risk factors (prior fragility fracture, parental hip fracture, smoking, systemic glucocorticoid use, excess alcohol intake, rheumatoid arthritis, and other secondary causes of osteoporosis) with age, sex, and body mass index and optionally, a femoral neck bone mineral density (BMD) measurement.

Despite being a well-known risk factor for fracture, previous falls were not included as a risk factor in the original FRAX algorithm [22, 23], whereas fall history is an input variable in other risk engines such as the Garvan fracture risk calculator [24] and the QFracture algorithm [25]. At the time of the launch of the FRAX calculator, there was a lack of reliable data with a uniform question construct [22, 23] and it remained unclear whether the fracture risk attributable to previous falls was amenable to pharmacological intervention [26]. Since 2008, assessment of previous falls has been shown to improve fracture prediction in addition to FRAX clinical risk factors and BMD in women and men [27, 28]. Moreover, pharmacological interventions, including menopausal hormone treatment [29, 30], clodronate [31], zoledronate [32] and omega-3 fatty acids [33] as well as non-pharmacological interventions [34–36] have been shown to have a beneficial effect in lowering the increased fracture risk associated with previous falls. Evidence that fall prevention interventions reduce subsequent fracture risk remains, however, limited [37–43]. With the update of the FRAX tool currently under development and the associated large resource assembled [44], data on previous falls are available both in a larger number of cohorts and with a uniform question construct, making it possible to consider falls history a new candidate input variable. The aim of the present study was to examine the risk of fracture associated with previous falls in an international setting and to determine its dependence on age, sex, duration of follow-up, 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 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 analyzed baseline and follow-up data from 906,359 women and men from 46 prospective cohorts, the majority of which were population-based. Of these 46 cohorts, 17 included only female participants, 6 included only male participants, whereas the remaining 23 included both. Details of each of the cohorts have been published previously [44] and are summarised in Table 1.

Identifying falls

A history of falls was obtained through questionnaires and was available in 46 cohorts that were assembled to construct the update of the FRAX algorithm. The question to ascertain self-reported falls was uniformly defined in 43 out of the 46 cohorts as "Have you fallen during the past year/12 months." The remaining three cohorts had a different question construct for previous falls (Bern, "2 or more falls in the last 12 months"; CaMos, "falls in the last month"; Sheffield, "2 or more falls within the previous months") (Table 1). Information on the number of previous falls was available in 30 cohorts. The number of previous falls was examined as a categorical variable (0, 1, 2, $\geq$ 3 falls in the past year).

Identifying fractures

Ascertainment of incident clinical fractures was undertaken by self-report and/or verified from hospital or central databases. Clinical fracture outcomes comprised any clinical fracture, osteoporotic fracture (defined according to Kanis et al. [45] as clinical vertebral, ribs, pelvis, humerus, clavicle, scapula, sternum, hip, other femoral fractures, tibia, fibula, distal forearm/wrist), MOF, and hip fracture.

Other variables of interest

Covariates of interest included current age since start of follow-up, current time since start of follow-up, and BMD at the femoral neck. Femoral neck BMD measurements were only available in a subset of individuals. Standardised BMD values were utilized to accommodate different DXA equipment. Corresponding femoral neck T-scores were calculated as previously described [46, 47].

Table 1 Description of cohort characteristics, previous falls, and incident fracture outcomes

Cohort	*n*	Person-years	Age (years)			Women (%)	Previous fall (%)	Number of falls	FN BMD (*n*)	Number of incident fractures			
			Mean	Min	Max					Any	Ost	MOF	Hip
AGES	5637	45,188	76.9	66.0	96.0	57.5	18.6	1: 694 2 or 3: 210 4 or 5: 38 6 or more: 35	4772	1600	1378	1120	525
BEH	2299	10,196	69.3	60.0	96.0	51.4	10.7	-	2291	98	76	46	40
Bern[a]	3690	13,840	59.9	20.1	94.3	77.6	12.2	2 or more: 452	3642	475	339	237	23
CaMos[b]	9423	121,634	62.1	25.0	103.0	69.4	6.7	-	8290	2435	1753	1188	340
DOES	2086	19,341	70.1	47.0	94.0	60.7	30.0	1: 447 2: 121 3: 46 4: 38	2057	480	404	299	95
DO-HEALTH	2156	5956	74.9	70.0	95.0	61.7	42.0	1: 658 2: 148 3: 48 4: 21 5: 6 6 or more: 8	1451	267	192	119	10
ECOSAP	5146	16,857	72.3	65.0	100.0	100.0	26.7	-	-	311	259	188	52
EPIFROS	284	2826	61.6	40.0	96.0	54.6	18.3	1: 34 2: 9 3: 3 4: 2 5: 1 12: 1	12	27	20	16	3
FORMEN	1886	16,265	72.5	65.0	93.0	0.0	16.3	-	1882	90	90	58	10
Framingham_offspring	3491	47,178	61.4	33.0	88.0	54.1	20.0	1: 488 2: 121 3: 36 4: 11 5: 8 6 or more: 15	2908	677	524	271	88
Framingham_original	1094	9390	79.5	72.0	101.0	64.7	29.9	1: 184 2: 80 3: 29 4: 7 5: 3 6 or more: 13	884	261	234	166	113
FRIDEX	815	8077	56.8	40.0	84.0	100.0	24.4	1: 128 2: 31 3: 25 4: 5 5: 4 6 or more: 6	815	112	56	41	15

Table 1 (continued)

Cohort	*n*	Person-years	Age (years)			Women (%)	Previous fall (%)	Number of falls	FN BMD (*n*)	Number of incident fractures			
			Mean	Min	Max					Any	Ost	MOF	Hip
FROCAT	1930	19174	69.3	32.0	111.0	55.5	25.9	1: 257 2: 104 3: 59 4: 22 5: 11 6 or more: 12	233	228	182	159	33
GERICO	758	2742	67.9	64.6	71.8	79.4	47.4	1: 218 2: 67 3: 34 4: 13 5: 1 6 or more: 26	744	71	51	26	2
GLOW	53673	214575	68.2	55.0	108.0	100.0	37.6	1: 12200 2 or more: 7968	-	5628	4233	2804	480
HAI	3515	9291	70.5	69.2	72.0	50.4	11.1	-	3436	125	113	77	10
HCS	251	2009	66.0	61.3	70.9	96.8	19.9	1: 39 2: 9 3: 1 4: 1	250	33	24	17	0
Health ABC	3064	36,348	73.6	68.0	80.0	51.5	21.3	-	3032	699	595	520	235
HUNT	6803	69,261	77.1	70.0	96.9	55.0	20.3	-	1859	2290	1998	1445	843
LASA	1472	7568	75.7	64.8	88.7	51.5	32.3	1: 249 2: 116 3: 37 4: 24 5: 17 6 or more: 29	519	132	96	-	39
Maccabi	83,577	757,792	65.4	37	91	64.8	5.0	-	7678	19,335	19,248	18,408	5780
Manitoba	37,246	105,145	66.6	20.0	104.3	89.0	20.9	1: 4654 2: 1641 3: 670 4: 270 5: 307 6 or more: 259	37,246	2064	1936	1437	342
MINOS	681	6152	65.2	50.0	86.0	0.0	24.1	1: 100 2 or more: 64	672	63	56	25	3
MrOS Hong Kong	2000	19,744	72.4	65.0	92.0	0.0	15.4	1: 234 2 or 3: 63 4 or 5: 7 6 or more: 3	2000	231	201	148	63
MrOS Sweden	3001	34,078	74.9	69.0	81.0	0.0	16.5	-	2809	964	869	724	338

Table 1 (continued)

Cohort	*n*	Person-years	Age (years)			Women (%)	Previous fall (%)	Number of falls	FN BMD (*n*)	Number of incident fractures			
			Mean	Min	Max					Any	Ost	MOF	Hip
MrOS USA	5994	75,015	73.7	64.0	100.0	0.0	21.2	1: 722 2 or 3: 448 4 or 5: 67 6 or more: 31	5993	1394	1082	814	330
MsOS Hong Kong	2000	17,528	72.6	65.0	98.0	100.0	24.1	1: 320 2 or 3: 137 4 or 5: 22 6 or more: 3	2000	338	298	247	69
OFELY	867	15,136	58.8	40.0	89.0	100.0	30.8	1: 157 2: 68 3: 22 4: 8 5: 5 6 or more: 7	861	245	207	180	40
OPRA	914	10,664	75.2	75.0	76.0	100.0	28.4	1: 126 2: 65 3: 40 4: 11 5: 10 7 or more: 8	825	457	413	398	173
OPUS	1978	12,135	62.0	20.2	80.0	100.0	29.0	1: 304 2: 120 3: 73	1970	234	146	112	14
OsteoLaus	1475	6726	64.5	50.2	81.5	100.0	25.4	-	1457	307	245	226	8
OSTPRE	9998	97,799	57.3	52.4	62.7	100.0	36.0	1: 1675 2: 1014 3: 429 4: 151 5: 147 6 or more: 187	2460	1635	1123	824	68
REFORM	1003	1482	77.9	65.0	99.0	60.5	65.2	1: 314 2: 186 3: 83 4: 33 5: 10 6 or more: 24	-	30	17	12	4
Rotterdam	10,382	133,691	68.7	55.0	106.2	59.0	18.7	-	7786	2885	2580	2103	790
SAOL-IPR-EPIPorto	916	11,139	55.9	40.0	89.0	77.6	22.8	1: 111 2: 42 3: 33 4: 4 5: 5 6 or more: 12	914	104	-	41	12

Table 1 (continued)

Cohort	*n*	Person-years	Age (years)			Women (%)	Previous fall (%)	Number of falls	FN BMD (*n*)	Number of incident fractures			
			Mean	Min	Max					Any	Ost	MOF	Hip
SarcoPhAge	228	440	75.9	68.2	93.4	57.0	37.3	-	217	13	8	5	1
SCOOP	12,368	58,845	75.6	70.0	86.0	100.0	27.8	-	2790	1932	1630	1288	375
SEMOF	7131	20,625	75.2	70.0	91.3	100.0	31.4	-	919	683	596	464	80
Sheffield[c]	2175	7441	80.0	74.3	100.9	100.0	6.0	2 or more: 131	2154	289	234	191	67
SOF	9654	135,907	71.6	65.0	89.0	100.0	30.0	1: 1875 2 or 3: 867 4 or 5: 127 6 or more: 32	7760	4346	3462	2801	1411
SOS	16,441	61,467	74.2	60.8	92.5	100.0	27.5	1: 2336 2: 1243 3: 537 4 or more: 401	4071	1365	1306	978	253
STRAMBO	821	7564	72.2	51.0	88.4	0.0	20.7	-	803	117	86	42	17
SUPERB	3025	10,752	77.8	74.7	81.0	100.0	29.6	-	3012	463	421	341	70
UK Biobank	499,867	5,735,643	56.5	38.0	73.0	54.4	19.8	1: 65,958 2 or more: 33,141	19,530	25,049	19,977	12,044	3925
WHI	78,612	1,072,537	64.4	49.0	79.0	100.0	32.3	1: 15,680 2: 6508 3 or more: 3232	5576	6377	5020	4392	2278
York	4532	9044	77.1	47.6	98.9	100.0	30.1	1: 699 2: 356	-	393	310	223	42
Overall (total/mean)	906,359	9,102,207	61.6	20.0	111.0	66.9	21.4		160,580	87,352	74,088	57,265	19,509

FN BMD femoral neck bone mineral density, *OST* osteoporotic fracture, *MOF* major osteoporotic fracture, *AGES* Age, Gene/Environment Susceptibility-Reykjavik 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, *EPIFROS* EPIdemiology and Fracture Risk factors for Osteoporosis in Spain, *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, *HAI* Healthy Ageing Initiative, *HCS* Hertfordshire Cohort Study, *Health ABC* Health, Aging and Body Composition, *HUNT* Trøndelag Health Study, *LASA* Longitudinal Aging Study Amsterdam, *MINOS* Montceau les MINes OSteoporosis, *MrOS* Osteoporotic Fractures in Men, *MsOS* Osteoporotic Fractures in Women, *OFELY* Os des Femmes de Lyon, *OPRA* Osteoporosis Prospective Risk Assessment, *OPUS* Osteoporosis and Ultrasound Study, *OSTPRE* Kuopio OSTeoporosis risk factor and PREvention study, *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, *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, *WHI* Women's Health Initiative

[a]2 or more falls in the last 12 months

[b]Falls in the last month

[c]2 or more falls within the previous months; all other cohorts, "fallen during the last year/12 months"

Statistical methods

The association between previous falls and the risk of fracture was estimated using an extension of the Poisson regression model [48, 49] applied separately to each cohort, irrespective of risk factor definition, and separately by sex for those cohorts contributing both women and men. 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 co-variances forwarded to the analysis team. The associations between previous falls and risk of fracture were described as hazard ratio (HR) for fracture with 95% confidence intervals (CIs) for any fall versus no fall. The number of falls in the previous year was also compared to no falls. The observation period of each participant was divided in intervals of 1 month. The first incident fracture per participant was counted for each relevant outcome. Covariates examined were current age at the start of follow-up, current time since start of follow-up, and BMD T-score at the femoral neck. The estimated value of the beta-coefficients and their variance was determined from the Poisson model for each age from 40 years. The results of each cohort and both sexes were weighted according to the variance and merged to determine the weighted means and standard deviations. Interaction terms were used to determine whether the strength of the association of previous falls and fracture risk changed with age, duration of follow-up, sex, or femoral neck T-score. Interactions with age, duration of follow-up, and femoral neck BMD were also explored using piecewise linear regression to check the adequacy of the Poisson model.

Heterogeneity between cohorts was tested by the I^2 statistic [50]. Random-effects models were used in the meta-analysis as moderate ($I^2 = 50$) to high ($I^2 = 75$) heterogeneity was noted between cohorts. Individuals with missing data were excluded. No data were imputed.

Sensitivity analyses

As indicated above, the effect of sex on the risk of fracture was computed in those cohorts that contributed both women and men. Similarly, differences in fracture risk with and without BMD were additionally explored in those cohorts that contributed probabilities both with and without BMD. Results were also computed for those cohorts with a uniformly defined question construct for previous falls (i.e., excluding the Bern, CaMos, and Sheffield cohorts). The evaluation of the effects of race and ethnicity was restricted to those cohorts recording more than one race or ethnic group (Asian, Black, Hispanic, and Caucasian), comprising CaMos, Health ABC, LASA, Manitoba, MrOS USA, SOF, UK Biobank, and WHI. Finally, fracture risk associated with a previous fall was explored according to study quality. 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, a score of 2 or 3 categorized as intermediate quality, and a score of 4 designated as high quality [44].

Results

The analysis population comprised 606,715 women and 299,644 men, aged 20–111 years, who were followed for 5.9 million person-years and 3.2 million person-years, respectively (Table and Appendix Table 8 and 9). During an average follow-up of 10.0 years, 67,308 women and 20,044 men sustained at least one fracture; 58,375 and 15,713 were characterized as a MOF in women and men, respectively, and 14,829 and 4680 were hip fractures. BMD measurements were available in 160,580 (17.7%) individuals. A previous fall was reported in 21.4% of individuals (148,382 women and 45,345 men). Falls were reported more frequently in women than in men (24.5% vs. 15.1%, respectively). The risk factor was uniformly defined in 43 out of 46 cohorts (Table 1). The prevalence of a previous fall among the

Table 2 Association of previous falls with subsequent fracture risk at the sites indicated in women and men

Outcome fracture	Number of cohorts	I^2 (%)	HR (95% CI)
Women			
Any	40	85	1.42 (1.33–1.51)
Hip	35	69	1.36 (1.23–1.50)
MOF	39	78	1.37 (1.28–1.46)
Ost	39	84	1.41 (1.32–1.51)
Men			
Any	27	51	1.53 (1.41–1.67)
Hip	20	39	1.59 (1.38–1.84)
MOF	25	59	1.50 (1.32–1.70)
Ost	25	54	1.59 (1.44–1.76)

Values are hazard ratios (HR) and 95% confidence intervals (CI), adjusted for age and duration of follow-up

BMD bone mineral density, *MOF* major osteoporotic fracture, *Ost* osteoporotic fracture, I^2 heterogeneity statistic

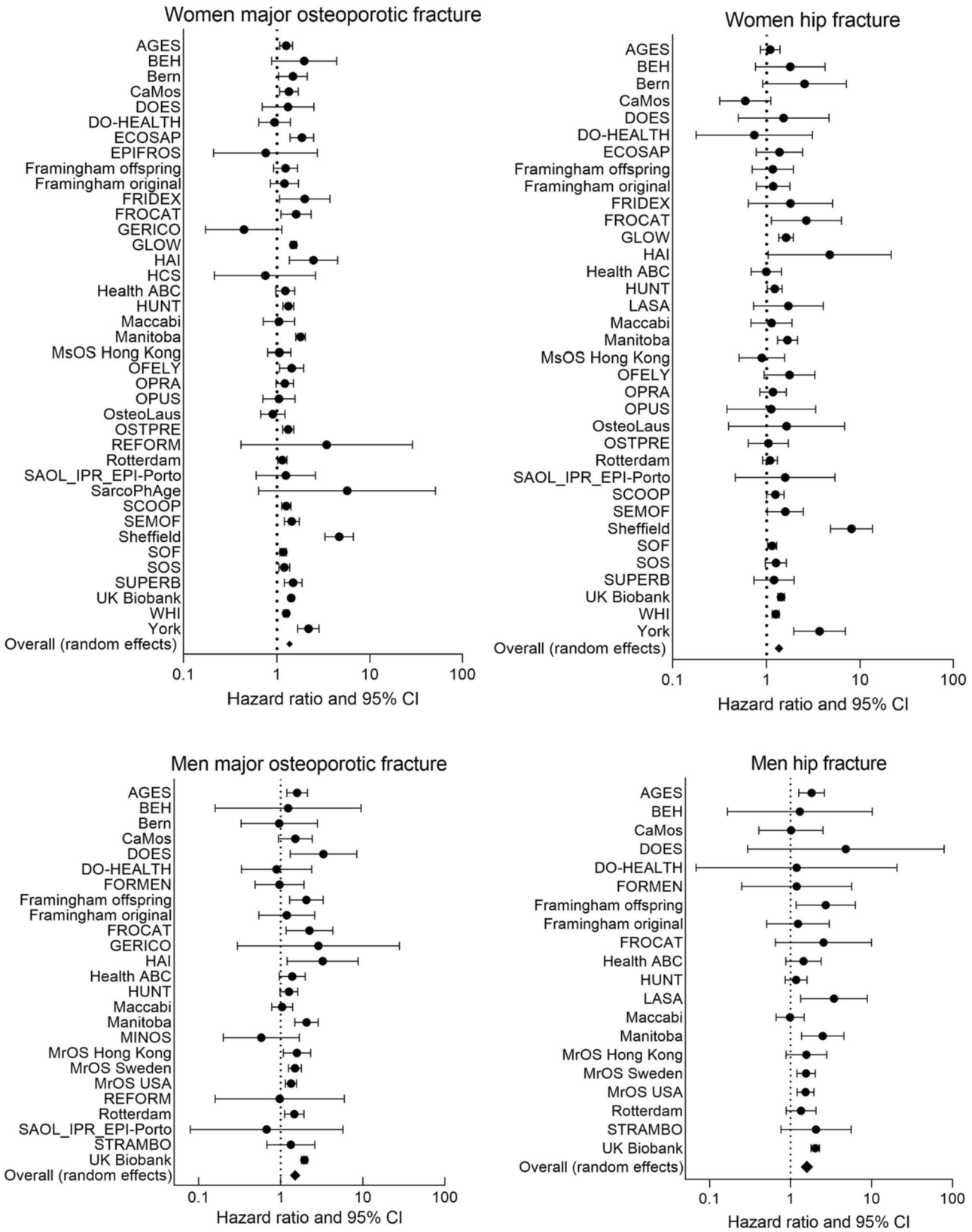

Fig. 1 Forest plots of the association of previous falls with subsequent risk of a major osteoporotic fractures or a hip fracture in women (upper panels) and men (lower panels). Effect estimates (hazard ratios) are shown for fracture (circles), adjusted for age and duration of follow-up. The horizontal lines represent 95% confidence intervals

cohorts increased (almost linearly) with age, being 16.3% at 20–29 years, to 22.2% at 50–59 years, and up to 45.8% at 90–99 years.

Previous falls and fracture

A previous fall in the past year was associated with a significantly increased risk of any subsequent fracture in both women (HR 1.42, 95% CI 1.33–1.51) and men (HR 1.53, 95% CI 1.41–1.67) (Table 2). The HRs were of similar magnitude for the specific fracture outcomes, ranging from 1.36 to 1.42 and 1.50 to 1.59 in women and men, respectively. Forest plots showing the effect size associated with a previous fall on the risk of a MOF and a hip fracture in women and men are shown in Fig. 1.

Previous falls and sex

Taking all cohorts into account, the HRs for the association between previous falls in the past year and fracture risk were consistently higher for men compared with women for all fracture outcomes (Table 2). When estimating the models using only those cohorts that contributed both women and men, a significant interaction between previous falls and sex was observed, with the predictive value of previous falls for fracture risk higher in men than in women by approximately 10–30% (Table 3). For example, in the case of the outcome MOF, the HR for previous falls was 1.32 (95% CI 1.20–1.45) for women and 1.53 (95% CI 1.27–1.84) for men (*P* value for the interaction, $P = 0.013$).

Previous falls and age

At all ages, previous falls in the past year were a risk factor for subsequent fracture. The HRs were highest at younger ages and decreased progressively with age (Table 4). A significant interaction between previous falls and age was observed in women for all fracture outcomes (Table 4). For hip fracture, the HR associated with previous falls

Table 3 Interaction between previous falls and sex in the association with subsequent fracture risk at the sites indicated in women and men

Outcome fracture	Number of cohorts	Women HR (95% CI)	Men HR (95% CI)	*P* value for interaction
Any	21	1.34 (1.23–1.46)	1.51 (1.32–1.73)	< 0.001
Hip	15	1.28 (1.13–1.44)	1.57 (1.24–1.98)	0.017
MOF	19	1.32 (1.20–1.45)	1.53 (1.27–1.84)	0.013
Ost	19	1.35 (1.22–1.48)	1.58 (1.35–1.85)	< 0.001

Values are hazard ratios (HR) and 95% confidence intervals (CI), adjusted for age and duration of follow-up

MOF major osteoporotic fracture, *Ost* osteoporotic fracture

Table 4 Interaction between previous falls and age at baseline in the association with subsequent fracture risk at the sites indicated in women and men

Outcome fracture	Number of cohorts	Age (years)						*P* value*
		40	50	60	70	80	90	
		HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	
Women								
Any	39	1.75 (1.53–2.01)	1.65 (1.47–1.84)	1.55 (1.42–1.68)	1.45 (1.36–1.54)	1.36 (1.31–1.41)	1.28 (1.25–1.30)	< 0.001
Hip	32	2.63 (1.85–3.76)	2.21 (1.68–2.90)	1.85 (1.53–2.25)	1.55 (1.38–1.74)	1.30 (1.23–1.38)	1.09 (1.00–1.19)	< 0.001
MOF	36	1.73 (1.44–2.08)	1.61 (1.39–1.87)	1.50 (1.34–1.68)	1.40 (1.29–1.51)	1.30 (1.24–1.36)	1.21 (1.17–1.25)	< 0.001
Ost	37	1.66 (1.41–1.96)	1.56 (1.35–1.79)	1.46 (1.30–1.63)	1.37 (1.25–1.49)	1.28 (1.20–1.36)	1.20 (1.15–1.25)	< 0.001
Men								
Any	25	1.96 (1.47–2.62)	1.83 (1.47–2.27)	1.70 (1.47–1.96)	1.58 (1.46–1.72)	1.47 (1.38–1.58)	1.37 (1.22–1.55)	0.068
Hip	17	2.21 (1.05–4.63)	2.03 (1.10–3.75)	1.87 (1.15–3.04)	1.72 (1.20–2.47)	1.58 (1.25–2.01)	1.46 (1.27–1.67)	0.21
MOF	23	2.05 (1.32–3.20)	1.90 (1.35–2.66)	1.75 (1.38–2.22)	1.62 (1.41–1.86)	1.50 (1.37–1.63)	1.38 (1.21–1.59)	0.15
Ost	23	2.02 (1.40–2.91)	1.89 (1.43–2.50)	1.77 (1.46–2.14)	1.65 (1.47–1.85)	1.54 (1.45–1.65)	1.44 (1.30–1.60)	0.13

Values are hazard ratios (HR) and 95% confidence intervals (CI), adjusted for duration of follow-up

MOF major osteoporotic fracture, *Ost* osteoporotic fracture

**P* value for the interaction term with age at baseline

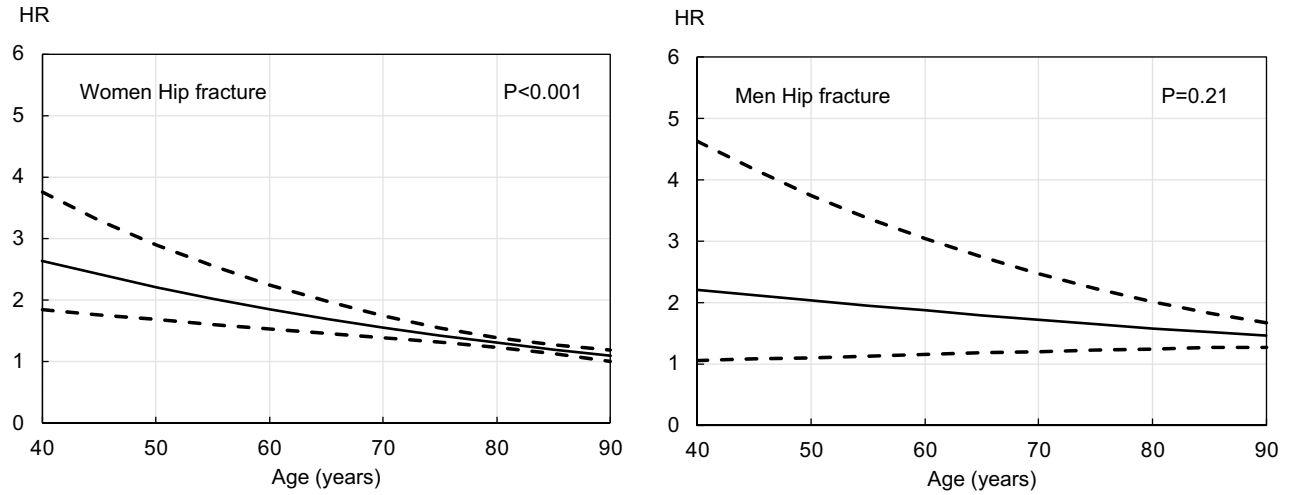

Fig. 2 Interaction between one or more falls in the year prior to baseline and age at baseline in the association with subsequent risk of a hip fracture in women (left panel) and men (right panel). Hazard ratios (HR), adjusted for duration of follow-up, and 95% confidence interval are shown. *P* values are for the interaction term with age at baseline

Table 5 Interaction between previous falls and duration of follow-up in the association with subsequent fracture risk at the sites indicated in women and men

Outcome fracture	Number of cohorts	Duration of follow-up (years)						*P* value*
		0	2	4	6	8	10	
		HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	
Women								
Any	39	1.49 (1.38–1.62)	1.44 (1.35–1.53)	1.39 (1.33–1.46)	1.34 (1.29–1.40)	1.30 (1.23–1.36)	1.25 (1.17–1.34)	0.0041
Hip	34	1.54 (1.36–1.74)	1.48 (1.33–1.65)	1.42 (1.29–1.55)	1.36 (1.25–1.47)	1.30 (1.22–1.40)	1.25 (1.17–1.33)	< 0.001
MOF	38	1.46 (1.34–1.59)	1.40 (1.31–1.50)	1.35 (1.29–1.42)	1.30 (1.25–1.36)	1.26 (1.19–1.32)	1.21 (1.13–1.30)	0.0036
Ost	38	1.52 (1.40–1.65)	1.45 (1.36–1.55)	1.39 (1.32–1.46)	1.33 (1.28–1.39)	1.28 (1.21–1.34)	1.22 (1.15–1.30)	< 0.001
Men								
Any	26	1.84 (1.65–2.05)	1.72 (1.61–1.84)	1.61 (1.52–1.71)	1.51 (1.37–1.66)	1.42 (1.22–1.64)	1.33 (1.09–1.62)	0.023
Hip	19	1.74 (1.32–2.28)	1.69 (1.36–2.10)	1.65 (1.40–1.95)	1.61 (1.41–1.85)	1.57 (1.37–1.80)	1.53 (1.30–1.81)	0.48
MOF	24	1.84 (1.66–2.03)	1.76 (1.67–1.86)	1.68 (1.56–1.82)	1.61 (1.41–1.85)	1.55 (1.26–1.90)	1.48 (1.12–1.96)	0.24
Ost	24	1.86 (1.70–2.04)	1.75 (1.66–1.84)	1.64 (1.53–1.76)	1.54 (1.36–1.73)	1.44 (1.21–1.72)	1.35 (1.07–1.72)	0.042

Values are hazard ratios (HR) and 95% confidence intervals (CI), adjusted for age

MOF major osteoporotic fracture, *Ost* osteoporotic fracture

**P* value for the interaction term with duration of follow-up

Table 6 Interaction between previous falls and femoral neck T-score in the association with subsequent fracture risk at the sites indicated in women and men

Femoral neck T-score	Outcome fracture			
	Any	Hip	MOF	Ost
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Women				
−4	1.29 (1.18–1.41)	1.40 (1.05–1.87)	1.27 (1.11–1.46)	1.24 (1.10–1.40)
−3	1.33 (1.25–1.42)	1.44 (1.20–1.72)	1.31 (1.20–1.43)	1.31 (1.21–1.41)
−2	1.38 (1.30–1.46)	1.48 (1.28–1.71)	1.36 (1.26–1.46)	1.38 (1.29–1.47)
−1	1.42 (1.31–1.55)	1.52 (1.21–1.91)	1.40 (1.27–1.55)	1.45 (1.32–1.59)
0	1.47 (1.30–1.65)	1.56 (1.10–2.22)	1.45 (1.24–1.68)	1.52 (1.33–1.75)
1	1.52 (1.29–1.78)	1.61 (0.99–2.60)	1.49 (1.21–1.84)	1.61 (1.33–1.94)
2	1.56 (1.28–1.91)	1.65 (0.89–3.07)	1.54 (1.18–2.02)	1.69 (1.33–2.15)
3	1.61 (1.27–2.06)	1.70 (0.80–3.62)	1.59 (1.14–2.22)	1.78 (1.32–2.39)
4	1.67 (1.25–2.22)	1.75 (0.71–4.28)	1.64 (1.11–2.43)	1.87 (1.32–2.66)
Number of cohorts	35	32	34	34
P value*	0.15	0.70	0.32	0.072
Men				
−4	1.71 (1.34–2.20)	0.88 (0.49–1.61)	1.24 (0.82–1.87)	1.58 (1.20–2.09)
−3	1.66 (1.40–1.97)	1.06 (0.70–1.60)	1.31 (0.98–1.75)	1.58 (1.31–1.91)
−2	1.61 (1.45–1.78)	1.27 (1.00–1.60)	1.39 (1.17–1.64)	1.58 (1.41–1.77)
−1	1.55 (1.44–1.68)	1.52 (1.31–1.75)	1.47 (1.34–1.60)	1.57 (1.45–1.71)
0	1.50 (1.33–1.70)	1.81 (1.41–2.33)	1.55 (1.34–1.79)	1.57 (1.38–1.79)
1	1.46 (1.20–1.76)	2.17 (1.42–3.32)	1.64 (1.27–2.12)	1.57 (1.27–1.94)
2	1.41 (1.07–1.84)	2.60 (1.41–4.79)	1.73 (1.18–2.53)	1.56 (1.16–2.11)
3	1.36 (0.96–1.93)	3.11 (1.39–6.95)	1.83 (1.10–3.04)	1.56 (1.06–2.30)
4	1.32 (0.86–2.03)	3.72 (1.37–10.09)	1.94 (1.03–3.64)	1.55 (0.96–2.51)
Number of cohorts	24	18	23	23
P value*	0.44	0.073	0.40	0.96

Values are hazard ratios (HR) and 95% confidence intervals (CI), adjusted for age and duration of follow-up

MOF major osteoporotic fracture, *Ost* osteoporotic fracture

**P* value for the interaction term with femoral neck T-score

Table 7 Association between number of previous falls and subsequent fracture risk at the sites indicated in women and men

Outcome fracture	1 fall vs. none		2 falls vs. none		≥3 falls vs. none	
	Number of cohorts	HR (95% CI)	Number of cohorts	HR (95% CI)	Number of cohorts	HR (95% CI)
Women						
Any	25	1.32 (1.24–1.41)	27	1.55 (1.38–1.74)	22	1.73 (1.55–1.93)
Hip	21	1.28 (1.16–1.41)	21	1.57 (1.27–1.95)	17	1.73 (1.49–2.02)
MOF	24	1.27 (1.19–1.36)	23	1.48 (1.30–1.68)	20	1.68 (1.51–1.87)
Ost	24	1.32 (1.22–1.42)	25	1.53 (1.35–1.73)	20	1.74 (1.55–1.96)
Men						
Any	15	1.46 (1.38–1.54)	15	2.03 (1.71–2.42)	12	2.27 (1.72–3.00)
Hip	10	1.58 (1.39–1.79)	8	2.43 (1.80–3.28)	8	4.00 (2.51–6.37)
MOF	13	1.48 (1.30–1.69)	13	2.13 (1.69–2.68)	9	2.45 (1.65–3.63)
Ost	14	1.50 (1.41–1.60)	13	2.12 (1.72–2.61)	12	2.53 (1.78–3.59)

Values are hazard ratios (HR) and 95% confidence intervals (CI), adjusted for age and duration of follow-up

MOF major osteoporotic fracture, *Ost* osteoporotic fracture, *BMD* bone mineral density

decreased from 2.63 (95% CI 1.85–3.76) at the age of 40 years to 1.09 (95% CI 1.00–1.19) at the age of 90 years ($P < 0.001$) (Fig. 2). In contrast, in men, the interaction term with age was not significant (Table 4). Similar relationships were observed using piecewise linear regression models (data not shown).

Previous falls and duration of follow-up

For all fracture outcomes, the risk following a previous fall in the past year decreased slowly over time since the start of follow-up (Table 5). A significant interaction was observed between previous falls and duration of follow-up for all fracture outcomes in women. In men, the interaction term was only significant for any and osteoporotic fractures. An almost identical relationship was observed using piecewise linear regression models (data not shown).

Previous falls and BMD

The predictive value of a previous fall on incident fracture risk was only marginally downward adjusted or not affected by the inclusion of femoral neck BMD in the models depending on the fracture outcome. In particular, the HRs from the models including only those cohorts contributing to both scenarios (i.e., in which femoral neck BMD had been measured) did not substantially differ (Appendix Table 10). When analyzing the interaction between previous falls and femoral neck T-score, the HRs tended to increase as the BMD increased in both women and men for all fracture outcomes (Table 6). The interaction terms were, however, not significant. Piecewise linear regression models with a knot at T-score − 2.5 largely confirmed these results (data not shown).

Number of previous falls and fracture

Information on the number of self-reported previous falls in the past year was available in 30 cohorts (Table 1). Fracture risk increased progressively with an increasing number of previous falls (Table 7). The HR for a MOF increased from 1.27 (95% CI 1.19–1.36) for one fall to 1.48 (95% CI 1.30–1.68) for two falls to 1.68 (95% CI 1.51–1.87) for ≥ 3 falls in women. The increment in risk for each additional fall was greater in men than in women. The HR for a MOF in men increased from 1.48 (95% CI 1.30–1.69) for one fall to 2.13 (95% CI 1.69–2.68) for two falls to 2.45 (95% CI 1.65–3.63) for > 3 falls. Similar HRs were observed for the other fracture outcomes.

Previous falls and risk of death

One or more previous falls was significantly associated with an increased risk of death in both women (HR 1.15, 95% CI 1.09–1.22) and men (HR 1.20, 95% CI 1.09–1.33). HRs remained essentially unchanged when femoral neck T-score was added to the models.

Sensitivity analyses

In sensitivity analyses, the association between a previous fall and subsequent fracture risk did not materially change when the analyses were restricted to those cohorts with a uniform risk factor definition ($n = 43$ cohorts, Appendix Table 11). No significant differences in HRs were observed according to race and ethnicity in those cohorts with these characteristics documented (Appendix Table 12). When analyzing the cohorts according to quality score, fracture risk was significantly increased following a previous fall in cohorts of intermediate quality (a quality score of 2 or 3) and cohorts of high quality (a quality score of 4), while this association did not reach statistical significance in the cohorts of poor quality (Appendix Table 13). Moreover, the predictive value of previous falls for fracture risk was significantly larger in cohorts of intermediate quality compared with cohorts of high quality for all fracture outcomes in women and all but MOF in men.

Discussion

With the second iteration of FRAX currently under development and the corresponding largest resource available to date, the predictive value of previous falls for subsequent fracture risk was investigated in 46 prospective cohorts. Our findings show that a previous fall in the past year confers a significantly increased risk of any clinical fracture, osteoporotic fracture, MOF, and hip fracture with the increase in risk varying between 36 and 59% depending on the fracture outcome and sex. Notably, the effect size was largely unaffected by race and ethnicity. Previous studies have similarly shown that assessment of falls history predicts fracture risk [5–20] and improves fracture risk prediction in addition to FRAX clinical risk factors and BMD [27, 28] in both women and men. Moreover, the availability of a standardized question construct in a large majority of the contributing cohorts and the increased risk

of fractures associated with previous falls being amenable to pharmacological treatment of the underlying bone fragility [29–32] support the consideration of falls history as an additional clinical risk factor in the update of the FRAX tool.

A significant interaction was observed between previous falls and sex for incident fracture risk with the predictive value of previous falls higher in men than in women. Also, in women, the increased risk mediated by previous falls decreased with age whereas the risk was not significantly associated with age in men such that it remained significantly increased at the age of 80 and 90 years. As previously reported [51], women fell more frequently than men. This suggests that the more frequent falls in women are less injurious than in men despite the fact they occur more often in older women. Thus, previous falls are an important risk factor for fracture in older men but less so for older women, i.e., those individuals who most often present with fractures in daily practice. This finding is in accordance with recent findings from the Osteoporotic Fractures in Men study showing fall history (previous year) is a strong risk factor for clinical fracture and hip fracture in late-life (over 80 years of age) men [52]. In addition, we observed a significant interaction between previous falls and follow-up time for the prediction of incident fractures with the risk diminishing over time. A previous study of elderly men showed that the association between previous falls and fracture risk decreased progressively with increasing follow-up time [27]. This may be a possible concern with the incorporation of previous falls into FRAX as falls history may provide less predictive power over longer periods. As with all risk variables to be used in FRAX, any interaction of effect over time is also important to incorporate in future probability models. Similarly, previous falls are associated with increased mortality, an important consideration when modelling 10-year fracture probability which, in the case of FRAX, is based on the hazards of both death and fracture [21].

Our findings indicate that the increased fracture risk mediated by previous falls is largely independent of BMD as the point estimates did not materially change after accounting for this measure. The predictive value of previous falls tended to increase with each unit increase in femoral neck T-score; the interaction terms were, however, not significant for the fracture outcomes investigated. The mechanism for the BMD-independent increase in fracture risk associated with falls history could not be determined from this study.

The predictive value of previous falls increased progressively with additional falls reported in the previous year in women and men. Our results are in line with previous findings of the risk of fracture increasing with the number of reported falls [6, 16, 28, 53] although the point estimates in this study were smaller compared with those previously reported. The clear dose–response indicates that the next generation of FRAX should incorporate the number of previous falls in the past year as an input variable. In the interim, conventional estimates of FRAX can be adjusted by hand [53] or electronically through the FRAXplus portal [54] (https://www.fraxplus.org/).

A particular strength of this study is that the estimates of fracture risk for previous falls are derived from the largest international resource available to date. The participating cohorts were identified partly through collaboration and through a systematic search of potentially available cohorts [44]. Computations were based on individual-level data, decreasing the risk of publication biases, and the extent of the data resource allowed for additional analyses such as interactions. We also acknowledge several limitations. Fall history was based on recall, which may not be accurate, especially since older adults who experience a fall may fear institutionalization, resulting in under reporting. This bias would most likely weaken rather than strengthen any associations with incident fractures. Also, it is not possible to examine all potential confounding factors that contribute to falls risk and previous falls such as physical activity levels and medications affecting balance. In addition, a simple question construct was used to ascertain falls, and it is possible that a more detailed questioning within the framework of a research protocol might have extracted more accurate information [55]. However, in the context of risk assessment undertaken in the clinic, optimized repeatability and simplicity are likely to be worth a modest sacrifice in accuracy. Finally, not all cohorts used a dose-responsive question construct on number of previous falls.

In summary, a uniform question construct regarding previous falls is associated with incident fracture risk, independent of BMD. Moreover, fracture risk increases with each additional fall in women and men. These data provide further support to incorporate previous falls into future iterations of FRAX to guide clinical management of those individuals at highest risk of fracture.

Appendix

Table 8 Description of cohort characteristics, previous falls, and incident fracture outcomes in women

Cohort	*n*	Person-years	Age (years)			Previous fall (%)	FN BMD (n)	Number of incident fractures			
			Mean	Min	Max			Any	Ost	MOF	Hip
AGES	3243	26,843	76.9	66.0	96.0	21.1	2673	1141	1011	839	368
BEH	1182	5269	69.2	60.0	94.0	14.4	1176	72	51	33	28
Bern	2863	10,783	60.9	20.1	94.3	12.5	2827	396	287	205	18
CaMos	6539	86,156	63.0	25.0	103.0	6.6	5712	1910	1384	981	270
DOES	1267	11,926	70.3	47.0	94.0	35.4	1256	349	296	233	73
DO-HEALTH	1331	3670	74.8	70.0	93.0	46.4	923	202	150	101	8
ECOSAP	5146	16,857	72.3	65.0	100.0	26.7	-	311	259	188	52
EPIFROS	155	1536	62.0	40.0	90.0	21.3	12	21	18	14	3
Framingham_offspring	1888	26,120	61.4	33.0	88.0	22.0	1620	474	359	194	66
Framingham_original	708	6324	80.0	72.0	101.0	29.4	554	208	188	141	95
FRIDEX	815	8077	56.8	40.0	84.0	24.4	815	112	56	41	15
FROCAT	1071	10,607	69.7	32.0	100.0	30.8	219	168	130	116	24
GERICO	602	2187	67.9	64.6	71.8	45.8	590	62	43	22	2
GLOW	53,673	214,575	68.2	55.0	108.0	37.6	-	5628	4233	2804	480
HAI	1770	4619	70.5	69.2	72.0	13.4	1719	83	75	55	7
HCS	243	1940	66.0	61.3	70.9	19.8	242	33	24	17	0
Health ABC	1578	19,838	73.5	68.0	80.0	24.1	1564	463	397	355	150
HUNT	3743	39,848	77.3	70.0	96.8	22.5	1310	1599	1452	1060	592
LASA	758	4076	75.7	64.8	88.6	34.2	260	81	60	0	21
Maccabi	54,175	497,082	65.5	37.0	91.0	5.1	6665	14,294	14,236	13,579	4071
Manitoba	33,136	94,303	66.9	20.0	104.3	20.5	33,136	1839	1718	1283	298
MsOS Hong Kong	2000	17,528	72.6	65.0	98.0	24.1	2000	338	298	247	69
OFELY	867	15,136	58.8	40.0	89.0	30.8	861	245	207	180	40
OPRA	914	10,664	75.2	75.0	76.0	28.4	825	457	413	398	173
OPUS	1978	12,135	62.0	20.2	80.0	29.0	1970	234	146	112	14
OsteoLaus	1475	6726	64.5	50.2	81.5	25.4	1457	307	245	226	8
OSTPRE	9998	97,799	57.3	52.4	62.7	36.0	2460	1635	1123	824	68
REFORM	607	899	77.6	65.0	99.0	63.9	-	23	12	7	2
Rotterdam	6125	81,489	69.5	55.0	106.2	23.3	4409	2155	1959	1645	613
SAOL-IPR_EPIPorto	711	8715	55.2	40.0	85.0	25.2	709	93	0	34	11
SarcoPhAge	130	251	75.7	68.2	93.4	41.5	124	12	8	5	1
SCOOP	12,368	58,845	75.6	70.0	86.0	27.8	2790	1932	1630	1288	375
SEMOF	7131	20,625	75.2	70.0	91.3	31.4	919	683	596	464	80
Sheffield	2175	7441	80.0	74.3	100.9	6.0	2154	289	234	191	67
SOF	9654	135,907	71.6	65.0	89.0	30.0	7760	4346	3462	2801	1411
SOS	16,441	61,467	74.2	60.8	92.5	27.5	4071	1365	1306	978	253
SUPERB	3025	10,752	77.8	74.7	81.0	29.6	3012	463	421	341	70
UK Biobank	272,086	3,143,813	56.4	39.0	71.0	23.1	9969	16,515	14,558	8913	2613
WHI	78,612	1,072,537	64.4	49.0	79.0	32.3	5576	6377	5020	4392	2278
YORK	4532	9044	77.1	47.6	98.9	30.1	-	393	310	223	42
Overall (total/mean)	606,715	5,864,409	62.6	20.0	108.0	24.5	114,339	67,308	58,375	45,530	14,829

FN BMD femoral neck bone mineral density, *OST* osteoporotic fracture, *MOF* major osteoporotic fracture

Table 9 Description of cohort characteristics, previous falls, and incident fracture outcomes in men

Cohort	*n*	Person-years	Age (years)			Previous fall (%)	FN BMD (*n*)	Number of incident fractures			
			Mean	Min	Max			Any	Ost	MOF	Hip
AGES	2394	18,345	77.0	67.0	96.0	15.2	2099	459	367	281	157
BEH	1117	4926	69.5	61.0	96.0	6.7	1115	26	25	13	12
Bern	827	3057	56.2	20.1	91.1	11.5	815	79	52	32	5
CaMos	2884	35,478	59.9	25.0	97.0	6.7	2578	525	369	207	70
DOES	819	7415	69.7	59.0	92.0	21.6	801	131	108	66	22
DO-HEALTH	825	2287	75.2	70.0	95.0	34.8	528	65	42	18	2
EPIFROS	129	1290	61.1	40.0	96.0	14.7	-	6	2	2	0
FORMEN	1886	16,265	72.5	65.0	93.0	16.3	1882	90	90	58	10
Framingham_offspring	1603	21,057	61.4	37.0	88.0	17.5	1288	203	165	77	22
Framingham_original	386	3065	78.7	72.0	99.0	30.8	330	53	46	25	18
FROCAT	859	8566	68.7	41.0	111.0	19.7	14	60	52	43	9
GERICO	156	555	68.1	65.5	71.8	53.2	154	9	8	4	0
HAI	1745	4671	70.5	69.9	71.7	8.8	1717	42	38	22	3
HCS	8	69	66.3	64.6	69.1	25.0	8	0	0	0	0
Health ABC	1486	16,510	73.8	69.0	80.0	18.3	1468	236	198	165	85
HUNT	3060	29,413	76.8	70.0	96.9	17.7	549	691	546	385	251
LASA	714	3492	75.7	64.8	88.7	30.3	259	51	36	0	18
Maccabi	29,402	260,710	65.0	40.0	91.0	5.0	1013	5041	5012	4829	1709
Manitoba	4110	10,862	64.7	20.0	101.2	24.3	4110	225	218	154	44
MINOS	681	6152	65.2	50.0	86.0	24.1	672	63	56	25	3
MrOS Hong Kong	2000	19,744	72.4	65.0	92.0	15.4	2000	231	201	148	63
MrOS Sweden	3001	34,078	74.9	69.0	81.0	16.5	2809	964	869	724	338
MrOS USA	5994	75,015	73.7	64.0	100.0	21.2	5993	1394	1082	814	330
REFORM	396	584	78.3	65.0	99.0	67.2	-	7	5	5	2
Rotterdam	4257	52,202	67.5	55.0	97.6	11.9	3377	730	621	458	177
SAOL-IPR-EPIPorto	205	2424	58.1	40.0	89.0	14.6	205	11	0	7	1
SarcoPhAge	98	189	76.2	68.5	89.4	31.6	93	1	0	0	0
STRAMBO	821	7564	72.2	51.0	88.4	20.7	803	117	86	42	17
UK Biobank	227,781	2,591,829	56.8	38.0	73.0	15.9	9561	8534	5419	3131	1312
Overall (total/mean)	299,644	3,237,814	59.5	20.0	111.0	15.1	46,241	20,044	15,713	11,735	4680

FN BMD femoral neck bone mineral density, *OST* osteoporotic fracture, *MOF* major osteoporotic fracture

Table 10 Association of previous falls with subsequent fracture risk at the sites indicated in women and men adjusted for age and duration of follow-up and additionally adjusted for BMD. Analysis includes only cohorts with femoral neck BMD

Outcome fracture	Number of cohorts	Cohorts with BMD		Adjusted for BMD
		I^2 (%)	HR (95% CI)	I^2 (%)	HR (95% CI)
Women					
Any	35	80	1.37 (1.27–1.47)	76	1.37 (1.26–1.49)
Hip	32	68	1.34 (1.18–1.53)	59	1.36 (1.18–1.56)
MOF	34	77	1.33 (1.22–1.44)	72	1.33 (1.21–1.46)
Ost	34	80	1.35 (1.25–1.47)	76	1.36 (1.24–1.49)
Men					
Any	24	54	1.49 (1.36–1.63)	0	1.51 (1.42–1.62)
Hip	19	36	1.55 (1.35–1.79)	0	1.55 (1.36–1.77)
MOF	23	61	1.46 (1.29–1.67)	0	1.47 (1.35–1.60)
Ost	23	54	1.53 (1.38–1.69)	0	1.51 (1.40–1.62)

Values are hazard ratios (HR) and 95% confidence intervals (CI), adjusted for age and duration of follow-up

BMD bone mineral density, *MOF* major osteoporotic fracture, *Ost* osteoporotic fracture, I^2 heterogeneity statistic

Table 11 Association of previous falls with subsequent fracture risk at the sites indicated in those cohorts with a uniform question construct

Outcome fracture	Number of cohorts	I^2 (%)	HR (95% CI)
Women			
Any	36	86	1.37 (1.29–1.45)
Hip	31	47	1.28 (1.19–1.37)
MOF	35	78	1.31 (1.23–1.40)
Ost	35	84	1.35 (1.27–1.44)
Men			
Any	24	92	1.53 (1.32–1.77)
Hip	18	85	1.61 (1.29–2.01)
MOF	22	91	1.48 (1.24–1.77)
Ost	22	77	1.57 (1.39–1.77)

Values are hazard ratios (HR) and 95% confidence intervals (CI), adjusted for age and duration of follow-up

MOF major osteoporotic fracture, *Ost* osteoporotic fracture, I^2 heterogeneity statistic

Table 12 Association of previous falls with subsequent fracture risk at the sites indicated in women and men combined according to race/ethnicity

Outcome fracture	Number of cohorts	HR (95% CI)	HR (95% CI)	*P* value for interaction
Asian vs. Caucasian		Caucasian	Asian	
Any	4	1.15 (0.64–2.08)	0.86 (0.37–2.01)	0.40
Hip	3	1.08 (0.58–2.01)	0.68 (0.14–3.38)	0.55
MOF	4	1.13 (0.63–2.02)	0.92 (0.37–2.27)	0.60
Black vs. Caucasian		Caucasian	Black	
Any	5	1.15 (0.68–1.94)	1.15 (0.53–2.50)	0.99
Hip	5	1.17 (0.73–1.88)	1.05 (0.48–2.31)	0.77
MOF	5	1.16 (0.69–1.93)	1.16 (0.53–2.54)	0.99
Hispanic vs. Caucasian		Caucasian	Hispanic	
Any	2	1.30 (1.19–1.41)	0.95 (0.69–1.32)	0.063
Hip	2	1.32 (1.12–1.56)	1.58 (0.05–45.67)	0.92
MOF	2	1.24 (1.17–1.32)	1.28 (0.47–3.52)	0.95
Other than Caucasian vs. Caucasian		Caucasian	Other than Caucasian	
Any	7	1.17 (0.79–1.74)	0.93 (0.50–1.73)	0.43
Hip	6	1.17 (0.80–1.70)	0.90 (0.45–1.82)	0.46
MOF	7	1.19 (0.80–1.75)	1.05 (0.57–1.91)	0.66

Values are hazard ratios (HR) and 95% confidence intervals (CI), adjusted for age, sex, and duration of follow-up

MOF major osteoporotic fracture

Table 13 Association of previous falls with subsequent fracture risk at the sites indicated in women and men according to quality score of the cohorts

Outcome fracture	Quality score 0–1			Quality score 2–3			Quality score 4		
	Number of cohorts	Person-years	HR (95% CI)	Number of cohorts	Person-years	HR (95% CI)	Number of cohorts	Person-years	HR (95% CI)
Women									
Any	3	3216	1.79 (0.59–5.44)	22	4,753,408	1.50 (1.38–1.64)[b]	15	771,719	1.27 (1.20–1.34)
Hip	0	0	–	21	4,938,300	1.54 (1.33–1.77)[c]	14	872,607	1.16 (1.07–1.27)
MOF	3	3288	1.64 (0.28–9.72)	22	4,856,680	1.45 (1.32–1.59)[b]	14	796,066	1.25 (1.18–1.32)
Ost	3	3253	1.38 (0.50–3.80)	21	4,799,082	1.50 (1.37–1.64)[b]	15	785,274	1.27 (1.20–1.34)
Men									
Any	2	1119	1.62 (0.41–6.39)	10	2,601,682	1.77 (1.56–2.01)[b]	15	541,337	1.44 (1.34–1.53)
Hip	0	0	–	5	2,624,302	2.01 (1.79–2.26)[c]	15	581,155	1.46 (1.29–1.67)
MOF	2	1130	1.48 (0.36–6.12)	9	2,631,427	1.71 (1.37–2.13)	14	553,866	1.41 (1.28–1.55)
Ost	2	1122	1.81 (0.54–6.04)	8	2,617,095	1.86 (1.73–2.01)[c]	15	549,659	1.47 (1.36–1.60)

Values are hazard ratios (HR) and 95% confidence intervals (CI), adjusted for age and duration of follow-up

MOF major osteoporotic fracture, *Ost* osteoporotic fracture

[a] $P < 0.05$

[b] $P < 0.01$

[c] $P < 0.001$, comparison with high quality (quality score 4)

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Declarations

Conflicts of interest JA Kanis led the team that developed FRAX as director of the WHO Collaborating Centre for Metabolic Bone Diseases; he is a director of Osteopoorosis Research Ltd that maintains FRAX. EV McCloskey, WD Leslie, M Lorentzon, NC Harvey, M Schini, 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. 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. 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Human and animal rights This study 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 is published, not allowing for identification of individual study participants. 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.

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Authors and Affiliations

Liesbeth Vandenput[1] · Helena Johansson[1,2,3] · Eugene V. McCloskey[2,4] · Enwu Liu[1] · Marian Schini[5] · Kristina E. Åkesson[6,7] · Fred A. Anderson[8] · Rafael Azagra[9,10,11,12] · Cecilie L. Bager[13] · Charlotte Beaudart[14,15] · Heike A. Bischoff-Ferrari[16,17] · Emmanuel Biver[18] · Olivier Bruyère[14] · Jane A. Cauley[19] · Jacqueline R. Center[20,21,22] · Roland Chapurlat[23] · Claus Christiansen[13] · Cyrus Cooper[24,25,26] · Carolyn J. Crandall[27] · Steven R. Cummings[28] · José A. P. da Silva[29,30] · Bess Dawson-Hughes[31] · Adolfo Diez-Perez[32] · Alyssa B. Dufour[33,34] · John A. Eisman[20,21,22] · Petra J. M. Elders[35] · Serge Ferrari[18] · Yuki Fujita[36] · Saeko Fujiwara[37] · Claus-Christian Glüer[38] · Inbal Goldshtein[39,40] · David Goltzman[41] · Vilmundur Gudnason[42,43] · Jill Hall[44] · Didier Hans[45] · Mari Hoff[46,47] · Rosemary J. Hollick[48] · Martijn Huisman[49,50] · Masayuki Iki[51] · Sophia Ish-Shalom[52] · Graeme Jones[53] · Magnus K. Karlsson[6,54] · Sundeep Khosla[55] · Douglas P. Kiel[34,56] · Woon-Puay Koh[57,58] · Fjorda Koromani[59,60] · Mark A. Kotowicz[61,62,63] · Heikki Kröger[64,65] · Timothy Kwok[66,67] · Olivier Lamy[68,69] · Arnulf Langhammer[70] · Bagher Larijani[71] · Kurt Lippuner[72] · Fiona E. A. McGuigan[6] · Dan Mellström[73,74] · Thomas Merlijn[35] · Tuan V. Nguyen[22,75,76] · Anna Nordström[77,78,79] · Peter Nordström[80] · Terence W. O'Neill[81,82] · Barbara Obermayer-Pietsch[83,84] · Claes Ohlsson[3,85] · Eric S. Orwoll[86] · Julie A. Pasco[61,62,63,87] · Fernando Rivadeneira[59] · Anne-Marie Schott[88] · Eric J. Shiroma[89] · Kristin Siggeirsdottir[42,90] · Eleanor M. Simonsick[91] · Elisabeth Sornay-Rendu[23] · Reijo Sund[65] · Karin M. A. Swart[92,93] · Pawel Szulc[23] · Junko Tamaki[94] · David J. Torgerson[95] · Natasja M. van Schoor[49] · Tjeerd P. van Staa[96] · Joan Vila[97] · Nicholas J. Wareham[98] · Nicole C. Wright[99] · Noriko Yoshimura[100] · MCarola Zillikens[59] · Marta Zwart[12,101,102,103] · Nicholas C. Harvey[24,25] · Mattias Lorentzon[1,3,104] · William D. Leslie[105] · John A. Kanis[1,2]

✉ John A. Kanis
w.j.Pontefract@sheffield.ac.uk; w.j.pontefract@shef.ac.uk

Liesbeth Vandenput
liesbeth.vandenput@acu.edu.au

Helena Johansson
helena@statiq.se

Eugene V. McCloskey
e.v.mccloskey@sheffield.ac.uk

Enwu Liu
enwu.liu@acu.edu.au

Marian Schini
m.schini@sheffield.ac.uk

Kristina E. Åkesson
kristina.akesson@med.lu.se

Fred A. Anderson
fred.anderson@umassmed.edu

Rafael Azagra
rafael.azagra@uab.cat

Cecilie L. Bager
cba@nordicbio.com

Charlotte Beaudart
c.beaudart@maastrichtuniversity.nl

Heike A. Bischoff-Ferrari
heike.bischoff@usz.ch

Emmanuel Biver
emmanuel.biver@hcuge.ch

Olivier Bruyère
olivier.bruyere@uliege.be

Jane A. Cauley
jcauley@edc.pitt.edu

Jacqueline R. Center
j.center@garvan.org.au

Roland Chapurlat
roland.chapurlat@inserm.fr

Claus Christiansen
cc@nordicbio.com

Cyrus Cooper
cc@mrc.soton.ac.uk

Carolyn J. Crandall
ccrandall@mednet.ucla.edu

Steven R. Cummings
steven.cummings@ucsf.edu

José A. P. da Silva
jdasilva@ci.uc.pt

Bess Dawson-Hughes
bess.dawson-hughes@tufts.edu

Adolfo Diez-Perez
adiez@psmar.cat

Alyssa B. Dufour
alyssadufour@hsl.harvard.edu

John A. Eisman
j.eisman@garvan.org.au

Petra J. M. Elders
p.elders@amsterdamumc.nl

Serge Ferrari
serge.ferrari@unige.ch

Yuki Fujita
yfujita@med.kindai.ac.jp

Saeko Fujiwara
fujiwara-s@yasuda-u.ac.jp

Claus-Christian Glüer
glueer@rad.uni-kiel.de

Inbal Goldshtein
inbalbarak@gmail.com

David Goltzman
david.goltzman@mcgill.ca

Vilmundur Gudnason
v.gudnason@hjarta.is

Jill Hall
jill.hall@ed.ac.uk

Didier Hans
didier.hans@chuv.ch

Mari Hoff
mari.hoff@ntnu.no

Rosemary J. Hollick
rhollick@abdn.ac.uk

Martijn Huisman
m.huisman@amsterdamumc.nl

Masayuki Iki
masa@med.kindai.ac.jp

Sophia Ish-Shalom
sishshalom@gmail.com

Graeme Jones
g.jones@utas.edu.au

Magnus K. Karlsson
magnus.karlsson@med.lu.se

Sundeep Khosla
khosla.sundeep@mayo.edu

Douglas P. Kiel
kiel@hsl.harvard.edu

Woon-Puay Koh
kohwp@nus.edu.sg

Fjorda Koromani
f.koromani@erasmusmc.nl

Mark A. Kotowicz
mark.kotowicz@deakin.edu.au

Heikki Kröger
heikki.kroger@kuh.fi

Timothy Kwok
tkwok@cuhk.edu.hk

Olivier Lamy
olivier.lamy@chuv.ch

Arnulf Langhammer
arnulf.langhammer@ntnu.no

Bagher Larijani
emrc@tums.ac.ir

Kurt Lippuner
kurt.lippuner@insel.ch

Fiona E. A. McGuigan
fiona.mcguigan@med.lu.se

Dan Mellström
dan.mellstrom@vgregion.se

Thomas Merlijn
tmerlijn@gmail.com

Tuan V. Nguyen
TuanVan.Nguyen@uts.edu.au

Anna Nordström
anna.h.nordstrom@umu.se

Peter Nordström
peter.nordstrom@umu.se

Terence W. O'Neill
terence.o'neill@manchester.ac.uk

Barbara Obermayer-Pietsch
barbara.obermayer@medunigraz.at

Claes Ohlsson
claes.ohlsson@medic.gu.se

Eric S. Orwoll
orwoll@ohsu.edu

Julie A. Pasco
julie.pasco@deakin.edu.au

Fernando Rivadeneira
f.rivadeneira@erasmusmc.nl

Anne-Marie Schott
anne-marie.schott@inserm.fr

Eric J. Shiroma
eric.shiroma@nih.gov

Kristin Siggeirsdottir
kristin@janus.is

Eleanor M. Simonsick
simonsickel@grc.nia.nih.gov

Elisabeth Sornay-Rendu
elisabeth.rendu@inserm.fr

Reijo Sund
reijo.sund@uef.fi

Karin M. A. Swart
karin.swart-polinder@pharmo.nl

Pawel Szulc
pawel.szulc@inserm.fr

Junko Tamaki
jtamaki@ompu.ac.jp

David J. Torgerson
david.torgerson@york.ac.uk

Natasja M. van Schoor
nm.vanschoor@amsterdamumc.nl

Tjeerd P. van Staa
tjeerd.vanstaa@manchester.ac.uk

Joan Vila
jvila@imim.es

Nicholas J. Wareham
nick.wareham@mrc-epid.cam.ac.uk

Nicole C. Wright
ncwright@uab.edu

Noriko Yoshimura
noripu@rc4.so-net.ne.jp

MCarola Zillikens
m.c.zillikens@erasmusmc.nl

Marta Zwart
marta.zwart@udg.edu

Nicholas C. Harvey
nch@mrc.soton.ac.uk

Mattias Lorentzon
mattias.lorentzon@medic.gu.se

William D. Leslie
bleslie@sbgh.mb.ca

[1] Mary McKillop Institute for Health Research, Australian Catholic University, Melbourne, Australia

[2] Centre for Metabolic Bone Diseases, University of Sheffield, Sheffield, UK

[3] Sahlgrenska Osteoporosis Centre, Department of Internal Medicine and Clinical Nutrition, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

[4] MRC and Arthritis Research UK Centre for Integrated Research in Musculoskeletal Ageing, Mellanby Centre for Musculoskeletal Research, University of Sheffield, Sheffield, UK

[5] Division of Clinical Medicine, School of Medicine and Population Health, University of Sheffield, Sheffield, UK

[6] Clinical and Molecular Osteoporosis Research Unit, Department of Clinical Sciences, Lund University, Lund, Sweden

[7] Department of Orthopedics, Skåne University Hospital, Malmö, Sweden

[8] GLOW Coordinating Center, Center for Outcomes Research, University of Massachusetts Medical School, Worcester, MA, USA

[9] Department of Medicine, Autonomous University of Barcelona, Barcelona, Spain

[10] Health Centre Badia del Valles, Catalan Institute of Health, Barcelona, Spain

[11] GROIMAP (Research Group), Unitat de Suport a La Recerca Metropolitana Nord, Institut Universitari d'Investigació en Atenció Primària Jordi Gol, Cerdanyola del Vallès, Barcelona, Spain

[12] PRECIOSA-Fundación Para La Investigación, Barberà del Vallés, Barcelona, Spain

[13] Nordic Bioscience A/S, Herlev, Denmark

[14] WHO Collaborating Centre for Public Health Aspects of Musculoskeletal Health and Aging, Division of Public Health, Epidemiology and Health Economics, University of Liège, Liège, Belgium

[15] Department of Health Services Research, University of Maastricht, Maastricht, The Netherlands

[16] Department of Aging Medicine and Aging Research, University Hospital, Zurich, and University of Zurich, Zurich, Switzerland

[17] Centre On Aging and Mobility, University of Zurich and City Hospital, Zurich, Switzerland

[18] Division of Bone Diseases, Department of Medicine, Geneva University Hospitals and Faculty of Medicine, University of Geneva, Geneva, Switzerland

[19] Department of Epidemiology, School of Public Health, University of Pittsburgh, Pittsburgh, PA, USA

[20] Skeletal Diseases Program, Garvan Institute of Medical Research, Sydney, NSW, Australia

[21] St Vincent's Clinical School, School of Medicine and Health, University of New South Wales Sydney, Sydney, NSW, Australia

[22] School of Medicine Sydney, University of Notre Dame Australia, Sydney, NSW, Australia

[23] INSERM UMR 1033, Université Claude Bernard-Lyon1, Hôpital Edouard Herriot, Lyon, France

[24] MRC Lifecourse Epidemiology Centre, University of Southampton, Southampton, UK

[25] NIHR Southampton Biomedical Research Centre, University of Southampton and University Hospitals Southampton NHS Foundation Trust, Southampton, UK

[26] NIHR Oxford Biomedical Research Unit, University of Oxford, Oxford, UK

[27] Division of General Internal Medicine and Health Services Research, David Geffen School of Medicine, University of California, Los Angeles, CA, USA

[28] San Francisco Coordinating Center, California Pacific Medical Center Research Institute, San Francisco, CA, USA

[29] Coimbra Institute for Clinical and Biomedical Research, Faculty of Medicine, University of Coimbra, Coimbra, Portugal

[30] Rheumatology Department, Centro Hospitalar E Universitário de Coimbra, Coimbra, Portugal

[31] Bone Metabolism Laboratory, Jean Mayer US Department of Agriculture Human Nutrition Research Center On Aging, Tufts University, Boston, MA, USA

[32] Department of Internal Medicine, Hospital del Mar and CIBERFES, Autonomous University of Barcelona, Barcelona, Spain

[33] Marcus Institute for Aging Research, Hebrew SeniorLife, Boston, MA, USA

[34] Department of Medicine, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA, USA

[35] Department of General Practice, Amsterdam UMC, Location AMC, Amsterdam Public Health Research Institute, Amsterdam, The Netherlands

[36] Center for Medical Education and Clinical Training, Kindai University Faculty of Medicine, Osaka, Japan

[37] Department of Pharmacy, Yasuda Women's University, Hiroshima, Japan

[38] Section Biomedical Imaging, Molecular Imaging North Competence Center, Department of Radiology and Neuroradiology, University Medical Center Schleswig-Holstein Kiel, Kiel University, Kiel, Germany

[39] Maccabitech Institute of Research and Innovation, Maccabi Healthcare Services, Tel Aviv, Israel

[40] Department of Epidemiology and Preventive Medicine, School of Public Health, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

[41] Department of Medicine, McGill University and McGill University Health Centre, Montreal, Canada

[42] Icelandic Heart Association, Kopavogur, Iceland

[43] University of Iceland, Reykjavik, Iceland

[44] MRC Centre for Reproductive Health, University of Edinburgh, Edinburgh, UK

[45] Interdisciplinary Centre of Bone Diseases, Bone and Joint Department, Lausanne University Hospital (CHUV) & University of Lausanne, Lausanne, Switzerland

[46] Department of Neuromedicine and Movement Science, Norwegian University of Science and Technology, Trondheim, Norway

[47] Department of Rheumatology, St. Olavs Hospital, Trondheim, Norway

[48] Aberdeen Centre for Arthritis and Musculoskeletal Health, Epidemiology Group, University of Aberdeen, Aberdeen, UK

[49] Department of Epidemiology and Data Science, Amsterdam Public Health Research Institute, VU University Medical Center, Amsterdam, The Netherlands

[50] Department of Sociology, VU University, Amsterdam, The Netherlands

[51] Department of Public Health, Kindai University Faculty of Medicine, Osaka, Japan

[52] Endocrine Clinic, Elisha Hospital, Haifa, Israel

[53] Menzies Institute for Medical Research, University of Tasmania, Hobart, Australia

[54] Department of Orthopaedics, Skåne University Hospital, Malmö, Sweden

[55] Robert and Arlene Kogod Center On Aging and Division of Endocrinology, Mayo Clinic College of Medicine, Mayo Clinic, Rochester, MN, USA

[56] Marcus Institute for Aging Research, Hebrew Senior Life, Boston, MA, USA

[57] Healthy Longevity Translational Research Programme, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore

[58] Singapore Institute for Clinical Sciences, Agency for Science Technology and Research (A*STAR), Singapore, Singapore

[59] Department of Internal Medicine, Erasmus University Medical Center, Rotterdam, The Netherlands

[60] Department of Radiology and Nuclear Medicine, Erasmus University Medical Center, Rotterdam, The Netherlands

[61] IMPACT (Institute for Mental and Physical Health and Clinical Translation), Deakin University, Geelong, VIC, Australia

[62] Barwon Health, Geelong, VIC, Australia

[63] Department of Medicine-Western Health, The University of Melbourne, St Albans, VIC, Australia

[64] Department of Orthopedics and Traumatology, Kuopio University Hospital, Kuopio, Finland

[65] Kuopio Musculoskeletal Research Unit, University of Eastern Finland, Kuopio, Finland

[66] Department of Medicine and Therapeutics, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong, Hong Kong

[67] Jockey Club Centre for Osteoporosis Care and Control, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong, Hong Kong

[68] Centre of Bone Diseases, Lausanne University Hospital, Lausanne, Switzerland

[69] Service of Internal Medicine, Lausanne University Hospital, Lausanne, Switzerland

[70] HUNT Research Centre, Department of Public Health and Nursing, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology, Trondheim, Norway

[71] Endocrinology and Metabolism Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran

[72] Department of Osteoporosis, Bern University Hospital, University of Bern, Bern, Switzerland

[73] Geriatric Medicine, Department of Internal Medicine and Clinical Nutrition, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

[74] Geriatric Medicine, Sahlgrenska University Hospital Mölndal, Mölndal, Sweden

[75] School of Biomedical Engineering, University of Technology Sydney, Sydney, Australia

[76] School of Population Health, UNSW Medicine, UNSW Sydney, Kensington, Australia

[77] School of Sport Sciences, UiT The Arctic University of Norway, Tromsø, Norway

[78] Department of Health Sciences, Swedish Winter Sports Research Centre, Mid Sweden University, Östersund, Sweden

[79] Department of Medical Sciences, Uppsala University, Uppsala, Sweden

[80] Department of Public Health and Caring Sciences, Uppsala University, Uppsala, Sweden

[81] National Institute for Health Research Manchester Biomedical Research Centre, Manchester University NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK

[82] Centre for Epidemiology Versus Arthritis, University of Manchester, Manchester, UK

[83] Department of Internal Medicine, Division of Endocrinology and Diabetology, Medical University Graz, Graz, Austria

[84] Center for Biomarker Research in Medicine, Graz, Austria

[85] Department of Drug Treatment, Sahlgrenska University Hospital, Region Västra Götaland, Gothenburg, Sweden

[86] Department of Medicine, Oregon Health and Science University, Portland, OR, USA

[87] Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Australia

[88] Université Claude Bernard Lyon 1, U INSERM 1290 RESHAPE, Lyon, France

[89] Laboratory of Epidemiology and Population Sciences, National Institute On Aging, Baltimore, MD, USA

[90] Janus Rehabilitation, Reykjavik, Iceland

[91] Translational Gerontology Branch, National Institute On Aging Intramural Research Program, Baltimore, MD, USA

[92] Department of General Practice, Amsterdam UMC, Location VUmc, Amsterdam Public Health Research Institute, Amsterdam, The Netherlands

[93] PHARMO Institute for Drug Outcomes Research, Utrecht, The Netherlands

[94] Department of Hygiene and Public Health, Faculty of Medicine, Educational Foundation of Osaka Medical and Pharmaceutical University, Osaka, Japan

[95] York Trials Unit, Department of Health Sciences, University of York, York, UK

[96] Centre for Health Informatics, Faculty of Biology, Medicine and Health, School of Health Sciences, University of Manchester, Manchester, UK

[97] Statistics Support Unit, Hospital del Mar Medical Research Institute, CIBER Epidemiology and Public Health (CIBERESP), Barcelona, Spain

[98] MRC Epidemiology Unit, University of Cambridge, Cambridge, UK

[99] Department of Epidemiology, University of Alabama at Birmingham, Birmingham, AL, USA

[100] Department of Preventive Medicine for Locomotive Organ Disorders, The University of Tokyo Hospital, Tokyo, Japan

[101] Health Center Can Gibert del Plà, Catalan Institute of Health, Girona, Spain

[102] Department of Medical Sciences, University of Girona, Girona, Spain

[103] GROIMAP/GROICAP (Research Groups), Unitat de Suport a La Recerca Girona, Institut Universitari d'Investigació en Atenció Primària Jordi Gol, Girona, Spain

[104] Region Västra Götaland, Geriatric Medicine, Sahlgrenska University Hospital, Mölndal, Sweden

[105] Department of Medicine, University of Manitoba, Winnipeg, MB, Canada