EXTENDED REPORT

The accuracy of osteoporotic fracture risk prediction tools: a systematic review and meta-analysis

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ABSTRACT

Objectives To identify and synthesise the best available evidence on the accuracy of the currently available tools for predicting fracture risk.

Methods We systematically searched PubMed MEDLINE, Embase and Cochrane databases to 2014. Two reviewers independently selected articles, collected data from studies, and carried out a hand search of the references of the included studies. The Quality Assessment Tool for Diagnostic Accuracy Studies (QUADAS) checklist was used, and the primary outcome was the area under the curve (AUC) and 95% CIs, obtained from receiver operating characteristic (ROC) analyses. We excluded tools if they had not been externally validated or were designed for specific disease populations. Random effects meta-analyses were performed with the selected tools.

Results Forty-five studies met inclusion criteria, corresponding to 13 different tools. Only three tools had been tested more than once in a population-based setting: FRAX (26 studies in 9 countries), GARVAN (6 studies in 3 countries) and QFracture (3 studies in the UK, 1 also including Irish participants). Twenty studies with these three tools were included in a total of 17 meta-analyses (for hip or major osteoporotic fractures; men or women; with or without bone mineral density).

Conclusions Most of the 13 tools are feasible in clinical practice. FRAX has the largest number of externally validated and independent studies. The overall accuracy of the different tools is satisfactory (>0.70), with QFracture reaching 0.89 (95% CI 0.88 to 0.89). Significant methodological limitations were observed in many studies, suggesting caution when comparing tools based solely on the AUC.

INTRODUCTION

The major clinical consequence of osteoporosis is the occurrence of fragility fractures.[1] Osteoporotic fractures lead to significant suffering, disability and mortality, resulting in enormous costs for individuals and society.[2] Predicting the absolute risk of osteoporotic fractures is, therefore, of the utmost importance to optimise prevention strategies.

The operational definition of osteoporosis provided by the WHO is a bone mineral density (BMD) 2.5 or more SDs below the average value for young healthy individuals of the same gender and ethnic background (T-score ≤−2.5).[3–5] However, BMD has limited sensitivity and specificity in the prediction of fracture.[6–8] In fact, a large number of conditions have been firmly established as risk factors for the occurrence of fragility fractures, independently of BMD, and include age, gender, body mass index, family history of fractures, ethnicity, premature menopause, glucocorticoid use, rheumatoid arthritis, hyperthyroidism, hyperparathryoidism, Cushing's, anorexia nervosa, malabsorption, falls, previous fractures, smoking, high caffeine intake and alcohol abuse.[9–16] These have been combined into prediction algorithms to estimate fracture probability. When applied upon the baseline epidemiology of fragility fractures in a given population, these algorithms or tools provide estimates of absolute risks. The use of these tools, combined with intervention thresholds, is recommended by many international treatment guidelines.[17–19] However, the existing tools differ from each in many relevant aspects: their feasibility, the number and availability of clinical risk factors included, the accessibility of BMD measurements and, finally, their performance in different settings. Such diversity calls for an integrative systematic review (SR) upon which the critical appraisal and selection of tools to be used in clinical practice and research can be based. The existing reviews[20–23] have a number of important limitations, such as exclusion of males, disregard of some relevant prediction algorithms, lack of meta-analysis where applicable and, naturally, omission of important subsequent publications.

The aim of this SR and meta-analysis is to bring together and describe all relevant evidence on the structure and performance of the currently available tools to predict fracture risk in the general population, while overcoming the above limitations.

METHODS

This study was conducted in line with the guidelines of the Cochrane Collaboration and our findings are reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[24 25]

Protocol and registration

The reviewers (AM, RJOF) and a mentor (JAPS) established the protocol for this SR. Advanced technical advice was obtained from experts (LC, EL, ES). This protocol was not published but is available upon request.

Eligibility criteria

We established the following inclusion criteria for studies:

A. Population—general adult population, both men and women
B. Intervention/test—any fracture risk prediction tool, score, algorithm or other instruments available to predict risk of fracture (with or without BMD measurement)
C. Comparator/control—because we wished to evaluate the performance of prediction tests, we defined the observed occurrence of the event of interest—osteoporotic fracture—as the 'gold standard'
D. Outcome/performance—the primary outcome measure was the area under the curve (AUC) of the fracture risk prediction and its SE, obtained from receiver operating characteristic (ROC) analysis, in the predetermined prediction time-interval. This was chosen as the primary outcome because the AUC represents the accuracy of the predictive model, that is, the probability that a randomly chosen subject with fracture is correctly rated or ranked with greater risk than a randomly chosen individual without fracture[26]
E. Design—cohort studies (either prospective or retrospective) and case–control studies if past data were available for all subjects.

Osteoporotic fracture risk prediction tools were only included in the final analyses if they were developed from an initial population (derivation model) and then externally validated in a different population (validation model), to prevent overestimated accuracy. Studies that included only specific disease populations (eg, chronic renal failure or rheumatoid arthritis patients) were also excluded. We also excluded studies that considered the performance of single variables, such as weight or age. We accepted the definition of major osteoporotic (MOP) fracture adopted by each tool (see below).

Information sources

We only searched published articles. One reviewer (RJOF) performed the electronic search, piloted in PubMed MEDLINE (2003–2014) and then adapted to run also in Cochrane (2003–2014) and Embase (2003–2014). The last search was run on 28 February 2014, with monthly automatic email updates until 6 September 2014. We supplemented electronic searches by checking references cited in published SR and in the articles extracted from the electronic searches. Conference abstracts and unpublished studies were not searched.

Search and study selection

The search strategies included free terms and medical descriptors (eg, MeSH terms) for each PICOD synonym. Some terms used were: Osteoporosis, 'Osteoporotic fractures', 'Risk Assessment', Algorithms, 'Area Under Curve', 'Sensitivity and Specificity', 'Validation Studies' and 'Cohort Studies'. The complete electronic string used for PubMed is provided in online supplementary table S1.

The following limits were applied: (a) articles published after 2003 (as no such studies had been published before then); (b) written in English, Spanish, French, Italian or Portuguese; and (c) performed in humans.

Studies were screened for inclusion over three phases, using Endnote software: (a) we searched and deleted duplicates; (b) two authors (AM and RJOF) independently assessed the electronic search results. They first screened by title and then by abstract. When a title seemed relevant, the abstract was reviewed for eligibility; (3) if any doubt remained, the full text of the article was retrieved and discussed. Arbitration by a third author (JAPS), applied in case of persistent disagreement, took place in two cases. The reason for exclusion was recorded after the full text screening. The inter-rater agreement between AM and RJOF for selection based on title, abstract and full text, measured with the κ statistic, was 0.99, 0.90 and 0.98, respectively.

The meta-analysis only included articles satisfying, cumulatively, the following four criteria: (a) only validation studies were considered (not the derivation models of the tool); (b) the tool had been validated for the country where the study was performed; (c) the tool had been validated for the outcome of the study (eg, studies employing in the prediction of vertebral fractures, a tool that had only been validated to predict hip fractures, were excluded); and (d) data were reported on at least 100 fracture events (as recommended by Vergouwe *et al*[27]).

Data collection

All the field researchers (AM, RJOF, ES, EL, LC and JAPS) validated the data extraction form, which was pilot-tested for feasibility and comprehensiveness with five studies and submitted to consensual minor adjustments. The data were extracted by one author (AM) into a Microsoft Excel spreadsheet. Data included the general characteristics of each study and the outcomes measured. A second author (RJOF) confirmed all the data extracted. We contacted some authors in order to obtain additional information, namely regarding required outcome statistical data (CIs and/or SE of AUCs).

Data items

We collected information on the following: (a) study (authors, year, country); (b) methods (study design, inclusion and exclusion criteria, tool(s) evaluated, factors/variables included in the fracture risk estimation, duration of follow-up, adjustment for time of follow-up, number of participants at the start and at the end of follow-up, reasons for loss to follow-up); (c) participants' characteristics (age, sex, race, diseases, medication); (d) fracture characteristics (number per site, ascertainment methods); and (e) outcome results for (i) all fractures, (ii) major fractures and (iii) hip fractures (AUC and SE or 95% CIs).

Risk of bias in individual studies

The quality of each study was independently appraised by two investigators (AM and RJOF) using the Quality Assessment Tool for Diagnostic Accuracy Studies (QUADAS-2) checklist,[28] and disagreements were solved by a third researcher (JAPS). We excluded some of the optional items of this checklist and added some new ones, as recommended by QUADAS authors[29] and described by other groups.[20] This resulted in a total of 14 items, all graded as adequate, inadequate or unclear (see online supplementary table S2). This quality assessment was not used to include/exclude data for meta-analysis, except for item 19, which refers to a minimum of 100 events of interest.

Summary measures and synthesis of results

For the synthesis of results, data were pooled and meta-analysis performed using Stata V.12 software (StataCorp, 2011). All results derived from primary studies (AUC and SE) were subjected to double data entry and the pooled AUC with 95% CIs were obtained from random effect meta-analyses by instrument type, fracture site, sex, and whether BMD was included or not.

To test heterogeneity among the studies, the I^2 of Higgins and Thompson was calculated. An I^2 value close to 0% indicates no heterogeneity between studies, close to 25% indicates low heterogeneity, close to 50% indicates moderate heterogeneity, and close to 75% indicates high heterogeneity.[30 31]

RESULTS

We included a total of 45 articles, evaluating 13 different tools. Figure 1 shows the study flow-chart. We identified 3546 articles from PubMed MEDLINE, 571 from Embase and 928 from Cochrane, and selected 60 for detailed review, of which 30 were excluded: 15 did not assess fracture risk prediction tools, 12 did not provide information regarding osteoporotic fracture outcome and 3 were SRs. We identified 15 additional articles through hand searching (n=13) and through saved search email updates (n=2). A total of 45 articles were finally included.

The main characteristics of the 13 tools identified are presented in table 1. The number of factors required for calculation varies from 4 in FRAMO to 31 in the updated QFracture (2012) (see online supplementary table S3). Seven tools include BMD as a risk factor (two as an optional item). Seven tools only predict fracture risk for women. Some tools are available on the internet, the algorithm's formula is published in the article for others, and some are available only on request from the authors. The age range of valid prediction is variable: limited to the interval of 70 to 100 years in FRAMO, to 30 to 99 years in updated QFracture (2012). Most tools were developed for populations above 40–50 years of age. Regarding the time-horizon of prediction, most tools calculate a 5-year (n=7) or a 10-year risk (n=7). Fracture and Immobilization Score (FRISC) and the updated QFracture (2012) allow the shortest time of prediction (1 year) while some tools provide more than one time-interval, like FRISC with four time-points (1, 3, 5 and 10 years) and the updated QFracture (2012) with 10 time-points (1–10 years). Regarding the types of fracture that is individually predicted, 10 of the 13 tools predict hip fractures and 7 predict major or any osteoporotic fractures. The definition of MOP fracture differs between tools. FRAX considers MOP as the combination of hip, clinical spine, wrist, and humerus.[32] The definition of the updated QFracture is similar, but all vertebral fractures are included, not only the clinical ones.[33] GARVAN's definition of MOP fracture includes all those considered by FRAX plus distal femur, proximal tibia/fibula, distal tibia/fibula, patella, pelvis, rib, sternum, hands and feet (excluding digits).[34]

In addition, FRAMO predicts the mortality risk, and FRISC the immobilisation risk. The 'Computer model for osteoporotic fracture risk' tool provides an estimation of risk reduction after osteoporosis treatment. Finally, regarding the number of published studies assessing each tool, FRAX (with 26 studies in 9 countries), GARVAN (also known as GRX, 6 studies in

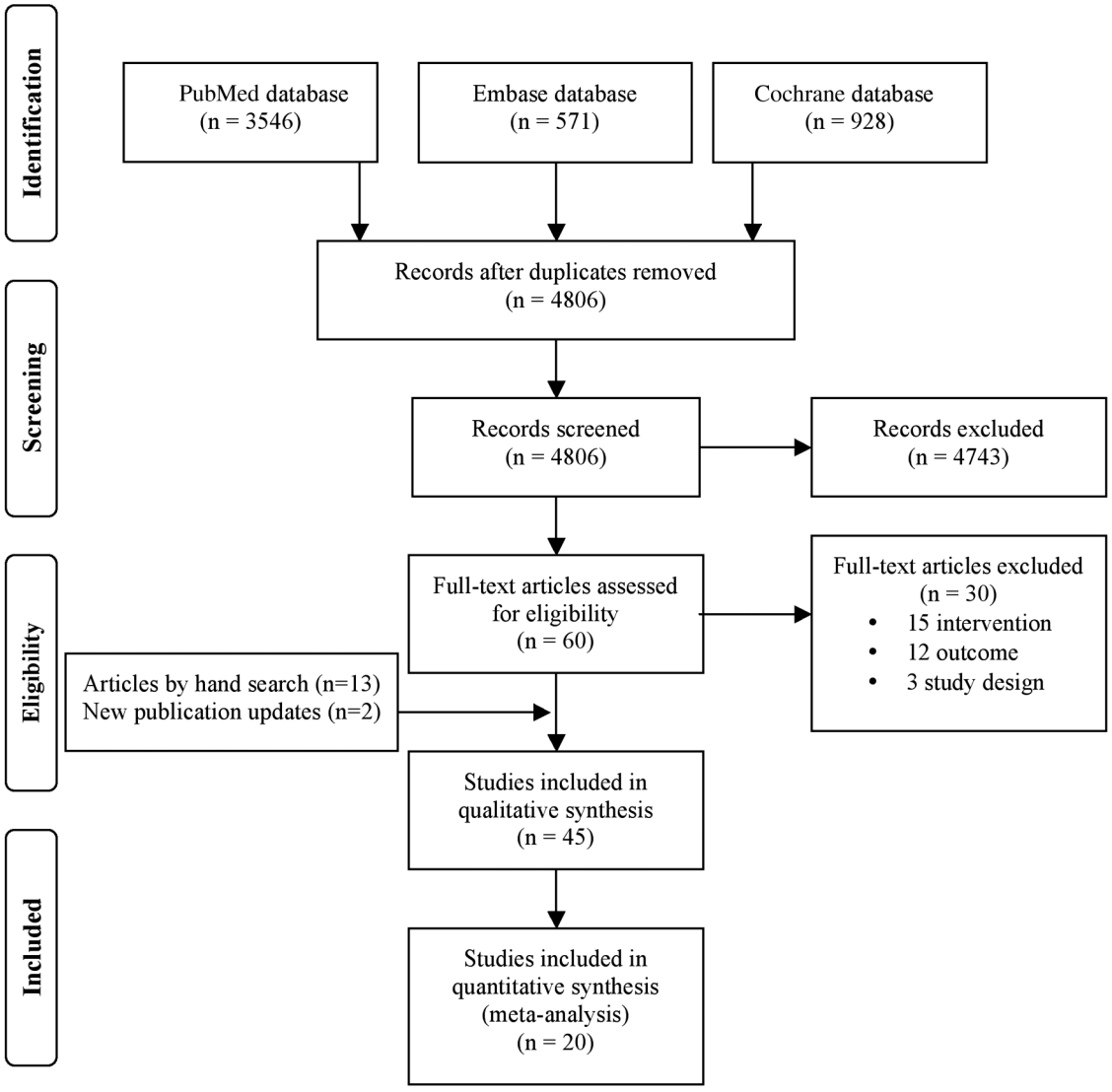

Figure 1 Flow-chart of the article selection.

Table 1 Characteristics of the fracture risk prediction tools

Tool	Characteristics				
	Number of clinical risk factors*	BMD	Tool accessibility Gender Age range	Prediction time(s) and outcome(s)	Number of studies
'Computer model for osteoporotic fracture risk'	8	Yes	Request from authors Female only 45–79	5 years Absolute fracture risk Expected absolute risk reduction after treatment	1[35]
FRAMO	4	No	Available in article Male/Female 70–100	2 years Hip fracture risk Mortality	2[36 37]
FRAX	11	Optional	http://www.shef.ac.uk/FRAX Male/Female 40–90	10 years Major osteoporotic fracture risk Hip fracture risk	26[32 38–62]
FRC	12†	Yes	https://riskcalculator.fore.org/ Male/Female ≥45	10 years Hip fracture risk	2[63 64]
FRISC	8	Yes	http://www.biostatistics.jp/prediction/frisc Female only 40–100	1, 3, 5 and 10 years Major osteoporotic fracture risk Immobilisation risk	2[59 65]
FRISK	5	Yes	Available in article Male/Female >60	5 and 10 years Major osteoporotic fracture risk	2[66 67]
GARVAN-GRX	5	Optional	http://garvan.org.au/promotions/bone-fracture-risk/calculator/ Male/Female 60–96	5 and 10 years Any osteoporotic/fragility fracture risk Hip fracture risk	6[34 39 54 55 68 69]
QFracture	19	No	Removed from website in 2012 Male/Female 30–85	1–10 years Any osteoporotic fracture risk Hip fracture risk	3[33 42 70]
Updated QFracture (2012)	31	No	http://www.qfracture.org/ Male/Female 30–99	1–10 years Any osteoporotic fracture risk Hip fracture risk	1[71]
Score for estimating the long-term risk of fracture in post-menopausal women	8	No	Available in article Females only ≥50	5 years Clinical vertebral fracture risk Clinical osteoporotic fracture risk Hip fracture risk	1[72]
Simplified fracture risk system	5	Yes	Available in article Female only ≥50	10 years Any fracture risk	1[73]
SOF	14	No	Available in article Female only Age unclear	5 years Hip fracture risk	1[74]
WHI	11	No	Request from authors Females only ≥50	5 years Hip fracture risk	1[75]

*Bone mineral density (BMD) was not considered.
Additional descriptions are provide in online supplementary table S3.
†An updated version of the website, dated September 2014, also includes BMD of spine, glucocorticoid exposure, and previous spine fracture, which were not part of the original publication included in this SR. No further publications supporting this change could be found.
FRISC, Fracture and Immobilization Score; FRISK, Fracture Risk prediction; SR, systematic review.

3 countries) and QFracture (3 studies in the UK, 1 including Irish participants) are the most extensively studied. All other tools have been evaluated by only one or two studies.

Methodological quality of the studies

A complete assessment of the quality of the 45 studies, using QUADAS-2, as well as a direct comparison between FRAX, QFracture and GARVAN studies, may be found in online supplementary figures S1 and S2.

Online supplementary table S4 shows the main characteristics of the 45 included articles. Thirty-five of the studies had a longitudinal prospective design, eight a longitudinal retrospective and one a cross-sectional.[66] We also included a randomised controlled trial (RCT).[43] The mean time of follow-up in the prospective cohorts ranged from 2[36 37 54] to 13.4 years[76] and from 1.7[55] to 11 years (median)[60] in the retrospective cohorts. Five studies evaluated two different tools, and most of them were conducted in North America, Scandinavian, Western Europe, Australia or Japan. Only two studies were multinational. The exclusion criteria were not described in 10 studies and were only briefly mentioned in many others. Only one study stated that no exclusion criteria were applied. The most common exclusion criteria were: unable to walk, use of corticosteroids, bisphosphonates or other bone-active agents, previous history of

hip or MOP fractures, hip replacement and secondary osteoporosis. Participants were mainly recruited from the general population (n=22), but also from osteoporosis screenings (n=12), or were post-menopausal women (n=9). Concerning the total population at baseline, only one study[33] provides this number for both the derivation and validation models, while 14 studies do not provide the baseline numbers, even for the validation model. This number varies from 390[37] to over 1 m.[33] All articles provide the number of participants available for event verification. The majority of studies included only women (n=30), while two studies included only men.[45 64] The participant's age in the validation model ranged from 30[33] to 116 years.[32] The numbers of fractures were usually given for hip and/or MOP fracture, but other sites and other specific outcomes were presented according to the tool (eg, immobilisation)[65] or specific aims of the study (eg, in obese and non-obese subjects).[62] Diagnosis of fractures was based principally on self-report, confirmed by X-rays in 35 studies, or medical records/hospital discharge registers. The highest performances (AUC) were reported for FRAX in China[41] (Hip_{Women} with BMD=0.88; Hip_{Women} without BMD=0.89) and for the updated QFracture[71] (Hip_{Women}=0.89; Hip_{Men}=0.88). The lowest AUCs ($FRAX_{Men;\ US;\ MOP}$=0.54; $FRAX_{Men;\ UK;\ MOP}$=0.57) were reported in a retrospective study using a FRAX model which had not been validated for that country and with a very small population.[55]

Meta-analysis

A total of 20 articles were selected for the meta-analysis. The reasons for exclusions are described in online supplementary table S5, the most relevant being number of fractures <100 and AUCs provided only for specific subgroups, for example, as defined by economic status. FRAX provides the greatest specification of outcomes: per site, per gender, with/without BMD. All studies with GARVAN included BMD, while QFracture excludes this measurement. Thus, we performed 10 different meta-analyses for FRAX (15 studies), 3 for GARVAN (5 studies) and 4 for QFracture (3 studies; we did not include updated QFracture published in 2012 because it only had one external validation study). Regarding the total number of participants included in the meta-analyses, GARVAN had the lowest numbers, QFracture was in between and FRAX had the largest numbers. All meta-analyses showed high heterogeneity, with the exception of one for FRAX and one for GARVAN (moderate heterogeneity). The results of all meta-analyses are presented in table 2. Overall, QFracture obtained the highest AUCs, being above 0.80 in three out of four studies. The three meta-analyses of GARVAN resulted in AUCs of around 0.70. Meta-analyses of studies with FRAX resulted in AUCs of between 0.61 and 0.79.

Pooled AUC data regarding hip fractures are presented in figure 2. This cannot be done for MOP fracture as the definition differs between the three tools.

We compared the risk prediction accuracy of excluded against included studies with meta analysis and found statistically significant higher AUC in the former studies (data not shown).

Summary appraisal of tools

In table 3 we compare aspects of the three different tools deemed relevant for their selection for clinical and research purposes. Most of these features have been mentioned above.

The countries and contexts in which these three major tools have been tested differ considerably. FRAX has been used to evaluate risk of fracture and death in 57 countries and has been the subject of 26 different validation studies in 9 countries. GARVAN was tested only in Australia, New Zealand and Canada. However, it has been proposed that this instrument does not require incorporation of national fracture data.[34 69] QFracture was only validated in the UK (with 88 participants from another country, Ireland, included) but by independent research teams; however, conversely, it has the largest number of participants.

Table 2 Meta-analyses of fracture risk assessment tools according to outcome specifications

Tool	Outcome specifications (BMD/site/sex)	Number of studies	Number of participants	Meta-analysis: random effect model AUC (95% CI)	Heterogeneity, I^2
FRAX (10-year prediction)	Y/MOP/W	n=5[39 41 43 44 60]	14 224	0.67 (0.64 to 0.71)*	80.2%*
	N/MOP/W	n=7[39 41 42 44 47 48 76]	24 726	0.65 (0.63 to 0.68)*	67.6%*
	N/Hip/W	n=9[39 41–44 47 48 53 57]	131 244	0.74 (0.68 to 0.80)*	94.3%*
	Y/Hip/W	n=5[39 41 44 53 57]	115 611	0.79 (0.73 to 0.85)*	93.3%*
	N/MOP/M	n=2[45 47]	11 199	0.63 (0.60 to 0.66)*	0.0%
	N/Hip/M	n=2[45 47]	11 199	0.71 (0.65 to 0.77)*	40.8%
	Y/MOP/B	n=3[46 51]	276 786	0.63 (0.60 to 0.66)*	97.1%*
	Y/Hip/B	n=3[46 51]	276 786	0.77 (0.73 to 0.81)*	69.8%*
	N/MOP/B	n=3[46 51]	276 786	0.61 (0.57 to 0.64)*	96.3%*
	N/Hip/B	n=3[46 51]	276 786	0.67 (0.61 to 0.73)*	94.7%*
GARVAN-GRX (10-year prediction)	Y/Hip/W	n=2[68 39]	5574	0.74 (0.61 to 0.87)*	88.2%*
	Y/MOP/W	n=3[39 68 69]	6932	0.70 (0.64 to 0.75)*	93.8%*
	Y/MOP/M	n=2[68 69]	5010	0.73 (0.68 to 0.78)*	59.0%
QFracture (10-years prediction)	N/MOP/W	n=3[33 70]	1 778 570	0.81 (0.78 to 0.834)*	97.8%*
	N/MOP/M	n=2[33 70]	1 741 983	0.72 (0.67 to 0.76)*	99.2%*
	N/Hip/W	n=3[33 42 70]	1 779 154	0.89 (0.88 to 0.89)*	96.3%*
	N/Hip/M	n=2[33 70]	1 741 983	0.87 (0.86 to 0.88)*	71.0%

Moderate heterogeneity: Higgins I^2 ~50%; high heterogeneity, Higgins I^2 ~75%.
*p<0.05.
AUC, area under the curve; B, both sexes; BMD, bone mass density; Hip, hip fractures; M, men; MOP, major osteoporotic fractures (MOPs are defined differently for the different instruments); N, without BMD; W, women; Y, with BMD.

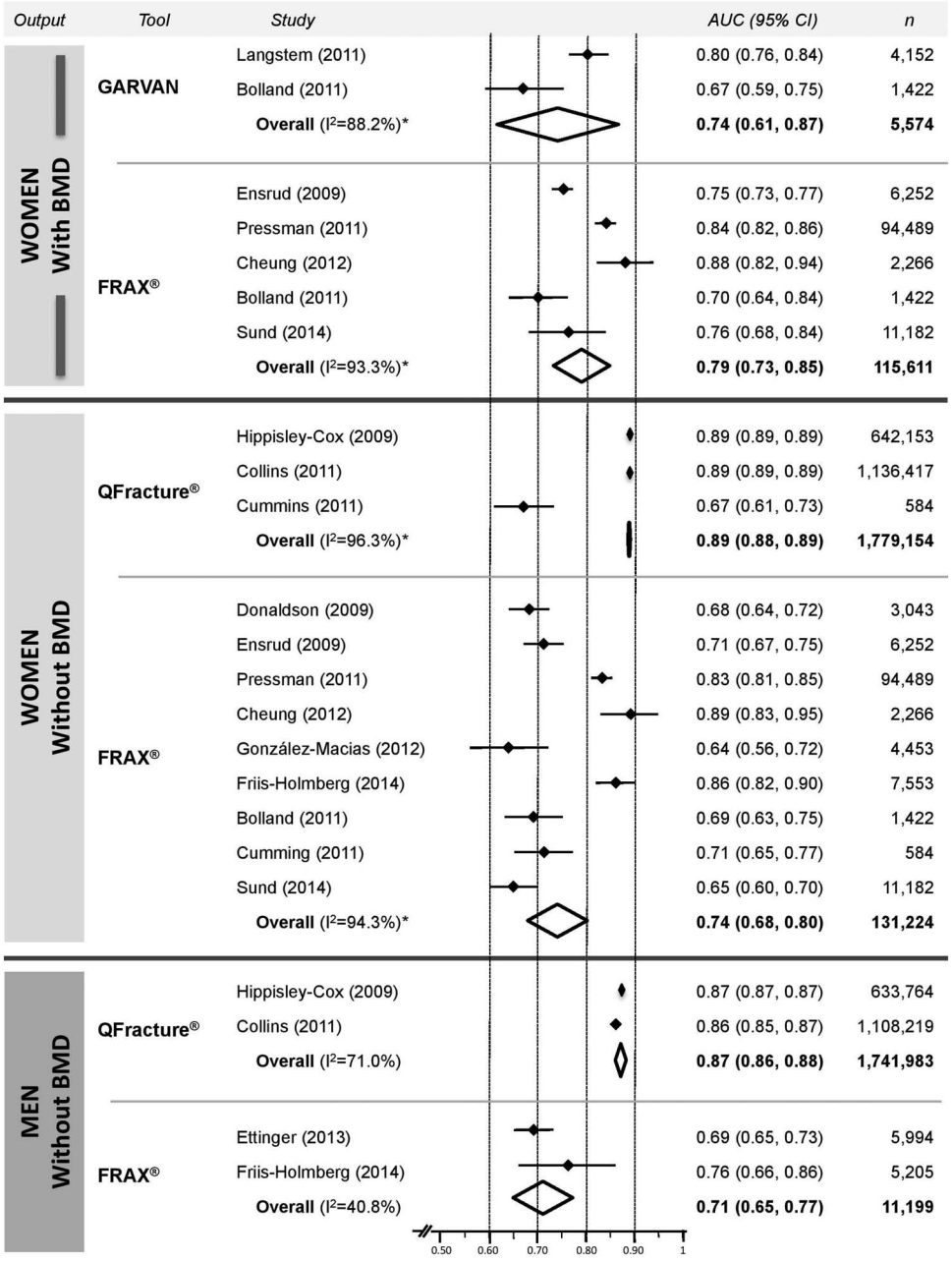

Figure 2 FRAX, GARVAN and QFracture pooled areas under the curve (AUCs) (95% CI) for 10-year hip fracture prediction, according to sex and bone mineral density (BMD) input.

QFracture is associated with the highest AUC, this being achieved at the cost of greater complexity and lower feasibility, given the large number of risk factors considered.

DISCUSSION

This SR identified 13 tools for osteoporotic fracture risk prediction, adding one new instrument (FRISK)[66 67] to the algorithms identified by previous SRs,[20–23] and updating the validation information regarding those already identified. This will help clinicians and researchers select those that best apply to their setting and needs. We have also performed a meta-analysis for 10-year risk prediction of hip and MOP fractures with FRAX, GARVAN and QFracture (for men, women and both genders, with and without BMD). To the best of our knowledge, this is the first meta-analysis on this topic.

The differences between the currently available fracture prediction tools must be emphasized, as caution is required when comparing the results obtained with different instruments. The number of risk factors considered (which varies between 4 and 31), as well as their nature, will have an important impact on feasibility. Differences in output (sex, age, types of fractures and time-intervals of prediction) might affect the applicability of the tool. All instruments predict the risk of osteoporotic fractures but not all provide separate estimations for hip and for major fractures.

On the other hand, our quality assessment of the included studies reveals, as with previous evaluations,[20–23] significant pitfalls in most of the studies, although recent publications appear to be of better quality.[45 47] Among the most important drawbacks is the lack of certainty of unbiased recruitment from the target population.

Table 3 Summary features of the three most studied tools, as deemed relevant for the selection of the instrument in clinical and research settings

	FRAX	QFracture	GARVAN
Feasibility			
Number of clinical risk factors	11	19	5
Requirement for BMD	Optional	No	Optional
Algorithm accessible for individual use	Yes	No*	Yes
Applicability			
Male and female	Yes	Yes	Yes
Age range	40–90	35–100	50–96
Prediction intervals	10	1, 2, …, 10	5, 10
Type of fracture—hip	Yes	Yes	Yes
Type of fracture—MOP	Yes	Yes	Yes
Countries	57	UK only	3
Inclusion in national guidelines	Yes	Yes	Yes
Validity			
Validated in a separate cohort	Yes	Yes	Y (BMD only)
Independent validation†	Yes	Yes	Y (BMD only)
Number of validation studies	26	3	6‡
Population basis for validation, N	4 624 438	3 485 952§	229 162
Population basis for validation, countries	9¶	UK only	3¶
Average quality of studies (QUADAS-2)	Globally similar (see online supplementary figure S2)		
Duration of follow-up equal to tool estimation interval	Yes	Yes (10 year only)	Yes (5 and 10 year)
Consideration of national fracture epidemiology	Yes	No	No
Consideration of background mortality	Yes	No	No
AUC (95% CI)—hip, females, without BMD	0.74 (0.68 to 0.80)	0.89 (0.88 to 0.89)	NA
AUC (95% CI)—hip, females, with BMD	0.79 (0.73 to 0.85)	NA	0.74 (0.61 to 0.87)
AUC (95% CI)—hip, males, without BMD	0.71 (0.65 to 0.77)	0.87 (0.86 to 0.88)	NA
AUC (95% CI)—hip, males, with BMD	0.77 (NA)**	NA	0.85 (NA)**
AUC (95% CI)—MOP	††	††	††

*QFracture was removed from the website in 2012. Only the updated version is now available, but is not suitable for meta-analysis as it has only been the subject of one validation study.
†That is, by independent research groups.
‡Only with BMD.
§Does not include the updated QFracture (2012) study.
¶We did not consider the study that included data from 10 countries.
**One study only.
††Comparison is inadequate because of different definitions of MOP for each tool.
AUC, area under the curve; BMD, bone mineral density; MOP, major osteoporotic fractures; NA, not applicable/not available; QUADAS, Quality Assessment Tool for Diagnostic Accuracy Studies.

There is also a lack of correspondence between the spectrum of participants and the population expected to receive the test in daily practice. This problem was observed in about 50% of included studies and in about 50% of the reports of the three major tools. All the instruments were validated for the general population, but several studies recruited participants from osteoporosis screening settings,[38 40 42 50–52 55 60 63 72 73] while some explicitly excluded people treated for osteoporosis.[41 42 53 55 56 58 63] Reports, unfortunately, do not provide the detailed data necessary for assessing the potential impact of treatment upon fracture prediction. We also verified that two studies excluded individuals previously exposed to glucocorticoids,[42 43] even though this risk factor was included in the risk algorithm under evaluation.

Follow-up time was consistent with the time-horizon of prediction validated for the tool in only a third of the studies. Furthermore, most of those without the required follow-up time[32 33 40 41 43–45 47–50 53–55 61 62 65 68 70 71] did not perform any statistical adjustments for this, which may have influenced the estimated AUCs.

Attrition is a well-known problem in longitudinal epidemiological studies.[77] The attrition rates vary considerably between the included studies, and most of them did not explain these rates. Death is a common cause of attrition in cohort studies of older people,[78] which affects the accuracy of the models. Only some studies in this SR took this into account.[39 41 45 47 48 57 58 61 62 64] One study[38] excluded women who died during follow-up, even though fracture, or its complications, might have been the cause of death.

For practical reasons we will focus our discussion below on FRAX, QFracture and GARVAN, as only these tools have been the subject of more than two validation studies testing exactly the same algorithm. FRISC has three validation studies, but each of them considered a different number of risk factors.

FRAX, GARVAN and QFracture can differentially predict risk in men and women and estimate the risk for hip and MOP fracture. However, the definition of the latter is different in each tool, thus precluding direct comparison.

QFracture and updated QFracture (2012) include a larger number and wider variety of clinical risk factors than FRAX and GARVAN. It is likely that algorithms with the longest lists of risk factors will have feasibility and adherence problems, but also greater accuracy. On the other hand, shorter lists may decrease the accuracy of the prediction. In some studies, the

authors excluded some of required risk factors, which inevitably weakens the robustness of the prediction, even if the impact upon the AUC and c-statistic is typically small.[79 80] In fact, even strong risk factors will have a minimal impact on the AUC if their prevalence in the studied population is low. This may be mistakenly reassuring and, as a rule, prediction tools should be used in strict accordance with the instructions provided by the authors, which in turn reflect the conditions of validation. There are, therefore, several potential caveats in the conclusion that deleting risk factors or opting for simpler ones is a good choice on the basis of the AUC alone.[81]

In FRAX, fracture probability is computed taking both the risk of fracture and the risk of death into account. Neither GARVAN nor QFracture include mortality. Kanis *et al*[81] have shown that this induces an inadequate continuous increase in the risk predicted by GARVAN in very advanced age. It is possible that the same may happen with QFracture.

Accuracy of estimates

Comparing instruments based on their AUCs, we found important pitfalls related, first and foremost, to differences in the definitions of events and to the participants' characteristics.[81] AUCs also tend to be smaller, the narrower the age range and the longer the duration of follow-up.[81]

To avoid these pitfalls we have: (a) appraised the quality of studies; (b) excluded the original studies, that is, derivation models from meta-analysis; and (c) restricted the comparative analysis to minimally comparable data (hip fractures).

We found that the meta-analysis of studies indicates higher AUCs with QFracture (0.89 and 0.87) than FRAX (0.74 and 0.71) when comparable data are available: hip fractures in women and men, respectively, both without BMD. The 95% CIs in the main two studies and the overall results of QFracture are practically residual and much smaller than those observed for FRAX (0.68 to 0.80 and 0.65 to 0.77), which reflects the larger number of participants in the QFracture studies. QFracture was designed for integration into electronic records systems where all necessary data have already been collected as part of routine care, as in the clinical research databases that served to derive and validate the model. The tool is incorporated into the electronic system allowing automatic calculation. The setting is very convenient but extremely hard to reproduce elsewhere. Derivation and validation were performed in different population samples, but from the same country, which favours a higher AUC. The fact that the tool amenable to meta-analysis (QFracture 2009) is no longer available adds to these difficulties.

Adding BMD to FRAX increases the AUC from 0.74 to 0.79 in women, and from 0.71 to 0.77 in men, but this is still below the values achieved with QFracture (0.89 and 0.87, respectively). Comparing the meta-analysis for GARVAN and FRAX, is only possible for hip fractures in women, using BMD—the results indicate a small numerical advantage for FRAX.

The performance of all these tools was validated for the general population. Thus, their application for specific settings (eg, osteoporosis population, secondary causes of osteoporosis) implies a risk of error. Further studies should also evaluate the threshold for use in clinical practice. Comparison between tools should, ideally, be made in the same population.

Limitations and strengths of this study

Assessing the quality of the studies with QUADAS-2 proved a difficult task, mostly due to poor reporting, and may be controversial as regards some points.

Concerning the meta-analysis, we frequently had to calculate the SE based on other parameters, which may have led to slightly different results (at a centesimal level).

We did not ask authors to provide data on age when this was missing from the publications. This may have slightly influenced the results of meta-analysis, as age may affect the AUC.[81] The only way to adjust our meta-analyses by age was to include studies with similar age bands or to stratify. We did the first but not the second as it was not possible to stratify with the published data.

Using AUC as the outcome for the meta-analysis could also be seen as a limitation, given its weaknesses as discussed above. Furthermore, given that fracture rates differ significantly from country to country, comparison of data obtained in different countries involves some risk of error. However, the vast majority of studies only provide these data.

Among the strengths of this study we would emphasise the comprehensiveness of the literature search and appraisal. Although we did not include so-called 'grey literature' (ie, congress abstracts and unpublished data), the hand search gives us a high degree of confidence that no major studies were missed. No study was excluded for language reasons. We limited our meta-analyses to sets of data that we found to be valid and directly comparable, thus avoiding most of the potential errors in similar exercises. Because we recognised significant heterogeneity, the analyses were performed using the random effects model,[30 31 82] which assumes that the effect of interest is not the same in all studies. This is a more conservative approach, resulting in wider 95% CIs, while, hopefully, reducing the risk of unrealistic assumptions.[30] This was the first meta-analysis performed on data from fracture risk prediction tools.

Conclusions

Thirteen externally validated algorithms designed to predict osteoporotic fracture risk are currently available to clinicians and researchers. Most of these tools are feasible in clinical practice and are simple to access and use. FRAX, QFracture and GARVAN are the most extensively studied tools, with FRAX having the greatest number of independent studies. FRAX was evaluated in a larger number of countries and also allows finer specification of outcomes. Adding BMD to FRAX increases the AUC for hip fractures in both men and women. Studies with QFracture present the highest AUCs; however, this tool has only been studied in the UK and Ireland and requires consideration of 19 clinical factors. This number was actually increased to 31 in the updated version, with a marginal increase in accuracy.

Methodological limitations and risk of bias are present in most studies, but to a lower extent than in the oldest studies. High-quality studies to assess the calibration of fracture prediction tools are still needed. Researchers should use the instruments in accordance with the requirements and indications for which they were validated, in order to allow international unbiased comparisons and better quantitative synthesis.

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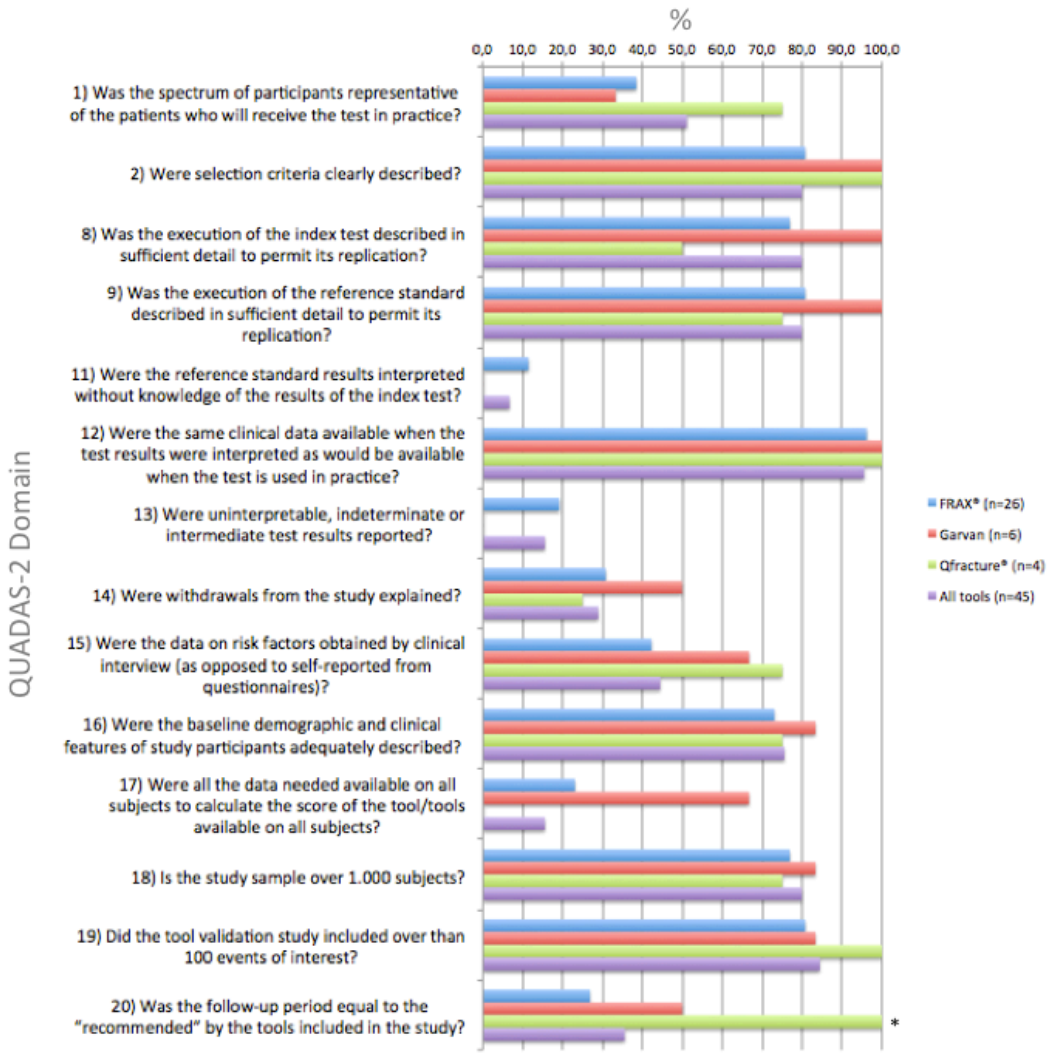
Supplementary Figures S1 and S2– *Methodological quality of the studies with QUADAS-2.*

According to our assessment with QUADAS-2 (Figure S1), the average quality of 45 studies was higher in item 12 - similarities between data available during study interpretation and clinical practice; item 2 - description of the selection criteria; and items 8 and 9 - provision of sufficient details to allow replication. However, many studies did not report enough data to analyse the accuracy of the tools at the end of study (item 17) or at interim/intermediate analysis (item 13). The reasons for withdrawal are also lacking in many articles (item 14). The number of participants lost during the follow up due to death is conspicuously missing in most studies. Adherence to the recommended time of follow-up for the used tool (item 20) was only present in 16 studies.

Figure S1 – Quality assessment of studies testing fracture risk prediction tools (n=45). Green= Yes; Yellow=unclear; Red= No.

We also compared the quality of reports dealing with the 3 most developed tools (Figure S2). Articles on FRAX® performed better than average on items 11 and 13, while GARVAN's articles performed better on items 2, 8, 9, 14, 16, 17 and 20 and QFracture® studies on items 1, 2, 15 and 19.

Figure S2 – Percentage of articles complying with quality criteria, according to risk prediction tool under evaluation. * QFracture® has only been validated for the 10-years prediction interval.



Supplementary Table S1 – Search Strategy in PubMed MEDLINE

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(hip fracture)))) AND (("Questionnaires"[Mesh] OR Questionnaire OR Questionnaire Design OR Designs, Questionnaire OR Designs, Questionnaire OR Questionnaire Designs OR NOF OR (National Osteoporosis Foundation) OR SCORE OR (Simple Calculated Osteoporosis Risk Estimation) OR ORAI OR (Osteoporosis Risk Assessment Instrument) OR ABONE OR (Aged Body Size No Estrogen) OR FRAX OR (fracture risk assessment tool) OR (FRACTUREindex) OR ("FRACTURE index") OR OSTT OR (Osteoporosis Self assessment Tool) OR "OST (OSTA)" OR DOEScore OR (Dubbo Osteoporosis Epidemiology Study) OR FOSTA OR (Female Osteoporosis Self assessment Tool for Asia) OR Self-assessment Tool OR SOFSURF OR EPIDOS study OR EPIDemiologie de l'OSteoporose OR EPIDOS fracture study OR Weight only EPIDOS OR "WOE" OR FNBMD OR "Bone mineral density at the femoral neck") OR "pBW" OR IOF OR (International Osteoporosis Foundation) OR Garvan OR KKOS OR OSIRIS OR DVO OR MORES OR Qfracture OR QFractureScores OR "Risk Assessment"[Mesh] OR 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Accuracy, Dimensional) OR "Area Under Curve"[Mesh] OR Area Under Curves OR Curve, Area Under OR Curves, Area Under OR Under Curve, Area OR Under Curves, Area OR AUC OR Harrell's C value OR likelihood ratio OR likelihood positive ratio OR likelihood negative ratio OR ROC curve OR ROC curves OR "Sensitivity and Specificity"[Mesh] OR Specificity and Sensitivity OR Specificity OR Sensitivity OR "Predictive Value of Tests"[Mesh] OR "False Positive Reactions"[Mesh] OR False Positive Reaction OR Positive Reaction, False OR Positive Reactions, False OR Reaction, False Positive OR Reactions, False Positive OR False positive OR False negative OR True positive OR True Negative OR "False Negative Reactions"[Mesh] OR False Negative Reaction OR Reaction, False Negative OR Reactions, False Negative OR "Reproducibility of Results"[Mesh] OR Reproducibility of Findings OR Reliability AND (Epidemiology) OR Reliabilities AND (Epidemiology) OR Validity AND (Epidemiology) OR Validities AND (Epidemiology) OR Validity of Results OR Reliability and Validity OR Validity and Reliability OR Reliability of Results OR "Feasibility Studies"[Mesh] OR Feasibility Study OR Studies, Feasibility OR Study, Feasibility OR Feasibility OR "Validation Studies as Topic"[Mesh] OR construct validity OR validation studies OR validation study OR validity reliability OR reliability validity OR validity OR validated OR validated study OR validated studies OR applicability OR clinimetric properties OR Psychometrics AND "[Mesh] OR Psychometric OR responsive OR responsiveness OR validation[tiab] OR validate[tiab] OR reproducib*[tiab] OR " AND psychometrics AND "[MeSH] OR psychometr*[tiab] OR clinimetr*[tiab] OR clinometr*[tiab] OR reliab* [tiab] OR valid*[tiab] OR reliability validity assessment OR " AND Evaluation Studies as Topic Mesh OR Evaluation OR Evaluations OR Evaluation Indexes OR Indexes, Evaluation OR Use Effectiveness OR Methodology, Evaluation OR Evaluation Methodologies OR Methodologies, Evaluation OR Evaluation Methodology OR PrePost Tests OR Pre Post Tests OR PrePost Test OR Test, PrePost OR Tests, PrePost OR Qualitative Evaluation OR Evaluation, Qualitative OR Evaluations, Qualitative OR Qualitative Evaluations OR Quantitative Evaluation OR Evaluation, Quantitative OR Evaluations, Quantitative OR Quantitative Evaluations OR Theoretical Effectiveness OR Effectiveness, Theoretical OR Critique OR Critiques)) Filters: Publication date from 2003/01/01

Supplementary Table S2 – Modified version of QUADAS-2. The checklist was used to assess the study quality. All items were scored with "yes", "no" or "unclear". Items 3-7 and 10 were excluded as they were not considered relevant in the current context. We added 6 new items to the checklist (items 15 to 20) as relevant for our review.

Item	Yes	No	Unclear
1. Was the spectrum of patients representative of the patients who will receive the test in practice? *(Unselected patients recruited from the general population?)*	( )	( )	( )
2. Were selection criteria clearly described? *(Clear definition of the criteria used in- and exclusion criteria for entry into the study)*	( )	( )	( )
3. ~~Is the reference standard likely to correctly classify the target condition?~~			
4. ~~Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?~~			
5. ~~Did the whole sample or a random selection of the sample, receive verification using a reference standard of diagnosis?~~			
6. ~~Did patients receive the same reference standard regardless of the index test result?~~			
7. ~~Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?~~			
8. Was the execution of the index test described in sufficient detail to permit its replication? *(Was the tool/tools described in sufficient detail to permit its replication (a final algorithm)?)*	( )	( )	( )
9. Was the execution of the reference standard described in sufficient detail to permit its replication? (*Was the fracture collection verified and not only self-reported?)*	( )	( )	( )
10. ~~Were the index test results interpreted without knowledge of the results of the reference standard?~~			
11. Were the reference standard results interpreted without knowledge of the results of the index test? (*Was the risk of fracture calculated without the knowledge of the outcome (fracture)?)*	( )	( )	( )
12. Were the same clinical data available when test results were interpreted as would be available when the test is used in practice? *(Is it possible to collect the risk factors included the tool in clinical practice?)*	( )	( )	( )
13. Were uninterpretable, indeterminate or intermediate test results reported? *(Were the any uninterpretable, indeterminate or intermediate results and were the results reported for all patients who were described as having been entered into the study?)*	( )	( )	( )
14. Were withdrawals from the study explained? *(A patient flow diagram or results available for all patients who were reported to have been entered into the study)*	( )	( )	( )
15. Were the data on risk factors obtained by clinical interview (as opposed to self-reported)?	( )	( )	( )
16. Were the baseline demographic and clinical features of study participants adequately described? *(Age, (BMD if measured) and risk factors for fracture included in the tool/tools used in the study (no more than 2 risk factors not reported in baseline description)?)*	( )	( )	( )
17. Were all the data needed to calculate the score of the tool/tools available on all subjects? ***(****No missing data on the risk factors included in the tool/tools?)*	( )	( )	( )
18. Is the study sample over 1.000 subjects?	( )	( )	( )
19. Did the tool validation study include over 100 events of interest?	( )	( )	( )
20. Was the follow-up period equal to the "recommended" by the tools included in the study? *(5 or 10 years for all subjects included in the study, depending on the outcome period of the tools)*	( )	( )	( )

Supplementary Table S3 – Risk factors included in the fracture risk prediction tools

Clinical Risk Factor / Tool	Previous fractures	Weight	Age	Smoking	Height	Sex	Parent's fractures or OP	BMD hip (neck)	Previous falls	Glucocorticoids	Alcohol consumption	Rheumatoid arthritis	BMD spine	Secondary causes of OP	Ethnicity	Type II Diabetes	Hormone replacement	Asthma	Cardiovascular disease	Menopausal symptoms	Gastrointestinal disease	Liver disease	Dementia	Chronic disease	Physical activity	Pulse (>80 bpm)	Early menopause	Impaired raise up (activity)	Back pain	Self reported health	Type I Diabetes	Kidney disease	Epilepsy	Parkinson	Living in a nursing home	Anti-depressive drugs	COPD	Cancer	SLE	Anti-convulsive drugs
Computer model for osteoporotic fracture risk																																								
FRAMO																																								
FRAX®																																								
FRC*																																								
FRISC																																								
FRISK																																								
GARVAN-GRX																																								
QFracture®																																								
updated QFracture® (2012)																																								
Score for estimating the long-term risk of fracture in post menopausal women																																								
Simplified fracture risk system																																								
SOF																																								
WHI																																								
N=	**12**	**12**	**11**	**8**	**7**	**6**	**6**	**6**	**5**	**5**	**4**	**4**	**4**	**3**	**3**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**

BMD, Bone Mass Index; COPD, Chronic Obstructive Pulmonary Disease; SLE, Systemic Lupus Erythematous; OP, Osteoporosis;

* Updated version of the website, dated Sep. 2014.

Supplementary Table S4 - Main characteristics of the studies included in this systematic literature review.

Study	Setting (Country)	Study design and duration of follow-up	Exclusion criteria	Population at baseline (N)	Population available for event verification	% women	Mean age (range)	Number of fractures per site	Fractures ascertainment	AUC
Computer model for osteoporotic fracture risk										
Ettinger (2005) [35]	Gen. Pop. (USA)	Prosp. Cohort 5 yrs	Any described	NA	DM - >400,000 VM-NA	100%	NA (45–79)	Hip, humerus, and wrist-14,528 Hip – 3,412	NA	NA
FRAMO										
Albertsson (2007) [36]	Gen. Pop. (Sweden)	Prosp. Cohort 2 yrs	NA	1,498	1.248	100%	78.8 yrs (70-100)	Hip-31	GP records	Hip-0.72 Mortality-0.75
Albertsson (2010) [37]	Gen. Pop. (Sweden)	Prosp. Cohort 2 yrs	NA	390	285	100%	79 yrs (72-98)	Hip, distal radius, proximal humerus, pubic bone, ischial bone, vertebrae - 14 Hip-7	Radiographic confirmed	NA
FRAX®										
Kanis (2007) [32]*	Differs with cohort (Several countries)	Prosp. Cohort DM-3,2 yrs VM-NA	Differs with cohort	NA	DM-46,340 VM-230,486	DM -68% VM-NA	DM - 65 yrs (20-106) VM - 63 yrs (35-116)	DM MOP -3,360 Hip - 850 VM MOP -15,183 Hip – 3,318	Depends on the study	DM With BMD MOP - 0.62 Hip - 0.74 Without BMD MOP -0.60 Hip – 0.66 VM With BMD MOP: - 0.63 Hip – 0.78 Without BMD MOP -0.62 Hip -0.67
Donaldson (2009) [43]*	Post. Menop. (USA)	RCT 3.8yrs	Use of systemic glucocorticoids	3,223	3,043	100%	68.2yrs (55-81)	MOP - 253 Vertebral only - 223	Self reported and radiographic confirmed. Vertebral frc confirmed by Xray	With BMD MOP-0.71 Without BMD MOP -0.68
Ensrud (2009) [44]*	Gen. Pop. (USA)	Prosp. Cohort MOP-8.7 yrs Hip- 9.2 yrs	Black women. Women unable to walk without assistance or with history of bilateral hip replacement	9,704	6,252	100%	71.3yrs (≥ 65)	MOP-1,037 Hip-389	Self reported and radiographic confirmed	With BMD MOP -0.68 Hip -0.75 Without BMD MOP-0.64

										Hip-0.71
Leslie (2010) [51]*	OP Screen. (Canada)	Prosp. Cohort NA	None	NA	39,603	92.8%	W 65.7yrs M 68.2yrs (≥50)	MOP-2,543 Hip-549	Radiographic confirmed	With BMD MOP -0.69 Hip -0.83 Without BMD MOP-0.66 Hip-0.79
Sornay-Rendu (2010) [56]	Gen. Pop. (France)	Prosp. Cohort 10yrs	Women with diseases or treatment that affect bone metabolism. HRT use in the last 12 months.	867	867	100%	58.8 yrs (≥ 40)	MOP-82 Hip-17	Self-reported and radiographic confirmed	With BMD MOP -0.78 Without BMD MOP -0.75
Tremollieres (2010) [76]*	Post. Menop. (France)	Prosp. Cohort 13.4yrs	Women treated for osteoporosis > 3 months (with the exception of parathyroid hormone and calcium/vitamin D supplementation.	4,024	2,651	100%	54 yrs (≥ 45)	MOP-145 Hip-13	Self-reported and radiographic confirmed	Without BMD MOP -0.63
Fraser (2011) [46]*	Gen. Pop. (Canada)	Prosp. Cohort 10yrs	Any described	NA	6,697	71.3%	W 65.8 yrs M 65.3yrs (≥50)	MOP: W-12%; M-6.4% Hip: W-2.7%; M-2.4%	Self reported and radiographic confirmed	With BMD MOP -0.69 Hip -0.80 Without BMD MOP-0.66 Hip-0.77
Hillier (2011) [49]	Gen. Pop. (USA)	Prosp. Cohort 9.4yrs	Women unable to walk without assistance and with bilateral hip replacements	7,963	6,252	100%	71 yrs (≥ 65)	MOP- 1,011 Hip-368	Self reported and radiographic confirmed	With BMD MOP (Normal- 0.64; Low bone mass-0.61; Osteoporotic-0.61) Hip (Normal- 0.78; Low bone mass-0.70; Osteoporotic-0.62) Without BMD MOP (Normal- 0.62; Low bone mass-0.59; Osteoporotic-0.61) Hip (Normal- 0.79; Low bone mass- 0.66; Osteoporotic-0.63)
Leslie (2011) [50]	OP Screen. (Canada)	Retr. Cohort 5.5yrs	Available on a different source	NA	36,368	93.1%	65.2 yrs (≥ 50)	MOP-2.321	Confirmed at the discharge diagnostics or hospital.	MOP-0.69 to 0.70
Leslie (2011)	OP Screen.	Retr. Cohort	Available on a different source	NA	37,032	100%	NA	MOP-1,748	Confirmed at the	MOP- 0.67 to 0.75

[52]	(Canada)	DM- 5.5 yrs VM- 5.6 yrs					(≥ 45)		discharge diagnostics or hospital.	
Pressman (2011) [53]*	OP Screen. (USA)	Retr. Cohort 6.6 yrs	Women who did not have at least 1 yr of continuous membership both before and after the DXA scan date, those in whom DXA data were not electronically accessible, and those with missing race/ethnicity and those who had filled a prescription for a bisphosphonate in the year before the DXA test.	NA	94,489	100%	NA (50-85)	Hip-1,579	Confirmed at the discharge diagnostics or hospital.	With BMD Hip -0.84 Without BMD Hip-0.83
Tamaki (2011) [58]	Post. Menop. (Japan)	Prosp. Cohort 10 yrs	Women who did not have femoral neck BMD measurements at the baseline survey, and women taking osteoporosis drugs or HRT at the baseline survey	1,040	815	100%	56.7yrs (40-74)	MOP-43 Hip - 4	Self-reported at each follow-up	With BMD MOP -0.69 Hip -0.88 Without BMD MOP-0.67 Hip-0.86
Cheung (2012) [41]*	Post. Menop. (China)	Prosp. Cohort 4.5 yrs	Women with prescribed osteoporosis treatment	NA	2,266	100%	62.1 yrs (40-90)	MOP- 106 Hip-21	Self-reported and radiographic confirmed	With BMD MOP -0.73 Hip -0.88 Without BMD MOP-0.71 Hip-0.89
González-Macías (2012) [48]*	Gen. Pop. (Spain)	Prosp. Cohort Median 36.1 months	Paget's disease, multiple myeloma, bone metastases, renal failure, hypercalcemia, immobilization for >3 months in the preceding year, anatomical anomalies of the right foot interfering with calcaneal ultrasound measurement, therapeutic doses of fluoride for more than 3 months in the past two yrs or for more than 2 yrs at any time in life, a life expectancy of less than 3 yrs, or participation in any other investigational study involving drugs.	5,146	4,453	100%	72.3 yrs (65–100)	MOP- 201 Hip-50	Self-reported and radiographic confirmed	Without BMD MOP-0.62 Hip-0.64
Ettinger (2013) [45]*	Gen. Pop. (USA)	Prosp. Cohort 8.4 yrs	Men who had used a bisphosphonate within 30 days prior to the baseline visit	5,994	4,291	0%	73.6 yrs (≥ 65)	MOP-374 Hip-161	Self-reported and radiographic confirmed	With BMD MOP-0.67 Hip-0.77 Without BMD MOP-0.63 Hip-0.69
Premaor (2013) [62]	Gen. Pop. (USA)	Prosp. Cohort Obese- 9.1 yrs Non-obese- 9.0	Women unable to walk without assistance, with bilateral hip replacements and black women	9,704	6,049	100%	NA (≥ 65)	MOP: Obese- 26.9% Non-obese- 32.7%	Self-reported and radiographic confirmed	No additional information provided by authors

		yrs								
Tebe Cordomi, 2013 [60]*	OP Screen. (Spain)	Retr. Cohort Median-11 yrs	NA	2,086	1,231	100%	56.8 yrs (40-90)	MOP-222 Hip-13	Self-reported	With BMD MOP-0.61
Azagra (2014) [38]	OP Screen. (Spain)	Prosp. Cohort 10 yrs	Women with wrong number for contact, no responders to 3 calls, treated to osteoporosis ate baseline or during follow up (with exception of supplements). Women died during follow up.	3,247	816	100%	56.8 yrs (40-90)	MOP-49 Hip-15	Confirmed at the GP or hospital.	With BMD MOP-0.74 Without BMD MOP- 0.73
Brennan (2014) [40]	OP Screen. (Canada)	Prosp. Cohort 6.2 yrs	NA	NA	51,327	100%	65.9yrs ≥ 50	MOP- 3723 Hip-1027	Confirmed at the discharge diagnostics or hospital	With BMD MOP- Q1- 0.68 Q5-0.71 Hip- Q1- 0.79 Q5-0.87 Without BMD MOP- Q1- 0.65 Q5-0.68 Hip- Q1- 0.76 Q5-0.85
Friis-Holmberg (2014) [47]*	Gen. Pop. (Denmark)	Prosp. Cohort 4.3 yrs	Participants were excluded if height or weight was missing	18,065	12,758	59.2%	56.8 yrs (40-90)	MOP- 395 Hip-54	Recorded on the GP computer	Without BMD MOP- M- 0.63; W-0.68 Hip- M- 0.76; W-0.86
Sund (2014) [57]*	Post. Menop. (Finland)	Prosp. Cohort 10 yrs	Women who experienced a hip fracture before 1994	13,917	11,182	100%	57.3 yrs (52.4-62.7)	Hip-117	Self-reported and radiographic confirmed	With BMD Hip-0.76 Without BMD Hip- 0.65
FRC										
Lo (2011) [63]	OP Screen. (USA)	Retr. Cohort 6.6 yrs	Women who did not have at least 1 yr of continuous membership both before and after the DXA scan date, those in whom DXA data were not electronically accessible, and those with missing race/ethnicity and those who had filled a prescription for a bisphosphonate in the year before the DXA.	120,972	94,489	100%	62.8 yrs (50-85)	Hip-1,579	Confirmed at the discharge diagnostics or hospital	With BMD Hip-0.85 Without BMD Hip- 0.83
Ettinger (2012) [64]	Gen. Pop. (USA)	Prosp. Cohort 9.2 yrs	Men who had used a bisphosphonate within 30 days prior to the baseline visit	5,994	5,893	0%	73.6 yrs (≥ 65)	MOP-335 Hip-156	Self-reported and radiographic confirmed	With BMD MOP-0.70 Hip-0.79 Without BMD MOP-0.66 Hip-0.71
FRISC										
Tanaka (2010) [65]	Post. Menop. (Japan)	Prosp. Cohort DM-5.3 yrs	DM-Women with metabolic bone disease and secondary osteoporosis	2,187	DM-1,787	100%	DM - 63.4 yrs (45-81)	DM MOP- 383	Available on a different source	VM With BMD

		VM- 10 yrs			VM-400		VM - 59.5 yrs (41-77)	Immobilization- 83 VM MOP- 60		MOP- 0.727
FRISC + FRAX®										
Tanaka (2011) [59]	Post. Menop. (Japan)	Prosp. Cohort 5.1 yrs	Women receiving treatment for osteoporosis, and diseases related to secondary osteoporosis	2,010	765	100%	63.3 yrs (NA)	Clinical and morphometric vertebral fractures- 141 Long bone fractures-49	Vertebral fractures were evaluated using radiographs taken at baseline and during the follow-up. No reference to the other types of fractures	Vertebral frt: FRAX® 0.690, FRISC 0.702, Pentosidine+FRISC 0.732. Vertebral frt and long bone frt: FRAX® 0.671, FRISC 0.685
FRISK										
Henry (2006) [66]	Gen. Pop. (Australia)	Cros. Cohort 2.0 yrs	NA	NA	Cases-231 Control-448	100%	Cases-74 yrs Control-72 yrs (≥60)	NA	Radiology reports	NA
Henry (2011) [67]	Gen. Pop. (Australia)	Prosp. Cohort Median-9.6 yrs	NA	600	600	100%	Median-74 yrs (≥50)	MOP-125 Hip-34	Radiology reports	With BMD MOP-0.66 Without BMD MOP-0.62
GARVAN										
Nguyen (2007) [34]	Gen. Pop. (Australia)	Prosp. Cohort Median-13 yrs	NA	3,676	1,768	58%	NA ≥ 60	Hip: W-96, M-31	Radiology reports	DM - With BMD Hip- W-0.85; M - 0.85
Nguyen (2008) [69]*	Gen. Pop. (Australia)	Prosp. Cohort W median 13 yrs; M median 12 yrs	NA	3,676	2,396	56.7%	W 71 yrs M 70 yrs (≥ 60)	MOP: W-426; M-149	Radiology reports	With BMD MOP W- 0.757; M - 0.754
Langsetm (2011) [68]*	Gen. Pop. (Canada)	Prosp. Cohort 8.6 yrs	NA	9,423	5,758	72.1%	68 yrs (55-95)	MOP: W-583; M-116	Self report annually and 78% Radiographic confirmed	With BMD MOP: W0.69; M- 0.70 Hip W-0.80; M- 0.85
GARVAN + FRAX®										
Sandhu (2010) [55]	OP Screen. (Australia)	Retr. Cohort Fct-1.7 yrs No Fct-3.7 yrs	If any prior MOP fracture, any treatment with bone-specific agent for > 30 months, or presence of metabolic bone disorder	530	200	72%	W Fct -73 yrs W No Fct -68 yrs M Fct- 75 yrs M No Fct – 68	MOP FRAX® W-69 MOP FRAX® M-31	Medical records	**FRAX®-US** MOP: W- 0.77;0.54 **FRAX®-UK** MOP: W-0.78; M-0.57 **GARVAN**

							yrs (60-90)			MOP: W-0.84; M-0.76
Bolland (2011) [39]*	Post. Menop. (New Zealand)	Prosp. Cohort 8.8 yrs	Women with major medical conditions, and if they were taking treatment for OP (including HRT or vitamin D supplements in doses > 1000 IU/day and had serum 25(OH)D levels ≥25 nmol/L. Not have a measurement of femoral neck BMD at baseline	1,471	1,422	100%	74.2 yrs (≥ 55)	MOP FRAX®- 16% MOP GARVAN-19.6% Hip- 4%	Self report	**FRAX** With BMD MOP-0.64 Hip-0.70 Without BMD MOP-0.62 Hip-0.69 **GARVAN** With BMD MOP-0.64 Hip-0.67
Sambrook (2011) [54]	Gen. Pop. (10 countries)	Prosp. Cohort 2 yrs	Women were excluded if they were unable to complete the study survey owing to cognitive impairment, language barriers, institutionalization, or illness, aged younger than 60 years, those on antiosteoporotic medication, and those with incomplete data	60,393	19,586	100%	NA (≥ 60)	MOP FRAX®- 468 MOP GARVAN- 538 Hip- 69	Self-reported	**FRAX®:** Without BMD MOP-0.60 Hip-0.65 **GARVAN** Without BMD MOP-0.64 Hip-0.61
QFracture®										
Hippisley-Cox (2009) [33]*	Gen. Pop. (England and Wales)	Prosp. Cohort DM- 7,898,208 person yrs VM- 4,401,261 person yrs	Patients with no previous recorded fracture, temporary residents, and patients with interrupted periods of registration with the practice and patients who did not have a valid Townsend deprivation score.	DM- 2,391,756 VM- 1,294,732	DM- 2,357,895 VM-1,275,917	DM- 50.2% VM- 50.3%	DM - Median W 48 yrs M 46 yrs VM - Median W 49 yrs M 46 yrs (30-85)	DM MOP-32,284 Hip-12,369 VM MOP-18,471 Hip- 7,162	Recorded on the GP computer records	VM MOP: W- 0.79; M-0.69 Hip: W- 0.89; M- 0.86
Collins (2011) [70]*	Gen. Pop. (UK)	Prosp. Cohort Median MOP - 5.98 yrs Hip - 6.03 yrs	Patients with no previously recorded fracture (hip, distal radius, or vertebra), temporary residents, and had no interrupted periods of registration with a practice	2,244,636	2,209,451	50.6%	Median W 48 yrs M 47 yrs (30-85)	MOP-25,208 Hip- 12,188	Recorded on the GP computer records	MOP: W- 0.82; M-0.74 Hip: W-0.89; M-0.86
Updated QFracture® (2012)										
Hippisley-Cox (2012) [71]*	Gen. Pop. (UK)	Prosp. Cohort DM- 23,608,337 person yrs, VM- 11,732,106 person yrs	Any described	NA	DM- 3,142,673 VM- 1,583,373	DM- 50.9% VM- 49.2%	DM - 50 yrs VM - 50 yrs (30-100)	DM MOP- 59,772 Hip-20,028 VM MOP- 28,685 Hip- 9,610	Recorded on the GP computer records	VM MOP: W- 0.79; M- 0.71 Hip: W- 0.89; M- 0.88
QFracture®+FRAX®										
Cummins (2011) [42]*	OP Screen. (UK and	Retr. Cohort NA	Subjects who were receiving treatment for osteoporosis, those on corticosteroids, and	NA	Cases-246 Controls-338	100%	Fct - 68 yrs Ctl – 66 yrs	MOP-246	NA	**FRAX®** Without BMD

	Ireland)		those with a secondary cause of osteoporosis such as malabsorption, chronic liver disease, renal failure, and malignant disease				(50-85)			MOP W- 0.67 HIP W - 0.71 **QFracture®** MOP W 0.67 HIP W- 0.64
Score for estimating the long-term risk of fracture in post menopausal women										
Van Staa (2006) [72]	OP Screen. (UK)	Prosp. Cohort DM-5.8 yrs VM-5.6 yrs	Women with recent use of oral glucocorticoids.	NA	DM- 366,104 VM- 32,728	100%	NA (≥ 50)	MOP-14,011 Clinical vertebral-1,610 Hip-6,453	Recorded on the GP computer records	DM MOP - 0.60 Hip - 0.84 Clinical vertebral - 0.69 VM NA
Simplified fracture risk system										
Leslie (2009) [73]	OP Screen. (Canada)	Retr. Cohort 3.1 yrs	NA	NA	16,205	100%	65 (≥ 50)	NA	NA	No AUC
SOF										
Ahmed (2006) [74]	Gen. Pop. (Norway)	Prosp. Cohort Max-5 yrs	History of previous hip fracture	5,795	1,410	100%	No Hip- 69.5 yrs Hip-70.4 yrs (65-84)	All non-vertebral Fct-170 Hip-49	Hospital codes discharge	No AUC
WHI										
Hundrup (2010) [75]	Post. Menop. (Denmark)	Prosp. Cohort 5 yrs	Premenopausal women with: 50<age<79 yrs; 42<weight <162 kg; 140<height<179 cm. If they had missing items in the questionnaire on smoking status, physical activity and self-reported health.	15,648	13,353	100%	61 yrs (≥ 45)	Hip-122	Recorded on the national register records	Hip-0.82

AUC, Area Under the Curve; CI, Confidence Interval; Cros. Cohort, Cross-sectional Cohort; Ctl, Control; DM, Derivation model; Frt, Fracture; Gen. Pop., General Population; GP – General Practitioner; HRT, Hormone Replacement Therapy; M, Man; MOP, Major Osteoporotic Fracture; NA, Not available; Post. Menop., Post Menopausal; Prosp. Cohort, Prospective Cohort; Retr. Cohort, Retrospective Cohort; OP Screen., Osteoporosis Screening; VM, Validation model; W, Women; yrs, Years

* Included in Meta-analysis

Supplementary Table S5 – Articles excluded from the meta-analysis. All studies with FRAX®.

Article	Reason of exclusion
Sornay-Rendu (2010) [55]	Number of fractures <100
Hillier (2011) [48]	Authors only provide AUC values for specific subgroups accordingly to specific objectives of the study (different BMD categories).
Leslie (2011) [49]	The AUC values were provided regarding specific objectives of study (Use of T-score of lumbar spine or femoral neck)
Leslie (2011) [51]	The AUC values were provided regarding specific objectives of study (Use of T-score of lumbar spine or femoral neck)
Tamaki (2011) [58]	Number of fractures <100
Premaor (2013) [61]	No additional information provided by authors
Azagra (2014) [37]	Number of fractures <100
Brennan (2014) [39]	Authors only provide AUC values for specific subgroups accordingly to specific objectives of the study (different socioeconomic status).
Sambrook (2011) [53]	No additional information provided by authors
Sandhu (2010) [54]	FRAX® model not validated for the country; Number of fractures <100

AUC, Area Under the Curve; BMD, Bone Mass Density.

Annals of the Rheumatic Diseases
The EULAR Journal
BMJ
ard.bmj.com

Simple tools predict whether people will suffer from osteoporotic fractures

Accurate, non-invasive clinical tools can help doctors to quickly and easily make informed treatment decisions for their osteoporosis patients.

INTRODUCTION

Most people lose bone density as a normal part of ageing. Osteoporosis is a condition where a person's bone density is reduced, making their bones fragile and more likely to fracture (break). Hip, wrist and spine (back) fractures are the most common types of fracture in people with osteoporosis.

There are several tools available to help doctors to work out whether people are at risk of developing osteoporotic bone fractures. These evaluate a person's risk factors without the need for laboratory tests. Risk factors may include age, weight, family history, caffeine and alcohol intake and whether they smoke or not, as well as what other health conditions they have and what medicines they may be taking.

WHAT DID THE AUTHORS HOPE TO FIND?

The authors hoped to find out how accurate the different tools to predict osteoporotic fractures are, and which are the easiest to use. They also wanted to know whether including the results of a bone mineral density examination could improve the accuracy.

WHO WAS STUDIED?

The authors looked at studies that had already been published. These all reported on the use of tools to predict osteoporotic bone fractures.

HOW WAS THE STUDY CONDUCTED?

A systematic review aims to identify all the published evidence on a particular topic and draw it together into one summary. This paper also included a meta-analysis, which means that statistical analyses were performed on the results in order to be sure that the conclusions being drawn are meaningful.

The authors used major electronic databases and clinical trial registries to search for trials and studies that reported on the quality of tools for predicting osteoporotic fractures in individuals. The search gave a long list of 4806 articles. Of these 45 had the correct type of information and were included in the review, and 20 articles were combined into the meta-analysis.

WHAT WERE THE MAIN FINDINGS OF THE STUDY?

The authors found that the tools currently available can predict with a high level of accuracy whether people will go on to suffer from osteoporotic fractures. Most of these tools could be used in clinical practice as they are simple to access and use.

The three tools that have been studied the most are called FRAX, QFracture and GARVAN. These are questionnaires that take personal details, such as age, height, weight, smoking status, family history and information about living arrangements, other diseases a person might have or medicines they might be using. A computer program then uses the answers to calculate the risk of developing a fracture.

All three of these tools provide information that can help a doctor to decide whether a particular patient needs treatment to prevent them from developing fractures.

ARE THESE FINDINGS NEW?

Although this study used previously published data, it was the first time that such an analysis has been performed for currently available tools for predicting fracture risk in the general population. Additionally, the authors provided calculations for both men and women with or without bone mineral density examination results wherever possible, which had not been done before.

HOW RELIABLE ARE THE FINDINGS?

These types of studies can only provide a combined view of what is available and published in the literature, and there may be some limitations arising from the definitions used in different studies, or from different ways of collecting or recording data. For example, the definition of "major osteoporotic fracture" is not the same for all the tools, and so this limits the comparison that can be made. However, the authors are confident that their findings are reliable.

WHAT DO THE AUTHORS PLAN ON DOING WITH THIS INFORMATION?

Osteoporotic fractures are a big problem, especially in countries with an ageing population. They can cause a lot of suffering and cost the health system a lot of money. The authors hope that these findings will help to raise awareness and to prevent fractures in people with osteoporosis.

WHAT DOES THIS MEAN FOR ME?

These findings may mean that it is possible for your doctor to use a tool to estimate how likely it is that you will suffer from an osteoporotic fracture in the future. This will mean that your doctor can then decide what treatment is best to help prevent fractures, and you can take measures to look after your bone health. Small lifestyle changes may help to prevent fractures – for example, avoid smoking, taking regular exercise, and eating a healthy diet with plenty of calcium and vitamin D which are both good for your bones.

If you are concerned about your bone health, you can also freely access some of the tools online: http://www.garvan.org.au/bone-fracture-risk http://www.qfracture.org/

These tools will help you to assess your own risk of fracture and decide what steps to take. If you are concerned, you should speak to your doctor.

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