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, Fred A Anderson, Rafael Azagra, Cecilie L Bager, Charlotte Beaudart, Heike A Bischoff-Ferrari, Emmanuel Biver, Olivier Bruyère, Jane A Cauley, Jacqueline R Center, Roland Chapurlat, Claus Christiansen, Cyrus Cooper, Carolyn J Crandall, Steven R Cummings, José AP da Silva, Bess Dawson-Hughes, Adolfo Diez-Perez , Alyssa B Dufour, John A Eisman, Petra JM Elders, Serge Ferrari, Yuki Fujita, Saeko Fujiwara, Claus-Christian Glüer, Inbal Goldshtein, David Goltzman, Vilmundur Gudnason, Jill Hall, Didier Hans, Mari Hoff, Rosemary J Hollick, Martijn Huisman, Masayuki Iki, Sophia Ish-Shalom, Graeme Jones, Magnus K Karlsson, Sundeep Khosla, Douglas P Kiel, Woon-Puay Koh, Fjorda Koromani, Mark A Kotowicz, Heikki Kröger, Timothy Kwok, Olivier Lamy, Arnulf Langhammer, Bagher Larijani, Kurt Lippuner, Fiona EA McGuigan, Dan Mellström, Thomas Merlijn, Tuan V Nguyen, Anna Nordström, Peter Nordström, Terence W O´Neill, Barbara Obermayer-Pietsch, Claes Ohlsson, Eric S Orwoll, Julie A Pasco, Fernando Rivadeneira, Anne-Marie Schott, Eric J Shiroma, Kristin Siggeirsdottir, Eleanor M Simonsick, Elisabeth Sornay-Rendu, Reijo Sund, Karin MA Swart, Pawel Szulc, Junko Tamaki, David J Torgerson, Natasja M van Schoor, Tjeerd P van Staa, Joan Vila , Nicholas J Wareham, Nicole C Wright, Noriko Yoshimura, M Carola Zillikens, Marta Zwart, Nicholas C Harvey, Mattias Lorentzon, William D Leslie, John A Kanis

Author	**Affiliation**	**Contact**
Liesbeth Vandenput	Mary McKillop Institute for Health Research, Australian Catholic University, Melbourne, Australia	liesbeth.vandenput@acu.edu.au ORCID: 0000-0002-1712-6131
Helena Johansson	Mary McKillop Institute for Health Research, Australian Catholic University, Melbourne, Australia	helena@statiq.se
	Centre for Metabolic Bone Diseases, University of Sheffield, Sheffield, UK	
	Sahlgrenska Osteoporosis Centre, Department of Internal Medicine and Clinical Nutrition, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden	
Eugene V McCloskey	Centre for Metabolic Bone Diseases, University of Sheffield, Sheffield, UK	e.v.mccloskey@sheffield.ac.uk ORCID: 0000-0003-0177-8140
	MRC and Arthritis Research UK Centre for Integrated research in Musculoskeletal	

	Ageing, Mellanby Centre for Musculoskeletal Research, University of Sheffield, UK	
Enwu Liu	Mary McKillop Institute for Health Research, Australian Catholic University, Melbourne, Australia	enwu.liu@acu.edu.au
Marian Schini	Division of Clinical Medicine, School of Medicine and Population Health, University of Sheffield, UK	m.schini@sheffield.ac.uk
Kristina E Åkesson	Clinical and Molecular Osteoporosis Research Unit, Department of Clinical Sciences, Lund University, Lund, Sweden	kristina.akesson@med.lu.se
	Department of Orthopedics, Skåne University Hospital, Malmö, Sweden	
Fred A Anderson	GLOW Coordinating Center, Center for Outcomes Research, University of Massachusetts Medical School, Worcester, MA, USA	fred.anderson@umassmed.edu
Rafael Azagra	Department of Medicine, Autonomous University of Barcelona, Barcelona, Spain	rafael.azagra@uab.cat
	Health Centre Badia del Valles, Catalan Institute of Health, Barcelona, Spain	
	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	
	PRECIOSA-Fundación para la investigación, Barberà del Vallés, Barcelona, Spain	
Cecilie L Bager	Nordic Bioscience A/S, Herlev, Denmark	cba@nordicbio.com
Charlotte Beaudart	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	c.beaudart@maastrichtuniversity.nl
	Department of Health Services Research, University of Maastricht, Maastricht, the Netherlands	

Heike A Bischoff-Ferrari	Department of Aging Medicine and Aging Research, University Hospital, Zurich, and University of Zurich, Zurich, Switzerland	heike.bischoff@usz.ch
	Centre on Aging and Mobility, University of Zurich and City Hospital, Zurich, Switzerland	
Emmanuel Biver	Division of Bone Diseases, Department of Medicine, Geneva University Hospitals and Faculty of Medicine, University of Geneva, Geneva, Switzerland	emmanuel.biver@hcuge.ch
Olivier Bruyère	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	olivier.bruyere@uliege.be
Jane A Cauley	Department of Epidemiology, School of Public Health, University of Pittsburgh, Pittsburgh, Philadelphia, United States.	jcauley@edc.pitt.edu
Jacqueline R Center	Skeletal Diseases Program, Garvan Institute of Medical Research, Sydney, NSW, Australia	j.center@garvan.org.au
	St Vincent's Clinical School, School of Medicine and Health, University of New South Wales Sydney, Sydney, NSW, Australia	
	School of Medicine Sydney, University of Notre Dame Australia, Sydney, NSW, Australia	
Roland Chapurlat	INSERM UMR 1033, Université Claude Bernard-Lyon1, Hôpital Edouard Herriot, Lyon, France	roland.chapurlat@inserm.fr
Claus Christiansen	Nordic Bioscience A/S, Herlev, Denmark	cc@nordicbio.com
Cyrus Cooper	MRC Lifecourse Epidemiology Centre, University of Southampton, Southampton, UK	cc@mrc.soton.ac.uk
	NIHR Southampton Biomedical Research Centre, University of Southampton and University Hospitals Southampton NHS Foundation Trust, Southampton, UK	

	NIHR Oxford Biomedical Research Unit, University of Oxford, Oxford, UK	
Carolyn J Crandall	Division of General Internal Medicine and Health Services Research, David Geffen School of Medicine, University of California, Los Angeles, CA, USA	ccrandall@mednet.ucla.edu
Steven R Cummings	San Francisco Coordinating Center, California Pacific Medical Center Research Institute, San Francisco, CA, USA	steven.cummings@ucsf.edu
José AP da Silva	Coimbra Institute for Clinical and Biomedical Research, Faculty of Medicine, University of Coimbra, Coimbra, Portugal	jdasilva@ci.uc.pt
	Rheumatology Department, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal	
Bess Dawson-Hughes	Bone Metabolism Laboratory, Jean Mayer US Department of Agriculture Human Nutrition Research Center on Aging, Tufts University, Boston, MA, USA	bess.dawson-hughes@tufts.edu
Adolfo Diez-Perez	Department of Internal Medicine, Hospital del Mar and CIBERFES, Autonomous University of Barcelona, Barcelona, Spain	adiez@psmar.cat
Alyssa B Dufour	Marcus Institute for Aging Research, Hebrew SeniorLife, Boston, MA, USA	alyssadufour@hsl.harvard.edu
	Department of Medicine, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA, USA	
John A Eisman	Skeletal Diseases Program, Garvan Institute of Medical Research, Sydney, NSW, Australia	j.eisman@garvan.org.au
	St Vincent's Clinical School, School of Medicine and Health, University of New South Wales Sydney, Sydney, NSW, Australia	
	School of Medicine Sydney, University of Notre Dame Australia, Sydney, NSW, Australia	
Petra JM Elders	Department of General Practice, Amsterdam UMC, location AMC,	p.elders@amsterdamumc.nl

	Amsterdam Public Health Research Institute, Amsterdam, The Netherlands	
Serge Ferrari	Division of Bone Diseases, Department of Medicine, Geneva University Hospitals and Faculty of Medicine, University of Geneva, Geneva, Switzerland	serge.ferrari@unige.ch
Yuki Fujita	Center for Medical Education and Clinical Training, Kindai University Faculty of Medicine, Osaka, Japan	yfujita@med.kindai.ac.jp
Saeko Fujiwara	Department of Pharmacy, Yasuda Women's University, Hiroshima, Japan	fujiwara-s@yasuda-u.ac.jp
Claus-Christian Glüer	Section Biomedical Imaging, Molecular Imaging North Competence Center, Department of Radiology and Neuroradiology, University Medical Center Schleswig-Holstein Kiel, Kiel University, Kiel, Germany	glueer@rad.uni-kiel.de
Inbal Goldshtein	Maccabitech Institute of Research and Innovation, Maccabi Healthcare Services, Tel Aviv, Israel	inbalbarak@gmail.com
	Department of Epidemiology and Preventive Medicine, School of Public Health, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel	
David Goltzman	Department of Medicine, McGill University and McGill University Health Centre, Montreal, Canada	david.goltzman@mcgill.ca
Vilmundur Gudnason	Icelandic Heart Association, Kopavogur, Iceland	v.gudnason@hjarta.is
	University of Iceland, Reykjavik, Iceland	
Jill Hall	MRC Centre for Reproductive Health, University of Edinburgh, Edinburgh, UK	jill.hall@ed.ac.uk
Didier Hans	Interdisciplinary Centre of Bone Diseases, Bone and Joint Department, Lausanne University Hospital (CHUV) & University of Lausanne, Lausanne, Switzerland	didier.hans@chuv.ch
Marie Hoff	Department of Neuromedicine and Movement Science, Norwegian University	mari.hoff@ntnu.no

	of Science and Technology, Trondheim, Norway	
	Department of Rheumatology, St Olavs Hospital, Trondheim, Norway	
Rosemary J Hollick	Aberdeen Centre for Arthritis and Musculoskeletal Health, Epidemiology Group, University of Aberdeen, Aberdeen, UK	rhollick@abdn.ac.uk
Martijn Huisman	Department of Epidemiology and Data Science, Amsterdam Public Health Research Institute, VU University Medical Center, Amsterdam, The Netherlands	m.huisman@amsterdamumc.nl
	Department of Sociology, VU University, Amsterdam, The Netherlands	
Masayuki Iki	Department of Public Health, Kindai University Faculty of Medicine, Osaka, Japan	masa@med.kindai.ac.jp
Sophia Ish-Shalom	Endocrine Clinic, Elisha Hospital, Haifa, Israel	sishshalom@gmail.com
Graeme Jones	Menzies Institute for Medical Research, University of Tasmania, Hobart, Australia	g.jones@utas.edu.au
Magnus K Karlsson	Clinical and Molecular Osteoporosis Research Unit, Department of Clinical Sciences, Lund University, Lund, Sweden	magnus.karlsson@med.lu.se
	Department of Orthopaedics, Skåne University Hospital, Malmö, Sweden	
Sundeep Khosla	Robert and Arlene Kogod Center on Aging and Division of Endocrinology, Mayo Clinic College of Medicine, Mayo Clinic, Rochester, MN, USA	khosla.sundeep@mayo.edu
Douglas P Kiel	Marcus Institute for Aging Research, Hebrew Senior Life, Boston, MA, USA	kiel@hsl.harvard.edu
	Department of Medicine, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA, USA	
Woon-Puay Koh	Healthy Longevity Translational Research Programme, Yong Loo Lin School of Medicine, National University of Singapore	kohwp@nus.edu.sg

	Singapore Institute for Clinical Sciences, Agency for Science Technology and Research (A*STAR), Singapore	
Fjorda Koromani	Department of Internal Medicine, Erasmus University Medical Center, Rotterdam, The Netherlands	f.koromani@erasmusmc.nl
	Department of Radiology and Nuclear Medicine, Erasmus University Medical Center, Rotterdam, The Netherlands	
Mark A Kotowicz	Deakin University, IMPACT (Institute for Mental and Physical Health and Clinical Translation), Geelong, Victoria, Australia	mark.kotowicz@deakin.edu.au
	Barwon Health, Geelong, Victoria, Australia	
	Department of Medicine - Western Health, The University of Melbourne, St Albans, Victoria, Australia	
Heikki Kröger	Department of Orthopedics and Traumatology, Kuopio University Hospital, Kuopio, Finland	heikki.kroger@kuh.fi
	Kuopio Musculoskeletal Research Unit, University of Eastern Finland, Kuopio, Finland	
Timothy Kwok	Department of Medicine and Therapeutics, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong	tkwok@cuhk.edu.hk
	Jockey Club Centre for Osteoporosis Care and Control, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong	
Olivier Lamy	Centre of Bone Diseases, Lausanne University Hospital, Lausanne, Switzerland	olivier.lamy@chuv.ch
	Service of Internal Medicine, Lausanne University Hospital, Lausanne, Switzerland	
Arnulf Langhammer	HUNT Research Centre, Department of Public Health and Nursing, Faculty of Medicine and Health Sciences, Norwegian	arnulf.langhammer@ntnu.no

	University of Science and Technology, Trondheim, Norway	
Bagher Larijani	Endocrinology and Metabolism Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran	emrc@tums.ac.ir
Kurt Lippuner	Department of Osteoporosis, Bern University Hospital, University of Bern, Bern, Switzerland	kurt.lippuner@insel.ch
Fiona EA McGuigan	Clinical and Molecular Osteoporosis Research Unit, Department of Clinical Sciences, Lund University, Lund, Sweden	fiona.mcguigan@med.lu.se
Dan Mellström	Geriatric Medicine, Department of Internal Medicine and Clinical Nutrition, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden	dan.mellstrom@vgregion.se
	Geriatric Medicine, Sahlgrenska University Hospital Mölndal, Mölndal, Sweden	
Thomas Merlijn	Department of General Practice, Amsterdam UMC, location AMC, Amsterdam Public Health Research Institute, Amsterdam, The Netherlands	tmerlijn@gmail.com
Tuan V Nguyen	School of Biomedical Engineering, University of Technology Sydney, Sydney, Australia	TuanVan.Nguyen@uts.edu.au
	School of Medicine Sydney, University of Notre Dame Australia, Sydney, Australia	
	School of Population Health, UNSW Medicine, UNSW Sydney, Kensington, Australia	
Anna Nordström	School of Sport Sciences, UiT The Arctic University of Norway, Tromsø, Norway	anna.h.nordstrom@umu.se
	Department of Health Sciences, Swedish Winter Sports Research Centre, Mid Sweden University, Östersund, Sweden	
	Department of Medical Sciences, Uppsala University, Sweden	

Peter Nordström	Department of public health and caring sciences, Uppsala University, Uppsala, Sweden	peter.nordstrom@umu.se
Terence W O´Neill	National Institute for Health Research Manchester Biomedical Research Centre, Manchester University NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK	terence.o'neill@manchester.ac.uk
	Centre for Epidemiology Versus Arthritis, University of Manchester, Manchester, UK	
Barbara Obermayer-Pietsch	Department of Internal Medicine, Division of Endocrinology and Diabetology, Medical University Graz, Graz, Austria	barbara.obermayer@medunigraz.at
	Center for Biomarker Research in Medicine, Graz, Austria	
Claes Ohlsson	Sahlgrenska Osteoporosis Centre, Department of Internal Medicine and Clinical Nutrition, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden	claes.ohlsson@medic.gu.se
	Department of Drug Treatment, Sahlgrenska University Hospital, Region Västra Götaland, Gothenburg, Sweden	
Eric S Orwoll	Department of Medicine, Oregon Health and Science University, Portland, Oregon, USA	orwoll@ohsu.edu
Julie A Pasco	Deakin University, Institute for Physical and Mental Health and Clinical Translation (IMPACT), Geelong, Australia	julie.pasco@deakin.edu.au
	Department of Medicine-Western Health, The University of Melbourne, St Albans, Australia	
	Barwon Health, Geelong, Australia	
	Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Australia	
Fernando Rivadeneira	Department of Internal Medicine, Erasmus University Medical Center, Rotterdam, The Netherlands	f.rivadeneira@erasmusmc.nl

Anne-Marie Schott	Université Claude Bernard Lyon 1, U INSERM 1290 RESHAPE, Lyon, France	anne-marie.schott@inserm.fr
Eric J Shiroma	Laboratory of Epidemiology and Population Sciences, National Institute on Aging, Baltimore, Maryland, USA	eric.shiroma@nih.gov
Kristin Siggeirsdottir	Icelandic Heart Association, Kopavogur, Iceland Janus Rehabilitation, Reykjavik, Iceland	kristin@janus.is
Eleanor M Simonsick	Translational Gerontology Branch, National Institute on Aging Intramural Research Program, Baltimore, Maryland	simonsickel@grc.nia.nih.gov
Elisabeth Sornay-Rendu	INSERM UMR 1033, University of Lyon, Hôpital Edouard Herriot, Lyon, France	elisabeth.rendu@inserm.fr
Reijo Sund	Kuopio Musculoskeletal Research Unit, University of Eastern Finland, Kuopio, Finland	reijo.sund@uef.fi
Karin MA Swart	Department of General Practice, Amsterdam UMC, location VUmc, Amsterdam Public Health Research Institute, Amsterdam, The Netherlands PHARMO Institute for Drug Outcomes Research, Utrecht, The Netherlands	karin.swart-polinder@pharmo.nl
Pawel Szulc	INSERM UMR 1033, University of Lyon, Hôpital Edouard Herriot, Lyon, France	pawel.szulc@inserm.fr
Junko Tamaki	Department of Hygiene and Public Health, Faculty of Medicine, Educational Foundation of Osaka Medical and Pharmaceutical University, Osaka, Japan	jtamaki@ompu.ac.jp
David J Torgerson	York Trials Unit, Department of Health Sciences, University of York, York, UK	david.torgerson@york.ac.uk
Natasja M van Schoor	Department of Epidemiology and Data Science, Amsterdam Public Health Research Institute, VU University Medical Center, Amsterdam, The Netherlands	nm.vanschoor@amsterdamumc.nl
Tjeerd P van Staa	Centre for Health Informatics, Faculty of Biology, Medicine and Health, School of Health Sciences, University of Manchester, Manchester, UK	tjeerd.vanstaa@manchester.ac.uk

Joan Vila	Statistics Support Unit, Hospital del Mar Medical Research Institute, CIBER Epidemiology and Public Health (CIBERESP), Barcelona, Spain	jvila@imim.es
Nicholas J Wareham	MRC Epidemiology Unit, University of Cambridge, Cambridge, United Kingdom	nick.wareham@mrc-epid.cam.ac.uk
Nicole C Wright	Department of Epidemiology, University of Alabama at Birmingham, Birmingham, Alabama, USA	ncwright@uab.edu
Noriko Yoshimura	Department of Preventive Medicine for Locomotive Organ Disorders, The University of Tokyo Hospital, Tokyo, Japan	noripu@rc4.so-net.ne.jp
M Carola Zillikens	Department of Internal Medicine, Erasmus University Medical Center, Rotterdam, The Netherlands	m.c.zillikens@erasmusmc.nl
Marta Zwart	Health Center Can Gibert del Plà, Catalan Institute of Health, Girona, Spain	marta.zwart@udg.edu
	Department of Medical Sciences, University of Girona, Girona, Spain	
	GROIMAP/GROICAP (research groups), Unitat de Suport a la Recerca Girona, Institut Universitari d'Investigació en Atenció Primària Jordi Gol, Girona, Spain	
	PRECIOSA-Fundación para la investigación, Barberà del Vallés, Barcelona, Spain	
Nicholas C Harvey	MRC Lifecourse Epidemiology Centre, University of Southampton, Southampton, UK	nch@mrc.soton.ac.uk
	NIHR Southampton Biomedical Research Centre, University of Southampton and University Hospital Southampton NHS Foundation Trust, Southampton, UK	
Mattias Lorentzon	Mary McKillop Institute for Health Research, Australian Catholic University, Melbourne, Australia	mattias.lorentzon@medic.gu.se
	Sahlgrenska Osteoporosis Centre, Department of Internal Medicine and Clinical Nutrition, Institute of Medicine,	

	Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden	
	Region Västra Götaland, Geriatric Medicine, Sahlgrenska University Hospital, Mölndal, Sweden	
William D Leslie	Department of Medicine, University of Manitoba, Winnipeg, Manitoba, Canada	bleslie@sbgh.mb.ca
John A Kanis	Mary McKillop Institute for Health Research, Australian Catholic University, Melbourne, Australia	w.j.pontefract@shef.ac.uk ORCID: 0000-0002-3129-4326
	Centre for Metabolic Bone Diseases, University of Sheffield, Sheffield, UK	

Corresponding author:
Prof. John A Kanis
Centre for Metabolic Bone Diseases
University of Sheffield Medical School
Sheffield, UK
Tel: +44 114 285 1109
Email: w.j.Pontefract@sheffield.ac.uk

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: previous falls – fracture risk – hip fracture – major osteoporotic fracture – meta-analysis – 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, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 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, 35, 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, 38, 39, 40, 41, 42, 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 analysed 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 utilised to accommodate different DXA equipment. Corresponding femoral neck T-scores were calculated as previously described [46, 47].

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 categorised 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 1, Appendix Table 1 and 2). 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 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 Figure 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 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 ($P<0.001$) (Figure 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 3). When analysing 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 $\geq$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 4). No significant differences in HRs were observed according to race and ethnicity in those cohorts with these characteristics documented (Appendix Table 5). When analysing 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 6). 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, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 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, 30, 31, 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. Falls 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, optimised 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.

Acknowledgements

We are grateful to Dr Östen Ljunggren for contributing the MrOS Sweden cohort. UK Biobank data are included under approved access agreement 3593. The authors acknowledge the Manitoba Centre for Health Policy for use of Manitoba data contained in the Population Health Research Data Repository (HIPC 2016/2017-29). The results and conclusions are those of the authors and no official endorsement by the Manitoba Centre for Health Policy, Manitoba Health, Seniors and Active Living, or other data providers is intended or should be inferred. NC Harvey acknowledges funding from the UK Medical Research Council [MC_PC_21003; MC_PC_21001]. The WHI program is funded by the National Heart, Lung, and Blood Institute, National Institutes of Health, U.S. Department of Health and Human Services through 75N92021D00001, 75N92021D00002, 75N92021D00003, 75N92021D00004, 75N92021D00005. Funding for the MrOS USA study comes from the National Institute on Aging (NIA), the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), the National Center for Advancing Translational Sciences (NCATS), and NIH Roadmap for Medical Research under the following grant numbers: U01 AG027810, U01 AG042124, U01 AG042139, U01 AG042140, U01 AG042143, U01 AG042145, U01 AG042168, U01 AR066160, and UL1 TR000128. Funding for the SOF study comes from the National Institute on Aging (NIA), and the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), supported by grants (AG05407, AR35582, AG05394, AR35584, and AR35583). Funding for the Health ABC study was from the Intramural research program at the National Institute on Aging under the following contract numbers: NO1-AG-6-2101, NO1-AG-6-2103 and NO1-AG-6-2106.

Compliance with ethical standards

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.

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 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.

JR Center has received honoraria for speaking at educational meetings and for advisory boards from Amgen and honoraria for an advisory board from Bayer, all unrelated to this work.

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

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

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

A Diez-Perez has no financial interest in FRAX, reports personal fees from Amgen, Lilly, Theramex and grants from Instituto Carlos III of the Spanish Ministry of Health and owns shares of Active Life Scientific, all outside the submitted work.

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

PJM Elders has no financial interest in FRAX. PJM Elders reports support for the SOS study by Stichting Achmea Gezondheidszorg, Achmea and VGZ zorgverzekeraar. Additional support was given by the stichting Artsenlaboratorium en Trombosedienst. Outside the submitted work, she did receive independent investigator driven grants by Zonmw, the Netherlands, de Hartstichting, the Netherlands, the European foundation for the study of Diabetes, Amgen the Netherlands, TEVA, the Netherlands and Takeda, the Netherlands.

CC Glüer reports honoraria and research support from AgNovos, Amgen, osteolabs and UCB unrelated to this work.

NC Harvey has received consultancy/lecture fees/honoraria/grant funding from Alliance for Better Bone Health, Amgen, MSD, Eli Lilly, Radius Health, Servier, Shire, UCB, Kyowa Kirin, Consilient Healthcare, Theramex, and Internis Pharma.

DP Kiel has no financial interest in FRAX but has received support for his work in the Framingham Study over the past 32 years by the National Institutes of Health, Astra Zeneca, Merck, Amgen, and Radius Health.

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

M Lorentzon has received lecture fees from Amgen, Lilly, Meda, Renapharma and UCB Pharma and consulting fees from Amgen, Radius Health, UCB Pharma, Renapharma, Parexel International, and Consilient Health, all outside the presented work.

EV McCloskey has received consultancy/lecture fees/grant funding/honoraria from AgNovos, Amgen, AstraZeneca, Consilient Healthcare, Fresenius Kabi, Gilead, GSK, Hologic, Internis, Lilly, Merck, Novartis, ObsEva, Pfizer, Radius Health, Redx Oncology, Roche, Sanofi Aventis, UCB, ViiV, Warner Chilcott and I3 Innovus.

C Ohlsson is listed as a coinventor on two patent applications regarding probiotics in osteoporosis treatment.

TW O'Neill reports honoraria from UCB unrelated to this work.

ES Orwoll reports consulting fees from Amgen, Biocon, Radius, and Bayer, and research support from Mereo.

JA Pasco has received funding from the National Health and Medical Research Council (NHMRC) Australia, and the Medical Research Future Fund (MRFF) Australia, and Amgen, all unrelated to this work.

M Schini received funding for her fellowship from the Medical Research Council Centre of Excellence for Musculoskeletal Ageing, from the Osteoporosis 2000 support group and from Roche Diagnostics and honoraria from MA Health care and Kyowa Kirin – all unrelated to this work.

KMA Swart is an employee of the PHARMO Institute for Drug Outcomes Research. This independent research institute performs financially supported studies for government and related healthcare authorities and several pharmaceutical companies.

NC Wright sits on the Board of Trustee of the US Bone Health and Osteoporosis Foundation, and has received consulting fees from Radius and ArgenX.

MC Zillikens has received honoraria in the past for lectures or advice from Alexion, Amgen, Eli Lilly, Kyowa Kirin, Shire and UCB, unrelated to the current work.

M Zwart has received research funding from national societies (SEMFYC and SEIOMM).

C Beaudart, E Biver, O Bruyère, JA Cauley, CJ Crandall, SR Cummings, JAP da Silva, B Dawson-Huges, AB Dufour, S Ferrari, Y Fujita, S Fujiwara, I Goldshtein, D Goltzman, V Gudnason, J Hall, D Hans, M Hoff, RJ Hollick, M Huisman, M Iki, S Ish-Shalom, H Johansson, G Jones, MK Karlsson, S Khosla, W-P Koh, F Koromani, H Kröger, T Kwok, O Lamy, A Langhammer, B Larijani, WD Leslie, K Lippuner, E Liu, FEA Mcguigan, D Mellström, T Merlijn, T Nguyen, A Nordström, P Nordström, B Obermayer-Pietsch, F Rivadeneira, A-M Schott, EJ Shiroma, K Sigeirsdottir, EM Simonsick, E Sornay-Rendu, R Sund, P Szulc, J Tamaki, DJ Torgerson, L Vandenput, NM van Schoor, TP van Staa, J Vila, NJ Wareham, and N Yoshimura declare no competing interests in relation to this work.

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.

Funding
No external funding

References

1. Morrison A, Fan T, Sen SS, Weisenfluh L (2013) Epidemiology of falls and osteoporotic fractures: a systematic review. ClinicoEconomics and outcomes research 5:9-18.

2. Masud T, Morris RO (2001) Epidemiology of falls. Age Ageing 30 Suppl 4:3-7

3. Garnett MF, Weeks JD, Spencer MR (2022) Unintentional fall deaths among adults aged 65 and over: United States, 2020. NCHS Data Brief. Nov;(449):1-8. PMID: 36454076.

4. Henry MJ, Pasco JA, Merriman EN, Zhang Y, Sanders KM, Kotowicz MA, Nicholson GC (2011) Fracture risk score and absolute risk of fracture. Radiology 2011;259(2):495-501.

5. Gardsell P, Johnell O, Nilsson BE, Nilsson JA (1989) The predictive value of fracture, disease, and falling tendency for fragility fractures in women. Calcif Tissue Int 45:327-330

6. Cummings SR, Nevitt MC, Browner WS, Stone K, Fox KM, Ensrud KE, Cauley J, Black D, Vogt TM (1995) Risk factors for hip fracture in white women. Study of Osteoporotic Fractures Research Group. N Engl J Med 332:767-773

7. Dargent-Molina P, Favier F, Grandjean H, Baudoin C, Schott AM, Hausherr E, Meunier PJ, Breart G (1996) Fall-related factors and risk of hip fracture: the EPIDOS prospective study. Lancet 348:145-149

8. Albrand G, Munoz F, Sornay-Rendu E, DuBoeuf F, Delmas PD (2003) Independent predictors of all osteoporosis-related fractures in healthy postmenopausal women: the OFELY study. Bone 32:78-85

9. Geusens P, Milisen K, Dejaeger E, Boonen S (2003) Falls and fractures in postmenopausal women: a review. J Br Menopause Soc 9:101-106

10. Kaptoge S, Benevolenskaya LI, Bhalla AK, Cannata JB, Boonen S, Falch JA, Felsenberg D, Finn JD, Nuti R, Hoszowski K, Lorenc R, Miazgowski T, Jajic I, Lyritis G, Masaryk P, Naves-Diaz M, Poor G, Reid DM, Scheidt-Nave C, Stepan JJ, Todd CJ, Weber K, Woolf AD, Roy DK, Lunt M, Pye SR, O'Neill T W, Silman AJ, Reeve J (2005) Low BMD is less predictive than reported falls for future limb fractures in women across Europe: results from the European Prospective Osteoporosis Study. Bone 36:387-398

11. Wainwright SA, Marshall LM, Ensrud KE, Cauley JA, Black DM, Hillier TA, Hochberg MC, Vogt MT, Orwoll ES, Study of Osteoporotic Fractures Research Group (2005) Hip fracture in women without osteoporosis. J Clin Endocrinol Metab 90:2787-2793

12. Sambrook PN, Cameron ID, Chen JS, Cumming RG, Lord SR, March LM, Schwarz J, Seibel MJ, Simpson JM (2007) Influence of fall related factors and bone strength on fracture risk in the frail elderly. Osteoporos Int 18:603-610

13. Frost M, Abrahamsen B, Masud T, Brixen K (2012) Risk factors for fracture in elderly men: a population-based prospective study. Osteoporos Int 23:521-531

14. Hoff M, Meyer HE, Skurtveit S, Langhammer A, Sogaard AJ, Syversen U, Dhainaut A, Skovlund E, Abrahamsen B, Schei B (2017) Validation of FRAX and the impact of self-reported falls among elderly in a general population: the HUNT study, Norway. Osteoporos Int 28:2935-2944

15. Weycker D, Edelsberg J, Barron R, Atwood M, Oster G, Crittenden DB, Grauer A (2017) Predictors of near-term fracture in osteoporotic women aged >/=65 years, based on data from the study of osteoporotic fractures. Osteoporos Int 28:2565-2571

16. Adachi JD, Berger C, Barron R, Weycker D, Anastassiades TP, Davison KS, Hanley DA, Ioannidis G, Jackson SA, Josse RG, Kaiser SM, Kovacs CS, Leslie WD, Morin SN, Papaioannou A, Prior JC, Shyta E, Silvia A, Towheed T, Goltzman D (2019) Predictors of imminent non-vertebral fracture in elderly women with osteoporosis, low bone mass, or a history of fracture, based on data from the population-based Canadian Multicentre Osteoporosis Study (CaMos). Arch Osteoporos 14:53

17. Barron RL, Oster G, Grauer A, Crittenden DB, Weycker D (2020) Determinants of imminent fracture risk in postmenopausal women with osteoporosis. Osteoporos Int 31:2103-2111

18. Yusuf AA, Hu Y, Chandler D, Crittenden DB, Barron RL (2020) Predictors of imminent risk of fracture in Medicare-enrolled men and women. Arch Osteoporos 15:120

19. Iconaru L, Charles A, Baleanu F, Surquin M, Benoit F, Mugisha A, Moreau M, Paesmans M, Karmali R, Rubinstein M, Rozenberg S, Body JJ, Bergmann P (2022) Prediction of an Imminent Fracture After an Index Fracture - Models Derived From the Frisbee Cohort. J Bone Miner Res 37:59-67

20. Kim KM, Lui LY, Cummings SR (2022) Recent fall and high imminent risk of fracture in older men and women. Age Ageing 51: afac141. doi: 10.1093/ageing/afac141

21. Kanis JA on behalf of the World Health Organization Scientific Group (2007) Assessment of osteoporosis at the primary health care level. Technical Report. World Health Organization Collaborating Centre for Metabolic Bone Diseases, University of Sheffield, UK. Available at: http://www.shef.ac.uk/FRAX/index.htm. Accessed 31 May 2023

22. Kanis JA, Hans D, Cooper C, Baim S, Bilezikian JP, Binkley N, Cauley JA, Compston JE, Dawson-Hughes B, El-Hajj Fuleihan G, Johansson H, Leslie WD, Lewiecki EM, Luckey M, Oden A, Papapoulos SE, Poiana C, Rizzoli R, Wahl DA, McCloskey EV, Task Force of the FI (2011) Interpretation and use of FRAX in clinical practice. Osteoporos Int 22:2395-2411

23. Masud T, Binkley N, Boonen S, Hannan MT, Members FPDC (2011) Official Positions for FRAX(R) clinical regarding falls and frailty: can falls and frailty be used in FRAX(R)? From Joint Official Positions Development Conference of the International Society for Clinical Densitometry and International Osteoporosis Foundation on FRAX(R). J Clin Densitom 14:194-204

24. Nguyen ND, Frost SA, Center JR, Eisman JA, Nguyen TV (2008) Development of prognostic nomograms for individualizing 5-year and 10-year fracture risks. Osteoporos Int 19:1431-1444

25. Hippisley-Cox J, Coupland C (2012) Derivation and validation of updated QFracture algorithm to predict risk of osteoporotic fracture in primary care in the United Kingdom: prospective open cohort study. BMJ 344:e3427

26. McClung MR, Geusens P, Miller PD, Zippel H, Bensen WG, Roux C, Adami S, Fogelman I, Diamond T, Eastell R, Meunier PJ, Reginster JY, Hip Intervention Program Study G (2001) Effect of risedronate on the risk of hip fracture in elderly women. Hip Intervention Program Study Group. N Engl J Med 344:333-340

27. Harvey NC, Oden A, Orwoll E, Lapidus J, Kwok T, Karlsson MK, Rosengren BE, Ljunggren O, Cooper C, McCloskey E, Kanis JA, Ohlsson C, Mellstrom D, Johansson H (2018) Falls Predict Fractures Independently of FRAX Probability: A Meta-Analysis of the Osteoporotic Fractures in Men (MrOS) Study. J Bone Miner Res 33:510-516

28. Leslie WD, Morin SN, Lix LM, Martineau P, Bryanton M, McCloskey EV, Johansson H, Harvey NC, Kanis JA (2019) Fracture prediction from self-reported falls in routine clinical practice: a registry-based cohort study. Osteoporos Int 30:2195-2203

29. Cauley JA, Robbins J, Chen Z, Cummings SR, Jackson RD, LaCroix AZ, LeBoff M, Lewis CE, McGowan J, Neuner J, Pettinger M, Stefanick ML, Wactawski-Wende J, Watts NB, Women's Health Initiative I (2003) Effects of estrogen plus progestin on risk of fracture and bone mineral density: the Women's Health Initiative randomized trial. JAMA 290:1729-1738

30. Lorentzon M, Johansson H, Harvey NC, Liu E, Vandenput L, Crandall CJ, Cauley JA, LeBoff MS, McCloskey EV, Kanis JA (2022) Menopausal hormone therapy reduces the risk of fracture regardless of falls risk or baseline FRAX probability-results from the Women's Health Initiative hormone therapy trials. Osteoporos Int 33:2297-2305

31. Kayan K, Johansson H, Oden A, Vasireddy S, Pande K, Orgee J, Kanis JA, McCloskey EV (2009) Can fall risk be incorporated into fracture risk assessment algorithms: a pilot study of responsiveness to clodronate. Osteoporos Int 20:2055-2061

32. Reid IR, Horne AM, Mihov B, Stewart A, Garratt E, Wiessing KR, Bolland MJ, Bastin S, Gamble GD (2019) Anti-fracture efficacy of zoledronate in subgroups of osteopenic postmenopausal women: secondary analysis of a randomized controlled trial. J Intern Med 286:221-229

33. Bischoff-Ferrari HA, Freystätter G, Vellas B, Dawson-Hughes B, Kressig RW, Kanis JA, Willett WC, Manson JE, Rizzoli R, Theiler R, Hofbauer LC, Armbrecht G, da Silva JAP, Blauth M, de Godoi Rezende Costa Molino C, Lang W, Siebert U, Egli A, Orav EJ, Wieczorek M; DO-HEALTH Research Group. (2022) Effects of vitamin D, omega-3 fatty acids, and a simple home strength exercise program on fall prevention: the DO-HEALTH randomized clinical trial. Am J Clin Nutr 115(5):1311-1321.

34. Zhao R, Feng F, Wang X (2017) Exercise interventions and prevention of fall-related fractures in older people: a meta-analysis of randomized controlled trials. Int J Epidemiol 46:149-161

35. Nørgaard JE, Andersen S, Ryg J, Stevenson AJT, Andreasen J, Oliveira AS, Danielsen MB, Jorgensen MG (2023) Effect of treadmill perturbation-based balance training on fall rates in community-dwelling older adults: A randomized clinical trial. JAMA Netw Open 6(4):e238422. doi: 10.1001/jamanetworkopen.2023.8422.

36. McCrum C, Bhatt TS, Gerards MHG, Karamanidis K, Rogers MW, Lord SR, Okubo Y (2022) Perturbation-based balance training: Principles, mechanisms and implementation in clinical practice. Front Sports Act Living. 2022 Oct 6;4:1015394. doi: 10.3389/fspor.2022.1015394.

37. Gill TM, Pahor M, Guralnik JM, McDermott MM, King AC, Buford TW, Strotmeyer ES, Nelson ME, Sink KM, Demons JL, Kashaf SS, Walkup MP, Miller ME; LIFE Study Investigators (2016) Effect of structured physical activity on prevention of serious fall injuries in adults aged 70-89: randomized clinical trial (LIFE Study). BMJ 352:i245

38. Cameron ID, Dyer SM, Panagoda CE, Murray GR, Hill KD, Cumming RG, Kerse N (2018) Interventions for preventing falls in older people in care facilities and hospitals. Cochrane Database Syst Rev 9:CD005465

39. Hopewell S, Adedire O, Copsey BJ, Boniface GJ, Sherrington C, Clemson L, Close JC, Lamb SE (2018) Multifactorial and multiple component interventions for preventing falls in older people living in the community. Cochrane Database Syst Rev 7:CD012221

40. Bhasin S, Gill TM, Reuben DB, Latham NK, Ganz DA, Greene EJ, Dziura J, Basaria S, Gurwitz JH, Dykes PC, McMahon S, Storer TW, Gazarian P, Miller ME, Travison TG, Esserman D, Carnie MB,

Goehring L, Fagan M, Greenspan SL, Alexander N, Wiggins J, Ko F, Siu AL, Volpi E, Wu AW, Rich J, Waring SC, Wallace RB, Casteel C, Resnick NM, Magaziner J, Charpentier P, Lu C, Araujo K, Rajeevan H, Meng C, Allore H, Brawley BF, Eder R, McGloin JM, Skokos EA, Duncan PW, Baker D, Boult C, Correa-de-Araujo R, Peduzzi P, Investigators ST (2020) A randomized trial of a multifactorial strategy to prevent serious fall injuries. N Engl J Med 383:129-140

41. Lamb SE, Bruce J, Hossain A, Ji C, Longo R, Lall R, Bojke C, Hulme C, Withers E, Finnegan S, Sheridan R, Willett K, Underwood M, Prevention of Fall Injury Trial Study G (2020) Screening and intervention to prevent falls and fractures in older people. N Engl J Med 383:1848-1859

42. Ganz DA, Yuan AH, Greene EJ, Latham NK, Araujo K, Siu AL, Magaziner J, Gurwitz JH, Wu AW, Alexander NB, Wallace RB, Greenspan SL, Rich J, Volpi E, Waring SC, Dykes PC, Ko F, Resnick NM, McMahon SK, Basaria S, Wang R, Lu C, Esserman D, Dziura J, Miller ME, Travison TG, Peduzzi P, Bhasin S, Reuben DB, Gill TM (2022) Effect of the STRIDE fall injury prevention intervention on falls, fall injuries, and health-related quality of life. J Am Geriatr Soc 70:3221-3229

43. Clemson L, Stark S, Pighills AC, Fairhall NJ, Lamb SE, Ali J, Sherrington C (2023) Environmental interventions for preventing falls in older people living in the community. Cochrane Database Syst Rev 3:CD013258

44. Vandenput L, Johansson H, McCloskey EV, Liu E, Akesson KE, Anderson FA, Azagra R, Bager CL, Beaudart C, Bischoff-Ferrari HA, Biver E, Bruyere O, Cauley JA, Center JR, Chapurlat R, Christiansen C, Cooper C, Crandall CJ, Cummings SR, da Silva JAP, Dawson-Hughes B, Diez-Perez A, Dufour AB, Eisman JA, Elders PJM, Ferrari S, Fujita Y, Fujiwara S, Gluer CC, Goldshtein I, Goltzman D, Gudnason V, Hall J, Hans D, Hoff M, Hollick RJ, Huisman M, Iki M, Ish-Shalom S, Jones G, Karlsson MK, Khosla S, Kiel DP, Koh WP, Koromani F, Kotowicz MA, Kroger H, Kwok T, Lamy O, Langhammer A, Larijani B, Lippuner K, Mellstrom D, Merlijn T, Nordstrom A, Nordstrom P, O'Neill TW, Obermayer-Pietsch B, Ohlsson C, Orwoll ES, Pasco JA, Rivadeneira F, Schei B, Schott AM, Shiroma EJ, Siggeirsdottir K, Simonsick EM, Sornay-Rendu E, Sund R, Swart KMA, Szulc P, Tamaki J, Torgerson DJ, van Schoor NM, van Staa TP, Vila J, Wareham NJ, Wright NC, Yoshimura N, Zillikens MC, Zwart M, Harvey NC, Lorentzon M, Leslie WD, Kanis JA (2022) Update of the fracture risk prediction tool FRAX: a systematic review of potential cohorts and analysis plan. Osteoporos Int 33:2103-2136

45. Kanis JA, Oden A, Johnell O, Jonsson B, de Laet C, Dawson A (2001) The burden of osteoporotic fractures: a method for setting intervention thresholds. Osteoporos Int 12:417-427

46. Looker AC, Wahner HW, Dunn WL, Calvo MS, Harris TB, Heyse SP, Johnston CC, Jr., Lindsay R (1998) Updated data on proximal femur bone mineral levels of US adults. Osteoporos Int 8:468-489

47. Lu Y, Fuerst T, Hui S, Genant HK (2001) Standardization of bone mineral density at femoral neck, trochanter and Ward's triangle. Osteoporos Int 12:438-444

48. Breslow NE, Day NE (1987) Statistical methods in cancer research. Volume II--The design and analysis of cohort studies. IARC Sci Publ 1-406

49. Albertsson-Wikland K, Martensson A, Savendahl L, Niklasson A, Bang P, Dahlgren J, Gustafsson J, Kristrom B, Norgren S, Pehrsson NG, Oden A (2016) Mortality Is not increased in recombinant human growth hormone-treated patients when adjusting for birth characteristics. J Clin Endocrinol Metab 101:2149-2159

50. Higgins JP, Thompson SG, Deeks JJ, Altman DG (2003) Measuring inconsistency in meta-analyses. BMJ 327:557-560

51. Moreland B, Kakara R, Henry A (2020) Trends in nonfatal falls and fall-related injuries among adults aged ≥65 years - United States, 2012-2018. MMWR Morb Mortal Wkly Rep 69(27):875-881.

52. Langsetmo L, Schousboe JT, Taylor BC, Cauley JA, Fink HA, Cawthon PM, Stefanick ML, Kado DM, Kats AM, Ensrud KE, Osteoporotic Fractures in Men Research Group (2022) Characteristics associated with 5-year fracture risk vs. 5-year mortality risk among late-life men. J Gerontol A Biol Sci Med Sci 78:683-689

53. Kanis JA, Johansson H, Harvey NC, Lorentzon M, Liu E, Vandenput L, Morin S, Leslie WD, McCloskey EV (2023) Adjusting conventional FRAX estimates of fracture probability according to the number of prior falls in the preceding year. Osteoporos Int 34:479-487

54. McCloskey EV, Johansson H, Harvey N, Lorentzon M, Liu E, Vandenput L Leslie W, Schini M, Kanis JA (2023) FRAXplus – Post hoc exploration of impact of additional risk factor information on FRAX probability calculations. Aging Clin Exp Res 35 (Supplement 1): S52

55. Teister CJ, Chocano-Bedoya PO, Orav EJ, Dawson-Hughes B, Meyer U, Meyer OW, Freystaetter G, Gagesch M, Rizzoli R, Egli A, Theiler R, Kanis JA, Bischoff-Ferrari HA (2018) Which Method of Fall Ascertainment Captures the Most Falls in Prefrail and Frail Seniors? Am J Epidemiol 187:2243-2251

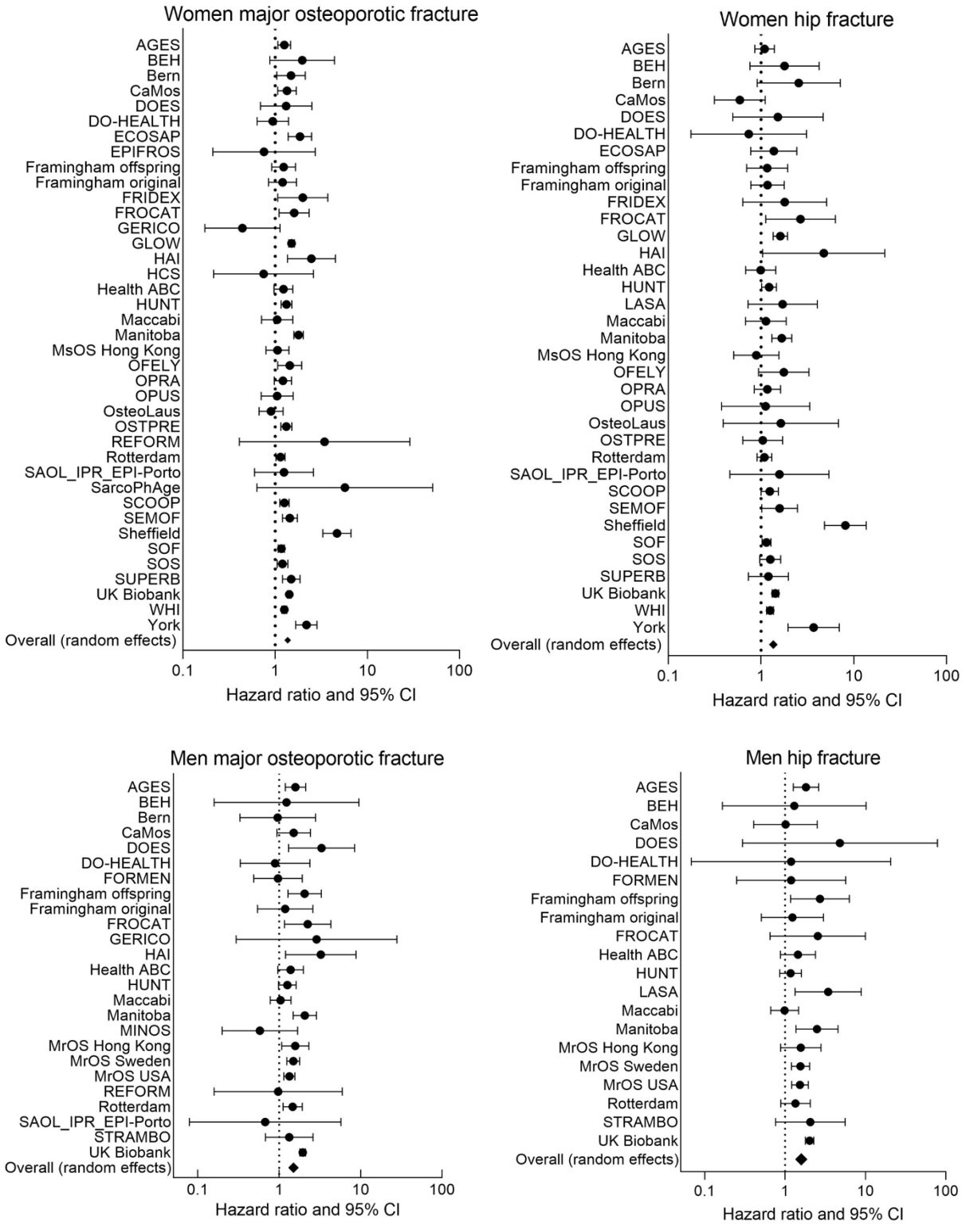

Fig 1 Forest plots of the association of previous falls with subsequent risk of a major osteoporotic fractures or a hip fracture in women (upper panels) and men (lower panels). Effect estimates (hazard ratios) are shown for fracture (circles), adjusted for age and duration of follow-up. The horizontal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

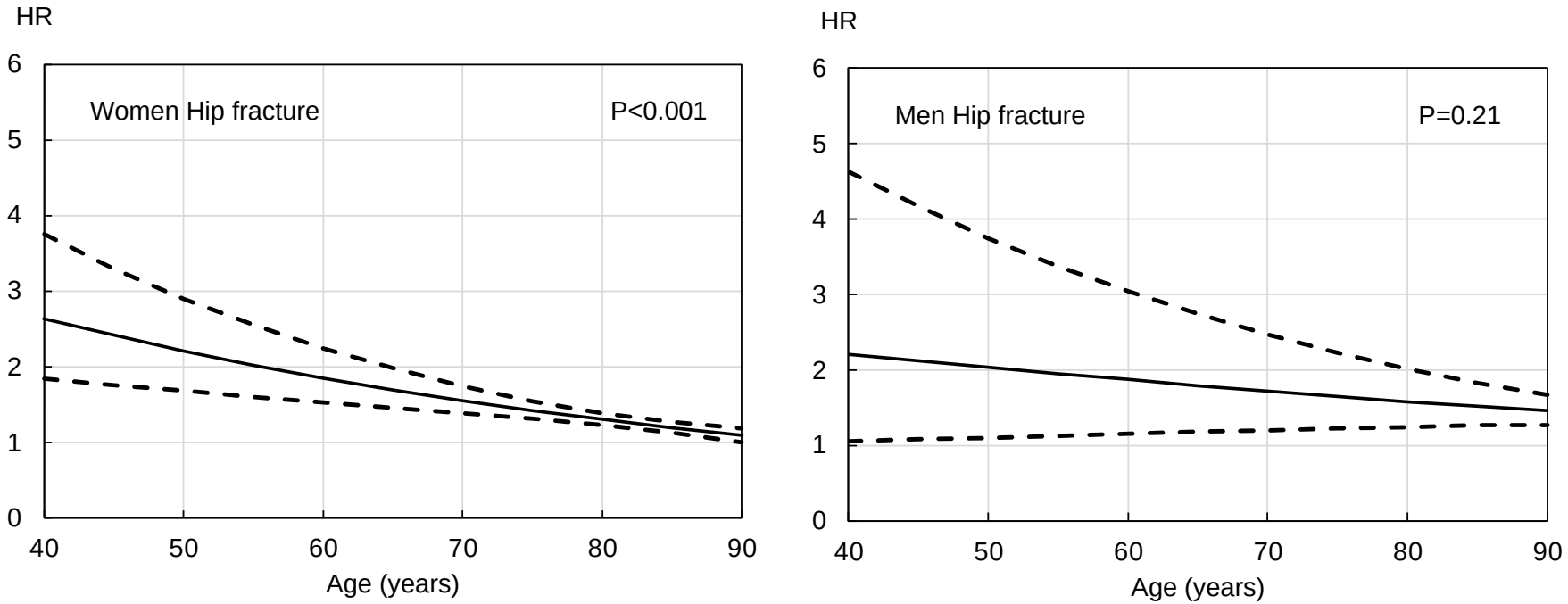

Fig 2 Interaction between one or more falls in the year prior to baseline and age at baseline in the association with subsequent risk of a hip fracture in women (left panel) and men (right panel). Hazard ratios (HR), adjusted for duration of follow-up, and 95% confidence interval are shown. P values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

Table 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	45188	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	10196	69.3	60.0	96.0	51.4	10.7	-	2291	98	76	46	40
Bern[a]	3690	13840	59.9	20.1	94.3	77.6	12.2	2 or more: 452	3642	475	339	237	23
CaMos[b]	9423	121634	62.1	25.0	103.0	69.4	6.7	-	8290	2435	1753	1188	340
DOES	2086	19341	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	16857	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	16265	72.5	65.0	93.0	0.0	16.3	-	1882	90	90	58	10
Framingham_offspring	3491	47178	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
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	744	71	51	26	2

								5: 1 6 or more: 26					
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	36348	73.6	68.0	80.0	51.5	21.3	-	3032	699	595	520	235
HUNT	6803	69261	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	83577	757792	65.4	37	91	64.8	5.0	-	7678	19335	19248	18408	5780
Manitoba	37246	105145	66.6	20.0	104.3	89.0	20.9	1: 4654 2: 1641 3: 670 4: 270 5: 307 6 or more: 259	37246	2064	1936	1437	342
MINOS	681	6152	65.2	50.0	86.0	0.0	24.1	1: 100	672	63	56	25	3

								2 or more: 64					
MrOS Hong Kong	2000	19744	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	34078	74.9	69.0	81.0	0.0	16.5	-	2809	964	869	724	338
MrOS USA	5994	75015	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	17528	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	15136	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	10664	75.2	75.0	76.0	100.0	28.4	1: 126 2: 65 3: 40 4: 11	825	457	413	398	173

								5: 10 7 or more: 8					
OPUS	1978	12135	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	97799	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	10382	133691	68.7	55.0	106.2	59.0	18.7	-	7786	2885	2580	2103	790
SAOL-IPR-EPIPorto	916	11139	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
SarcoPhAge	228	440	75.9	68.2	93.4	57.0	37.3	-	217	13	8	5	1
SCOOP	12368	58845	75.6	70.0	86.0	100.0	27.8	-	2790	1932	1630	1288	375
SEMOF	7131	20625	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	135907	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	16441	61467	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	10752	77.8	74.7	81.0	100.0	29.6	-	3012	463	421	341	70
UK Biobank	499867	5735643	56.5	38.0	73.0	54.4	19.8	1: 65958 2 or more: 33141	19530	25049	19977	12044	3925
WHI	78612	1072537	64.4	49.0	79.0	100.0	32.3	1: 15680 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)	906359	9102207	61.6	20.0	111.0	66.9	21.4		160580	87352	74088	57265	19509

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/12months"

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

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	Men	P value for interaction
		HR (95% CI)	HR (95% CI)	
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

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

Table7. 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

Appendix

Appendix Table 1. 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	26843	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	10783	60.9	20.1	94.3	12.5	2827	396	287	205	18
CaMos	6539	86156	63.0	25.0	103.0	6.6	5712	1910	1384	981	270
DOES	1267	11926	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	16857	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	26120	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	10607	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	53673	214575	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	19838	73.5	68.0	80.0	24.1	1564	463	397	355	150
HUNT	3743	39848	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	54175	497082	65.5	37.0	91.0	5.1	6665	14294	14236	13579	4071
Manitoba	33136	94303	66.9	20.0	104.3	20.5	33136	1839	1718	1283	298
MsOS Hong Kong	2000	17528	72.6	65.0	98.0	24.1	2000	338	298	247	69
OFELY	867	15136	58.8	40.0	89.0	30.8	861	245	207	180	40
OPRA	914	10664	75.2	75.0	76.0	28.4	825	457	413	398	173
OPUS	1978	12135	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	97799	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	81489	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	12368	58845	75.6	70.0	86.0	27.8	2790	1932	1630	1288	375
SEMOF	7131	20625	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	135907	71.6	65.0	89.0	30.0	7760	4346	3462	2801	1411
SOS	16441	61467	74.2	60.8	92.5	27.5	4071	1365	1306	978	253
SUPERB	3025	10752	77.8	74.7	81.0	29.6	3012	463	421	341	70
UK Biobank	272086	3143813	56.4	39.0	71.0	23.1	9969	16515	14558	8913	2613
WHI	78612	1072537	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)	606715	5864409	62.6	20.0	108.0	24.5	114339	67308	58375	45530	14829

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

Appendix Table 2. 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	18345	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	35478	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	16265	72.5	65.0	93.0	16.3	1882	90	90	58	10
Framingham_offspring	1603	21057	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	16510	73.8	69.0	80.0	18.3	1468	236	198	165	85
HUNT	3060	29413	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	29402	260710	65.0	40.0	91.0	5.0	1013	5041	5012	4829	1709
Manitoba	4110	10862	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	19744	72.4	65.0	92.0	15.4	2000	231	201	148	63
MrOS Sweden	3001	34078	74.9	69.0	81.0	16.5	2809	964	869	724	338
MrOS USA	5994	75015	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	52202	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	227781	2591829	56.8	38.0	73.0	15.9	9561	8534	5419	3131	1312
Overall (total/mean)	299644	3237814	59.5	20.0	111.0	15.1	46241	20044	15713	11735	4680

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

Appendix Table 3. 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

			Cohorts with BMD		Adjusted for BMD
Outcome fracture	Number of cohorts	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

Appendix Table 4. 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

Appendix Table 5. 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

Appendix Table 6. Association of previous falls with subsequent fracture risk at the sites indicated in women and men according to quality score of the cohorts

	Quality score 0-1			Quality score 2-3			Quality score 4		
Outcome fracture	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	4753408	1.50 (1.38-1.64)[b]	15	771719	1.27 (1.20-1.34)
Hip	0	0	-	21	4938300	1.54 (1.33-1.77)[c]	14	872607	1.16 (1.07-1.27)
MOF	3	3288	1.64 (0.28-9.72)	22	4856680	1.45 (1.32-1.59)[b]	14	796066	1.25 (1.18-1.32)
Ost	3	3253	1.38 (0.50-3.80)	21	4799082	1.50 (1.37-1.64)[b]	15	785274	1.27 (1.20-1.34)
Men									
Any	2	1119	1.62 (0.41-6.39)	10	2601682	1.77 (1.56-2.01)[b]	15	541337	1.44 (1.34-1.53)
Hip	0	0	-	5	2624302	2.01 (1.79-2.26)[c]	15	581155	1.46 (1.29-1.67)
MOF	2	1130	1.48 (0.36-6.12)	9	2631427	1.71 (1.37-2.13)	14	553866	1.41 (1.28-1.55)
Ost	2	1122	1.81 (0.54-6.04)	8	2617095	1.86 (1.73-2.01)[c]	15	549659	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)