**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

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| **Author** | **Affiliation** | **Contact** |

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| Liesbeth Vandenput | Mary McKillop Institute for Health Research, Australian Catholic University, Melbourne, Australia | liesbeth.vandenput@acu.edu.auORCID: 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.ukORCID: 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, Amsterdam Public Health Research Institute, Amsterdam, The Netherlands  | p.elders@amsterdamumc.nl |
| 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 of Science and Technology, Trondheim, Norway | mari.hoff@ntnu.no |
| 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 University of Science and Technology, Trondheim, Norway | arnulf.langhammer@ntnu.no |
| 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 | kristin@janus.is |
| Janus Rehabilitation, Reykjavik, Iceland |
| 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  | karin.swart-polinder@pharmo.nl |
| PHARMO Institute for Drug Outcomes Research, Utrecht, The Netherlands |
| 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.ukORCID: 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 >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 I2 statistic [50]. Random-effects models were used in the meta-analysis as moderate (I2=50) to high (I2=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 >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.

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**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.

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

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*Human and animal rights*
This study does not contain any original studies with human participants or animals performed by any of the authors.

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

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**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: 6942 or 3: 2104 or 5: 386 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 |
| Berna | 3690 | 13840 | 59.9 | 20.1 | 94.3 | 77.6 | 12.2 | 2 or more: 452 |  3642  | 475 | 339 | 237 | 23 |
| CaMosb | 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: 4472: 1213: 464: 38 |  2057 | 480 | 404 | 299 | 95 |
| DO-HEALTH | 2156 | 5956 | 74.9 | 70.0 | 95.0 | 61.7 | 42.0 | 1: 6582: 1483: 484: 215: 66 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: 342: 93: 34: 25: 112: 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: 4882: 1213: 364: 115: 86 or more: 15 |  2908  | 677 | 524 | 271 | 88 |
| Framingham\_original | 1094 | 9390 | 79.5 | 72.0 | 101.0 | 64.7 | 29.9 | 1: 1842: 803: 294: 75: 36 or more: 13 |  884  | 261 | 234 | 166 | 113 |
| FRIDEX | 815 | 8077 | 56.8 | 40.0 | 84.0 | 100.0 | 24.4 | 1: 1282: 313: 254: 55: 46 or more: 6 |  815  | 112 | 56 | 41 | 15 |
| FROCAT | 1930 | 19174 | 69.3 | 32.0 | 111.0 | 55.5 | 25.9 | 1: 2572: 1043: 594: 225: 116 or more: 12 |  233  | 228 | 182 | 159 | 33 |
| GERICO | 758 | 2742 | 67.9 | 64.6 | 71.8 | 79.4 | 47.4 | 1: 2182: 673: 344: 135: 16 or more: 26 |  744  | 71 | 51 | 26 | 2 |
| GLOW | 53673 | 214575 | 68.2 | 55.0 | 108.0 | 100.0 | 37.6 | 1: 122002 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: 392: 93: 14: 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: 2492: 1163: 374: 245: 176 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: 46542: 16413: 6704: 2705: 3076 or more: 259 | 37246 | 2064 | 1936 | 1437 | 342 |
| MINOS | 681 | 6152 | 65.2 | 50.0 | 86.0 | 0.0 | 24.1 | 1: 1002 or more: 64 |  672  | 63 | 56 | 25 | 3 |
| MrOS Hong Kong | 2000 | 19744 | 72.4 | 65.0 | 92.0 | 0.0 | 15.4 | 1: 2342 or 3: 634 or 5: 76 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: 7222 or 3: 4484 or 5: 676 or more: 31 |  5993  | 1394 | 1082 | 814 | 330 |
| MsOS Hong Kong | 2000 | 17528 | 72.6 | 65.0 | 98.0 | 100.0 | 24.1 | 1: 3202 or 3: 1374 or 5: 226 or more: 3 |  2000  | 338 | 298 | 247 | 69 |
| OFELY | 867 | 15136 | 58.8 | 40.0 | 89.0 | 100.0 | 30.8 | 1: 1572: 683: 224: 85: 56 or more: 7 |  861  | 245 | 207 | 180 | 40 |
| OPRA | 914 | 10664 | 75.2 | 75.0 | 76.0 | 100.0 | 28.4 | 1: 1262: 653: 404: 115: 107 or more: 8 |  825  | 457 | 413 | 398 | 173 |
| OPUS | 1978 | 12135 | 62.0 | 20.2 | 80.0 | 100.0 | 29.0 | 1: 3042: 1203: 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: 16752: 10143: 4294: 1515: 1476 or more: 187 |  2460  | 1635 | 1123 | 824 | 68 |
| REFORM | 1003 | 1482 | 77.9 | 65.0 | 99.0 | 60.5 | 65.2 | 1: 3142: 1863: 834: 335: 106 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: 1112: 423: 334: 45: 56 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 |
| Sheffieldc | 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: 18752 or 3: 8674 or 5: 1276 or more: 32 |  7760 | 4346 | 3462 | 2801 | 1411 |
| SOS | 16441 | 61467 | 74.2 | 60.8 | 92.5 | 100.0 | 27.5 | 1: 23362: 12433: 5374 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: 659582 or more: 33141 |  19530 | 25049 | 19977 | 12044 | 3925 |
| WHI | 78612 | 1072537 | 64.4 | 49.0 | 79.0 | 100.0 | 32.3 | 1: 156802: 65083 or more: 3232 |  5576  | 6377 | 5020 | 4392 | 2278 |
| York | 4532 | 9044 | 77.1 | 47.6 | 98.9 | 100.0 | 30.1 | 1: 6992: 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

|  |  |  |  |
| --- | --- | --- | --- |
| Outcomefracture | Numberofcohorts | I2(%) | 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; I2, 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

|  |  |  |  |
| --- | --- | --- | --- |
| Outcomefracture | Numberof 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.

|  |  |  |  |
| --- | --- | --- | --- |
| Outcomefracture | Numberof 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 |
| Outcomefracture | Number ofcohorts | I2 (%) | HR (95% CI) | I2 (%) | 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; I2, 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.

|  |  |  |  |
| --- | --- | --- | --- |
| Outcomefracture | Numberofcohorts | I2(%) | 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; I2, 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** |
| Outcomefracture | Numberofcohorts | Person years | HR (95% CI) | Numberofcohorts | Person years | HR (95% CI) | Numberofcohorts | 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)