



# Update of the fracture risk prediction tool FRAX: a systematic review of potential cohorts and analysis plan

L. Vandenput<sup>1,2</sup> · H. Johansson<sup>1,3</sup> · E. V. McCloskey<sup>3,4</sup> · E. Liu<sup>1</sup> · K. E. Åkesson<sup>5,6</sup> · F. A. Anderson<sup>7</sup> · R. Azagra<sup>8,9,10</sup> · C. L. Bager<sup>11</sup> · C. Beaudart<sup>12</sup> · H. A. Bischoff-Ferrari<sup>13,14</sup> · E. Biver<sup>15</sup> · O. Bruyère<sup>12</sup> · J. A. Cauley<sup>16</sup> · J. R. Center<sup>17,18,19</sup> · R. Chapurlat<sup>20</sup> · C. Christiansen<sup>11</sup> · C. Cooper<sup>21,22,23</sup> · C. J. Crandall<sup>24</sup> · S. R. Cummings<sup>25</sup> · J. A. P. da Silva<sup>26,27</sup> · B. Dawson-Hughes<sup>28</sup> · A. Diez-Perez<sup>29</sup> · A. B. Dufour<sup>30,31</sup> · J. A. Eisman<sup>18,19,32</sup> · P. J. M. Elders<sup>33</sup> · S. Ferrari<sup>15</sup> · Y. Fujita<sup>34</sup> · S. Fujiwara<sup>35</sup> · C.-C. Glüer<sup>36</sup> · I. Goldshtein<sup>37,38</sup> · D. Goltzman<sup>39</sup> · V. Gudnason<sup>40,41</sup> · J. Hall<sup>42</sup> · D. Hans<sup>43</sup> · M. Hoff<sup>44,45</sup> · R. J. Hollick<sup>46</sup> · M. Huisman<sup>47,48</sup> · M. Iki<sup>34</sup> · S. Ish-Shalom<sup>49</sup> · G. Jones<sup>50</sup> · M. K. Karlsson<sup>5,51</sup> · S. Khosla<sup>52</sup> · D. P. Kiel<sup>30,31</sup> · W.-P. Koh<sup>53,54</sup> · F. Koromani<sup>55,56</sup> · M. A. Kotowicz<sup>57,58,59</sup> · H. Kröger<sup>60,61</sup> · T. Kwok<sup>62,63</sup> · O. Lamy<sup>64,65</sup> · A. Langhammer<sup>66</sup> · B. Larijani<sup>67</sup> · K. Lippuner<sup>68</sup> · D. Mellström<sup>69,70</sup> · T. Merlijn<sup>33</sup> · A. Nordström<sup>71,72</sup> · P. Nordström<sup>73</sup> · T. W. O'Neill<sup>74,75</sup> · B. Obermayer-Pietsch<sup>76,77</sup> · C. Ohlsson<sup>2,78</sup> · E. S. Orwoll<sup>79</sup> · J. A. Pasco<sup>80,81,82,83</sup> · F. Rivadeneira<sup>55</sup> · B. Schei<sup>84,85</sup> · A.-M. Schott<sup>86</sup> · E. J. Shiroma<sup>87</sup> · K. Siggeirsdottir<sup>40,88</sup> · E. M. Simonsick<sup>89</sup> · E. Sornay-Rendu<sup>90</sup> · R. Sund<sup>61</sup> · K. M. A. Swart<sup>33</sup> · P. Szulc<sup>20</sup> · J. Tamaki<sup>91</sup> · D. J. Torgerson<sup>92</sup> · N. M. van Schoor<sup>47</sup> · T. P. van Staa<sup>93</sup> · J. Vila<sup>94</sup> · N. J. Wareham<sup>95</sup> · N. C. Wright<sup>96</sup> · N. Yoshimura<sup>97</sup> · M. C. Zillikens<sup>55</sup> · M. Zwart<sup>98,99,100</sup> · N. C. Harvey<sup>101,102</sup> · M. Lorentzon<sup>1,103,104</sup> · W. D. Leslie<sup>105</sup> · J. A. Kanis<sup>1,3,106</sup>

Received: 10 February 2022 / Accepted: 18 May 2022

© International Osteoporosis Foundation and National Osteoporosis Foundation 2022

## Abstract

**Summary** We describe the collection of cohorts together with the analysis plan for an update of the fracture risk prediction tool FRAX with respect to current and novel risk factors. The resource comprises 2,138,428 participants with a follow-up of approximately 20 million person-years and 116,117 documented incident major osteoporotic fractures.

**Introduction** The availability of the fracture risk assessment tool FRAX® has substantially enhanced the targeting of treatment to those at high risk of fracture with FRAX now incorporated into more than 100 clinical osteoporosis guidelines worldwide. The aim of this study is to determine whether the current algorithms can be further optimised with respect to current and novel risk factors.

**Methods** A computerised literature search was performed in PubMed from inception until May 17, 2019, to identify eligible cohorts for updating the FRAX coefficients. Additionally, we searched the abstracts of conference proceedings of the American Society for Bone and Mineral Research, European Calcified Tissue Society and World Congress of Osteoporosis. Prospective cohort studies with data on baseline clinical risk factors and incident fractures were eligible.

**Results** Of the 836 records retrieved, 53 were selected for full-text assessment after screening on title and abstract. Twelve cohorts were deemed eligible and of these, 4 novel cohorts were identified. These cohorts, together with 60 previously identified cohorts, will provide the resource for constructing an updated version of FRAX comprising 2,138,428 participants with a follow-up of approximately 20 million person-years and 116,117 documented incident major osteoporotic fractures. For each known and candidate risk factor, multivariate hazard functions for hip fracture, major osteoporotic fracture and death will be tested using extended Poisson regression. Sex- and/or ethnicity-specific differences in the weights of the risk factors will be investigated. After meta-analyses of the cohort-specific beta coefficients for each risk factor, models comprising 10-year probability of hip and major osteoporotic fracture, with or without femoral neck bone mineral density, will be computed.

**Conclusions** These assembled cohorts and described models will provide the framework for an updated FRAX tool enabling enhanced assessment of fracture risk (PROSPERO (CRD42021227266)).

**Keywords** Epidemiology · Fracture probability · FRAX · Hip fracture · Major osteoporotic fracture · Risk assessment

Extended author information available on the last page of the article

## Introduction

Accurate assessment of fracture risk is critical for the optimal management of osteoporosis. The fracture risk assessment tool FRAX®, released by the then World Health Organization Collaborating Centre in Sheffield, UK, in 2008 [1], estimates individualised 10-year probability of hip and major osteoporotic fracture (MOF; hip, clinical spine, distal forearm and proximal humerus). The algorithm integrates seven dichotomous clinical risk factors (prior fragility fracture, parental hip fracture, smoking, excess alcohol consumption, glucocorticoid use, rheumatoid arthritis and other causes of secondary osteoporosis) with age, sex and body mass index and optionally, a bone mineral density (BMD) measurement [2]. Since its release, 86 FRAX models have been made available for 78 countries. Furthermore, the FRAX tool has widely influenced clinical decision-making as emphasised by the more than 100 guidelines worldwide incorporating FRAX as a valuable aid in the setting of intervention thresholds for osteoporosis [3, 4].

The FRAX tool has been appreciated for its simplicity for use in primary care but criticised for the same reason because of the use of dichotomous clinical risk factors (yes/no response) that does not take account of exposure response. Exposure response is not considered for glucocorticoids, alcohol consumption, smoking and the number of prior fractures. Moreover, lumbar spine BMD is not specifically considered and parameters relating to the material and structural properties of bone are lacking. Some of these limitations have been addressed by relatively simple arithmetic procedures to adjust the conventional FRAX estimates [4]. The most recent FRAX adjustment relates to the recency of fracture with probability ratios providing adjustments to the FRAX probability estimates depending on the site of the recent sentinel fracture [5]. These adjustment algorithms are external to FRAX and will remain so in the absence of international databases with the relevant granularity of data.

Notwithstanding, an update of the FRAX tool is timely and keenly anticipated. One strategy to improve the predictive value of FRAX is to consider novel risk factors not currently accommodated in the algorithm. A complementary approach is to expand the resource with additional cohorts, especially male and ethnic-specific cohorts, and with a longer follow-up than those that already contributed to FRAX, which will permit more precise, race/ethnicity- and sex-specific, estimates of the existing beta-coefficients. Many population-based cohorts worldwide have already provided data for the development of the original FRAX tool and its validation [6] or subsequent application. In order to assure that all possible eligible cohorts are included in the update of FRAX, a systematic review was conducted.

## Methods

We conducted a systematic review to identify potential cohort studies for the update of FRAX. This review was registered with the International prospective register of systematic reviews, PROSPERO (CRD42021227266), and followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [7].

### Search strategy

To identify eligible cohorts, a computerised literature search was performed in PubMed from its inception to May 17, 2019, with no language restrictions. The following MeSH and free text terms were used to restrict studies to those involving prospective, preferably population-based cohorts with available data on fracture outcomes as well as the clinical risk factors currently incorporated in FRAX: “age factors” OR “age” OR “gender” OR “sex” OR “previous fractures” OR “prior fractures” OR “previous fracture” OR “prior fracture” OR “smoking” OR “adrenal cortex hormones” OR “corticosteroid” OR “corticosteroids” OR “corticoids” OR “arthritis, rheumatoid” OR “rheumatoid arthritis” OR “diabetes” OR “diabetes mellitus” OR “falling” OR “falls” OR “accidental falls” OR “malnutrition” OR “nutritional deficiencies” OR “nutritional deficiency” OR “malnourishment” OR “undernutrition” OR “medical history taking” OR “family medical history” OR “family health history” OR “recurrence” OR “recurrences” AND (“risk factors” OR “risk factor”) AND (“prospective cohort” OR “prospective studies” OR “prospective study”) AND (“fractures, Bone” OR “fracture” OR “fractures”). The terms malnutrition, nutritional deficiencies, nutritional deficiency, malnourishment or undernutrition were included to identify disorders such as inflammatory bowel disease (Crohn’s disease and ulcerative colitis) and celiac disease, which are considered secondary causes of osteoporosis. All the above listed terms were combined with specific filters to simultaneously exclude cohorts that had already contributed to FRAX. Reference lists of identified records were also screened for potential cohorts. Two reviewers (JAK and EVM) first independently screened titles and abstracts for relevance, and reports deemed potentially relevant were examined in full to evaluate eligibility. Any disagreements were resolved by discussion and the opinion of a third reviewer, as needed. Records were stored using a citation manager and a web-based tool, Rayyan [8], was used to code screening. In addition, reference lists from the original studies, reviews and meta-analyses were examined to identify additional possible studies.

## Eligibility

Studies were eligible if the cohort described was prospective, included at least 200 participants, assessed an adequate number of clinical risk factors and reported an adequate number of incident fracture outcomes. Cohorts that had already contributed to FRAX as source or validation cohorts or that were previously identified but have not been used in any previous analysis were collectively categorised separately as “cohorts previously identified” (Fig. 1).

## Results

### Literature search

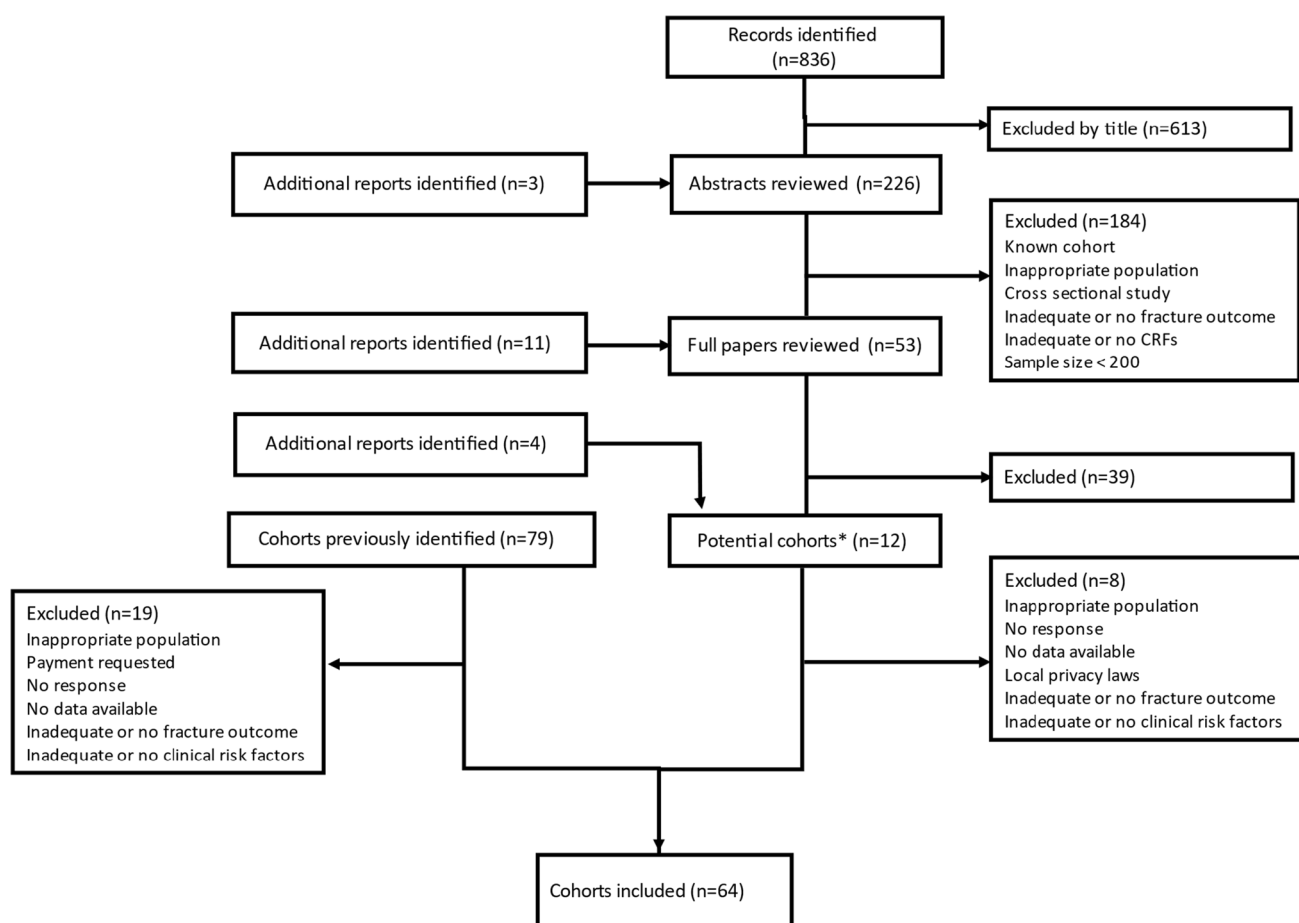
The computerised literature search yielded 836 records. After excluding by title screening, 226 records remained for abstract screening. Of these, a further 184 records were excluded (inappropriate study population ( $n=55$ ),

cross-sectional design ( $n=16$ ), sample size  $<200$  ( $n=23$ ), inadequate or no fracture outcome ( $n=7$ ), inadequate or no clinical risk factors ( $n=49$ ), reviews ( $n=15$ ) or cohorts already contributing to FRAX (“known cohort”,  $n=19$ )). Additional hand searching found another 11 records, leaving 53 reports for full-text assessment (Fig. 1).

### Included studies

After assessing 53 full reports, 12 novel cohorts were identified to be potentially eligible for contributing to the update of the FRAX tool (Fig. 1). Of these, 4 met the inclusion criteria and the principal investigator agreed to contribute their data (Table 1). The reasons for the exclusion of the other potential cohorts ( $n=8$ ) are indicated in Appendix Table 3.

The previously identified cohorts ( $n=79$ ), including the source ( $n=9$ ) and validation ( $n=10$ ) cohorts for the original FRAX algorithm as well as other previously identified cohorts, were also considered. All source and validation cohorts were included and 41 of the remaining 60 previously



**Fig. 1** PRISMA flow chart. Cohorts previously identified: source and validation cohorts used to develop the existing FRAX tool as well as other cohorts that were previously identified but have not been used

in any previous analysis; Known cohort: additional publication of a previously identified cohort. \*After reviewing 18 reports, 12 cohorts were identified as several reports described the same cohort

**Table 1** Characteristics of the cohorts included in the update of FRAX

Cohort (quality score)	Type	Origin	N	N*	Women (%)	Age (years) (mean (range))†	Diabetes (%)†	Falls (%)	FN BMD (N)	Any fracture (%)	Hip fracture (%)	MOF (%)	Mortality (%)	Follow-up (years) (mean (range))‡
AGES (4)	C	Iceland	5706	10	57.6	77 (66–98)	0.01 13.0 II	18.6	4782	28.4	9.4	19.9	41.3	8.0 (0.0–11.6)
AHS (2)	A	Japan	2613	7	69.6	65 (47–95)	12.5	-	2596	14.1	1.2	10.8	5.8	3.9 (0.0–6.8)
APOSS (4)	C	UK	5119	10	100.0	48 (44–56)	1.0	-	5112	8.7	0.1	3.7	-	8.8 (0.0–13.3)
AUSTRIOS B (1)	C	Austria	2064	5	84.2	84 (68–103)	1.4	-	-	8.5	3.7	-	-	1.2 (0.0–1.5)
BEH (3)	C	Iran	2426	11	51.9	69 (60–96)	31.8 33.5 II	0.0	2417	4.4	1.7	-	10.5	4.2 (0.0–5.8)
Bern (2)	C	Switzerland	23,185	11	84.9	59 (20–95)	0.41 0.7 II	12.2	22,830	21.7	1.3	12.6	0.8	7.8 (0.0–31.0)
CaMos (4)	A	Canada	9423	10	69.4	62 (25–103)	1.11 5.9 II	6.7	8290	25.8	3.6	12.6	22.4	12.9 (0.0–22.6)
DOES (4)	A	Australia	2654	9	62.4	70 (47–94)	6.0 II	25.9	2116	25.9	5.2	16.7	12.4	8.8 (0.1–13.9)
DO-HEALTH (3)	C	Europe	2157	11	61.7	75 (70–95)	0.61 5.7 II	42.0	1452	12.4	0.5	5.5	-	2.8 (0.0–3.5)
ECOSAP (2)	C	Spain	5201	9	100.0	72 (65–100)	-	26.7	-	6.0	1.0	3.7	1.9	3.3 (0.0–8.4)
EPIC-Norfolk (4)	C	UK	25,636	7	54.7	59 (39–79)	2.3	-	-	11.9	5.3	9.1	37.9	19.3 (0.0–25.4)
EPIDOS (2)	B	France	7598	8	100.0	80 (70–100)	-	-	7562	13.5	3.0	7.5	6.4	2.8 (0.0–4.0)
EPiFROS (3)	D	Spain	284	11	54.6	62 (40–96)	0.71 8.5 II	18.3	12	9.5	1.1	5.7	-	10.0 (1.4–10.0)
EVOS/EPOS (3)	A	Europe	17,342	8	53.6	64 (41–95)	9.2	-	5296	4.0	0.4	2.1	-	3.1 (0.1–5.9)
FORMEN (4)	C	Japan	1888	11	0.0	72 (65–93)	0.21 9.6 II	16.3	1884	4.8	0.5	3.1	18.8	8.6 (0.0–12.9)
Framingham_off-spring (4)	C	USA	3539	10	54.1	61 (33–90)	11.2 II	20.0	2939	21.4	3.0	8.9	24.9	16.5 (0.0–20.3)
Framingham_original (4)	C	USA	1166	10	65.3	80 (72–101)	13.0 II	29.9	896	23.9	11.7	16.0	95.1	9.6 (0.0–24.0)
FRIDEX (3)	D	Spain	815	10	100.0	57 (40–84)	2.7	24.4	815	13.8	1.8	5.0	-	9.9 (1.0–10.0)
PROCAT (4)	D	Spain	1954	9	55.7	69 (32–111)	-	25.9	238	11.7	1.7	8.2	-	9.9 (0.0–10.3)
GERICO (1)	C	Switzerland	765	11	79.5	68 (65–72)	0.01 3.4 II	47.3	751	9.3	0.3	3.4	1.0	3.6 (0.8–5.3)
GLOW (2)	C	Worldwide	60,393	10	100.0	69 (55–108)	3.9	37.9	-	10.5	0.9	5.2	-	4.0 (0.0–6.0)
GOS (4)	B	Australia	1865	9	100.0	63 (35–95)	-	-	1807	9.3	1.7	6.2	10.0	6.9 (0.1–10.9)
Gothenburg I (4)	A	Sweden	2375	5	60.9	86 (70–96)	-	-	-	29.4	20.4	24.9	83.2	9.2 (0.0–24.4)
Gothenburg II (4)	A	Sweden	11,376	8	100.0	59 (21–84)	2.0	-	-	16.9	2.3	10.4	9.6	13.2 (0.1–16.2)
HAI (2)	C	Sweden	3618	9	50.2	70 (69–72)	8.5	11.1	3535	3.5	0.3	2.2	1.9	2.6 (0.2–5.6)
HCS (4)	C	UK	632	9	50.3	65 (59–71)	-	19.9	631	10.6	0.5	5.5	-	8.9 (2.7–12.6)
Health ABC (4)	C	USA	3075	10	51.5	74 (68–80)	15.0	21.3	3047	22.8	7.6	16.9	64.7	11.9 (0.0–17.4)
HUNT (4)	C	Norway	50,213	10	54.6	53 (20–101)	0.51 3.3 II	20.3	11,583	20.4	3.3	9.4	13.1	12.4 (0.0–14.1)
JPOS (3)	C	Japan	1950	10	100.0	58 (40–82)	0.31 3.3 II	-	1935	13.6	1.5	5.1	3.8	13.3 (2.6–20.3)

**Table 1** (continued)

Cohort (quality score)	Type	Origin	N	N*	Women (%)	Age (years) (mean (range))	Diabetes (%) <sup>†</sup>	Falls (%)	FN BMD (N)	Any fracture (%)	Hip fracture (%)	MOF (%)	Mortality (%)	Follow-up (years) (mean (range)) <sup>‡</sup>
LASA (4)	D	The Netherlands	1509	10	51.8	76 (65–89)	8.0	32.3	522	8.9	2.6	-	33.5	5.1 (0.0–7.2)
Maccabi (4)	C	Israel	659,266	9	52.0	56 (30–91)	11.8 II	5.0	35,829	8.2	1.7	7.9	9.3	9.6 (0.0–10.0)
Manitoba (3)	C	Canada	92,277	11	89.8	63 (20–104)	11.2	22.7	92,102	13.3	3.1	9.9	-	9.0 (0.0–22.2)
MINOS (3)	C	France	841	10	0.0	65 (50–86)	7.2	24.8	675	10.1	0.6	4.0	23.5	8.9 (0.1–10.4)
Miyama (4)	B	Japan	400	7	50.0	59 (40–79)	-	-	400	15.3	1.8	8.8	13.8	9.3 (0.5–19.0)
MrOS Hong Kong (3)	C	Hong Kong	2000	11	0.0	72 (65–92)	14.7	15.4	2000	11.6	3.2	7.4	42.7	9.9 (0.1–12.2)
MrOS Sweden (4)	C	Sweden	3014	11	0.0	75 (69–81)	9.5	16.5	2820	32.2	11.3	24.2	69.6	11.4 (0.0–18.2)
MrOS USA (4)	C	USA	5994	11	0.0	74 (64–100)	10.9	21.2	5994	23.3	5.5	13.6	58.6	12.5 (0.0–18.8)
MsOS Hong Kong (3)	C	Hong Kong	2000	11	100.0	73 (65–98)	14.1	24.1	2000	16.9	3.4	12.4	25.9	8.8 (0.2–10.4)
NHEFS (4)	C	USA	12,220	5	59.6	49 (25–74)	4.9	-	-	-	0.9	-	13.8	10.0 (0.0–14.0)
OFELY (4)	C	France	867	11	100.0	59 (40–89)	0.1 I	30.8	861	28.3	4.6	20.8	16.1	17.5 (0.0–21.0)
OPRA (4)	C	Sweden	1044	9	100.0	75 (75–76)	-	28.4	947	50.2	18.7	43.4	57.3	11.6 (0.0–16.9)
OPUS (2)	B	Europe	2882	11	100.0	61 (20–81)	4.9	27.5	2836	12.0	0.7	5.8	-	6.1 (0.1–8.2)
OsteoLaus (3)	C	Switzerland	1475	10	100.0	65 (50–82)	4.1	25.4	1457	20.8	0.5	15.3	2.2	4.6 (0.0–7.4)
OSTPRE (3)	C	Finland	11,200	11	100.0	57 (52–63)	0.8 I	36.3	2761	16.5	0.7	8.2	23.1	9.8 (0.0–10.0)
PERF (2)	B	Denmark	4225	6	100.0	63 (44–81)	-	-	2446	5.6	0.3	3.4	6.2	7.3 (0.1–24.3)
REFORM (0)	C	UK, Ireland	1010	5	60.4	78 (65–99)	-	65.2	-	3.0	0.4	1.2	2.7	1.5 (0.2–2.6)
Rochester (4)	A	USA	1003	7	65.3	57 (21–94)	-	-	995	32.6	3.7	24.3	-	7.7 (0.0–19.1)
Rotterdam (4)	A	The Netherlands	14,619	11	58.8	66 (45–106)	11.3 II	18.7	11,040	22.7	5.7	15.9	41.8	10.8 (0.0–23.5)
SAOL_IPR, EPL-Porto (4/2/3)	C	Portugal	1227	11	76.5	56 (40–89)	4.4	22.9	1225	11.5	1.3	1.0	13.5	12.3 (0.1–29.1)
SarcoPhAge (0)	C	Belgium	260	11	58.1	76 (68–93)	0.8	38.8	247	5.7	0.4	2.2	5.3	1.9 (0.1–3.1)
SCHS (4)	C	Singapore	52,042	7	57.4	62 (48–84)	14.3	-	-	-	2.1	-	-	8.9 (0.0–11.5)
SCOOP (4)	C	UK	12,483	10	100.0	76 (70–86)	-	27.8	2718	15.6	3.1	10.4	8.0	4.8 (0.0–5.0)
SEMOF (3)	B	Switzerland	7133	9	100.0	75 (70–91)	-	31.4	920	9.6	1.1	6.5	-	2.9 (0.0–4.9)
Sheffield (2)	A	UK	2606	11	100.0	80 (74–101)	0.6 I	5.5	2584	13.3	3.1	8.8	9.9	3.4 (0.0–5.1)
SOF (3)	B	USA	9704	11	100.0	72 (65–89)	1.2 I	30.0	8074	47.5	14.7	29.0	-	14.1 (0.0–23.4)
SOS (2)	C	The Netherlands	16,945	11	100.0	74 (61–93)	0.8 I	27.3	4167	8.4	1.6	6.0	9.5	3.7 (0.0–6.0)
STOP/IT (2)	C	USA	446	6	55.3	71 (65–87)	4.5	-	444	11.8	0.5	5.7	-	4.3 (0.4–5.2)
STRAMBO (4)	C	France	1167	11	0.0	63 (21–88)	10.2	19.9	1145	14.2	2.1	5.1	28.6	9.2 (0.4–12.1)
SUPERB (3)	C	Sweden	3028	10	100.0	78 (75–81)	-	29.6	3015	15.3	2.3	11.3	4.2	3.6 (0.2–5.2)
TASOAC (3)	C	Australia	1099	7	48.9	63 (51–81)	6.3	-	1094	13.3	0.5	4.5	28.6	10.0 (0.4–18.4)
THIN (4)	B	UK	366,104	8	100.0	64 (50–116)	-	-	-	8.6	1.8	-	15.1	5.8 (0.0–13.0)
UK Biobank (3)	C	UK	502,536	10	54.4	57 (37–73)	5.3	19.8	19,692	5.0	0.8	2.4	6.5	11.5 (0.0–14.6)

**Table 1** (continued)

Cohort (quality score)	Type	Origin	N	N*	Women (%)	Age (years) (mean (range))	Diabetes (%) <sup>†</sup>	Falls (%)	FN BMD (N)	Any fracture (%)	Hip fracture (%)	MOF (%)	Mortality (%)	Follow-up (years) (mean (range)) <sup>‡</sup>
WHI (2)	B	USA	82,238	11	100.0	64 (49–79)	7.2	32.3	6181	8.4	2.9	5.7	19.8	13.7 (0.0–21.5)
York (2)	B	UK	4532	7	100.0	77 (48–99)	-	30.1	-	8.7	0.9	4.9	2.3	2.0 (0.5–2.0)

\*Number of clinical risk factors available (age, sex, BMI, prior fragility fracture, parental hip fracture, smoking, excess alcohol consumption, glucocorticoid use, rheumatoid arthritis and the new clinical risk factors diabetes and history of falls)

<sup>†</sup>I, type 1 diabetes; II, type 2 diabetes; otherwise, no type reported

<sup>‡</sup>Until time of death; if mortality data not available, then follow-up time for hip fracture

A, cohort used in the initial FRAX development; B, cohort used in the validation; C, cohort previously identified but not used in any previous analysis; D, newly identified cohort

FN BMD, femoral neck bone mineral density; MOF, major osteoporotic fracture; AGES, Age, Gene/Environment Susceptibility-Reykjavik Study; AHS, Adult Health Study; APOSS, Aberdeen Prospective Osteoporosis Screening Study; BEH, Bushehr Elderly Health; CaMos, Canadian Multicentre Osteoporosis Study; DOES, Dubbo Osteoporosis Epidemiology Study; DO-HEALTH, VitaminD3-Omega3-Home Exercise-Healthy Aging and Longevity Trial; ECOSAP, Ecografía Osea en Atención Primaria; EPIC-Norfolk, European Prospective Investigation of Cancer-Norfolk; EPIDOS, Epidemiologie de l'Ostéoporose; EPIFROS, Epidemiology and Fracture Risk factors for Osteoporosis in Spain; EVOS/EPOS, European Vertebral Osteoporosis Study/European Prospective Osteoporosis Study; FORMEN, Fujiwara-kyo Osteoporosis Risk in Men; FRIDEX, Fracture Risk factors and bone Densitometry type central dual X-ray; FROCAT, Fracture Risk factors for Osteoporosis in Catalonia; GERICO, Geneva Retirees Cohort; GLOW, Global Longitudinal Study of Osteoporosis in Women; GOS, Geelong Osteoporosis Study; HAL, Healthy Ageing Initiative; HCS, Hertfordshire Cohort Study; Health ABC, Health, Aging and Body Composition; HUNT, Helseundersøkelsen i Nord-Trøndelag; JPOS, Japanese Population-based Osteoporosis Study; LASA, Longitudinal Aging Study Amsterdam; MINOS, Montceau les Mines Osteoporosis; MrOS, Osteoporotic Fractures in Men; MsOS, Osteoporotic Fractures in Women; NHEFS, National Health and Nutrition Examination Survey (NHANES) I Epidemiologic Follow-up Study; OFELY, Os des Femmes de Lyon; OPRA, Osteoporosis Prospective Risk Assessment; OPUS, Osteoporosis and Ultrasound Study; OSTPRE, Osteoporosis risk factor and PREvention; PERF, Prospective Epidemiologic Risk Factor; REFORM, Reducing Falls with ORtheses and a Multifaceted podiatry intervention; SAOL-IPR-EPIPorto, Santo António dos Olivais, Instituto Português de Reumatologia and EPIPorto; SurcoPhAge, Sarcopenia and Physical Impairment with advancing Age; SCHS, Singapore Chinese Health Study; SCOOP, screening for prevention of fractures in older women; SEMOF, Swiss Evaluation of the Methods of Measurement of Osteoporotic Fracture risk; SOF, Study of Osteoporotic Fractures; SOS, SALT Osteoporosis Study; STRAMBO, Structure of the Aging Men's Bone; SUPERB, Sahlgrenska University hospital Prospective Evaluation of Risk of Bone fractures; TASOAC, Tasmanian Older Adult Cohort; THIN, The Health Improvement Network; WHI, Women's Health Initiative

identified cohorts were also eligible to contribute (Table 1). The reasons for the other cohorts to be excluded ( $n=19$ ) are indicated in Appendix Table 3.

The 60 eligible previously identified cohorts will be combined with the 4 newly identified cohorts to construct the updated FRAX tool. Details of each of the cohorts are summarised below and in Table 1.

## AGES

The Age, Gene/Environment Susceptibility-Reykjavik Study (AGES) was initiated in 2002 to examine risk factors, including genetic susceptibility and gene/environment interactions, in relation to disease and disability in old age. The AGES-Reykjavik sample is drawn from the established population-based cohort, the Reykjavik Study, a cohort of men and women born between 1907 and 1935 and followed in Iceland since 1967. Between 2002 and 2006, the AGES-Reykjavik study re-examined 5764 survivors of the Reykjavik Study [9, 10]. Participants were assessed with quantitative computed tomography (QCT) and the obtained CT images were processed to derive dual-energy X-ray absorptiometry (DXA)-equivalent areal BMD measures. The cohort was previously identified. For this study, 5706 participants (2419 men) were included with a mean age of 77 years and a mean follow-up time of 8.0 years. BMD was measured in 4782 individuals.

## AHS

The Adult Health Study (AHS) documents the late health effects of radiation exposure among atomic bomb survivors in Hiroshima and Nagasaki. The original AHS cohort consisted of about 15,000 atomic bomb survivors and 5000 controls selected from residents in Hiroshima and Nagasaki using the 1950 national census supplementary schedules and the Atomic Bomb Survivors Survey. AHS subjects have been followed through biennial medical examinations since 1958 with a participation rate of approximately 80% throughout this period [11, 12]. BMD was measured at each biennial health examination using DXA (Hologic QDR 2000) since December 1993. The cohort was a source cohort for the original FRAX tool. For this study, 2613 participants (749 men) were included with a mean age of 65 years and a mean follow-up time of 3.9 years. BMD was measured in 2596 individuals.

## APOSS

The Aberdeen Prospective Osteoporosis Screening Study (APOSS) is a population-based screening programme for osteoporotic fracture risk [13]. All residents in Grampian, northeast Scotland, are issued with a unique number known

as the Community Health Index when they register with their primary care physician. Approximately 7200 women 45–54 years of age were randomly selected from this community-based register, and 5119 women came for the initial visit that took place between 1990 and 1994. All participants underwent bone densitometry and risk factor assessment by questionnaire, and the women were invited to undergo further assessment between 1997 and 2000. A total of 3883 women attended the second visit. Finally, a postal questionnaire was sent in 2002 to ascertain further fractures and to collect data on medical conditions and treatments. BMD was measured by DXA using Norland scanners. At the first visit, all the women were scanned using the same machine. At the second visit, the majority of women were scanned using an XR26, but 357 women (11.5%) were scanned using an XR36. The cohort was previously identified. For this study, 5119 women were included with a mean age of 48 years and a mean follow-up time of 8.8 years. BMD was measured in 5112 individuals.

## AUSTRIOS B

The AUSTRIOS B cohort is a prospective cohort study of elderly female patients above 70 recruited in 95 nursing homes in four counties in Austria [14]. The study centre was located in Graz. Patients were screened, enrolled and followed up by five mobile study teams consisting of a physician, a nurse and a medical student. Comorbidities and medication as well as laboratory data and bone ultrasound were documented. Outcomes included major fractures and other health complications. The patients, all Caucasian because of the ethnic composition of that age group in Austria, had to be able to walk a short distance independently, with the use of canes or a walker, or with the support of a nurse. The cohort was previously identified. For this study, 2064 participants (327 men) were included with a mean age of 84 years and a mean follow-up time of 1.2 years.

## BEH

The Bushehr Elderly Health (BEH) programme is a prospective population-based study with multistage stratified-cluster sampling aimed at investigating the prevalence of non-communicable diseases and its associated risk factors. Between March 2013 and October 2014, 3000 men and women were enrolled as a representative urban sample of people aged 60 years and older residing in the city of Bushehr, the capital city of a province located in South Iran [15, 16]. BMD was measured by DXA (Discovery WI, Hologic). The cohort was previously identified. For this study, 2426 participants (1166 men) were included with a mean age of 69 years and a mean follow-up time of 4.2 years. BMD was measured in 2417 individuals.



## Bern

The Bern cohort is a referral population of about 40,000 men and women from the Osteoporosis Clinic at the University Hospital in Bern, Switzerland. The participants, usually with one or more risk factors for osteoporosis, were recruited between 1988 and 2018. BMD was measured by DXA (Hologic QDR®, 1000, 2000, 4500A/W, Discovery A/C) with cross-calibration (Personal communication of primary data on the Bern cohort with Kurt Lippuner, May 1, 2019). The cohort was previously identified. For this study, 23,185 participants (3493 men) were included with a mean age of 59 years and a mean follow-up time of 7.8 years. BMD was measured in 22,830 individuals.

## CaMos

The Canadian Multicentre Osteoporosis Study (CaMos) is a population-based, prospective age-stratified cohort. The study documented the incidence of fractures and risk factors in a random sample of 9423 men and women aged 25 years or more selected from regional residential telephone listings during 1995–1997. The sampling frame is from nine study centres (St John's, Halifax, Quebec City, Kingston, Toronto, Hamilton, Saskatoon, Calgary and Vancouver) in nine provinces [17]. BMD was measured by DXA using Hologic QDR 1000 or 2000 or Lunar DPX densitometers. The cohort was a source cohort for the original FRAX tool. For this study, 9423 participants (2884 men) were included with a mean age of 62 years and a mean follow-up time of 12.9 years. BMD was measured in 8290 individuals.

## DOES

The Dubbo Osteoporosis Epidemiology Study (DOES), started in 1989, is a longitudinal population-based study of women and men aged 60 years and older living in Dubbo, 400 km northwest of Sydney, Australia [18]. Participation in the study was 56% of the population. Baseline measurements included BMD assessed using DXA (GE-Lunar, DPX and Prodigy). The cohort was a source cohort for the original FRAX tool. For this study, 2654 participants (1068 men) were included with a mean age of 70 years and a mean follow-up time of 8.8 years. BMD was measured in 2116 individuals.

## DO-HEALTH

The VitaminD3-Omega3-Home Exercise-Healthy Aging and Longevity Trial (DO-HEALTH) is a multicentre clinical trial among 2157 community-dwelling European men

and women age 70 years and older at 7 recruitment centres located in 5 different countries (Zurich, Basel, Geneva, Toulouse, Berlin, Innsbruck and Coimbra) [19, 20]. Enrolment occurred between December 2012 and November 2014. The randomised, placebo-controlled trial has a  $2 \times 2 \times 2$  factorial design testing a simple home exercise programme and/or vitamin D, and/or omega-3 fatty acids, over a 3-year period. BMD was assessed at four recruiting centres equipped with Lunar iDXA machines. The cohort was previously identified. For this study, 2157 participants (826 men) were included with a mean age of 75 years and a mean follow-up time of 2.9 years. BMD was measured in 1452 individuals.

## ECOSAP

The Ecografía Osea en Atención Primaria (ECOSAP) is a referral population of 5201 women aged 65 or older who were enrolled in a 3-year, prospective study by a nonrandomised sampling of consecutive cases in 58 primary care centres in Spain between March 2000 and June 2001, regardless of the reason for consultation [21, 22]. An average of 90 women were included from each centre (range, 26–161). The cohort was previously identified. For this study, 5201 women were included with a mean age of 72 years and a mean follow-up time of 3.3 years.

## EPIC-Norfolk

The European Prospective Investigation of Cancer (EPIC) study is a prospective cohort study designed to investigate the aetiology of major chronic diseases. The Norfolk cohort was recruited between 1993 and 1997 and comprised men and women aged 45 to 74 years identified from general practice listings [23, 24]. The cohort was previously identified. For this study, 25,636 participants (11,606 men) were included with a mean age of 59 years and a mean follow-up time of 19.3 years.

## EPIDOS

The Epidémiologie de l'Ostéoporose (EPIDOS) is a prospective multicentre study on risk factors for hip fracture in elderly ambulatory women aged 75–95 years recruited through mailings using large population-based listings such as electoral rolls in five French centres (Amiens, Lyon, Montpellier, Paris, Toulouse) between April 1992 and December 1993 [25, 26]. BMD was measured by DXA (Lunar DPX Plus). The cohort was a validation cohort for the original FRAX tool. For this study, 7598 women were included with a mean age of 80 years and a mean follow-up time of 2.8 years. BMD was measured in 7562 individuals.



## EPIFROS

The EPIde miology and Fracture Risk factors for Osteoporosis in Spain (EPIFROS) cohort is a population-based sample of men and women between 40 and 96 years of age, recruited between 2007 and 2009 from the Asturias region in the Northwest of Spain [27, 28]. The cohort was identified through the systematic review. For this study, 284 participants (129 men) were included with a mean age of 62 years and a mean follow-up time of 10.0 years. BMD was measured in 12 individuals.

## EVOS/EPOS

The European Vertebral Osteoporosis Study (EVOS), started in 1989, is comprised of age- and sex-stratified random samples from 36 centres in 19 European countries [29]. Equal numbers of men and women were drawn in each centre within six 5-year age bands (50–54 up to 75–79 years) during 1989. BMD was measured in 13 centres by DXA using pencil beam machines that were cross-calibrated using the European spine phantom. The sample provided the framework for the European Prospective Osteoporosis study (EPOS) where repeated assessment was undertaken in 29 of the centres [30, 31]. The cohort was a source cohort for the original FRAX tool. For this study, 17,342 participants (8050 men) were included with a mean age of 64 years and a mean follow-up time of 3.1 years. BMD was measured in 5296 individuals.

## FORMEN

The Fujiwara-kyo Osteoporosis Risk in Men (FORMEN) study is an ancillary study of a larger prospective, community-based cohort study, the Cohort Study for Functioning Capacity and Quality of Life in Elderly Japanese, also referred to as the Fujiwara-kyo Study. The FORMEN study examines elderly male participants (65 years and older) of the Fujiwara-kyo Study, enrolled between June 2007 and October 2008, for bone health [32, 33]. BMD measurement was undertaken using a Hologic QDR 4500 device. The cohort was previously identified. For this study, 1888 men were included with a mean age of 72 years and a mean follow-up time of 8.6 years. BMD was measured in 1884 individuals.

## Framingham–offspring

In 1971, the Framingham Offspring Study ( $n = 5124$ ) enrolled the adult offspring (and their spouses) of the original Framingham cohort participants. DXA scans were obtained up to 3 times every 4 years between 1996 and 2008 using a Lunar DPX-L densitometer (GE Lunar Corp,

Madison, WI, USA) [34, 35]. For this study, 3539 participants (1625 men) were included with a mean age of 61 years and a mean follow-up time of 16.5 years. BMD was measured in 2939 individuals.

## Framingham–original

The Framingham Original Cohort, initiated in 1948, is comprised of 5209 Caucasians who were systematically recruited as a two thirds sample of the population of Framingham, MA, USA, for the purpose of determining risk factors for cardiovascular disease [36]. Since 1948, these participants have been examined every 20 years. From 1987 through 1999, all surviving participants were invited for 3 BMD tests, approximately 4 years apart. BMD was measured using a dual-photon absorptiometer from 1987 through 1991 and a DXA from 1992 through 1999 (both manufactured by Lunar Corp) [34, 35]. The cohort was previously identified. For this study, 1166 participants (405 men) were included with a mean age of 80 years and a mean follow-up time of 9.6 years. BMD was measured in 896 individuals.

## FRIDEX

The Fracture Risk factors and bone DEnsitometry type central dual X-ray (FRIDEX) cohort is constituted of women referred by general practitioners and specialists for undergoing central bone densitometry by DXA for the initial study of osteoporosis or treatment follow-up, who accept to answer an extensive questionnaire on risk factors for osteoporotic fracture (family history of osteoporosis and hip fracture, clinical risk factors and lifestyle habits related to diet and toxic substances). This cohort was initiated in 1999 at the Bone Densitometry Unit of the Department of Nuclear Medicine of the University Hospital Vall d'Hebrón in Barcelona [37, 38]. BMD was measured by DXA (Lunar Prodigy). The cohort was identified through the systematic review. For this study, 815 women were included with a mean age of 57 years and a mean follow-up time of 9.9 years. BMD was measured in 815 individuals.

## FROCAT

The Fracture Risk factors for Osteoporosis in CATalonia (FROCAT) cohort represents a Spanish cohort of men and women between 40 and 90 years old assigned to family physicians participating in the study that were working in the Public Health Services and practices managed by the Catalan Health Institute. The sample of patients was taken from those who were assigned to the family physicians in 2001 and who had been previously selected by simple randomization by stratified age and sex groups according to the Catalan population census and province [39]. A

subgroup of the patients underwent BMD measurements by DXA. The cohort was identified through the systematic review. For this study, 1954 participants (865 men) were included with a mean age of 69 years and a mean follow-up time of 9.9 years. BMD was measured in 238 individuals.

### GERICO

The Geneva Retirees Cohort (GERICO) is a prospective ongoing cohort study designed to identify the gene loci and musculoskeletal factors related to fracture risk in recently retired workers from the Geneva area. Healthy community-dwelling postmenopausal women and men were recruited at the age of 63 to 67 years between 2008 and 2011 by advertisement in the local press, the Geneva University Hospitals or local large companies at time of retirement [40]. BMD was assessed using a Hologic QDR Discovery. The cohort was previously identified. For this study, 765 participants (157 men) were included with a mean age of 68 years and a mean follow-up time of 3.6 years. BMD was measured in 751 individuals.

### GLOW

The Global Longitudinal Study of Osteoporosis in Women (GLOW) is an observational study of women aged 55 years and older sampled from 17 primary care practices in 10 countries (Australia, Belgium, Canada, France, Germany, Italy, Netherlands, Spain, UK and USA) [41]. Sampling took place from October 2006 to February 2008 and was stratified by age to ensure that two-thirds of the women surveyed were 65 years of age and older. The cohort was previously identified. For this study, 60,393 women were included with a mean age of 69 years and a mean follow-up time of 4.0 years.

### GOS

The Geelong Osteoporosis Study (GOS) is an ongoing population-based, prospective age-stratified cohort of women aged 20 years and older. Subjects were randomly selected from electoral rolls of the Barwon Statistical Division that includes the Geelong region in south-eastern Australia during the years 1993–1997 [42]. BMD measurements were performed using DXA (Lunar DPX-L, GE-Prodigy). The cohort was a validation cohort for the original FRAX tool. For this study, 1865 women were included with a mean age of 63 years and a mean follow-up time of 6.9 years. BMD was measured in 1807 individuals.

### Gothenburg I

The Gothenburg I study comprised four birth cohorts of 2375 randomly sampled men and women aged 70 years or more followed for up to 20 years after a baseline BMD measurement [43, 44]. The participation rate was 73%. The participants were drawn randomly from the population register in Gothenburg by the date of birth to provide cohorts aged 70, 76, 79 and 85 years at the time of investigation (1985–1993). The cohort was a source cohort for the original FRAX tool. For this study, 2375 participants (929 men) were included with a mean age of 86 years and a mean follow-up time of 9.2 years.

### Gothenburg II

The Gothenburg II study comprised a randomly drawn population cohort of women aged 21–89 years between 1992 and 1997 [45]. Risk factors for osteoporosis were recorded by use of a standardised questionnaire. The cohort was a source cohort for the original FRAX tool. For this study, 11,376 women were included with a mean age of 59 years and a mean follow-up time of 13.2 years.

### HAI

The Healthy Ageing Initiative (HAI) is an ongoing observational cohort study of 70-year-old adults in Umeå, northern Sweden, since 2012. Its goal is to investigate traditional and novel risk factors for cardiovascular disease and injurious falls and fractures. Inclusion criteria for the HAI were residency in the Umeå municipal area and an age of 70 years at the time of participation. Eligible participants were drawn from population registers and invited via letter and subsequent telephone call [46]. BMD measurements were performed with a Lunar iDXA device. The cohort was previously identified. For this study, 3618 participants (1800 men) were included with a mean age of 70 years and a mean follow-up time of 2.6 years. BMD was measured in 3535 individuals.

### HCS

The Hertfordshire Cohort Study (HCS) is a population-based study of men and women born between 1931 and 1939 in the county of Hertfordshire, UK [47]. It was initiated to evaluate interactions between the genome, the intrauterine and early postnatal development and adult diet and lifestyle in the aetiology of chronic disorders in later life. BMD was measured using a Hologic QDR 4500 instrument. The cohort was previously identified. For this study, 632 participants

(314 men) were included with a mean age of 65 years and a mean follow-up time of 8.9 years. BMD was measured in 631 individuals.

### Health ABC

The Health, Aging and Body Composition (Health ABC) study is a prospective observational cohort study examining the relationship between changes in body composition and disability, morbidity and mortality. The cohort is comprised of men and women who were between 70 and 79 years of age in the recruitment period from March 1997 to July 1998. Participants were recruited from all age-eligible Blacks residing in Pittsburgh, PA, and Memphis, TN, and a random sample of White Medicare beneficiaries [48]. The cohort is approximately 40% Black and evenly divided between male and female participants. BMD was assessed at both field centres by DXA (Hologic QDR 4500A). The cohort was previously identified. For this study, 3075 participants (1491 men) were included with a mean age of 74 years and a mean follow-up time of 11.9 years. BMD was measured in 3047 individuals.

### HUNT

Helse Undersøkelsen i Trøndelag (HUNT) study is an ongoing population-based study, which has collected data in four surveys: HUNT1 (1984–86), HUNT2 (1995–97), HUNT3 (2006–08) and HUNT 4 (2017–2019). In each survey, all inhabitants in Nord-Trøndelag County in central Norway, aged 20 years or older, were invited to participate [49, 50]. In HUNT 3, BMD was measured by DXA using a Lunar Prodigy scanner. The cohort was previously identified. For this study, 50,213 participants (22,799 men) were included with a mean age of 53 years and a mean follow-up time of 12.4 years. BMD was measured in 11,583 individuals.

### JPOS

The Japanese Population-based Osteoporosis Study (JPOS) is a population-based study launched in 1996 to produce a BMD reference database using DXA (Hologic QDR 4500 device) to evaluate bone turnover markers in Japanese women and to determine risk factors related to osteoporotic fractures [51]. Subjects were randomly selected according to resident registrations at seven municipalities distributed throughout Japan. The cohort was previously identified. For this study, 1950 women were included with a mean age of 58 years and a mean follow-up time of 13.3 years. BMD was measured in 1935 individuals.

### LASA

The Longitudinal Aging Study Amsterdam (LASA) is an ongoing multidisciplinary cohort study on predictors and consequences of changes in physical, cognitive, emotional and social functioning in older people in The Netherlands [52–54]. Briefly, a sample of 3107 older men and women aged 55–85 years, stratified by age, sex and urbanization, was drawn from the population registers of 11 municipalities in areas in the west, northeast and south of The Netherlands. Data collection took place in 1992–1993 (baseline), in 1995–1996 and in 1998–1999. BMD was measured by DXA (Hologic QDR 2000). The cohort was identified through the systematic review. For this study, 1509 participants (728 men) studied at wave C (1995) were included with a mean age of 76 years and a mean follow-up time of 5.1 years. BMD was measured in 522 individuals.

### Maccabi

The Maccabi database comprises the electronic medical records of all patients from the Maccabi Healthcare Services, a large Israeli government-funded health maintenance organization insuring and providing medical care for 2.5 million current members (i.e. approximately 25% of the Israeli population) [55]. All BMD scans were conducted using the same standardised model of the Lunar Prodigy. The cohort was previously identified. For this study, 659,266 participants (316,287 men) were included with a mean age of 56 years and a mean follow-up time of 9.6 years. BMD was measured in 35,829 individuals, with scanning performed up to 1 year before or after the baseline visit.

### Manitoba

The Manitoba cohort is a population-based registry that captures all referrals for DXA testing in the Province of Manitoba, Canada, with linkage to health services databases for longitudinal analyses [56, 57]. From 1990 to 2000, DXA measurements were performed with a pencil-beam instrument (Lunar DPX; Lunar Corporation, Madison, WI) and after this date, cross-calibrated fan-beam instruments were used (Lunar Prodigy until 2012, Lunar iDXA from 2012 onwards, GE Healthcare). The cohort was previously identified. Age 20 years or older at the time of baseline DXA performed between January 1996 and March 2018 were included with a mean age of 63 years and a mean follow-up time of 9.0 years. BMD was measured in 92,102 individuals.

## MINOS

The Montceau les MINes OSteoporosis (MINOS) study is a prospective study of osteoporosis and of its determinants in men aged 50 to 85 years that was initiated in 1995 as a collaboration between the INSERM (the French National Institute of Health and Medical Research) and the Société de Secours Minière de Bourgogne (SSMB), a health insurance company, in Montceau les Mines, a town situated 130 km northwest of Lyon in the Department (district) Saône et Loire [58]. BMD was measured by DXA (Hologic QDR 1500). The cohort was previously identified. For this study, 841 men were included with a mean age of 65 years and a mean follow-up time of 8.9 years. BMD was measured in 675 individuals.

## Miyama

This population-based epidemiological study, initiated in 1990, was conducted in Miyama, a mountain village in Wakayama Prefecture, Japan. Subjects ( $n=400$ ) for the BMD cohort were selected by sex and age stratum from the full list of residents born in 1910–1949, with 50 men and 50 women in each age decade [59]. BMD was measured using DXA (Lunar DPX). The cohort was a validation cohort for the original FRAX tool. For this study, 400 participants (200 men) were included with a mean age of 59 years and a mean follow-up time of 9.3 years. BMD was measured in 400 individuals.

## MrOS Hong Kong

The Osteoporotic Fractures in Men (MrOS) Hong Kong study included Chinese men of Asian ethnicity aged 65 years and older who were enrolled between 2001 and 2003. This cohort was an age-stratified cohort giving 33% of subjects in each of the following age groups: 65 to 69, 70 to 74 and  $\geq 75$  years. Subjects were recruited in housing estates and community centres for the elderly [60, 61]. Subjects had BMD evaluation using Hologic QDR 4500 devices. The cohort was previously identified. For this study, 2000 men were included with a mean age of 72 years and a mean follow-up time of 9.9 years. BMD was measured in 2000 individuals.

## MrOS Sweden

The Osteoporotic Fractures in Men (MrOS) Sweden cohort is a multicentre prospective cohort of mainly white men aged 69 to 81 years. Subjects were enrolled between October 2001 and December 2004 in three sites (Malmö, Göteborg and Uppsala) by identifying men using national population

registers [62, 63]. Both Hologic QDR 4500 (Göteborg) and GE Lunar Prodigy (Malmö and Uppsala) devices were used to measure BMD. The cohort was previously identified. For this study, 3014 men were included with a mean age of 75 years and a mean follow-up time of 11.4 years. BMD was measured in 2820 individuals.

## MrOS USA

The Osteoporotic Fractures in Men (MrOS) USA study enrolled men, 65 years of age or older, from March 2000 through April 2002. Community-based recruitment occurred at six US academic medical centres in Birmingham, AL; Minneapolis, MN; Palo Alto, CA; Pittsburgh, PA; Portland, OR; and San Diego, CA [64, 65]. Participants had BMD measured using Hologic QDR 4500 devices. The cohort was previously identified. For this study, 5994 men were included with a mean age of 74 years and a mean follow-up time of 12.5 years. BMD was measured in 5994 individuals.

## MsOS Hong Kong

The Osteoporotic Fractures in Women (MsOS) Hong Kong included Chinese women of Asian ethnicity aged 65 years and older who were recruited between 2002 and 2003. This cohort was an age-stratified cohort giving 33% of subjects in each of the following age groups: 65 to 69, 70 to 74 and  $\geq 75$  years. Subjects were recruited from housing estates and community centres for the elderly [66]. Participants had BMD measured using Hologic QDR 4500 devices. The cohort was previously identified. For this study, 2000 women were included with a mean age of 73 years and a mean follow-up time of 8.8 years. BMD was measured in 2000 individuals.

## NHEFS

The National Health and Nutrition Examination Survey (NHANES) I Epidemiologic Follow-up Study (NHEFS) was a national longitudinal study designed to investigate the relationships between clinical, nutritional and behavioural factors assessed in NHANES I and subsequent mortality, morbidity and hospital utilization, as well as changes in risk factors, functional limitations and institutionalization [67]. The NHEFS cohort includes all persons 25–74 years of age who completed a medical examination at NHANES I in 1971–1975 ( $n=14,407$ ). The follow-up data collection was conducted from 1982 through 1984 for all members of the NHEFS cohort who were still alive and residing in their baseline location. The cohort was previously identified. For this study, 12,220 participants (4941 men) were included with a mean age of 49 years and a mean follow-up time of 10.0 years.



## OFELY

The Os des Femmes de Lyon (OFELY) cohort comprises an age-stratified cohort of women aged 31–89 years randomly recruited from the affiliates of a large health insurance company from the Rhone district (Mutuelle Générale d'Éducation Nationale, Lyon, France) between February 1992 and December 1993 [68]. BMD was measured by DXA using a Hologic QDR 2000 or Hologic QDR 4500. The cohort was previously identified. For this study, 867 women were included with a mean age of 59 years and a mean follow-up time of 17.5 years. BMD was measured in 861 individuals.

## OPRA

From December 1995 to May 1999, women, picked randomly from the city files of Malmö, Sweden, were invited to participate in the Malmö Osteoporosis Prospective Risk Assessment (OPRA) study. Of the 1604 women initially invited, 1044 (65%) participated in the baseline investigation, which took place all year round. All women were 75 years old at the initial visit [69]. BMD was assessed by DXA technique (Lunar DPX-L). The cohort was previously identified. For this study, 1044 women were included with a mean age of 75 years and a mean follow-up time of 11.6 years. BMD was measured in 947 individuals.

## OPUS

The Osteoporosis and Ultrasound Study (OPUS) is a multi-centre age-stratified population-based female cohort involving 5 centres from different European countries (Sheffield and Aberdeen in the UK, Berlin and Kiel in Germany and Paris in France) [70]. Participants of the OPUS study were recruited from random population samples between April 1999 and April 2001. Women of two different age segments (20–39 years of age, “younger women”, or 55–79 years of age, “older women”) were included. Bone densitometry was performed using DXA (Hologic QDR 4500 in the Kiel, Paris and Sheffield centres; Lunar Expert devices in the Aberdeen and Berlin centres). The cohort was a validation cohort for the original FRAX tool. For this study, 2882 women were included with a mean age of 61 years and a mean follow-up time of 6.1 years. BMD was measured in 2836 individuals.

## OsteoLaus

The OsteoLaus study is a single-centre nested population-based cohort of postmenopausal women living in the city of Lausanne, Switzerland. It is a substudy of the CoLaus/

PsyColaUS study, an ongoing prospective study aiming to assess the determinants of cardiovascular and psychiatric diseases using a population-based sample drawn from the city of Lausanne. Between September 2009 and September 2012, all women aged between 50 and 80 years from the CoLaus/PsyCoLaus study (first follow-up) were invited to participate in the OsteoLaus study, and 85% accepted ( $n = 1475$ ). The first follow-up of the OsteoLaus study was between September 2012 and June 2015 ( $n = 1349$ ) and the second follow-up between March 2015 and February 2018 ( $n = 1234$ ). The mean follow-up period for each visit is 2.5 years, and the study is projected to have at least four follow-up visits. The aims of the OsteoLaus study are to compare different models of fracture risk prediction and to assess the relationship between osteoporosis and cardiovascular diseases [71, 72]. DXA scans were performed to measure BMD using the Discovery A System (Hologic). The cohort was previously identified. For this study, 1475 women were included with a mean age of 65 years and a mean follow-up time of 4.6 years. BMD was measured in 1457 individuals.

## OSTPRE

The Kuopio OSTeoporosis risk factor and PREvention (OST-PRE) study in Finland was initiated through a postal inquiry sent to all 14,220 women aged 47–56 who were residents of Kuopio province in 1989 [73, 74]. A total of 13,100 women responded to the inquiry, of whom 1214 were excluded for incomplete information. This left a study population of 11,886 women. A random stratified sample underwent BMD testing by DXA using the Lunar DPX. The cohort was previously identified. For this study, 11,200 women were included with a mean age of 57 years and a mean follow-up time of 9.8 years. BMD was measured in 2761 individuals.

## PERF

The Prospective Epidemiologic Risk Factor (PERF) study aimed to find risk factors associated with age-related diseases. Women who had previously either participated in clinical randomised placebo-controlled studies or had been screened for previous studies at the Centre for Clinical and Basic Research in Denmark were invited to participate in PERF. A total of 5855 Danish postmenopausal women aged 48 to 89 years were enrolled in the PERF study during 1999 to 2001 [75]. BMD was measured by DXA using either a Hologic QDR 2000 or a Lunar Prodigy scanner. The cohort was a validation cohort for the original FRAX tool. For this study, 4225 women were included with a mean age of 63 years and a mean follow-up time of 7.3 years. BMD was measured in 2446 individuals.

## REFORM

The REducing Falls with ORthoses and a Multifaceted podiatry intervention (REFORM) study is a pragmatic open two-arm cohort randomised controlled trial. Community dwelling men and women aged 65 years and over from National Health Service (NHS) podiatry clinics in England and from one podiatry clinic at the National University of Ireland, Galway, were recruited between October 2012 and August 2014 [76]. In total, 1010 participants were randomised to either a podiatry intervention, including foot and ankle exercises, foot orthoses and, if required, new footwear, and a falls prevention leaflet ( $n=493$ ) or usual podiatry treatment plus a falls prevention leaflet ( $n=517$ ). The cohort was previously identified. For this study, 1010 participants (400 men) were included with a mean age of 78 years and a mean follow-up time of 1.5 years.

## Rochester

The Rochester cohort was recruited from two random population samples stratified by decade of age, one from 1980 comprising women who were subsequently followed for up to 20 years [77] and another sample of women and men from 1990 followed for 8 years [78]. BMD was measured by dual photon absorptiometry in the first cohort (cross-calibrated to DXA) and by DXA (Hologic QDR 2000) in the second group. The cohort was a source cohort for the original FRAX tool. For this study, 1003 participants (348 men) were included with a mean age of 57 years and a mean follow-up time of 7.7 years. BMD was measured in 995 individuals.

## Rotterdam

The Rotterdam Study (RS) is a single-centre population-based follow-up study conducted in the suburb of Ommoord in Rotterdam, where all inhabitants aged 55 years or older were invited [79–83]. The baseline study comprised a home interview followed by two visits at the research centre for clinical examinations. The initial cohort (RS-I) recruited men and women in 1990 with follow-up visits in 1993–1995 (RS-I-2), 1997–1999 (RS-I-3), 2002–2004 (RS-I-4), 2009–2011 (RS-I-5) and 2014–2015 (RS-I-6). In 2000–2001, a second cohort was established (RS-II) with participants aged above 55 years having follow-up examinations in 2004–2005 (RS-II-2), 2011–2012 (RS-II-3) and 2015–2016 (RS-II-4). Between 2006 and 2008, a third, younger cohort (RS-III-1) was established with participants aged above 45 years with follow-up visit in 2012–2014 (RS-III-2). BMD was assessed by DXA using a Lunar DPX-L (RS-I-1, RS-I-2, RS-I-3 and RS-II-1), Lunar Prodigy (RS-I-4, RS-II-2, RS-III-1) and iDXA (RS-I-5, RS-I-6, RS-II-3, RS-II-4, RS-III-2). The cohort was a source cohort for

the original FRAX tool. For this study, 14,619 participants (6024 men) were included with a mean age of 66 years and a mean follow-up time of 10.8 years. BMD was measured in 11,040 individuals.

## SAOL-IPR-EPIPorto

Data of three different Portuguese cohorts, Santo António dos Olivais (SAOL) in Coimbra, Instituto Português de Reumatologia (IPR) in Lisbon and EPIPorto in Porto (from the centre, south and north of the country, respectively), were combined [84]. The SAOL study is a population-based cohort, designed to examine the association between a variety of potential risk factors and osteoporosis and fragility fractures. From March 1998 to April 2000, 1745 persons, aged > 18 years, were identified, contacted and recruited, with the method of random numbers selection from the electoral register of the county, stratified by gender and 5-year age strata. The population of the prospective IPR study consists of 819 women and men aged 40 years or older at baseline, of whom a DXA was performed between December 1999 and July 2001. Participants were referred by physicians, including general practitioners, rheumatologists, endocrinologists, orthopaedic surgeons and gynaecologists. The EPIPorto study is a population-based cohort study, with the aim of assessing determinants of health in the adult population of Porto. For this purpose, 2485 community-dwellers aged > 18 years, selected in 1999–2003 by random digit phone dialling, have been repeatedly evaluated. The second evaluation, performed in 2005–2006, including 1466 persons, recorded all clinical parameters relevant to FRAX. Only persons aged > 40 years and with a complete set of data on FRAX clinical risk factors were included. DXA scans were performed using a Hologic QDR 4500 bone densitometer in all cases. The cohorts were previously identified. For this study, 1227 participants (288 men) were included with a mean age of 56 years and a mean follow-up time of 12.3 years. BMD was measured in 1225 individuals.

## SarcoPhAge

The Sarcopenia and Physical Impairment with advancing Age (SarcoPhAge) study, a 5-year prospective longitudinal study, was developed in Liège, Belgium, in June 2013 with the purpose of assessing the health and functional outcomes of sarcopenia [85]. Elderly subjects aged 65 years and older were recruited in different departments of an outpatient clinic in Liège and through advertisements in the press. BMD measurements were performed with a Hologic Discovery A device. The cohort was previously identified. For this study, 260 participants (109 men) were included with a mean age of 76 years and a mean follow-up time of 1.9 years. BMD was measured in 247 individuals.

## SCHS

The Singapore Chinese Health Study (SCHS) is a community-based prospective cohort study to investigate diet, lifestyle factors and risk of chronic diseases. Between April 1993 and December 1998, 63,257 middle-aged to older men and women were enrolled. The study participants were restricted to two major dialect groups in Singapore, the Hokkiens and the Cantonese, who originated from Fujian and Guangdong provinces in Southern China. During the enrolment period, all study participants were residents of government housing estates, where 86% of the Singapore population was housed [86, 87]. The cohort was previously identified. For this study, 52,042 participants (22,160 men) were included with a mean age of 62 years and a mean follow-up time of 8.9 years.

## SCOOP

The screening for prevention of fractures in older women (SCOOP) study has been designed as a multi-centre, unblinded, pragmatic, randomised controlled trial with 5-year follow-up to assess the effectiveness and cost-effectiveness of a community-based screening programme to prevent fractures in older women [88, 89]. Women aged 70–85 years were recruited from primary care in seven regions in England (Norwich, Southampton, Bristol, Birmingham, Manchester, York and Sheffield). Consenting participants were randomised between April 2008 and July 2009 to either a screening arm ( $n=6233$  receiving a care algorithm including FRAX and drug targeting) or the control arm ( $n=6250$  receiving usual primary care for osteoporosis based on opportunistic case finding). BMD measurements were performed with DXA in selected participants. The cohort was previously identified. For this study, 12,483 women were included with a mean age of 76 years and a mean follow-up time of 4.8 years. BMD was measured in 2718 individuals.

## SEMOF

The Swiss Evaluation of the Methods of Measurement of Osteoporotic Fracture risk (SEMOF) study is a prospective, multi-centre, population-based study. Elderly women (70 to 80 years old) were randomly recruited from official state registries between January 1998 and April 2000 [90]. The cohort was a validation cohort for the original FRAX tool. For this study, 7133 women were included with a mean age of 75 years and a mean follow-up time of 2.9 years [91]. BMD was measured in 920 individuals (Hologic QDR 4500A). Those who decided to attend their visit at the SEMOF site of the Osteoporosis Policlinic of the

University Hospital of Bern, Switzerland ( $n=701$ ) had their BMD remeasured [90].

## Sheffield

The Sheffield cohort comprised women aged 75 years or more selected randomly from the population of Sheffield, UK, and surrounding districts between 1993 and 1999. Approximately 35,000 women, identified from general practitioner listings, were contacted by letter and invited to attend for assessment of their skeletal status. Five thousand eight hundred and seventy-three women were willing to attend for the screening visit. Of these, 281 were excluded, and the remainder randomly allocated after informed consent to treatment with the bisphosphonate clodronate, or to an identical placebo [92, 93]. The participants for this study comprised women allocated to treatment with placebo only. All women had baseline assessment of BMD undertaken the Hologic QDR 4500. The cohort was a source cohort for the original FRAX tool. For this study, 2606 women were included with a mean age of 80 years and a mean follow-up time of 3.4 years. BMD was measured in 2584 individuals.

## SOF

The Study of Osteoporotic Fractures (SOF) is a multicentre study of risk factors for fracture in women aged 65 years and older. The participants were community-based ambulatory women recruited between September 1986 through October 1988, from population-based listings at four clinical centres in Portland, OR; Minneapolis, MN; Baltimore, MD; and the Monongahela Valley near Pittsburgh, PA [94, 95]. Women unable to walk without assistance and women with bilateral hip replacements were excluded. In addition, black women were excluded because of their low incidence of hip fracture. From January 1989 to December 1990, all participants were invited to undergo a second evaluation. BMD was measured at the second visit using Hologic QDR 1000 scanners. The cohort was a validation cohort for the original FRAX tool. For this study, 9704 women were included with a mean age of 72 years and a mean follow-up time of 14.1 years. BMD was measured in 8074 individuals.

## SOS

The SALT Osteoporosis Study (SOS) is a randomised pragmatic trial including women aged 65 to 90 years in 225 general practitioner practices in the northern part of the Netherlands [96, 97]. Women who are not prescribed bone sparing drugs or corticosteroids are eligible for the study and those with at least one clinical risk factor for fractures, as determined by questionnaires, were randomly assigned to an intervention or control group between July 2010 and



April 2014. DXA measurements for the intervention group were performed at six different locations with all locations using a Hologic Discovery device. The cohort was previously identified. For this study, 16,945 women were included with a mean age of 74 years and a mean follow-up time of 3.7 years. BMD was measured in 4167 individuals.

### STOP/IT

The STOP/IT calcium and vitamin D intervention trial is a 3-year, double-blind, placebo-controlled trial in healthy, ambulatory men and women 65 years of age or older who were recruited through direct mailings and presentations in the larger Boston, MA community from February 1992 through February 1993 [98]. Eligible subjects were enrolled and randomly assigned to either the placebo or the calcium–vitamin D group with stratification according to sex, race and decade of age. BMD was measured by a Lunar DPX-L scanner. The cohort was previously identified. For this study, 446 participants (200 men) were included with a mean age of 71 years and a mean follow-up time of 4.3 years. BMD was measured in 444 individuals.

### STRAMBO

The Structure of the Aging Men's Bone (STRAMBO) cohort is a single-centre prospective cohort study evaluating skeletal fragility and its determinants in men. This cohort is the result of a collaboration between INSERM (National Institute of Health and Medical Research) and MTRL (Mutuelle des Travailleurs de la Région Lyonnaise). MTRL is a complementary health insurance company open to all citizens. Men aged 20 to 85 years old living in the greater Lyon were randomly selected from the MTRL lists in 2006–2008 [99]. BMD assessment occurred with the Hologic Discovery A device. The cohort was previously identified. At baseline, 1167 men were included with a mean age of 63 years. BMD was measured in 1145 individuals. Follow-up was undertaken in 823 men aged 60 years or more with a mean follow-up time of 9.2 years.

### SUPERB

The Sahlgrenska University hospital Prospective Evaluation of Risk of Bone fractures (SUPERB) study is a prospective, population-based study that was performed in the greater Gothenburg area and included 3028 ambulant women aged 75 to 80 years, randomly recruited via the Swedish national population register between the years 2013 and 2016. The subjects first received an invitation letter and were then contacted by telephone [100–102]. BMD measurements were performed using a Hologic

Discovery A device. The cohort was previously identified. For this study, 3028 women were included with a mean age of 78 years and a mean follow-up time of 3.6 years. BMD was measured in 3015 individuals.

### TASOAC

The Tasmanian Older Adult Cohort (TASOAC) study is a prospective, population-based study that included 1099 community-dwelling men and women (98% of European descent) aged 50–79 years at baseline. The study was established to identify the environmental, genetic and biochemical factors associated with the development and progression of osteoarthritis and other diseases such as osteoporosis, stroke, ischemic heart disease, diabetes and cancer. Participants in TASOAC were selected from electoral rolls in Southern Tasmania using stratified random sampling by sex and enrolled between March 2002 and September 2004 [103, 104]. BMD was measured using DXA (Hologic Delphi). The cohort was previously identified. For this study, 1099 participants (562 men) were included with a mean age of 63 years and a mean follow-up time of 10.0 years. BMD was measured in 1094 individuals.

### THIN

The Health Improvement Network (THIN) research database contains computerised medical records of a sample of general practitioners in the UK between 1995 and 2004, similar to the General Practice Research Database. The study population consisted of all women aged 50 years or older who were registered at one of THIN practices [105, 106]. The cohort was a validation cohort for the original FRAX tool. For this study, 366,104 women were included with a mean age of 64 years and a mean follow-up time of 5.8 years.

### UK Biobank

The UK Biobank is a long-term study that aims to identify the contribution of genetic and environmental factors to disease. From 2006 to 2010, the UK Biobank recruited 502,647 individuals aged 37 to 76 years from across the UK. Detailed characterization was undertaken using self-completed questionnaires, brief interviews, physical and functional measures and blood collection [107, 108]. BMD was measured using a Lunar iDXA instrument in a subset as part of the ongoing (at the time of writing) imaging study. The cohort was previously identified. For this study, 502,536 participants (229,134 men) were included with a mean age of 57 years and a mean follow-up time of 11.5 years. BMD was measured in 19,692 individuals.

## WHI

The Women's Health Initiative (WHI), carried out at 40 US clinical centres, is a study of postmenopausal women aged 50 to 79 years and free of serious medical conditions at baseline (1993 to 1998) [109, 110]. The study comprises three overlapping randomised controlled studies and an observational study. The WHI Observational Study ( $n=93,676$ ) was designed to examine important causes of morbidity and mortality in postmenopausal women and the trials ( $n=68,132$ ) comprised dietary modification (low-fat diet), menopausal hormone therapy in women with or without uterus and supplementation with calcium and vitamin D. For this analysis, women taking bone-active medication were excluded. BMD was measured at three clinic sites (Pittsburgh, PA; Birmingham, AL; Phoenix/Tucson, AZ), using Hologic QDR 2000, 2000+ or 4500 instruments [111]. The cohort was a validation cohort for the original FRAX tool. For this study, 82,238 women were included with a mean age of 64 years and a mean follow-up time of 13.7 years. BMD was measured in 6181 individuals.

## York

The Primary Care Hip Protector Trial is a pragmatic randomised controlled trial with women aged 70 years or over with one or more risk factors for hip fracture (i.e. low body weight, current smoker, a prior fracture, family history of hip fracture) recruited from registers of general practices in primary care or through the media between September 1999 and November 2000. Participants with risk factors were allocated in a control group or a hip protector intervention group [112, 113]. Additionally, women who had declined to take part in the trial but agreed to take part in other subsequent studies were included. The cohort was a validation cohort for the original FRAX tool. For this study, 4532 women were included with a mean age of 77 years and a mean follow-up time of 2.0 years.

Overall, baseline and follow-up data from 2,138,428 participants (69% women) followed for approximately 20 million person-years will be used as the resource to update FRAX. Of the 64 cohorts, 24 (38%) contribute with only female participants and 6 (9%) only with male participants (Table 1). The smallest cohort contributing to the update of FRAX includes 260 participants (SarcoPhAge), the largest 659,266 participants (Maccabi). The majority of the cohorts are from Europe. However, all continents are represented except for Africa. Most of the cohorts are population-based whereas the remainder are referral cohorts, randomised controlled trials or convenience samples. In the case of randomised controlled trials, individuals allocated to bone

active medication were excluded from analysis in the Sheffield and WHI cohorts.

The mean age of all participants at baseline was 60 years with a range from 20 to 116 years (Table 1). When considering the potential candidates for additional risk factors, the prevalence of diabetes mellitus and falls history is shown in Table 1, with data available in 48 (75%) and 46 (72%) of the cohorts, respectively. BMD measurements were available in 83% of the cohorts. During a mean follow-up of 9.3 years, 194,369 (9.1%) participants sustained a fracture; 116,117 (5.4%) were MOFs, of which 42,468 were at the hip. Specifically, 8557 hip fractures and 27,440 MOFs were sustained in men and 33,911 hip fractures and 88,677 MOFs were documented in women.

Each cohort was assessed for quality 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. Quality scores are given in Table 1.

## Development of the FRAX update

### Established risk factors for fracture

The risk factors in the present FRAX tool comprise body mass index, prior fragility fracture, parental history of hip fracture, current tobacco smoking, long-term oral glucocorticoid use, rheumatoid arthritis, excessive alcohol consumption and other causes of secondary osteoporosis. Femoral neck bone mineral density (BMD) is an optional variable. Each has been subject to meta-analyses to determine their association with fracture risk and dependence on age, sex and time (duration of observation) [1].

The risk factors used for the current version of the FRAX tool remain crucial elements for its update. Baseline assessments in the various cohorts will provide information on participants' age, sex and BMI (computed from height and weight) and the dichotomised clinical risk factors. BMD testing is undertaken by DXA and standardised BMD measurements are used to take into account different equipment manufacturers [114]. Femoral neck T-scores will be calculated from the NHANES III White female reference values [115, 116]. Data on novel risk factors (e.g. severity and

treatment of type 2 diabetes, site, number of and time since previous fracture, prevalent falls) will also be gathered in an as consistent format as possible.

The inclusion of new cohorts with the established risk factors will increase the general applicability of FRAX. This is particularly important for men who were under-represented in the original version of FRAX. Indeed, it is anticipated that sex-dependent differences in risk will emerge [117]. In addition to expanding the resource with additional cohorts, especially male cohorts, a longer follow-up than that used to derive FRAX will increase the precision of time-dependent effects and effects of calendar year. The additional cohorts are expected to provide substantially increased power to explore interaction terms. The original FRAX model was based on 12 population-based cohorts in which there were 1141 hip fractures in individuals followed for 252,000 person years. For the present analysis, there are more than 40,000 hip fractures in 64 cohorts with a follow-up of 19.9 million-person years.

### New risk factors for fracture

In exploring new cohorts and updating cohorts previously used in FRAX, a number of new clinical risk factors will be sought. The risk indicators sought are shown in Appendix Table 4. Criteria for inclusion of clinical risk factors includes their simplicity of use in primary care and international validity. An important additional criterion is to demonstrate the “reversibility of risk” [1, 118]. This concept differs from reversible risk. For example, age is a risk factor for fracture but is not a reversible risk in that age cannot be reversed. Notwithstanding, patients identified on the basis of age respond to pharmacological intervention irrespective of age [119]. Thus, age demonstrates reversibility of risk. Levels of evidence

for reversibility of risk are shown in Table 2. The highest level of evidence is where the risk factor is used as an entry criterion in placebo-controlled trials. The next level is the demonstration that the risk factor does not adversely affect the therapeutic response to treatment. All the current risk factors qualify as level A or B. Additional risk factors will need to satisfy the same criteria. The strongest candidates as additional risk factors are diabetes mellitus and falls history, neither of which scored well in 2007 [1] (Table 2).

**Diabetes** Diabetes (both type 1 and type 2, but particularly type 1) is associated with an increase in risk of hip and non-vertebral fracture. In type 2 diabetes, a longer duration of disease and insulin use is associated with an increased risk [120–122]. Diabetes is not a primary entry variable in the current FRAX construction. Type 1 diabetes is indirectly considered in FRAX as one of the secondary causes of osteoporosis, increasing the calculated fracture probability when BMD is not known but not when BMD is included in the risk calculation. At the time that FRAX was released in 2008, the effect of secondary causes on fracture risk was conservatively assumed to be mediated by their effect to decrease bone density. Rheumatoid arthritis and exposure to glucocorticoids were the only secondary causes of osteoporosis demonstrated to have impact on fracture risk additional to their impact on BMD in the FRAX algorithm, with uncertainty as to whether this was true for other disorders [123]. Several recent reports have shown that for a given FRAX probability or T-score and age, the risk of fracture among individuals with diabetes is higher than the risk in nondiabetics [124–126]. Together, these studies provide compelling evidence that FRAX underestimates the risk of osteoporotic fractures in individuals with type 2 diabetes. Recent evidence has shown that the association between diabetes

**Table 2** Categorization of risk factors for fracture according to evidence for reversibility of risk [1]

Grade	Description	Risk factor
A	Validated by use as inclusion criteria in randomised controlled trials	Low BMD (DXA spine or hip) Prior vertebral fracture Long-term glucocorticoid treatment
B	Does not affect fracture outcomes adversely in randomised controlled trials	Family history of fracture Prior non-vertebral fracture Biochemical markers of bone turnover QUS (at the heel) Smoking Body weight or BMI Age Alcohol intake
C	Untested	Other risk factors
D	Adversely affect intervention outcome	Risk factors for falling

*BMD*, bone mineral density; *DXA*, dual energy X-ray absorptiometry; *QUS*, quantitative ultrasound; *BMI*, body mass index

and future fractures can be influenced by the severity of the disease, with insulin-treated type 2 diabetes patients having a higher fracture risk compared to those on oral antidiabetics [121, 127]. Adding severity of the disease to the updated FRAX algorithm, if possible, might substantially improve predictive performance.

With regard to reversibility of risk, post hoc analyses of pivotal clinical trials would have low power to show a beneficial effect in the small subgroups of individuals with diabetes. Notwithstanding, subgroup analyses have shown similar effects of a wide range of pharmacological interventions on BMD and vertebral fracture in patients with or without diabetes [128]. Additionally, in a nationwide cohort study from Denmark, users of antiresorptive drugs were compared with age-matched and gender-matched controls from the general population [129]. No difference was observed in the effects of treatment on fracture, including hip fracture, between patients with diabetes and nondiabetic controls, or between patients with type 1 and type 2 diabetes. Thus, the criterion of reversibility of risk is fulfilled.

**History of falls** Falls are common in the elderly, with the prevalence of prior falls estimated as 42% in community-dwelling people age 75 years or more [130]. Many previous studies, in different populations, have documented strong associations between propensity to fall and risk of future fracture [25, 95, 131–139]. There is, however, limited evidence that an intervention aimed at reducing falls will lead to a subsequent reduction in fractures [140–144]. Indeed, a lack of uniformly reliable data [123, 145] and a dearth of evidence indicating that fracture risk attributable to falls risk might be amenable to pharmacological treatment [146] meant that “past falls” was not incorporated as an input variable to the FRAX calculator.

Since then, assessment of falls risk has been demonstrated to improve fracture prediction in addition to FRAX clinical risk factors and BMD in both men and women [147, 148]. Moreover, several interventions have been shown to have a beneficial effect in lowering the increased risk associated with a falls history, including menopausal hormone treatment [111, 149], clodronate [150] and zoledronate [151].

A possible concern with the incorporation of falls into FRAX relates to a possible interaction with time. In one study of elderly men, past falls were a significant predictor of incident fractures even after adjustment for FRAX. The hazard ratio decreased markedly with increasing follow-up time [147]. These findings suggest that history of past falls may provide less robust predictive power over longer periods.

**Outcome measures** Outcome measures will include the sites and date of all incident fractures, date of death and date at end of follow-up. Ascertainment of fractures in the individual cohorts has been undertaken by self-report and/or verified from hospital or central databases. The sites of primary interest are vertebra, proximal humerus, distal forearm and hip since the probability of fractures at these sites forms a major output of FRAX. Nevertheless, fractures at all sites will be assessed to determine whether the spectrum of fracture outcomes differs according to the presence or absence of the relevant risk factor. There are precedents for this in our work on obesity, suggesting that the association between BMI and future fracture risk is site-specific, with low BMI being a risk factor for all osteoporotic fractures but a protective factor for lower leg fracture [152]. Another outcome of importance is mortality since the estimates of fracture probability depend on the integrated effect of the risk factor on death as well as fracture risk. Probability models will be computed for hip fracture and MOF (vertebral, humerus, forearm or hip fracture).

## Power

For the calculation of statistical power, a conservative assumption would include approximately 400,000 participants with 8800 experiencing one or more hip fractures (assuming an average age of 65 and a short follow-up of on average 4 years). Based on our previous findings on smoking and corticosteroid use as risk factors for hip fracture (HR 1.5 and 2.2, respectively) [153, 154], with smoking having a relatively low HR and corticosteroid use having low prevalence, we would have > 99% power to detect associations between these exposures and incident hip fracture with an alpha of 0.05.

## Analytic framework

The output of FRAX is the probability of fracture. This metric differs from other risk engines [155–157] in that probability integrates the risk of fracture and the risk of death [158]. A FRAX variable strongly affected in this way is smoking, which carries a moderate risk of fracture [154] but has a minor effect on fracture probability because smoking increases the risk of death as well as the risk of fracture. Type 2 diabetes is also associated with approximately a two-fold increase in mortality [125] and this will compete with the fracture hazard. The consideration of fracture and death hazards is, however, more complex.

One of the strengths of FRAX is that it is derived from the primary data in population-based cohorts from around the world. The use of primary data for the model construct permits the determination of the predictive importance in a multivariable context of each of the risk factors,

as well as interactions between risk factors, and in this way, optimises the accuracy with which fracture probability can be computed [1]. This FRAX matrix of covariates is used both for the fracture hazard and for the death hazard. If a candidate risk factor were totally independent of the other risk factors, then incorporation into a FRAX model would be relatively straightforward. We already know this not to be the case for type 2 diabetes in that there is a significant interaction with age such that the hazard ratio for fracture appears to be higher in younger individuals [125].

It is important to recognise that the strength of the risk factors varies according to fracture outcome. In general, risk factors were more strongly associated with hip fracture risk than with the risk of any osteoporotic fracture. This consideration indicates that integrated models to assess overall fracture risk should use risk ratios separately determined for hip fracture and for other osteoporotic fracture (without hip fracture).

### Meta-analyses

For each available cohort and for each candidate risk factor, a special extension of Poisson regression model will be used to study the relationship between the candidate risk factor, current age, current time since baseline, other covariates and the risk of fracture [2, 159, 160]. The methodology has been well rehearsed in previous publications [6, 152–154, 161–168]. The observation period of each participant will be divided in intervals of 1 month. The first fracture per person will be counted for each relevant outcome. In contrast to a logistic model, the Poisson regression utilises person years of follow-up and the instantaneous hazard function is assumed to be  $\exp(\beta_0 + \beta_1 \times \text{current time from baseline} + \beta_2 \times \text{current age} + \beta_3 \times \text{variable of interest})$ . The beta coefficients reflect the effect size of the variables as in a logistic model, and  $\beta_x = 0$  denotes that the corresponding variable does not contribute to fracture risk. Interactions with age or time since baseline will also be investigated. An identical analysis will examine the risk of death since estimates of fracture probability depend on the integrated effect of the risk factor on death as well as fracture risk.

For each variable, the dependence on age, sex and time (duration of observation) will be examined to elicit significant interactions. For continuous variables (BMI and BMD), interaction terms will be sought with the variable itself (e.g.  $\text{BMD} \cdot \text{BMD}$ ) since previous analyses have identified trends that might now be of statistical and clinical significance [165]. Results of studies reporting BMD will be compared with those in which BMD was not measured. Results categorised by quality scores of cohorts will be compared.

The  $\beta$ -coefficients from each cohort will be weighted according to the variance and then merged to determine the weighted mean of the coefficient and its standard deviation. Heterogeneity between cohorts will be tested by means of the  $I^2$  statistic. A fixed effects or a random effects model will be chosen dependent on the result of the test for heterogeneity.

### Construct of the updated FRAX (integration of all FRAX variables)

By introducing interactions, i.e. products between variables, the model can be made more realistic (with a better fit to the data). Interactions may not however be linear between a continuous variable and the risk of fracture; therefore, also piecewise linear functions, spline functions or quadratic functions will be explored. An example is the inter-relationship between BMI and fracture risk, where a BMI has a different significance at different levels of BMI [166]. Thus, it is necessary to determine the interactions between each of the risk factors, e.g. to what extent does the risk of glucocorticoid treatment depend upon smoking and how does this affect the interaction of smoking with age. This requires a meta-analysis of the meta-analyses (referred to as a mega-analysis).

When several variables are considered simultaneously, the beta coefficients will differ from the coefficients obtained when each variable is studied alone. However, the change in a beta coefficient may be small if the corresponding risk variable is of great importance and not correlated to other variables included in the model. In order to estimate the beta coefficients for a model that includes several variables, we generally need sufficient data for all the variables. In the types of models mentioned (logistic regression model, Cox and Poisson regression models), the importance of different variables is reflected by beta coefficients. The linear combination  $\beta_1 \cdot x_1 + \dots + \beta_k \cdot x_k$  of the variables gives a risk score, which can be considered as a new variable. When the goodness of the combination as a predictor is studied, the same type of description (gradient of risk per standard deviation, area under the ROC curve, etc.) can be applied as for a single variable.

Not all cohorts have complete information on all the dichotomous risk factors. For example, a current history of smoking is not available from CaMos and Rochester. Where one dichotomous variable (e.g. smoking) is deleted from the model and has a very minor effect on the  $\beta$  coefficients for the other variables, the original  $\beta$  coefficients will be used as previously described [6].

For each risk factor, all significant interaction terms that are identified by the previous meta-analyses will be entered (with age, time, sex and the risk factor) with and without BMD. Where interactions noted in the “mega-analyses” are no longer



significant for hip fracture and other osteoporotic fractures, these will be omitted in a stepwise manner by dropping the interaction with the largest  $p$  value. In the first FRAX model, interactions that were retained were age · sex, BMD · age, BMD · BMD, BMD · current age, family history · age, prior fracture · age, BMI · BMI and age · age [6]. The much greater power of the updated FRAX is thus expected to generate more interactions of biological and statistical significance.

**Model characteristics** The performance of the model will be assessed as the gradient of risk, i.e. the increase in fracture risk per SD increase in risk score. Gradients of risk will be computed for the prediction of hip fracture and other MOF (clinical spine, forearm, proximal humerus) with BMD alone, the clinical risk factors alone and the combination. The gradient of risk is likely to be age dependent [6].

The incremental value of the models can be compared in two ways. In effect, there will be three models at our disposal. These comprise the new model incorporating the novel indices of risk, the new model that uses the traditional risk factors (but with project-specific weights) and the traditional FRAX model as currently used. Thus, we can assess the increment in performance characteristics that is related to the re-weighting of the traditional FRAX risk factors and that which is related to the incorporation of the novel risk factors.

**Validation** Following meta-analysis but before mega-analysis, source and validation cohorts (10–20% of cohorts available) will be identified and matched to ensure representation by age range, sex distribution and population basis (sampling frame). The performance characteristics as described above will be compared in the source and validation cohorts. If the characteristics observed in the discovery cohorts are comparable to those in the validation cohorts, then all cohorts together will be used to form the final model. Construction and validation of the prediction model will follow the framework of PROGRESS (Prognosis Research Strategy) [169] that promotes how prognostic models are developed, validated and assessed.

**Calibration** All FRAX models are calibrated with regard to the epidemiology of hip fracture (preferably from national sources) and mortality (usually UN source). Thus, were the population of each country to be “FRAXed”, the number of hip fractures and deaths estimated would match that provided from the source data [4]. It follows that the calibration of the FRAX algorithms is only as good as the epidemiology with which the tools are populated. Additionally, any validation exercise will be critically dependent on the representativeness of the population tested for the index country. Several investigators have studied populations that were considered to represent national populations, including the UK, Canada

and Norway [155, 170–172]. In these studies, FRAX appears to be well calibrated. As more recent or higher quality epidemiological information on fracture and death risks become available, country-specific models will be recalibrated.

## Discussion

FRAX represents a significant advance in the assessment of both women and men at risk for osteoporosis-related fracture and allows the tailoring of pharmacological interventions to high-risk subjects. While FRAX does not define intervention thresholds, which depend on country-specific considerations, it provides a platform to assess fracture probability which is needed to make rational treatment decisions by clinicians and public health agencies. The tool is, however, far from perfect, but better than BMD alone. The widespread use and interest in FRAX and its adoption into management guidelines have fuelled interest as to how models can be improved, extended to other countries and, in particular, how the limitations of FRAX should temper clinical judgement. The wish list of clinicians for the modulation of FRAX is large, and in many instances, these wishes cannot presently be fulfilled, but an explanation and understanding of the reasons may be helpful in translating the information provided by FRAX into clinical practice.

In this report, we have described the identification and characteristics of 64 cohorts eligible to participate in the construct of the FRAX update. The included cohorts form the largest database to date, comprising 2,138,428 participants (69% women) followed for approximately 20 million person-years with 116,117 documented MOFs. This reflects an increase in the percentage of men included as well as a longer average follow-up time compared with the cohorts used to develop and validate the original FRAX algorithm [6]. Also, including new cohorts and updating the previously identified cohorts increases the likelihood of identifying potential novel risk factors for fracture that are now more adequately characterised and available in a larger number of populations. The strongest candidates as additional risk factors are diabetes mellitus and falls history. These will be the first novel risk factors to be tested in the risk assessment algorithms and incorporated in the meta-analytical framework according to the analysis plan described.

We anticipate that the development and implementation of the updated FRAX algorithm will benefit researchers and health care professionals through refined risk assessment models with additional risk factors for fractures. The improved performance characteristics of the updated FRAX platform will facilitate the identification of those at highest fracture risk and instruct guideline developers and policy makers on optimal treatment strategies for osteoporosis.

## Appendix

Tables 3 and 4

**Table 3** Excluded cohorts

Cohort	Classification	Origin	Reason for exclusion
APCaPS	A	India	No incident fractures
AUSTRIOS A	A	Austria	Inappropriate population
BioPersMed	A	Austria	Inappropriate population
Bolland et al.*	B	New Zealand	No data available
Cantabria/Cantabria-Camargo	A	Spain	Inappropriate population
CHAMP	A	Australia	Payment requested
CLSA	A	Canada	Inappropriate population
H70	B	Sweden	Inappropriate population
HALST	A	Taiwan	No response to invitation
Hong Kong Osteoporosis Study	B	Hong Kong	No response to invitation
IWHP	A	Singapore	No response to invitation
Lau et al.†	A	Hong Kong	Inappropriate population
MEDOS	A	Europe	Inappropriate population
MENOS	B	France	Data no longer exist
NHIRD cohorts	A	Taiwan	No response to invitation
Northumbria	A	UK	Difficulties with data access
PLSAW	B	Australia	No data available
Qfracture	B	UK	No response to invitation
QUALYOR	A	France	Inappropriate population
ROAD	A	Japan	No response to invitation
ROSE	A	Denmark	Unable to provide individual-level data
Rubin et al.‡	B	Denmark	Unable to provide data due to Danish privacy laws
TLSA	A	Taiwan	No contact details
Tromsø	B	Norway	No response to invitation
Vietnam	A	Vietnam	No response to invitation
WGHS	A	USA	Payment requested
WHAP	A	Australia	No incident fractures

*APCaPS*, Andhra Pradesh Children and Parents Study; *BioPersMed*, Biomarkers for Personalised Medicine in Common Metabolic Disorders; *CHAMP*, Concord Health and Ageing in Men Project; *CLSA*, Canadian Longitudinal Study on Aging; *H70*, Gothenburg H70 Birth Cohort; *HALST*, Healthy Aging Longitudinal Study in Taiwan; *IWHP*, Integrated Women's Health Programme; *MEDOS*, Mediterranean Osteoporosis Study; *MENOS*, Menopause et Os; *NHIRD*, National Health Insurance Research Database; *PLSAW*, Perth Longitudinal Study of Aging in Women; *QUALYOR*, Qualité Osseuse Lyon Orléans; *ROAD*, Research on Osteoarthritis/Osteoporosis Against Disability; *ROSE*, Risk-stratified Osteoporosis Strategy Evaluation; *TLSA*, Taiwan Longitudinal Study on Aging; *WGHS*, Women's Genome Health Study; *WHAP*, Women's Healthy Ageing Project

A, cohort previously identified but not used in any previous analysis; B, cohort identified through the systematic review

\*Bolland et al. (2011) *J Bone Miner Res* 26(2), 420–427

†Lau et al. (2001) *Osteoporos Int* 2(3), 239–243 and personal communication of primary data on the cohort with Edith Lau, 2004

‡Rubin et al. (2013) *Bone* 56(1), 16–22



**Table 4** Additional risk factors for consideration for the update of FRAX

Age at menopause
Androgen deprivation therapy
Aromatase inhibitors
Cancer
Chair stand test
Chronic kidney disease
Chronic obstructive pulmonary disease
Diabetes type 2
Resident in a nursing or care home
Epilepsy or taking anticonvulsants
Gait speed/walking speed
Grip strength
Morphometric vertebral fracture (grade)
Muscle mass/lean mass at various sites
Parkinson's disease
Previous falls
Previous fracture (site and number of and time since fracture)
Stroke (previous 6 months)
Timed Up and Go (TUG) test
Trabecular bone score

**Acknowledgements** We thank the Gothenburg University Library for assistance with the systematic review. We are grateful to Dr Östen Ljunggren for contributing the MrOS Sweden cohort.

## Declarations

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

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

**Conflicts of interest** JA Kanis led the team that developed FRAX as director of the WHO Collaborating Centre for Metabolic Bone Diseases; he has no financial interest in FRAX. EV McCloskey, WD Leslie, M Lorentzon, NC Harvey, E Liu, L Vandenput and H Johansson are members of the FRAX team. JA Kanis, NC Harvey and EV McCloskey are members of the advisory body to the National Osteoporosis Guideline Group. JA Kanis reports no additional competing interests. KE Åkesson has no financial interest related to FRAX; chaired the National SALAR Group for Person-Centered Care Pathway Osteoporosis. FA Anderson led the team that developed GLOW, while director of the Center for Outcomes Research at the University of Massachusetts Medical School; he has no financial interest in FRAX. R Azagra has received funding for research from Instituto Carlos III of Spanish Ministry of Health, IDIAP Jordi Gol of Catalan Government and from Scientific Societies SEMFYC and SEIOMM. CL Bager is employed at Nordic Bioscience and owns stock in Nordic Bioscience. She de-

clares 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. Furthermore, Prof. Bischoff-Ferrari reports non-financial support from Roche Diagnostics and personal fees from Wild, Sandoz, Pfizer, Vifor, Mylan, Roche, Meda Pharma, outside the submitted work with regard to speaker fees and travel fees. JR Center has received honoraria for speaking at educational meetings and for advisory boards from Amgen and honoraria for an advisory board from Bayer. R Chapurlat has no financial interest in FRAX. He has received grant funding from Amgen, UCB, Chugai, MSD, Mylan and Medac. He has received honoraria from Amgen, UCB, Chugai, Galapagos, Biocon, Abbvie, Haoma Medica, Pfizer, Amolyt, MSD, Lilly, BMS, Novartis, Arrow, PKMed, Kyowa-Kirin and Sanofi. C Christiansen owns stock in Nordic Bioscience. He declares no competing interests in relation to this work. C Cooper reports personal fees from Alliance for Better Bone Health, Amgen, Eli Lilly, GSK, Medtronic, Merck, Novartis, Pfizer, Roche, Servier, Takeda and UCB. A Diez-Perez reports personal fees from Amgen, Lilly, Theramex and grants from Instituto Carlos III 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. 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, Consilient Healthcare 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 30 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. He has served on advisory boards for Amgen Australia, Novartis and Eli Lilly — all unrelated to this work and is the Director of the Geelong Bone Densitometry Service. M Lorentzon has received lecture fees from Amgen, Lilly, Meda, Renapharma and UCB Pharma and consulting fees from Amgen, Radius Health, UCB Pharma, Renapharma 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, 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. 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, all unrelated to this work. 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, C-C Gluer, 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, D Mellström, T Merlijn, A Nordström, P Nordström, TW O'Neill, B Obermayer-Pietsch, F Rivadeneira, B Schei, A-M Schott, EJ Shiroma, K Siggeirsdottir, EM Simonsick, E Sornay-Rendu, R Sund, KMA Swart, P Szulc, J Tamaki, DJ Torgerson, L Vandenput, NM van Schoor, TP van Staa, J Vila, NJ Wareham, NC Wright and N Yoshimura declare no competing interests in relation to this work.

## References

- 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: [https://www.sheffield.ac.uk/FRAX/pdfs/WHO\\_Technical\\_Report.pdf](https://www.sheffield.ac.uk/FRAX/pdfs/WHO_Technical_Report.pdf) (Accessed December 23, 2020)
- Kanis JA, Johnell O, Oden A, Johansson H, McCloskey E (2008) FRAX and the assessment of fracture probability in men and women from the UK. *Osteoporos Int* 19:385–397
- Kanis JA, Harvey NC, Cooper C, Johansson H, Oden A, McCloskey EV, Advisory Board of the National Osteoporosis Guideline G (2016) A systematic review of intervention thresholds based on FRAX : a report prepared for the National Osteoporosis Guideline Group and the International Osteoporosis Foundation. *Arch Osteoporos* 11:25
- Kanis JA, Harvey NC, Johansson H, Liu E, Vandenput L, Lorentzon M, Leslie WD, McCloskey EV (2020) A decade of FRAX: how has it changed the management of osteoporosis? *Aging Clin Exp Res* 32:187–196
- Kanis JA, Johansson H, Harvey NC, Gudnason V, Sigurdsson G, Siggeirsdottir K, Lorentzon M, Liu E, Vandenput L, McCloskey EV (2020) Adjusting conventional FRAX estimates of fracture probability according to the recency of sentinel fractures. *Osteoporos Int* 31:1817–1828
- Kanis JA, Oden A, Johnell O, Johansson H, De Laet C, Brown J, Burckhardt P, Cooper C, Christiansen C, Cummings S, Eisman JA, Fujiwara S, Gluer C, Goltzman D, Hans D, Krieg MA, La Croix A, McCloskey E, Mellstrom D, Melton LJ 3rd, Pols H, Reeve J, Sanders K, Schott AM, Silman A, Torgerson D, van Staa T, Watts NB, Yoshimura N (2007) The use of clinical risk factors enhances the performance of BMD in the prediction of hip and osteoporotic fractures in men and women. *Osteoporos Int* 18:1033–1046
- Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hrobjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA, Whiting P, Moher D (2021) The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 372:n71
- Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A (2016) Rayyan-a web and mobile app for systematic reviews. *Syst Rev* 5:210
- Sigurdsson G, Aspelund T, Chang M, Jonsdottir B, Sigurdsson S, Eiriksdottir G, Gudmundsson A, Harris TB, Gudnason V, Lang TF (2006) Increasing sex difference in bone strength in old age: the Age, Gene/Environment Susceptibility-Reykjavik Study (AGES-REYKJAVIK). *Bone* 39:644–651
- Harris TB, Launer LJ, Eiriksdottir G, Kjartansson O, Jonsson PV, Sigurdsson G, Thorgeirsson G, Aspelund T, Garcia ME, Cotch MF, Hoffman HJ, Gudnason V (2007) Age, Gene/Environment Susceptibility-Reykjavik Study: multidisciplinary applied phenomics. *Am J Epidemiol* 165:1076–1087
- Fujiwara S, Kasagi F, Yamada M, Kodama K (1997) Risk factors for hip fracture in a Japanese cohort. *J Bone Miner Res* 12:998–1004
- Fujiwara S, Kasagi F, Masunari N, Naito K, Suzuki G, Fukunaga M (2003) Fracture prediction from bone mineral density in Japanese men and women. *J Bone Miner Res* 18:1547–1553
- Macdonald HM, McGuigan FE, Stewart A, Black AJ, Fraser WD, Ralston S, Reid DM (2006) Large-scale population-based study shows no evidence of association between common polymorphism of the VDR gene and BMD in British women. *J Bone Miner Res* 21:151–162
- Dobnig H, Piswanger-Solkner JC, Roth M, Obermayer-Pietsch B, Tiran A, Strele A, Maier E, Maritschnegg P, Sieberer C, Fahrleitner-Pammer A (2006) Type 2 diabetes mellitus in nursing home patients: effects on bone turnover, bone mass, and fracture risk. *J Clin Endocrinol Metab* 91:3355–3363
- Ostovar A, Nabipour I, Larijani B, Heshmat R, Darabi H, Vahdat K, Ravanipour M, Mehrdad N, Raeisi A, Heidari G, Shafiee G, Haeri M, Pourbehi M, Sharifi F, Noroozi A, Tahmasebi R, Aghaei Meybodi H, Assadi M, Farrokhi S, Nemat R, Amini MR, Barekat M, Amini A, Salimpour H, Dobaradaran S, Moshtaghi D (2015) Bushehr Elderly Health (BEH) Programme, phase I (cardiovascular system). *BMJ Open* 5:e009597
- Shafiee G, Ostovar A, Heshmat R, Darabi H, Sharifi F, Raeisi A, Mehrdad N, Shadman Z, Razi F, Amini MR, Arzaghi SM, Meybodi HA, Soltani A, Nabipour I, Larijani B (2017) Bushehr Elderly Health (BEH) programme: study protocol and design of musculoskeletal system and cognitive function (stage II). *BMJ Open* 7:e013606
- Kreiger N, Tenenhouse A, Joseph L, Mackenzie T, Poliquin S, Brown JP, Prior JC, Rittmaster RS (1999) The Canadian Multicentre Osteoporosis Study (CaMos): background, rationale, methods. *Can J Aging* 18:376–387
- Jones G, Nguyen T, Sambrook PN, Kelly PJ, Gilbert C, Eisman JA (1994) Symptomatic fracture incidence in elderly men and women: the Dubbo Osteoporosis Epidemiology Study (DOES). *Osteoporos Int* 4:277–282
- Bischoff-Ferrari HA, Molino C, Rival S, Vellas B, Rizzoli R, Kressig RW, Kanis JA, Manson JE, Dawson-Hughes B, Orav EJ, da Silva JAP, Blauth M, Felsenberg D, Ferrari SM, Theiler R, Egli A, Group D-HR (2021) DO-HEALTH: Vitamin D3 - Omega3 - Home Exercise - Healthy Aging And Longevity Trial - design of a multinational clinical trial on healthy aging among European seniors. *Contemp Clin Trials* 100
- Bischoff-Ferrari HA, Vellas B, Rizzoli R, Kressig RW, da Silva JAP, Blauth M, Felson DT, McCloskey EV, Watzl B, Hofbauer LC, Felsenberg D, Willett WC, Dawson-Hughes B, Manson JE, Siebert U, Theiler R, Staehelin HB, de Godoi Rezende Costa Molino C, Chocano-Bedoya PO, Abderhalden LA, Egli A, Kanis JA, Orav EJ, Group D-HR (2020) Effect of vitamin D supplementation, omega-3 fatty acid supplementation, or a strength-training exercise program on clinical outcomes in older adults: the DO-HEALTH randomized clinical trial. *JAMA* 324:1855–1868
- Hernandez JL, Marin F, Gonzalez-Macias J, Diez-Perez A, Vila J, Gimenez S, Galan B, Arenas MS, Suarez F, Gayola L, Guillen G, Sagredo T, Belenguer R, Moron A, Arriaza E, ECOSAP study investigators (2004) Discriminative capacity of calcaneal quantitative ultrasound and of osteoporosis and fracture risk factors in postmenopausal women with osteoporotic fractures. *Calcif Tissue Int* 74:357–365
- Diez-Perez A, Gonzalez-Macias J, Marin F, Abizanda M, Alvarez R, Gimeno A, Pegenaute E, Vila J, Osea E, enAtencionPrimaria study i, (2007) Prediction of absolute risk of non-spinal

- fractures using clinical risk factors and heel quantitative ultrasound. *Osteoporos Int* 18:629–639
23. Day NOS, Luben R, Khaw KT, Bingham S, Welch A, Wareham N (1999) EPIC-Norfolk: study design and characteristics of the cohort. *Br J Cancer* 80(Suppl 1):95–103
  24. Khaw KT, Reeve J, Luben R, Bingham S, Welch A, Wareham N, Oakes S, Day N (2004) Prediction of total and hip fracture risk in men and women by quantitative ultrasound of the calcaneus: EPIC-Norfolk prospective population study. *Lancet* 363:197–202
  25. 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
  26. Schott AM, Cormier C, Hans D, Favier F, Hausherr E, Dargent-Molina P, Delmas PD, Ribot C, Sebert JL, Breart G, Meunier PJ (1998) How hip and whole-body bone mineral density predict hip fracture in elderly women: the EPIDOS prospective study. *Osteoporos Int* 8:247–254
  27. Zwart M, Azagra R, Tranche S, Gil Y, Tudela N, Quijónes O, Alonso J, Alvarez G, Saez M, Aguye A, Martin C, Gabriel P (2021) Epidemiology of osteoporotic fractures and subsequent fractures in the Asturian Region of Spain. the EPIFROS cohort. *Osteoporos Int* 32:in press
  28. Zwart M, Azagra R, Aguye A, Tranche S, Saez M, Alvarez G, Alonso J, Quijónes O, Tudela N, Gil Y, Martin C, Diaz-Herrera MA, Gabriel P (2021) FRAX® predictive ability to predict major osteoporotic fractures and hip fractures in the Spanish population. the EPIFROS Asturias cohort. *Osteoporos Int* 32:in press
  29. O'Neill TW, Felsenberg D, Varlow J, Cooper C, Kanis JA, Silman AJ (1996) The prevalence of vertebral deformity in European men and women: the European Vertebral Osteoporosis Study. *J Bone Miner Res* 11:1010–1018
  30. European Prospective Osteoporosis Study Group, Felsenberg D, Silman AJ, Lunt M, Armbricht G, Ismail AA, Finn JD, Cockerill WC, Banzer D, Benevolenskaya LI, Bhalla A, Bruges Armas J, Cannata JB, Cooper C, Dequeker J, Eastell R, Felsch B, Gowin W, Havelka S, Hoszowski K, Jajic I, Janott J, Johnell O, Kanis JA, Kragl G, Lopes Vaz A, Lorenc R, Lyritis G, Masaryk P, Matthis C, Miazgowski T, Parisi G, Pols HA, Poor G, Raspe HH, Reid DM, Reisinger W, Schedit-Nave C, Stepan JJ, Todd CJ, Weber K, Woolf AD, Yershova OB, Reeve J, O'Neill TW (2002) Incidence of vertebral fracture in Europe: results from the European Prospective Osteoporosis Study (EPOS). *J Bone Miner Res* 17:716–724
  31. Ismail AA, Pye SR, Cockerill WC, Lunt M, Silman AJ, Reeve J, Banzer D, Benevolenskaya LI, Bhalla A, Bruges Armas J, Cannata JB, Cooper C, Delmas PD, Dequeker J, Dilsen G, Falch JA, Felsch B, Felsenberg D, Finn JD, Gennari C, Hoszowski K, Jajic I, Janott J, Johnell O, Kanis JA, Kragl G, Lopez Vaz A, Lorenc R, Lyritis G, Marchand F, Masaryk P, Matthis C, Miazgowski T, Naves-Diaz M, Pols HA, Poor G, Rapado A, Raspe HH, Reid DM, Reisinger W, Scheidt-Nave C, Stepan J, Todd C, Weber K, Woolf AD, O'Neill TW (2002) Incidence of limb fracture across Europe: results from the European Prospective Osteoporosis Study (EPOS). *Osteoporos Int* 13:565–571
  32. Iki M, Fujita Y, Tamaki J, Kouda K, Yura A, Kadowaki E, Sato Y, Moon JS, Okamoto N, Kurumatani N, Study Group for Functioning C, Quality of Life in Elderly J (2009) Design and baseline characteristics of a prospective cohort study for determinants of osteoporotic fracture in community-dwelling elderly Japanese men: the Fujiwara-kyo Osteoporosis Risk in Men (FORMEN) study. *BMC Musculoskelet Disord* 10:165
  33. Fujita Y, Tamaki J, Kouda K, Yura A, Sato Y, Tachiki T, Hamada M, Kajita E, Kamiya K, Kaji K, Tsuda K, Ohara K, Moon JS, Kitagawa J, Iki M, group Fs, (2021) Determinants of bone health in elderly Japanese men: study design and key findings of the Fujiwara-kyo Osteoporosis Risk in Men (FORMEN) cohort study. *Environ Health Prev Med* 26:51
  34. Berry SD, Samelson EJ, Pencina MJ, McLean RR, Cupples LA, Broe KE, Kiel DP (2013) Repeat bone mineral density screening and prediction of hip and major osteoporotic fracture. *JAMA* 310:1256–1262
  35. Hannan MT, Weycker D, McLean RR, Sahni S, Bornheimer R, Barron R, Travison TG, Kiel DP (2019) Predictors of imminent risk of nonvertebral fracture in older, high-risk women: the Framingham Osteoporosis Study. *JBM Plus* 3:e10129
  36. Feinleib M, Kannel WB, Garrison RJ, McNamara PM, Castelli WP (1975) The Framingham Offspring Study. Design and preliminary data *Prev Med* 4:518–525
  37. Azagra R, Roca G, Encabo G, Prieto D, Aguye A, Zwart M, Guell S, Puchol N, Gene E, Casado E, Sancho P, Sola S, Toran P, Iglesias M, Sabate V, Lopez-Exposito F, Ortiz S, Fernandez Y, Diez-Perez A (2011) Prediction of absolute risk of fragility fracture at 10 years in a Spanish population: validation of the WHO FRAX tool in Spain. *BMC Musculoskelet Disord* 12:30
  38. Azagra R, Roca G, Encabo G, Aguye A, Zwart M, Guell S, Puchol N, Gene E, Casado E, Sancho P, Sola S, Toran P, Iglesias M, Gisbert MC, Lopez-Exposito F, Pujol-Salud J, Fernandez-Hermida Y, Puente A, Rosas M, Bou V, Anton JJ, Lansberg G, Martin-Sanchez JC, Diez-Perez A, Prieto-Alhambra D (2012) FRAX(R) tool, the WHO algorithm to predict osteoporotic fractures: the first analysis of its discriminative and predictive ability in the Spanish FRIDEX cohort. *BMC Musculoskelet Disord* 13:204
  39. Azagra R, Zwart M, Aguye A, Martin-Sanchez JC, Casado E, Diaz-Herrera MA, Morina D, Cooper C, Diez-Perez A, Dennison EM, Groinmap, Group FS (2016) Fracture experience among participants from the FROCAT study: what thresholding is appropriate using the FRAX tool? *Maturitas* 83:65–71
  40. Hars M, Biver E, Chevalley T, Herrmann F, Rizzoli R, Ferrari S, Trombetti A (2016) Low lean mass predicts incident fractures independently from FRAX: a prospective cohort study of recent retirees. *J Bone Miner Res* 31:2048–2056
  41. Hooven FH, Adachi JD, Adams S, Boonen S, Compston J, Cooper C, Delmas P, Diez-Perez A, Gehlbach S, Greenspan SL, LaCroix A, Lindsay R, Netelenbos JC, Pfeilschifter J, Roux C, Saag KG, Sambrook P, Silverman S, Siris E, Watts NB, Anderson FA Jr (2009) The Global Longitudinal Study of Osteoporosis in Women (GLOW): rationale and study design. *Osteoporos Int* 20:1107–1116
  42. Pasco JA, Nicholson GC, Kotowicz MA (2012) Cohort profile: Geelong Osteoporosis Study. *Int J Epidemiol* 41:1565–1575
  43. Svanborg A (1977) Seventy-year-old people in Gothenburg a population study in an industrialized Swedish city. II. General presentation of social and medical conditions. *Acta Med Scand Suppl* 611:5–37
  44. Johansson C, Black D, Johnell O, Oden A, Mellstrom D (1998) Bone mineral density is a predictor of survival. *Calcif Tissue Int* 63:190–196
  45. Stenström M, Olsson J-O, Mellström D (2000) Thyroid hormone replacement is not related to increased risk of osteoporosis. *Osteoporos Int* 11:S114
  46. Johansson J, Nordstrom A, Nordstrom P (2015) Objectively measured physical activity is associated with parameters of bone in 70-year-old men and women. *Bone* 81:72–79
  47. Syddall HE, Aihie Sayer A, Dennison EM, Martin HJ, Barker DJ, Cooper C (2005) Cohort profile: the Hertfordshire Cohort Study. *Int J Epidemiol* 34:1234–1242
  48. Visser M, Kritchevsky SB, Goodpaster BH, Newman AB, Nevitt M, Stamm E, Harris TB (2002) Leg muscle mass and composition in relation to lower extremity performance in men and

- women aged 70 to 79: the Health, Aging and Body Composition study. *J Am Geriatr Soc* 50:897–904
49. Krokstad S, Langhammer A, Hveem K, Holmen TL, Midthjell K, Stene TR, Bratberg G, Heggland J, Holmen J (2013) Cohort profile: the HUNT study, Norway. *Int J Epidemiol* 42:968–977
  50. Gulati AM, Hoff M, Salvesen O, Dhainaut A, Semb AG, Kavanaugh A, Haugeberg G (2017) Bone mineral density in patients with psoriatic arthritis: data from the Nord-Trøndelag Health Study 3. *RMD Open* 3:e000413
  51. Iki M, Tamaki J, Sato Y, Morita A, Ikeda Y, Kajita E, Nishino H, Akiba T, Matsumoto T, Kagamimori S, Kagawa Y, Yoneshima H, Matsukura T, Yamagami T, Kitagawa J, Group JS (2015) Cohort profile: the Japanese Population-based Osteoporosis (JPOS) Cohort Study. *Int J Epidemiol* 44:405–414
  52. Pluijm SM, Visser M, Smit JH, Popp-Snijders C, Roos JC, Lips P (2001) Determinants of bone mineral density in older men and women: body composition as mediator. *J Bone Miner Res* 16:2142–2151
  53. Huisman M, Poppelaars J, van der Horst M, Beekman AT, Brug J, van Tilburg TG, Deeg DJ (2011) Cohort profile: the Longitudinal Aging Study Amsterdam. *Int J Epidemiol* 40:868–876
  54. Hoogendijk EO, Deeg DJH, de Breij S, Klokgieters SS, Kok AAL, Stringa N, Timmermans EJ, van Schoor NM, van Zutphen EM, van der Horst M, Poppelaars J, Malhoe P, Huisman M (2020) The Longitudinal Aging Study Amsterdam: cohort update 2019 and additional data collections. *Eur J Epidemiol* 35:61–74
  55. Goldstein I, Gerber Y, Ish-Shalom S, Leshno M (2018) Fracture risk assessment with FRAX using real-world data in a population-based cohort from Israel. *Am J Epidemiol* 187:94–102
  56. Leslie WD, MacWilliam L, Lix L, Caetano P, Finlayson GS (2005) A population-based study of osteoporosis testing and treatment following introduction of a new bone densitometry service. *Osteoporos Int* 16:773–782
  57. Leslie WD, Caetano PA, Macwilliam LR, Finlayson GS (2005) Construction and validation of a population-based bone densitometry database. *J Clin Densitom* 8:25–30
  58. Szulc P, Munoz F, Duboeuf F, Marchand F, Delmas PD (2005) Bone mineral density predicts osteoporotic fractures in elderly men: the MINOS study. *Osteoporos Int* 16:1184–1192
  59. Yoshimura N, Kinoshita H, Danjoh S, Takijiri T, Morioka S, Kasamatsu T, Sakata K, Hashimoto T (2002) Bone loss at the lumbar spine and the proximal femur in a rural Japanese community, 1990–2000: the Miyama study. *Osteoporos Int* 13:803–808
  60. Kwok T, Khoo CC, Leung J, Kwok A, Qin L, Woo J, Leung PC (2012) Predictive values of calcaneal quantitative ultrasound and dual energy X ray absorptiometry for non-vertebral fracture in older men: results from the MrOS study (Hong Kong). *Osteoporos Int* 23:1001–1006
  61. Kwok AW, Gong JS, Wang YX, Leung JC, Kwok T, Griffith JF, Leung PC (2013) Prevalence and risk factors of radiographic vertebral fractures in elderly Chinese men and women: results of Mr. OS (Hong Kong) and Ms. OS (Hong Kong) studies. *Osteoporos Int* 24:877–885
  62. Mellstrom D, Johnell O, Ljunggren O, Eriksson AL, Lorentzon M, Mallmin H, Holmberg A, Redlund-Johnell I, Orwoll E, Ohlsson C (2006) Free testosterone is an independent predictor of BMD and prevalent fractures in elderly men: MrOS Sweden. *J Bone Miner Res* 21:529–535
  63. Jutberger H, Lorentzon M, Barrett-Connor E, Johansson H, Kanis JA, Ljunggren O, Karlsson MK, Rosengren BE, Redlund-Johnell I, Orwoll E, Ohlsson C, Mellstrom D (2010) Smoking predicts incident fractures in elderly men: Mr OS Sweden. *J Bone Miner Res* 25:1010–1016
  64. Blank JB, Cawthon PM, Carrion-Petersen ML, Harper L, Johnsson JP, Mitson E, Delay RR (2005) Overview of recruitment for the Osteoporotic Fractures in Men Study (MrOS). *Contemp Clin Trials* 26:557–568
  65. Orwoll E, Blank JB, Barrett-Connor E, Cauley J, Cummings S, Ensrud K, Lewis C, Cawthon PM, Marcus R, Marshall LM, McGowan J, Phipps K, Sherman S, Stefanick ML, Stone K (2005) Design and baseline characteristics of the Osteoporotic Fractures in Men (MrOS) Study—a large observational study of the determinants of fracture in older men. *Contemp Clin Trials* 26:569–585
  66. Wong SY, Kwok T, Woo J, Lynn H, Griffith JF, Leung J, Tang YY, Leung PC (2005) Bone mineral density and the risk of peripheral arterial disease in men and women: results from Mr. and Ms Os. *Hong Kong Osteoporos Int* 16:1933–1938
  67. NHEFS The NHANES I Epidemiologic Follow-up Study. <https://www.ncdc.gov/nchs/nhanes/nhefs/default.aspx> (Accessed January 30, 2021)
  68. Garnero P, Sornay-Rendu E, Chapuy MC, Delmas PD (1996) Increased bone turnover in late postmenopausal women is a major determinant of osteoporosis. *J Bone Miner Res* 11:337–349
  69. Gerdhem P, Ringsberg KA, Obrant KJ, Akesson K (2005) Association between 25-hydroxy vitamin D levels, physical activity, muscle strength and fractures in the prospective population-based OPRA Study of Elderly Women. *Osteoporos Int* 16:1425–1431
  70. Gluer CC, Eastell R, Reid DM, Felsenberg D, Roux C, Barkmann R, Timm W, Blenk T, Armbrrecht G, Stewart A, Clowes J, Thomasius FE, Kolta S (2004) Association of five quantitative ultrasound devices and bone densitometry with osteoporotic vertebral fractures in a population-based sample: the OPUS study. *J Bone Miner Res* 19:782–793
  71. Lamy O, Krieg M-A, Stoll D, Aubry-Rozier B, Metzger M, Hans D (2012) The OsteoLaus cohort study. *Osteologie* 21:77–82
  72. Shevroja E, Marques-Vidal P, Aubry-Rozier B, Hans G, Rivade-neira F, Lamy O, Hans D (2019) Cohort profile: the OsteoLaus study. *Int J Epidemiol* 48:1046–1047g
  73. Honkanen R, Kroger H, Tuppurainen M, Alhava E, Saarikoski S (1995) Fractures and low axial bone density in perimenopausal women. *J Clin Epidemiol* 48:881–888
  74. Sund R, Honkanen R, Johansson H, Oden A, McCloskey E, Kanis J, Kroger H (2014) Evaluation of the FRAX model for hip fracture predictions in the population-based Kuopio Osteoporosis Risk Factor and Prevention Study (OSTPRE). *Calcif Tissue Int* 95:39–45
  75. Bagger YZ, Tanko LB, Alexandersen P, Hansen HB, Mollgaard A, Ravn P, Qvist P, Kanis JA, Christiansen C (2004) Two to three years of hormone replacement treatment in healthy women have long-term preventive effects on bone mass and osteoporotic fractures: the PERF study. *Bone* 34:728–735
  76. Cockayne S, Adamson J, Clarke A, Corbacho B, Fairhurst C, Green L, Hewitt CE, Hicks K, Kenan AM, Lamb SE, McIntosh C, Menz HB, Redmond AC, Richardson Z, Rodgers S, Vernon W, Watson J, Torgerson DJ, study R, (2017) Cohort randomised controlled trial of a multifaceted podiatry intervention for the prevention of falls in older people (the REFORM trial). *PLoS ONE* 12:e0168712
  77. Melton LJ 3rd, Crowson CS, O'Fallon WM, Wahner HW, Riggs BL (2003) Relative contributions of bone density, bone turnover, and clinical risk factors to long-term fracture prediction. *J Bone Miner Res* 18:312–318
  78. Melton LJ 3rd, Atkinson EJ, O'Connor MK, O'Fallon WM, Riggs BL (1998) Bone density and fracture risk in men. *J Bone Miner Res* 13:1915–1923
  79. Hofman A, Grobbee DE, de Jong PT, van den Ouweland FA (1991) Determinants of disease and disability in the elderly: the Rotterdam Elderly Study. *Eur J Epidemiol* 7:403–422
  80. De Laet CE, Van Hout BA, Burger H, Weel AE, Hofman A, Pols HA (1998) Hip fracture prediction in elderly men and women: validation in the Rotterdam Study. *J Bone Miner Res* 13:1587–1593

81. Schuit SC, van der Klift M, Weel AE, de Laet CE, Burger H, Seeman E, Hofman A, Uitterlinden AG, van Leeuwen JP, Pols HA (2004) Fracture incidence and association with bone mineral density in elderly men and women: the Rotterdam Study. *Bone* 34:195–202
82. Ikram MA, Brusselle GGO, Murad SD, van Duijn CM, Franco OH, Goedegebure A, Klaver CCW, Nijsten TEC, Peeters RP, Stricker BH, Tiemeier H, Uitterlinden AG, Vernooij MW, Hofman A (2017) The Rotterdam Study: 2018 update on objectives, design and main results. *Eur J Epidemiol* 32:807–850
83. Ikram MA, Brusselle G, Ghanbari M, Goedegebure A, Ikram MK, Kavousi M, Kieboom BCT, Klaver CCW, de Knecht RJ, Luik AI, Nijsten TEC, Peeters RP, van Rooij FJA, Stricker BH, Uitterlinden AG, Vernooij MW, Voortman T (2020) Objectives, design and main findings until 2020 from the Rotterdam Study. *Eur J Epidemiol* 35:483–517
84. Marques A, Lucas R, Simoes E, Verstappen SMM, Jacobs JWG, da Silva JAP (2017) Do we need bone mineral density to estimate osteoporotic fracture risk? A 10-year prospective multicentre validation study. *RMD Open* 3:e000509
85. Beaudart C, Reginster JY, Petermans J, Gillain S, Quabron A, Locquet M, Slomian J, Buckinx F, Bruyere O (2015) Quality of life and physical components linked to sarcopenia: the SarcoPhAge study. *Exp Gerontol* 69:103–110
86. Koh WP, Wu AH, Wang R, Ang LW, Heng D, Yuan JM, Yu MC (2009) Gender-specific associations between soy and risk of hip fracture in the Singapore Chinese Health Study. *Am J Epidemiol* 170:901–909
87. Dai Z, Wang R, Ang LW, Low YL, Yuan JM, Koh WP (2014) Protective effects of dietary carotenoids on risk of hip fracture in men: the Singapore Chinese Health Study. *J Bone Miner Res* 29:408–417
88. Shepstone L, Fordham R, Lenaghan E, Harvey I, Cooper C, Gittoes N, Heawood A, Peters T, O'Neill T, Torgerson D, Holland R, Howe A, Marshall T, Kanis J, McCloskey E (2012) A pragmatic randomised controlled trial of the effectiveness and cost-effectiveness of screening older women for the prevention of fractures: rationale, design and methods for the SCOOP study. *Osteoporos Int* 23:2507–2515
89. Shepstone L, Lenaghan E, Cooper C, Clarke S, Fong-Soe-Khioe R, Fordham R, Gittoes N, Harvey I, Harvey N, Heawood A, Holland R, Howe A, Kanis J, Marshall T, O'Neill T, Peters T, Redmond N, Torgerson D, Turner D, McCloskey E, Team SS (2018) Screening in the community to reduce fractures in older women (SCOOP): a randomised controlled trial. *Lancet* 391:741–747
90. Popp AW, Senn C, Franta O, Krieg MA, Perrelet R, Lippuner K (2009) Tibial or hip BMD predict clinical fracture risk equally well: results from a prospective study in 700 elderly Swiss women. *Osteoporos Int* 20:1393–1399
91. Krieg MA, Cornuz J, Ruffieux C, Van Melle G, Buche D, Dambacher MA, Hans D, Hartl F, Hauselmann HJ, Kraenzlin M, Lippuner K, Neff M, Pancaldi P, Rizzoli R, Tanzi F, Theiler R, Tyndall A, Wimpfheimer C, Burckhardt P (2006) Prediction of hip fracture risk by quantitative ultrasound in more than 7000 Swiss women > or =70 years of age: comparison of three technologically different bone ultrasound devices in the SEMOF study. *J Bone Miner Res* 21:1457–1463
92. Johansson H, Oden A, Johnell O, Jonsson B, de Laet C, Oglesby A, McCloskey EV, Kayan K, Jalava T, Kanis JA (2004) Optimization of BMD measurements to identify high risk groups for treatment—a test analysis. *J Bone Miner Res* 19:906–913
93. McCloskey EV, Beneton M, Charlesworth D, Kayan K, deTakats D, Dey A, Orgee J, Ashford R, Forster M, Cliffe J, Kerish L, Brazier J, Nichol J, Aropuu S, Jalava T, Kanis JA (2007) Clodronate reduces the incidence of fractures in community-dwelling elderly women unselected for osteoporosis: results of a double-blind, placebo-controlled randomized study. *J Bone Miner Res* 22:135–141
94. Cummings SR, Black DM, Nevitt MC, Browner WS, Cauley JA, Genant HK, Mascioli SR, Scott JC, Seeley DG, Steiger P et al (1990) Appendicular bone density and age predict hip fracture in women. The Study of Osteoporotic Fractures Research Group. *JAMA* 263:665–668
95. 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
96. Elders PJM, Merlijn T, Swart KMA, van Hout W, van der Zwaard BC, Niemeijer C, Heymans MW, van der Heijden AA, Rutters F, van der Horst HE, Lips P, Netelenbos JC, van Schoor NM (2017) Design of the SALT Osteoporosis Study: a randomised pragmatic trial, to study a primary care screening and treatment program for the prevention of fractures in women aged 65 years or older. *BMC Musculoskelet Disord* 18:424
97. Merlijn T, Swart KM, van Schoor NM, Heymans MW, van der Zwaard BC, van der Heijden AA, Rutters F, Lips P, van der Horst HE, Niemeijer C, Netelenbos JC, Elders PJ (2019) The effect of a screening and treatment program for the prevention of fractures in older women: a randomized pragmatic trial. *J Bone Miner Res* 34:1993–2000
98. Dawson-Hughes B, Harris SS, Krall EA, Dallal GE (1997) Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. *N Engl J Med* 337:670–676
99. Szulc P, Boutroy S, Vilaythiou N, Chaitou A, Delmas PD, Chapurlat R (2011) Cross-sectional analysis of the association between fragility fractures and bone microarchitecture in older men: the STRAMBO study. *J Bone Miner Res* 26:1358–1367
100. Nilsson AG, Sundh D, Johansson L, Nilsson M, Mellstrom D, Rudang R, Zoulakis M, Wallander M, Darelid A, Lorentzon M (2017) Type 2 diabetes mellitus is associated with better bone microarchitecture but lower bone material strength and poorer physical function in elderly women: a population-based study. *J Bone Miner Res* 32:1062–1071
101. Lorentzon M, Nilsson AG, Johansson H, Kanis JA, Mellstrom D, Sundh D (2019) Extensive undertreatment of osteoporosis in older Swedish women. *Osteoporos Int* 30:1297–1305
102. Johansson L, Sundh D, Magnusson P, Rukmangatharajan K, Mellstrom D, Nilsson AG, Lorentzon M (2020) Grade 1 vertebral fractures identified by densitometric lateral spine imaging predict incident major osteoporotic fracture independently of clinical risk factors and bone mineral density in older women. *J Bone Miner Res* 35:1942–1951
103. Scott D, Blizzard L, Fell J, Giles G, Jones G (2010) Associations between dietary nutrient intake and muscle mass and strength in community-dwelling older adults: the Tasmanian Older Adult Cohort study. *J Am Geriatr Soc* 58:2129–2134
104. Cervo MM, Shivappa N, Hebert JR, Oddy WH, Winzenberg T, Balogun S, Wu F, Ebeling P, Aitken D, Jones G, Scott D (2020) Longitudinal associations between dietary inflammatory index and musculoskeletal health in community-dwelling older adults. *Clin Nutr* 39:516–523
105. Walley T, Mantgani A (1997) The UK general practice research database. *Lancet* 350:1097–1099
106. van Staa TP, Geusens P, Kanis JA, Leufkens HG, Gehlbach S, Cooper C (2006) A simple clinical score for estimating the long-term risk of fracture in post-menopausal women. *QJM* 99:673–682
107. Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, Downey P, Elliott P, Green J, Landray M, Liu B, Matthews P, Ong G, Pell J, Silman A, Young A, Sprosen T, Peakman T, Collins R (2015) UK biobank: an open access resource for



- identifying the causes of a wide range of complex diseases of middle and old age. *PLoS Med* 12:e1001779
108. Littlejohns TJ, Holliday J, Gibson LM, Garratt S, Oesingmann N, Alfaro-Almagro F, Bell JD, Boultonwood C, Collins R, Conroy MC, Crabtree N, Doherty N, Frangi AF, Harvey NC, Leeson P, Miller KL, Neubauer S, Petersen SE, Sellers J, Sheard S, Smith SM, Sudlow CLM, Matthews PM, Allen NE (2020) The UK Biobank imaging enhancement of 100,000 participants: rationale, data collection, management and future directions. *Nat Commun* 11:2624
  109. WHI The Women's Health Initiative Study Group (1998) Design of the Women's Health Initiative clinical trial and observational study. *Control Clin Trials* 19:61–109
  110. Hays J, Hunt JR, Hubbell FA, Anderson GL, Limacher M, Allen C, Rossouw JE (2003) The Women's Health Initiative recruitment methods and results. *Ann Epidemiol* 13:S18–77
  111. 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
  112. Birks YF, Porthouse J, Addie C, Loughney K, Saxon L, Baverstock M, Francis RM, Reid DM, Watt I, Torgerson DJ, Trial PCHP, G, (2004) Randomized controlled trial of hip protectors among women living in the community. *Osteoporos Int* 15:701–706
  113. Mann R, Birks Y, Hall J, Torgerson D, Watt I (2006) Exploring the relationship between fear of falling and neuroticism: a cross-sectional study in community-dwelling women over 70. *Age Ageing* 35:143–147
  114. 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
  115. 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
  116. Binkley N, Kiebzak GM, Lewiecki EM, Krueger D, Gangnon RE, Miller PD, Shepherd JA, Drezner MK (2005) Recalculation of the NHANES database SD improves T-score agreement and reduces osteoporosis prevalence. *J Bone Miner Res* 20:195–201
  117. Kanis JA, Johansson H, Harvey NC, Gudnason V, Sigurdsson G, Siggeirsdottir K, Lorentzon M, Liu E, Vandenput L, McCloskey E (2021) The effect on subsequent fracture risk of age, sex and prior fracture site by recency of prior fracture. *Osteoporos Int* 32:1547–1555
  118. Kanis JA, McCloskey E, Johansson H, Oden A, Leslie WD (2012) FRAX((R)) with and without bone mineral density. *Calcif Tissue Int* 90:1–13
  119. Strom O, Lauppe R, Ljunggren O, Spangeus A, Ortsater G, O'Kelly J, Akesson K (2020) Real-world effectiveness of osteoporosis treatment in the oldest old. *Osteoporos Int* 31:1525–1533
  120. Vestergaard P (2007) Discrepancies in bone mineral density and fracture risk in patients with type 1 and type 2 diabetes—a meta-analysis. *Osteoporos Int* 18:427–444
  121. Vilaca T, Schini M, Harnan S, Sutton A, Poku E, Allen IE, Cummings SR, Eastell R (2020) The risk of hip and non-vertebral fractures in type 1 and type 2 diabetes: a systematic review and meta-analysis update. *Bone* 137:115457
  122. Bai J, Gao Q, Wang C, Dai J (2020) Diabetes mellitus and risk of low-energy fracture: a meta-analysis. *Aging Clin Exp Res* 32:2173–2186
  123. 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
  124. Schwartz AV, Vittinghoff E, Bauer DC, Hillier TA, Strotmeyer ES, Ensrud KE, Donaldson MG, Cauley JA, Harris TB, Koster A, Womack CR, Palermo L, Black DM, Study of Osteoporotic Fractures Research Group, Osteoporotic Fractures in Men Research Group, Health And Body Composition Research Group (2011) Association of BMD and FRAX score with risk of fracture in older adults with type 2 diabetes. *JAMA* 305:2184–2192
  125. Giangregorio LM, Leslie WD, Lix LM, Johansson H, Oden A, McCloskey E, Kanis JA (2012) FRAX underestimates fracture risk in patients with diabetes. *J Bone Miner Res* 27:301–308
  126. Leslie WD, Rubin MR, Schwartz AV, Kanis JA (2012) Type 2 diabetes and bone. *J Bone Miner Res* 27:2231–2237
  127. Wallander M, Axelsson KF, Nilsson AG, Lundh D, Lorentzon M (2017) Type 2 diabetes and risk of hip fractures and non-skeletal fall injuries in the elderly: a study from the fractures and fall injuries in the elderly cohort (FRAILCO). *J Bone Miner Res* 32:449–460
  128. Schacter GI, Leslie WD (2021) Diabetes and osteoporosis: part II, clinical management. *Endocrinol Metab Clin North Am* 50:287–297
  129. Vestergaard P, Rejnmark L, Mosekilde L (2011) Are antiresorptive drugs effective against fractures in patients with diabetes? *Calcif Tissue Int* 88:209–214
  130. Masud T, Morris RO (2001) Epidemiology of falls. *Age Ageing* 30(Suppl 4):3–7
  131. 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
  132. 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
  133. Gillespie LD, Gillespie WJ, Robertson MC, Lamb SE, Cumming RG, Rowe BH (2003) Interventions for preventing falls in elderly people. *Cochrane Database Syst Rev* CD000340
  134. Geusens P, Milisen K, Dejaeger E, Boonen S (2003) Falls and fractures in postmenopausal women: a review. *J Br Menopause Soc* 9:101–106
  135. 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, Lyrakis 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 TW, 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
  136. 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
  137. 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
  138. 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
  139. Henry MJ, Pasco JA, Sanders KM, Nicholson GC, Kotowicz MA (2006) Fracture Risk (FRISK) Score: Geelong Osteoporosis Study. *Radiology* 241:190–196
  140. Cameron ID, Gillespie LD, Robertson MC, Murray GR, Hill KD, Cumming RG, Kerse N (2012) Interventions for preventing


- falls in older people in care facilities and hospitals. *Cochrane Database Syst Rev* 12:CD005465
141. Gillespie LD, Robertson MC, Gillespie WJ, Sherrington C, Gates S, Clemson LM, Lamb SE (2012) Interventions for preventing falls in older people living in the community. *Cochrane Database Syst Rev* CD007146
  142. 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, Trivison 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, Boulton 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
  144. 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 Group (2020) Screening and intervention to prevent falls and fractures in older people. *N Engl J Med* 383:1848–1859
  145. 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
  146. 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
  147. 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
  148. Leslie WD, Morin SN, Lix LM, Martineau P, Bryant 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
  149. Lorentzon M, Johansson H, Harvey N, Liu E, Vandenput L, Crandall C, McCloskey E, Kanis J (2020) Hormone therapy reduces the risk of fracture regardless of baseline FRAX probability or prior falls – results from the Women's Health Initiative hormone therapy trials. *J Bone Miner Res* 33 (Suppl 1) (Available at <https://www.asbmr.org/education/AbstractDetail?aid=14f38954-f17b-4c7f-a336-d2cd794f4a0a>) Accessed December 23, 2020
  150. 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
  151. 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
  152. Johansson H, Kanis JA, Oden A, McCloskey E, Chapurlat RD, Christiansen C, Cummings SR, Diez-Perez A, Eisman JA, Fujiwara S, Gluer CC, Goltzman D, Hans D, Khaw KT, Krieg MA, Kroger H, LaCroix AZ, Lau E, Leslie WD, Mellstrom D, Melton LJ 3rd, O'Neill TW, Pasco JA, Prior JC, Reid DM, Rivadeneira F, van Staa T, Yoshimura N, Zillikens MC (2014) A meta-analysis of the association of fracture risk and body mass index in women. *J Bone Miner Res* 29:223–233
  153. Kanis JA, Johansson H, Oden A, Johnell O, de Laet C, Melton IL, Tenenhouse A, Reeve J, Silman AJ, Pols HA, Eisman JA, McCloskey EV, Mellstrom D (2004) A meta-analysis of prior corticosteroid use and fracture risk. *J Bone Miner Res* 19:893–899
  154. Kanis JA, Johnell O, Oden A, Johansson H, De Laet C, Eisman JA, Fujiwara S, Kroger H, McCloskey EV, Mellstrom D, Melton LJ, Pols H, Reeve J, Silman A, Tenenhouse A (2005) Smoking and fracture risk: a meta-analysis. *Osteoporos Int* 16:155–162
  155. Hippisley-Cox J, Coupland C (2009) Predicting risk of osteoporotic fracture in men and women in England and Wales: prospective derivation and validation of QFractureScores. *BMJ* 339:b4229
  156. Nguyen ND, Frost SA, Center JR, Eisman JA, Nguyen TV (2007) Development of a nomogram for individualizing hip fracture risk in men and women. *Osteoporos Int* 18:1109–1117
  157. 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
  158. Kanis JA, Oden A, Johansson H, McCloskey E (2012) Pitfalls in the external validation of FRAX. *Osteoporos Int* 23:423–431
  159. Breslow NE, Day NE (1987) Statistical methods in cancer research. Volume II—The design and analysis of cohort studies. *IARC Sci Publ* 1–406
  160. 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
  161. Kanis JA, Johnell O, De Laet C, Johansson H, Oden A, Delmas P, Eisman J, Fujiwara S, Garnero P, Kroger H, McCloskey EV, Mellstrom D, Melton LJ, Pols H, Reeve J, Silman A, Tenenhouse A (2004) A meta-analysis of previous fracture and subsequent fracture risk. *Bone* 35:375–382
  162. Kanis JA, Johansson H, Oden A, Johnell O, De Laet C, Eisman JA, McCloskey EV, Mellstrom D, Melton LJ 3rd, Pols HA, Reeve J, Silman AJ, Tenenhouse A (2004) A family history of fracture and fracture risk: a meta-analysis. *Bone* 35:1029–1037
  163. Kanis JA, Johansson H, Johnell O, Oden A, De Laet C, Eisman JA, Pols H, Tenenhouse A (2005) Alcohol intake as a risk factor for fracture. *Osteoporos Int* 16:737–742
  164. Kanis JA, Johansson H, Oden A, De Laet C, Johnell O, Eisman JA, McCloskey E, Mellstrom D, Pols H, Reeve J, Silman A, Tenenhouse A (2005) A meta-analysis of milk intake and fracture risk: low utility for case finding. *Osteoporos Int* 16:799–804
  165. Johnell O, Kanis JA, Oden A, Johansson H, De Laet C, Delmas P, Eisman JA, Fujiwara S, Kroger H, Mellstrom D, Meunier PJ, Melton LJ 3rd, O'Neill T, Pols H, Reeve J, Silman A, Tenenhouse A (2005) Predictive value of BMD for hip and other fractures. *J Bone Miner Res* 20:1185–1194
  166. De Laet CE, Kanis JA, Oden A, Johansson H, Johnell O, Delmas P, Eisman JA, Kroger H, Fujiwara S, Garnero P, McCloskey EV, Mellstrom D, Melton LJ 3rd, Meunier PJ, Pols HA, Reeve J, Silman A, Tenenhouse A (2005) Body mass index as a predictor of fracture risk: a meta-analysis. *Osteoporos Int* 16:1330–1338
  167. Johansson H, Kanis JA, Oden A, Leslie WD, Fujiwara S, Gluer CC, Kroger H, LaCroix AZ, Lau E, Melton LJ 3rd, Eisman JA, O'Neill TW, Goltzman D, Reid DM, McCloskey E (2014) Impact of femoral neck and lumbar spine BMD discordances on FRAX probabilities in women: a meta-analysis of international cohorts. *Calcif Tissue Int* 95:428–435
  168. McCloskey EV, Oden A, Harvey NC, Leslie WD, Hans D, Johansson H, Barkmann R, Boutroy S, Brown J, Chapurlat R,



- Elders PJM, Fujita Y, Gluer CC, Goltzman D, Iki M, Karlsson M, Kindmark A, Kotowicz M, Kurumatani N, Kwok T, Lamy O, Leung J, Lippuner K, Ljunggren O, Lorentzon M, Mellstrom D, Merlijn T, Oei L, Ohlsson C, Pasco JA, Rivadeneira F, Rosengren B, Sornay-Rendu E, Szulc P, Tamaki J, Kanis JA (2016) A meta-analysis of trabecular bone score in fracture risk prediction and its relationship to FRAX. *J Bone Miner Res* 31:940–948
169. Steyerberg EW, Moons KG, van der Windt DA, Hayden JA, Perel P, Schroter S, Riley RD, Hemingway H, Altman DG, for the PROGRESS Group (2013) Prognosis Research Strategy (PROGRESS) 3: prognostic model research. *PLoS Med* 10:e1001381
170. Leslie WD, Lix LM, Johansson H, Oden A, McCloskey E, Kanis JA, Program MBD (2010) Independent clinical validation of a Canadian FRAX tool: fracture prediction and model calibration. *J Bone Miner Res* 25:2350–2358
171. Fraser LA, Langsetmo L, Berger C, Ioannidis G, Goltzman D, Adachi JD, Papaioannou A, Josse R, Kovacs CS, Olszynski WP, Towheed T, Hanley DA, Kaiser SM, Prior J, Jamal S, Kreiger N, Brown JP, Johansson H, Oden A, McCloskey E, Kanis JA, Leslie WD, CaMos Research G (2011) Fracture prediction and calibration of a Canadian FRAX(R) tool: a population-based report from CaMos. *Osteoporos Int* 22:829–837
172. 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

**Publisher's Note** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

## Authors and Affiliations

L. Vandenput<sup>1,2</sup>  · H. Johansson<sup>1,3</sup> · E. V. McCloskey<sup>3,4</sup> · E. Liu<sup>1</sup> · K. E. Åkesson<sup>5,6</sup> · F. A. Anderson<sup>7</sup> · R. Azagra<sup>8,9,10</sup> · C. L. Bager<sup>11</sup> · C. Beaudart<sup>12</sup> · H. A. Bischoff-Ferrari<sup>13,14</sup> · E. Biver<sup>15</sup> · O. Bruyère<sup>12</sup> · J. A. Cauley<sup>16</sup> · J. R. Center<sup>17,18,19</sup> · R. Chapurlat<sup>20</sup> · C. Christiansen<sup>11</sup> · C. Cooper<sup>21,22,23</sup> · C. J. Crandall<sup>24</sup> · S. R. Cummings<sup>25</sup> · J. A. P. da Silva<sup>26,27</sup> · B. Dawson-Hughes<sup>28</sup> · A. Diez-Perez<sup>29</sup> · A. B. Dufour<sup>30,31</sup> · J. A. Eisman<sup>18,19,32</sup> · P. J. M. Elders<sup>33</sup> · S. Ferrari<sup>15</sup> · Y. Fujita<sup>34</sup> · S. Fujiwara<sup>35</sup> · C.-C. Glüer<sup>36</sup> · I. Goldshtein<sup>37,38</sup> · D. Goltzman<sup>39</sup> · V. Gudnason<sup>40,41</sup> · J. Hall<sup>42</sup> · D. Hans<sup>43</sup> · M. Hoff<sup>44,45</sup> · R. J. Hollick<sup>46</sup> · M. Huisman<sup>47,48</sup> · M. Iki<sup>34</sup> · S. Ish-Shalom<sup>49</sup> · G. Jones<sup>50</sup> · M. K. Karlsson<sup>5,51</sup> · S. Khosla<sup>52</sup> · D. P. Kiel<sup>30,31</sup> · W.-P. Koh<sup>53,54</sup> · F. Koromani<sup>55,56</sup> · M. A. Kotowicz<sup>57,58,59</sup> · H. Kröger<sup>60,61</sup> · T. Kwok<sup>62,63</sup> · O. Lamy<sup>64,65</sup> · A. Langhammer<sup>66</sup> · B. Larijani<sup>67</sup> · K. Lippuner<sup>68</sup> · D. Mellström<sup>69,70</sup> · T. Merlijn<sup>33</sup> · A. Nordström<sup>71,72</sup> · P. Nordström<sup>73</sup> · T. W. O'Neill<sup>74,75</sup> · B. Obermayer-Pietsch<sup>76,77</sup> · C. Ohlsson<sup>2,78</sup> · E. S. Orwoll<sup>79</sup> · J. A. Pasco<sup>80,81,82,83</sup> · F. Rivadeneira<sup>55</sup> · B. Schei<sup>84,85</sup> · A.-M. Schott<sup>86</sup> · E. J. Shiroma<sup>87</sup> · K. Siggeirsdottir<sup>40,88</sup> · E. M. Simonsick<sup>89</sup> · E. Sornay-Rendu<sup>90</sup> · R. Sund<sup>61</sup> · K. M. A. Swart<sup>33</sup> · P. Szulc<sup>20</sup> · J. Tamaki<sup>91</sup> · D. J. Torgerson<sup>92</sup> · N. M. van Schoor<sup>47</sup> · T. P. van Staa<sup>93</sup> · J. Vila<sup>94</sup> · N. J. Wareham<sup>95</sup> · N. C. Wright<sup>96</sup> · N. Yoshimura<sup>97</sup> · M. C. Zillikens<sup>55</sup> · M. Zwart<sup>98,99,100</sup> · N. C. Harvey<sup>101,102</sup> · M. Lorentzon<sup>1,103,104</sup> · W. D. Leslie<sup>105</sup> · J. A. Kanis<sup>1,3,106</sup>

✉ J. A. Kanis  
w.j.pontefract@shef.ac.uk

L. Vandenput  
liesbeth.vandenput@acu.edu.au

H. Johansson  
helena@statiq.se

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

E. Liu  
enwu.liu@acu.edu.au

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

F. A. Anderson  
fred.anderson@umassmed.edu

R. Azagra  
rafael.azagra@uab.cat

C. L. Bager  
cba@nordicbio.com

C. Beaudart  
c.beaudart@uliege.be

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

E. Biver  
emmanuel.biver@hcuge.ch

O. Bruyère  
olivier.bruyere@uliege.be

J. A. Cauley  
jcauley@edc.pitt.edu

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

R. Chapurlat  
roland.chapurlat@inserm.fr

C. Christiansen  
cc@nordicbio.com

C. Cooper  
cc@mrc.soton.ac.uk

C. J. Crandall  
ccrandall@mednet.ucla.edu

S. R. Cummings  
steven.cummings@ucsf.edu

J. A. P. da Silva  
jdasilva@ci.uc.pt

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

A. Diez-Perez  
adiez@psmar.cat

A. B. Dufour  
alyssadufour@hsl.harvard.edu

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

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

S. Ferrari  
serge.ferrari@unige.ch

Y. Fujita  
yfujita@med.kindai.ac.jp

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

C.-C. Glüer  
glueer@rad.uni-kiel.de

I. Goldshtein  
goldst\_in@mac.org.il

D. Goltzman  
david.goltzman@mcgill.ca

V. Gudnason  
v.gudnason@hjarta.is

J. Hall  
jill.hall@ed.ac.uk

D. Hans  
didier.hans@chuv.ch

M. Hoff  
mari.hoff@ntnu.no

R. J. Hollick  
rhollick@abdn.ac.uk

M. Huisman  
m.huisman@amsterdamumc.nl

M. Iki  
masa@med.kindai.ac.jp

S. Ish-Shalom  
sishshalom@gmail.com

G. Jones  
g.jones@utas.edu.au

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

S. Khosla  
khosla.sundeep@mayo.edu

D. P. Kiel  
kiel@hsl.harvard.edu

W.-P. Koh  
kohwp@nus.edu.sg

F. Koromani  
f.koromani@erasmusmc.nl

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

H. Kröger  
heikki.kroger@kuh.fi

T. Kwok  
tkwok@cuhk.edu.hk

O. Lamy  
olivier.lamy@chuv.ch

A. Langhammer  
arnulf.langhammer@ntnu.no

B. Larijani  
emrc@tums.ac.ir

K. Lippuner  
kurt.lippuner@insel.ch

D. Mellström  
dan.mellstrom@vgregion.se

T. Merlijn  
tmerlijn@gmail.com

A. Nordström  
anna.h.nordstrom@umu.se

P. Nordström  
peter.nordstrom@umu.se

T. W. O'Neill  
terence.oneill@manchester.ac.uk

B. Obermayer-Pietsch  
barbara.obermayer@medunigraz.at

C. Ohlsson  
claes.ohlsson@medic.gu.se

E. S. Orwoll  
orwoll@ohsu.edu

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

F. Rivadeneira  
f.rivadeneira@erasmusmc.nl

B. Schei  
berit.schei@ntnu.no

A.-M. Schott  
anne-marie.schott-pethelaz@chu-lyon.fr

E. J. Shiroma  
eric.shiroma@nih.gov

K. Siggeirsdottir  
kristin@janus.is

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

E. Sornay-Rendu  
elisabeth.rendu@inserm.fr

R. Sund  
reijo.sund@uef.fi

- K. M. A. Swart  
karin.swart-polinder@pharmo.nl
- P. Szulc  
pawel.szulc@inserm.fr
- J. Tamaki  
jtamaki@ompu.ac.jp
- D. J. Torgerson  
david.torgerson@york.ac.uk
- N. M. van Schoor  
nm.vanschoor@amsterdamumc.nl
- T. P. van Staa  
tjeerd.vanstaa@manchester.ac.uk
- J. Vila  
jvila@imim.es
- N. J. Wareham  
nick.wareham@mrc-epid.cam.ac.uk
- N. C. Wright  
ncwright@uab.edu
- N. Yoshimura  
noripu@rc4.so-net.ne.jp
- M. C. Zillikens  
m.c.zillikens@erasmusmc.nl
- M. Zwart  
marta.zwart@udg.edu
- N. C. Harvey  
nch@mrc.soton.ac.uk
- M. Lorentzon  
mattias.lorentzon@medic.gu.se
- W. D. Leslie  
bleslie@sbgh.mb.ca
- <sup>1</sup> Mary McKillop Institute for Health Research, Australian Catholic University, Melbourne, Australia
  - <sup>2</sup> Sahlgrenska Osteoporosis Centre, Department of Internal Medicine and Clinical Nutrition, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden
  - <sup>3</sup> Centre for Metabolic Bone Diseases, University of Sheffield, Sheffield, UK
  - <sup>4</sup> MRC Versus Arthritis Centre for Integrated Research in Musculoskeletal Ageing, Mellanby Centre for Musculoskeletal Research, University of Sheffield, Sheffield, UK
  - <sup>5</sup> Clinical and Molecular Osteoporosis Research Unit, Department of Clinical Sciences, Lund University, Lund, Sweden
  - <sup>6</sup> Department of Orthopedics, Skåne University Hospital, Malmö, Sweden
  - <sup>7</sup> GLOW Coordinating Center, Center for Outcomes Research, University of Massachusetts Medical School, Worcester, MA, USA
  - <sup>8</sup> Department of Medicine, Autonomous University of Barcelona, Barcelona, Spain
  - <sup>9</sup> Health Center Badia del Valles, Catalan Institute of Health, Barcelona, Spain
  - <sup>10</sup> GROIMAP (Research Group), Unitat de Suport a La Recerca Metropolitana Nord, Institut Universitari d'Investigació en Atenció Primària Jordi Gol, Santa Coloma de Gramenet, Barcelona, Spain
  - <sup>11</sup> Nordic Bioscience A/S, Herlev, Denmark
  - <sup>12</sup> 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
  - <sup>13</sup> Department of Aging Medicine and Aging Research, University Hospital, Zurich, and University of Zurich, Zurich, Switzerland
  - <sup>14</sup> Centre On Aging and Mobility, University of Zurich and City Hospital, Zurich, Switzerland
  - <sup>15</sup> Division of Bone Diseases, Department of Medicine, Geneva University Hospitals and Faculty of Medicine, University of Geneva, Geneva, Switzerland
  - <sup>16</sup> Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, Philadelphia, USA
  - <sup>17</sup> Bone Biology, Healthy Ageing Theme, Garvan Institute of Medical Research, Sydney, NSW, Australia
  - <sup>18</sup> St Vincent's Clinical School, Faculty of Medicine, University of New South Wales Sydney, Sydney, NSW, Australia
  - <sup>19</sup> School of Medicine Sydney, University of Notre Dame Australia, Sydney, NSW, Australia
  - <sup>20</sup> INSERM UMR 1033, University of Lyon, Hôpital Edouard Herriot, Lyon, France
  - <sup>21</sup> MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton, UK
  - <sup>22</sup> National Institute for Health Research Southampton Biomedical Research Centre, University of Southampton and University Hospitals Southampton NHS Foundation Trust, Southampton, UK
  - <sup>23</sup> National Institute for Health Research Oxford Biomedical Research Unit, University of Oxford, Oxford, UK
  - <sup>24</sup> Division of General Internal Medicine and Health Services Research, David Geffen School of Medicine, University of California, Los Angeles, CA, USA
  - <sup>25</sup> San Francisco Coordinating Center, California Pacific Medical Center Research Institute, San Francisco, CA, USA
  - <sup>26</sup> Coimbra Institute for Clinical and Biomedical Research, Faculty of Medicine, University of Coimbra, Coimbra, Portugal
  - <sup>27</sup> Rheumatology Department, University Hospital and University of Coimbra, Coimbra, Portugal
  - <sup>28</sup> Bone Metabolism Laboratory, Jean Mayer US Department of Agriculture Human Nutrition Research Center On Aging, Tufts University, Boston, MA, USA
  - <sup>29</sup> Department of Internal Medicine, Hospital del Mar and CIBERFES, Autonomous University of Barcelona, Barcelona, Spain

- 30 Marcus Institute for Aging Research, Hebrew SeniorLife, Boston, MA, USA
- 31 Department of Medicine, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA, USA
- 32 Osteoporosis and Bone Biology Division, Garvan Institute of Medical Research, Sydney, NSW, Australia
- 33 Department of General Practice, Amsterdam UMC, Location VUmc, Amsterdam Public Health Research Institute, Amsterdam, The Netherlands
- 34 Department of Public Health, Faculty of Medicine, Kindai University, Osaka, Japan
- 35 Department of Pharmacy, Yasuda Women's University, Hiroshima, Japan
- 36 Section Biomedical Imaging, Molecular Imaging North Competence Center, Department of Radiology and Neuroradiology, University Medical Center Schleswig-Holstein Kiel, Kiel University, Kiel, Germany
- 37 Maccabitech Institute of Research and Innovation, Maccabi Healthcare Services, Tel Aviv, Israel
- 38 Department of Epidemiology and Preventive Medicine, School of Public Health, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
- 39 Department of Medicine, McGill University and McGill University Health Centre, Montreal, Canada
- 40 Icelandic Heart Association, Kopavogur, Iceland
- 41 University of Iceland, Reykjavik, Iceland
- 42 MRC Centre for Reproductive Health, University of Edinburgh, Edinburgh, UK
- 43 Centre of Bone Diseases, Bone and Joint Department, Lausanne University Hospital, Lausanne, Switzerland
- 44 Department of Neuromedicine and Movement Science, Norwegian University of Science and Technology, Trondheim, Norway
- 45 Department of Rheumatology, St Olavs Hospital, Trondheim, Norway
- 46 Aberdeen Centre for Arthritis and Musculoskeletal Health, Epidemiology Group, University of Aberdeen, Aberdeen, UK
- 47 Department of Epidemiology and Data Science, Amsterdam Public Health Research Institute, VU University Medical Center, Amsterdam, The Netherlands
- 48 Department of Sociology, VU University, Amsterdam, The Netherlands
- 49 Endocrine Clinic, Elisha Hospital, Haifa, Israel
- 50 Menzies Institute for Medical Research, University of Tasmania, Hobart, Australia
- 51 Department of Orthopaedics, Skåne University Hospital, Malmö, Sweden
- 52 Robert and Arlene Kogod Center On Aging and Division of Endocrinology, Mayo Clinic College of Medicine, Mayo Clinic, Rochester, MN, USA
- 53 Healthy Longevity Translational Research Programme, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore
- 54 Singapore Institute for Clinical Sciences, Agency for Science Technology and Research (A\*STAR), Singapore, Singapore
- 55 Department of Internal Medicine, Erasmus University Medical Center, Rotterdam, The Netherlands
- 56 Department of Radiology and Nuclear Medicine, Erasmus University Medical Center, Rotterdam, The Netherlands
- 57 IMPACT (Institute for Mental and Physical Health and Clinical Translation), Deakin University, Geelong, VIC, Australia
- 58 Barwon Health, Geelong, VIC, Australia
- 59 Department of Medicine - Western Health, The University of Melbourne, St Albans, Victoria, Australia
- 60 Department of Orthopedics and Traumatology, Kuopio University Hospital, Kuopio, Finland
- 61 Kuopio Musculoskeletal Research Unit, University of Eastern Finland, Kuopio, Finland
- 62 Department of Medicine and Therapeutics, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong, Hong Kong
- 63 Jockey Club Centre for Osteoporosis Care and Control, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong, Hong Kong
- 64 Centre of Bone Diseases, Lausanne University Hospital, Lausanne, Switzerland
- 65 Service of Internal Medicine, Lausanne University Hospital, Lausanne, Switzerland
- 66 Department of Public Health and Nursing, Faculty of Medicine and Health Sciences, HUNT Research Centre, Norwegian University of Science and Technology, Trondheim, Norway
- 67 Endocrinology and Metabolism Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran
- 68 Department of Osteoporosis, Bern University Hospital, University of Bern, Bern, Switzerland
- 69 Geriatric Medicine, Department of Internal Medicine and Clinical Nutrition, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden
- 70 Geriatric Medicine, Sahlgrenska University Hospital Mölndal, Mölndal, Sweden
- 71 Division of Sustainable Health, Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden
- 72 School of Sport Sciences, Arctic University of Norway, Tromsø, Norway
- 73 Unit of Geriatric Medicine, Department of Community Medicine and Rehabilitation, Umeå University, Umeå, Sweden
- 74 National Institute for Health Research Manchester Biomedical Research Centre, Manchester University NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK
- 75 Centre for Epidemiology Versus Arthritis, University of Manchester, Manchester, UK

- <sup>76</sup> Department of Internal Medicine, Division of Endocrinology and Diabetology, Medical University Graz, Graz, Austria
- <sup>77</sup> Center for Biomarker Research in Medicine, Graz, Austria
- <sup>78</sup> Department of Drug Treatment, Sahlgrenska University Hospital, Region Västra Götaland, Gothenburg, Sweden
- <sup>79</sup> Department of Medicine, Oregon Health and Science University, Portland, OR, USA
- <sup>80</sup> Institute for Physical and Mental Health and Clinical Translation (IMPACT), Deakin University, Geelong, Australia
- <sup>81</sup> Department of Medicine-Western Health, The University of Melbourne, St Albans, Australia
- <sup>82</sup> Barwon Health, Geelong, Australia
- <sup>83</sup> Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Australia
- <sup>84</sup> Department of Public Health and Nursing, Norwegian University of Science and Technology, Trondheim, Norway
- <sup>85</sup> Department of Gynecology, St Olavs Hospital, Trondheim, Norway
- <sup>86</sup> Université Claude Bernard Lyon 1, U INSERM 1290 RESHAPE, Lyon, France
- <sup>87</sup> Laboratory of Epidemiology and Population Sciences, National Institute On Aging, Baltimore, MD, USA
- <sup>88</sup> Janus Rehabilitation, Reykjavik, Iceland
- <sup>89</sup> Translational Gerontology Branch, National Institute On Aging Intramural Research Program, Baltimore, MD, USA
- <sup>90</sup> INSERM Research Unit 1033, Lyon, France
- <sup>91</sup> Department of Hygiene and Public Health, Faculty of Medicine, Educational Foundation of Osaka Medical and Pharmaceutical University, Osaka, Japan
- <sup>92</sup> York Trials Unit, Department of Health Sciences, University of York, York, UK
- <sup>93</sup> Centre for Health Informatics, Faculty of Biology, Medicine and Health, School of Health Sciences, University of Manchester, Manchester, UK
- <sup>94</sup> Statistics Support Unit, Hospital del Mar Medical Research Institute, CIBER Epidemiology and Public Health (CIBERESP), Barcelona, Spain
- <sup>95</sup> MRC Epidemiology Unit, University of Cambridge, Cambridge, UK
- <sup>96</sup> Department of Epidemiology, University of Alabama at Birmingham, Birmingham, AL, USA
- <sup>97</sup> Department of Preventive Medicine for Locomotive Organ Disorders, The University of Tokyo Hospital, Tokyo, Japan
- <sup>98</sup> Health Center Can Gibert del Plà, Catalan Institute of Health, Girona, Spain
- <sup>99</sup> Department of Medical Sciences, University of Girona, Girona, Spain
- <sup>100</sup> GROIMAP (Research Group), Institut Universitari d'Investigació en Atenció Primària Jordi Gol, Barcelona, Spain
- <sup>101</sup> MRC Lifecourse Epidemiology Centre, University of Southampton, Southampton, UK
- <sup>102</sup> NIHR Southampton Biomedical Research Centre, University of Southampton and University Hospital Southampton NHS Foundation Trust, Southampton, UK
- <sup>103</sup> Sahlgrenska Osteoporosis Centre, Institute of Medicine, University of Gothenburg, Gothenburg, Sweden
- <sup>104</sup> Geriatric Medicine, Region Västra Götaland, Sahlgrenska University Hospital, Mölndal, Sweden
- <sup>105</sup> Department of Medicine, University of Manitoba, Winnipeg, MB, Canada
- <sup>106</sup> Centre for Metabolic Bone Diseases, University of Sheffield Medical School, Sheffield, UK