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ORIGINAL ARTICLE

Family history of fracture and fracture risk: a meta-analysis to update the FRAX® risk assessment tool

Eugene V. McCloskey · Helena Johansson · Enwu Liu · Kristina E. Åkesson · Fred A. Anderson · Rafael Azagra-Ledesma, et al. ***[full author details at the end of the article]***

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Abstract

Summary In the largest meta-analysis of international cohorts to date, a family history of fracture is confirmed as a significant BMD-independent predictor of future fracture risk. Parental and sibling histories of fracture carry the same significance for future fracture, including the impact of family hip fracture on future hip fracture risk.

Purpose We have undertaken a meta-analysis of international prospective cohorts to quantify the relationship between a family history of fracture and future fracture incidence.

Methods The analysis dataset comprised 350,542 men and women from 42 cohorts in 29 countries followed for 2.8 million person-years. We investigated the relationship between family history of hip fracture or any fracture and the risk of any clinical fracture, any osteoporotic fracture, major osteoporotic fracture (MOF), and hip fracture alone using an extended Poisson model in each cohort. Models were adjusted for current age, sex, BMD, and follow-up time.

Results As no difference in influence of family history of fracture was seen between genders, results are presented for men and women combined. A parental history of hip fracture was associated with a higher risk of incident fracture across all fracture outcome categories, with a stronger relationship with future hip fracture (hazard ratios (HR, 95% CI) for hip and MOF 1.37, 1.23–1.52 and 1.19, 1.12–1.27, respectively). Associations were slightly reduced but remained significant when additionally adjusted for BMD and did not vary by baseline offspring age, follow-up time, or parent affected. In a more limited analysis, parental history of any fracture or a sibling history of hip or any fracture showed similar associations to those observed with parental history of hip fracture.

Conclusions A family history of fracture is confirmed as a significant BMD-independent predictor of future fracture risk. While parental hip fracture appears the strongest factor for future hip fracture, a family history of other fractures might be appropriate for inclusion in future iterations of the FRAX tool.

Keywords Family history · FRAX · Hip fracture · Meta-analysis · Osteoporotic fractureF · Parental history

Introduction

The role of a family history of fracture in informing an individual's risk of future fracture is well established from multiple cross-sectional and prospective studies [1–10]. Most studies have been based on a self-reported history of parental fracture, but at least one study has shown good concordance with self-reported and documented parental hip fracture [11]. Estimates suggest that the heritability of fracture risk is of the order of 30%, but the mechanisms conveying this hereditary component remain unclear. In a recent GWAS meta-analysis for fracture, 15 genetic determinants were identified, all of which also influenced bone mineral density (BMD) [12] with the latter showing heritability of 50–80% [12, 13]. Nonetheless, other heritable or shared environmental factors are important, as family history remains a predictor following adjustment for BMD. Other heritable factors might include bone size, shape, architecture, matrix properties, bone turnover, and height [14]. Indeed, the heritability of height is comparable to, or greater than, that of BMD [15].

Irrespective of the mechanism, the fact that the risk of fractures is greater in individuals with a family history of fractures than in those with the same level of BMD but no family history was confirmed in a meta-analysis of international cohorts in the development of the FRAX® fracture risk assessment tool [16]. The meta-analysis comprised data from 34,928 men and women drawn from seven prospective population studies followed for a total of 134,000 person-years. The magnitude of the association was greatest for a parental history of hip fracture and appeared of similar magnitude in women and men, though the number of outcome fractures in men was relatively limited [16]. The analysis resulted in a parental history of hip fracture being included as an input variable within FRAX when launched in 2008. Since then, many more prospectively studied cohorts have become available that have the potential to improve the accuracy of FRAX [17]. Using an expanded FRAX cohort collection, the aim of the present study was to quantify the risk for future fracture associated with a family history of fracture, particularly parental hip fracture, in an international setting and to explore the dependence of this risk on age, sex, time since baseline assessment, and BMD.

Methods

The analysis dataset comprised up to 42 cohorts from 29 countries, with data on women provided within 36 cohorts and on men within 20 cohorts. Details of the cohorts studied have been given previously [17] and are summarized in Table 1. The review identifying these cohorts was registered with the International Prospective Register of Systematic Reviews, PROSPERO (CRD42021227266), and followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Baseline family history of fracture

A parental history of hip fracture was captured by questionnaire. Of the 42 cohorts, 36 (85.7%) had captured a history of hip fracture in both parents, while the remaining studies had only recorded a maternal history of hip fracture (Table 1). A smaller number of studies had recorded data on parental history of any fracture, and an even smaller number had reported a history of hip or any fracture in siblings (details provided below).

Outcome fractures

Incident fractures were classified as all clinical fractures ("any fracture") with further sub-categories used including fractures considered to be associated with osteoporosis ("osteoporotic fractures"—excluded fractures of the skull, face, hands, feet, ankle, and patella in both genders as well as tibial and fibular fractures in men) [18]. Hip fracture and major osteoporotic fracture (MOF—distal forearm, proximal humerus, hip, and vertebral) were also analyzed. No distinction was made according to trauma since both high- and low-trauma fractures show similar relationships with low BMD and future fracture risk [19–22].

Statistical methods

The primary analysis focused on the relationship between parental hip fracture history and fracture risk. 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]. In this approach, each observation period was divided into short consecutive intervals and evaluated to generate a complete continuous hazard model as opposed to the commonly used Cox proportional hazards model. Complete continuous hazard functions can incorporate virtually any covariate or interaction, including time, and can be applied to an arbitrary population to compute the expected outcome in that population. Because of an embargo on data transfer, Cox regression was used on the Manitoba cohort. Covariates included current time since start of follow up, current age, parental history of hip 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 [17, 25, 26]. Differences in risk with and without BMD were additionally explored in those cohorts that contributed information on family history and BMD. Further models included the interaction term "parental hip fracture sex" or "parental hip fracture current time since baseline" to determine whether the strength of the association of parental hip fracture and fracture risk differed with sex or time. An additional model included the interaction term "parental hip fracture current age" to determine whether the strength of the association of parental hip fracture and fracture risk changed with age. The hazard ratio (HR) for parental hip fracture was determined for each cohort from the Poisson model, without a time interaction; inverse-variance weighted β-coefficients were used to merge the cohort-specific, gender-specific results and determine the weighted means and standard deviations. The HR of those with a prior parental hip fracture history versus those without such a history was equal to $e^{\text{weighted mean of }\beta}$. Heterogeneity between cohorts was tested on the major co-variate (a parental history of hip fracture) by the I^2 statistic [27]. There was moderate heterogeneity in risk between cohorts (index of heterogeneity I^2 = 0–50% depending on fracture outcome), and a random effects model was used in the meta-analysis. Secondary analyses, using the same analytic approach, were undertaken to examine the relationship between fracture risk and parental history of any fracture as well as sibling history of hip or any fracture.

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 using a method and assumptions that have been previously published [28–30].

Table 1 Characteristics of the cohorts studied

Cohort	*n*	Person-years	Age (years)		Female (%)	Parental history of hip fracture (%)	Parent captured (Mo/Fa)	Incident fractures (*n*)				
			Mean	Range				Hip	Any	MOF	MOF minus hip	Osteoporotic
AGES	5706	45,508	77	66–98	58	6.8	Mo+Fa	535	1619	1134	766	1395
APOSS	1804	14,996	47.7	44–51	100	7.2	Mo+Fa	2	143	65	65	76
BEH	2217	9840	69.2	61–96	51	12.5	Mo+Fa	35	93	41	5	71
Bern	23,104	181,352	58.9	20–95	85	7.4	Mo+Fa	294	5033	2913	2730	3891
DO-HEALTH	2136	5905	75	70–95	62	10.7	Mo+Fa	10	264	119	112	190
ECOSAP	5146	16,857	72.3	65–100	100	4.1	Mo	52	311	188	136	259
EPIDOS	7595	21,192	80.5	70–100	100	9.0	Mo+Fa	226	1026	568	376	837
EPIFROS	284	2826	61.6	40–96	55	8.1	Mo+Fa	3	27	16	13	20
EVOS/EPOS	12,554	38,517	63.7	41–91	52	8.6	Mo+Fa	40	508	266	228	508
FORMEN	1884	16,252	72.5	65–93	0	6.1	Mo+Fa	10	89	57	48	89
FRIDEX	815	8077	56.8	40–84	100	14.0	Mo+Fa	15	112	41	28	56
FROCAT	1952	19,394	69.2	32–111	56	11.1	Mo+Fa	33	229	160	135	183
GERICO	762	2757	67.9	65–72	79	14.3	Mo+Fa	2	71	26	24	51
GLOW	54,258	216,703	68.2	55–108	100	15.5	Mo+Fa	490	5690	2848	2437	4285
GOS	1405	9732	62.5	35–95	100	8.8	Mo+Fa	24	134	88	68	115
Gothenburg_II	2597	31,528	58.4	49–73	100	13.6	Mo	43	294	183	163	210
HCS	632	5595	64.9	59–71	50	3.3	Mo+Fa	3	67	35	33	51
JPOS	1944	25,812	57.5	40–82	100	4.3	Mo+Fa	29	265	99	-	-
Manitoba	56,575	351,401	64.3	20–104	87	10.6	Mo+Fa	1269	5783	4060	3027	5374
MINOS	681	6152	65.2	50–86	0	15.6	Mo+Fa	3	63	25	22	56
MrOS Hong Kong	1669	16,474	72.4	65–91	0	5.0	Mo+Fa	53	187	122	77	162
MrOS USA	4557	57,586	73.5	64–99	0	16.7	Mo+Fa	242	1031	595	352	787
MrOS Sweden	1913	22,065	74.9	69–81	0	13.4	Mo+Fa	221	614	463	301	548
MsOS Hong Kong	1635	14,383	72.4	65–98	100	5.3	Mo+Fa	54	273	206	161	242
OFELY	867	15,136	58.8	40–89	100	11.8	Mo+Fa	40	245	180	159	207
OPRA	1044	12,133	75.2	75–76	100	0.5	Mo	195	524	453	-	473
OPUS	1942	11,912	62	20–80	100	9.6	Mo+Fa	12	231	108	98	143
OsteoLaus	1468	6691	64.5	50–82	100	10.8	Mo+Fa	8	304	225	220	242
OSTPRE	10,048	98,284	57.3	52–63	100	9.2	Mo+Fa	67	1638	811	753	1117
Rochester	1000	7685	56.8	21–94	65	32.5	Mo+Fa	37	326	243	229	283
Rotterdam	8531	114,069	69	55–106	60	9.9	Mo+Fa	694	2452	1808	1323	2201
SAOL_IPR_EPIPorto	929	11,284	55.9	40–89	77	11.6	Mo+Fa	12	105	41	18	-
SarcoPhAge	228	440	75.9	68–93	57	14.9	Mo+Fa	1	13	5	4	8
SCOOP	11,564	55,080	75.5	70–86	100	10.0	Mo+Fa	337	1791	1192	915	1509
SEMOF	6873	19,930	75.2	70–91	100	9.7	Mo	76	665	451	375	580

Table 1 (continued)

Cohort	*n*	Person-years	Age (years)		Female (%)	Parental history of hip fracture (%)	Parent captured (Mo/Fa)	Incident fractures (*n*)				
			Mean	Range				Hip	Any	MOF	MOF minus hip	Osteoporotic
Sheffield	1698	6228	79.7	74–96	100	4.9	Mo	44	219	141	106	176
SOF	5935	84,383	71.6	65–89	100	19.3	Mo + Fa	885	2675	1752	1155	2152
SOS	16,624	62,111	74.2	61–93	100	16.9	Mo + Fa	260	1383	992	702	1324
STRAMBO	811	7503	72	51–88	0	16.8	Mo + Fa	17	115	42	26	85
SUPERB	2979	23,067	77.8	75–81	100	17.5	Mo + Fa	234	1060	789	637	1020
WHI	79,682	1,096,015	64.3	49–79	100	12.6	Mo + Fa	2328	6703	4578	2474	5253
York	4494	8968	77.1	48–99	100	8.0	Mo	42	387	220	186	306
Total	350,542	2,781,823						8977	44,762	28,349	20,687	36,535
Mean			66.9		89.1	11.7						

MOF, major osteoporotic fracture; *Mo*, mother; *Fa*, father; *AGES*, Age, Gene/Environment Susceptibility-Reykjavik Study; *APOSS*, Aberdeen Prospective Osteoporosis Screening Study; *BEH*, Bushehr Elderly Health; *DO-HEALTH*, VitaminD3-Omega3-Home Exercise-Healthy Aging and Longevity Trial; *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; *HCS*, Hertfordshire Cohort Study; *Health ABC*, Health, Aging, and Body Composition; *JPOS*, Japanese Population-based Osteoporosis Study; *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; *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

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. We additionally excluded BMD from the model, and in a separate model included height as another potentially inherited trait. Assessment of the effects of race and ethnicity was confined to those cohorts recording more than one self-reported race or ethnic group (Asian, Black, Hispanic, White), comprising WHI, SOF, MrOS USA, and Manitoba. Results were also computed according to study quality as previously defined [17]. In brief, each cohort was assessed for quality based on a 0/1 score for four criteria: population-based cohort—yes scores 1, other scores 0; fracture ascertainment—self-report scores 0, others score 1; duration of follow-up—>2 years scores 1, else scores 0; and average loss to follow-up/year—less than 10% scores 1, others score 0. With a possible range of scores from 0 to 4, poor quality was classified as a score of 0-1, intermediate quality as 2-3, and high quality as 4.

Results

The mean age of the total analysis population was 66.9 years (range 20–111 years), comprising 312,366 women and 38,176 men in 42 cohorts (Table 1). The total follow-up was 2.78 million person-years. Overall, a parental history of hip fracture was present in 11.7% of the individuals, with a similar overall prevalence in men and women (9.6% and 12.0%, respectively). Baseline BMD measurements were available in 164,579 individuals (46.9% of the whole study population).

During follow up, 44,762 individuals (4802 men and 39,960 women) were identified as having a subsequent fracture of any kind, with 36,535 classified as incident osteoporotic fractures and 8977 characterized as hip fractures (Table 1).

Parental history of hip fracture

Risk of fracture associated with parental history of hip fracture in women and men including adjustment for BMD

The prevalence of parental history of hip fracture rose with age from the age of 40 years in both men and women and peaked in the 60–69 years age group (Supplementary Data, Table A). The HR for future fractures was very similar in men and women (Supplementary Data, Table B), and when tested in those cohorts that contributed both genders to the analysis, there was no statistical difference in the HR between men and women for all fracture outcomes (Supplementary Data, Table C). Thus, further analyses were performed in men and women combined; for additional information, some of the analyses in each sex are provided in the supplementary data.

In men and women combined, a parental history of hip fracture was associated with an increased risk of subsequent fracture regardless of the outcome fracture category (Table 2). The HRs ranged from 1.15 for any fracture to 1.37 for hip fracture and were similar whether analyzed in all the cohorts or when confined to those cohorts with measurements of BMD available (Table 2). Adjustment for BMD in the latter cohorts reduced the HRs slightly, but a parental history of hip fracture remained a significant predictor of fracture risk across all fracture outcomes. In the case of hip fracture, if it is assumed that the risk of any fracture increases 2.07-fold for each standard deviation (SD) decrease in hip BMD, then the difference in risk between those individuals with and without a parental history of hip fracture is equivalent to an expected difference in BMD of 0.35SD. However, the difference in BMD was only approximately 0.12SD demonstrating that lower BMD accounted for only a minority (35.0%) of the difference in risk of hip fracture.

In those cohorts where it was possible to identify whether the parental history of hip fracture was in the mother (21 cohorts comprising 203,705 individuals) and/or the father (16 cohorts comprising 18,281 individuals), the

Table 2 Hazard ratio (HR) and 95% confidence interval (CI) of fracture at the sites indicated associated with a history of parental hip fracture in women and men combined

Outcome fracture	All cohorts[a]			Cohorts with BMD[a]			Cohorts with BMD[b]		
	Cohorts (*N*)	I^2	HR (95% CI)	Cohorts (*N*)	I^2	HR (95% CI)	Cohorts (*N*)	I^2	HR (95% CI)
Any	41	52	1.15 (1.09–1.21)	36	52	1.12 (1.05, 1.20)	36	41	1.08 (1.02, 1.15)
Hip	33	47	1.37 (1.23–1.52)	28	47	1.29 (1.11, 1.49)	28	46	1.18 (1.03, 1.37)
MOF	40	47	1.19 (1.12–1.27)	36	46	1.17 (1.08, 1.27)	36	34	1.11 (1.04, 1.20)
Osteoporotic	38	49	1.16 (1.10–1.23)	34	41	1.13 (1.05, 1.20)	34	29	1.07 (1.01, 1.14)

[a]HRs are adjusted for sex, age, and time since baseline

[b]HRs are adjusted for sex, age, time since baseline, and BMD

MOF, major osteoporotic fractures

prevalence of paternal hip fracture was substantially lower than that of maternal hip fracture (2.7% vs 10.7%, respectively, $p < 0.001$). Nonetheless, the risk of future fracture related to a parental history of hip fracture was similar if the fracture had occurred in the mother or father (Table 3).

Despite the moderate heterogeneity observed across the studies, the increase in fracture risk amongst those who reported a parental history of hip fracture was reasonably consistent as shown in the Forest plots in Fig. 1 for hip and MOF fracture outcomes in women and men combined.

Table 3 Hazard ratio (HR) and 95% confidence interval (CI) of fracture at the sites indicated associated with a history of parental hip fracture in the mother or father in women and men combined. HRs are adjusted for sex, age, and time since baseline

Outcome fracture	Parent with hip fracture	
	Mother	Father
	HR (95% CI) (*n*)	HR (95% CI) (*n*)
Any	1.19 (1.13–1.26) (21)	1.20 (1.11–1.29) (15)
Hip	1.47 (1.29–1.67) (20)	1.54 (1.22–1.94) (10)
MOF	1.26 (1.16–1.37) (21)	1.25 (1.13–1.38) (15)
Osteoporotic	1.20 (1.12–1.29) (20)	1.24 (1.14–1.35) (14)

MOF, major osteoporotic fractures; *n*, number of cohorts included in analysis

Interaction with age and time since baseline

A parental history of hip fracture was a significant risk factor for fracture at all ages, with no significant interaction with age for any of the fracture outcomes in women, men, or both genders combined. The relationship between the HR for MOF and age is shown in Fig. 2A for women and men combined. The HR at age 40 years was 1.21 and that at 90 years was 1.08, with a p-value for the interaction of 0.53. Likewise, the fracture risk associated with a parental history of hip fracture showed no interaction with time since baseline (Fig. 2B).

Sensitivity analyses including height and race/ethnicity

Eighteen cohorts contributed data on baseline height and a parental history of hip fracture. Adjustment for height had

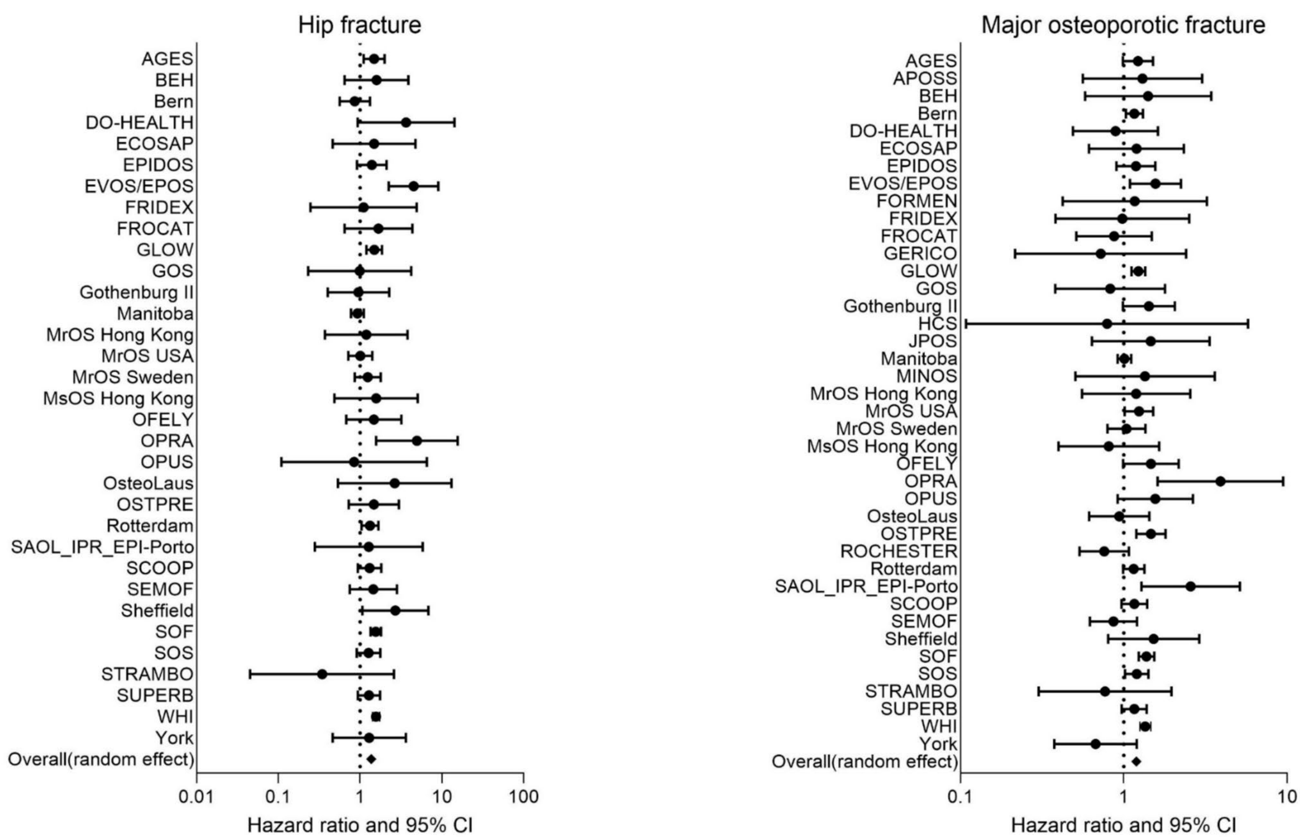

Fig. 1 Forest plot showing effect size on hip fracture risk (left panel) and MOF risk (right panel) in women and men combined associated with a parental history of hip fracture adjusted for sex, age, and time since baseline

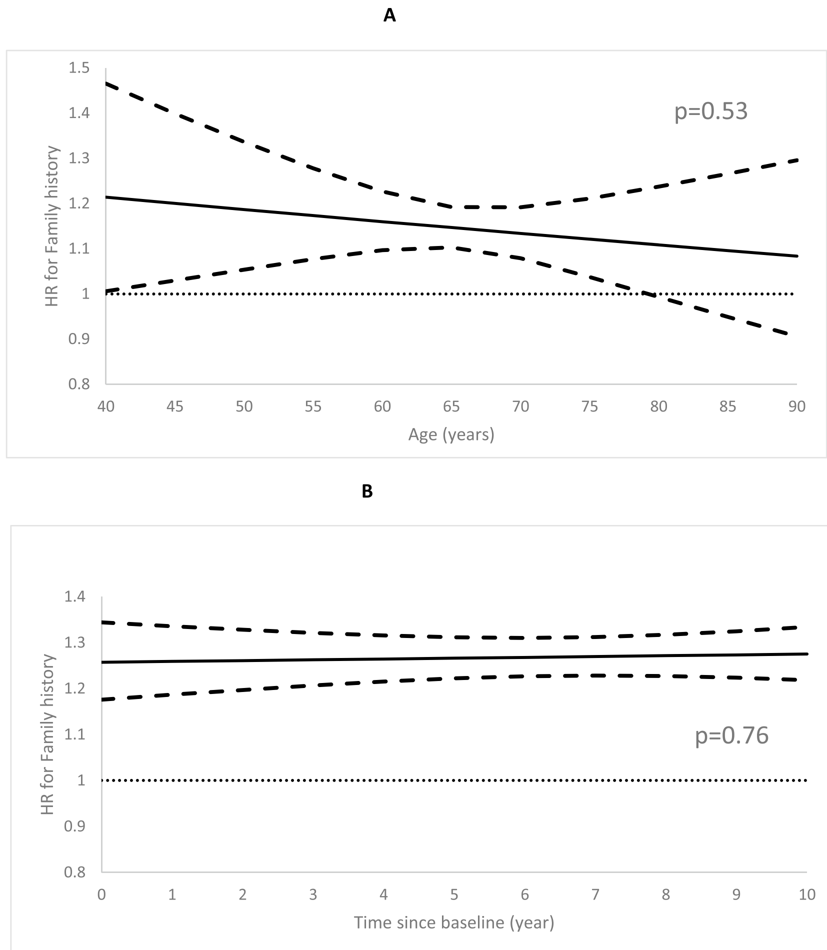

Fig. 2 Hazard ratio (HR) and 95% confidence interval (CI) of MOF fracture by age (**A**) and time since baseline (**B**) associated with a history of parental hip fracture in men and women combined. HRs are adjusted for sex, age, and time since baseline

no significant impact on the relationship between parental hip fracture and subsequent fracture risk (Supplementary Data Table D).

The ability to examine the relationship between ethnicity and parental history of hip fracture was confined to four cohorts (WHI, SOF, MrOS USA, and Manitoba). The HRs for hip and MOF outcomes, adjusted for age and time since baseline, suggest that the relationship between parental history and fracture risk is largely independent of ethnicity (Table 4).

Risk of death

A parental history of hip fracture was associated with a significant decrease in the risk of death in men and women combined (HR 0.90, 0.83–0.96, $p = 0.0032$) (Table 5) with very similar effect sizes in both genders. Hazard ratios remained unchanged when adjusted for femoral neck BMD.

Risk of fracture associated with a parental history of any fracture and sibling history of fracture

A total of 12 cohorts contained baseline data on a history of any fracture in the mother or the father or both. In a total of 131,270 men and women, 32.0% reported such a history. The risk (HR) conferred by a parental history of any fracture on future fracture risk was similar to that observed for a parental history of hip fracture across the range of fracture outcomes, other than hip fracture (HRs for any fracture, MOF, and osteoporotic fracture were 1.23, 1.22, 1.27, and 1.25, respectively; all $p > 0.28$ compared to any fracture). In contrast, the HR for the hip fracture outcome was somewhat lower for parental history of any fracture than that for a parental history of hip fracture (1.22 vs 1.38, respectively, when adjusted for age and time since baseline) (Fig. 3).

A sibling history of hip fracture was only recorded in six cohorts comprising 25,887 individuals, and a sibling history of any fracture in four cohorts with a total of 16,624 men and women. The overall prevalence of sibling hip fracture

Table 4 Hazard ratio (HR) and 95% confidence interval (CI) of fracture at the sites indicated associated with a parental history of hip fracture in men and women combined according to race/ethnicity (analysis within WHI, MrOs USA, Manitoba, and SOF cohorts). HRs are adjusted for sex, age, and time since baseline. No significant difference was observed in HRs across the ethnicities

Outcome fracture	Cohorts (*N*)	HR	95% CI	HR	95% CI	*p*-value
Asian vs White		**White**		**Asian**		
Hip	3a	1.12	0.75–1.66	1.77	0.69–4.49	0.32
MOF	3a	1.16	0.96–1.41	1.34	0.75–2.40	0.62
Black vs White		**White**		**Black**		
Hip	3a	1.12	0.76–1.65	1.31	0.59–2.95	0.68
MOF	3a	1.16	0.96–1.41	0.96	0.51–1.80	0.54
Hispanic vs White		**White**		**Hispanic**		
Hip	1b	1.51	1.36–1.68	1.23	0.43–3.53	0.71
MOF	1b	1.30	1.20–1.40	1.66	0.99–2.79	0.36
Other than White vs White		**White**		**Other than White**		
Hip	4c	1.23	0.95–1.60	1.39	0.85–2.26	0.61
MOF	4c	1.22	1.04–1.42	1.35	0.99–1.83	0.50

Table 5 Hazard ratio (HR) and 95% confidence interval (CI) of death associated with a parental history of hip fracture in men and women combined. HRs are adjusted for sex, age, and time since baseline. Where possible to examine, no significant difference was observed in HRs across ethnicities

Outcome	Adjusted for age and time since baseline		Adjusted for age and time since baseline—for those with BMD		Adjusted for age, time since baseline and BMD	
	Cohorts (*N*)	HR (95% CI)	Cohorts (*N*)	HR (95% CI)	Cohorts (*N*)	HR (95% CI)
Death	27	0.90 (0.83–0.96) $\boldsymbol{p}=0.0032$	25	0.86 (0.80–0.92) $p<0.001$	25	0.86 (0.80–0.92) $p<0.001$

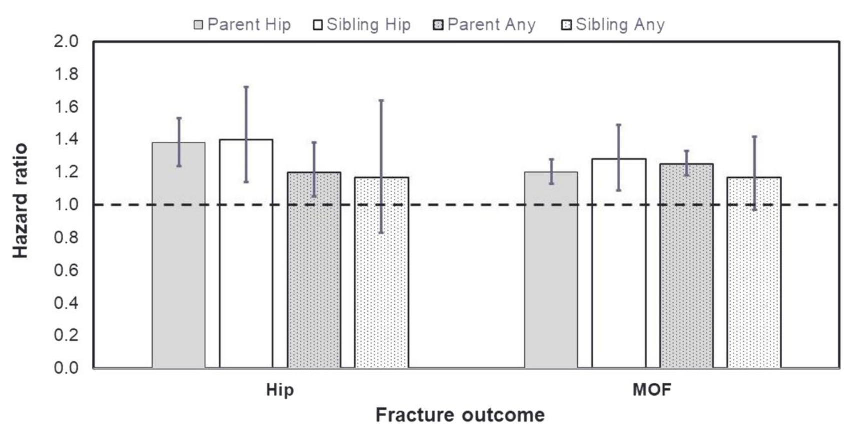

Fig. 3 Hazard ratio (HR) and 95% confidence interval (CI) of hip and MOF fracture outcomes associated with a family history of fractures in men and women combined. The hazard ratios were similar for parental and sibling histories. HRs are adjusted for age and time since baseline

was 3.5% and that of any fracture was 24.2%. Both were also associated with an increase in future fracture risk, similar to that of a history of comparable fracture in a parent (Fig. 3).

Quality scores

While the HRs were slightly higher in moderate quality studies than in those judged to be high quality, there was no statistically significant difference in fracture outcome HRs when cohorts of high quality were compared with those of moderate quality and a single low quality study (Supplementary Data Table E).

Discussion

The present study, undertaken using primary data from a large number of international population-based cohorts, confirms that a family history of fracture confers an increase in fracture risk as shown in a previous meta-analysis [16]. Since that publication, several other individual cohort studies have confirmed the association [6, 9, 10]. As seen in the previous meta-analysis, a parental history of hip fracture is a stronger predictor of future hip fracture risk than parental fractures at other sites but also predicts other fracture outcomes [16]. Notably, this predictive performance is now observed to be similar in the presence of a sibling history of hip fracture. In addition, both a parental and sibling history of any fracture show similar relationships with future fracture risk, though the performance for hip fracture risk is somewhat weaker than that for a parental or sibling history of hip fracture. Additionally, the associations are similar in men and women, and the parental history is of equivalent performance regardless of whether the history of fracture is maternal or paternal. Importantly, the associations are independent of age, duration of follow-up, and, as demonstrated previously, are largely independent of BMD. Some of these results differ from those derived in the previous smaller meta-analysis, and these are discussed in more detail below.

A major difference in the present analysis from our previous meta-analysis [16] is the observation that a family history of fracture (hip or any) has very similar effects on fracture risk in men and women. In the earlier analysis, probably due to a relatively small sample size of men, a paternal history of any fracture was a significant risk factor for hip fracture in women (RR = 2.04), but not in men (RR = 0.99). The earlier analysis also showed that a maternal history of fracture was also apparently a stronger risk factor for hip fracture amongst men (RR = 2.18) than amongst women (RR = 1.29). The current analysis clearly shows that the impact of parental history of fracture is the same in men and women and is the same regardless of whether the fracture had occurred in the mother or father. Given that the relationships reflect a genetic component of risk, predominantly related to small effects of multiple autosomal genes, one might expect a similar impact from maternal or paternal fracture as the offspring inherits approximately half of their genome from each. In addition, siblings on average share half of their genes with each other [31], so that a similar genetic relationship in siblings and parents is not unexpected.

The hazard ratios reported here for family history of hip fracture on the outcomes of hip and osteoporotic fractures are somewhat lower than those from the previous meta-analysis. For example, parental history of hip fracture previously had a hazard ratio of 1.75 (95% CI 1.17–2.63) for offspring hip fracture [16], compared to 1.37 (1.23–1.52) in the present analysis. The respective ratios for the outcome of osteoporotic fracture are 1.38 (1.16–1.65) and 1.16 (1.10–1.23). The increased sample size has improved the certainty of the estimates with substantially narrower confidence limits, but it should be noted that the new point estimates for the hazard ratios still lie within the confidence limits from the earlier analysis. Furthermore, the hazard ratio reported here for subsequent MOF associated with parental hip fracture (1.19, 1.12–1.27) is similar to that observed in two analyses from a single cohort using electronic record linkage to examine the relationship between parental hip fracture risk and subsequent MOF fracture risk (HRs 1.26 and 1.30, respectively) [9, 10].

It is worth noting the additional new information about the interaction, or more correctly the lack of interaction, between age and a family history of fracture for subsequent fracture risk. One could speculate that an age interaction might be expected; for example, fewer parental hip fractures are likely to be observed for younger offspring as their parents may also not be that old and have not yet sustained a fracture. However, in those younger offspring with a parental history of hip fracture, the latter may also have occurred at a relatively young age and relate more to heritable factors. In the earlier meta-analysis, the HR for osteoporotic and/or hip fractures showed a decrease with age, an effect that was observed for both a parental history of any fracture and was particularly marked for parental hip fracture [16]. For example, for the latter risk factor and an outcome of hip fracture, the HR decreased from 2.34 at the age of 40 years to 1.33 at the age of 85 years. However, the confidence intervals were wide and the *p*-values for age interaction did not reach statistical significance [16]. In this updated analysis, the decrease in HR with age is much more subtle and, in the presence of a much greater sample size, shows no interaction with age. Again, this analysis does not contain information about the age of parents at the time of hip fracture; recent analysis from a single large cohort suggests that the increase in risk is significantly lower at older age of hip fracture in the parents [10]. Both the earlier and present meta-analyses also confirm no interaction between a family history of hip fracture and time of follow-up.

As FRAX probabilities are derived using age-specific incidences of fracture and mortality, this analysis also examined the relationship between a family history of fracture and mortality. Perhaps surprisingly, it shows that a parental history of hip fracture is associated with an approximate 10% lower mortality risk, an effect that persists following adjustment for age, time since baseline, and BMD. In the absence of information about the age of death in the parents, it could be speculated that the occurrence of hip fracture provides a surrogate measure of longevity in the parent (those living into older age being at increased risk of hip fracture). While lifespan has a relatively low heritability (25% or less), longevity (survival to extreme ages, e.g., top 10% of long-term survivors) clusters strongly within families [32].

The study has a number of strengths and limitations. The family history is based on self-reported data and may be open to recall bias. However, studies have reported that the validity of self-reported fractures, particularly non-vertebral fractures, is generally good [33, 34], and a single well-conducted study has also confirmed good agreement between offspring reports and diagnosis of parental hip fracture using hospitalization data in Manitoba (kappa = 0.68, sensitivity 70%, specificity 96%) [11]. As a further strength, the estimates of risk are derived in an international setting largely from population-based cohorts, and the calculations, based on primary data, decrease the risk of publication bias. Additionally, non-response biases, for example from frail individuals, which might result in an underestimate of the probability associated with a family history of fracture, are unlikely to affect risk ratios. The construct of the question(s) to capture family history differed somewhat between cohorts, especially on the breadth of family history, particularly of sibling history. Nonetheless, there is good evidence for a degree of homogeneity across the cohorts and family histories that are consistent with genetic and/or shared environmental effects. The study suggests that family history is also an important risk factor across ethnicities, though this conclusion is somewhat limited by the relatively small non-white populations included. Importantly, the use of a family history as a risk factor to identify patients also appears to identify a risk that is amenable to treatment with bone-active medications. For example, there was no difference in treatment efficacy according to family history of fracture or osteoporosis in studies of raloxifene or strontium ranelate [35, 36]. More recently, in the SCOOP study of screening for high hip fracture risk in the UK, family history of fracture was a major driver of identifying a high-risk subgroup for subsequent treatment [37]. Treatment was associated with a 28% overall reduction in hip fracture incidence in the screening arm, with an approximate 45% reduction in hip fracture risk in those at highest risk and receiving treatment, of whom 39% had a history of parental hip fracture [37, 38].

The mechanism for the BMD-independent increase in risk, including skeletal factors such as bone size, shape, and microarchitecture [39], remains elusive and could not be addressed in our analysis. As previously, we have determined that height, a relatively highly genetic component, did not affect the relationship between family history and fracture outcome [16] despite a strong genetic component to height [40]. That family history is independent of other risk factors used in FRAX, in addition to age, sex, and BMD, will also need to be examined in further analyses before a final update of the FRAX tool.

In summary, this updated and much enlarged meta-analysis has quantified the magnitude of the risk for future fractures conferred by a family history of hip or any fracture. A family history of hip fracture remains the strongest family-based predictor of future hip fracture, and this is true if the hip fracture occurs in either parent or a sibling. Nonetheless, a family history of any fracture is also a significant contributor to future fracture risk, and the effect is similar in men and women. As shown previously, and irrespective of the mechanism, these data indicate that the risk of hip or all osteoporotic fractures is greater in men and women with a family history of fractures than in individuals with the same level of BMD but with no family history. The consistency of the association between family history and fracture risk in an international setting provides the rationale for the continuing use of family history of fracture in the next iteration of FRAX.

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Declarations

Ethical approval and consent to participate 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 all cohorts is also given by the University of Sheffield. This study does not contain any original studies with human participants or animals performed by any of the authors. Participant data are stored in coded, de-identified form. Only summary statistics and aggregate data are published, not allowing for the identification of individual study participants.

Conflict 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 Osteoporosis Research Ltd., which 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 of the National Osteoporosis Guideline Group. He is a director of Osteoporosis Research Ltd., which maintains FRAX.

KE Akesson has no financial interest related to FRAX and chaired the National SALAR Group for Person-Centered Care Pathway Osteoporosis.
FA Anderson led the team that developed GLOW while being the director of the Center for Outcomes Research at the University of Massachusetts Medical School; he has no financial interest in FRAX.
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Authors and Affiliations

Eugene V. McCloskey[1,2] · Helena Johansson[1] · Enwu Liu[3] · Kristina E. Åkesson[4,5] · Fred A. Anderson[6] · Rafael Azagra-Ledesma[7,8,9,10] · Cecilie L. Bager[11] · Charlotte Beaudart[14] · Heike A. Bischoff-Ferrari[77,78] · Emmanuel Biver[15] · Olivier Bruyère[16] · Jane A. Cauley[17] · Jacqueline R. Center[18,19] · Roland Chapurlat[20] · Claus Christiansen[11] · Cyrus Cooper[21,22,23] · Carolyn J. Crandall[24] · Steven R. Cummings[25] · José A. P. da Silva[26,27] · Bess Dawson-Hughes[28] · Adolfo Diez-Perez[29] · Alyssa B. Dufour[30,31] · John A. Eisman[19,32,33] · Petra J. M. Elders[34] · Serge Ferrari[15] · Yuki Fujita[35] · Saeko Fujiwara[36] · Claus-Christian Glüer[37] · Inbal Goldshtein[38,39] · David Goltzman[40] · Vilmundur Gudnason[41,42] · Jill Hall[43] · Didier Hans[44] · Mari Hoff[45,46] · Rosemary J. Hollick[47] · Martijn Huisman[48,49] · Masayuki Iki[50] · Sophia Ish-Shalom[51] · Graeme Jones[52] · Magnus K. Karlsson[4,53] · Sundeep Khosla[54] · Douglas P. Kiel[30,31] · Woon-Puay Koh[55,56] · Fjorda Koromani[57,58] · Mark A. Kotowicz[59,60,61] · Heikki Kröger[62,63] · Timothy Kwok[64,65] · Olivier Lamy[66,67] · Arnulf Langhammer[68,69] · Bagher Larijani[70] · Kurt Lippuner[71] · Dan Mellström[72,73] · Fiona E. A. McGuigan[4] · Thomas Merlijn[34] · Tuan V. Nguyen[74,75,76] · Anna Nordström[12,13] · Peter Nordström[79] · Terence W. O´Neill[98] · Barbara Obermayer-Pietsch[81] · Claes Ohlsson[82,83] · Eric S. Orwoll[84] · Julie A. Pasco[59,60,61,85] · Fernando Rivadeneira[57] · Berit Schei[106,107] · Anne-Marie Schott[86] · Eric J. Shiroma[87] · Kristin Siggeirsdottir[41,88] · Eleanor M. Simonsick[89] · Elisabeth Sornay-Rendu[90] · Reijo Sund[63] · Karin M. A. Swart[91,92] · Pawel Szulc[90] · Junko Tamaki[93] · David J. Torgerson[94] · Natasja M. van Schoor[48] · Tjeerd P. van Staa[95] · Joan Vila[80] · Nicholas J. Wareham[97] · Nicole C. Wright[96] · Noriko Yoshimura[99] · M. Carola Zillikens[57] · Marta Zwart[100,101,102] · Marian Schini[2] · Liesbeth Vandenput[82] · Nicholas C. Harvey[21,22] · Mattias Lorentzon[103,104] · William D. Leslie[105] · John A. Kanis[1]

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

Helena Johansson
helena@statiq.se

Enwu Liu
enwu.liu@flinders.edu.au

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

Fred A. Anderson
fred.anderson@umassmed.edu

Rafael Azagra-Ledesma
rafael.azagra@uab.cat

Cecilie L. Bager
cba@nordicbio.com

Charlotte Beaudart
charlotte.beaudart@unamur.be

Heike A. Bischoff-Ferrari
HA.Bischoff-Ferrari@felixplatter.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
Ccrandal@g.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
adiezperez@hotmail.com

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
fujityuu@hirakata.kmu.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
ma.huisman@amsterdamumc.nl

Masayuki Iki
iki.mas@kmu.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@unibe.ch

Dan Mellström
dan.mellstrom@gu.se

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

Thomas Merlijn
tmerlijn@gmail.com

Tuan V. Nguyen
tuanvan.nguyen@uts.edu.au

Anna Nordström
anna.nordstrom@uu.se

Peter Nordström
peter.nordstrom@uu.se

Terence W. O´Neill
terence.oneill@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

Berit Schei
berit.schei@ntnu.no

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
joanviladomenech@gmail.com

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

Nicole C. Wright
nwright6@tulane.edu

Noriko Yoshimura
noripu2yoshi@gmail.com

M. Carola Zillikens
m.c.zillikens@erasmusmc.nl

Marta Zwart
marta.zwart@udg.edu

Marian Schini
m.schini@sheffield.ac.uk

Liesbeth Vandenput
liesbeth.vandenput@medic.gu.se

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

Mattias Lorentzon
mattias.lorentzon@medic.gu.se

William D. Leslie
bleslie@sbgh.mb.ca

John A. Kanis
w.j.pontefract@shef.ac.uk

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

[2] Centre for Integrated Research in Musculoskeletal Ageing, Mellanby Centre for Musculoskeletal Research, Division of Clinical Medicine, School of Medicine & Population Health, University of Sheffield Medical School, Sheffield, UK

[3] College of Medicine and Public Health, Flinders University, Adelaide, Australia

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

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

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

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

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

[9] 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

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

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

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

[13] School of Sport Sciences, Arctic University of Norway, Tromsø, Norway

[14] Public Health Aging Research & Epidemiology (PHARE) Group, Research Unit in Clinical Pharmacology and Toxicology (URPC), NAmur Research Institute for LIfe Sciences (NARILIS), University of Namur, Namur, Belgium

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

[16] Research Unit in Public Health, Epidemiology and Health Economics, University of Liège, Liège, Belgium

[17] Department of Epidemiology, School of Public Health, University of Pittsburgh, Pittsburgh, Philadelphia, USA

[18] Garvan Institute of Medical Research, Sydney, NSW, Australia

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

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

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

[22] NIHR Southampton Biomedical Research Centre, University of Southampton and University Hospital Southampton NHS Foundation Trust, Southampton, UK

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

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

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

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

[27] Rheumatology Department, University Hospital and University of Coimbra, Coimbra, Portugal

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

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

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

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

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

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

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

[35] Department of Hygiene and Public Health, Faculty of Medicine, Kansai Medical University, Osaka, Japan

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

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

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

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

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

[41] Icelandic Heart Association, Kopavogur, Iceland

[42] University of Iceland, Reykjavik, Iceland

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

[44] Centre of Bone Diseases, Bone and Joint Department, Lausanne University Hospital, Lausanne, Switzerland

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

[46] Department of Rheumatology, St Olavs Hospital, Trondheim, Norway

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

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

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

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

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

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

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

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

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

[56] A*STAR Institute for Human Development and Potential, Singapore, Singapore

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

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

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

[60] Barwon Health, Geelong, VIC, Australia

[61] Department of Medicine - Western Health, The University of Melbourne, St Albans, Victoria, Australia

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

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

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

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

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

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

[68] HUNT Research Centre, Department of Public Health and Nursing, NTNU, Norwegian University of Science and Technology, Levanger, Norway

[69] Levanger Hospital, Nord-Trøndelag Hospital Trust, Levanger, Norway

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

[71] Faculty of Medicine, ARTORG Center for Biomedical Engineering Research, University of Bern, Bern, Switzerland

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

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

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

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

[76] Tam Anh Research Institute, Tam Anh Hospital, Ho Chi Minh City, Vietnam

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

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

[79] Department of Public Health and Caring Sciences, Clinical Geriatrics, Uppsala University, Uppsala, Sweden

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

[81] Div. of Endocrinology and Diabetology, Dept. of Internal Medicine, Medical University Graz, Endocrine Lab Platform, Auenbruggerplatz 15, 8036 Graz, Austria

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

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

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

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

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

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

[88] Janus Rehabilitation, Reykjavik, Iceland

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

[90] UMR 1033, INSERM, University of Lyon, Hôpital Edouard Herriot, Lyon, France

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

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

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

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

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

[96] Center for Health Outcomes, Implementation, Community-Engaged Sciences, School of Medicine, Tulane University, New Orleans, LA, USA

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

[98] Caring Sciences, Clinical Geriatrics, Centre for Epidemiology Versus Arthritis, University of Manchester, Manchester, UK

[99] Department of Preventive Medicine for Locomotive Organ Disorders, 22Nd Century Medical and Research Center, The University of Tokyo, Tokyo, Japan

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

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

[102] GROICAP (Research Group), Institut Universitari d'Investigació en Atenció Primària Jordi Gol, Girona, Spain

[103] Sahlgrenska Osteoporosis Centre, Institute of Medicine, University of Gothenburg, Gothenburg, Sweden

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

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

[106] Department of Public Health and Nursing, Norwegian University of Science and Technology, Trondheim, Norway

[107] Department of Gynecology, St Olavs Hospital, Trondheim, Norway