Osteoporosis: assessing the risk of fragility fracture

Appendices

Short clinical guideline

27 January 2012

Draft for Consultation

Commissioned by the National Institute for Health and Clinical Excellence

Contents

1 Appendices

2 Appendix A: Declarations of interests

3 All members of the GDG and all members of the NCGC staff were required to make formal
4 declarations of interest at the outset, and these were updated at every subsequent meeting
5 throughout the development process. No interests were declared that required actions.

6 **Dr Peter Barry**

GDG meeting	Declaration of Interests
Chair recruitment	None
First GDG meeting (31 August–1 September 2011)	No change to declarations
Second GDG Meeting (5 October 2011)	No change to declarations
Third GDG Meeting (18 November 2011)	No change to declarations
Fourth GDG Meeting (19–20 December 2011)	No change to declarations

7 **Dr Terry Aspray**

GDG meeting	
GDG recruitment	I am consultant in charge of a fracture liaison service delivering care to the population of Newcastle upon Tyne. In a recent national audit (excluding Scotland), the outcomes for providing advice and treatment for secondary prevention of fractures was the fifth best in the country. Others might fear that I would be biased about service design. However, I recognise that the Newcastle service model has developed over 11 years and is appropriate for our local population and service configuration. Other areas may require a different model of service
First GDG meeting (31 August–1 September 2011)	No change to declarations
Second GDG Meeting (5 October 2011)	Speaker fees from Amgen, paid into a hospital fund.
Third GDG Meeting (18 November 2011)	No change to declarations
Fourth GDG Meeting (19–20 December 2011)	No change to declarations

8 **Mrs Kathleen Briers**

GDG meeting	
GDG recruitment	None
First GDG meeting (31 August–1 September 2011)	No change to declarations
Second GDG Meeting (5 October 2011)	No change to declarations

GDG meeting	
Third GDG Meeting (18 November 2011)	No change to declarations
Fourth GDG Meeting (19–20 December 2011)	No change to declarations

1 **Dr Gary Collins**

GDG meeting	
GDG recruitment	None
First GDG meeting (31 August–1 September 2011)	No change to declarations
Second GDG Meeting (5 October 2011)	No change to declarations
Third GDG Meeting (18 November 2011)	No change to declarations
Fourth GDG Meeting (19–20 December 2011)	No change to declarations

2 **Professor Juliet Compston**

GDG meeting	
GDG recruitment	None
First GDG meeting (31 August–1 September 2011)	Advisory board/speaking commitments for Amgen, Novartis, MSD, Servier, Warner-Chilcott, Gilead, and GlaxoSmithKline & Nycomed. Grant funding from GlaxoSmithKline. Chairman of National Osteoporosis Guideline Group.
Second GDG Meeting (5 October 2011)	No change to declarations
Third GDG Meeting (18 November 2011)	No change to declarations
Fourth GDG Meeting (19–20 December 2011)	No change to declarations

3 **Dr Frances Dockery**

GDG meeting	
GDG recruitment	None
First GDG meeting (31 August–1 September 2011)	No change to declarations
Second GDG Meeting (5 October 2011)	No change to declarations
Third GDG Meeting (18 November 2011)	No change to declarations
Fourth GDG Meeting (19–20 December 2011)	No change to declarations

4 **Ms Sheila Ruddick**

GDG meeting	

GDG meeting	
GDG recruitment	None
First GDG meeting (31 August–1 September 2011)	Received reimbursement of expenses from GSK April 2011. Received reimbursement of expenses (BSR Conference) April 2011 AMGEN.
Second GDG Meeting (5 October 2011)	No change to declarations
Third GDG Meeting (18 November 2011)	No change to declarations
Fourth GDG Meeting (19–20 December 2011)	No change to declarations

1   **Dr Peter Selby**

GDG meeting	
GDG recruitment	None
First GDG meeting (31 August–1 September 2011)	Amgen supporting research in Primary hyperparathyroidism in my department. Amgen supporting research in Primary hyperparathyroidism in my department.
Second GDG Meeting (5 October 2011)	Lecture fee for Shire. Amgen sponsoring trial of primary hyperparathyroidism in my department. Author of WOGG guideline.
Third GDG Meeting (18 November 2011)	No change to declarations
Fourth GDG Meeting (19–20 December 2011)	No change to declarations

2   **Dr David Stephens**

GDG meeting	
GDG recruitment	None
First GDG meeting (31 August–1 September 2011)	I am a member of the SIGN GDG on Osteoporosis
Second GDG Meeting (5 October 2011)	No change to declarations
Third GDG Meeting (18 November 2011)	No change to declarations
Fourth GDG Meeting (19–20 December 2011)	No change to declarations

3   **Mrs Angela Thornhill**

GDG meeting	
GDG recruitment	None
First GDG meeting (31 August–1 September 2011)	Voluntary role - stepped down from chair Nottingham support group of NOS in March 2011, Member of NOS.
Second GDG Meeting (5 October 2011)	No change to declarations

GDG meeting	
Third GDG Meeting (18 November 2011)	No change to declarations
Fourth GDG Meeting (19–20 December 2011)	No change to declarations

1   **Professor Jonathan Tobias**

GDG meeting	
GDG recruitment	Within the last two months, I have received honoraria from Amgen in relation to two educational meetings they have organised concerning Denosumab, in which I participated as either chair or speaker.
First GDG meeting (31 August–1 September 2011)	No change to declarations
Second GDG Meeting (5 October 2011)	No change to declarations
Third GDG Meeting (18 November 2011)	No change to declarations
Fourth GDG Meeting (19–20 December 2011)	No change to declarations

2   **Declarations of interests of NCGC members**

GDG meeting	Declaration of Interests of NCGC members
First GDG meeting (31 August–1 September 2011)	None
Second GDG Meeting (5 October 2011)	No change to declarations
Third GDG Meeting (18 November 2011)	No change to declarations
Fourth GDG Meeting (19–20 December 2011)	No change to declarations

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Appendix B: High priority research recommendations

The Guideline Development Group has made the following recommendations for research, based on its review of evidence, to improve NICE guidance and patient care in the future.

B.1 Risk assessment of fragility fracture

B.1.1 Research question 1: Using GP practice lists to identify people at high risk

What is the clinical and cost effectiveness of using GP practice lists to identify people at high risk of fracture, leading to formal risk assessment and possible treatment?

Why this is important:

Assessment of fracture risk is currently done opportunistically. GP records are now universally computerised and contain information that may be useful in identifying patients at high risk of fracture for example, age, record of prescriptions, major diagnoses, and previous fracture. A study is required to assess whether people at higher risk can be identified by using risk assessment tools to obtain an estimate of risk based on pre-existing information and inviting people at highest risk for a clinical assessment and risk factor estimation. This could result in a more effective and efficient use of staff time and health service resources than an opportunistic approach.

Criteria for selecting high-priority research recommendations:

Criterion	Explanation
Importance to patients or the population	The aim of assessment would be to use preventative measures to prevent fragility fractures. Direct medical costs to the UK healthcare economy from fragility fractures have been estimated at £2.3 billion, with the potential to increase to more than £6 billion by 2036. Most of these costs relate to hip fracture care. Projections show that on current trends, by 2036, there could be as many as 140,000 hospital admissions for hip fracture a year in the UK – this would be an increase of 57% on 2008 admissions.
Relevance to NICE guidance	Medium - High: the research would provide evidence for how assessment could be targeted to those at highest risk.
Relevance to the NHS	The findings could inform a strategy of reduction of fracture risk resulting in better use of resources in short and long term.
Study design	A prospective study is required to (1) Interrogate general practice records and develop an estimate of risk for people registered (2) Invite individuals for assessment and carry out formal risk assessment (3) Compare estimate and formal risk assessment. (4) Use findings to model cost effectiveness of this approach
National priorities	

Current evidence base	There is no research into the effectiveness of targeting people for risk assessment of fracture in this way.
Equality	Assessment is currently done opportunistically and particularly when people visit general practice surgeries/clinics. People at high risk who do not attend, for example because of frailty, mobility problems, alcohol problems are less likely to visit surgeries and clinics and less likely to be assessed. A more systematic approach would highlight which patients required assessment.
Feasibility	Similar studies have been carried out in other areas where risk scores are validated and prevention is being considered e.g. cardiovascular disease. The accuracy of recording in general practice records of factors influencing fracture risk is however disputed.
Other comments	Any other important issues should be mentioned, such as potential funders or outcomes of previous attempts to address this issue, or methodological problems. However, this is not a research protocol.

1 **B.1.2 Research question 2: FRAX and QFracture in adults receiving bone protective therapy**

2 What is the utility of FRAX and QFracture in adults receiving bone protective therapy?

3 **Why this is important**:

4 Because of concerns about rare but serious side-effects of long-term anti-resorptive therapy, many
5 physicians prescribe these drugs for a finite period of time, usually 3-5 years. Reassessment of
6 fracture risk at the end of this treatment period is important, since some people remain at high risk
7 of fracture and require continued treatment whereas others may benefit from a 'drug holiday' for 1
8 or more years. Neither FRAX nor QFracture has been tested in treated patients and it is unknown
9 whether the ability of clinical risk factors with or without measurement of bone mineral density to
10 predict fracture risk is similar in untreated and treated patients. There is therefore a need for
11 prospective studies to investigate the predictive power of these tools to assess fracture risk in
12 patients after a period of bone protective therapy.

13 **Criteria for selecting high-priority research recommendations**:

Criterion	Explanation
Importance to patients or the population	Many patients are concerned about possible side-effects of long-term bone protective therapy, but worry that stopping treatment may increase their risk of fracture. A risk assessment tool that could be applied after 3-5 years of treatment would aid decisions about the risk/benefit balance of a drug holiday.
Relevance to NICE guidance	High, since the guideline addresses fracture risk assessment.
Relevance to the NHS	High, because of the large number of women and men receiving bone protective therapy.
Study design	Prospective study of fracture incidence in patients who have finished a course of bone protective therapy, using FRAX and/or QFracture to assess risk immediately after withdrawal of therapy.
National priorities	

Current evidence base	None published.
Equality	N/A
Feasibility	Good. Would require fracture as primary outcome, therefore would need large sample size and follow-up for minimum two years.
Other comments	

1 **B.1.3 Research question 3: FRAX and QFracture in adults with secondary causes of osteoporosis**

2 What is the utility of FRAX and QFracture in detecting risk of fragility fracture in adults with
3 secondary causes of osteoporosis?

4 **Why this is important**:

5 If secondary osteoporosis is entered as a risk factor in FRAX, the algorithm assumes that the effect is
6 mediated solely through effects on bone mineral density. Input of bone mineral density into the
7 questionnaire in such patients will therefore generate the same fracture risk whether or not
8 secondary osteoporosis is entered. However, it is likely that at least some secondary causes of
9 osteoporosis, for example inflammatory bone disease, affect fracture risk by mechanisms that are
10 partially independent of BMD and fracture risk may therefore be underestimated in such patients.
11 There is therefore a need to investigate the accuracy of FRAX in predicting fracture risk in patients
12 with secondary causes of osteoporosis other than rheumatoid arthritis and to establish whether their
13 effect on fracture risk is mediated solely through effects on bone mineral density.

14 **Criteria for selecting high-priority research recommendations**:

Criterion	Explanation
Importance to patients or the population	Up to one-third of women and one half of men with osteoporosis have an underlying secondary cause. Accurate fracture risk assessment tools are important for this population.
Relevance to NICE guidance	High, since the guideline addresses fracture risk assessment.
Relevance to the NHS	High, since this population comprises a substantial proportion of patients at risk of fracture.
Study design	Prospective study to investigate the ability of FRAX and/or QFracture to predict fracture risk in different secondary causes of osteoporosis.
National priorities	
Current evidence base	Reasonable for rheumatoid arthritis but no good evidence for other secondary causes.
Equality	
Feasibility	Good for the more common conditions such as COPD and IBD, less easy for rarer causes.

Other comments	

1 **B.1.4 Research question 4: BMD with FRAX**

2 What is the added prognostic value of BMD in the assessment of fracture risk with FRAX?

3 **Why this is important**:

4 The 10-year fracture risk as estimated by FRAX is calculated using clinical risk factors with or without
5 BMD. The clinical risk factors are routinely available making calculation of fracture risk at the time of
6 consultation. However, refinement of a patient's 10-year fracture risk using BMD requires
7 assessment using DXA scanning equipment.

8 Currently, there are no definitive studies in primary or secondary care evaluating whether the
9 addition of BMD to FRAX improves the accuracy of the predicted fracture risk. There is a need for
10 studies to examine whether adding BMD to FRAX results in the correct reclassification of patients
11 from low risk to high risk (and vice-versa). Furthermore, studies are also needed to evaluate the
12 clinical usefulness (net benefit) of adding BMD to FRAX; that is, how many more patients are
13 correctly classified as high risk (true positives) at the same rate of correctly classifying patients as low
14 risk (true negatives).

15 **Criteria for selecting high-priority research recommendations**:

Criterion	Explanation
Importance to patients or the population	Identifying individuals who would be at an increased risk of fracture is an important challenge. Direct medical costs to the UK healthcare economy from fragility fractures have been estimated at £1.8 billion in 2000, with the potential to increase to £2.2 billion by 2025[1]. Most of these costs relate to hip fracture care. Determining whether BMD, which incurs a cost, actually improves the accuracy of FRAX for predicting the 10-year fracture risk is an important issue to be resolved.
Relevance to NICE guidance	Medium-High: the research would provide evidence of whether BMD could improve the accuracy of predictions of fracture risk using FRAX.
Relevance to the NHS	The findings could inform a strategy of reduction of fracture risk resulting in better use of resources in short and long term.
Study design	A prospective study is required to determine the added value of BMD to FRAX. The studies should: • compare risk predictions between FRAX with and without BMD; • compare FRAX with and without BMD and focus on whether those classified at low risk using FRAX without BMD are reclassified correctly as high risk and vice versa; • determine the added value of BMD in both primary and secondary care; • identify any subgroups where adding BMD to FRAX improves the 10-year predicted fracture risks.
National priorities	
Current evidence	There are no definitive studies in UK primary or secondary care evaluating

base	whether the addition of FRAX improves the accuracy of predicted 10- year fracture risk.
Equality	
Feasibility	Similar studies have been carried out in other areas where risk scores are validated and prevention is being considered, for example in cardiovascular disease.
Other comments	An important issue to be considered when evaluating whether BMD has added value to FRAX, is to ensure the appropriate statistical methods are used [2,3]. To date, studies have been characterized by the use of poor and largely uninformative methods that make judging whether BMD adds to the predictive accuracy of FRAX of limited value. Traditional performance measures, such as the area under the receiver operating characteristic curve (c-statistic) have limited utility in determining whether BMD has added value to FRAX. Instead, studies should focus on quantifying the added value of BMD using reclassification methods [2] or net benefit methods[4]. Studies should also be sufficiently large, with a minimum of 100 events[5] and missing data should be appropriately handled[6].

1   **B.1.5   Research question 5: FRAX and QFracture in adults living in long-term care**

2   What is the utility of FRAX and QFracture in detecting risk of fragility fracture in adults living in
3   residential and nursing homes?

4   **Why this is important**:

5   Care home residents are at high risk of fragility fracture[7, 8]). This is probably related to increased age
6   and frailty with multiple co-morbidities, which increase fracture risk. There is also evidence that care
7   home residents have lower bone mineral density, with 70% having osteoporosis using densitometry
8   criteria alone[9]. However, tools such as FRAX and QFracture, which only estimate fracture risk up to
9   the ninth decade and use 10-year fracture risk, may under-estimate short-term risk in care home
10   residents, who have a mean age of approximately 85 years and a life expectancy of less than 5
11   years[10].

12   A study is required to assess whether care home residents should have targeted fracture risk
13   assessment and whether residents at higher risk of fracture can be identified, using FRAX or
14   QFracture. This could result in a more effective and efficient strategy for fracture prevention
15   targeting health service resources on those at the very highest fracture risk.

16   **Criteria for selecting high-priority research recommendations**:

Criterion	Explanation
Importance to patients or the population	There are approximately 330,000 people aged over 65 years living in care homes in England, with a projected increase by 51% to a total of 500,000 residents by 2025[11]. Fractures and their consequences currently cost the UK healthcare economy an estimated £2.3 billion and costs are projected to increase to more than £6 billion by 2036. Care home residents have more than three times the risk of hip fracture (RR=3.3 to 3.96) compared with community residents of the same age[78]) Projections of demographic change and particularly a 61% increase in the oldest old population by 2025 anticipate residential and nursing home residents suffering even higher rates of fracture.

Relevance to NICE guidance	Medium - High: the research would provide evidence on the performance of these risk assessment tools when used in those at highest risk.
Relevance to the NHS	The findings could inform a strategy of reduction of fracture risk resulting in better use of resources in short and long term.
Study design	A prospective study is required to (1) Interrogate care home and general practice records to identify individual estimated fracture risk (using FRAX or QFracture) (2) Compare fracture risk estimates for individuals using both tools (3) Estimate proportion of patients who warrant intervention (threshold to be agreed) and identify their characteristics.
National priorities	The national service framework for older people targets the prevention of and serious injury.
Current evidence base	There is no research into the effectiveness of targeting people for risk assessment of fracture in this way. There is epidemiological evidence of high fracture risk in this population [78] and of an extremely high prevalence of osteoporosis[9].
Equality	Despite knowledge that fracture rates are high[7][8] and levels of treatment targeted to prevent fracture are low[9], there are no current strategies for fracture risk assessment in care homes. Moreover, we do not know whether the tools developed to assess fracture risk will perform adequately in this vulnerable high-risk group. As the *short clinical guideline on osteoporosis: fragility risk* is for opportunistic assessment in primary and secondary care, there is a risk that this population at greatest risk will not benefit from appropriate assessment.
Feasibility	Targeting an evaluation of interventions within care homes is extremely feasible and there are precedents with regard to other long term conditions such as diabetes mellitus[9], vaccination[12] and infection control[13].
Other comments	

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Appendix C: How this guideline was developed

1 This guideline was developed in accordance with the process for short clinical guidelines set out in
2 'The guidelines manual' (2009) (see www.nice.org.uk/GuidelinesManual). There is more information
3 about how NICE clinical guidelines are developed on the NICE website
4 (www.nice.org.uk/HowWeWork). A booklet, 'How NICE clinical guidelines are developed: an
5 overview for stakeholders, the public and the NHS' (fourth edition, published 2009), is available from
6 NICE publications (phone 0845 003 7783 or email publications@nice.org.uk and quote reference
7 N1739).

C.1 Additional methods used

C.1.1 Developing the review questions

10 Review questions were developed based on the scope. They were drafted by the review team and
11 refined and validated by the GDG. This short guideline is concerned exclusively with prognosis,
12 investigating either simple prognostic factors for osteoporotic fracture or the accuracy of risk
13 stratification tools to predict fracture. Prognostic review protocols were written to address these
14 issues and the principles adopted are described in more detail below.

15   A framework similar to the PICO format for intervention studies was used for these questions and
16 covered three main factors: –Population, prognostic factor or risk stratification tool and outcomes.
17 This framework guided the literature searching process and facilitated GDG discussions and their
18 development of recommendations. Review questions and protocols can be seen in section C5.

19 For all review questions across this guideline, standard systematic reviewing methods were used
20 which involved five main steps: writing a review protocol in discussion with the GDG; searching the
21 literature; selecting relevant studies against the pre-defined inclusion criteria; quality assessment of
22 the included studies, analysis of the data and interpretation of the results.

23 Following literature search, systematic reviewers sifted the set of titles and abstracts, and identified
24 and retrieved potentially relevant studies, according to the pre-specified inclusion/exclusion criteria
25 set in the protocols that were agreed by the GDG. The systematic reviewers then read the retrieved
26 full-text papers and papers were excluded if they failed to meet the inclusion criteria. Quality
27 assurance was carried out by a second reviewer to eliminate any potential of selection bias or error
28 (10% of sifting and selection of papers, 10-20% data extraction). Quality assessment of studies was
29 carried out using appropriate methodology checklists (see section C4 for more details about quality
30 assessment with respect to each review question). Key information reported in the included studies
31 was then extracted, such as study and population characteristics, prognostic factors measurements,
32 outcome measurements, number of incident fractures, length of follow up, loss to follow up, analysis
33 details, main results findings and study limitations. In addition, evidence statements were produced.
34 They are brief statement summarising key results and quality of the studies for a review question.

35 The methods used for the two review questions are different and further details are now given
36 separately for each type of prognostic review.

C.1.2 Review question 1: How useful are simple clinical measures for targeting people for risk assessment of fragility fracture?

39 This review is concerned with the feasibility of "triaging" patients presenting to health care settings,
40 in order to determine which patients should be given a full risk assessment for fragility fracture (as
41 described in question 2, see section C3). It was not thought practicable or likely cost effective to carry
42 out a full risk assessment for all patients presenting, for instance, to their General Practitioner, not
43 least because many patients would have a very low risk of fracture; for example, a 23 year old man
44 presenting with a sprained ankle. Therefore, this review sought to explore if there are some simple
45 clinical measures or prognostic factors that can be used for targeting people for full risk assessment

of fragility fracture (leading to appropriate treatment). The GDG determined that there were two important features that would influence the usefulness of these simple measures:

- how strong the predictor is (magnitude of association);
- how common the condition is (prevalence).

Accordingly, the GDG pre-specified the following simple measures / prognostic factors in the protocol: body mass index (BMI), prior oral corticosteroid use, family history of fracture, previous fracture, smoking, alcohol, history of falls, age, and other secondary causes of osteoporosis. Some of these are continuous variables (e.g. age), some are treated as categorical variables (e.g. alcohol, BMI) and some are truly dichotomous variables (e.g. family history of fracture). The GDG did not pre-specify particular cut-off points for prognostic factors that were continuous variables, so all cut-offs were included and reported (as well as the effect for the continuous variable). We also noted the reference category for variables that had more than one category.

C.1.2.1 Methods used for this type of prognostic review

At the protocol stage, the approach to the question was discussed, principally to decide whether we should review <u>any</u> simple clinical measure/prognostic factor (in which case, univariate analyses would have been acceptable) or whether the review should be restricted to <u>independent</u> risk factors (in which case, only appropriate multivariable analyses would be acceptable). The GDG agreed that the review was not intended to establish whether factors were independent risk factors for development of fragility fractures and so univariate analyses were acceptable if these were what was available. The most appropriate study design for this type of prognostic review is the prospective cohort study in which both of the following are satisfied:

1. patients with/without the prognostic factor are followed over time to see if the prognostic factor predicts the outcome of interest (fracture) **and**

2. the important confounders are taken into account in the (multivariable) analysis.

Furthermore, it was noted that prognostic questions examining the outcome, fragility fracture are concerned with time-to-event data, and the analysis should indicate that this was taken into account (e.g. by conducting a Cox regression analysis adjusted for the key confounders).

The protocol covered several prognostic systematic reviews, one for each prognostic factor, and the GDG also pre-specified the important prognostic factors (confounders) which had to be included in the multivariable analyses for validity.

Individual patient data analyses

The GDG recognised that the ideal study design was a meta-analysis of individual patient data (IPD), again taking into account the important confounders and using time-to-event data, rather than using aggregate data to conduct systematic reviews. This study design is often considered the gold standard because the analysis is based on original raw data for each participant in each study. Having access to the raw data for each study enables checking, detailed exploration and re-analysis of the data in a consistent way. IPD meta-analyses usually involve more than one study and generally have large representative sample size.

The GDG noted that a number of IPD meta-analyses are available in the literature (published in 2004-2005), mainly for the prognostic factors used in the FRAX algorithm. A literature search was done from 2005 to 2011 to identify and retrieve relevant IPD meta-analyses published on the included prognostic factors for completeness. Having gone through the literature searches, one IPD meta-analysis was identified for each of body mass index, prior oral corticosteroid use, family history of fracture, previous fracture, smoking and alcohol intake. All of them were meta-analyses of cohort studies that were drawn from the original populations used to derive the FRAX score (the "WHO cohort").

1 Other IPD analyses have been conducted using large datasets, particularly those used to derive or
2 validate the QFracture algorithm used as a risk stratification tool in question 2 (section C3). We note
3 that the QFracture derivation study[14] used data from the QResearch database, in which outcomes
4 are collected prospectively but the appropriate baseline characteristics (e.g. family history of
5 fracture) are obtained from patient records (i.e. retrospectively). This gives a risk of inaccurate
6 recording and data for some prognostic factors and confounders are not recorded at all (and have to
7 be ignored or imputed). This gives potential for bias. Similar limitations may occur for IPD meta-
8 analyses too.

9 Regression coefficients (reported as hazard ratios) given by the QFracture derivation cohort[14] were
10 reported, enabling a comparison with the evidence given in the IPD meta-analyses. Prevalence of
11 each prognostic factor in the QResearch data was also noted, in order to assess how rare or common
12 the condition was in the population. These data were thought to be appropriate as it contained a
13 large representative sample size that was applicable to the UK setting.

14 **Systematic reviews of study level data in cohort studies for other prognostic factors**

15 No IPD meta-analysis was found for falls history, therefore a comprehensive systematic review was
16 conducted for this factor, and only prospective cohort studies were included and reviewed.

17 Summary data from each if the different studies were presented visually in forest plots using Review
18 Manager version 5.1 but pooling was not conducted. To represent the data in forest plots, standard
19 errors of the natural logarithm of the effect estimates (e.g. ln (OR))were calculated from the 95%
20 confidence intervals reported by individual studies and entered into the generic inverse-variance
21 method of Review Manager. Forest plots were included in the evidence report and presented to the
22 GDG. In addition, evidence was described in evidence statements which reflect the key finding as
23 well as quality of the studies for a specific review question.

24 For age as a prognostic factor, the GDG were interested in determining the age at which the risk of
25 fragility fracture starts increasing more rapidly in men and women. The GDG wanted an estimate
26 only, partly because they anticipated that the cut point was likely to vary a lot across studies,
27 depending on population setting and its underlying fracture prevalence and prevalence of baseline
28 risk factors. Therefore, the GDG agreed that it would be adequate to restrict the review to three
29 studies, reporting the incidence of fracture by age, in the QFracture internal and external validation
30 studies[14] and a cohort that was included during the development of the FRAX score[15].

31 Systematic reviews were not conducted for secondary causes of osteoporosis. These covered the
32 whole spectrum of health conditions, and recommendations were made based on expert opinions.

33 **C.1.3 Review question 2: Which risk assessment tools are the most accurate in predicting the**
34 **risk of fragility fracture in adults, including those without known osteoporosis or previous**
35 **fragility fracture?**

36 This question is concerned with whether different combinations of prognostic factors (algorithms)
37 accurately predict fragility fracture. Risk stratification algorithms or risk prediction models are
38 derived using time-dependent regression analyses of patient level data - as discussed in question 1.

39 This review focuses on validation studies and is much less concerned with analysing the derivation
40 studies, except when examining whether the algorithms are clinically realistic.

41 **C.1.3.1 Background**

42 The purpose of a risk prediction model is to provide accurate predictions for new patients[16]. An
43 important aspect when introducing a new prediction model is to demonstrate the reproducibility and

1 generalisability of the prediction model; that is, to establish whether the prediction model works in
2 new patients and to quantify this performance[17].

3 **Design of a validation study**

4 Evaluating the performance of a risk prediction model can generally be evaluated in a hierarchy of
5 three increasingly stringent strategies[18,19]:

6 1. Internal validation: using a single data set.

7 2. Temporal validation: using a data set from the same centre(s) but at a different moment in time.

8 3. External validation: using a data set from a different centres (than those used to develop the
9 prediction model).

10 **Internal validation**: this can be evaluated by splitting the data set into two parts. The model is
11 developed on one portion of the data 'training data' whilst the resulting model is evaluated on the
12 second portion of the data 'test data'. Data are often randomly split, however, this strategy is weak
13 as it essentially produces two (apart from chance) similar data sets. A non-random split (i.e. by time
14 or geographical location) will provide a tougher test. Preferably, investigators should use all the data
15 to derive the model and use bootstrapping or cross-validation to evaluate the prediction model and
16 to quantify any over-fitting.

17 **Temporal validation**: ideally, prospective in design, temporal validation is an intermediate step
18 between internal and external validation. Evaluation of the model is on subsequent patients within
19 the same centre(s) as the data set used to develop the prediction model but at a later period in time.

20 **External validation**: the primary aim of validation is to demonstrate satisfactory performance of the
21 prediction model on patients from a different population than those used to derive the model
22 (preferably carried out by independent investigators). Whilst prospective studies are desirable,
23 retrospective data can be used to evaluate the generalisability of the model.

24 Validation studies can provide preliminary (yet important) evidence to support potential usefulness
25 of a risk prediction model[20,21]. However, validation studies are unable to evaluate whether
26 prediction rules change clinical behaviour and ultimately patient outcomes. Impact studies aim to
27 determine whether prediction models change clinical management, doctors' behaviour and
28 ultimately improve patient outcomes. The preferred design is a randomised trial, typically using a
29 cluster design, whereby centres are randomised to either to use the prediction model or to standard
30 care/management. Outcomes are then evaluated in terms of clinical decision-making and patient
31 outcomes.

32 **Sample size**

33 Sample size considerations for validation studies are less established than those for say randomised
34 trials. However, simulation studies for models based on logistic regression have suggested that
35 validation studies should be carried out on data sets that have a minimum of 100 events (i.e. 100
36 fractures)[5]. Evaluating the performance on data sets with less than 100 events can provide
37 unreliable and potentially misleading performance data and should be avoided.

38 **Treatment of missing data**

39 Missing data is common in most clinical data sets, which can be a serious problem in studies deriving
40 or validating a prediction model. Regardless of study design, collecting all data on all risk predictors
41 for all individuals is a difficult task that is rarely achieved. The most common (yet flawed) approach
42 to handling missing data is to omit patents with missing data (complete-case analysis). Omitting
43 patients with missing data has been shown to produce biased and misleading results[22]. Instead of
44 omitting patients that have missing (recorded) data on one or more risk factors, investigators should
45 (1) examine any potential reasons for why data are missing for particular risk factors and (2) use

1 more advanced statistical methods such as multiple imputation to handle missing data. Investigators
2 should be aware, that multiple imputation makes fewer assumptions on the reason for missing data
3 than omitting patients with missing data and makes full use of all the data[23,24]. Missing data should
4 be appropriately handled in both development and validation studies.

5 **Model performance**

6 Evaluating the performance of a prediction model is typically evaluated by examining discrimination
7 and calibration[25]. Discrimination refers to the ability of the prediction model to distinguish between
8 those who do or do not experience the event of interest (i.e fracture)[18]. Calibration concerns how
9 well the predicted risks compare to observed risks. A model is well calibrated if, for every 100
10 patients given a prediction of p%, the observed number of events is close to p11. Discrimination is
11 typically assessed by calculating the area under the receiver operating characteristic curve (c-
12 statistic), where a value of 0.5 implies the model is no better than flipping a coin. However, there are
13 limitations in the usefulness and interpretation of the area under the receiver operating
14 characteristic curve to conclude whether the model is of any use[3,26,27]. Other measures to evaluate
15 the discrimination (or separation) of a prediction model include the D-statistic[28]. Calibration is
16 evaluated either by calculating the Hosmer-Lemeshow test statistic, or preferably by plotting
17 predicted risks against observed risks (calibration plot). The resulting calibration plot, if there is close
18 agreement will be have points lying on around line of 45°, with a slope value around 1.0. Other
19 informative measures of model performance include the R2 (explained variation) and the Brier
20 score[16].

21 **Evaluating the added value of risk factors to a model**

22 Once a model has been developed and shown to provide useful and accurate predictions, new risk
23 factors, tests or biomarkers often become available that are believed to have the potential to
24 improve accuracy of model predictions and ultimately improve decision making. However, many of
25 the traditional approaches to evaluating the added-value of a new risk factor (such as the c-statistic)
26 have limited ability to demonstrate whether adding a new risk factor to an existing prediction model
27 will actually improve the model[26,27]. Alternative methods that are more sensitive to examining the
28 added-value of new risk factors have been proposed. These include reclassification tables, net
29 reclassification improvement and the integrated discrimination improvement. Reclassification tables
30 describe the change in risk categories (low, high risk) between models with and without the new risk
31 factor[29,30]. Net reclassification improvement, which quantifies the amount of reclassification
32 introduced by using a model with the new risk factor[2,31-33] whilst the integrated discrimination
33 improvement quantifies the increase in separation of events and non-events[31]. Reclassification and
34 net reclassification improvement both require pre-defined (accepted) thresholds to designate
35 patients low or high risk. An alternative method to these approaches without imposing a specific
36 threshold and enabling an evaluation over all clinically relevant thresholds is using decision analytic
37 methods[4]. This approach is based on weighing up the relative harms of false-positives (unnecessary
38 treatment) against the harms of false-negative results (delayed treatment).

39 **Evaluating more than one model**

40 There is often more than one model to predict a particular outcome of interest (QFracture, FRAX).
41 Deciding which model to use can be a difficult task. Prediction models are typically developed using
42 different data sets at a different moment in time, yet users are required to choose between two or
43 more competing models. Deciding which model to consider requires absorbing all available evidence
44 on discrimination and calibration. In addition, more recently developed methods such as decision
45 curves (net benefit), as described above, can provide invaluable insights into the clinical usefulness of
46 one model over another[3].

47 **Reporting**

1　Deciding which model (from multiple models) to use can be a difficult task. This task is often made
2　more difficult when investigators fail to report all the relevant details in both development and
3　validation of a risk prediction model. Only when all the key details of study design, statistical
4　methodology and model evaluation have been reported can potential users of the models objectively
5　judge scientific evidence supporting the model. Full and transparent reporting of all aspects in the
6　development and validation of a prediction model is vital. Systematic reviews of methodological
7　conduct and reporting of risk prediction models have all identified major flaws in methodology and
8　reporting which compromise the accuracy of the prediction models and make deciding whether to
9　use one particular model over another a difficult task[34-40]. There are currently no reporting
10　guidelines (similar to the CONSORT statement for randomised trials) to assist authors, editors and
11　readers. However, recent initiatives have begun to rectify this[41].

12　**C.1.3.2　Methods used for this review**

13　FRAX and QFracture are the two main risk assessment tools in predicting the risk of fragility fracture
14　in adults in the UK for which UK validation studies are available. There are two FRAX algorithms
15　available, one including bone mineral density (BMD) and the other without BMD; the QFracture
16　algorithm does not include BMD. This review question also asks whether measuring BMD alone using
17　Dual-energy X-ray absorptiometry (DXA) is likely to be adequate in predicting risk of fragility fracture;
18　and whether FRAX using the algorithm including BMD improves the predictive accuracy of the FRAX
19　tool based on clinical risk factors alone.

20　**Predictive test accuracy and discrimination**

21　We wished to know how accurate the risk stratification tools are in predicting fracture outcomes.
22　This means we want to know across a population if:

23　• a high risk score in an individual is reflected in a fracture occurring in that same individual over
24　the next 10 years;

25　• a low risk score in an individual is reflected in freedom from fracture in that same individual over
26　the next 10 years.

27　This is very similar, in principle, to how we look at diagnostic test accuracy (for diagnosis) and we
28　take an analogous approach here – and use the term "predictive test accuracy". Accordingly we can
29　use similar methods to determine predictive test accuracy statistics and similar quality assessments
30　to diagnostic test accuracy. There are however some important differences, mainly related to the
31　time dependence of prognosis, including the play of chance (i.e. the fact that the event is yet to
32　happen when we measure risk) and these mean we have to modify our quality assessment and to
33　carry out additional analyses to truly answer these types of question (see below).

34　By analogy with diagnostic test accuracy, we considered the risk stratification tool as the "index
35　test"; and the outcome (observed fracture) as the "reference standard". The understanding of
36　"population" is similar (although "prior tests" are generally less common for risk stratification tools
37　than for diagnostic tests). We can also record pseudo 2x2 tables and calculate sensitivity and
38　specificity, but doing this simplistically means we lose the time-to-event nature of the analysis. To
39　calculate the sensitivity and specificity we have to define the cut-off threshold for high and low risk –
40　and this may be difficult to do because it is often related to treatment thresholds.

41　Partly to overcome this dilemma, authors have used risk stratification tools to calculate the area
42　under the receiver operating characteristics (ROC) curve, abbreviated to area under the curve (AUC).
43　The ROC curve is a curve fitted to the set of combinations of sensitivity and (1-specificity), across all
44　possible (theoretical) cut-off points. The AUC is actually calculated using alternative computational
45　methods that also allow for the time-to-event nature of the fracture data.

Area under the curve (and its 95% confidence intervals), a measure of or discrimination, was a common outcome reported by the studies. The GDG agreed on the following criteria for AUC: 90%-100% indicates perfect discrimination; 70%-89% indicates moderate discrimination; 50-69% indicates poor discrimination and <50% not discriminatory at all.

As discussed above, AUC is not a good method of discriminating between risk stratification tools because the statistics are very insensitive even to major changes in the algorithm[26], and we also investigated calibration and reclassification methods, where reported.

Differences between prognostic tests are best determined by both discrimination and calibration

The AUC data provided by the studies were initially plotted in a graph by outcome and sex using Microsoft EXCEL for each tool examined. The review team then compared the AUCs across studies and produced narrative summaries, looking at inconsistency between studies. Data other than AUC (e.g. sensitivity/specificity for certain thresholds, R2, D statistics, Brier score etc.) were also presented if given, and we contacted the authors of all papers for test accuracy statistics such as sensitivity, specificity, positive predictive value, negative predictive value for several thresholds defined by the GDG (thresholds for major osteoporotic fracture: 10%, 20% and 30%; thresholds for hip fracture: 3% and 5%). Sensitivity and specificity were calculated from raw data supplied by the authors, where appropriate. The raw data were used for generating forest plots using Review Manager (version no. 5.1) and for examining ROC curves.

Calibration data were not often reported in the studies, so the authors were contacted for further information on calibration, as well as data such as the number of patients classified as having true positive, true negative, false positive, false negative results. We also requested reclassification data from authors reporting more than one risk score.

C.1.3.3 Simple clinical measures/ prognostic factors

For the evidence review of simple clinical measures, a methodology checklist for systematic reviews of prognostic studies was used for quality assessment[42].The quality assessment checklist consists of six main areas. Each area contains a number of items to be considered for assessment of potential bias. An overall rating (yes, partly, no, unclear) is then given for each area. Additional comments are made to support the rating, when needed.

The methodology checklist includes the following:
- selection of study population (adequate source of population, adequately described inclusion/exclusion criteria, recruitment method clearly described, table of baseline factors reported);
- study attrition (response rate, reasons for loss to follow up, no important differences between key characteristics and outcomes in study participants who completed the studies and those who did not);
- prognostic factor measurement (prognostic factor measurement clearly defined, data collection procedure adequate, any incomplete data taken into account for in the analysis, method/setting of measurement consistent across included studies);
- outcome measurement (clear definition of outcome, outcome measurement valid, method of measuring outcome consistent across included studies);
- confounding (all important confounders considered and measured, clear definition, adequate measurement of confounders, method of confounding measurement is consistent across included studies, appropriate imputation techniques applied for missing data if used, important potential confounders accounted for in the analysis, etc.);

1 • analysis (no selective reporting of results, analysis addressed missing data if appropriate,
2 appropriate strategy for model building, selected model was adequate for the design of the
3 review, including taking account of the time-to-event nature of the data).

4 Reviewers assessed the risk of bias associated with each item and then estimated an overall risk of
5 bias; the overall applicability was also assessed.

6 **C.1.3.4 Risk assessment tools**

7 QUADAS-2 was adapted for quality assessment of risk assessment tools. Adaptation was necessary to
8 take into account the time dependence of prognosis, including the play of chance (i.e. the fact that
9 the event is yet to happen when we measure risk).

10 QUADAS-2 is a tool for the quality assessment of diagnostic accuracy studies[43]. The tool comprises
11 four domains- patient selection, index test, reference standard and flow and timing. Each domain is
12 assessed on risk of bias and concerns about applicability. Where more than one test is compared
13 within a study, there is an additional domain for multiple index tests. A rating is given for each
14 domain and an overall risk of bias is then generated for each study. Applicability was assessed to
15 decide whether the study population had direct or indirect applicability (appropriate to review
16 question or population very different from the UK), whether the risk stratification tool was directly
17 applicable and whether the outcome (facture) was recorded or measured appropriately.

18 The following items were added to QUADAS-2, in consultation with the senior statistician in the GDG,
19 to capture some of the elements in prognostic studies and make it more relevant to prognostic
20 evidence review (see also section C.3.1):

21 • validation method (internal or external validation);

22 • imputation and exclusions for the prognostic factors in the index test (Level of imputation (above
23 or below 50%) including the number of factors requiring imputation; level of exclusions, including
24 the number of factors with exclusions; assumed diagnosis for 1 or more factors[a]);

25 • is the analysis based on incidence data or time to event data?

26 • source of data (index test/reference standard) – data from a clinical database or a cohort

27 • number of events (fractures) (Event rate above or below 100).

28 The GDG considered length of follow up (or interval between index tests and reference standard) to
29 be less important when the number of fracture included in the study is adequate, i.e. more than 100
30 fractures. Blinding of outcome assessors to the risk stratification tool was also considered less
31 important.
32

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a Some studies made the assumption that if there was no recorded value of a diagnosis, then the patient did not have
   that risk factor.

C.2 Review questions and review protocols

C.2.1 Review question 1

How useful are simple clinical measures for targeting people for risk assessment of fragility fracture?

Population	Adult men or women (over 18 years), including those without known osteoporosis or previous fragility fracture.
Prognostic factor	BMI, oral glucocorticoid use, family history of fracture, previous fracture, smoking, alcohol, history of falls.
Outcomes	Risk of fractures including: • vertebral • hip • forearm • any fragility fracture.
Inclusion/exclusion criteria	Where meta-analyses based on individual patient data are available, these are reviewed and other types of evidence such as meta-analysis, systematic reviews, cohort studies, case-control studies and cross-sectional studies are not included. Hierarchy of evidence (only go down a level if there is a lack of literature): • pooled analysis of patient-level data • systematic reviews • cohort studies. Minimum number of fractures reported in study (event rate): 100.
Study types	IPD meta-analyses (when available); prospective cohort

C.2.2 Review question 2

Which risk assessment tools are the most accurate for predicting the risk of fragility fracture in adults, including those without known osteoporosis or previous fragility fracture?

Population	Adult men or women (over 18 years) at risk of fragility fracture, including those without known osteoporosis or previous fragility fracture
Index tests (risk assessment tools)	• QFracture • FRAX, with or without BMD • BMD alone
Reference standard or target conditions	Fractures including: • vertebral • hip • forearm • any fragility fracture.
Outcomes (in terms of discrimination/ calibration)	• Area under the curve. • Sensitivity, specificity, predictive values. • Predicted risk, observed risk. • Other outcomes: D statistics, R^2 statistic and Brier score.
Study types	• Cohort (preferably prospective)

1 # C.3 Search strategies

2 ## C.3.1 Introduction

3 Systematic search strategies were used to identify published evidence for the Osteoporosis guideline,
4 and were run in accordance with the NICE Guidelines Manual 2009:
5 http://www.nice.org.uk/media/5F2/44/The_guidelines_manual_2009_-_All_chapters.pdf

6 Searches for clinical evidence were undertaken between Sept-Nov 2011. Any studies added to the
7 databases after this date were not included unless specifically stated in the text.

8 ## C.3.2 Scoping searches

9 Scoping searches were conducted in January 2011 using the following websites and databases (listed
10 below in alphabetical order). Browsing or simple search strategies were employed. The search results
11 were used to provide information for scope development and project planning.

12

Guidelines	Website address
CMA Infobase (Canadian guidelines)	www.cma.ca/cpgs
Guidelines International Network	www.g-i-n.net/
Health Technology Assessments	www.crd.york.ac.uk/
Medline/Embase Guideline Search (Population and Filter)	N/A
National Guidelines Clearinghouse	www.guideline.gov/
New Zealand Guidelines Group	www.nzgg.org.nz/
NHMRC (Australian Guidelines)	http://www.nhmrc.gov.au/guidelines/
NICE Guidelines	http://guidance.nice.org.uk/
Scottish Intercollegiate Guidelines Network	www.sign.ac.uk/
Specialist Organisations	Various
Reviews, clinical evidence sources, economic evaluations	**Website address**
BMJ Clinical Evidence	clinicalevidence.bmj.com/
Cochrane Library (Systematic Reviews)	www.thecochranelibrary.com/
Kings Fund Database	www.kingsfund.org.uk/library/
NHS Evidence	www.nelh.nhs.uk/
TRIP Database	www.tripdatabase.com/
Other sources as agreed by reviewers	**Website address**
Drugs List (BNF and eMC)	bnf.org/ www.medicines.org.uk/

13 ## C.3.3 Clinical searches

14 Search strategies for review questions were developed by the Information Scientist, with advice from
15 the NCGC Clinical Guidelines Technical Team. Searches for **clinical reviews** were run in Medline and
16 Embase (OVID), and in the Cochrane Library (Wiley) databases for question C.3.7.2. Typically,
17 searches were constructed in the following way:

18 • Clinical questions were translated into search strategies using subject heading and free text
19 terms, following a PEO format. In this format **Population** (P) terms are combined with
20 **Exposure/Intervention** (E) terms (as indicated in the tables under each individual question in
21 section C.3.7), and sometimes Outcome (O) terms. Study type filters were added where
22 appropriate (see C.3.5 and question summary tables).

1 **C.3.4   Economic searches**

2   Searches for **economic reviews** were run in Medline (Ovid), Embase (Ovid), the NHS Economic
3   Evaluations Database (NHS EED), the Health Technology Assessment (HTA) database, and the Health
4   Economic Evaluation Database (HEED). NHS EED and HTA were searched via the Centre for Reviews
5   and Dissemination (CRD) interface. For Medline and Embase an economic filter C.3.5.4 was added to
6   population terms C.3.6.

7 **C.3.5   Study filter terms**

8 **C.3.5.1   Systematic review (SR) search terms**

9   **Medline search terms**

1.	Meta-analysis/
2.	Meta-analysis as topic/
3.	(meta analy* or metanaly* or metaanaly*).ti,ab.
4.	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
5.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
6.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
7.	(search* adj4 literature).ab.
8.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
9.	cochrane.jw.
10.	or/1-9

10   **Embase search terms**

1.	Systematic review/
2.	Meta-analysis/
3.	(meta analy* or metanaly* or metaanaly*).ti,ab.
4.	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
5.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
6.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
7.	(search* adj4 literature).ab.
8.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
9.	((pool* or combined) adj2 (data or trials or studies or results)).ab.
10.	cochrane.jw.
11.	or/1-10

11 **C.3.5.2   Risk search terms**

12   **Medline search terms**

1.	((decision or predict* or assess* or screen* or score* or scoring or stratif*) adj3 (tool* or rule* or instrument*1 or index* or test* or technique* or analys*)).mp.
2.	risk stratif*.mp.
3.	decision support.mp.
4.	(risk* adj2 (factor* or assessment*)).mp.
5.	exp Risk/
6.	Incidence/
7.	prognos*.tw.
8.	predict*.tw.
9.	course*.tw.

10.	monitor*.tw.
11.	risk*.ti,ab.
12.	or/1-11

1 **Embase search terms**

1.	((decision or predict* or assess* or screen* or score* or scoring or stratif*) adj3 (tool* or rule* or instrument*1 or index* or test* or technique* or analys*)).mp.
2.	risk stratif*.mp.
3.	decision support.mp.
4.	(risk* adj2 (factor* or assessment*)).mp.
5.	exp Risk/
6.	Incidence/
7.	prognos*.tw.
8.	predict*.tw.
9.	course*.tw.
10.	monitor*.tw.
11.	risk*.ti.
12.	or/1-11

2 **C.3.5.3 Observational studies search terms**

3 **Medline search terms**

1.	Epidemiologic studies/
2.	exp Case control studies/
3.	exp Cohort studies/
4.	Cross-sectional studies/
5.	case control.ti,ab.
6.	(cohort adj (study or studies or analys*)).ti,ab.
7.	((follow up or observational or uncontrolled or non randomi#ed or nonrandomi#ed or epidemiologic*) adj (study or studies)).ti,ab.
8.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort*)).ti,ab.
9.	or/1-8

4 **Embase search terms**

1.	Clinical study/
2.	exp Case control study/
3.	Family study/
4.	Longitudinal study/
5.	Retrospective study/
6.	Prospective study/
7.	Cross-sectional study/
8.	Cohort analysis/
9.	Follow-up/
10.	cohort*.ti,ab.
11.	9 and 10
12.	case control.ti,ab.
13.	(cohort adj (study or studies or analys*)).ti,ab.
14.	((follow up or observational or uncontrolled or non randomi#ed or nonrandomi#ed or epidemiologic*) adj (study or studies)).ti,ab.
15.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or

	analys* or cohort*)).ti,ab.
16.	or/1-8,11-15

1 C.3.5.4 Health economic search terms

2 Medline search terms

1.	Economics/
2.	Value of life/
3.	exp "Costs and cost analysis"/
4.	exp Economics, Hospital/
5.	exp Economics, medical/
6.	Economics, nursing/
7.	Economics, pharmaceutical/
8.	exp "Fees and Charges"/
9.	exp Budgets/
10.	budget*.ti,ab.
11.	cost*.ti.
12.	(economic* or pharmaco?economic*).ti.
13.	(price* or pricing*).ti,ab.
14.	(cost* adj2 (effectiv* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
15.	(financ* or fee or fees).ti,ab.
16.	(value adj2 (money or monetary)).ti,ab.
17.	or/1-16

3 Embase search terms

1.	Health economics/
2.	exp Economic evaluation/
3.	exp Health care cost/
4.	exp Fee/
5.	Budget/
6.	Funding/
7.	budget*.ti,ab.
8.	cost*.ti.
9.	(economic* or pharmaco?economic*).ti.
10.	(price* or pricing*).ti,ab.
11.	(cost* adj2 (effectiv* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
12.	(financ* or fee or fees).ti,ab.
13.	(value adj2 (money or monetary)).ti,ab.
14.	or/1-13

4 C.3.6 Standard population search strategy

5 Medline search terms

1.	Osteoporotic fractures/
2.	fracture*.ti,ab.
3.	Fractures, Cartilage/ or exp Fractures, Bone/
4.	or/1-3
5.	Letter/
6.	Editorial/
7.	News/

8.	exp Historical article/
9.	Anecdotes as topic/
10.	Comment/
11.	Case report/
12.	(letter or comment*).ti.
13.	or/5-12
14.	Randomized controlled trial/ or random*.ti,ab.
15.	13 not 14
16.	Animals/ not Humans/
17.	exp Animals, Laboratory/
18.	exp Animal experimentation/
19.	exp Models, Animal/
20.	exp Rodentia/
21.	(rat or rats or mouse or mice).ti.
22.	or/15-21
23.	4 not 22
24.	Limit 23 to english language

1 **Embase search terms**

1.	Osteoporotic fractures/
2.	exp Fracture/
3.	fracture*.ti,ab.
4.	or/1-3
5.	letter.pt. or Letter/
6.	note.pt.
7.	editorial.pt.
8.	Case report/ or Case study/
9.	(letter or comment*).ti.
10.	or/5-9
11.	Randomized controlled trial/ or random*.ti,ab.
12.	10 not 11
13.	Animal/ not Human/
14.	Nonhuman/
15.	exp Animal experiment/
16.	exp Experimental animal/
17.	Animal model/
18.	exp Rodent/
19.	(rat or rats or mouse or mice).ti.
20.	or/12-19
21.	4 not 20
22.	Limit 21 to english language

2 **Cochrane search terms**

#1	MeSH descriptor Osteoporotic Fractures explode all trees
#2	(fracture*):ti,ab,kw
#3	MeSH descriptor Fractures, Cartilage explode all trees
#4	MeSH descriptor Fractures, Bone explode all trees
#5	(#1 OR #2 OR #3 OR #4)

1 **C.3.7 Searches by specific question**

2 **C.3.7.1 Clinical measures**

3 Review question 1: How useful are simple clinical measures for targeting people for risk assessment
4 of fragility fracture?

5 Searches were conducted for particular clinical measures as outlined below.

6 **Steroids**

7 Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Exposure/Intervention	Study filter used	Date parameters
Fragility fracture	Oral steroids	Risk	2004-3/11/11

8 **Medline search terms**

1.	exp Adrenal cortex hormones/
2.	exp Glucocorticoids/
3.	(glucocorticoid* or steroid* or corticosteroid*).ti,ab.
4.	Budesonide/
5.	(budesonide or entocort or budenofalk).ti,ab.
6.	(mometasone furoate or asmanex).ti,ab.
7.	exp Betamethasone/
8.	(betamethasone or betametasone or betnelan or betnesol).ti,ab.
9.	cortisone.ti,ab.
10.	(deflazacort or calcot).ti,ab.
11.	exp Dexamethasone/
12.	dexamethasone.ti,ab.
13.	exp Hydrocortisone/
14.	(hydrocortisone or efcortesol or solu-cortef).ti,ab.
15.	exp Methylprednisolone/
16.	(methylprednisolone or medrone or solu-medrone).ti,ab.
17.	Prednisolone/
18.	(prednisolone or prednisone or lodotra).ti,ab.
19.	or/1-18

9 **Embase search terms**

1.	exp Corticosteroid/
2.	exp Glucocorticoid/
3.	(glucocorticoid* or steroid* or corticosteroid*).ti,ab.
4.	Budesonide/
5.	(budesonide or entocort or budenofalk).ti,ab.
6.	exp Betamethasone/
7.	(betamethasone or betametasone or betnelan or betnesol).ti,ab.
8.	cortisone.ti,ab.
9.	(deflazacort or calcot).ti,ab.
10.	exp Dexamethasone/
11.	dexamethasone.ti,ab.
12.	exp Hydrocortisone/
13.	(hydrocortisone or efcortesol or solu-cortef).ti,ab.
14.	exp Methylprednisolone/

15.	(methylprednisolone or medrone or solu-medrone).ti,ab.
16.	Prednisolone/
17.	(prednisolone or prednisone or lodotra).ti,ab.
18.	or/1-17

1   **Falls history**

2   Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Exposure/intervention	Study filter used	Date parameters
Fragility fracture	Falls history	Risk	2004-10/10/11

3   **Medline search terms**

1.	*Accidental Falls/
2.	fall*.ti,ab.
3.	1 or 2

4   **Embase search terms**

1.	*Falling/
2.	fall*.ti,ab.
3.	1 or 2

5   **Previous/family history of fracture**

6   Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Exposure/Intervention	Study filter used	Date parameters
Fragility fracture	Previous or family history	Risk	2004-2/11/11

7   **Medline search terms**

1.	exp Genetic predisposition to disease/
2.	Family/
3.	exp Medical history taking/
4.	((family or maternal or parental) adj6 histor*).ti,ab.
5.	(familial or inherit* or heredit* or predispos* or susceptib*).ti,ab.
6.	((take* or taking) adj3 (history or histories)).ti,ab.
7.	((recurrent or recurring or repeated or history or chronic or previous or prior or habitual) adj6 fracture*).ti,ab.
8.	or/1-7

8   **Embase search terms**

1.	exp Genetic predisposition/
2.	Disease predisposition/
3.	Family history/
4.	Family/
5.	Familial disease/ or Familial incidence/
6.	exp Anamnesis/
7.	((family or maternal or parental) adj6 histor*).ti,ab.
8.	(familial or inherit* or heredit* or predispos* or susceptib*).ti,ab.
9.	((take* or taking) adj3 (history or histories)).ti,ab.
10.	((recurrent or recurring or repeated or history or chronic or previous or prior or habitual) adj6 fracture*).ti,ab.
11.	or/1-10

9   **BMI**

1   Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Exposure/Intervention	Study filter used	Date parameters
Fragility fracture	Body Mass Index	Risk	2005-1/1/11

2   **Medline search terms**

1.	Body weight/ or exp Body weight changes/
2.	exp Body Mass Index/
3.	BMI.ti,ab.
4.	body mass ind*.ti,ab.
5.	(adipos* or obes* or thinness or anorex*).ti,ab.
6.	(under?weight or over?weight).ti,ab.
7.	(low adj2 (weight or bodyweight or bodymass or "body mass")).ti,ab.
8.	exp Overweight/
9.	Thinness/
10.	or/1-9

3   **Embase search terms**

1.	Body weight/ or Lean body weight/ or Weight change/ or Weight fluctuation/ or Weight gain/ or Weight reduction/
2.	Body weight disorder/ or exp Obesity/ or Underweight/ or Wasting syndrome/
3.	Body mass/
4.	BMI.ti,ab.
5.	body mass ind*.ti,ab.
6.	(adipos* or obes* or thinness or anorex*).ti,ab.
7.	(under?weight or over?weight).ti,ab.
8.	(low adj2 (weight or bodyweight or bodymass or "body mass")).ti,ab.
9.	or/1-8

4   **Smoking**

5   Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Exposure/Intervention	Study filter used	Date parameters
Fragility fracture	Smoking	Risk	2004-1/1/11

6   **Medline search terms**

1.	Smoking/
2.	exp Tobacco/
3.	exp Tobacco smoke pollution/
4.	"Tobacco use disorder"/
5.	Nicotine/
6.	(smok* or nonsmok* or cigar* or tobacco or nicotine).ti,ab.
7.	or/1-6

7   **Embase search terms**

1.	exp Smoking/
2.	Tobacco/
3.	Nicotine/
4.	Cigarette smoke/ or Cigarette smoke condensate/ or Tobacco smoke/
5.	Tobacco dependence/
6.	Smokeless tobacco/
7.	(smok* or cigar* or tobacco or nicotine).ti,ab.

8.	or/1-7

1   **Alcohol**

2   Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Exposure/Intervention	Study filter used	Date parameters
Fragility fracture	Alcohol	Risk	2004-2/11/11

3   **Medline search terms**

1.	Alcohol drinking/
2.	exp Alcoholic beverages/
3.	exp Alcohol-related disorders/
4.	Temperance/
5.	(alcohol* or beer* or wine* or liquor* or drinker* or drunk* or intoxicat*).ti,ab.
6.	(non-drink* or nondrink*).ti,ab.
7.	((bing* or problem) adj3 drink*).ti,ab.
8.	or/1-7

4   **Embase search terms**

1.	Drinking behavior/
2.	exp Alcoholic beverage/
3.	Alcohol consumption/
4.	Alcohol abstinence/
5.	Alcohol intoxication/
6.	Drunkenness/
7.	Alcohol abuse/
8.	Alcoholism/
9.	(nondrink* or non-drink*).ti,ab.
10.	(alcohol* or beer* or wine* or liquor* or drunk* or drinker* or intoxicat*).ti,ab.
11.	((bing* or problem) adj3 drink*).ti,ab.
12.	or/1-11

5   **C.3.7.2   Risk assessment tools**

6   Review question 2: Which risk assessment tools are the most accurate in predicting the risk of
7   fragility fracture in adults, including those without known osteoporosis or previous fragility fracture?

8   Two searches were conducted as below.

9   **Bone Mineral Density**

10   Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Exposure/Intervention	Study filters used	Date parameters
Fragility fracture	Bone Mineral Density or densitometry	Risk or Observational studies [Medline and Embase only]	All years – 8/9/11

11   **Medline search terms**

1.	exp Bone density/
2.	(bone adj3 density).ti,ab.
3.	BMD.ti,ab.
4.	exp Densitometry/
5.	densitometry.ti,ab.

6.	(areal adj2 density).ti,ab.
7.	(z-score or t-score).ti,ab.
8.	Absorptiometry, Photon/
9.	absorptiometry.ti,ab.
10.	photodensitometry.ti,ab.
11.	(scan* adj2 (DXA or DEXA or densitometric)).ti,ab.
12.	(densigraphy or densimetry or densitography).ti,ab.
13.	or/1-12

Embase search terms

1.	exp Bone Density/
2.	(bone adj3 density).ti,ab.
3.	BMD.ti,ab.
4.	exp Densitometry/
5.	densitometry.ti,ab.
6.	(areal adj2 density).ti,ab.
7.	(z-score or t-score).ti,ab.
8.	Absorptiometry, Photon/
9.	absorptiometry.ti,ab.
10.	photodensitometry.ti,ab.
11.	(densigraphy or densimetry or densitography).ti,ab.
12.	(scan* adj2 (DXA or DEXA or densitometric)).ti,ab.
13.	or/1-12

Cochrane search terms

#1	MeSH descriptor Bone Density explode all trees
#2	(bone near density):ti,ab,kw
#3	(BMD):ti,ab,kw
#4	MeSH descriptor Densitometry explode all trees
#5	(densitometry):ti,ab,kw
#6	(areal near density):ti,ab,kw
#7	(z-score or t-score):ti,ab,kw
#8	MeSH descriptor Absorptiometry, Photon explode all trees
#9	absorptiometry:ti,ab,kw or photodensitometry :ti,ab,kw
#10	(scan* near (DXA or DEXA or densitometric)):ti,ab,kw
#11	(densigraphy or densimetry or densitography):ti,ab,kw
#12	(#1 or #2 o r#3 or #4 o r#5 o r#6 o r#7 or #8 or #9 or #10 or #11)

FRAX and QFracture

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Exposure/Intervention	Study filter used	Date parameters
FRAX or QFracture*	None	None	All years -21/7/11 and a top up on 14/9/11

Non-standard population used.

Medline search terms

1.	(FRAX or FRAXTM or qfracture*).ti,ab.
2.	(risk* and assess* and tool*).ti,ab.
3.	fracture*.ti,ab.

4.	2 and 3
5.	(fracture* adj3 risk adj3 assess* adj3 tool*).ti,ab.
6.	1 or 4 or 5
7.	Letter/
8.	Editorial/
9.	News/
10.	exp Historical article/
11.	Anecdotes as topic/
12.	Comment/
13.	Case report/
14.	(letter or comment* or abstracts).ti.
15.	or/7-14
16.	6 not 15

1 **Embase search terms**

1.	(FRAX or FRAXTM or qfracture*).ti,ab.
2.	(risk* and assess* and tool*).ti,ab.
3.	fracture*.ti,ab.
4.	2 and 3
5.	(fracture* adj3 risk adj3 assess* adj3 tool*).ti,ab.
6.	1 or 4 or 5
7.	letter.pt. or Letter/
8.	note.pt.
9.	editorial.pt.
10.	Case report/ or Case study/
11.	(letter or comment*).ti.
12.	or/7-11
13.	Randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	Animal/ not Human/
16.	Nonhuman/
17.	exp Animal experiment/
18.	exp Experimental animal/
19.	Animal model/
20.	exp Rodent/
21.	(rat or rats or mouse or mice).ti.
22.	or/14-21
23.	6 not 22
24.	Limit 23 to english language

2 **Cochrane search terms**

#1	(FRAX or FRAXTM or qfracture*):ti,ab,kw
#2	(fracture* risk assess* tool*):ti,ab,kw
#3	(risk* and assess* and tool*):ti,ab
#4	fracture*:ti,ab
#5	(#3 AND #4)
#6	(#1 OR #2 OR #5)

1 C.3.8 Economic searches

2 Economic searches were run in Medline and Embase by combining population terms with the
3 economic filter and limiting by date range. Economic searches were executed in the NHS EED and
4 HTA (CRD) databases by simply running population terms without a date limitation. Initial searches
5 were conducted on 19/5/11. The population subsequently changed and a top up search was run on
6 13/9/11.

7 C.3.8.1 Initial search

8 Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Exposure/Intervention	Study filter used	Date parameters
Osteoporosis or Osteoporotic fractures	Risk assessment tools	Risk, Economic [only Embase and Medline]	2009 – 19/05/11 (Medline and Embase) All years – 19/5/11

9 **Medline search terms**

1.	(FRAX or FRAXTM or WHO fracture risk assessment tool).ti,ab. not fragile X.mp.
2.	(osteoporosis self-assessment tool or (OST and osteoporo*)).ti,ab.
3.	(osteoporosis risk assessment instrument or (ORAI and osteoporo*)).ti,ab.
4.	simple calculated osteoporosis risk estimation.ti,ab.
5.	(osteoporosis index of risk or (OSIRIS and osteoporo*)).ti,ab.
6.	garvan fracture risk calculator.ti,ab.
7.	(age body size no estrogen or ABONE).ti,ab.
8.	(SOFSURF or DOEScore).ti,ab.
9.	or/1-8
10.	Osteoporotic fractures/
11.	((fragility or osteoporo*) adj2 fracture*).ti,ab.
12.	10 or 11
13.	exp Osteoporosis/
14.	Bone diseases, Metabolic/
15.	osteoporo*.ti,ab.
16.	or/13-15
17.	Bone density/
18.	(bone adj6 densit*).ti,ab.
19.	bmd.ti,ab.
20.	(bone or bones).mp.
21.	exp densitometry/ or DXA.ti,ab.
22.	20 and 21
23.	17 or 18 or 19 or 22
24.	Fractures, Cartilage/ or exp Fractures, Bone/
25.	fracture*.ti,ab.
26.	24 or 25
27.	16 and 26
28.	23 and 26
29.	12 or 27 or 28
30.	exp "Analysis of variance"/ or Factor analysis, Statistical/ or exp Models, Statistical/ or exp Probability/ or exp Survival analysis/
31.	"Predictive value of tests"/ or exp Regression analysis/ or Prognosis/ or Disease-free survival/ or Nomograms/

32.	Algorithms/
33.	"Severity of illness index"/
34.	(risk or prognosis or prognostic or diagnosed or predictor or predictive value or accurac*).ti,ab.
35.	body weight criterion.ti,ab.
36.	((scor* or screen* or assess* or predict* or probability) adj3 (system* or tool* or method* or instrument*)).ti,ab.
37.	(sensitiv* or cohort).mp.
38.	or/30-37
39.	9 or (29 and 38)

1

Embase search terms

1.	(FRAX or FRAXTM or WHO fracture risk assessment tool).ti,ab. not fragile X.mp.
2.	(osteoporosis self-assessment tool or (OST and osteoporo*)).ti,ab.
3.	(osteoporosis risk assessment instrument or (ORAI and osteoporo*)).ti,ab.
4.	simple calculated osteoporosis risk estimation.ti,ab.
5.	(osteoporosis index of risk or (OSIRIS and osteoporo*)).ti,ab.
6.	garvan fracture risk calculator.ti,ab.
7.	(age body size no estrogen or ABONE).ti,ab.
8.	(SOFSURF or DOEScore).ti,ab.
9.	or/1-8
10.	Osteoporotic fractures/
11.	((fragility or osteoporo*) adj2 fracture*).ti,ab.
12.	10 or 11
13.	exp Osteoporosis/
14.	Bone demineralization/ or Metabolic bone disease/
15.	osteoporo*.ti,ab.
16.	or/13-15
17.	Bone density/
18.	(bone adj6 densit*).ti,ab.
19.	bmd.ti,ab.
20.	Bone densitometry/
21.	(bone or bones).mp.
22.	exp Densitometry/ or DXA.ti,ab.
23.	21 and 22
24.	17 or 18 or 19 or 20 or 23
25.	exp fracture/
26.	fracture*.ti,ab.
27.	25 or 26
28.	16 and 27
29.	24 and 27
30.	12 or 28 or 29
31.	exp Statistical analysis/
32.	Statistical model/
33.	exp Survival/
34.	Probability/
35.	exp Risk/
36.	exp Algorithm/
37.	Disease severity/ or Prognosis/
38.	exp Predictive value/ or Scoring system/

39.	Diagnostic value/
40.	(risk or prognosis or prognostic or diagnosed or predictor or predictive value or accurac*).ti,ab.
41.	body weight criterion.ti,ab.
42.	(cohort or sensitiv*).mp.
43.	((scor* or screen* or assess* or predict* or probability) adj3 (system* or tool* or method* or instrument*)).ti,ab.
44.	or/31-43
45.	9 or (30 and 44)

1   **HEED search terms**

1.	ax=osteoporosis fracture within 3
2.	ax=osteoporosis fractures within 3
3.	ax=fragility fracture within 3
4.	ax=fragility fractures within 3
5.	ax=bone density within 3
6.	ax=fracture*
7.	cs=5 and 6
8.	cs =1 or 2 or 3 or 4 or 7
9.	ax=risk* or FRAX or FRAXTM or OST or OSIRIS or ORAI or ABONE or SOFSURF or DOEScore OR garvan fracture risk calculator OR simple calculated osteoporis risk estimation
10.	cs=8 and 9

2   **CRD search terms**

1.	MeSH DESCRIPTOR osteoporosis EXPLODE ALL TREES WITH QUALIFIER undefined IN NHSEED,HTA
2.	(osteoporo*) IN NHSEED, HTA
3.	MeSH DESCRIPTOR bone density EXPLODE ALL TREES WITH QUALIFIER undefined IN NHSEED,HTA
4.	(bone adj6 densit*) IN NHSEED, HTA
5.	#1 OR #2 OR #3 OR #4
6.	MeSH DESCRIPTOR Fractures, Bone EXPLODE ALL TREES
7.	MeSH DESCRIPTOR Fractures, Cartilage EXPLODE ALL TREES
8.	(fracture*) IN NHSEED, HTA
9.	#6 OR #7 OR #8
10.	#5 AND #9
11.	((fragility or osteoporo*) adj2 fracture*) IN NHSEED, HTA
12.	(FRAX or FRAXTM or OST or OSIRIS or ORAI or ABONE or SOFSURF or DOEScore) OR ("garvan fracture risk calculator") OR ("simple calculated osteoporis risk estimation") IN NHSEED, HTA
13.	(risk*) OR (((scor* or screen* or assess* or predict* or probability*) adj3 (system* or tool* or method* or instrument*))) IN NHSEED, HTA
14.	MeSH DESCRIPTOR probability EXPLODE ALL TREES WITH QUALIFIER undefined IN NHSEED,HTA
15.	MeSH DESCRIPTOR regression analysis EXPLODE ALL TREES WITH QUALIFIER undefined IN NHSEED,HTA
16.	MeSH DESCRIPTOR algorithms EXPLODE ALL TREES WITH QUALIFIER undefined IN NHSEED,HTA
17.	MeSH DESCRIPTOR Severity of Illness Index EXPLODE ALL TREES
18.	MeSH DESCRIPTOR Analysis of Variance EXPLODE ALL TREES
19.	MeSH DESCRIPTOR Factor Analysis, Statistical EXPLODE ALL TREES
20.	MeSH DESCRIPTOR Models, Statistical EXPLODE ALL TREES
21.	MeSH DESCRIPTOR survival analysis EXPLODE ALL TREES WITH QUALIFIER undefined IN NHSEED,HTA
22.	(cohort or sensitiv*) OR (prognosis or prognostic or diagnosed or predictor or "predictive value" or accurac*) IN NHSEED, HTA
23.	MeSH DESCRIPTOR Predictive Value of Tests EXPLODE ALL TREES
24.	MeSH DESCRIPTOR prognosis EXPLODE ALL TREES WITH QUALIFIER undefined IN NHSEED,HTA
25.	#13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24

26.	#10 OR #11
27.	#25 AND #26
28.	#12 OR #27
29.	(#28) IN NHSEED
30.	(#28) IN HTA

1 **C.3.8.2 Top-up search**

2 A top up search was conducted as the intial population was limited to oseoporotic fractures and
3 changed post-scoping to encompass fragility fractures.

4 Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Exposure/Intervention	Study filter used	Date parameters
FRAX or QFracture*	None	Economic [only Embase and Medline]	All years -13/9/11

5 *Non-standard population used.*

6 **Medline search terms**

1.	(FRAX or FRAXTM or qfracture*).ti,ab.
2.	(risk* and assess* and tool*).ti,ab.
3.	fracture*.ti,ab.
4.	2 and 3
5.	(fracture* adj3 risk adj3 assess* adj3 tool*).ti,ab.
6.	1 or 4 or 5
7.	Letter/
8.	Editorial/
9.	News/
10.	exp Historical article/
11.	Anecdotes as topic/
12.	Comment/
13.	Case report/
14.	(letter or comment* or abstracts).ti.
15.	or/7-14
16.	6 not 15
17.	Limit 16 to english language

7 **Embase search terms**

1.	(FRAX or FRAXTM or qfracture*).ti,ab.
2.	(risk* and assess* and tool*).ti,ab.
3.	fracture*.ti,ab.
4.	2 and 3
5.	(fracture* adj3 risk adj3 assess* adj3 tool*).ti,ab.
6.	1 or 4 or 5
7.	letter.pt. or Letter/
8.	note.pt.
9.	editorial.pt.
10.	Case report/ or Case study/
11.	(letter or comment*).ti.

12.	or/7-11
13.	Randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	Animal/ not Human/
16.	Nonhuman/
17.	exp Animal experiment/
18.	exp Experimental animal/
19.	Animal model/
20.	exp Rodent/
21.	(rat or rats or mouse or mice).ti.
22.	or/14-21
23.	6 not 22
24.	Limit 23 to english langauge

1 **HEED search terms**

1.	ax=FRAX
2.	ax=FRAXTM
3.	ax=qfracture*
4.	ax=assess*
5.	ax=risk*
6.	ax=tool*
7.	cs=4 and 5 and 6
8.	ax=fracture*
9.	cs=7 and 8
10.	cs=1 or 2 or 3
11.	cs=9 or 10

2 **CRD search terms**

1.	(FRAX) OR (FRAXTM) OR (qfracture*) IN NHSEED, HTA
2.	(Risk* and Assess* and tool*) IN NHSEED, HTA
3.	#1 OR #2
4.	(fracture*) IN NHSEED, HTA
5.	#3 AND #4

3

4

1   # C.4   Excluded studies

2   ## C.4.1   Studies excluded from the clinical review on simple clinical measures for targeting people
3   for risk assessment of fragility fracture (history of falls)

Author/title	Reason for exclusion
Abolhassani F, Moayyeri A, Naghavi M, Soltani A, Larijani B, Shalmani HT. Incidence and characteristics of falls leading to hip fracture in Iranian population. Bone. United States 2006; 39(2):408-413. (Guideline Ref ID ABOLHASSANI2006)	Not question of interest
Albertsson D, Gause-Nilsson I, Mellstrom D, Eggertsen R. Risk group for hip fracture in elderly women identified by primary care questionnaire--clinical implications. Upsala Journal of Medical Sciences. Sweden 2006; 111(2):179-187. (Guideline Ref ID ALBERTSSON2006)	Less than 100 fracture outcomes reported
Albrand G, Munoz F, Sornay-Rendu E, Duboeuf F, Delmas PD. Independent predictors of all osteoporosis-related fractures in healthy postmenopausal women: the OFELY study. Bone. United States 2003; 32(1):78-85. (Guideline Ref ID ALBRAND2003)	Less than 100 fracture outcomes reported
Assantachai P, Praditsuwan R, Chatthanawaree W, Pisalsarakij D, Thamlikitkul V. Risk factors for falls in the Thai elderly in an urban community. Journal of the Medical Association of Thailand. Thailand 2003; 86(2):124-130. (Guideline Ref ID ASSANTACHAI2003)	Not cohort study; survey
Balzini L, Vannucchi L, Benvenuti F, Benucci M, Monni M, Cappozzo A et al. Clinical characteristics of flexed posture in elderly women. Journal of the American Geriatrics Society. United States 2003; 51(10):1419-1426. (Guideline Ref ID BALZINI2003)	Not question of interest
Bow CH, Tsang SW, Loong CH, Soong CS, Yeung SC, Kung AW. Bone mineral density enhances use of clinical risk factors in predicting ten-year risk of osteoporotic fractures in Chinese men: the Hong Kong Osteoporosis Study. Osteoporosis International. England 2011; 22(11):2799-2807. (Guideline Ref ID BOW2011)	Less than 100 fracture outcomes reported
Chen Z, Maricic M, Bassford TL, Pettinger M, Ritenbaugh C, Lopez AM et al. Fracture risk among breast cancer survivors: results from the Women's Health Initiative Observational Study. Archives of Internal Medicine. Division of Epidemiology and Biostatistics, Zuckerman College of Public Health, University of Arizona, PO Box 245203, 1540 E. Drachman, Tucson, AZ 85724, USA. zchen@u.arizona.edu 2005; 165(5):552-558. (Guideline Ref ID CHEN2005)	Not cohort study; case control study
Chen Z, Maricic M, Aragaki AK, Mouton C, Arendell L, Lopez AM et al. Fracture risk increases after diagnosis of breast or other cancers in postmenopausal women: results from the Women's Health Initiative. Osteoporosis International. England 2009; 20(4):527-536. (Guideline Ref ID CHEN2009B)	Not question of interest
Dargent-Molina P, Favier F, Grandjean H, Baudoin C, Schott AM, Hausherr E et al. Fall-related factors and risk of hip fracture: the EPIDOS prospective study. Lancet.	Cohort study subsequently published with longer follow-up (that is included)

Author/title	Reason for exclusion
ENGLAND 1996; 348(9021):145-149. (Guideline Ref ID DARGENT1996)	
Egan M, Jaglal S, Byrne K, Wells J, Stolee P. Factors associated with a second hip fracture: a systematic review. Clinical Rehabilitation. England 2008; 22(3):272-282. (Guideline Ref ID EGAN2008)	Narrative of systematic review without data-analysis
Geusens P, Autier P, Boonen S, Vanhoof J, Declerck K, Raus J. The relationship among history of falls, osteoporosis, and fractures in postmenopausal women. Archives of Physical Medicine & Rehabilitation. United States 2002; 83(7):903-906. (Guideline Ref ID GEUSENS2002)	Not cohort study; survey
Gibson RE, Harden M, Byles J, Ward J. Incidence of falls and fall-related outcomes among people in aged-care facilities in the Lower Hunter region, NSW. New South Wales Public Health Bulletin. Australia 2008; 19(9-10):166-169. (Guideline Ref ID GIBSON2008)	Not cohort study; survey
Henry MJ, Pasco JA, Sanders KM, Nicholson GC, Kotowicz MA. Fracture Risk (FRISK) Score: Geelong Osteoporosis Study. Radiology. United States 2006; 241(1):190-196. (Guideline Ref ID HENRY2006)	Not question of interest
Henry MJ, Pasco JA, Merriman EN, Zhang Y, Sanders KM, Kotowicz MA et al. Fracture risk score and absolute risk of fracture. Radiology. 2011; 259(2):495-501. (Guideline Ref ID HENRY2011)	Not question of interest
Honkanen R, Tuppurainen M, Kroger H, Alhava E, Puntila E. Associations of early premenopausal fractures with subsequent fractures vary by sites and mechanisms of fractures. Calcified Tissue International. UNITED STATES 1997; 60(4):327-331. (Guideline Ref ID HONKANEN1997)	Not question of interest
Johnell O, Kanis JA, Oden A, Sernbo I, Redlund-Johnell I, Petterson C et al. Fracture risk following an osteoporotic fracture. Osteoporosis International. England 2004; 15(3):175-179. (Guideline Ref ID JOHNELL2004A)	Not question of interest
Khazzani H, Allali F, Bennani L, Ichchou L, El ML, Abourazzak FE et al. The relationship between physical performance measures, bone mineral density, falls, and the risk of peripheral fracture: a cross-sectional analysis. BMC Public Health. England 2009; 9:297. (Guideline Ref ID KHAZZANI2009)	Not cohort study; case control study
Khine H, Dorfman DH, Avner JR. Applicability of Ottawa knee rule for knee injury in children. Pediatric Emergency Care. United States 2001; 17(6):401-404. (Guideline Ref ID KHINE2001)	Wrong population
Kim YM, Hyun NR, Shon HS, Kim HS, Park SY, Park IH et al. Assessment of clinical risk factors to validate the probability of osteoporosis and subsequent fractures in Korean women. Calcified Tissue International. United States 2008; 83(6):380-387. (Guideline Ref ID KIM2008)	Not question of interest
Langsetmo L, Hanley DA, Kreiger N, Jamal SA, Prior J, Adachi JD et al. Geographic variation of bone mineral density and selected risk factors for prediction of incident fracture among Canadians 50 and older. Bone. United	Not question of interest

Author/title	Reason for exclusion
States 2008; 43(4):672-678. (Guideline Ref ID LANGSETMO2008)	
Leslie WD, Anderson WA, Metge CJ, Manness LJ, Maximizing Osteoporosis Management in Manitoba Steering Committee. Clinical risk factors for fracture in postmenopausal Canadian women: a population-based prevalence study. Bone. United States 2007; 40(4):991-996. (Guideline Ref ID LESLIE2007A)	Not cohort study; survey
Luukinen H, Koski K, Jokelainen J. Temporal changes in the frequency of falling accidents among the elderly during the 1990s: A population-based study. Public Health. 2006; 120(5):418-420. (Guideline Ref ID LUUKINEN2006)	Not cohort study; survey
Nguyen ND, Frost SA, Center JR, Eisman JA, Nguyen TV. Development of prognostic nomograms for individualizing 5-year and 10-year fracture risks. Osteoporosis International. England 2008; 19(10):1431-1444. (Guideline Ref ID NGUYEN2008)	Not question of interest
Nguyen ND, Eisman JA, Center JR, Nguyen TV. Risk factors for fracture in nonosteoporotic men and women. Journal of Clinical Endocrinology & Metabolism. United States 2007; 92(3):955-962. (Guideline Ref ID NGUYEN2007A)	Cohort study subsequently published with longer follow-up
Nguyen TV, Eisman JA, Kelly PJ, Sambrook PN. Risk factors for osteoporotic fractures in elderly men. American Journal of Epidemiology. UNITED STATES 1996; 144(3):255-263. (Guideline Ref ID NGUYEN1996)	Cohort study subsequently published with longer follow-up (that is included)
Nguyen TV, Center JR, Sambrook PN, Eisman JA. Risk factors for proximal humerus, forearm, and wrist fractures in elderly men and women: the Dubbo Osteoporosis Epidemiology Study. American Journal of Epidemiology. United States 2001; 153(6):587-595. (Guideline Ref ID NGUYEN2001)	Cohort study subsequently published with longer follow-up (that is included)
Ojo F, Al SS, Ray LA, Raji MA, Markides KS. History of fractures as predictor of subsequent hip and nonhip fractures among older Mexican Americans. Journal of the National Medical Association. United States 2007; 99(4):412-418. (Guideline Ref ID OJO2007)	Not question of interest
Piirtola M, Vahlberg T, Isoaho R, Aarnio P, Kivela SL. Incidence of fractures and changes over time among the aged in a Finnish municipality: a population-based 12-year follow-up. Aging-Clinical & Experimental Research. Italy 2007; 19(4):269-276. (Guideline Ref ID PIIRTOLA2007)	Not cohort study; survey
Pinheiro MM, Ciconelli RM, Martini LA, Ferraz MB. Clinical risk factors for osteoporotic fractures in Brazilian women and men: the Brazilian Osteoporosis Study (BRAZOS). Osteoporosis International. England 2009; 20(3):399-408. (Guideline Ref ID PINHEIRO2009)	Not cohort study; survey
Pluskiewicz W, Adamczyk P, Franek E, Leszczynski P, Sewerynek E, Wichrowska H et al. Ten-year probability of osteoporotic fracture in 2012 Polish women assessed by FRAX and nomogram by Nguyen et al.-Conformity between methods and their clinical utility. Bone. United States 2010; 46(6):1661-1667. (Guideline Ref ID PLUSKIEWICZ2010)	Not question of interest

Author/title	Reason for exclusion
Poor G, Atkinson EJ, O'Fallon WM, Melton LJ, III. Predictors of hip fractures in elderly men. Journal of Bone & Mineral Research. UNITED STATES 1995; 10(12):1900-1907. (Guideline Ref ID POOR1995A)	Not cohort study; case control study
Rubin KH, Abrahamsen B, Hermann AP, Bech M, Gram J, Brixen K. Prevalence of risk factors for fractures and use of DXA scanning in Danish women. A regional population-based study. Osteoporosis International. 2011; 22(5):1401-1409. (Guideline Ref ID RUBIN2011)	Not cohort study; survey
Shimada H, Suzukawa M, Ishizaki T, Kobayashi K, Kim H, Suzuki T. Relationship between subjective fall risk assessment and falls and fall-related fractures in frail elderly people. BMC Geriatrics. England 2011; 11:40. (Guideline Ref ID SHIMADA2011)	Not question of interest
Singh MF, Singh NA, Hansen RD, Finnegan TP, Allen BJ, Diamond TH et al. Methodology and baseline characteristics for the sarcopenia and hip fracture study: A 5-year prospective study. Journals of Gerontology - Series A Biological Sciences and Medical Sciences. 2009; 64(5):568-574. (Guideline Ref ID SINGH2009)	Not question of interest
Van Iersel M, Verbeek ALM, Bloem BR, Munneke M, Esselink RAJ, Olde R. Frail elderly patients with dementia go too fast. Journal of Neurology, Neurosurgery and Psychiatry. 2006; 77(7):874-876. (Guideline Ref ID VANIERSEL2006A)	Wrong population
Vestergaard P, Jorgensen NR, Schwarz P, Mosekilde L. Effects of treatment with fluoride on bone mineral density and fracture risk--a meta-analysis. Osteoporosis International. England 2008; 19(3):257-268. (Guideline Ref ID VESTERGAARD2008A)	Not question of interest

1 **C.4.2   Studies excluded from the clinical review on FRAX and QFracture assessment tools**

Author/title	Reason for exclusion
McCloskey. From relative risk to absolute fracture risk calculation: The FRAX Algorithm.	Review
Cevei. Evaluation of osteoporotic fracture risk according to the risk factors.	Not relevant to review question
Saylor. Application of a fracture risk algorithm to men treated with androgen deprivation therapy for prostate cancer.	Not relevant to review question. Subgroup - prostate cancer patients
Adler. Treatment thresholds for osteoporosis in men on androgen deprivation therapy: T-score versus FRAX	Not relevant to review question. Subgroup – prostate cancer patients
McCloskey. Ten-year fracture probability identifies women who will benefit from clodronate therapy – additional results from a double-blind, placebo-controlled randomised study.	Not relevant to review question
Franek. WHO fracture risk calculator (FRAX) in the assessment of obese patients with osteoporosis	Not relevant to review question. Subgroup – obese patients with osteoporosis, reassessment of fracture risk and reassignment to treatment
Kanis. Bazedoxifene reduces vertebral and clinical fractures in postmenopausal women at high risk assessed	Not relevant to review question. Subgroup – people currently receiving osteoporosis

Author/title	Reason for exclusion
with FRAX.	treatment
Kanis. Guidance for the adjustment of FRAX according to the dose of glucocorticoids.	Not relevant to review question.
Jager. Combined vertebral fracture assessment and bone mineral density measurement: a patient-friendly new tool with an important impact on the Canadian risk fracture classification.	Not relevant to review question
Fujiwara. Development and application of a Japanese model of the WHO fracture risk assessment tool (FRAX).	Did not report relevant data (10 year fracture probability)
Schwartz. Association of BMD and FRAX score with risk of fracture in older adults with Type 2 diabetes.	Did not report relevant data (10 year fracture probability)
Lippuner. Remaining lifetime and absolute 10-year probabilities of osteoporotic fracture in Swiss men and women.	Did not report relevant data (10 year fracture probability)
Tseng. Ten-year fracture probability in Hong Kong Southern Chinese according to age and BMD femoral neck T-scores.	Did not report relevant data (10 year fracture probability)
Curtis. Population-based fracture risk assessment and osteoporosis treatment disparities by race and gender.	Did not report relevant data (10 year fracture probability)
Van Staa. A simple clinical score for estimating the long-term risk of fracture in post-menopausal women.	Not relevant to review question
Leslie. Construction of a FRAX model for the assessment of fracture probability in Canada and implications for treatment.	Not relevant to review question
Leslie. Imputation of 10-year osteoporotic fracture rates from hip fractures: a clinical validation study.	Updated results published in a more recent paper [Leslie 2010. Independent Clinical Validation of Canadian FRAX tool: fracture prediction and model calibration].
Leslie. Construction and validation of a simplified fracture risk assessment tool for Canadian women and women: results from the CaMos and Manitoba cohorts.	Not relevant to review question
Kanis. A meta-analysis of the effect of strontium ranelate on the risk of vertebral and non-vertebral fracture in postmenopausal osteoporosis and the interaction with FRAX.	Meta-analysis
Hamdy. Variance in 10-year fracture risk calculated with and without T-scores in select subgroups of normal and osteoporotic patients.	Not relevant to review question
Rubin. Fracture risk assessed by fracture risk assessment tool (FRAX) compared with fracture derived from population fracture rates.	Did not report relevant data (10 year fracture probability by age strata)
Goodhand. Application of the WHO fracture risk assessment tool (FRAX) to predict need for DEXA scanning and treatment in patients with inflammatory bowel disease at risk of osteoporosis.	Did not report relevant data (10 year fracture probability). No reference standard/outcome of interest.
Dimic. Potential role of FRAX analysis in postmenopausal women with osteopenia.	Not relevant to review question.
Francis. (ii) Fracture risk assessment.	Review
Johansson. A FRAX model for the assessment of fracture probability in Belgium.	Did not report relevant data (10 year fracture probability by age strata)
Ensrud. A comparison of prediction models for fractures	Duplicate

Author/title	Reason for exclusion
in older women: Is more better?	
Lewiecki. Bone densitometry and vertebral fracture assessment.	Review
Van Gee. Comparing FRAX and Garvan fracture risk calculator in postmenopausal women: A prospective 5-year follow-up study.	Conference abstract
Planas. Accuracy of FRAX and Garvan nomograms to predict osteoporotic fracture risk in prostate cancer patients subjected to androgen suppression.	Conference abstract
Borissova. FRAX implementation in fracture risk assessment. Is it superior to T-score alone in identifying subjects with probable vertebral fracture?	Conference abstract
Bonaccorsi. A comparison between FRAX and osteoporosis Canada's tool in assessment of major osteoporotic fracture risk in postmenopausal women.	Conference abstract
Crabtree. Impact of UK national guidelines based on FRAX (registered) – comparison with current clinical practice.	Review
Lekamwasam. Application of FRAX model to Sri Lankan postmenopausal women.	Not relevant to review question (not Sri Lankan specific FRAX)
Skowronska-Jozwiak. Comparison of selected methods for fracture risk assessment in postmenopausal women.	Not relevant to review question (treatment threshold)
Kanis. FRAX and the assessment of fracture probability in men and women from the UK.	Did not report relevant data (10 year fracture probability)
Kanis. Development and use of FRAX in osteoporosis.	Review
Strom. FRAX and its applications in health economics – cost-effectiveness and intervention thresholds using bazedoxifene in a Swedish setting as an example.	Not relevant to review question [health economics]
Kanis. FRAX and its applications to clinical practice.	Review
Chen. Vertebral fracture status and the World Health Organisation risk factors for predicting osteoporotic fracture risk.	Updated results published in a more recent paper [Fraser 2011. Fracture prediction and calibration of a Canadian FRAX tool: a population based report from CaMos].
Enrud. A comparison of prediction models for fractures in older women: is more better?	Duplicate
Hippisley-Cox. Predicting risk of osteoporotic fracture in men and women in England and Wales: prospective derivation and validation of QFracture Scores	Duplicate
Skowronska-Jozwiak. Comparison of selected methods for fracture risk assessment in postmenopausal women.	Duplicate
Johansson. BMD, clinical risk factors and their combination for hip fracture prevention.	Based on simulation data

1   ## C.4.3   Studies excluded from the clinical review on BMD

Author, year	Exclusion reason
Abrahamsen B, Vestergaard P, Rud B et al. Ten-year absolute risk of osteoporotic fractures according to BMD T score at menopause: the Danish Osteoporosis Prevention Study. Journal of Bone & Mineral Research. 2006; 21(5):796-800. Ref ID: ABRAHAMSEN2006	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Ahlborg HG, Nguyen ND, Center JR et al. Incidence and	Paper did not report area under curve (results

Author, year	Exclusion reason
risk factors for low trauma fractures in men with prostate cancer. Bone. 2008; 43(3):556-560. Ref ID: AHLBORG2008	reported as odds ratios, risk ratios, etc.)
Akaberi S, Simonsen O, Lindergard B et al. Can DXA predict fractures in renal transplant patients? American Journal of Transplantation. 2008; 8(12):2647-2651. Ref ID: AKABERI2008	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Albertsson D et al. Hip and fragility fracture prediction by 4-item clinical risk score and mobile heel BMD: a women cohort study. BMC Musculoskeletal Disorders. 2010; 11(55) Ref ID: Albertsson2010	Risk score (RR)
Albrand G, Munoz F, Sornay-Rendu E et al. Independent predictors of all osteoporosis-related fractures in healthy postmenopausal women: the OFELY study. Bone. 2003; 32(1):78-85. Ref ID: ALBRAND2003	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Atroshi I, Ahlander F, Billsten M et al. Low calcaneal bone mineral density and the risk of distal forearm fracture in women and men: a population-based case-control study. Bone. 2009; 45(4):789-793. Ref ID: ATROSHI2009	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Augat P, Fan B, Lane NE et al. Assessment of bone mineral at appendicular sites in females with fractures of the proximal femur. Bone. 1998; 22(4):395-402. Ref ID: AUGAT1998	Case-control study
Azagra R, Roca G, Encabo G et al. Prediction of absolute risk of fragility fracture at 10 years in a Spanish population: Validation of the WHO FRAX tool in Spain. BMC Musculoskeletal Disorders. 2011; 12(30) Ref ID: AZAGRA2011	Protocol
Bagger YZ, Tanko LB, Alexandersen P et al. The long-term predictive value of bone mineral density measurements for fracture risk is independent of the site of measurement and the age at diagnosis: results from the Prospective Epidemiological Risk Factors study. Osteoporos Int. 2006; 17(3):471-477. Ref ID: BAGGER2006A	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Bainbridge KE, Sowers M, Lin X et al. Risk factors for low bone mineral density and the 6-year rate of bone loss among premenopausal and perimenopausal women. Osteoporos Int. 2004; 15(6):439-446. Ref ID: BAINBRIDGE2004	Did not report fracture risk as outcome
Banks E, Reeves GK, Beral V et al. Hip fracture incidence in relation to age, menopausal status, and age at menopause: prospective analysis. PLoS Medicine / Public Library of Science. 2009; 6(11):e1000181. Ref ID: BANKS2009	Not relevant to review question (not BMD)
Barrett-Connor E, Siris ES, Wehren LE et al. Osteoporosis and fracture risk in women of different ethnic groups. Journal of Bone and Mineral Research. 2005; 20 (2): 185-194. Ref ID: BARRETTCONNOR2005	Index test not relevant to review protocol (peripheral DXA device)
Bauer DC, Gluer CC, Cauley JA et al. Broadband ultrasound attenuation predicts fractures strongly and independently of densitometry in older women. A prospective study. Study of Osteoporotic Fractures Research Group. Arch Intern Med. 1997; 157(6):629-634. Ref ID: BAUER1997	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)

Author, year	Exclusion reason
Ben Sedrine W, Devogelaer JP, Kaufman JM et al. Evaluation of the simple calculated osteoporosis risk estimation (SCORE) in a sample of white women from Belgium. Bone. 2001; 29(4):374-380. Ref ID: BENSEDRINE2001	Not relevant to review question (assessing risk of osteoporosis rather than fragility fracture)
Bensen R, Adachi JD, Papaioannou A et al. Evaluation of easily measured risk factors in the prediction of osteoporotic fractures. BMC Musculoskeletal Disorders. 2005; 6:47. Ref ID: BENSEN2005	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Berger C, Langsetmo L, Joseph L et al. Association between change in BMD and fragility fracture in women and men. Journal of Bone & Mineral Research. 2009; 24(2):361-370. Ref ID: BERGER2009	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Bergot C, Bousson V, Meunier A et al. Hip fracture risk and proximal femur geometry from DXA scans. Osteoporos Int. 2002; 13(7):542-550. Ref ID: BERGOT2002	Correlation only
Bessette L, Jean S, Davison S et al. Comparison of clinical risk factors for osteoporosis between subjects who sustained a traumatic or a fragility fracture. J Rheumatol. 2010; Conference(var.pagings):6-1280. Ref ID: BESSETTE2010	Abstract
Bjarnason NH, Sarkar S, Duong T et al. Six and twelve month changes in bone turnover are related to reduction in vertebral fracture risk during 3 years of raloxifene treatment in postmenopausal osteoporosis. Osteoporos Int. 2001; 12(11):922-930. Ref ID: BJARNASON2001	Not relevant to review question (treatment response)
Black DM, Bouxsein ML, Marshall LM et al. Proximal femoral structure and the prediction of hip fracture in men: a large prospective study using QCT. Journal of Bone & Mineral Research. 2008; 23(8):1326-1333. Ref ID: BLACK2008	Replaced by Bauer 2007 (more fracture incidence)
Blaizot S, Delmas PD, Marchand F et al. Risk factors for peripheral fractures vary by age in older men--the prospective MINOS study. Osteoporos Int. 2011; 22(6):1755-1764. Ref ID: BLAIZOT2011	BMD with other risk factors
Broe KE, Hannan MT, Kiely DK et al. Predicting fractures using bone mineral density: a prospective study of long-term care residents. Osteoporos Int. 2000; 11(9):765-771. Ref ID: BROE2000	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Bruyere O, Varela AR, Adami S et al. Loss of hip bone mineral density over time is associated with spine and hip fracture incidence in osteoporotic postmenopausal women. Eur J Epidemiol. 2009; 24(11):707-712. Ref ID: BRUYERE2009	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Buist DS, LaCroix AZ, Manfredonia D et al. Identifying postmenopausal women at high risk of fracture in populations: a comparison of three strategies. J Am Geriatr Soc. 2002; 50(6):1031-1038. Ref ID: BUIST2002	Not relevant to review question
Cadarette SM, McIsaac WJ, Hawker GA et al. The validity of decision rules for selecting women with primary osteoporosis for bone mineral density testing. Osteoporos Int. 2004; 15(5):361-366. Ref ID: CADARETTE2004	Not relevant to review question (assessing risk of osteoporosis rather than fragility fracture)
Carroll J, Testa MA, Erat K et al. Modeling fracture risk	Cross-sectional study (Sen, spec)

Author, year	Exclusion reason
using bone density, age, and years since menopause. Am J Prev Med. 1997; 13(6):447-452. Ref ID: CARROLL1997	
Cauley JA, Hochberg MC, Lui LY et al. Long-term risk of incident vertebral fractures. JAMA. 2007; 298(23):2761-2767. Ref ID: CAULEY2007	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Cauley JA, Lui LY, Ensrud KE et al. Bone mineral density and the risk of incident nonspinal fractures in black and white women. JAMA. 2005; 293(17):2102-2108. Ref ID: CAULEY2005A	Age- adjusted BMD
Cauley JA, Zmuda JM, Wisniewski SR et al. Bone mineral density and prevalent vertebral fractures in men and women. Osteoporos Int. 2004; 15(1):32-37. Ref ID: CAULEY2004	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Center JR, Nguyen TV, Pocock NA et al. Volumetric bone density at the femoral neck as a common measure of hip fracture risk for men and women. Journal of Clinical Endocrinology & Metabolism. 2004; 89(6):2776-2782. Ref ID: CENTER2004	Replaced by Nguyen 2008 (Dubbo)
Cevei M, Stoicanescu D. Evaluation of osteoporotic fracture risk according to the risk factors. Archives of the Balkan Medical Union. 2009; 44(3):190-195. Ref ID: CEVEI2009	Abstract
Chandler JM, Zimmerman SI, Girman CJ et al. Low bone mineral density and risk of fracture in white female nursing home residents. JAMA. 2000; 284(8):972-977. Ref ID: CHANDLER2000	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Chapurlat RD, Bauer DC, Nevitt M et al. Incidence and risk factors for a second hip fracture in elderly women. The Study of Osteoporotic Fractures. Osteoporos Int. 2003; 14(2):130-136. Ref ID: CHAPURLAT2003	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Chapurlat RD, Palermo L, Ramsay P et al. Risk of fracture among women who lose bone density during treatment with alendronate. The Fracture Intervention Trial. Osteoporos Int. 2005; 16(7):842-848. Ref ID: CHAPURLAT2005	Not relevant to review question (treatment response)
Chen JS, Sambrook PN, Simpson JM et al. Risk factors for hip fracture among institutionalised older people. Age & Ageing. 2009; 38(4):429-434. Ref ID: CHEN2009A	Not relevant to review question (not BMD)
Chen JS, Simpson JM, March LM et al. Risk factors for fracture following a fall among older people in residential care facilities in Australia. J Am Geriatr Soc. 2008; 56(11):2020-2026. Ref ID: CHEN2008	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Cheng S, Suominen H, Sakari-Rantala R et al. Calcaneal bone mineral density predicts fracture occurrence: a five-year follow-up study in elderly people. Journal of Bone & Mineral Research. 1997; 12(7):1075-1082. Ref ID: CHENG1997C	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Clayton RA, Gaston MS, Ralston SH et al. Association between decreased bone mineral density and severity of distal radial fractures. Journal of Bone & Joint Surgery - American Volume. 2009; 91(3):613-619. Ref ID: CLAYTON2009	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Cleghorn DB, Polley KJ, Bellon MJ et al. Fracture rates as a	Paper did not report area under curve (results

Author, year	Exclusion reason
function of forearm mineral density in normal postmenopausal women: retrospective and prospective data. Calcif Tissue Int. 1991; 49(3):161-163. Ref ID: CLEGHORN1991	reported as odds ratios, risk ratios, etc.)
Colon-Emeric CS, Lyles KW, Su G et al. Clinical risk factors for recurrent fracture after hip fracture: a prospective study. Calcif Tissue Int. 2011; 88(5):425-431. Ref ID: COLONEMERIC2011	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Cook RB, Collins D, Tucker J et al. Comparison of questionnaire and quantitative ultrasound techniques as screening tools for DXA. Osteoporos Int. 2005; 16(12):1565-1575. Ref ID: COOK2005	Not relevant to review question (assessing risk of osteoporosis rather than fragility fracture)
Cranney A, Jamal SA, Tsang JF et al. Low bone mineral density and fracture burden in postmenopausal women. CMAJ Canadian Medical Association Journal. 2007; 177(6):575-580. Ref ID: CRANNEY2007A	Paper did not report area under curve (fracture burden by measuring fracture rate)
Cummings SR, Black D. Bone mass measurements and risk of fracture in Caucasian women: a review of findings from prospective studies. [Review] [26 refs]. Am J Med. 1995; 98(2A):24S-28S. Ref ID: CUMMINGS1995	Review
Cummings SR, Black DM, Nevitt MC et al. Appendicular bone density and age predict hip fracture in women. The Study of Osteoporotic Fractures Research Group. JAMA. 1990; 263(5):665-668. Ref ID: CUMMINGS1990	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Cummings SR, Black DM, Nevitt MC et al. Bone density at various sites for prediction of hip fractures. The Study of Osteoporotic Fractures Research Group. Lancet. 1993; 341(8837):72-75. Ref ID: CUMMINGS1993	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Cummings SR, Cawthon PM, Ensrud KE et al. BMD and risk of hip and nonvertebral fractures in older men: a prospective study and comparison with older women. Journal of Bone & Mineral Research. 2006; 21(10):1550-1556. Ref ID: CUMMINGS2006	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Damilakis J, Papadokostakis G, Perisinakis K et al. Hip fracture discrimination by the Achilles Insight QUS imaging device. Eur J Radiol. 2007; 63(1):59-62. Ref ID: DAMILAKIS2007	Case-control study
Dargent-Molina P, Douchin MN, Cormier C et al. Use of clinical risk factors in elderly women with low bone mineral density to identify women at higher risk of hip fracture: The EPIDOS prospective study. Osteoporos Int. 2002; 13(7):593-599. Ref ID: DARGENTMOLINA2002	Not relevant to review question
Dargent-Molina P, Piault S, Breart G et al. A comparison of different screening strategies to identify elderly women at high risk of hip fracture: results from the EPIDOS prospective study. Osteoporos Int. 2003; 14(12):969-977. Ref ID: DARGENTMOLINA2003	Not relevant to review questionc
Dargent-Molina P, Piault S, Breart G et al. A triage strategy based on clinical risk factors for selecting elderly women for treatment or bone densitometry: the EPIDOS prospective study. Osteoporos Int. 2005; 16(8):898-906. Ref ID: DARGENTMOLINA2005	Paper did not report area under curve
Dargent-Molina P, Piault S, Breart G. Identification of	Not relevant to review question (assessing risk

Author, year	Exclusion reason
women at increased risk of osteoporosis: no need to use different screening tools at different ages. Maturitas. 2006; 54(1):55-64. Ref ID: DARGENT2006	of osteoporosis rather than fragility fracture)
Dargent-Molina P, Schott AM, Hans D et al. Separate and combined value of bone mass and gait speed measurements in screening for hip fracture risk: results from the EPIDOS study. Epidemiologie de l'Osteoporose. Osteoporos Int. 1999; 9(2):188-192. Ref ID: DARGENTMOLINA1999	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Davis SR, Kirby C, Weekes A et al. Simplifying screening for osteoporosis in Australian primary care: The Prospective Screening for Osteoporosis; Australian Primary Care Evaluation of Clinical Tests (PROSPECT) study. Menopause. 2011; 18(1):53-59. Ref ID: DAVIS2011	Not relevant to review question
De Laet CE, van Hout BA, Burger H et al. Bone density and risk of hip fracture in men and women: cross sectional analysis.[Erratum appears in BMJ 1997 Oct 11;315(7113):916]. BMJ. 1997; 315(7102):221-225. Ref ID: DELAET1997	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
De Laet CE, van Hout BA, Burger H et al. Hip fracture prediction in elderly men and women: validation in the Rotterdam study. Journal of Bone & Mineral Research. 1998; 13(10):1587-1593. Ref ID: DELAET1998	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
De LC, Kanis JA, Oden A et al. Body mass index as a predictor of fracture risk: a meta-analysis. Osteoporos Int. 2005; 16(11):1330-1338. Ref ID: DELAET2005	Not relevant to review question (meta-analysis)
Dequeker J, Tobing L, Rutten V et al. Relative risk factors for osteoporotic fracture: a pilot study of the MEDOS questionnaire. Clin Rheumatol. 1991; 10(1):49-53. Ref ID: DEQUEKER1991	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Di MM, Vallero F, Di MR et al. Type of hip fracture in patients with Parkinson disease is associated with femoral bone mineral density. Archives of Physical Medicine & Rehabilitation. 2008; 89(12):2297-2301. Ref ID: DIMONACO2008	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Diamond TH, Bucci J, Kersley JH et al. Osteoporosis and spinal fractures in men with prostate cancer: risk factors and effects of androgen deprivation therapy. J Urol. 2004; 172(2):529-532. Ref ID: DIAMOND2004	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Dincel VE, Sengelen M, Sepici V et al. The association of proximal femur geometry with hip fracture risk. Clin Anat. 2008; 21(6):575-580. Ref ID: DINCEL2008A	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Duan Y, Duboeuf F, Munoz F et al. The fracture risk index and bone mineral density as predictors of vertebral structural failure. Osteoporos Int. 2006; 17(1):54-60. Ref ID: DUAN2006	Nested case-control study
Duboeuf F, Jergas M, Schott AM et al. A comparison of bone densitometry measurements of the central skeleton in post-menopausal women with and without vertebral fracture. Br J Radiol. 1995; 68(811):747-753. Ref ID: DUBOEUF1995	Case-control study
Duppe H, Gardsell P, Johnell O et al. Bone mineral density, muscle strength and physical activity. A population-based	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)

Author, year	Exclusion reason
study of 332 subjects aged 15-42 years. Acta Orthop Scand. 1997; 68(2):97-103. Ref ID: DUPPE1997	
Eklund F, Nordstrom A, Bjornstig U et al. Bone mass, size and previous fractures as predictors of prospective fractures in an osteoporotic referral population. Bone. 2009; 45(4):808-813. Ref ID: EKLUND2009	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
El Maghraoui A, Habbassi A, Ghazi M et al. Validation and comparative evaluation of four osteoporosis risk indexes in Moroccan menopausal women. Archives of Osteoporosis. 2006; 1(1-2):1-6. Ref ID: ELMAGHRAOUI2006	Not relevant to review question (assessing risk of osteoporosis rather than fragility fracture)
El Maghraoui A, Mounach A, Gassim S et al. Vertebral fracture assessment in healthy men: prevalence and risk factors. Bone. 2008; 43(3):544-548. Ref ID: ELMAGHRAOUI2008	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Ensrud KE, Lipschutz RC, Cauley JA et al. Body size and hip fracture risk in older women: a prospective study. Study of Osteoporotic Fractures Research Group. Am J Med. 1997; 103(4):274-280. Ref ID: ENSRUD1997	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
EPOS. The relationship between bone density and incident vertebral fracture in men and women. Journal of Bone & Mineral Research. 2002; 17(12):2214-2221. Ref ID: EPOS2002	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Espallargues M, Sampietro-Colom L, Estrada MD et al. Identifying bone-mass-related risk factors for fracture to guide bone densitometry measurements: a systematic review of the literature. [Review] [176 refs]. Osteoporos Int. 2001; 12(10):811-822. Ref ID: ESPALLARGUES2001	Review
Ettinger B et al. Simple computer model for calculating and reporting 5-year osteoporotic fracture risk in postmenopausal women. Journal of Women's Health. 2005; 159-171. Ref ID: Ettinger2005	Risk score (not AUC)
Faulkner KG, Cummings SR, Black D et al. Simple measurement of femoral geometry predicts hip fracture: the study of osteoporotic fractures. Journal of Bone & Mineral Research. 1993; 8(10):1211-1217. Ref ID: FAULKNER1993	Not AUC (OR)
Finigan J, Greenfield DM, Blumsohn A et al. Risk factors for vertebral and nonvertebral fracture over 10 years: a population-based study in women. Journal of Bone & Mineral Research. 2008; 23(1):75-85. Ref ID: FINIGAN2008	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Formica CA, Nieves JW, Cosman F et al. Comparative assessment of bone mineral measurements using dual X-ray absorptiometry and peripheral quantitative computed tomography. Osteoporos Int. 1998; 8(5):460-467. Ref ID: FORMICA1998	Cross-sectional study
Fox KM, Cummings SR, Williams E et al. Femoral neck and intertrochanteric fractures have different risk factors: a prospective study. Osteoporos Int. 2000; 11(12):1018-1023. Ref ID: FOX2000	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Frediani B, Acciai C, Falsetti P et al. Calcaneus ultrasonometry and dual-energy X-ray absorptiometry for the evaluation of vertebral fracture risk. Calcif Tissue Int.	Case-control study

Author, year	Exclusion reason
2006; 79(4):223-229. Ref ID: FREDIANI2006	
Fujiwara S, Hamaya E, Goto W et al. Vertebral fracture status and the World Health Organization risk factors for predicting osteoporotic fracture risk in Japan. Bone. 2011; 49(3):520-525. Ref ID: FUJIWARA2011	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Fujiwara S, Kasagi F, Masunari N et al. Fracture prediction from bone mineral density in Japanese men and women. Journal of Bone & Mineral Research. 2003; 18(8):1547-1553. Ref ID: FUJIWARA2003	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Gardsell P, Johnell O, Nilsson BE. Predicting fractures in women by using forearm bone densitometry. Calcif Tissue Int. 1989; 44(4):235-242. Ref ID: GARDSELL1989	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Garnero P, Dargent-Molina P, Hans D et al. Do markers of bone resorption add to bone mineral density and ultrasonographic heel measurement for the prediction of hip fracture in elderly women? The EPIDOS prospective study. Osteoporos Int. 1998; 8(6):563-569. Ref ID: GARNERO1998	Replaced by Hans 2004 (EPIDOS)
Geater S, Leelawattana R, Geater A. Validation of the OSTA index for discriminating between high and low probability of femoral neck and lumbar spine osteoporosis among Thai postmenopausal women. J Med Assoc Thai. 2004; 87(11):1286-1292. Ref ID: GEATER2004	Not relevant to review question (assessing risk of osteoporosis rather than fragility fracture)
Ghazi M, Mounach A, Nouijai A et al. Performance of the osteoporosis risk assessment tool in Moroccan men. Clin Rheumatol. 2007; 26(12):2037-2041. Ref ID: GHAZI2007	Not relevant to review question (assessing risk of osteoporosis rather than fragility fracture)
Gluer CC, Eastell R, Reid DM et al. Association of five quantitative ultrasound devices and bone densitometry with osteoporotic vertebral fractures in a population-based sample: the OPUS Study. Journal of Bone & Mineral Research. 2004; 19(5):782-793. Ref ID: GLUER2004	Not AUC
Gluer MG, Minne HW, Gluer CC et al. Prospective identification of postmenopausal osteoporotic women at high vertebral fracture risk by radiography, bone densitometry, quantitative ultrasound, and laboratory findings: results from the PIOS study. Journal of Clinical Densitometry. 2005; 8(4):386-395. Ref ID: GLUER2005	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Gnudi S, Gualtieri G, Malavolta N. Simultaneous densitometry and quantitative bone sonography in the estimation of osteoporotic fracture risk. Br J Radiol. 1998; 71(846):625-629. Ref ID: GNUDI1998	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Gnudi S, Malavolta N, Lisi L et al. Bone mineral density and bone loss measured at the radius to predict the risk of nonspinal osteoporotic fracture. Journal of Bone & Mineral Research. 2001; 16(6):1130-1135. Ref ID: GNUDI2001	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Gnudi S, Malavolta N. Comparison between T-score-based diagnosis of osteoporosis and specific skeletal site measurements: prognostic value for predicting fracture risk. Journal of Clinical Densitometry. 2003; 6(3):267-273. Ref ID: GNUDI2003	Not relevant to review question (assessing risk of osteoporosis rather than fragility fracture)
Gnudi S, Ripamonti C, Malavolta N. Quantitative ultrasound and bone densitometry to evaluate the risk of	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)

Author, year	Exclusion reason
nonspine fractures: a prospective study. Osteoporos Int. 2000; 11(6):518-523. Ref ID: GNUDI2000	
Gnudi S, Sitta E. Clinical risk factor evaluation to defer postmenopausal women from bone mineral density measurement: An Italian study. Journal of Clinical Densitometry. 2009; 8(2):9-205. Ref ID: GNUDI2009	Not relevant to review question (assessing risk of osteoporosis rather than fragility fracture)
Gomez AC, Diaz CM, Hawkins CF et al. Femoral bone mineral density, neck-shaft angle and mean femoral neck width as predictors of hip fracture in men and women. Osteoporos Int. 2000; 11(8):714-720. Ref ID: GOMEZ2000	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Gonnelli S, Caffarelli C, Maggi S et al. Utility of QUS assessment in COPD patients treated with GCS: The EOLO study. Bone. 2009; Conference(var.pagings):S144-S145. Ref ID: GONNELLI2009	Conference abstract
Gonnelli S, Cepollaro C, Gennari L et al. Quantitative ultrasound and dual-energy X-ray absorptiometry in the prediction of fragility fracture in men. Osteoporos Int. 2005; 16(8):963-968. Ref ID: GONNELLI2005	Not relevant to review question (assessing risk of osteoporosis rather than fragility fracture)
Grados F, Fechtenbaum J, Flipon E et al. Radiographic methods for evaluating osteoporotic vertebral fractures. [Review] [61 refs]. Joint, Bone, Spine: Revue du Rhumatisme. 2009; 76(3):241-247. Ref ID: GRADOS2009	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Grampp S, Genant HK, Mathur A et al. Comparisons of noninvasive bone mineral measurements in assessing age-related loss, fracture discrimination, and diagnostic classification. Journal of Bone & Mineral Research. 1997; 12(5):697-711. Ref ID: GRAMPP1997	Cross-sectional study
Greenspan SL, Myers ER, Maitland LA et al. Fall severity and bone mineral density as risk factors for hip fracture in ambulatory elderly. JAMA. 1994; 271(2):128-133. Ref ID: GREENSPAN1994A	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Grgurevic A, Gledovic Z, Vujasinovic-Stupar N. Factors associated with postmenopausal osteoporosis: a case-control study of Belgrade women. Women & Health. 2010; 50(5):475-490. Ref ID: GRGUREVIC2010	Not relevant to review question (not BMD)
Gronholz MJ. Prevention, diagnosis, and management of osteoporosis-related fracture: a multifactoral osteopathic approach. [Review] [90 refs]. J Am Osteopath Assoc. 2008; 108(10):575-585. Ref ID: GRONHOLZ2008	Review
Gudmundsdottir SL, Oskarsdottir D, Indridason OS et al. Risk factors for bone loss in the hip of 75-year-old women: a 4-year follow-up study. Maturitas. 2010; 67(3):256-261. Ref ID: GUDMUNDSDOTTIR2010	Did not report fracture as outcome
Hain SF. DXA scanning for osteoporosis. Clinical Medicine, Journal of the Royal College of Physicians of London. 2006; 6(3):254-258. Ref ID: HAIN2006	Review
Hamdy RC. Fracture risk assessment in postmenopausal women. [Review]. Reviews in Endocrine & Metabolic Disorders. 2010; 11(4):229-236. Ref ID: HAMDY2010	Review
Hawker GA, Jamal SA, Ridout R et al. A clinical prediction rule to identify premenopausal women with low bone mass. Osteoporos Int. 2002; 13(5):400-406. Ref ID: HAWKER2002	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)

Author, year	Exclusion reason
Henry MJ, Pasco JA, Sanders KM et al. Fracture Risk (FRISK) Score: Geelong Osteoporosis Study. Radiology. 2006; 241(1):190-196. Ref ID: HENRY2006	Risk score (cross-sectional and cohort study)
Hochberg MC, Ross PD, Black D et al. Larger increases in bone mineral density during alendronate therapy are associated with a lower risk of new vertebral fractures in women with postmenopausal osteoporosis. Fracture Intervention Trial Research Group. Arthritis Rheum. 1999; 42(6):1246-1254. Ref ID: HOCHBERG1999	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Hodsman AB, Leslie WD, Tsang JF et al. 10-year probability of recurrent fractures following wrist and other osteoporotic fractures in a large clinical cohort: an analysis from the Manitoba Bone Density Program. Arch Intern Med. 2008; 168(20):2261-2267. Ref ID: HODSMAN2008	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Holmberg AH, Johnell O, Nilsson PM et al. Risk factors for fragility fracture in middle age. A prospective population-based study of 33,000 men and women.[Erratum appears in Osteoporos Int. 2006;17(11):1704]. Osteoporos Int. 2006; 17(7):1065-1077. Ref ID: HOLMBERG2006	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Hongsdusit N, Von MD, Barrett-Connor E. A comparison between peripheral BMD and central BMD measurements in the prediction of spine fractures in men. Osteoporos Int. 2006; 17(6):872-877. Ref ID: HONGSDUSIT2006	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Huang C, Ross PD, Wasnich RD. Short-term and long-term fracture prediction by bone mass measurements: a prospective study. Journal of Bone & Mineral Research. 1998; 13(1):107-113. Ref ID: HUANG1998A	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Huang C, Ross PD, Yates AJ et al. Prediction of fracture risk by radiographic absorptiometry and quantitative ultrasound: a prospective study. Calcif Tissue Int. 1998; 63(5):380-384. Ref ID: HUANG1998	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Hung LK, Wu HT, Leung PC et al. Low BMD is a risk factor for low-energy Colles' fractures in women before and after menopause. Clinical Orthopaedics & Related Research. 2005;(435):219-225. Ref ID: HUNG2005	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Itoh S, Tomioka H, Tanaka J et al. Relationship between bone mineral density of the distal radius and ulna and fracture characteristics. Journal of Hand Surgery - American Volume. 2004; 29(1):123-130. Ref ID: ITOH2004	Not relevant to review question
Jager PL, Jonkman S, Koolhaas W et al. Combined vertebral fracture assessment and bone mineral density measurement: a new standard in the diagnosis of osteoporosis in academic populations. Osteoporos Int. 2011; 22(4):1059-1068. Ref ID: JAGER2011	Risk of osteoporosis as outcome, not fracture
Jagtap VR, Ganu JV, Nagane NS. BMD and serum intact osteocalcin in postmenopausal osteoporosis women. Indian Journal of Clinical Biochemistry. 2011; 26(1):70-73. Ref ID: JAGTAP2011	Did not report fracture risk as outcome
Jergas M, Genant HK. Spinal and femoral DXA for the assessment of spinal osteoporosis. Calcif Tissue Int. 1997; 61(5):351-357. Ref ID: JERGAS1997A	Case-control study
Jergas M, Gluer CC. Assessment of fracture risk by bone	Review

Author, year	Exclusion reason
density measurements. [Review] [69 refs]. Semin Nucl Med. 1997; 27(3):261-275. Ref ID: JERGAS1997	
Jitapunkul S, Yuktananandana P, Parkpian V. Risk factors of hip fracture among Thai female patients. J Med Assoc Thai. 2001; 84(11):1576-1581. Ref ID: JITAPUNKUL2001	Not relevant to review question (not BMD)
Johnell O, Kanis JA, Black DM et al. Associations between baseline risk factors and vertebral fracture risk in the Multiple Outcomes of Raloxifene Evaluation (MORE) Study. Journal of Bone & Mineral Research. 2004; 19(5):764-772. Ref ID: JOHNELL2004	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Johnell O, Kanis JA, Oden A et al. Predictive value of BMD for hip and other fractures.[Erratum appears in J Bone Miner Res. 2007 May;22(5):774]. Journal of Bone & Mineral Research. 2005; 20(7):1185-1194. Ref ID: JOHNELL2005B	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Jokinen H, Pulkkinen P, Keinanen-Kiukaanniemi S et al. Risk factors for cervical and trochanteric hip fractures; A 10-year follow-up study. Bone. 2009; Conference(var.pagings):S107. Ref ID: JOKINEN2009	Conference abstract
Jokinen H, Pulkkinen P, Korpelainen J et al. Risk factors for cervical and trochanteric hip fractures in elderly women: a population-based 10-year follow-up study. Calcif Tissue Int. 2010; 87(1):44-51. Ref ID: JOKINEN2010	Not relevant to review question (not BMD)
Kanis JA, Johnell O, Oden A et al. The use of multiple sites for the diagnosis of osteoporosis. Osteoporos Int. 2006; 17(4):527-534. Ref ID: KANIS2006A	Risk of osteoporosis as outcome
Kanis JA, Oden A, Johnell O et al. The use of clinical risk factors enhances the performance of BMD in the prediction of hip and osteoporotic fractures in men and women. [Review] [79 refs]. Osteoporos Int. 2007; 18(8):1033-1046. Ref ID: KANIS2007A	Review
Kaptoge S, Armbrecht G, Felsenberg D et al. Whom to treat? The contribution of vertebral X-rays to risk-based algorithms for fracture prediction. Results from the European Prospective Osteoporosis Study. Osteoporos Int. 2006; 17(9):1369-1381. Ref ID: KAPTOGE2006	Not relevant to review question (model without BMD)
Kaptoge S, Benevolenskaya LI, Bhalla AK et al. Low BMD is less predictive than reported falls for future limb fractures in women across Europe: results from the European Prospective Osteoporosis Study. Bone. 2005; 36(3):387-398. Ref ID: KAPTOGE2005	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Kiebzak GM, Binkley N, Lewiecki EM et al. Diagnostic agreement at the total hip using different DXA systems and the NHANES III database. Journal of Clinical Densitometry. 2007; 10(2):132-137. Ref ID: KIEBZAK2007	Did not report fracture as outcome
Kim YM, Hyun NR, Shon HS et al. Assessment of clinical risk factors to validate the probability of osteoporosis and subsequent fractures in Korean women. Calcif Tissue Int. 2008; 83(6):380-387. Ref ID: KIM2008	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Kroger H, Huopio J, Honkanen R et al. Prediction of fracture risk using axial bone mineral density in a perimenopausal population: a prospective study. Journal of Bone & Mineral Research. 1995; 10(2):302-306. Ref ID:	Not AUC (OR)

Author, year	Exclusion reason
KROGER1995	
Kumagai S, Kawano S, Atsumi T et al. Vertebral fracture and bone mineral density in women receiving high dose glucocorticoids for treatment of autoimmune diseases.[Erratum appears in J Rheumatol. 2005 Jul;32(7):1414 Note: Kanai, Yoshiki [corrected to Kanai, Yoshinori]]. J Rheumatol. 2005; 32(5):863-869. Ref ID: KUMAGAI2005	Cross-sectional study
Kung AW, Lee KK, Ho AY et al. Ten-year risk of osteoporotic fractures in postmenopausal Chinese women according to clinical risk factors and BMD T-scores: a prospective study. Journal of Bone & Mineral Research. 2007; 22(7):1080-1087. Ref ID: KUNG2007	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
LaFleur J, McAdam-Marx C, Alder SS et al. Clinical risk factors for fracture among postmenopausal patients at risk for fracture: a historical cohort study using electronic medical record data. Journal of Bone & Mineral Metabolism. 2011; 29(2):193-200. Ref ID: LAFLEUR2011	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
LaFleur J, McAdam-Marx C, Kirkness C et al. Clinical risk factors for fracture in postmenopausal osteoporotic women: a review of the recent literature. [Review] [93 refs]. Ann Pharmacother. 2008; 42(3):375-386. Ref ID: LAFLEUR2008	Review
Langsetmo L, Hanley DA, Kreiger N et al. Geographic variation of bone mineral density and selected risk factors for prediction of incident fracture among Canadians 50 and older. Bone. 2008; 43(4):672-678. Ref ID: LANGSETMO2008	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Langsetmo L, Morin S, Kovacs CS et al. Determining whether women with osteopenic bone mineral density have low, moderate, or high clinical fracture risk. Menopause. 2010; 17(5):1010-1016. Ref ID: LANGSETMO2010	BMD with other risk factors (age)
Lee SH, Dargent-Molina P, Breart G et al. Risk factors for fractures of the proximal humerus: results from the EPIDOS prospective study. Journal of Bone & Mineral Research. 2002; 17(5):817-825. Ref ID: LEE2002A	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Lee SH, Khang YH, Lim KH et al. Clinical risk factors for osteoporotic fracture: a population-based prospective cohort study in Korea. Journal of Bone & Mineral Research. 2010; 25(2):369-378. Ref ID: LEE2010B	Not relevant to review question (not BMD)
Legrand E, Chappard D, Pascaretti C et al. Bone mineral density and vertebral fractures in men. Osteoporos Int. 1999; 10(4):265-270. Ref ID: LEGRAND1999	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Legrand E, Chappard D, Pascaretti C et al. Trabecular bone microarchitecture, bone mineral density, and vertebral fractures in male osteoporosis. Journal of Bone & Mineral Research. 2000; 15(1):13-19. Ref ID: LEGRAND2000	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Leslie WD, Lix LM, Manitoba Bone Density Program. Absolute fracture risk assessment using lumbar spine and femoral neck bone density measurements: derivation and validation of a hybrid system. Journal of Bone & Mineral Research. 2011; 26(3):460-467. Ref ID: LESLIE2011B	Not relevant to review question (not BMD alone)

Author, year	Exclusion reason
Leslie WD, Lix LM, Manitoba Bone Density Program. Simplified 10-year absolute fracture risk assessment: a comparison of men and women. Journal of Clinical Densitometry. 2010; 13(2):141-146. Ref ID: LESLIE2010	Not relevant to review question
Leslie WD, Lix LM, Tsang JF et al. Single-site vs multisite bone density measurement for fracture prediction. Arch Intern Med. 2007; 167(15):1641-1647. Ref ID: LESLIE2007	Replaced by Leslie 2007a (Manitoba)
Leslie WD, Pahlavan PS, Roe EB et al. Bone density and fragility fractures in patients with developmental disabilities. Osteoporos Int. 2009; 20(3):379-383. Ref ID: LESLIE2009A	Cross-sectional study
Leslie WD, Tsang JF, Caetano PA et al. Effectiveness of bone density measurement for predicting osteoporotic fractures in clinical practice. Journal of Clinical Endocrinology & Metabolism. 2007; 92(1):77-81. Ref ID: LESLIE2007D	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Leslie WD, Tsang JF, Caetano PA et al. Number of osteoporotic sites and fracture risk assessment: a cohort study from the Manitoba Bone Density Program. Journal of Bone & Mineral Research. 2007; 22(3):476-483. Ref ID: LESLIE2007C	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Leslie WD, Tsang JF, Lix LM. Effect of total hip bone area on osteoporosis diagnosis and fractures. Journal of Bone & Mineral Research. 2008; 23(9):1468-1476. Ref ID: LESLIE2008A	Replaced by Leslie 2007a
Lespessailles E, Poupon S, Adriambelosoa N et al. Glucocorticoid-induced osteoporosis: is the bone density decrease the only explanation? Joint, Bone, Spine: Revue du Rhumatisme. 2000; 67(2):119-126. Ref ID: LESPESSAILLES2000	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Lewis CE, Ewing SK, Taylor BC et al. Predictors of non-spine fracture in elderly men: the MrOS study. Journal of Bone & Mineral Research. 2007; 22(2):211-219. Ref ID: LEWIS2007	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Lillholm M, Ghosh A, Pettersen PC et al. Vertebral fracture risk (VFR) score for fracture prediction in postmenopausal women. Osteoporos Int. 2011; 22(7):2119-2128. Ref ID: LILLHOLM2011	Case-control study
Link TM, Vieth V, Matheis J et al. Bone structure of the distal radius and the calcaneus vs BMD of the spine and proximal femur in the prediction of osteoporotic spine fractures. Eur Radiol. 2002; 12(2):401-408. Ref ID: LINK2002	Case-control study
Lo JC, Pressman AR, Chandra M et al. Fracture risk tool validation in an integrated healthcare delivery system. Am J Manag Care. 2011; 17(3):188-194. Ref ID: LO2011	Not relevant to review question (not BMD alone)
Lopes JB, Danilevicius CF, Takayama L et al. Prevalence and risk factors of radiographic vertebral fracture in Brazilian community-dwelling elderly. Osteoporos Int. 2011; 22(2):711-719. Ref ID: LOPES2011	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Lopez AM, Pena MA, Hernandez R et al. Fracture risk in patients with prostate cancer on androgen deprivation therapy. Osteoporos Int. 2005; 16(6):707-711. Ref ID:	Not relevant to review question (not BMD)

Author, year	Exclusion reason
LOPEZ2005	
Lynn HS, Woo J, Leung PC et al. An evaluation of osteoporosis screening tools for the osteoporotic fractures in men (MrOS) study. Osteoporos Int. 2008; 19(7):1087-1092. Ref ID: LYNN2008	Not relevant to review question (assessing risk of osteoporosis rather than fragility fracture)
Machado P, da Silva JA. Performance of decision algorithms for the identification of low bone mineral density in Portuguese postmenopausal women. Acta Reumatologica Portuguesa. 2008; 33(3):314-328. Ref ID: MACHADO2008	Not relevant to review question (assessing risk of osteoporosis rather than fragility fracture)
Mackey DC, Eby JG, Harris F et al. Prediction of clinical non-spine fractures in older black and white men and women with volumetric BMD of the spine and areal BMD of the hip: the Health, Aging, and Body Composition Study*. Journal of Bone & Mineral Research. 2007; 22(12):1862-1868. Ref ID: MACKEY2007	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Marcus R, Wang O, Satterwhite J et al. The skeletal response to teriparatide is largely independent of age, initial bone mineral density, and prevalent vertebral fractures in postmenopausal women with osteoporosis. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research. 2003; 18(1):18-23. Ref ID: MARCUS2003	Not relevant to review question (treatment response)
Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. BMJ. 1996; 312(7041):1254-1259. Ref ID: MARSHALL1996	Meta-analysis
Mayhew P, Kaptoge S, Loveridge N et al. Discrimination between cases of hip fracture and controls is improved by hip structural analysis compared to areal bone mineral density. An ex vivo study of the femoral neck. Bone. 2004; 34(2):352-361. Ref ID: MAYHEW2004	Case-control study
McCloskey EV, Vasireddy S, Threlkeld J et al. Vertebral fracture assessment (VFA) with a densitometer predicts future fractures in elderly women unselected for osteoporosis. Journal of Bone & Mineral Research. 2008; 23(10):1561-1568. Ref ID: MCCLOSKEY2008	Not relevant to review question – not BMD
Melamed A, Vittinghoff E, Sriram U et al. BMD reference standards among South Asians in the United States. Journal of Clinical Densitometry. 2010; 13(4):379-384. Ref ID: MELAMED2010	Not relevant to review question
Melton LJ, III, Atkinson EJ, O'Fallon WM et al. Long-term fracture prediction by bone mineral assessed at different skeletal sites. Journal of Bone & Mineral Research. 1993; 8(10):1227-1233. Ref ID: MELTON1993	Not AUC (RR)
Melton LJ, III, Beck TJ, Amin S et al. Contributions of bone density and structure to fracture risk assessment in men and women. Osteoporos Int. 2005; 16(5):460-467. Ref ID: MELTON2005	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Melton LJ, III, Christen D, Riggs BL et al. Assessing forearm fracture risk in postmenopausal women. Osteoporos Int. 2010; 21(7):1161-1169. Ref ID: MELTON2010	Case-control study
Melton LJ, III, Crowson CS, O'Fallon WM et al. Relative	Paper did not report area under curve (results

Author, year	Exclusion reason
contributions of bone density, bone turnover, and clinical risk factors to long-term fracture prediction. Journal of Bone & Mineral Research. 2003; 18(2):312-318. Ref ID: MELTON2003	reported as odds ratios, risk ratios, etc.)
Miller PD, Barlas S, Brenneman SK et al. An approach to identifying osteopenic women at increased short-term risk of fracture. Arch Intern Med. 2004; 164(10):1113-1120. Ref ID: MILLER2004	Descriptive study
Miller RG, Segal JB, Ashar BH et al. High prevalence and correlates of low bone mineral density in young adults with sickle cell disease. Am J Hematol. 2006; 81(4):236-241. Ref ID: MILLER2006	Not relevant to review question
Moayyeri A, Kaptoge S, Dalzell N et al. Is QUS or DXA better for predicting the 10-year absolute risk of fracture? Journal of Bone & Mineral Research. 2009; 24(7):1319-1325. Ref ID: MOAYYERI2009	Not relevant to review question (not BMD alone)
Morden NE, Sullivan SD, Bartle B et al. Skeletal health in men with chronic lung disease: rates of testing, treatment, and fractures. Osteoporos Int. 2011; 22(6):1855-1862. Ref ID: MORDEN2011	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Morin S, Tsang JF, Leslie WD. Weight and body mass index predict bone mineral density and fractures in women aged 40 to 59 years. Osteoporos Int. 2009; 20(3):363-370. Ref ID: MORIN2009	Not relevant to review question (assessing risk of osteoporosis rather than fragility fracture)
Morse LR, Geller A, Battaglino RA et al. Barriers to providing dual energy x-ray absorptiometry services to individuals with spinal cord injury. American Journal of Physical Medicine & Rehabilitation. 2009; 88(1):57-60. Ref ID: MORSE2009	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Mussolino ME, Looker AC, Madans JH et al. Risk factors for hip fracture in white men: the NHANES I Epidemiologic Follow-up Study. Journal of Bone & Mineral Research. 1998; 13(6):918-924. Ref ID: MUSSOLINO1998	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Nahas EA, Kawakami MS, Nahas-Neto J et al. Assessment of risk factors for low bone mineral density in Brazilian postmenopausal women. Climacteric. 2011; 14(2):220-227. Ref ID: NAHAS2011	Not relevant to review question (assessing risk of osteoporosis rather than fragility fracture)
Nakaoka D, Sugimoto T, Kaji H et al. Determinants of bone mineral density and spinal fracture risk in postmenopausal Japanese women. Osteoporos Int. 2001; 12(7):548-554. Ref ID: NAKAOKA2001	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Naves M, Diaz-Lopez JB, Gomez C et al. Prevalence of osteoporosis in men and determinants of changes in bone mass in a non-selected Spanish population. Osteoporos Int. 2005; 16(6):603-609. Ref ID: NAVES2005A	Not relevant to review question (did not report fracture risk as outcome)
Neumann T, Samann A, Lodes S et al. Glycaemic control is positively associated with prevalent fractures but not with bone mineral density in patients with Type 1 diabetes. Diabet Med. 2011; 28(7):872-875. Ref ID: NEUMANN2011	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Nevitt MC, Johnell O, Black DM et al. Bone mineral density predicts non-spine fractures in very elderly women. Osteoporos Int. 1994; 4(6):325-331. Ref ID: NEVITT1994B	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Nguyen ND, Frost SA, Center JR et al. Development of a	Risk score

Author, year	Exclusion reason
nomogram for individualizing hip fracture risk in men and women. Osteoporos Int. 2007; 18(8):1109-1117. Ref ID: NGUYEN2007	
Nguyen ND, Pongchaiyakul C, Center JR et al. Identification of high-risk individuals for hip fracture: a 14-year prospective study. Journal of Bone & Mineral Research. 2005; 20(11):1921-1928. Ref ID: NGUYEN2005A	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Nguyen T, Sambrook P, Kelly P et al. Prediction of osteoporotic fractures by postural instability and bone density. BMJ. 1993; 307(6912):1111-1115. Ref ID: NGUYEN1993	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Nguyen TV, Center JR, Pocock NA et al. Limited utility of clinical indices for the prediction of symptomatic fracture risk in postmenopausal women. Osteoporos Int. 2004; 15(1):49-55. Ref ID: NGUYEN2004	Risk score
Nguyen TV, Eisman JA, Kelly PJ et al. Risk factors for osteoporotic fractures in elderly men. Am J Epidemiol. 1996; 144(3):255-263. Ref ID: NGUYEN1996	Paper reported BMD as outcome
Nordstrom P, Eklund F, Bjornstig U et al. Do Both Areal BMD and Injurious Falls Explain the Higher Incidence of Fractures in Women than in Men? Calcif Tissue Int. 2011; 89(3):203-210. Ref ID: NORDSTROM2011	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Nyquist F, Gardsell P, Sernbo I et al. Assessment of sex hormones and bone mineral density in relation to occurrence of fracture in men: a prospective population-based study. Bone. 1998; 22(2):147-151. Ref ID: NYQUIST1998	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Ofluoglu D, Gunduz OH, Bekirolu N et al. A method for determining the grade of osteoporosis based on risk factors in postmenopausal women. Clin Rheumatol. 2005; 24(6):606-611. Ref ID: OFLUOGLU2005	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Oyen J, Brudvik C, Gjesdal CG et al. Osteoporosis as a risk factor for distal radial fractures: a case-control study. Journal of Bone & Joint Surgery - American Volume. 2011; 93(4):348-356. Ref ID: OYEN2011B	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Oyen J, Rohde G, Hochberg M et al. Low bone mineral density is a significant risk factor for low-energy distal radius fractures in middle-aged and elderly men: a case-control study. BMC Musculoskeletal Disorders. 2011; 12(67) Ref ID: OYEN2011	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Pande I, O'Neill TW, Pritchard C et al. Bone mineral density, hip axis length and risk of hip fracture in men: results from the Cornwall Hip Fracture Study. Osteoporos Int. 2000; 11(10):866-870. Ref ID: PANDE2000	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Papaioannou A, Joseph L, Ioannidis G et al. Risk factors associated with incident clinical vertebral and nonvertebral fractures in postmenopausal women: the Canadian Multicentre Osteoporosis Study (CaMos). Osteoporos Int. 2005; 16(5):568-578. Ref ID: PAPAIOANNOU2005	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Park HM, Sedrine WB, Reginster JY et al. Korean experience with the OSTA risk index for osteoporosis: a validation study. Journal of Clinical Densitometry. 2003;	Not relevant to review question (assessing risk of osteoporosis rather than fragility fracture)

Author, year	Exclusion reason
6(3):247-250. Ref ID: PARK2003	
Partanen J, Heikkinen J, Jamsa T et al. Characteristics of lifetime factors, bone metabolism, and bone mineral density in patients with hip fracture. Journal of Bone & Mineral Metabolism. 2002; 20(6):367-375. Ref ID: PARTANEN2002	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Peacock M, Turner CH, Liu G et al. Better discrimination of hip fracture using bone density, geometry and architecture. Osteoporos Int. 1995; 5(3):167-173. Ref ID: PEACOCK1995	Case-control study
Peretz A, De M, V, Moris M et al. Evaluation of quantitative ultrasound and dual X-Ray absorptiometry measurements in women with and without fractures. Journal of Clinical Densitometry. 1999; 2(2):127-133. Ref ID: PERETZ1999	Cross-sectional (Sen, spec)
Persson GR, Berglund J, Persson RE et al. Prediction of hip and hand fractures in older persons with or without a diagnosis of periodontitis. Bone. 2011; 48(3):552-556. Ref ID: PERSSON2011	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Peter I, Crosier MD, Yoshida M et al. Associations of APOE gene polymorphisms with bone mineral density and fracture risk: A meta-analysis. Osteoporos Int. 2011; 22(4):1199-1209. Ref ID: PETER2011	Not relevant to review question
Pinheiro MM, Reis Neto ET, Machado FS et al. Risk factors for osteoporotic fractures and low bone density in pre and postmenopausal women. Rev Saude Publica. 2010; 44(3):479-485. Ref ID: PINHEIRO2010	Cross-sectional descriptive study
Pongchaiyakul C, Nguyen ND, Eisman JA et al. Clinical risk indices, prediction of osteoporosis, and prevention of fractures: diagnostic consequences and costs. Osteoporos Int. 2005; 16(11):1444-1450. Ref ID: PONGCHAIYAKUL2005	Not relevant to review question (assessing risk of osteoporosis rather than fragility fracture)
Rabier B, Heraud A, Grand-Lenoir C et al. A multicentre, retrospective case-control study assessing the role of trabecular bone score (TBS) in menopausal Caucasian women with low areal bone mineral density (BMDa): Analysing the odds of vertebral fracture. Bone. 2010; 46(1):176-181. Ref ID: RABIER2010	Case-control study
Rasheed A, Khurshid R, Aftab L. Bone mass measurement and factors associated with risk of fracture in a group of peri- and postmenoupasal women. Journal of Ayub Medical College, Abbottabad: JAMC. 2008; 20(1):48-51. Ref ID: RASHEED2008	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Reginster JY, Ben SW, Viethel P et al. Validation of OSIRIS, a prescreening tool for the identification of women with an increased risk of osteoporosis. Gynecol Endocrinol. 2004; 18(1):3-8. Ref ID: REGINSTER2004	Not relevant to review question (assessing risk of osteoporosis rather than fragility fracture)
Rehman Q, Lang T, Modin G et al. Quantitative computed tomography of the lumbar spine, not dual x-ray absorptiometry, is an independent predictor of prevalent vertebral fractures in postmenopausal women with osteopenia receiving long-term glucocorticoid and hormone-replacement therapy. Arthritis & Rheumatism.	Not relevant to review question (prevalent vertebral fracture as outcome)

Author, year	Exclusion reason
2002; 46(5):1292-1297. Ref ID: REHMAN2002	
Rivadeneira F, Zillikens MC, De Laet CE et al. Femoral neck BMD is a strong predictor of hip fracture susceptibility in elderly men and women because it detects cortical bone instability: the Rotterdam Study. Journal of Bone & Mineral Research. 2007; 22(11):1781-1790. Ref ID: RIVADENEIRA2007	Not relevant to review question (not BMD alone)
Robbins JA, Schott AM, Garnero P et al. Risk factors for hip fracture in women with high BMD: EPIDOS study. Osteoporos Int. 2005; 16(2):149-154. Ref ID: ROBBINS2005	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Rodriguez-Soto AE, Fritscher KD, Schuler B et al. Texture analysis, bone mineral density, and cortical thickness of the proximal femur: fracture risk prediction. J Comput Assist Tomogr. 2010; 34(6):949-957. Ref ID: RODRIGUEZSOTO2010	Case-control study
Romagnoli E, Del FR, Russo S et al. Secondary osteoporosis in men and women: Clinical challenge of an unresolved issue. J Rheumatol. 2011; 38(8):1671-1679. Ref ID: ROMAGNOLI2011	Not relevant to review question
Ross PD, Genant HK, Davis JW et al. Predicting vertebral fracture incidence from prevalent fractures and bone density among non-black, osteoporotic women. Osteoporos Int. 1993; 3(3):120-126. Ref ID: ROSS1993A	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Ross PD, Huang C, Davis JW et al. Vertebral dimension measurements improve prediction of vertebral fracture incidence. Bone. 1995; 16(4 Suppl):257S-262S. Ref ID: ROSS1995	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Ross PD, Kress BC, Parson RE et al. Serum bone alkaline phosphatase and calcaneus bone density predict fractures: a prospective study. Osteoporos Int. 2000; 11(1):76-82. Ref ID: ROSS2000	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Roux C, Briot K, Horlait S et al. Assessment of non-vertebral fracture risk in postmenopausal women. Ann Rheum Dis. 2007; 66(7):931-935. Ref ID: ROUX2007	Not relevant to review question (not BMD alone)
Rozas-Moreno P, Reyes-Garca R, Luque-Fernandez I et al. Utility of FRAX index in the evaluation of type 2 diabetes patients. Bone. 2011; Conference(var.pagings):S198. Ref ID: ROZASMORENO2011	Conference abstract
Saeed I, Carpenter RD, Leblanc AD et al. Quantitative computed tomography reveals the effects of race and sex on bone size and trabecular and cortical bone density. Journal of Clinical Densitometry. 2009; 12(3):330-336. Ref ID: SAEED2009	Did not report risk of fracture as outcome
Sakai A, Oshige T, Zenke Y et al. Association of bone mineral density with deformity of the distal radius in low-energy Colles' fractures in Japanese women above 50 years of age. Journal of Hand Surgery - American Volume. 2008; 33(6):820-826. Ref ID: SAKAI2008	Not relevant to review question
Sakkers R, Kok D, Engelbert R et al. Skeletal effects and functional outcome with olpadronate in children with osteogenesis imperfecta: a 2-year randomised placebo-controlled study. Lancet. 2004; 363(9419):1427-1431. Ref	Not relevant to review question (treatment response in children)

Author, year	Exclusion reason
ID: SAKKERS2004	
Salaffi F, Silveri F, Stancati A et al. Development and validation of the osteoporosis prescreening risk assessment (OPERA) tool to facilitate identification of women likely to have low bone density. Clin Rheumatol. 2003; 24(3):3-211. Ref ID: SALAFFI2003	Not relevant to review question (assessing risk of osteoporosis rather than fragility fracture)
Sarkar S, Mitlak BH, Wong M et al. Relationships between bone mineral density and incident vertebral fracture risk with raloxifene therapy. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research. 2002; 17(1):1-10. Ref ID: SARKAR2002	Not relevant to review question (treatment response measured by change in BMD)
Sato Y, Kanoko T, Satoh K et al. Risk factors for hip fracture among elderly patients with Alzheimer's disease. J Neurol Sci. 2004; 223(2):107-112. Ref ID: SATO2004	Not measure of effect
Schneider DL, Worley K, Beard MK et al. The primary care osteoporosis risk of fracture screening (POROS) study: design and baseline characteristics. Contemporary Clinical Trials. 2010; 31(4):336-344. Ref ID: SCHNEIDER2010	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Schneyer CR, Lopez H, Concannon M et al. Assessing population risk for postmenopausal osteoporosis: a new strategy using data from the Behavioral Risk Factor Surveillance System (BRFSS). Journal of Bone & Mineral Research. 2008; 23(1):151-158. Ref ID: SCHNEYER2008	Not relevant to review question (assessing risk of osteoporosis rather than fragility fracture)
Schott AM, Cormier C, Hans D et al. How hip and whole-body bone mineral density predict hip fracture in elderly women: the EPIDOS Prospective Study. Osteoporos Int. 1998; 8(3):247-254. Ref ID: SCHOTT1998	Replaced by Hans 2004 (EPIDOS)
Schott AM, Kassai KB, Hans D et al. Should age influence the choice of quantitative bone assessment technique in elderly women? The EPIDOS study. Osteoporos Int. 2004; 15(3):196-203. Ref ID: SCHOTT2004	Replaced by Hans 2004 (EPIDOS)
Schott AM, Weill-Engerer S, Hans D et al. Ultrasound discriminates patients with hip fracture equally well as dual energy X-ray absorptiometry and independently of bone mineral density. Journal of Bone & Mineral Research. 1995; 10(2):243-249. Ref ID: SCHOTT1995	Case-control study (Sen, spec)
Schuit SC, van der Klift M, Weel AE et al. Fracture incidence and association with bone mineral density in elderly men and women: the Rotterdam Study.[Erratum appears in Bone. 2006 Apr;38(4):603]. Bone. 2004; 34(1):195-202. Ref ID: SCHUIT2004	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Seeley DG, Kelsey J, Jergas M et al. Predictors of ankle and foot fractures in older women. The Study of Osteoporotic Fractures Research Group. Journal of Bone & Mineral Research. 1996; 11(9):1347-1355. Ref ID: SEELEY1996	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Sen SS, Rives VP, Messina OD et al. A risk assessment tool (OsteoRisk) for identifying Latin American women with osteoporosis. J Gen Intern Med. 2005; 20(3):245-250. Ref ID: SEN2005	Not relevant to review question (assessing risk of osteoporosis rather than fragility fracture)
Shaw CK, Li YM, Wang LY et al. Prediction of bone fracture by bone mineral density in Taiwanese. J Formos Med Assoc. 2001; 100(12):805-810. Ref ID: SHAW2001	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)

Author, year	Exclusion reason
Shepherd AJ, Cass AR, Carlson CA et al. Development and internal validation of the male osteoporosis risk estimation score. Annals of Family Medicine. 2007; 5(6):540-546. Ref ID: SHEPHERD2007	Not relevant to review question (assessing risk of osteoporosis rather than fragility fracture)
Shepherd AJ, Cass AR, Ray L. Determining risk of vertebral osteoporosis in men: validation of the male osteoporosis risk estimation score. Journal of the American Board of Family Medicine: JABFM. 2010; 23(2):186-194. Ref ID: SHEPHERD2010	Reported risk of osteoporosis as outcome, not fracture risk
Sheu Y, Zmuda JM, Boudreau RM et al. Bone strength measured by peripheral quantitative computed tomography and the risk of nonvertebral fractures: the osteoporotic fractures in men (MrOS) study. Journal of Bone & Mineral Research. 2011; 26(1):63-71. Ref ID: SHEU2011	Subset of cohort (2 centres only); replaced by Bauer 2007
Shin CS, Choi HJ, Kim MJ et al. Prevalence and risk factors of osteoporosis in Korea: a community-based cohort study with lumbar spine and hip bone mineral density. Bone. 2010; 47(2):378-387. Ref ID: SHIN2010	Not relevant to review question (assessing risk of osteoporosis rather than fragility fracture)
Siris ES, Baim S, Nattiv A. Primary care use of FRAX: absolute fracture risk assessment in postmenopausal women and older men. [Review] [48 refs]. Postgrad Med. 2010; 122(1):82-90. Ref ID: SIRIS2010	Systematic review
Siris ES, Brenneman SK, Barrett-Connor E et al. The effect of age and bone mineral density on the absolute, excess, and relative risk of fracture in postmenopausal women aged 50-99: results from the National Osteoporosis Risk Assessment (NORA). Osteoporos Int. 2006; 17(4):565-574. Ref ID: SIRIS2006	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Siris ES, Chen YT, Abbott TA et al. Bone mineral density thresholds for pharmacological intervention to prevent fractures. Arch Intern Med. 2004; 164(10):1108-1112. Ref ID: SIRIS2004A	Not relevant to review question (treatment threshold)
Siris ES, Miller PD, Barrett-Connor E et al. Identification and fracture outcomes of undiagnosed low bone mineral density in postmenopausal women: results from the National Osteoporosis Risk Assessment. JAMA. 2001; 286(22):2815-2822. Ref ID: SIRIS2001	Not relevant to review question (not BMD)
Sirola J, Koistinen A, Rikkonen T et al. Risk factors for perimenopausal fractures are dependent on pattern of BMD change - A 15-year population-based study. Bone. 2009; Conference(Procter and Gamble Pharm. and sanofi-aventis):var-S409. Ref ID: SIROLA2009	Conference abstract
Skedros JG, Sybrowsky CL, Stoddard GJ. The osteoporosis self-assessment screening tool: a useful tool for the orthopaedic surgeon. Journal of Bone & Joint Surgery - American Volume. 2007; 89(4):765-772. Ref ID: SKEDROS2007	Not relevant to review question (assessing risk of osteoporosis rather than fragility fracture)
Sornay-Rendu E, Munoz F, Garnero P et al. Identification of osteopenic women at high risk of fracture: the OFELY study. Journal of Bone & Mineral Research. 2005; 20(10):1813-1819. Ref ID: SORNAYRENDU2005A	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Sosa M, Saavedra P, Jodar E et al. Bone mineral density	Paper did not report area under curve (results

Author, year	Exclusion reason
and risk of fractures in aging, obese post-menopausal women with type 2 diabetes. The GIUMO Study. Aging-Clinical & Experimental Research. 2009; 21(1):27-32. Ref ID: SOSA2009	reported as odds ratios, risk ratios, etc.)
Spangler L, Scholes D, Brunner RL et al. Depressive symptoms, bone loss, and fractures in postmenopausal women. J Gen Intern Med. 2008; 23(5):567-574. Ref ID: SPANGLER2008	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Srikanth R, Cassidy G, Joiner C et al. Osteoporosis in people with intellectual disabilities: a review and a brief study of risk factors for osteoporosis in a community sample of people with intellectual disabilities. [Review]. J Intellect Disabil Res. 2011; 55(1):53-62. Ref ID: SRIKANTH2011	Review
Steiner ML, Fernandes CE, Strufaldi R et al. Application of Osteorisk to postmenopausal patients with osteoporosis. Sao Paulo Medical Journal = Revista Paulista de Medicina. 2010; 128(1):24-29. Ref ID: STEINER2010	Paper reported risk of osteoporosis as outcome, not fracture risk
Stewart A, Reid DM, Porter RW. Broadband ultrasound attenuation and dual energy X-ray absorptiometry in patients with hip fractures: which technique discriminates fracture risk. Calcif Tissue Int. 1994; 54(6):466-469. Ref ID: STEWART1994	Case-control study
Stewart A, Walker LG, Porter RW et al. Predicting a second hip fracture. Journal of Clinical Densitometry. 1999; 2(4):363-370. Ref ID: STEWART1999	Second hip fracture
Stone KL, Seeley DG, Lui LY et al. BMD at multiple sites and risk of fracture of multiple types: long-term results from the Study of Osteoporotic Fractures. Journal of Bone & Mineral Research. 2003; 18(11):1947-1954. Ref ID: STONE2003	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Sturtridge W, Lentle B, Hanley DA et al. 2. The use of bone density measurement in the diagnosis and management of osteoporosis. Can Med Assoc J. 1996; 155(7):924-929. Ref ID: STURTRIDGE1996B	Review
Szulc P, Boutroy S, Vilayphiou N et al. Cross-sectional analysis of the association between fragility fractures and bone microarchitecture in older men: the STRAMBO study. Journal of Bone & Mineral Research. 2011; 26(6):1358-1367. Ref ID: SZULC2011	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Taes Y, Lapauw B, Griet V et al. Prevalent fractures are related to cortical bone geometry in young healthy men at age of peak bone mass. Journal of Bone & Mineral Research. 2010; 25(6):1433-1440. Ref ID: TAES2010	Not relevant to review question (prevalent fracture)
Taes Y, Lapauw B, Vanbillemont G et al. Early smoking is associated with peak bone mass and prevalent fractures in young, healthy men. Journal of Bone & Mineral Research. 2010; 25(2):379-387. Ref ID: TAES2010A	Not relevant to review question (not BMD)
Taylor BC, Schreiner PJ, Stone KL et al. Long-term prediction of incident hip fracture risk in elderly white women: study of osteoporotic fractures. J Am Geriatr Soc. 2004; 52(9):1479-1486. Ref ID: TAYLOR2004	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Tebe, C., Espallargues, M., Estrada, M. D., Casas, L., and	Abstract

Author, year	Exclusion reason
Di, Gregorio S. Risk factor analysis and probability of fragility fracture in a cohort of women with bone densitometry indication (Structured abstract). 2010. Ref ID: TEBE2010 http://www.mrw.interscience.wiley.com/cochrane/clhta/articles/HTA-32010000691/frame.html	
Thomas CD, Mayhew PM, Power J et al. Femoral neck trabecular bone: loss with aging and role in preventing fracture. Journal of Bone & Mineral Research. 2009; 24(11):1808-1818. Ref ID: THOMAS2009	Descriptive study
Thompson PW. A fracture risk profile using single-site bone density assessment and clinical risk factors.[Erratum appears in J Clin Densitom. 2004 Summer;7(2):253]. Journal of Clinical Densitometry. 2000; 3(1):73-77. Ref ID: THOMPSON2000	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Timmer MH, Samson MM, Monninkhof EM et al. Predicting osteoporosis in patients with a low-energy fracture. Archives of Gerontology & Geriatrics. 2009; 49(1):e32-e35. Ref ID: TIMMER2009	Not relevant to review question (assessing risk of osteoporosis rather than fragility fracture)
Toogood JH, Baskerville JC, Markov AE et al. Bone mineral density and the risk of fracture in patients receiving long-term inhaled steroid therapy for asthma. Journal of Allergy & Clinical Immunology. 1995; 96(2):157-166. Ref ID: TOOGOOD1995	No measure of effect
Torgerson DJ, Campbell MK, Thomas RE et al. Prediction of perimenopausal fractures by bone mineral density and other risk factors. Journal of Bone & Mineral Research. 1996; 11(2):293-297. Ref ID: TORGERSON1996	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Travison TG, Araujo AB, Esche GR et al. The relationship between body composition and bone mineral content: threshold effects in a racially and ethnically diverse group of men. Osteoporos Int. 2008; 19(1):29-38. Ref ID: TRAVISON2008A	Did not report fracture risk as outcome
Trimpou P, Landin-Wilhelmsen K, Oden A et al. Male risk factors for hip fracture-a 30-year follow-up study in 7,495 men. Osteoporos Int. 2010; 21(3):409-416. Ref ID: TRIMPOU2010	Not relevant to review question (not BMD)
Tsang SWY, Bow CH, Chu EYW et al. Clinical risk factor assessment had better discriminative ability than bone mineral density in identifying subjects with vertebral fracture. Osteoporos Int. 2011; 22(2):667-674. Ref ID: TSANG2011	Cross-sectional study (not BMD)
Tuppurainen M, Kroger H, Honkanen R et al. Risks of perimenopausal fractures--a prospective population-based study. Acta Obstet Gynecol Scand. 1995; 74(8):624-628. Ref ID: TUPPURAINEN1995	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Turner CH, Peacock M, Timmerman L et al. Calcaneal ultrasonic measurements discriminate hip fracture independently of bone mass. Osteoporos Int. 1995; 5(2):130-135. Ref ID: TURNER1995	Case-control study
Vaidya SV, Dholakia D, Yadav S. An age- and sex-controlled matched pair analysis of T scores in ethnic Indians with hip fractures. Journal of Orthopaedic Surgery.	Descriptive study

Author, year	Exclusion reason
2003; 11(1):22-27. Ref ID: VAIDYA2003	
van der Klift M, De Laet CE, McCloskey EV et al. Risk factors for incident vertebral fractures in men and women: the Rotterdam Study. Journal of Bone & Mineral Research. 2004; 19(7):1172-1180. Ref ID: VANDERKLIFT2004	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
van der Klift M, De Laet CE, McCloskey EV et al. The incidence of vertebral fractures in men and women: the Rotterdam Study. Journal of Bone & Mineral Research. 2002; 17(6):1051-1056. Ref ID: VANDERKLIFT2002	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
van Geel AC, Geusens PP, Nagtzaam IF et al. Timing and risk factors for clinical fractures among postmenopausal women: a 5-year prospective study. BMC Medicine. 2006; 4(24) Ref ID: VANGEEL2006	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
van Geel TA, Geusens PP, Nagtzaam IF et al. Risk factors for clinical fractures among postmenopausal women: a 10-year prospective study. Menopause International. 2007; 13(3):110-115. Ref ID: VANGEEL2007	Not relevant to review question
van Geel TA, Nguyen ND, Geusens PP et al. Development of a simple prognostic nomogram for individualising 5-year and 10-year absolute risks of fracture: a population-based prospective study among postmenopausal women. Ann Rheum Dis. 2011; 70(1):92-97. Ref ID: VANGEEL2011	Risk score (not AUC – HR)
Van GT, Geusens P, Dinant G-J et al. Comparing FRAX and Garvan Fracture Risk Calculator in postmenopausal women: A prospective 5-year follow-up study. Bone. 2011; Conference(var.pagings):S63. Ref ID: VANGEEL2011A	Conference abstract
van Staa TP, Laan RF, Barton IP et al. Bone density threshold and other predictors of vertebral fracture in patients receiving oral glucocorticoid therapy. Arthritis Rheum. 2003; 48(11):3224-3229. Ref ID: VANSTAA2003	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
van Staa TP, Leufkens HG, Cooper C. The epidemiology of corticosteroid-induced osteoporosis: a meta-analysis. [Review] [130 refs]. Osteoporos Int. 2002; 13(10):777-787. Ref ID: VANSTAA2002A	Not relevant to review question (meta-analysis)
Vokes T, Lauderdale D, Ma SL et al. Radiographic texture analysis of densitometric calcaneal images: relationship to clinical characteristics and to bone fragility. Journal of Bone & Mineral Research. 2010; 25(1):56-63. Ref ID: VOKES2010	Not relevant to review question (prevalent fracture)
Vokes TJ, Gillen DL, Pham AT et al. Risk factors for prevalent vertebral fractures in black and white female densitometry patients. Journal of Clinical Densitometry. 2007; 10(1):1-9. Ref ID: VOKES2007	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Von MD, Visby LA, Barrett-Connor E et al. Evaluation of the simple calculated osteoporosis risk estimation (SCORE) in older Caucasian women: the Rancho Bernardo study. Osteoporos Int. 1999; 10(1):79-84. Ref ID: VONMUHLEN1999	Not relevant to review question (assessing risk of osteoporosis rather than fragility fracture)
Wadhwa VK, Weston R, Mistry R et al. Long-term changes in bone mineral density and predicted fracture risk in patients receiving androgen-deprivation therapy for	Not relevant to review question (change in BMD and fracture risk in patients with prostate cancer)

Author, year	Exclusion reason
prostate cancer, with stratification of treatment based on presenting values. BJU Int. 2009; 104(6):800-805. Ref ID: WADHWA2009	
Walsh LJ, Lewis SA, Wong CA et al. The impact of oral corticosteroid use on bone mineral density and vertebral fracture. American Journal of Respiratory & Critical Care Medicine. 2002; 166(5):691-695. Ref ID: WALSH2002	Not relevant to review question
Watts NB, Cooper C, Lindsay R et al. Relationship between changes in bone mineral density and vertebral fracture risk associated with risedronate: greater increases in bone mineral density do not relate to greater decreases in fracture risk. Journal of Clinical Densitometry. 2004; 7(3):255-261. Ref ID: WATTS2004	Not relevant to review question (treatment response measured by change in BMD)
Wehrli FW, Hopkins JA, Hwang SN et al. Cross-sectional study of osteopenia with quantitative MR imaging and bone densitometry. Radiology. 2000; 217(2):527-538. Ref ID: WEHRLI2000	Not relevant to review question
Wei TS, Hu CH, Wang SH et al. Fall characteristics, functional mobility and bone mineral density as risk factors of hip fracture in the community-dwelling ambulatory elderly. Osteoporos Int. 2001; 12(12):1050-1055. Ref ID: WEI2001	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Wilkin TJ, Devendra D. Bone densitometry is not a good predictor of hip fracture. BMJ. 2001; 323(7316):795-797. Ref ID: WILKIN2001	Review
Winzenrieth R, Dufour R, Pothuaud L et al. A retrospective case-control study assessing the role of trabecular bone score in postmenopausal Caucasian women with osteopenia: analyzing the odds of vertebral fracture. Calcif Tissue Int. 2010; 86(2):104-109. Ref ID: WINZENRIETH2010	Case-control study
Yamamoto M, Yamaguchi T, Yamauchi M et al. Bone mineral density is not sensitive enough to assess the risk of vertebral fractures in type 2 diabetic women. Calcif Tissue Int. 2007; 80(6):353-358. Ref ID: YAMAMOTO2007	Paper did not report area under curve (results reported as odds ratios, risk ratios, etc.)
Zehnder Y, Luthi M, Michel D et al. Long-term changes in bone metabolism, bone mineral density, quantitative ultrasound parameters, and fracture incidence after spinal cord injury: a cross-sectional observational study in 100 paraplegic men. Osteoporos Int. 2004; 15(3):180-189. Ref ID: ZEHNDER2004A	Cross-sectional descriptive study

1

Appendix D: Evidence tables and forest plots

D.1 Evidence tables for review question 1 (How useful are simple clinical measures for targeting people for risk assessment of fragility fracture?)

D.1.1 Prognostic factor: Body mass index

Table 1: Evidence table for BMI

Reference	Study type	Number of patients	Patient characteristics				Baseline and outcome variables	Statistical Methods	Source of funding
Osteoporos Int. 2005 Nov;16(11):1330-8. Body mass index as a predictor of fracture risk: a meta-analysis. De Laet C, Kanis JA, Odén A, Johanson 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.	Meta-analyses from 12 cohorts Rotterdam (Netherlands), EVOS/EPOS (Europe), CaMos (Canada), Rochester (USA), Sheffield (UK), DOES (Australia), EPIDOS (France), OFELY (France), Kuopio (Finland), Hiroshima (Japan), Gothenburg I and II	N=59 644 (75% Women)		All men	All women	Overall	Height and weight measured using standardised methods. BMI calculated as weight in kg / height squared in metres. 2 cohorts (Gothenburg I and II) used DXA at the distal forearm, or by DPA at right heal. 10 cohorts assessed BMI assessed at femoral neck by DXA. Outcomes Any hip fracture Hip fracture Osteoporotic fracture Fracture ascertained by self-report (Sheffield, EVOS/EPOS, Kuopio,	Risk of fracture; Poisson regression model in each cohort separately for any fracture, hip fracture, and osteoporotic fracture. Covariates included; current age, time since start of follow-up, analyses for both sexes separately, with and without taking BMD information into account. BMD expresses ad sex- and cohort-specific Z scores. BMD measured either continuously	European Community (EU FP 3/5), International Osteoporosis Foundation, International Society for Clinical Densitometry
			N	14 887	44 757	59 644			
			Person-years	60 427	191 607	2520344			
			Any fracture1	837	4484	5321			
			Hip fracture2	188	953	1141			
			Osteo-porotic fracture3	644	2674	3318			
			Mean age (years)	66.4	62.2	63.2			
			Mean BMI4 (kg/m2)	26.2	25.9	26.0			
			Mean height(cm)	172.6	160.4	163.3			
			Mean	77.9	66.9	69.5			

Reference	Study type	Number of patients	Patient characteristics	Baseline and outcome variables	Statistical Methods	Source of funding
	(Sweden)		weight(kg) [ ] [ ] [ ] 1information available for about 58 000 participants 2information available for about 46 000 participants 3information available for about 47 000 participants 4BMI available in 65% of individuals	Hiroshima, OFELY, EPIDOS) and/or verified from hospital or central databases (Gothenburg, CaMos, DOES, Kuopio, Sheffield, EVOS/EPOS, Rochester, Rotterdam). For EVOS/EPOS and CaMos investigator determined if fracture was osteoporotic. For EVOS/EPO, osteoporotic fracture comprised hip, forearm, humeral or spine fractures. For CaMos study fracture comprised spine, pelvis, ribs, distal forearm, forearm and hip. In other cohorts, fractures at sites considered to be characteristic for osteoporosis were extracted from data (Kanis et al, 2002, Osteoporos Int 12, 417-427).	or using specific thresholds. β-coefficient of each cohort and sex weighted according to the variance and merged to determine weighted mean difference (WMD) of β-coefficient and it standard deviation (SD). RR at different BMI given by e (weighted mean coefficient) RR per unit difference of BMI (BMI = 25 kg/m2 as reference). I2 statistic used for heterogeneity between cohorts.	

Results

Without information on BMD; adjusted for current age and time since start of follow up
Any fracture: RR per unit increase BMI (gradient of risk; GR) = 0.98 (95%CI 0.97 to 0.99)

Reference	Study type	Number of patients	Patient characteristics	Baseline and outcome variables	Statistical Methods	Source of funding

Osteoporotic fracture: RR = 0.97 (95%CI 0.97 to 0.98)

Hip fracture: RR = 0.93 (95%CI 0.91 to 0.94)

RR per unit change in men versus women similar (p > 0.30, shown graphically)

Excluding hip fractures in osteoporotic fractures; GR < 1 in men and women combined (shown graphically)

Adjusted for BMD, current age and time since start of follow up

GR change compared without BMD (increase in RR, shown graphically)

Only hip fractures in women GR < 1 (shown graphically)

Excluding Gothenburg I and II (BMD not measured at femoral neck; GR for hip fracture in women not < 1

Relative fracture risk per unit increase by age for men and women combined: adjusted for time since start of follow-up

Any fracture and osteoporotic fracture; GR per unit BMI increased with advancing age (without adjustment for BMD) (shown graphically)

Hip fracture; GR decreased with age (shown graphically)

Excluding hip fracture from osteoporotic fractures; similar trend with age as seen for all osteoporotic fractures (hown graphically)

Relative fracture risk per unit increase by age for men and women combined: adjusted for BMD and adjusted for time since start of follow-up

Any fracture, osteoporotic fracture and hip fracture; GR similar, most ages not different from 1

Distribution (%) of men and women categorised by intervals of BMI			
BMI			
kg/m2	men	Women	Total
< 20	7.5	8.9	8.5
20-24	30.9	38.5	36.5
25-29	47.2	35.8	38.8
30-34	12.4	12.9	12.8
35-39	1.7	3.1	2.7
40+	0.2	0.8	0.7

Reference	Study type	Number of patients	Patient characteristics		Baseline and outcome variables		Statistical Methods	Source of funding
RR for fracture at various levels BMI (kg/m2) men and women combined, adjusted for current age and time, without and with adjustment for BMD. Reference BMI = 25 (kg/m2)								
BMI	Any fracture			Osteoporotic fracture			Hip fracture	
	RR	95%CI		RR	95%CI		RR	95%CI
Not adjusted for BMD								
15	1.66	1.31 to 2.09		1.79	1.35 to 2.37		4.48	3.11 to 6.45
20	1.21	1.12 to 1.30		1.27	1.16 to 1.38		1.95	1.71 to 2.22
25	1.00	reference		1.00	reference		1.00	reference
30	0.92	0.85 to 1.00		0.89	0.81 to 0.98		0.83	0.69 to 0.99
35	0.85	0.75 to 0.98		0.74	0.62 to 0.90		0.75	0.50 to 1.11
Adjusted for BMD								
15	1.00	0.75 to 1.33		1.07	0.78 to 1.48		2.16	1.42 to 3.28
20	0.98	0.90 to 1.08		1.02	0.92 to 1.13		1.42	1.23 to 1.65
25	1.00	reference		1.00	reference		1.00	reference
30	1.01	0.91 to 1.11		0.96	0.86 to 1.08		1.00	0.82 to 1.21
35	0.99	0.82 to 1.19		0.91	0.73 to 1.13		1.18	0.78 to 1.80

Re-analysing data from cohorts with uniform acquisition of data on fractures (Rotterdam, Rochester, Sheffield, DOES, Hiroshima)

Hip fracture; no change in relation with BMI (data not shown)

Osteoporotic fracture; a high BMI had greater protective effect in absence of BMD (data not shown)

Unadjusted BMD data reanalysed in 65% who didn't have BMD test, findings didn't differ from entire cohort (data not shown)

No differences observed between men and women across data (data not shown)

Heterogeneity

Osteoporotic fractures; I^2 = 49% (95%CI 8 to 71). Adjusted for age I^2 = 0.

Hip fractures I^2 = 8% (95%CI 0 to 44)

Table 2: **Methodology checklist* for quality assessment of systematic reviews of prognostic studies**
(*Adapted from Ann Intern Med. 2006 Mar 21;144(6):427-37. Evaluation of the quality of prognosis studies in systematic reviews. Hayden JA, Côté P, Bombardier C.)
Reference: Osteoporos Int. 2005 Nov;16(11):1330-8. Body mass index as a predictor of fracture risk: a meta-analysis. De Laet C, Kanis JA, Odén A, Johanson 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.

Potential Bias	Items To Be Considered for Assessment of Potential Opportunity for Bias	Overall	Comments on methodology and identified limitations
Cohort study populations in review The review includes studies with the population of interest on key characteristics that are adequately similar in pooled data sufficient to limit potential bias.	1. The source populations in included cohort studies are adequate for key characteristics. 2. The literature review is sufficiently rigorous and adequately reported. 3. Inclusion and exclusion criteria for cohort studies are adequately described. 4. Recruitment in included cohort studies is adequately described (e.g. sequential recruitment). 5. The review reports key characteristics for individual patient data at baseline.	Partly	1. Yes. 2. No details of a literature search given in methods. No details given of the characteristics of the populations in either the included or excluded cohorts 3. No excluded studies are reported. 4. Partly. 5. Yes.
Study attrition Loss to follow-up of the individual patient data is not associated with key characteristics sufficient to limit potential bias.	1. Response rate (i.e. proportion individual patient data) providing outcome is adequate. 2. Reasons for loss to follow-up in review population are provided. 3. Cohort participants lost to follow-up are adequately described for key characteristics. 4. There are no important differences between key characteristics and outcomes in cohort study participants who completed the studies and those who did not.	Unclear	1. Of N = 59 644; information on any fracture, osteoporotic data and hip fracture was available for approx. 58 000, 46 000 and 47 000 participants, respectively. 2. No reasons given for loss to follow-up. 3. Not addressed. 4. Not addressed.
Prognostic factor measurement The review adequately describes measurement of prognostic factor of interest in the included	1. Clear definition or description of the prognostic factor measured is provided for included cohort studies. 2. The prognostic factor measure and method are adequately valid and reliable to limit misclassification bias. 3. Any variation between cohort studies for prognostic factor measurement is adequately addressed in statistical methods.	Unclear	1. Yes. 2. Yes. 3. All cohorts used standard techniques. 4. Unclear. 5. Unclear.

Potential Bias	Items To Be Considered for Assessment of Potential Opportunity for Bias	Overall	Comments on methodology and identified limitations
cohort studies sufficient to limit potential bias.	4. Individual patient data has complete data for prognostic factors or this has been accounted for in analysis 5. The method and setting of measurement are the same for included cohort studies.		
Outcome measurement The outcome of interest is adequately measured in included cohort studies sufficient to limit potential bias.	1. A clear definition of the outcome of interest is provided, including duration of follow-up. 2. The outcome measure and method are adequately valid and reliable to limit misclassification bias. 3. The method and setting of measurement are the same for included cohort studies.	Partly	1. Yes. 2. Yes. Fracture verified by radiology report or hospital/centre database in 11/12 cohorts. I cohort self report. Definition of osteoporotic fracture differed between studies. 3. Unclear.
Confounding measurement and account Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest.	1. All important confounders are measured. 2. Clear definitions of the important confounders measured are provided. 3. Measurement of all important confounders is adequately valid and reliable. 4. The method and setting of confounding measurement are the same for all study participants. 5. Appropriate methods are used if imputation is used for missing confounder data. 6. Important potential confounders are accounted for in the review design. 7. Important potential confounders are accounted for in the analysis (i.e. appropriate adjustment).	Partly	1. Confounders; BMD, current age, time since follow-up, gender. 2. Yes. 3. Yes. 4. No. 5. Not done. 6. Yes. 7. Yes.
Analysis The statistical analysis is appropriate for the design of the review, limiting potential for presentation of invalid results.	1. There is sufficient presentation of data to assess the adequacy of the analysis. 2. The selected model is adequate for the design of the review. 3. The strategy for model building (i.e. inclusion of variables) is appropriate and is based on a conceptual framework or model. 4. Analysis addresses missing data if appropriate	Yes	1. Yes. 2. Model; Poisson regression model in each cohort separately for any fracture, hip fracture, and osteoporotic fracture. β-coefficient of each cohort and sex is a linear function of age; $\beta k + \beta k+1 x age$. Estimated value of β-coefficients and their variance determined for each sex from age 50 years. The results of each cohort and the two sexes were weighted means and

Potential Bias	Items To Be Considered for Assessment of Potential Opportunity for Bias	Overall	Comments on methodology and identified limitations
	5. There is no selective reporting of results.		standard deviations .RR of those with a family history versus those with no family history given by e (weighted mean coefficient). 3. Included variables; current age, time since start of follow-up, analyses for both sexes separately, with and without taking BMD information into account. 4. Not done. 5. No selective reporting.

D.1.2 Prognostic factor: Prior oral corticosteroid use

Table 3:   Evidence table for prior oral corticosteroid use

Reference	Study type	Number of patients	Patient characteristics								Baseline and outcome variables	Statistical Methods	Source of funding
J Bone Miner Res. 2004 Jun;19(6):893-9. A meta-analysis of prior corticosteroid use and fracture risk. Kanis JA, Johansson H, Oden A, Johnell O, de Laet C, Melton III LJ, Tenenhouse A, Reeve J, Silman AJ, Pols HA, Eisman JA, McCloskey EV, Mellstrom D.	Meta-analyses from 7 cohorts EVOS/ EPO (Europe), CaMos (Canada), Rotterdam (Netherlands), DOES (Australia), Sheffield (UK), Rochester (USA), Gothenburg (Sweden)	N=42542 overall, 14171 men, 27825 women (65% Women)	Patients studied and fracture outcomes. Person-years = 176 286								Corticosteroid use Duration of use was not analysed. CaMos study; identified participants who had ever taken corticosteroids > 1 month. Rochester; participants taken who had ever taken corticosteroids > 6 months. 3 cohorts current use available. Rotterdam; current use n = 159, noncurrent use = 7624. DOES; never use n = 159,	Risk of fracture; Poisson regression model in each cohort and sex separately for any fracture, hip fracture, and osteoporotic fracture. Covariates included; current age, time since start of follow-up, use of corticoid steroids, age x use of corticoid steroids, and BMD In addition, BMD	NCCHTA acting on behalf of the NHS ExecutiveUK.
				Age (years)		Cortico-steroid use (%)	Number of fractures			Prior fracture			
				Mean	Range		Hip	Osteo-porotic	Any				
			Men										
			EVOS/EPOS	65	43 to 95	3.6	16	202	202	40			
			CaMos	60	25 to 97	2.8	9	59	124	50			
			Rotterdam	68	55 to 98	2.2	61	146	201	11			
			Rochester	55	23 to 90	2.3	0	25	38	18			
			DOES	70	60 to 92	6.0	21	90	116	-			
			Sheffield	-	-	-	-	-	-	-			
			Gothenburg	-	-	-	-	-	-	-			
			Women										
			EVOS/EPOS	64	41 to 93	5.9	23	486	486	32			
			CaMos	63	23 to	5.3	33	258	46	41			

			103				1	
Rotterdam	72	55 to 106	1.9	22 3	621	78 8	16	
Rochester	58	21 to 94	3.5	42	219	25 1	18	
DOES	71	57 to 96	6.0	64	211	28 9	-	
Sheffield	80	74 to 96	9.2	62	242	29 1	51	
Gothenbur g	59	21 to 89	3.8	29	308	43 5	18	

past but not current use n = 25, current use = 58. Sheffield; never use n = 1963, ever use n = 137, current use = 64.

BMD assessed at femoral neck by DXA except Gothenburg which assessed at distal forearm by DXA.

Outcomes
Any hip fracture
Hip fracture
Osteoporotic fracture
Fracture ascertained by self-report (Sheffield, EVOS/EPOS) and/or verified from hospital or

excluded from the model, and in further analysis included history of previous fragility fracture and rheumatoid arthritis.

β-coefficient of each cohort and sex weighted according to the variance and merged to determine weighted mean difference (WMD) of β-coefficient and it standard deviation (SD). The estimated value of the β-coefficient and their variance was determined for each age

Osteoporosis: fragility fracture risk

| | | | | central databases (Gothenburg, CaMos, DOES, Sheffield, Rochester, EVOS/EPOS Rotterdam).

An osteoporotic fracture was one considered to be caused by osteoporosis by investigator. For EVOS/EPO, osteoporotic fracture comprised hip, forearm, humeral or spine fractures. For CaMos study fracture comprised spine, pelvis, ribs, distal forearm, forearm and hip. In other cohorts, | from the age of 50 to 85 years.

RR at different of those treated with corticosteroids versus not treated given by e (weighted mean coefficient) | |

| | | | fractures at sites considered to be characteristic for osteoporosis were extracted (Kanis et al, 2002, Osteoporos Int 12, 417-424). | | |

Results

Risk ratio of fracture and 95%CI associated with ever use of corticosteroids according to age and adjusted for BMD						
	Any fracture		Osteoporotic fracture		Hip fracture	
Age	Risk ratio1	95%CI	Risk ratio	95%CI	Risk ratio	95%CI
50	1.98	1.35 to 2.92	2.63	1.68 to 4.13	4.42	1.26 to 15.49
55	1.83	1.35 to 2.47	2.32	1.63 to 3.30	4.15	1.50 to 11.49
60	1.67	1.33 to 2.09	2.00	1.52 to 2.62	3.71	1.67 to 8.23
65	1.56	1.29 to 1.88	1.81	1.43 to 2.27	2.98	1.55 to 5.74
70	1.55	1.30 to 1.86	1.76	1.42 t0 2.19	2.44	1.37 to 4.36
75	1.64	1.37 to 1.97	1.70	1.36 to 2.11	2.22	1.35 to 3.63
80	1.62	1.31 to 2.00	1.59	1.26 to 2.02	2.13	1.39 to 3.27
85	1.66	1.26 to 2.17	1.71	1.29 to 2.28	2.48	1.58 to 3.89
All ages	1.572	1.37 to 1.80	1.66	1.42 to 1.92	2.25	1.60 to 3.15
All ages (ever use versus population risk)	1.53		1.61		2.13	

BMD measurements available in 72% individuals

1 ever use of corticosteroids versus no use

2ever use of corticosteroids versus population

When BMD excluded from model, RR was lower up to age 75 years (data shown graphically)

Rheumatoid arthritis

Rheumatoid arthritis, documented in 3 cohorts (CaMos, DOES, Sheffield) when current corticosteroid use was recorded, was given as reason for treatment in 14%).

In a further model there was an independent fracture risk of corticosteroid use adjusted for arthritis for; any fracture RR = 1.68 (95%CI 1.47 to 2.01), osteoporotic fracture RR = 1.80 (95%CI 1.47 to 2.20), hip fracture RR = 2.30 (95%CI 1.50 to 3.55).

Conversely, rheumatoid arthritis was associated with risk of any fracture RR = 1.45 (95%CI 1.16 to 1.80), osteoporotic fracture RR = 11.56 (95%CI 1.20 to 2.02), hip fracture RR = 21.95 (95%CI 1.11 to 3.42). Risk persisted after adjustment for corticosteroid use in the case of any fracture RR = 1.38 (95%CI 1.11 to 1.72) and osteoporotic fracture RR = 1.46 (95%CI 1.12 to 1.90), not for hip fracture RR = 1.76 (95%CI 0.97 to 3.19, p = 0.06).

Independent RR (95%CI) of ever use of corticosteroids and prior fracture according to type of fracture and gender			
Fracture type	Gender	Corticosteroid use	Prior fracture
Any fracture	M	1.67 (1.10 to 2.51)	1.68 (1.39 to 2.02)
	F	1.39 (1.18 to 1.64)	1.71 (1.58 to 1.86)
Osteoporotic fracture	M	2.16 (1.42 to 3.27)	1.68 (1.35 to 2.08)
	F	1.42 (1.18 to 1.70)	1.72 (1.57 to 1.89)
Hip fracture	M	2.62 (0.91 to 7.51)	1.69 (0.98 to 2.94)
	F	2.07 (1.38 to 3.10)	1.66 (1.33 to 2.06)

Table 4:   Methodology checklist* for quality assessment of systematic reviews of prognostic studies
(*Adapted from Ann Intern Med. 2006 Mar 21;144(6):427-37. Evaluation of the quality of prognosis studies in systematic reviews. Hayden

JA, Côté P, Bombardier C.)

Reference: J Bone Miner Res. 2004 Jun;19(6):893-9. A meta-analysis of prior corticosteroid use and fracture risk. Kanis JA, Johansson H, Oden A, Johnell O, de Laet C, Melton III LJ, Tenenhouse A, Reeve J, Silman AJ, Pols HA, Eisman JA, McCloskey EV, Mellstrom D.

Potential Bias	Items To Be Considered for Assessment of Potential Opportunity for Bias	Overall	Comments on methodology and identified limitations
Cohort study populations in review The review includes studies with the population of interest on key characteristics that are adequately similar in pooled data sufficient to limit potential bias.	1. The source populations in included cohort studies are adequate for key characteristics. 2. The literature review is sufficiently rigorous and adequately reported. 3. Recruitment in included cohort studies is adequately described (e.g. sequential recruitment). 4. Inclusion and exclusion criteria for cohort studies are adequately described. 5. The review reports key characteristics for individual patient data at baseline.	Partly	1. Yes. 2. No details of a literature search given in methods. No details given of the characteristics of the populations in either the included or excluded cohorts 3. No excluded studies are reported. 4. Partly. 5. Yes.
Study attrition Loss to follow-up of the individual patient data is not associated with key characteristics sufficient to limit potential bias.	1. Response rate (i.e. proportion individual patient data) providing outcome is adequate. 2. Reasons for loss to follow-up in review population are provided. 3. Cohort participants lost to follow-up are adequately described for key characteristics. 4. There are no important differences between key characteristics and outcomes in cohort study participants who completed the studies and those who did not.	No	1. No, not addressed. 2. Not addressed. 3. Not addressed. 4. Not addressed.
Prognostic factor measurement The review adequately describes measurement of prognostic factor of interest in the included cohort studies sufficient to limit potential bias.	1. Clear definition or description of the prognostic factor measured is provided for included cohort studies. 2. The prognostic factor measure and method are adequately valid and reliable to limit misclassification bias. 3. Any variation between cohort studies for prognostic factor measurement is adequately addressed in statistical methods. 4. Individual patient data has complete data for prognostic factors or this has been accounted for in analysis	No	1. No; factor defined as 'ever use', duration of use not examined. 2. No. 3. No; 1 study definition was steroids > 1 month, 3 cohorts current use available, 1 cohort current and noncurrent use available, 1 cohort never use, past but not present and current use, 1 cohort never and current. 4. Unclear.

Potential Bias	Items To Be Considered for Assessment of Potential Opportunity for Bias	Overall	Comments on methodology and identified limitations
	5. The method and setting of measurement are the same for included cohort studies.		5. Unclear.
Outcome measurement The outcome of interest is adequately measured in included cohort studies to sufficient to limit potential bias.	1. A clear definition of the outcome of interest is provided, including duration of follow-up. 2. The outcome measure and method are adequately valid and reliable to limit misclassification bias. 3. The method and setting of measurement are the same for included cohort studies.	Yes	1. Yes. 2. Yes. Fracture verified by radiology report or hospital/centre database in all cohorts. Definition of osteoporotic fracture differed between cohorts. 3. Unclear.
Confounding measurement and account Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest.	1. All important confounders are measured. 2. Clear definitions of the important confounders measured are provided. 3. Measurement of all important confounders is adequately valid and reliable. 4. The method and setting of confounding measurement are the same for all study participants. 5. Appropriate methods are used if imputation is used for missing confounder data. 6. Important potential confounders are accounted for in the review design. 7. Important potential confounders are accounted for in the analysis (i.e. appropriate adjustment).	Unclear	1. Confounders; BMD, current age, gender, prior fracture, arthritis. 2. Yes. 3. Unclear. 4. No. 5. Not done. 6. Yes. 7. Yes.
Analysis The statistical analysis is appropriate for the design of the review, limiting potential for presentation of invalid results.	1. There is sufficient presentation of data to assess the adequacy of the analysis. 2. The selected model is adequate for the design of the review. 3. The strategy for model building (i.e. inclusion of variables) is appropriate and is based on a conceptual framework or model. 4. Analysis addresses missing data if appropriate. 5. There is no selective reporting of results.	Yes	1. Yes. 2. Model; Poisson regression model in each cohort and sex separately for any fracture, hip fracture, and osteoporotic fracture. Included variables; current age, time since start of follow-up, use of corticoid steroids, age x use of corticoid steroids, and BMD/ 3. Covariates; time since start of follow-up, current age x steroids, BMD. 4. Yes. 5. No selective reporting.

D.1.3   Prognostic factor: Family history of fracture and fracture risk

Table 5:   Evidence table for family history of fracture

Reference	Study type	Number of patients	Patient characteristics		Baseline and outcome variables	Statistical Methods	Source of funding
Bone. 2004 Nov;35(5):1029-37. A family history of fracture and fracture risk: a meta-analysis. 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.	Meta-analyses from 7 cohorts EVOS/EPOS (Europe), CaMos (Canada), Rotterdam (Netherlands), DOES (Australia), Sheffield (UK), Rochester (USA), Gothenburg (Sweden)	N=34 928 (64% Women)	<table><tr><td></td><td>Total</td></tr><tr><td>N</td><td>34 928</td></tr><tr><td>Person-years</td><td>134 374</td></tr><tr><td>Mean age (range) years</td><td>65 (21 to 106)</td></tr><tr><td>Any fracture number (incidence/10000 years)</td><td>3189 (237)</td></tr><tr><td>Hip fracture number (incidence/10000 years)</td><td>505 (38)</td></tr><tr><td>Osteoporotic fracture number (incidence/10000 years)</td><td>2530 (188)</td></tr></table>		Family history of fracture provided by questionnaire and information collected concerning a history in first degree relatives. Maternal family history with information on age, sex, fracture outcome and time of fracture; Available for total 12 567 men and 22 361 women. Paternal family history with information on age, sex, fracture outcome and time of fracture; No data from Sheffield, Gothenburg, available data 12 451 men and 18 964 women. Sibling family history with information on age, sex, fracture outcome and time of fracture;	Risk of fracture; Poisson regression model in each cohort and each sex separately for any fracture, hip fracture, and osteoporotic fracture. Covariates included; current age, time since start of follow-up, age at baseline, family history of fracture (and of hip fracture), with and without taking BMD information into account, current age x family history with BMD. Height as separate model. Separate analyses undertaken for a family history involving father, mother and siblings.	GE Lunar, Lilly, Hologic, Roche, IGEA, Alliance for Better Bone Health, Novartis, Wyeth (unrestricted support). National Osteoporosis Foundation, International, Osteoporosis Foundation, International Society for Clinical Densitometry, European Community (EU FP 3/5).

				No data from Rotterdam, Rochester or Gothenburg, available data 7873 men and 13 412 women.	β-coefficient of each cohort and sex is a linear function of age; βk + βk+1xage. Estimated value of β-coefficients and their variance determined for each sex from age 50 years. The results of each cohort and the two sexes were weighted means and standard deviations.	
				Family history of hip fracture; Not available for CaMos, DOES, Rochester. Paternal family history; 8896 men and 19 524 women followed for 33 800, and 77 874 person-years, respectively.	RR of those with a family history versus those with no family history given by e (weighted mean coefficient)	
				BMD assessed by multiple techniques, purpose of this study, data for BMD assessed at femoral neck by DXA with exception Gothenburg cohort where BMD assessed by DXA at distal forearm. BMD available for 63% of individuals. Z-score of BMD for each sex and age cohort computed from the regression of BMD by age.	I2 statistic used for heterogeneity for major co-variate (a parental history of hip fracture). No heterogeneity noted for a parental history of osteoporotic fracture (I2 = 0%) moderate for hip fracture (I2 = 49%), and a fixed-effects model was used.	
				Outcomes Any hip fracture Hip fracture Osteoporotic fracture		

Fracture ascertained by self-report (Sheffield, EVOS/EPOS,) and/or verified from hospital or central databases (Gothenburg, CaMos, DOES, Sheffield, EVOS/EPOS, Rochester, Rotterdam).

For EVOS/EPOS and CaMos investigator determined if fracture was osteoporotic. For EVOS/EPO, osteoporotic fracture comprised hip, forearm, humeral or spine fractures. For CaMos study fracture comprised spine, pelvis, ribs, distal forearm, forearm and hip. In other cohorts, fractures at sites considered to be characteristic for osteoporosis were extracted (Kanis et al, 2002, Osteoporos Int 12, 417-424).

Results

RR at sites shown with 95%CI associated with a family history of fracture in mothers, fathers, siblings or combination				
Outcome fracture	Men		Women	
	RR	95%CI	RR	95%CI
Parental history				

Any	1.17	0.93 to 1.48	1.17	1.06 to 1.29
Osteoporotic	1.17	0.89 to 1.54	1.18	1.05 to 1.32
Hip	2.02	1.18 to 3.46	1.38	1.33 to 1.43
Maternal history				
Any	1.25	0.99 to 1.59	1.15	1.04 to 1.28
Osteoporotic	1.30	0.98 to 1.72	1.15	1.02 to 1.30
Hip	2.18	1.25 to 3.80	1.29	0.98 to 1.69
Paternal history				
Any	1.17	0.86 to 1.58	1.12	0.99 to 1.27
Osteoporotic	1.11	0.74 to 1.65	1.13	0.97 to 1.31
Hip	2.04	0.98 to 4.22	0.99	0.70 to 1.42
Sibling history				
Any	1.66	1.23 to 2.241	1.11	0.96 to 1.20
Osteoporotic	1.58	1.07 to 2.32	1.13	0.94 to 1.36
Hip	1.11	0.39 to 3.11	1.45	0.94 to 2.25
Maternal, paternal or sibling history				
Any	1.30	1.04 to 1.62	1.17	1.07 to 1.29
Osteoporotic	1.23	0.95 to 1.59	1.21	1.09 to 1.35
Hip	1.86	1.12 to 3.08	1.40	1.09 to 1.80

1 Difference between men and women p = 0.018

For family history hip fracture; total number individuals = 28 420 men and women, followed for 111 675 years. In this subgroup; 219 fractures of which 1838 considered related to osteoporosis and 322 were hip fractures.

In all, 16% individuals reported a maternal history any fracture. A parental and sibling history of fractures was reported by 13% and 15%, respectively. A maternal, paternal or sibling history of hip fracture was reported by 6%, 4% and 2% individuals respectively.

RR and 95%CI for fractures at sites shown in men and women combined according to family history of fracture in first degree relatives						
Family history	Size of fracture					
	Any		Osteoporotic		Hip	
	RR	95%CI	RR	95%CI	RR	95%CI
Parental	1.17	1.07 to 1.28	1.18	1.06 to 1.31	1.49	1.17 to 1.89
Maternal	1.17	1.06 to 1.28	1.17	1.05 to 1.31	1.43	1.12 to 1.83
Paternal	1.13	1.00 to 1.27	1.13	0.98 to 1.30	1.14	0.83 to 1.57
Sibling	1.21	1.05 to 1.38	1.20	1.02 to 1.42	1.39	0.93 to 2.08
Maternal/sibling	1.19	1.09 to 1.30	1.21	1.09 to 1.34	1.43	1.14 to 1.80
Paternal/sibling	1.51	1.04 to 1.27	1.16	1.03 to 1.30	1.19	0.92 to 1.55
All	1.19	1.09 to 1.34	1.22	1.10 to 1.34	1.48	1.18 to 1.85

Data not adjusted for BMD

RR and 95%CI for fractures at sites shown in men and women associated with a family history of hip fracture in the mother, father and siblings				
	Men		Women	
	RR	95%CI	RR	95%CI
Parental history				
Any	1.01	0.69 to 1.47	1.34	1.13 to 1.58
Osteoporotic	1.01	0.67 to 1.52	1.38	1.16 to 1.65
Hip	1.73	0.82 to 3.63	1.75	1.17 to 2.63
Maternal history				
Any	1.02	0.69 to 1.52	1.29	1.09 to 1.54
Osteoporotic	1.03	0.67 to 1.59	1.33	1.11 to 1.60
Hip	1.56	0.71 to 3.42	1.61	1.07 to 2.43

Paternal history				
Any	0.93	0.56 to 1.54	1.34	1.07 to 1.68
Osteoporotic	0.91	0.51 to 1.63	1.33	1.11 to 1.81
Hip	1.51	0.65 to 3.51	1.61	0.59 to 1.69
Sibling history				
Any	2.21	0.91 to 5.41	1.25	0.82 to 1.90
Osteoporotic	2.21	0.91 to 5.41	1.43	0.94 to 2.19
Hip	5.71	0.72 to 44.98	2.47	0.96 to 6.39

Data not adjusted for BMD

RR with 95%CI for osteoporotic fracture and for hip fracture with a parental history of fracture by age in men and women combined (as there was no difference found between men and women (p > 0.30)				
Age (years)	Osteoporotic fracture		Hip fracture	
	RR	95%CI	RR	95%CI
50	1.31	1.02 to 1.69	1.63	0.69 to 3.86
55	1.29	1.05 to 1.59	1.73	0.84 to 3.58
60	1.28	1.08 to 1.51	1.82	1.01 to 3.27
65	1.27	1.11 to 1.46	1.86	1.17 to 3.27
70	1.25	1.10 to 1.42	1.79	1.24 to 2.96
75	1.20	1.06 to 1.35	1.53	1.14 to 2.57
80	1.12	0.98 to 1.28	1.35	1.04 to2.07
85	1.08	0.91 to 1.28	1.31	0.99 to 1.75

RR decline with time in case of hip fracture p > 0.30. RR decline for osteoporotic fracture p = 0.078.

RR with 95%CI for osteoporotic fracture and for hip fracture with a parental history of any fracture by age in men and women combined				
Age (years)	Osteoporotic fracture		Hip fracture	

	RR	95%CI	RR	95%CI
50	1.80	1.19 to 2.72	2.43	0.64 to 8.52
55	1.66	1.21 to 2.30	2.36	0.81 to 6.90
60	1.56	1.22 to 1.98	2.41	1.03 to 5.64
65	1.50	1.23 to 1.82	2.44	1.27 to 4.68
70	1.47	1.21 to 1.77	2.57	1.53 to 4.30
75	1.31	1.07 to 1.67	1.75	1.08 to 2.82
80	1.14	0.91 to 1.44	1.26	0.82 to 1.94
85	1.14	0.86 to 1.51	1.33	0.87 to 2.02

RR with 95%CI associated with parental history of fracture and parental history of hip fracture				
Outcome fracture	Without BMD		With BMD	
	RR	95%CI	RR	95%CI
Parental history of fracture				
Any	1.18	1.06 to 1.31	1.18	1.07 to 1.31
Osteoporotic	1.22	1.08 to 1.37	1.22	1.08 to 1.38
Hip	1.63	1.25 to 2.12	1.63	1.24 to 2.13
Parental history of hip fracture				
Any	1.42	1.19 to 1.71	1.41	1.17 to 1.71
Osteoporotic	1.54	1.25 to 1.88	1.54	1.25 to 1.88
Hip	2.27	1.47 to 3.49	2.28	1.48 to 3.51

Adjusted for BMD

Effect of height

Increasing height

Osteoporotic fracture; RR increased by 1.02 (95%CI = 1.01 to 1.03) for each cm increase in height. Similar effect noted for hip fracture (RR = 1.03; 95%CI 1.01 to 1.05).

There was little or no adjustment for the RR of parental history.For osteoporotic fracture RR = 1.49 (95%CI = 1.21 to 1.84) and for hip fracture RR = 2.10 (95%CI 1.32 to 3.33)

Table 6: **Methodology checklist* for quality assessment of systematic reviews of prognostic studies**
(*Adapted from Ann Intern Med. 2006 Mar 21;144(6):427-37. Evaluation of the quality of prognosis studies in systematic reviews. Hayden JA, Côté P, Bombardier C.)
Reference: Bone. 2004 Nov;35(5):1029-37. A family history of fracture and fracture risk: a meta-analysis. 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.

Potential Bias	Items To Be Considered for Assessment of Potential Opportunity for Bias	Overall	Comments on methodology and identified limitations
Cohort study populations in review The review includes studies with the population of interest on key characteristics that are adequately similar in pooled data sufficient to limit potential bias.	1. The source populations in included cohort studies are adequate for key characteristics. 2. The literature review is sufficiently rigorous and adequately reported. 3. Recruitment in included cohort studies is adequately described (e.g. sequential recruitment). 4. Inclusion and exclusion criteria for cohort studies are adequately described. 5. The review reports key characteristics for individual patient data at baseline.	Partly	1. Yes. 2. No details of a literature search given in methods. No details given of the characteristics of the populations in either the included or excluded cohorts 3. No excluded studies are reported. 4. Partly. 5. Yes.
Study attrition Loss to follow-up of the individual patient data is not associated with key characteristics sufficient to limit potential bias.	1. Response rate (i.e. proportion individual patient data) providing outcome is adequate. 2. Reasons for loss to follow-up in review population are provided. 3. Cohort participants lost to follow-up are adequately described for key characteristics. 4. There are no important differences between key characteristics and outcomes in cohort study participants who completed the studies and those who did not.	Unclear	1. Unclear. 2. Not addressed. 3. Not addressed. 4. Not addressed.
Prognostic factor measurement The review adequately	1. Clear definition or description of the prognostic factor measured is provided for included cohort studies. 2. The prognostic factor measure and method are adequately	No	1. Yes. 2. No; data provided by self report. 3. Unclear if report was by interview or self report from

Potential Bias	Items To Be Considered for Assessment of Potential Opportunity for Bias	Overall	Comments on methodology and identified limitations
describes measurement of prognostic factor of interest in the included cohort studies sufficient to limit potential bias.	valid and reliable to limit misclassification bias. 3. Any variation between cohort studies for prognostic factor measurement is adequately addressed in statistical methods. 4. Individual patient data has complete data for prognostic factors or this has been accounted for in analysis 5. The method and setting of measurement are the same for included cohort studies.		questionnaire. Paternal history for women not available in 2 cohorts. Sibling history not available in 3 cohorts. 4. Unclear. 5. Unclear.
Outcome measurement The outcome of interest is adequately measured in included cohort studies to sufficient to limit potential bias.	1. A clear definition of the outcome of interest is provided, including duration of follow-up. 2. The outcome measure and method are adequately valid and reliable to limit misclassification bias. 3. The method and setting of measurement are the same for included cohort studies.	Yes	1. Yes 2. Yes. Fracture verified by radiology report or hospital/centre database in all cohorts. Definition of osteoporotic fracture differed between cohorts. 3. Unclear.
Confounding measurement and account Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest.	1. All important confounders are measured. 2. Clear definitions of the important confounders measured are provided. 3. Measurement of all important confounders is adequately valid and reliable. 4. The method and setting of confounding measurement are the same for all study participants. 5. Appropriate methods are used if imputation is used for missing confounder data. 6. Important potential confounders are accounted for in the review design. 7. Important potential confounders are accounted for in the analysis (i.e. appropriate adjustment).	Unclear	1. Confounders; BMD, age at baseline, gender. 2. Yes. 3. Unclear. 4. Unclear; different techniques. 5. Not done. 6. Yes. 7. Yes.
Analysis The statistical analysis is appropriate for the design of the review, limiting potential for	1. There is sufficient presentation of data to assess the adequacy of the analysis. 2. The selected model is adequate for the design of the review. 3. The strategy for model building (i.e. inclusion of variables) is	Yes	1. Yes. 2. Model; Poisson regression model in each cohort and each sex separately for any fracture, hip fracture, and osteoporotic fracture. β-coefficient of each cohort and sex is a linear function of age;$\beta k + \beta k+1xage$. Estimated

Potential Bias	Items To Be Considered for Assessment of Potential Opportunity for Bias	Overall	Comments on methodology and identified limitations
presentation of invalid results.	appropriate and is based on a conceptual framework or model. 4. Analysis addresses missing data if appropriate 5. There is no selective reporting of results.		value of β-coefficients and their variance determined for each sex from age 50 years. The results of each cohort and the two sexes were weighted means and standard deviations.RR of those with a family history versus those with no family history given by e (weighted mean coefficient). 3. Covariates; current age, time since start of follow-up, age at baseline, family history of fracture (and of hip fracture), with and without taking BMD information into account, current age x family history with BMD. Height as separate model. Separate analyses undertaken for a family history involving father, mother and siblings. 4. Not addressed. 5. No selective reporting.

D.1.4 Prognostic factor: Previous fracture and subsequent fracture risk

Table 7: Evidence table for previous fracture

Reference	Study type	Number of patients	Patient characteristics		Baseline and outcome variables	Statistical Methods	Source of funding
Bone. 2004 Aug;35(2): 375-82. A meta-analysis of previous fracture and subsequent	Meta-analyses from 7 cohorts Rotterdam, (Netherlands), EVOS/EPOS (Europe), CaMos	N=60 161 (75% Women)		Total	Prospective fracture ascertained by self-report (Sheffield, Kuopio EVOS/EPOS, Hiroshima) and/or verified from hospital or central databases (Gothenburg I and II, CaMos, DOES, Sheffield, EVOS/EPOS, Rochester, Rotterdam,	Risk of fracture; Poisson regression model in each cohort and each sex separately. Covariates included; current age, time since start of follow-up, prior history of fracture and BMD. Additionally BMD was excluded	GE Lunar, Lilly, Hologic, Roche, IGEA, Alliance for Better Bone Health, Novartis, Wyeth, Pfizer (unrestricted support).
			N	60 161			
			Person-years	254 582			
			Mean age (range) years	62.9 (21 to 106)			

fracture risk.
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.

(Canada),
Rochester
(USA), Sheffield
(UK), DOES
(Australia),
Gothenburg II
(Sweden)

Fracture history (%)	26%
Any fracture	5563
Hip fracture	978
Osteoporotic fracture	3350

Kuopio).

For Kuopio and OFELY all fractures recorded and no distinction made between fracture sites. For EVOS/EPOS and Gothenburg I, osteoporotic fractures only were recorded. In other cohorts, an osteoporotic fracture was considered to be due to osteoporosis either by investigator or by the Co-ordinating Centre. For EVOS study osteoporotic fracture comprised hip, forearm, humeral or limb fractures. For CaMos study fracture comprised spine, pelvis, ribs, distal forearm, forearm and hip. I

In other cohorts (Rochester, Rotterdam, Sheffield, DOES, Hiroshima, Gothenburg I) fractures at sites considered to be characteristic for osteoporosis were extracted from data (Kanis et al, 2002, Osteoporos Int 12, 417-427).

Outcomes
Any hip fracture
Hip fracture
Osteoporotic fracture

from the model. Further model included interaction term prior fracture x time to determine whether the strength of association of prior fracture and fracture risk waned with time.

β-coefficient for each sex in each cohort is a linear function of age; $\beta k + \beta k+1 \times age$. Estimated value of β-coefficients and their variance determined from age 50 to 80 years. The results of each cohort and the two sexes were weighted means and standard deviations.

The component of the RR explained by BMD was computed from meta-analysis of BMD and fracture risk. The risk of any fracture was assumed to increase 1.6 fold for each SD decrease in BMD. For hip fracture, the gradient of risk was assumed to be 2.6 per SD. The proportion of risk attributed to a low BMD was commuted as;
[log RRa/logGR] -[log RRb/logGR]
[log RRa/logGR]

Where log RRa is the unadjusted risk ratio. Where log RRb is the adjusted risk ratio for BMD and GR is the gradient of risk.

National Osteoporosis Foundation, International, Osteoporosis Foundation, International Society for Clinical Densitometry, European Community (EU FP 3/5).

Results

Prevalence of a prior fracture in men and women by age			
Age (years)	Probability of fracture (%)		
	Men	Women	Combined
30	44	15	24
40	43	18	27
50	42	23	30
60	41	29	34
70	40	35	37
80	39	41	41
90	38	48	45

Probability of recording a history of a prior fracture was higher in men than in women; OR = 1.19 (95%CI 1.14 to 1.25)

RR and 95%CI of fracture associated with a history of prior fracture in men and women, with and without adjustment for BMD						
	Men		Women		Combined	
	RR	95%CI	RR	95%CI	RR	95%CI
Without BMD						
Any	2.02	1.73 to 2.38	1.84	1.72 to 1.96	1.86	1.75 to 1.98
Osteoporotic	1.93	1.61 to 2.33	1.85	1.70 to 2.01	1.86	1.72 to 2.01
Hip	2.30	1.56 to 3.41	1.77	1.49 to 2.11	1.85	1.58 to 2.17
With BMD						
Any	2.04	1.67 to 2.48	1.77	1.59 to 1.88	1.77	1.64 to 1.91
Osteoporotic	1.91	1.50 to 2.43	1.76	1.57 to 1.92	1.76	1.60 to 1.93
Hip	1.97	1.12 to 3.48	1.62	1.23 to 1.98	1.62	1.30 to 2.01

The RR was marginally lower by approximately 10% taking in to account BMD. Assuming risk of any fracture increases 1.60 fold for each SD decrease in hip BMD, then difference in risk between those with and without a prior fracture is equal to an expected difference of 1.32 SD [log(1.86)/log(1.60)]. In reality, the difference in BMD at all ages in men and women combined was approximately 0.11 SD ([log(1.86)/log(1.60)] - log(1.77)/log(1.60)]). Thus, low BMD accounts for the minority (8%; 0.11/1.32) of the difference in risk between those with or without a prior fracture.

Fracture risk decreased by age by about 10% (p = 0.089) (shown graphically)

RR for any fracture and 95%CI comparing men and women with and without a previous fracture by age, with and without adjustment for BMI				
Age	RR without BMD1		RR with BMD1	
	Mean	95%CI	Mean	95%CI
50	1.92	1.63 to 2.20	1.91	1.59 to 2.29
55	1.90	1.73 to 2.09	1.83	1.60 to 2.10
60	1.98	1.80 to 2.18	1.94	1.73 to 2.17
65	2.02	1.86 to 2.20	1.99	1.81 to 2.20
70	2.03	1.87 to 2.21	1.98	1.79 to 2.18
75	1.96	1.80 to 2.13	1.82	1.65 to 2.02
80	1.88	1.72 to 2.06	1.72	1.54 to 1.91
85	1.83	1.65 to 2.04	1.72	1.51 to 1.96
All ages	1.86	1.75 to 1.98	1.77	1.64 to 1.91

1 prior fracture versus no fracture

RR for hip fracture and 95%CI comparing men and women with and without a previous fracture by age, with and without adjustment for BMD				
Age	RR without BMD1		RR with BMD1	
	Mean	95%CI	Mean	95%CI
50	5.04	2.66 to 9.56	3.88	1.79 to 8.43
55	4.20	2.46 to 7.15	3.98	2.08 to 7.62

60	3.40	2.21 to 5.24	3.16	1.88 to 5.32
65	2.60	1.85 to 3.64	2.28	1.52 to 3.41
70	2.31	1.76 to 3.02	1.90	1.37 to 2.65
75	2.14	1.71 to 2.68	1.64	1.24 to 2.17
80	1.90	1.58 to 2.28	1.41	1.12 to 1.78
85	1.66	1.39 to 1.98	1.32	1.04 to 1.68
All ages	1.85	1.58 to 2.17	1.62	1.30 to 2.01

1 prior fracture versus no fracture

Risk ratio highest at younger ages and decreased progressively with age (p < 0.002 for interaction arm). Risk decreased by 3% (95%CI = 1 to 5%) for each year of age. In men and women combined, low BMD explained 22% of the increase in RR and was constant by age (assuming a gradient of risk for hip fracture of 2.6/SD decrease in BMD)

Table 8:   Methodology checklist* for quality assessment of systematic reviews of prognostic studies
(*Adapted from Ann Intern Med. 2006 Mar 21;144(6):427-37. Evaluation of the quality of prognosis studies in systematic reviews. Hayden JA, Côté P, Bombardier C.)
Reference: Bone. 2004 Aug;35(2): 375-82. A meta-analysis of previous fracture and subsequent fracture risk. 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.

Potential Bias	Items To Be Considered for Assessment of Potential Opportunity for Bias	Overall	Comments on methodology and identified limitations
Cohort study populations in review The review includes studies with the population of interest on key characteristics that are adequately similar in pooled data sufficient to limit potential bias.	1. The source populations in included cohort studies are adequate for key characteristics. 2. The literature review is sufficiently rigorous and adequately reported. 3. Recruitment in included cohort studies is adequately described (e.g. sequential recruitment). 4. Inclusion and exclusion criteria for cohort studies are adequately described. 5. The review reports key characteristics for individual patient	Partly	1. Yes. 2. No details of a literature search given in methods. No details given of the characteristics of the populations in either the included or excluded cohorts 3. No excluded studies are reported. 4. Partly. 5. Yes.

Potential Bias	Items To Be Considered for Assessment of Potential Opportunity for Bias	Overall	Comments on methodology and identified limitations
	data at baseline.		
Study attrition Loss to follow-up of the individual patient data is not associated with key characteristics sufficient to limit potential bias.	1. Response rate (i.e. proportion individual patient data) providing outcome is adequate. 2. Reasons for loss to follow-up in review population are provided. 3. Cohort participants lost to follow-up are adequately described for key characteristics. 4. There are no important differences between key characteristics and outcomes in cohort study participants who completed the studies and those who did not.	Unclear	1. Unclear. 2. Not addressed. 3. Not addressed. 4. Not addressed.
Prognostic factor measurement The review adequately describes measurement of prognostic factor of interest in the included cohort studies sufficient to limit potential bias.	1. Clear definition or description of the prognostic factor measured is provided for included cohort studies. 2. The prognostic factor measure and method are adequately valid and reliable to limit misclassification bias. 3. Any variation between cohort studies for prognostic factor measurement is adequately addressed in statistical methods. 4. Individual patient data has complete data for prognostic factors or this has been accounted for in analysis 5. The method and setting of measurement are the same for included cohort studies.	Unclear	1. Yes. 2. Unclear; prior fracture ascertained differently in cohorts; self report and / or database. 3. Unclear if report was by interview or self report from questionnaire. 4. Unclear. 5. Unclear.
Outcome measurement The outcome of interest is adequately measured in included cohort studies to sufficient to limit potential bias.	1. A clear definition of the outcome of interest is provided, including duration of follow-up. 2. The outcome measure and method are adequately valid and reliable to limit misclassification bias. 3. The method and setting of measurement are the same for included cohort studies.	Yes	1. Yes. 2. Yes. Fracture verified by radiology report or hospital/centre database in all cohorts. Definition of osteoporotic fracture differed between cohorts. 3. Unclear.
Confounding measurement and account	1. All important confounders are measured. 2. Clear definitions of the important confounders measured are provided.	Unclear	1. Confounders; BMD, age, gender. 2. Yes. 3. Unclear.

Potential Bias	Items To Be Considered for Assessment of Potential Opportunity for Bias	Overall	Comments on methodology and identified limitations
Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest.	3. Measurement of all important confounders is adequately valid and reliable. 4. The method and setting of confounding measurement are the same for all study participants. 5. Appropriate methods are used if imputation is used for missing confounder data. 6. Important potential confounders are accounted for in the review design. 7. Important potential confounders are accounted for in the analysis (i.e. appropriate adjustment).		4. Unclear; different techniques. 5. Not done. 6. Yes.
Analysis The statistical analysis is appropriate for the design of the review, limiting potential for presentation of invalid results.	1. There is sufficient presentation of data to assess the adequacy of the analysis. 2. The selected model is adequate for the design of the review. 3. The strategy for model building (i.e. inclusion of variables) is appropriate and is based on a conceptual framework or model. 4. Analysis addresses missing data if appropriate 5. There is no selective reporting of results.	Yes	1. Yes. 2. Risk of fracture; Poisson regression model in each cohort and each sex separately. β-coefficient for each sex in each cohort is a linear function of age; $\beta k + \beta k+1 x age$. Estimated value of β-coefficients and their variance determined from age 50 to 80 years. The results of each cohort and the two sexes were weighted means and standard deviations. The component of the RR explained by BMD was computed from meta-analysis of BMD and fracture risk. The risk of any fracture was assumed to increase 1.6 fold for each SD decrease in BMD. For hip fracture, the gradient of risk was assumed to be 2.6 per SD. 3. Covariates included; current age, time since start of follow-up, prior history of fracture and BMD. Additionally BMD was excluded from the model. Further model included interaction term prior fracture x time to determine whether the strength of association of prior fracture and fracture risk waned with time. 4. Not done. 5. No selective reporting.

D.1.5   Prognostic factor: Smoking

Table 9:   Evidence table for smoking

Reference	Study type	Number of patients	Patient characteristics		Baseline and outcome variables	Statistical Methods	Source of funding
Osteoporos Int. 2005 Feb;16(2):155-62. Smoking and fracture risk: a meta-analysis. 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	Meta-analyses from 10 cohorts EVOS/EPOS (Europe), CaMos (Canada), Rotterdam (Netherlands, DOES (Australia), Sheffield (UK), Rochester (USA), Gothenburg I and II(Sweden), Hiroshima (Japan), Kupio (Finland)	N=59 232 (74% Women)	_(see sub-table below)_		History of current or past smoking obtained by self report. EVOS/EPOS, Hiroshima, Gothenburg I; recorded as past or present. Gothenburg II; past or present, but use for 6 months qualified as past or current use. Rotterdam, Sheffield DOES; recorded as previous, current or never. CaMos, Rochester; data on current use not available Height and weight measured by standard techniques in all cohorts. BMI calculated as weight in kg / height squared in metres. For purpose of this study,	Risk of fracture; Poisson regression model in each cohort and each sex separately for any fracture, hip fracture, and osteoporotic fracture. Covariates included; current age, time since start of follow-up, current age, history of smoking, and BMD. BMD was also excluded from model. β-coefficient for each cohort is age-dependent; $\beta k + \beta k = 1 \times age$. Estimated value of β-coefficients and their variance determined for each sex within age range 50-80 years. The results of each cohort and the both sexes were weighted according to variance and merged to determine weighted means and standard deviations. RR of those who currently	National Osteoporosis Foundation, International Society for Clinical Densitometry, European Community (EU FP 3/5). GE Lunar, Lilly, Hologic, Roche, IGEA, Alliance for Better Bone Health, Novartis, Pfizer, Wyeth (unrestricted support).

	Total
N	59 232
Person-years	249 897
Mean age	62.8
Smoking history (%) Current	18
Smoking history (%) Ever	52
Any fracture number	5444
Hip fracture number	957
Osteoporotic fracture number	3494

| | | | | data for BMD assessed at femoral neck by DXA with exception Gothenburg cohorts where BMD assessed by DPA at heal and DXA at distal forearm.

Fracture ascertained by self-report (Sheffield, EVOS/EPOS,Kupio, Hiroshima) and/or verified from hospital or central databases (Gothenburg, CaMos, DOES, Sheffield, EVOS/EPOS, Rochester, Rotterdam).

For EVOS/EPOS and CaMos investigator determined if fracture was osteoporotic. For EVOS/EPO, osteoporotic fracture comprised hip, forearm, humeral or spine fractures. For CaMos study fracture comprised spine, pelvis, ribs, distal forearm, forearm and hip. In other cohorts, fractures at sites considered to be characteristic for osteoporosis were extracted (Kanis et al, 2002, Osteoporos Int 12, 417-424). | smoked or ever smoked versus those who never smoked given by e (weighted mean coefficient)

Further models; effects including BMI with and without BMD.

Little heterogeneity noted between cohorts for relationship hip fracture risk and smoking (I2 = 12%, 95%CI 0 to 53%), a fixed-effects model was used.

The component of the RR explained by BMD was computed from meta-analysis of BMD and fracture risk. The risk of any fracture was assumed to increase 1.6 fold for each SD decrease in BMD. For hip fracture, the gradient of risk was assumed to be 2.6 per SD. The proportion of risk attributed to a low BMD was commuted as; [log RRa/logGR] -[log RRb/logGR] [log RRa/logGR] | |
|---|---|---|---|---|---|---|

Results

Outcome data			
	All men	All women	Overall
N			59 232
Total follow-up (person-years)	61 563	188 334	249 897
Any fracture	867	4577	5444
Hip fracture	207	750	957
Osteoporotic fracture	677	2817	3494
Available BMD (numbers (%))			36 550 (64%)
Available BMI (%)			96%

Prevalence of smoking history in men and women by age			
Age (years)	Probability of smoking (%)		
	Men	Women	Combined
50	41.3	26.8	32.9
55	37.2	22.3	28.4
60	33.3	18.3	28.3
65	29.6	15.0	20.6
70	26.1	12.1	17.4
75	22.9	9.7	14.6
80	20.0	7.8	12.1
85	17.4	6.2	10.0

Prevalence smoking among cohorts decreased almost linearly with age in men and women (p < 0.001. At all ages; current smoking higher in men than women.

Risk ratio of fracture and 95%confidence interval associated with current smoking by fracture outcome in men and women

Outcome	Sex	RR	95%CI	RR1	95%CI
Any kind of fracture	M	1.50	1.26 to 1.77	1.49	1.20 to 1.84
	F	1.18	1.07 to 1.30	1.02	0.90 to 1.16
	M + F	1.25	1.15 to 1.36	1.13	1.01 to 1.25
Osteoporotic fracture	M	1.53	1.27 to 1.83	1.54	0.21 to 1.95
	F	1.20	1.06 to 1.35	1.01	0.87 to 1.17
	M + F	1.29	1.17 to 1.43	1.13	1.00 to 1.28
Hip fracture	M	1.82	1.34 to 2.49	1.69	1.16 to 2.48
	F	1.85	1.46 to 2.34	1.55	1.16 to 2.07
	M + F	1.84	1.52 to 2.22	1.60	1.27 to 2.02

1 RR adjusted for BMD

Women; RR for any fracture or osteoporotic fracture lower when adjusted for BMD. Men; reduction less marked.

For fractures overall 45% of risk explained by BMD, osteoporotic alone 40% and for hip fracture 23%

Risk ratio for fracture and 95% confidence interval in men and women combined ; adjusted for age, BMD, BMI and both BMD and BMI						
Adjustment	Outcome fracture					
	Any fracture		Osteoporotic fracture		Hip fracture	
	RR	95%CI	RR	95%CI	RR	95%CI
Age	1.25	1.15 to 1.36	1.29	1.17 to 1.43	1.84	1.55 to 2.22
Age BMD	1.13	1.01 to 1.25	1.13	1.00 to 1.28	1.60	1.27 to 2.02
Age BMI	1.19	1.09 to 1.30	1.21	1.08 to 1.34	1.65	1.34 to 2.03
Age, BMI, BMD	1.12	1.01 to 1.25	1.11	0.98 to 1.26	1.55	1.23 to 1.96

RRs for smokers were adjusted downward when accounting for BMI. The downward adjustment was less than the adjustment for BMD alone. For BMI and BMD together slight RR reduction compared with BMD.

Risk ratios and 95% confidence intervals for osteoporotic and hip fractures in current smokers for men and women combined

Age	Without BMD		With BMD	
	RR	95%CI	RR	95%CI
Osteoporotic fracture				
50	1.05	0.80 to 1.37	0.82	0.57 to 1.18
55	1.06	0.86 to 1.30	0.85	0.65 to 1.12
60	1.08	0.92 to 1.26	0.88	0.72 to 1.08
65	1.14	1.00 to 1.30	0.91	0.76 to 1.09
70	1.27	1.12 to 1.45	1.01	0.85 to 1.20
75	1.45	1.28 to 1.65	1.20	1.01 to 1.43
80	1.54	1.34 to 1.77	1.30	1.08 to 1.57
85	1.52	1.28 to 1.80	1.28	1.00 to 1.63
Hip fracture				
50	2.52	1.24 to 5.10	2.28	0.94 to 5.51
55	2.35	1.32 to 4.19	2.09	1.03 to 4.24
60	2.17	1.38 to 3.44	1.87	1.07 to 3.25
65	1.98	1.38 to 2.86	1.68	1.07 to 2.65
70	1.92	1.42 to 2.60	1.69	1.15 to 2.48
75	1.94	1.52 to 2.49	1.76	1.30 to 2.37
80	1.91	1.55 to 2.35	1.69	1.31 to 2.19
85	1.80	1.43 to 2.26	1.57	1.16 to 2.13

Risk ratio of fracture and 95% confidence interval associated with smoking history by subsequent fracture outcome in men and women (not adjusted for BMD)			
Outcome	Sex	RR	95%CI
Any kind of fracture	M	1.27	1.07 to 1.51
	F	1.18	1.10 to 1.26
	M + F	1.19	1.12 to 1.27

Osteoporotic fracture	M	1.34	1.10 to 1.63	
	F	1.15	1.07 to 1.63	
	M + F	1.18	1.09 to 1.27	
Hip fracture	M	1.11	0.67 to 1.83	
	F	1.42	1.18 to 1.72	
	M + F	1.38	1.15 to 1.65	

A history smoking (ever smoked); increase risk for any fracture, osteoporotic and hip fracture. Similar risk in men and women. No difference when adjusted for BMD (data not shown). No effect of age (data not shown). Exclusion of Gothenburg cohorts (BMD assessed as heal or forearm) no effect (data not shown)

Table 10: **Methodology checklist* for quality assessment of systematic reviews of prognostic studies**
(*Adapted from Ann Intern Med. 2006 Mar 21;144(6):427-37. Evaluation of the quality of prognosis studies in systematic reviews. Hayden JA, Côté P, Bombardier C.
Reference: Osteoporos Int. 2005 Feb;16(2):155-62. Smoking and fracture risk: a meta-analysis. 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.

Potential Bias	Items To Be Considered for Assessment of Potential Opportunity for Bias	Overall	Comments on methodology and identified limitations
Cohort study populations in review The review includes studies with the population of interest on key characteristics that are adequately similar in pooled data sufficient to limit potential bias.	1. The source populations in included cohort studies are adequate for key characteristics. 2. The literature review is sufficiently rigorous and adequately reported. 3. Recruitment in included cohort studies is adequately described (e.g. sequential recruitment). 4. Inclusion and exclusion criteria for cohort studies are adequately described. 5. The review reports key characteristics for individual patient data at baseline.	Partly	1. Yes. 2. No details of a literature search given in methods. No details given of the characteristics of the populations in either the included or excluded cohorts 3. No excluded studies are reported. 4. Partly. 5. Yes.
Study attrition Loss to follow-up of the individual patient data is not associated with key characteristics	1. Response rate (i.e. proportion individual patient data) providing outcome is adequate. 2. Reasons for loss to follow-up in review population are provided. 3. Cohort participants lost to follow-up are adequately described	Unclear	1. Unclear. 2. Not addressed. 3. Not addressed. 4. Not addressed.

Potential Bias	Items To Be Considered for Assessment of Potential Opportunity for Bias	Overall	Comments on methodology and identified limitations
sufficient to limit potential bias.	for key characteristics. 4. There are no important differences between key characteristics and outcomes in cohort study participants who completed the studies and those who did not.		
Prognostic factor measurement The review adequately describes measurement of prognostic factor of interest in the included cohort studies sufficient to limit potential bias.	1. Clear definition or description of the prognostic factor measured is provided for included cohort studies. 2. The prognostic factor measure and method are adequately valid and reliable to limit misclassification bias. 3. Any variation between cohort studies for prognostic factor measurement is adequately addressed in statistical methods. 4. Individual patient data has complete data for prognostic factors or this has been accounted for in analysis 5. The method and setting of measurement are the same for included cohort studies.	No	1. Yes 2. No; smoking data obtained by self report. 3. No; definition of smoking past or current differed between cohorts. 4. Unclear. 5. Not applicable.
Outcome measurement The outcome of interest is adequately measured in included cohort studies to sufficient to limit potential bias.	1. A clear definition of the outcome of interest is provided, including duration of follow-up. 2. The outcome measure and method are adequately valid and reliable to limit misclassification bias. 3. The method and setting of measurement are the same for included cohort studies.	Yes	1. Yes. 2. Yes. Fracture verified by radiology report or hospital/centre database in all cohorts. Definition of osteoporotic fracture differed between cohorts 3. Unclear.
Confounding measurement and account Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of	1. All important confounders are measured. 2. Clear definitions of the important confounders measured are provided. 3. Measurement of all important confounders is adequately valid and reliable. 4. The method and setting of confounding measurement are the same for all study participants. 5. Appropriate methods are used if imputation is used for missing confounder data.	Partly	1. Confounders; BMD, age, gender. 2. Yes. 3. Yes. 4. No. 5. Not done. 6. Yes. 7. Yes.

Potential Bias	Items To Be Considered for Assessment of Potential Opportunity for Bias	Overall	Comments on methodology and identified limitations
interest.	6. Important potential confounders are accounted for in the review design. 7. Important potential confounders are accounted for in the analysis (i.e. appropriate adjustment).		
Analysis The statistical analysis is appropriate for the design of the review, limiting potential for presentation of invalid results.	1. There is sufficient presentation of data to assess the adequacy of the analysis. 2. The selected model is adequate for the design of the review. 3. The strategy for model building (i.e. inclusion of variables) is appropriate and is based on a conceptual framework or model. 4. Analysis addresses missing data if appropriate 5. There is no selective reporting of results.	Yes	1. Yes. 2. Risk of fracture; Poisson regression model in each cohort and each sex separately for any fracture, hip fracture, and osteoporotic fracture. β-coefficient for each cohort is age-dependent; βk + βk =1xage. Estimated value of β-coefficients and their variance determined for each sex within age range 50-80 years. The results of each cohort and the both sexes were weighted according to variance and merged to determine weighted means and standard deviations. RR of those who currently smoked or ever smoked versus those who never smoked given by e (weighted mean coefficient) . 3. Covariates; current age, time since start of follow-up, current age, history of smoking, BMD. 4. Not done. 5. No selective reporting.

D.1.6 Prognostic factor: Alcohol

Table 11: Evidence table for alcohol

Reference	Study type	Number of patients	Patient characteristics		Baseline and outcome variables	Statistical Methods	Source of funding
Osteoporos Int. 2005 Jul;16(7):737-42. 2004	Meta-analyses from 3 cohorts	N=16 971 (65% Women)		Total	Assessment alcohol intake Rotterdam and DOES; intake documented as	Risk of fracture; Poisson regression model in each cohort and each sex separately for any fracture,	International Osteoporosis Foundation, National
			N	N=16 971			

Alcohol intake as a risk factor for fracture. Kanis JA, Johansson H, Johnell O, Oden A, De Laet C, Eisman JA, Pols H, Tenenhouse A	CaMos (Canada), Rotterdam (Netherlands), DOES (Australia)					

Person-years	75 433
Mean age (years) (range)	65.0
Any fracture number	5444
Hip fracture number	957
Osteoporotic fracture number	3494

g/day. DOES intake documented as g/day. Review used units/day as the metric and divided the daily intake recorded in Rotterdam and DOES by 8 (the definition of a unit in the UK).

Fracture ascertained by self-report and verified from hospital central databases (Gothenburg, CaMos, DOES, Sheffield, EVOS/EPOS, Rochester, Rotterdam). Investigator determined if fracture was osteoporotic. For CaMos study; fracture comprised spine, pelvis, ribs, distal forearm, forearm and hip. For Rotterdam and DOES; fractures at sites considered to be characteristic for osteoporosis were extracted (Kanis et al, 2002, Osteoporos Int 12, 417-424).

 BMD assessed was undertaken at femoral neck by DXA in all centres.

hip fracture, and osteoporotic fracture.

Covariates included; current time' current age, alcohol intake, and alcohol intake x current age. Intake of alcohol was examined as a continuous or dichotomous variable. Additional models included covariates listed with BMD, current smoking and BMI.

β-coefficient for each cohort is age-dependent; $\beta k + \beta k =1xage$. Estimated value of β-coefficients and their variance determined for each sex from age 50 years. The results of each cohort and the both sexes were weighted according to variance and merged to determine weighted means and standard deviations.

RR of those on a given intake or less versus those on a higher intake was given by e (weighted mean coefficient)

Little heterogeneity noted between cohorts (p > 0.30), a fixed-effects model was used.

Osteoporosis Foundation, International Society for Clinical Densitometry, European Community (EU FP 3/5).

GE Lunar, Lilly, Hologic, Roche, IGEA, Alliance for Better Bone Health, Novartis, Wyeth (unrestricted support).

Results

Units of alcohol	Men		Women	
	N	%	N	%
0	2982	49.4	8692	77.2
1	1250	20.7	1598	14.2
2	605	10.0	479	4.3
3	433	7.2	292	2.6
4	292	4.8	109	1.0
5	178	3.0	52	0.5
6	92	1.5	19	0.2
7	52	0.9	14	0.1
8	57	0.9	4	
9	25	0.4	2	
10	22	0.4	0	
> 10	47	0.8	4	
Total	6036		11 265	

Alcohol intake was higher in men versus women.

49% of men and 77% of women took no alcohol.

8% of men and 1% women took 5 units or greater per day of alcohol.

Risk ratio and 95% confidence interval for osteoporotic and hip fracture per unit increase in alcohol intake in men and women. Gradient of risk is not adjusted for BMD. The reference base is 1 unit per day.			
Outcome	Sex	RR	95%CI
Osteoporotic fracture	M	1.04	1.01 to 1.07
	F	1.08	1.02 to 1.14

	M + F	1.05	1.02 to 1.08
Hip fracture	M	1.07	1.00 to 1.13
	F	1.11	0.98 to 1.26
	M + F	1.07	1.02 to 1.14

Assessing alcohol as a continuous variable, high intake associated with increased risk of osteoporotic and hip fracture.

For example; in men and women combined, risk of hip fracture increased by 7% for each additional unit of alcohol intake above 1 unit daily.

Risk ratio and 95% confidence interval for osteoporotic and hip fracture per according to intake of alcohol in men and women								
Alcohol intake (units/day)	Men				Women			
	Osteoporotic fracture		Hip fracture		Osteoporotic fracture		Hip fracture	
	RR	95%CI	RR	95%CI	RR	95%CI	RR	95%CI
0	1.06	0.83 to 1.34	0.94	0.58 to 1.54	0.96	1.85 to 1.08	0.98	1.75 to 1.27
1	1.00	-	1.00	-	1.00	-	1.00	-
2	1.05	0.92 to 1.20	1.21	0.92 to 1.59	1.07	0.99 to 1.16	1.09	0.91 to 1.29
3	1.38	0.87 to 2.18	1.91	1.21 to 3.03	1.20	0.91 to 1.58	1.33	1.01 to 1.75
4	1.81	1.24 to 2.64	2.84	1.21 to 6.64	1.38	1.12 to 1.69	1.72	1.08 to 2.73

Risk ratio increased with more than 2 units/day, but not increased below this level

Risk ratio and 95% confidence interval for fracture according to intake of alcohol in men and women combined, with and without BMD				
Categorisation (units/day)	Without BMD		Adjusted for BMD	
	RR	95%CI	RR	95%CI
Any fracture				
> 2	1.23	1.06 to 1.43	1.24	1.06 to 1.45
> 3	1.33	1.10 to 1.60	1.34	1.11 to 1.62
> 4	1.51	1.20 to 1.91	1.51	1.19 to 1.93
Any osteoporotic fracture				

> 2	1.38	1.16 to 1.65	1.36	1.13 to 1.63
> 3	1.55	1.26 to 1.92	1.53	1.23 to 1.91
> 4	1.70	1.30 to 2.22	1.64	1.24 to 2.17
Any hip fracture				
> 2	1.68	1.19 to 2.36	1.70	1.35 to 3.79
> 3	1.92	1.28 to 2.88	2.05	1.35 to 3.11
> 4	2.26	1.35 to 3.79	2.39	1.39 to 4.09

No effect on risk ratio when BMD was added to the model.

No difference in femoral neck BMD in individuals who abstained from alcohol (Z-score = -0.03 ±SD 1.02) from those taking 1 to 2 units daily (Z-score = -0.02 ±SD 0.99) and from those taking > 2 units daily (Z-score = -0.01±SD 1.00).

Risk ratio and 95% confidence interval associated with a consumption of > 2 units/day of alcohol with and without adjustment for smoking, body mass index and bone marrow density						
Model	Outcome fracture					
	Any fracture		Osteoporotic fracture		Hip fracture	
	RR	95%CI	RR	95%CI	RR	95%CI
Base case	1.23	1.06 to 1.43	1.38	1.16 to 1.65	1.68	1.19 to 2.36
+ smoking	1.22	1.03 to 1.43	1.36	1.13 to 1.63	1.50	1.50 to 2.15
+ smoking + BMD	1.24	1.05 to 1.46	1.38	1.14 to 1.66	1.54	1.07 to 2.22
+ BMD	1.21	1.04 to 1.41	1.35	1.13 to 1.61	1.64	1.16 to 2.32
+ BMI + BMD	1.22	1.14 to 1.43	1.34	1.11 to 1.61	1.67	1.16 to 2.38

When outcome dichotomised at > 2 units daily, no confounding effect of smoking or BMI on the association

Table 12: Methodology checklist* for quality assessment of systematic reviews of prognostic studies
(*Adapted from Ann Intern Med. 2006 Mar 21;144(6):427-37. Evaluation of the quality of prognosis studies in systematic reviews. Hayden JA, Côté P, Bombardier C.

Reference: Osteoporos Int. 2005 Jul;16(7):737-42. 2004 Alcohol intake as a risk factor for fracture. Kanis JA, Johansson H, Johnell O, Oden A, De Laet C, Eisman JA, Pols H, Tenenhouse A.

Potential Bias	Items To Be Considered for Assessment of Potential Opportunity for Bias	Overall	Comments on methodology and identified limitations
Cohort study populations in review The review includes studies with the population of interest on key characteristics that are adequately similar in pooled data sufficient to limit potential bias.	1. The source populations in included cohort studies are adequate for key characteristics. 2. The literature review is sufficiently rigorous and adequately reported. 3. Recruitment in included cohort studies is adequately described (e.g. sequential recruitment). 4. Inclusion and exclusion criteria for cohort studies are adequately described. 5. The review reports key characteristics for individual patient data at baseline.	Partly	1. Yes. 2. No details of a literature search given in methods. No details given of the characteristics of the populations in either the included or excluded cohorts 3. No excluded studies are reported. 4. Partly. 5. Yes.
Study attrition Loss to follow-up of the individual patient data is not associated with key characteristics sufficient to limit potential bias.	1. Response rate (i.e. proportion individual patient data) providing outcome is adequate. 2. Reasons for loss to follow-up in review population are provided. 3. Cohort participants lost to follow-up are adequately described for key characteristics. 4. There are no important differences between key characteristics and outcomes in cohort study participants who completed the studies and those who did not.	Unclear	1. Unclear. 2. Not addressed. 3. Not addressed. 4. Not addressed.
Prognostic factor measurement The review adequately describes measurement of prognostic factor of interest in the included cohort studies sufficient to limit potential bias.	1. Clear definition or description of the prognostic factor measured is provided for included cohort studies. 2. The prognostic factor measure and method are adequately valid and reliable to limit misclassification bias. 3. Any variation between cohort studies for prognostic factor measurement is adequately addressed in statistical methods. 4. Individual patient data has complete data for prognostic factors or this has been accounted for in analysis 5. The method and setting of measurement are the same for	No	1. Yes. 2. Unclear. 3. Unclear; assessment differed between cohorts 4. Not addressed, 5. No.

Potential Bias	Items To Be Considered for Assessment of Potential Opportunity for Bias	Overall	Comments on methodology and identified limitations
	included cohort studies.		
Outcome measurement The outcome of interest is adequately measured in included cohort studies to sufficient to limit potential bias.	1. A clear definition of the outcome of interest is provided, including duration of follow-up. 2. The outcome measure and method are adequately valid and reliable to limit misclassification bias. 3. The method and setting of measurement are the same for included cohort studies.	Yes	1. Yes. 2. Yes; fractures verified by hospital database. 3. Unclear.
Confounding measurement and account Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest.	1. All important confounders are measured. 2. Clear definitions of the important confounders measured are provided. 3. Measurement of all important confounders is adequately valid and reliable. 4. The method and setting of confounding measurement are the same for all study participants. 5. Appropriate methods are used if imputation is used for missing confounder data. 6. Important potential confounders are accounted for in the review design. 7. Important potential confounders are accounted for in the analysis (i.e. appropriate adjustment).	Partly	1. Confounders; BMD, age, gender. 2. Yes. 3. Yes. 4. No. 5. Not done. 6. Yes. 7. Yes.
Analysis The statistical analysis is appropriate for the design of the review, limiting potential for presentation of invalid results.	1. There is sufficient presentation of data to assess the adequacy of the analysis. 2. The selected model is adequate for the design of the review. 3. The strategy for model building (i.e. inclusion of variables) is appropriate and is based on a conceptual framework or model. 4. Analysis addresses missing data if appropriate 5. There is no selective reporting of results.	Unclear	1. Yes. 2. Model; Poisson regression model in each cohort and each sex separately for any fracture, hip fracture, and osteoporotic fracture. β-coefficient for each cohort is age-dependent; $\beta k + \beta k = 1 x age$. Estimated value of β-coefficients and their variance determined for each sex from age 50 years. The results of each cohort and the both sexes were weighted according to variance and merged to determine weighted means and standard deviations.RR of those on a given intake or less versus those on a higher intake was given by e (weighted

Potential Bias	Items To Be Considered for Assessment of Potential Opportunity for Bias	Overall	Comments on methodology and identified limitations
			mean coefficient). 3. Covariates; current time' current age, alcohol intake, and alcohol intake x current age, BMD, current smoking and BMI. 4. Not addressed. 5. No selective reporting.

D.1.7 Evidence tables for history of falls

Fall in past 12 months

Table 13: Evidence table, Chen 2009

Bibliographic reference	Study type	Number of patients	Patient characteristics	Prognostic factor	Length of follow-up	Outcome measures	Source of funding	Study quality / additional comments
Age Ageing. 2009 Jul;38(4):429-34. Risk factors for hip fracture among institution-alised older people. Chen JS, Sambrook	Prognostic cohort study	1894 men and women	The Fracture Risk Epidemiology in the frail Elderly (FREE) study' Subjects recruited from 52 nursing homes and 30 intermediate-care nursing care facilities in Northern Sydney Health Services area during March 1999 and February 2003. 461 men and 1433 women. Mean age (SD) = 86(7.1) Baseline characteristics by subsequent hip fracture status |	N subjects measured	Subjects without	Subjects with new		Fall in past 12 months	Mean (SD) 2.65 (1.38) years	Hip fracture	Australian National Health and Medical Research Council and Osteoporosis Australia.	Subjects followed-up for hip fracture every 6–12 weeks. Hip fractures were validated by X-ray reports. HR for fall in last 12

PN, Simpson JM, Cameron ID, Cumming RG, Seibel MJ, Lord SR, March LM.

		new hip (N = 1703)	hip (N = 191)
Mean(SD) age (years)	1894	85.4(7.1)	86.6(6.4)
Female number (%)	1894	1280(75.2)	153(80.1)
Mean(SD) weight (kg)	1777	60.5(14.4)	57.7(12.5)
Past fall, number (%)	1841	865(52.3)	96(51.3)
Previous fracture number (%)	1877	772(42.8)	104(54.7)

month not adjusted for any con-founders. 15 residents were lost to follow-up.

Results

201 hip fractures were recorded in 191 subjects (overall hip fracture incidence rate = 4.0% per person year).

Univariate analysis

HR(95%CI) for risk of hip fracture; fall in past year

Fall in past 12 months

0.95(0.72 to 1.26)

Table 14: **Quality assessment, Chen 2009 (reference: Age Ageing. 2009 Jul;38(4):429-34. Risk factors for hip fracture among institutionalised older people. Chen JS, Sambrook PN, Simpson JM, Cameron ID, Cumming RG, Seibel MJ, Lord SR, March LM).**

	Items To Be Considered for Assessment of Potential Opportunity for Bias	Overall
1.1	The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results	Yes

	Items To Be Considered for Assessment of Potential Opportunity for Bias	Overall
1.2	Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias	Yes
1.3	The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias	Unclear
1.4	The outcome of interest is adequately measured in study participants, sufficient to limit bias	Yes
1.5	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest	No
1.6	The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results	Yes

Table 15: Evidence table, Wolinsky 2009

Bibliographic reference	Study type	Number of patients	Patient characteristics	Prognostic factor	Length of follow-up	Outcome measures	Source of funding	Study quality / additional comments
J Gerontol A Biol Sci Med Sci. 2009 Feb;64(2):249-55. Recent hospitalization and the risk of hip fracture among older Americans. Wolinsky FD, Bentler SE, Liu L, Obrizan M, Cook EA, Wright KB, Geweke JF, Chrischilles EA, Pavlik CE,	Prognostic cohort study	5511 men and women	Survey on Asset and Health Dynamics Among the Oldest Old (AHEAD) study. Subjects were aged ≥ 70 years recruited from 1993 to 1994 in USA. 38% male. Subjects had to have clinical data linked to their Medicare claims. Baseline characteristics (N = 5511): Characteristic / Value; Age range 69 to 74 (%) (years) 38; Age range 75 to 79 (%) (years) 29	Fall in past 112 months	Mean per person 7.1 years	Hip fractures	National Institute of Health.	Hip fractures identified by ICD9-CM principle admitting diagnostic codes 820.xx. Unclear description of baseline interview.

Bibliographic reference	Study type	Number of patients	Patient characteristics		Prognostic factor	Length of follow-up	Outcome measures	Source of funding	Study quality / additional comments
Ohsfeldt RL, Jones MP, Richardson KK, Rosenthal GE, Wallace RB			Age range 80 to 84 (%) (years)	19					
			Age range 85+ (%) (years)	19					
			Hip fracture (%)	4					
			Any fall past 12 months (%)	25					

Results

Total number of person-years surveillance = 39112

8.9% sustained hip fracture.

Multivariate adjusted* HR for hip fracture; fall in past 12 months

1.35 (P < 0.001)

* adjusted for age, sex, race, residence type, body mass, smoking history, diabetes, psychological problems, heart disease, cognitive function.

Table 16:   Quality assessment, Wolinsky 2009 (Reference: J Gerontol A Biol Sci Med Sci. 2009 Feb;64(2):249-55. Recent hospitalization and the risk of hip fracture among older Americans. Wolinsky FD, Bentler SE, Liu L, Obrizan M, Cook EA, Wright KB, Geweke JF, Chrischilles EA, Pavlik CE, Ohsfeldt RL, Jones MP, Richardson KK, Rosenthal GE, Wallace RB)

	Items To Be Considered for Assessment of Potential Opportunity for Bias	Overall
1.1	The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results	Yes
1.2	Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias	Yes
1.3	The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias	Unclear

	Items To Be Considered for Assessment of Potential Opportunity for Bias	Overall
1.4	The outcome of interest is adequately measured in study participants, sufficient to limit bias	Yes
1.5	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest	Yes
1.6	The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results	Yes

Table 17:   Evidence table, Guessous 2008

Bibliographic reference	Study type	No. of patients	Patient characteristics	Prognostic factor	Length of follow-up	Outcome measures	Source of funding	Study quality / additional comments
Radiology. 2008 Jul;248(1):179-84. Osteoporotic fracture risk in elderly women: estimation with quantitative heel US and clinical risk factors. Guessous I, Cornuz J, Ruffieux C, Burckhardt P, Krieg MA.	Prognostic cohort study	6714 women	Swiss Evaluation of the Methods of Measurement of Osteoporosis Fracture Risk (SEMOF) study. Women aged ≥ 70 years recruited from ten major Swiss osteoporosis centres; 7609 women were contacted, 495 women did not answer the 6 month questionnaire and were considered lost to follow-up. Of the remaining 7114 women eligible for analysis, 930 were exclude due to missing data and 10 women were older than 85 years. Final cohort was 6174 women with age range 70 to 85 years). Exclusions History of hip fracture, bilateral hip replacement, renal failure, active cancer or dementia. Baseline characteristics (N = 6714) Characteristic / Value	Fall in past 12 months	2.8 years	Fracture of hip, wrist or arm	Concordat des Caisses-Maladies Suisses.	Falls data obtained by interview with trained research assistants. Fractures were confirmed by medical report from treating physician.

Mean (SD) age (years)	75.1 (3.1)
Mean (SD) height (cm)	158.6 (6.1)
Mean (SD) weight (kg)	65.1 (11.2)
Mean (SD) BMI (kg/m2)	25.9 (4.3)
Falls in past year N (%)	1915 (31)
Fracture history N (%)	3186 (52)

Results

Fractures

317 women had fractures giving an incidence of 17 per 1000 women-years. The incidence amongst excluded women was similar (14 per 1000 women-years).

Univariate analysis

Falls in past 12 months statistically significant predictor of hip, wrist or arm fracture (P < 0.001).

Mutivariate Cox Model falls in past 12 months HR (95%CI)

1.40 (1.11 to 1.76) (P < 0.003)

Table 18: **Evidence table, Guessous 2008 (reference: Radiology. 2008 Jul;248(1):179-84. Osteoporotic fracture risk in elderly women: estimation with quantitative heel US and clinical risk factors. Guessous I, Cornuz J, Ruffieux C, Burckhardt P, Krieg MA.)**

	Items To Be Considered for Assessment of Potential Opportunity for Bias	Overall
1.1	The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results	Yes
1.2	Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias	Yes
1.3	The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias	Yes
1.4	The outcome of interest is adequately measured in study participants, sufficient to limit bias	Yes
1.5	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest	Yes
1.6	The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results	Yes

Table 19: Evidence table, Hans 2008

Bibliographic reference	Study type	Number of patients	Patient characteristics	Prognostic factor	Length of follow-up	Outcome measures	Source of funding	Study quality / additional comments
J Bone Miner Res. 2008 Jul;23(7):1045-51. Assessment of the 10-year probability of osteoporotic hip fracture combining clinical risk factors and heel bone ultrasound: the EPISEM prospective cohort of 12,958 elderly women. Hans D, Durosier C, Kanis JA, Johansson H, Schott-Pethelaz AM, Krieg MA.	Prospective cohort study	12 958 women	EPISEM database which combined 2 prospective multicentre population-based cohorts; EPIDOS (Epidemiology of osteoporosis) cohort of 7598 French women aged ≥ 75 years SEMOF (Swiss evaluation of the Methods of measurement of osteoporotic fracture risk) cohort of 7062 Swiss women aged ≥ 70 years	Fall in past 12 months	Mean (S D) 3.2 (0.9) years	Hip fracture	None stated	Fall in past year determined by structured questionnaire. Incident fractures determined (1) through direct contact with subjects at 4 month intervals for EPIDOS and 6 month intervals for SEMOF (2) from family members or (3) from subject's physician. Fracture events were confirmed from subject's medical record.

Baseline characteristics (N = 12 958)	
Characteristic	Value
Mean age(SD) Range (years)	77.6(4.3) 70 to 100
Mean(SD) height (cm)	154(5.9)
Mean(SD) weight (kg)	62.7(11.1)
Mean(SD) BMI (kg/m2)	25.7(4.2)
Fall in past 12 months (%)	28.0
Prior history of fracture (%)	48.5

Results

During follow; 307 hip fractures with incidence of 7.32 per 1000 woman-years.

Univariate HR (95%CI) risk of hip fracture; fall in past 12 months

1.36(1.08 to 1.73)

Multivariate* HR (95%CI) risk of hip fracture; fall in past 12 months

1.27(1.00 to 1.61)

* adjusted for age, BMI, history of fracture after age 50 years, results of chair test, current cigarette smoking, diabetes mellitus

Multivariate* HR (95%CI) risk of hip fracture; fall in past 12 months

1.29(1.01 to 1.65)

* adjusted for age, BMI, history of fracture after age 50 years, results of chair test, current cigarette smoking, diabetes mellitus, stiffness index

Table 20: Quality assessment, Hans 2008 (Reference: J Bone Miner Res. 2008 Jul;23(7):1045-51. Assessment of the 10-year probability of osteoporotic hip fracture combining clinical risk factors and heel bone ultrasound: the EPISEM ospective cohort of 12,958 elderly women. Hans D, Durosier C, Kanis JA, Johansson H, Schott-Pethelaz AM, Krieg MA.)

	Items To Be Considered for Assessment of Potential Opportunity for Bias	Overall
1.1	The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results	Yes
1.2	Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias	Unclear
1.3	The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias	Unclear
1.4	The outcome of interest is adequately measured in study participants, sufficient to limit bias	Yes
1.5	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest	Yes
1.6	The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results	Yes

Table 21: Evidence table, Lewis 2007

Bibliographic reference	Study type	Number of patients	Patient characteristics	Prognostic factor	Length of follow-up	Outcome measures	Source of funding	Study quality / additional comments
J Bone Miner Res. 2007 Feb;22(2):211-9.	Prognostic cohort study	5995 men	5995 men ≥ 65 years of age recruited from Mar 2000 to April 2002 from populations of Birmingham AL, Minneapolis MN,	Any falls in past 12 months	Mean (SD) 4.1(0.9) years	Non-spine fracture	National Institute of Health, National	Reports of fracture verified by physician adjudication of medical records and X-ray

Predictors of non-spine fracture in elderly men: the MrOS study. Lewis CE, Ewing SK, Taylor BC, Shikany JM, Fink HA, Ensrud KE, Barrett-Connor E, Cummings SR, Orwoll E;			Pittsburgh PA, Palo Alto CA, Portland OR, San Diego CA: USA. Osteoporotic Fractures in Men (MrOS) Study			Institute Arthritis and Musculoskeletal and Skin Diseases. National Institute on Aging. National Cancer Institute.	reports. Unclear if fall data verified. Fall HR adjusted for age, and age and BMD. 112 men excluded who reported taking osteoporosis medication at baseline, 3 men receiving testosterone injections, 4 men missing data at follow-up. 5876 men (98%) in analyses.

Baseline characteristics (N = 5876)	
Characteristic	Value
Age ≥ 80 years	17.6%
Any fall in past year	20.9%
Mean(SD) weight (kg)	83.3(3.3)
Mean(SD) height (cm)	174.2(6.8)

Results

Of 5876 men, 4.7% (N = 275) reported an incident nonspine fracture during follow-up (11.46/1000 person-years). Considering all fracture, the most common were; ribs 18.6%, hip 16.4%, wrist 13.8% and ankle 7.6%.

Any falls in previous year HR (95%CI)
Age-adjusted
1.82(1.42 to 2.35)
Age and BMD adjusted
1.82(1.41 to 2.34)

Multivariate analysis*
Any falls in previous year HR (95%CI) excluding BMD
1.56(1.21 to 2.02)
controlling for BMD
1.59(1.23 to 2.05)
including BMD
1.58(1.22 to 2.04)

*adjusted for total hip BMD, fracture at or after age 50, age ≥ 80 years, use of tricyclic antidepressants, unable to complete any narrow walk trial, depressed mood, clinical site and race ethnicity

Table 22: Quality assessment, Lewis 2007 (Reference: J Bone Miner Res. 2007 Feb;22(2):211-9. Predictors of non-spine fracture in elderly men: the MrOS study. Lewis CE, Ewing SK, Taylor BC, Shikany JM, Fink HA, Ensrud KE, Barrett-Connor E, Cummings SR, Orwoll E.)

	Items To Be Considered for Assessment of Potential Opportunity for Bias	**Overall**
1.1	The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results	Yes
1.2	Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias	Yes
1.3	The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias	Unclear
1.4	The outcome of interest is adequately measured in study participants, sufficient to limit bias	Yes
1.5	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest	Yes
1.6	The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results	Yes

Table 23: Evidence table, Diez-Perez 2007

Bibliographic reference	**Study type**	**Number of patients**	**Patient characteristics**	**Prognostic factor**	**Length of follow-up**	**Outcome measures**	**Source of funding**	**Study quality / additional comments**
Osteoporos Int. 2007 May;18(5):629-39. Prediction of absolute risk of non-spinal fractures using clinical risk factors and heel quantitative	Prognostic cohort study	5201 women	Ecografía Osea en Atención Primaria (ECOSAP) study. Women ≥ 65 years recruited from throughout Spain primary care centres from Mar 2000 to June 2001. Exclusion Paget's disease of bone, multiple myeloma, known bone metastases, serum creatinine > 265 micromole/dl, serum calcium > 11.0 mg/dl, immobilisation > 3 months previous year, anomalies of right foot, therapeutic doses	Fall in past 12 months	Mean (SD) 2.83 (0.72) years	Non-spinal low-trauma fracture Excluded Severe trauma fracture, fractures of skull, face	Department Medical Research, Ely Lilly and Company (Madrid) Spain.	Women returned to study centre every 6 months for evaluation. Investigators conducted questionnaire with the

						metacarpals and phalanges		subject. All fractures confirmed by site investigator who viewed original X-ray file or radiological or surgery report. 99 women (1.9%) died during follow-up.
ultrasound. Díez-Pérez A, González-Macías J, Marín F, Abizanda M, Alvarez R, Gimeno A, Pegenaute E, Vila J; for the Ecografía Osea en Atención Primaria study investigators.			fluoride for > 3 months in past 2 years, estimated life expectancy < 3 years, participation in study involving drug therapy.					

Baseline characteristics (N = 5201)	
Characteristic	Value
Mean age(SD) Range (years)	68(10.3) 50 to 99
Mean(SD) height (cm)	164.6(6.5)
Mean(SD) weight (kg)	62.9(10.3)
Mean(SD) BMI (kg/m2)	28.11(8.4)
Fall in last 12 months N(%)	257(14.2)

Results

Total follow-up 14 999 women years, 311 women suffered at least one incident low-trauma fracture, a cumulative fracture rate of 6.0%, incident rate of 2420 per 100 000 women years. Overall adjudicated non-vertebral fractures was 363 including 133 forearm/wrist, 54 hip, 50 humerus, 37 leg and 17 pelvic fractures. 52% (1.0%) women sustained 2 or fractures, 99 women (1.9%) died from unrelated causes during follow-up

Multivariate Cox regression analysis for independent prediction of fall in last 12 months versus none risk factor for fracture, HR(95%CI)

Overall non-spinal fractures; 1.70(1.35 to 2.15)	Main non-spinal fractures; 1.66(1.28 to 2.15)	Humerus fractures; 1.53(0.86 to 2.27)
Hip fractures; 1.23(0.68 to 2.22)	Wrist/forearm fractures; 2.05(1.39 to 3.01)	

Table 24: Quality assessment, Diez-Perez 2007 (Reference: Osteoporos Int. 2007 May;18(5):629-39. Prediction of absolute risk of non-spinal fractures using clinical risk factors and heel quantitative ultrasound. Díez-Pérez A, González-Macías J, Marín F, Abizanda M, Alvarez R, Gimeno A, Pegenaute E, Vila J; for the Ecografía Osea en Atención Primaria study investigators)

	Items To Be Considered for Assessment of Potential Opportunity for Bias	Overall
1.1	The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results	Yes
1.2	Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias	Yes

	Items To Be Considered for Assessment of Potential Opportunity for Bias	Overall
1.3	The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias	Yes
1.4	The outcome of interest is adequately measured in study participants, sufficient to limit bias	Yes
1.5	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest	Yes
1.6	The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results	Yes

Table 25:   Evidence table, Nguyen 2005

Bibliographic reference	Study type	Number of patients	Patient characteristics	Prognostic factor	Length of follow-up	Outcome measures	Source of funding	Study quality / additional comments
J Bone Miner Res. 2005 Nov;20(11):1921-8. Epub 2005 May 31. Identification of high-risk individuals for hip fracture: a 14-year prospective study. Nguyen ND, Pongchaiyakul C, Center JR, Eisman JA, Nguyen TV	Prognostic cohort study	1669 men and women	Dubbo Osteoporosis Epidemiology Study (DOES). Men and women ≥ 60 years recruited in 1989 from Dubbo, Australia.	Fall in past 12 months	Median (IQR) 12 (6 to 13) years	Hip fracture	National Health and Medical Council AU, GE-Lunar, Merck AU, Eli Lilly, Inter-national Aventis AU.	Baseline assessment question-naire completed during interview by nurse co-ordinator. Fractures confirmed by radiology report, and confirmed as low trauma at interview.

Baseline characteristics by fracture status
Women (N =960)

	Hip fracture N = 86	Non hip fracture N = 874	P value
Mean (SD) age(years)	78.0(7.7)	70.3(7.4)	<0.001
Mean (SD) height (cm)	155.5(6.6)	160.0(6.2)	<0.001
Mean (SD) weight (kg)	55.4(11.0)	66.2(12.4)	<0.001
Mean (SD) BMI (kg/m2)	23(4)	26(5)	<0.001

Fall past 12 months N (%)	55(64.0)	407(34.0)	0.001
Previous fracture N (%)	18(20.9)	85(9.7)	0.001

Baseline characteristics by fracture status Men (N = 689)			
	Hip fracture N = 29	Non hip fracture N = 660	P value
Mean (SD) age(years)	77.0(7.5)	68.9(6.1)	<0.001
Mean (SD) height (cm)	169.5(7.5)	173.6(6.9)	0.002
Mean (SD) weight (kg)	72.0(14.2)	78.9(2.4)	0.005
Mean (SD) BMI (kg/m2)	25(4)	26(4)	0.070
Fall past 12 months N (%)	13(44).0)	191(24.0)	0.067
Previous fracture N (%)	9(31.0)	39(4.7)	<0.001

Follow-up; 9961 person-years for women and 6643 person-years for men.

Hip fracture

86 women with incidence of 9.4 years (95%CI 5.0 to 17.6 per-person years).

29 men with incidence of 4.4 years (95%CI 1.8 to 10.8 per person years).

Univariate Cox's proportional model HR (95%CI) for risk of hip fracture; fall in past 12 months

Women; 2.0(1.3 to 3.2)

Men; 2.0(1.0 to 4.4)

Multivariate Cox's proportional model: HR (95%CI) for risk of hip fracture; fall in past 12 months

Adjusted for age
Women and men; 2.0(1.4 to 2.9)

Adjusted for femoral neck BMD
Women and men; 2.0(1.6 to 2.4)

Adjusted for femoral neck BMD, age, gender
Women and men; 1.4(0.9 to 2.1)

Table 26: Quality assessment, Nguyen 2005 (Reference: J Bone Miner Res. 2005 Nov;20(11):1921-8. Identification of high-risk individuals for hip fracture: a 14-year prospective study. Nguyen ND, Pongchaiyakul C, Center JR, Eisman JA, Nguyen TV)

	Items To Be Considered for Assessment of Potential Opportunity for Bias	Overall
1.1	The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results	Yes
1.2	Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias	Unclear
1.3	The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias	Yes
1.4	The outcome of interest is adequately measured in study participants, sufficient to limit bias	Yes
1.5	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest	Yes
1.6	The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results	Yes

Table 27: Evidence table, Porthouse 2004

Bibliographic reference	Study type	Number of patients	Patient characteristics	Prognostic factor	Length of follow-up	Outcome measures	Source of funding	Study quality / additional comments
QJM. 2004	Prognostic	8933	Women aged ≥ 70 years in North Yorkshire	Fall in past	24 months	Any non-	None	Fall in last 12

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Sep;97(9):569-74. Risk factors for fracture in a UK population: a prospective cohort study. Porthouse J, Birks YF, Torgerson DJ, Cockayne S, Puffer S, Watt I.	cohort study	women	and North Cumbria, UK. Recruited from Nov 1999 to Mar 2001.	12 months		vertebral fracture (fingers, toes, ribs excluded) Hip fracture Wrist fracture	stated.	months and fracture data obtained by self questionnaire. At follow-up 248 women died, and *4393 didn't respond or had withdrawn from the study, hence complete data available on 4292 women.

Baseline characteristics (N = 4292)*	
Characteristic	Value
Mean(SD) age (years)	76.9(5.14)
Mean(SD) weight (kg)	64.25(11.05)
Previous fracture N(%)	1867(43.6%)
Maternal hip fracture N(%)	498(11.6)
Current smoker N(%)	335(7.8%)
Fall in past 12 months N(%)	1253(29.3)
Low body weight (<58kg) N(%)	1247(29.10
Anti-fracture treatments	
HRT N(%)	107(2.5)
Calcium /vitamin D N(%)	429(10)
Bi-phosphonates N(%)	257(6)
SERMS N(%)	9(0.2)

Results

Incidence of fracture

any non-vertebral fracture = 330

hip fracture = 57

wrist fracture = 125

Univariate analysis OR(95%CI for risk of fracture; fall in last 12 months;

any non-vertebral fracture;

2.06 (1.63 to 2.59), P < 0.0001

hip fracture;

2.92 (1.70 to 5.01), P < 0.0001

wrist fracture;

1.60 (1.10–2.31), P = 0.012

Table 28: **Quality assessment, Porthouse 2004 (Reference: QJM. 2004 Sep;97(9):569-74. Risk factors for fracture in a UK population: a prospective cohort study. Porthouse J, Birks YF, Torgerson DJ, Cockayne S, Puffer S, Watt I.)**

	Items To Be Considered for Assessment of Potential Opportunity for Bias	Overall
1.1	The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results	Yes
1.2	Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias	No
1.3	The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias	Unclear
1.4	The outcome of interest is adequately measured in study participants, sufficient to limit bias	Unclear
1.5	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest	No
1.6	The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results	Unclear

Table 29: Evidence table, Seeley 1996

Bibliographic reference	Study type	Number of patients	Patient characteristics	Prognostic factor	Length of follow-up	Outcome measures	Source of funding	Study quality / additional comments
J Bone Miner Res. 1996 Sep;11(9):1347-55. Predictors of ankle and foot fractures in older women. The Study of	Prognostic cohort study	9704 women	Study of Osteoporotic Fractures (SOF) study. Women aged ≥ 65 years recruited at 4 clinical sites in USA (Baltimore MA, Minneapolis MN, Monongahela Valley PE, Portland OR) from 1986 to 1988. Baseline characteristics (N = 9704)	Fall in past year	Mean (SD) 5.9 (1.2) years	Ankle fracture Foot fracture	National Institute Health.	Baseline assessment questionnaire completed during interview. Women followed every 4 months by telephone or mail to record incident

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Osteoporotic Fractures Research Group. Seeley DG, Kelsey J, Jergas M, Nevitt MC.			Group/characteristic	Value						fracture. Fracture confirmed by X-ray.
			Ankle fracture (N=191) Mean age (SD) (years)	71.2(5.0)						
			Foot fracture (N=204) Mean age (SD) (years)	71.4(5.2)						
			No fracture (N=9147) Mean age (SD) (years)	71.7(5.3)						
			Ankle fracture (N=191) Fracture since age 50 (%)	40						
			Foot fracture (N=204) Fracture since age 50 (%)	44						
			No fracture (N=9147) Fracture since age 50 (%)	37						
			Ankle fracture (N=191) Fall in 12 months (%)	39						
			Foot fracture (N=204) Fall in past year (%)	29						
			No fracture (N=9147) Fall in past year (%)	30						

Results

191 women sustained at least 1 ankle fracture, 204 women sustained foot fractures. 10 women sustained both. Incidence ankle fractures = 3.4 per 1000 women-years, foot fractures = 3.4 women-years. 85% all ankle fractures associated with fall, 62% foot fractures associated with fall.

RR(95%) of ankle fracture adjusting for age; fall in past 12 months

1.76(1.26 to 2.46)

Multivariate* of fall in past year

1.53(1.14 to 2.06)

*adjusting for age, bone mass, weight gain since 25 years, vigorous activity ≤ 1trip out of house/week, history of osteoarthritis, sister fractured hip after age 50, oestrogen and/or vitamin D use, grip strength, use arm to stand from chair, low contrast sensitivity (vision)

No data given for ankle fracture.

Table 30: Quality assessment, Seeley 1996 (Reference: J Bone Miner Res. 1996 Sep;11(9):1347-55. Predictors of ankle and foot fractures in older women. The Study of Osteoporotic Fractures Research Group. Seeley DG, Kelsey J, Jergas M, Nevitt MC.)

	Items To Be Considered for Assessment of Potential Opportunity for Bias	Overall
1.1	The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results	Yes
1.2	Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias	Yes
1.3	The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias	Yes
1.4	The outcome of interest is adequately measured in study participants, sufficient to limit bias	Yes
1.5	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest	Yes
1.6	The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results	Yes

Table 31: Evidence table, Vogt 2002

Bibliographic reference	Study type	Number of patients	Patient characteristics	Prognostic factor	Length of follow-up	Outcome measures	Source of funding	Study quality / additional comments
J Am Geriatr Soc. 2002 Jan;50(1):97-103. Distal radius fractures in older women: a 10-year follow-up study of descriptive characteristics and risk factors. The study of osteoporotic fractures. Vogt MT, Cauley JA, Tomaino MM, Stone K, Williams JR, Herndon JH.	Prognostic cohort study	9704 women	Study of Osteoporotic Fractures (SOF) study. Women aged ≥ 65 years recruited at 4 clinical sites in USA (Baltimore MA, Minneapolis MN, Monongahela Valley PE, Portland OR) from 1986 to 1988.	Fall(s) in past 12 months	Mean 9.8 years	Distal radius fracture	Public Health Service Grants	Baseline assessment questionnaire completed during interview. Women followed every 4 months by telephone or mail to record incident fracture. Follow-up 99% complete. Fracture confirmed by 2 orthopaedic surgeons re-reviewing radiology reports.

Results

527 distal radius fractures during 9.8 years of follow-up (72 932 person years). Incidence of fractures = 7.3 fractures per 1000 person years. 73% fractures were extra-articular and 27% were intra-articular (incidence 5.3 and 1.9 per 1000 person years, respectively). More than 98% of fractures occurred after a minor fall.

RR (95%CI) for fall(s) (adjusted for age)

Prognostic factor	All distal radius fractures (N = 527) RR(95%CI)	Extra-articular fractures (N = 527) RR(95%CI)	Intra-articular fractures (N = 527) RR(95%CI)
Fell in past year	1.2(1.0 to 1.2)	1.4(0.0 to 1.7)	0.9(0.9 to 1.4)
Fell 2 or more times in past year	1.6(1.2 to 2.0)	1.4(1.0 to 1.9)	2.1(1.4 to 3.2)

Mutivariate RR(95%CI) for falls

Prognostic factor	All distal radius fractures (N = 527) RR(95%CI)	Extra-articular fractures (N = 527) RR(95%CI)	Intra-articular fractures (N = 527) RR(95%CI)
Fell 2 or more times in past year	1.6(1.2 to 2.0)	1.4(1.0 to 1.9)	2.2(1.5 to 3.4)

Table 32: Quality assessment, Vogt 2002 (reference: J Am Geriatr Soc. 2002 Jan;50(1):97-103. Distal radius fractures in older women: a 10-year follow-up study of descriptive characteristics and risk factors. The study of osteoporotic fractures. Vogt MT, Cauley JA, Tomaino MM, Stone K, Williams JR, Herndon JH.)

	Items To Be Considered for Assessment of Potential Opportunity for Bias	Overall
1.1	The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results	Yes
1.2	Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias	Yes
1.3	The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias	Yes
1.4	The outcome of interest is adequately measured in study participants, sufficient to limit bias	Yes
1.5	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic	Yes

	Items To Be Considered for Assessment of Potential Opportunity for Bias	Overall
	factor of interest	
1.6	The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results	Yes

Fall in past 6 months

Table 33:   Evidence table, van Staa 2005

Bibliographic reference	Study type	Number of patients	Patient characteristics	Prognostic factor	Length of follow-up	Outcome measures	Source of funding	Study quality / additional comments
QJM. 2005 Mar;98(3):191-8. A simple score for estimating the long-term risk of fracture in patients using oral glucocorticoids. van Staa TP, Geusens P, Pols HA, de Laet C, Leufkens HG, Cooper C.	Prognostic cohort study	191 752 men and women	Subjects taking oral glucocorticoids aged ≥ 40 years (39.8% men), from General Practice Research Database (GPRD), which comprises the computerized medical records of general practitioners UK.	Fall in past 6 months	Mean 2.5 years per person	Fracture	Proctor and Gamble Pharmaceuticals.	Fall in past 6 months and fracture determined from GPRD. 59.5% of total follow-up classified as past exposure to oral glucocorticoids.

Within the Patient characteristics cell:

Baseline characteristics N = 191 752	
	Prevalence
BMI < 20	4.8%
BMI ≥ 20	43.5%
Fall in past 6 months	1.6%
Fracture history	10.7%
Indication for oral glucocorticoids	
Rheumatoid arthritis	8.1%
Polymyalgia rheumatica	11.0%
Non-infectious enteritis and colitis	7.1%

| | Respiratory disease | 53.5% | | | | | |
| | Hospitalisation for oral glucocorticoids indication in year before | 5.5% | | | | | |

Results

RR(95%CI) for fracture*; falls in past 6 months

Clinical osteoporotic fracture; 2.57(2.30 to 2.86)

Femur/hip fracture; 2.52(2.12 to 3.00)

Clinical vertebral fracture; 2.24(1.71 to 2.92)

*adjusted for age and sex

Table 34: Quality assessment, van Staa 2005 (reference: QJM. 2005 Mar;98(3):191-8. A simple score for estimating the long-term risk of fracture in patients using oral glucocorticoids. van Staa TP, Geusens P, Pols HA, de Laet C, Leufkens HG, Cooper C.)

	Items To Be Considered for Assessment of Potential Opportunity for Bias	Overall
1.1	The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results	Yes
1.2	Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias	Yes
1.3	The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias	Unclear
1.4	The outcome of interest is adequately measured in study participants, sufficient to limit bias	Unclear
1.5	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest	Yes
1.6	The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results	Yes

Table 35: Evidence table, Dargent-Molina 2002

Bibliographic reference	Study type	Number of patients	Patient characteristics	Prognostic factor	Length of follow-up	Outcome measures	Source of funding	Study quality / additional comments

Osteoporos Int. 2002 Jul;13(7):593-9. Use of clinical risk factors in elderly women with low bone mineral density to identify women at higher risk of hip fracture: The EPIDOS prospective study. Dargent-Molina P, Douchin MN, Cormier C, Meunier PJ, Bréart G; EPIDOS Study Group.	Prognostic cohort study	6933 women	EPIDemiologie de l'OSteoporose (EPIDOS) Study	Fall in past 6 months	Mean (SD) 3.7 (0.8)	Hip fracture	INSERM-MSD-Chibret	Women followed every 4 months by telephone or mail to record incident fracture. History of falls by self report.

EPIDemiologie de l'OSteoporose (EPIDOS) Study

Caucasian women ≥ 75 years recruited in France from Jan 1992 to Jan 1995

Women ≥ 75 years with no missing value for femoral hip BMD and weight.

Exclusion

Previous hip fracture, bilateral hip replacement, prolonged corticotherapy, immobilisation

Baseline characteristics (N = 6933)	
Characteristic	Value
Mean(SD) age (years)	80.5(3.7)
Mean(SD) femoral neck BMD (g/cm2)	0.71(0.11)
Mean(SD) weight (kg)	59.8(10.4)

Results

25 380 women years of follow-up; 276 women suffered hip fracture. Risk of hip fracture in population = 10.9 per 1000 woman-years.

Multivariate Cox regression model adjusted* RR (95%CI) for hip fracture

Falll during past 6 months;

1.4(0.9 to 2.0)

*adjusted for age, tandem walk(able after several trials, unable, not performed), gait speed, visual acuity.

Table 36: **Quality assessment, Dargent-Molina 2002 (reference: Osteoporos Int. 2002 Jul;13(7):593-9. Use of clinical risk factors in elderly women with low bone mineral density to identify women at higher risk of hip fracture: The EPIDOS prospective study. Dargent-Molina P, Douchin MN, Cormier C, Meunier PJ, Bréart G; EPIDOS Study Group.)**

	Items To Be Considered for Assessment of Potential Opportunity for Bias	Overall
1.1	The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results	Yes
1.2	Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias	Yes
1.3	The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias	Unclear
1.4	The outcome of interest is adequately measured in study participants, sufficient to limit bias	Unclear
1.5	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest	Yes
1.6	The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results	Yes

Table 37: **Evidence table, Lee 2002**

Bibliographic reference	Study type	Number of patients	Patient characteristics	Prognostic factor	Length of follow-up	Outcome measures	Source of funding	Study quality / additional comments
J Bone Miner Res. 2002 May;17(5):817-25. Risk factors for fractures of the proximal humerus: results from the EPIDOS prospective study. Lee SH, Dargent-Molina P, Bréart G; EPIDOS Group.	Prognostic cohort study	6901 women	EPIDemiologie de l'OSteoporose (EPIDOS) Study Caucasian women ≥ 75 years recruited in France from Jan 1992 to Jan 1995

Exclusion

Previous hip fracture, history of hip replacement, prolonged immobilisation, history of proximal | Fall in past 6 months | Mean (SD) 3.6 (0.8) | Humeral fracture | INSERM-MSD-Chibret | Women followed every 4 months by telephone or mail to record incident fracture. Fracture confirmed by X-ray or radiological report. Baseline examination performed by trained nurse, questionnaire, |

Epidemiologie de l'Osteoporose Study			humeral fracture.					clinical and functional assessment, BMD and ultrasound measurement. 83 (1.2%) lost to follow-up, 629 (9.1%) women died.

Baseline characteristics (N = 6901)	
Characteristic	Value
Mean (SD) age (years)	80.5(3.7)
N(%) women with falls in past 6 months	1626(23%)

Results

25 033 person-years of follow-up; 439 (6.4%) discontinued,

165 women had first incident humeral fractures (incident rate 6.6 per 1000 person-years) occurring at mean (SD) age 82.2(4).

Multivariate adjusted* RR (95%CI)for risk of humeral fracture; fall in past 6 months

First year of follow-up

1.1(0.6 to 2.0)

Second year of follow-up

1.50(1.0 to 2.3)

Third year of follow-up 2.2

(1.4 to 3.4)

Fourth year of follow-up for osteoporotic fracture

3.0(1.5 to 6.1)

*adjusted for femoral neck BMD, calcaneal SOS, maternal history of hip fracture, number of physical activities, closed-eye static balance score, ankle or foot pain.

Table 38: Quality assessment, Lee 2002 (reference: J Bone Miner Res. 2002 May;17(5):817-25. Risk factors for fractures of the proximal humerus: results from the EPIDOS prospective study. Lee SH, Dargent-Molina P, Bréart G; EPIDOS Group. Epidemiologie de l'Osteoporose Study)

	Items To Be Considered for Assessment of Potential Opportunity for Bias	Overall
1.1	The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results	Yes
1.2	Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias	Yes
1.3	The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias	Yes

	Items To Be Considered for Assessment of Potential Opportunity for Bias	Overall
1.4	The outcome of interest is adequately measured in study participants, sufficient to limit bias	Yes
1.5	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest	Yes
1.6	The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results	Yes

Fall in past 90 days

Table 39: Evidence table, Stolee 2009

Bibliographic reference	Study type	Number of patients	Patient characteristics	Prognostic factor	Length of follow-up	Outcome measures	Source of funding	Study quality / additional comments
J Gerontol A Biol Sci Med Sci. 2009 Mar;64(3):403-10. Risk factors for hip fracture in older home care clients. Stolee P, Poss J, Cook RJ, Byrne K, Hirdes JP.	Prospective cohort study	40 279 men and women	Subjects aged ≥ 60 years who had received an intake assessment on entering residential home (long-stay >60 days) in Ontario Canada. Subjects were assessed between 18th January 2002 and 22nd August 2006 and had at least 1 follow-up assessment. Mean age (SD) = 81.5 (7.1), 68.5% female.\n\nExcluded\nSubjects who had had a hip fracture at intake assessment.	One or more fall in past 90 days	180 to 1440 days	Hip fracture	Canadian Institutes of Health Research Institute of Musculoskeletal Health and Arthritis	Fall history determined as part of the Resident Assessment Instrument (RAI)/Minimum Data Set–Home Care assessment instrument. Unclear how fracture data ascertained.

Results

Total number of assessments = 110 928 assessments. 1003 subjects (2.5) had hip fracture on follow-up assessment (incidence rate = 24.4/1,000 person-years of follow-up; 27.8/1,000 for females; 17.1/1,000 for males).

Falls in past 90 days for subjects with hip fracture = 44.9%. Falls in past 90 days for subjects without hip fracture = 37.9%

Univariate RR(95%CI) for hip fracture; one or more fall in past 90 days (age and sex adjusted)

1.44(1.27 to 1.64)

Multivariate RR(95%CI) for hip fracture; one or more fall in past 90 days (age and sex adjusted)

1.28(1.12 to 1.46)

Subjects with osteoporosis RR (95%CI) = 1.59(1.27 to 2.00). Subjects without osteoporosis RR (95%CI) = 1.23(1.05 to 1.43).

Table 40: Quality assessment, Stolee 2009 (reference: J Gerontol A Biol Sci Med Sci. 2009 Mar;64(3):403-10. Risk factors for hip fracture in older home care clients. Stolee P, Poss J, Cook RJ, Byrne K, Hirdes JP.)

	Items To Be Considered for Assessment of Potential Opportunity for Bias	Overall
1.1	The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results	Yes
1.2	Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias	Yes
1.3	The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias	Yes
1.4	The outcome of interest is adequately measured in study participants, sufficient to limit bias	Unclear
1.5	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest	Yes
1.6	The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results	Yes

Fall in past month

Table 41: Evidence table, Papaioannou 2005

Bibliographic reference	Study type	Number of patients	Patient characteristics	Prognostic factor	Length of follow-up	Outcome measures	Source of funding	Study quality / additional comments
Osteoporos Int. 2005 May;16(5):568-78. Risk factors associated with incident clinical	Prognostic cohort study	5143 women	Canadian Multicentre Osteoporosis Study (CaMos). Postmenopausal women aged > 25 years recruited from 1995 to 1997 in Canada. Baseline characteristics by fracture status	Falls in past month	3 years	Number of falls past month	National Health Research and Development Programme.	Falls determined at baseline interview with by investigator

vertebral and nonvertebral fractures in postmen-opausal women: the Canadian Multicentre Osteoporosis Study (CaMos).

Papaioannou A, Joseph L, Ioannidis G, Berger C, Anastassiades T, Brown JP, Hanley DA, Hopman W, Josse RG, Kirkland S, Murray TM, Olszynski WP, Pickard L, Prior JC, Siminoski K, Adachi JD.

	None (N = 4829)	Vertebral (N = 34)
Mean(SD) age (years)	66.4(9.6)	74.4(10.0)
Mean(SD) height (cm)	159.3(6.5)	155.8(7.4)
Mean(SD) weight (kg)	68.6(13.5)	59.4(10.5)
Mean(SD) BMI Lumbar spine (g/cm2)	0.92(0.17)	0.79(0.17)
Mean(SD) BMI Femoral neck (g/cm2)	0.69(0.12)	0.56(0.10)
Fall in past month N(%)	0.1(0.4)	0.1(0.2)

Baseline characteristics by fracture status

	Main non Vertebral fracture (N = 163)	Any non vertebral fracture (N = 74)
Mean(SD) age (years)	70.4(7.5)	69.9(6.1)
Mean(SD) height (cm)	150.0(6.7)	159.5(6.8)
Mean(SD) weight (kg)	67.3(13.1)	67.9(13.2)
Mean(SD) BMI Lumbar spine (g/cm2)	0.84(0.15)	0.85(0.15)

and fractures ascertain by self report and confirmed by physician.

	Mean(SD) BMI Femoral neck (g/cm2)	0.63(0.11)	0.65(0.10)					
	Fall in past month N (%)	0.1(0.3)	0.1(0.3)					

Results

Fracture

314 (6.2%) women sustained a fracture, 34 vertebral, 163 main non-vertebral, 280 any non-vertebral fracture.

Multivariate HR (95%CI) for fracture; fall in past month

Main nonvertebral fracture

0.970(0.562 to 1.675)

Any non-vertebral fracture

1.028(0.689 to 1.532)

Table 42: Quality assessment, Papaioannou 2005 (reference: Osteoporos Int. 2005 May;16(5):568-78. Risk factors associated with incident clinical vertebral and nonvertebral fractures in postmenopausal women: the Canadian Multicentre Osteoporosis Study (CaMos). Papaioannou A, Joseph L, Ioannidis G, Berger C, Anastassiades T, Brown JP, Hanley DA, Hopman W, Josse RG, Kirkland S, Murray TM, Olszynski WP, Pickard L, Prior JC, Siminoski K, Adachi JD.)

	Items To Be Considered for Assessment of Potential Opportunity for Bias	Overall
1.1	The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results	Yes
1.2	Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias	Yes
1.3	The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias	Yes
1.4	The outcome of interest is adequately measured in study participants, sufficient to limit bias	Yes
1.5	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest	Yes
1.6	The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results	Yes

History of falls

Table 43:   Evidence table, Hippisley-Cox 2009

Bibliographic reference	Study type	Number of patients	Patient characteristics	Prognostic factor	Length of follow-up	Outcome measures	Source of funding	Study quality / additional comments
BMJ. 2009 Nov 19;339:b4229. Predicting risk of osteoporotic fracture in men and women in England and Wales: prospective derivation and validation of QFractureScores Hippisley-Cox J, Coupland C.	Prognostic cohort study	2 357 865 men and women	Inclusion Primary care patients (England and Wales) aged 30 to 85 years at study entry from eligible practices during 15 years from 1/1/1993-30/6/2008. At least 1 year patient data. Open cohort design (entry throughout whole study period); 183 633 women and 1 174 232 men. Exclusion Previous recorded fracture (hip, distal radius, or vertebral), temporary / interrupted registration, no valid Townsend deprivation score.	History of falls	15 years	Osteoporotic fracture (distal radius, or vertebral) Hip fracture	David Stables (medical director of EMIS) as part of larger study on risks and benefits of HRT.	Study stated 'history of falls' unclear timing. Recorded in primary care database; QResearch, before baseline. Unclear if fracture data confirmed by radiology. Imputed data to replace missing values for smoking status, alcohol, BMI.

Baseline characteristics N = 2 357 865		
	Women	Men
N	1 183 633	1 174 232
Mean (IQR) age (years)	48 (37-62)	46 (37-59)
BMI recorded (%)	884 523 (74.73)	781 619 (66.56)
Mean (SD) BMI (kg/m2)	25.88 (4.86)	26.43 (4.08)
History of falls	8801 (0.74)	4676

			(%)		(0.39)					

Results

Incident rates of osteoporotic fracture per 1000 person years

Women

Total = 24 350

Rate/1000(95%CI)

3.08 (3.04 to 3.12)

Men

Total = 7934

Rate/1000(95%CI)

0.99 (0.96 to 1.01)

Incident rates of hip fracture per 1000 person years

Women

Total = 9302

Rate/1000(95%CI)

1.15 (1.13 to 1.17)

Men

Total = 3067

Rate/1000(95%CI)

0.38 (0.36 to 0.39)

Multivariate adjusted* HR(95%CI) for osteoporotic fractures in women; history of falls

Complete case analysis; 1.65(1.45 to 1.87)

Multiply imputed data; 1.82(1.66 to 1.99)

Multivariate adjusted* HR(95%CI) for hip fracture in women; history of falls

Complete case analysis; 1.69(1.40 to 2.05)

Multiply imputed data; 2.03(1.80 to 2.29)

Multivariate adjusted* HR(95%CI) for osteoporotic fractures in men; history of falls

Complete case analysis; 2.17(1.60 to 2.93)
Multiply imputed data; 2.23(1.80 to 2.75)

Multivariate adjusted* HR(95%CI) for hip fracture in men; history of falls
Complete case analysis; 2.29(1.46 to 3.61)
Multiply imputed data; 2.66(2.03 to 3.49)

*adjusted for smoking, alcohol consumption, rheumatoid arthritis, CVD, Type 2 diabetes, asthma, current tricyclic antidepressants, current corticosteroids, liver disease, fractional polynomial terms for age and BMI.

Table 44: Quality assessment, Hippisley-Cox 2009 (reference: BMJ. 2009 Nov 19;339:b4229. Predicting risk of osteoporotic fracture in men and women in England and Wales: prospective derivation and validation of QFractureScores. Hippisley-Cox J, Coupland C.)

	Items To Be Considered for Assessment of Potential Opportunity for Bias	Overall
1.1	The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results	Yes
1.2	Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias	Yes
1.3	The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias	Unclear
1.4	The outcome of interest is adequately measured in study participants, sufficient to limit bias	Unclear
1.5	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest	Yes
1.6	The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results	Yes

Table 45: Evidence table, van Staa 2006

Bibliographic reference	Study type	Number of patients	Patient characteristics	Prognostic factor	Length of follow-up	Outcome measures	Source of funding	Study quality / additional comments
QJM. 2006	Prognostic	366 104	Women aged ≥ 50 years	History of	Mean 5.8	Fracture	Proctor and	Study stated

Oct;99(10):673-82. A simple clinical score for estimating the long-term risk of fracture in post-menopausal women. van Staa TP, Geusens P, Kanis JA, Leufkens HG, Gehlbach S, Cooper C	cohort study	women	included in the THIN Research Database (containing computerized medical records of UK general practices).	falls	years (median 4.7 years)	Femur/hip Clinical vertebrate Other clinical osteoporotic	Gamble Pharmaceuticals Ltd.	'history of falls' unclear timing. Hip fracture confirmed in 91.0% of fracture cases by GP. Missing data reported for BMI and smoking only.

Prevalence	
Age (years)	
50 to 59	33.7%
60 to 69	27.2%
70 to 79	23.2%
80 to 89	13.0%
90 +	2.9%
BMI	
< 20	6.2%
≥ 20	44.8%
Fracture history	8.1%
Fall history	1.7%

Results

6453 women suffered a hip fracture (1610 clinical vertebral and 14 011 other osteoporotic fractures).

Age-adjusted RR of fracture (95%CI); history of fall

Femur/hip; 1.96(1.79 to 2.15)

Clinical vertebrate; 1.82(1.47 to 2.25)

Other clinical osteoporotic; 1.74(1.60 to 1.89)

Table 46: Quality assessment, van Staa 2006 (reference: QJM. 2006 Oct;99(10):673-82. A simple clinical score for estimating the long-term risk of fracture in post-menopausal women. van Staa TP, Geusens P, Kanis JA, Leufkens HG, Gehlbach S, Cooper C.)

	Items To Be Considered for Assessment of Potential Opportunity for Bias	Overall
1.1	The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential	Yes

	Items To Be Considered for Assessment of Potential Opportunity for Bias	Overall
	bias to the results	
1.2	Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias	Yes
1.3	The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias	Unclear
1.4	The outcome of interest is adequately measured in study participants, sufficient to limit bias	Unclear
1.5	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest	Yes
1.6	The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results	Yes

Greater than 2 falls last year of follow-up

Table 47: Evidence table, Cauley 2007

Bibliographic reference	Study type	Number of patients	Patient characteristics	Prognostic factor	Length of follow-up	Outcome measures	Source of funding	Study quality / additional comments
J Bone Miner Res. 2007 Nov;22(11):1816-26. Clinical risk factors for fractures in multi-ethnic women: the Women's Health Initiative. Cauley JA, Wu L, Wampler NS, Barnhart JM, Allison M, Chen Z, Jackson R, Robbins J.	Prognostic cohort study	159 579 women	Women's Health Initiative (WHI); composed of an observational cohort (N = 92 368) and three overlapping clinical trials (N = 67 211) of hormone therapy, dietary modification and calcium and vitamin D supplementation. Postmenopausal women aged 50 to 79 years recruited from 1993 to 1998, USA. Age at screening; mean(SD) Caucasian (N = 133 533) 63.6(7.2) Black (N = 14 627) 61.6(7.1) Hispanic (N= 6512) 60.2(6.8) Asian/Pacific Islander (N = 4192) 63.0(7.5)	> 2 falls during last year follow-up year	Mean (SD) 9.8(2.6) years	Fracture (except those of fingers, toes, skull, face or sternum)	None stated.	Fall history determined by self report. Fracture confirmed by radiology report. At study end, 5.7% subjects were deceased, 4.3% subjects had withdrawn or were lost to follow-up.

	American Indian (N = 715) 61.6(7.5) Number of falls during last follow-up year > 2 times; N(%) Caucasian; 8910(6.7) Black; 739(5.1) Hispanic; 328(5.0) Asian/Pacific Islander; 185(4.4) American Indian; 58(8.1)

Results

Incident fractures occurred in 23 270 women; hip fractures 7%, and clinical spine fractures 9%

1.7 (1.9, 2.0)

Mutivariate HR(95%CI) for risk of any fracture; > 2 falls during last year follow-up

Caucasian; 1.27(1.22 to 1.32)

Black; 1.67(1.38 to 2.02)

Hispanic; 1.80(1.40 to 2.32)

Asian/Pacific Islander; 1.41(1.04 to 1.91)

American Indian; 1.38(0.75 to 2.55)

Table 48: Quality assessment, Cauley 2007 (reference: J Bone Miner Res. 2007 Nov;22(11):1816-26. Clinical risk factors for fractures in multi-ethnic women: the Women's Health Initiative. Cauley JA, Wu L, Wampler NS, Barnhart JM, Allison M, Chen Z, Jackson R, Robbins J.)

	Items To Be Considered for Assessment of Potential Opportunity for Bias	Overall
1.1	The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results	Yes
1.2	Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias	Yes
1.3	The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias	Unclear
1.4	The outcome of interest is adequately measured in study participants, sufficient to limit bias	Yes
1.5	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest	Yes

	Items To Be Considered for Assessment of Potential Opportunity for Bias	Overall
1.6	The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results	Yes

Fall rate and history of fall

Table 49: Evidence table, Sambrook 2007

Bibliographic reference	Study type	Number of patients	Patient characteristics	Prognostic factor	Length of follow-up	Outcome measures	Source of funding	Study quality / additional comments
Osteoporos Int. 2007 May;18(5):603-10. Influence of fall related factors and bone strength on fracture risk in the frail elderly. Sambrook PN, Cameron ID, Chen JS, Cumming RG, Lord SR, March LM, Schwarz J, Seibel MJ, Simpson JM.	Prognostic cohort study	2005 men and women	Fracture Risk Epidemiology in Elderly (FREE) study. 473 men and 1532 women in residential care facilities (mean age(SD) 85.7(7.1), range 65 to 104 years), 30 intermediate care or 52 nursing homes in Northern Sydney Health Services area, Australia **Baseline characteristics by fracture status** 	Mean (SD) or ratio (%)	Subjects with any fractures N = 315	Subjects without fractures N = 1690	P value
---	---	---	---
Age (years)	89.6 (6.5)	85.5 (7.2)	0.001
Male: Female)	16.5:83.5	24.9:75.1	0.001
Weight (kg)	57.1(11.8)	60.7(14.5)	<0.001
Previous fall, yes: no	54.7:45.3	52.8:47.2	0.54		History of fall Fall rate per (person year) ≥ 3.08 1.05 to > 3.08 0.5 to < 1.00 0	Median 705 days	Fracture	Australian Health and Medical Research Council, Osteoporosis Australian, Arthritis Australia.	Fracture ascertained from records every 6 weeks and confirmed by radiology, falls ascertained every 6 weeks.

			Previous fracture, yes: no	57.1:42.9	43.1:56.9	<0.001					
			Subjects with any fracture versus no fracture; no difference in incidence of stroke, Parkinson's, number of medications								

Results

Follow-up (median 705 days) ; falls

Of 2005 subjects; 663 subjects had no falls, 1342 subjects sustained 6646 falls giving fall rate of 214 falls per 100 person years (30% fell once, 36% fell 2 to 4 times).

Follow-up (median 705 days): Fracture

375 fracture events in 316 subjects, some subjects had > 1 fracture in separate falls, or > 1 fracture in the same fall/event (405 total fractures).

Fracture sites;

hip: 118, vertebral: 75, pelvic: 47, wrist: 34, humeral: 31, rib: 26, femoral shaft: 17, miscellaneous: 57. Of 375 fracture events, 82% attributed to fall.

Overall fracture rate: 12.1 / 100 person years.

Fall related fracture rate; 4.6 / 100 falls for total fracture and 1.7 / 100 falls for hip fracture.

Univariate analysis for fracture risk; Incident risk ratio per unit of measurement (IRR) (95%CI)

History of fall

1.14(0.90 to 1.43)

Univariate analysis for fracture risk; IRR(95% CI); Fall rate (per person year)

≥ 3.08

3.05 (2.21 to 4.20)

1.05 to < 3.08

2.22 (1.59 to 3.09)

0.5 to < 1.00

1.67 (1.19 to 2.34)

0

1

Multivariate analysis for fracture risk by method of negative binomial regression; IRR(95% CI)

≥ 3.08

3.35 (2.38 to 4.72)

1.05 to < 3.08

2.42 (1.71 to 3.42)

0.5 to < 1.00

1.65 (1.17 to 2.34)

0

1

Table 50: Quality assessment, Sambrook 2007 (reference: Osteoporos Int. 2007 May;18(5):603-10. Influence of fall related factors and bone strength on fracture risk in the frail elderly. Sambrook PN, Cameron ID, Chen JS, Cumming RG, Lord SR, March LM, Schwarz J, Seibel MJ, Simpson JM.)

	Items To Be Considered for Assessment of Potential Opportunity for Bias	Overall
1.1	The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results	Yes
1.2	Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias	Yes
1.3	The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias	Yes
1.4	The outcome of interest is adequately measured in study participants, sufficient to limit bias	Yes
1.5	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest	Yes
1.6	The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results	Yes

Table 51: Evidence table, Schwartz 2005

Bibliographic reference	Study type	Number of patients	Patient characteristics	Prognostic factor	Length of follow-up	Outcome measures	Source of funding	Study quality / additional comments

Am J Epidemiol. 2005 Jan 15;161(2):180-5. Increased falling as a risk factor for fracture among older women: the study of osteoporotic fractures. Schwartz AV, Nevitt MC, Brown BW Jr, Kelsey JL.	Prognostic cohort study	9485 women	Study of Osteoporotic Fractures (SOF) study. Women aged ≥ 65 years recruited at 4 clinical sites in USA (Baltimore MA, Minneapolis MN, Monongahela Valley PE, Portland OR) from 1986 to 1988.	Fall rate. Following baseline visit, subject's falls were monitored ever 4 months. Information on falls from the first 12 postcards, or approximately 4 years of follow-up, was used to determine the rate of falling for each participant.	Median 6.3 years	Fractures approx 4 years after baseline visit. Hip Proximal humerus Distal forearm Ankle Foot All none-spine fractures	US Public Health Service grants.	Study examined increase in rate of falls during approximately first 4 years of follow-up and subsequent fracture rate reported for median 6.3 years. Falls determined by self-report. Fractures confirmed by radiology report.

Baseline characteristics (N = 9485)

Characteristic	Value
Mean age (SD)	71.6 (5.3)
Range (years)	65 to 99

Results

Of 9704 cohort, 522 were deceased and 76 were lost to follow-up leaving 9106 participants available for analysis of fracture risk. All of these women had returned at least six of the 12 postcards; 99.8 percent had returned at least 10, and 92.3 percent had returned all 12. Only the first fracture occurring after the 12th postcard at each specific site considered included in analysis.

Age-specific rate of falling was higher at older ages (range from 43 falls per 100 person-years for women aged 65 to 69 years to 87 falls per 100 person-years among women aged > 85 years). 40% of women reported no falls in the 4-year period. Approximately 5% of women fell at an average rate of more than 1.75 falls per year.

During follow-up, the rate of falls increased for approximately 30 percent of the participants and decreased for another 30 percent. The average change in the rate of falls increased with age, ranging from an annual increase of 1.2 falls per 100 years per year for women aged 65 to 69 years to 17.4 falls per 100 years per year for women aged ≥ 85 years.

During follow-up after the 12th postcard

1541 women reported at least one confirmed non-spine fracture, excluding fractures due to severe trauma or pathology. The 1933 confirmed fractures included fractures of the hip (n = 388), distal forearm (n = 326), proximal humerus (n = 212), ankle (n = 148), foot (n = 144), and other sites.

Age-adjusted rate ratios* for the association between rate of falling in the first 4 years of follow-up and subsequent fractures among women aged 65 years or more, by fracture site.

Rate of falls in the first 4 years (no of falls/ year)	N Women	Site of fracture											
		Hip		Proximal humerus		Distal forearm		Ankle		Foot		All non-spine fractures	
		RR	95%CI†	RR	95%CI	RR	95%CI	RR	95%CI	RR	95%CI	RR	95% CI
0	3.634	1.00‡		1.00‡		1.00‡		1.00‡		1.00‡		1.00‡	
0.01-0.75	4.034	1.30	1.03 to 1.64	1.06	0.79 to 1.43	1.17	0.92 to 1.49	1.04	0.73 to 1.48	1.63	1.13 to 2.36	1.22	1.09 to 1.36
0.76-1.75	1.014	1.48	1.07 to 2.03	0.99	0.62 to 1.58	1.01	0.69 to 1.49	1.35	0.81 to 2.24	1.18	0.64 to 2.15	1.51	1.29 to 1.77
>1.75	424	1.85	1.24 to 2.74	1.17	0.62 to 2.20	1.87	1.20 to 2.90	1.24	0.57 to 2.73	1.50	0.67 to 3.34	1.88	1.52 to 2.32

* Rate ratios were calculated by means of the Cox proportional hazards model. Data in all models were adjusted for age at baseline.

†RR, rate ratio; CI confidence interval

‡ Reference category

Compared with the 3634 women who had no falls in the first 4 years, women who reported an average rate of more than 1.75 falls per year in the first 4 years of follow-up ("frequent fallers") had nearly double the rate of subsequent hip fracture (rate ratio (RR) = 1.85) and distal forearm fracture (RR = 1.87). Frequent fallers had at increased rate of foot fracture (RR = 1.50) but a reduced increased rate of ankle (RR = 1.24) and proximal humerus (RR = 1.17) fracture in comparison with women who never fell. Frequent fallers also had an increased rate of all non-spine fractures (RR = 1.88).

Rate ratios* for the association between increasing rate of falls in the first 4 years of follow-up and subsequent fractures among women aged 65 years or more, by fracture site, with adjustment for age at baseline and rate of falls in the first 4 years.

Change of rate of falls in the first 4 years (no of falls /year)	N women	Site of fracture											
		Hip		Proximal humerus		Distal forearm		Ankle		Foot		All non-spine fractures	
		RR	95%CI†	RR	95%CI	RR	95%CI	RR	95%CI	RR	95%CI	RR	95% CI
No change or decrease	6.379	1.00‡		1.00‡		1.00‡		1.00‡		1.00‡		1.00‡	
Quartile of increasing fall rate													
0.001-0.13	681	1.01	0.67 to 1.51	0.84	0.47 to 1.50	0.85	0.55 to 1.31	0.96	0.51 to 1.81	0.84	0.45 to 1.57	0.89	0.73 to 1.09
0.14-0.27	634	0.99	0.65 to 1.49	0.85	0.47 to 1.54	0.66	0.40 to 1.09	0.70	0.33 to 1.48	0.84	0.44 to 1.61	0.83	0.67 to 1.03
0.28-0.44	740	1.44	1.02 to 2.04	0.92	0.53 to 1.59	0.67	0.42 to 1.07	0.89	0.48 to 1.67	0.87	0.4 to 1.59	1.02	0.85 to 1.23
>0.44	672	1.57	1.10 to 2.23	1.65	1.00 to 2.72	0.98	0.64 to 1.51	0.53	0.23 to 1.20	0.64	0.30 to 1.39	1.15	0.95 to 1.40

* Rate ratios were calculated by means of the Cox proportional hazards model. Data in all models were adjusted for age at baseline and rate of falling during the first 4 years of follow up.

†RR, rate ratio; CI confidence interval

‡ Reference category

Adjustment for the average rate of falls in the first 4 years

In the top quartile of increasing falls continued to be associated with hip (RR = 1.57) and proximal humerus (RR = 1.65) fracture. An increasing rate of falls was not associated with a higher rate of distal forearm, ankle, or foot fracture, with or without controlling for the average rate of falls.

Multivariate adjusted rate ratios* for the associations between change in the rate of falls during the first 4 years of follow up and subsequent hip and proximal fractures among women aged 65 years or more				
Measurement	Site of fracture			
	Hip†		Proximal humerus‡	
	RR§	95%CI§	RR	95%CI
Change in rate of falls in the first 4 years (no. of falls/year/year)				
No change or decrease	1.00¶		1.00¶	

Quartile of increasing rate of falls				
0.001-0.13	1.04	0.69 to 1.55	0.89	0.50 to 1.60
0.14-0.27	0.97	0.64 to 1.47	0.87	0.48 to 1.60
0.28-0.44	1.33	0.93 to 1.91	0.97	0.56 to 1.69
>0.44	1.42	0.99 to 2.04	1.79	1.08 to 2.95
Rate of falls in the first 4 years (no. of falls/year)				
0	1.00¶		1.00¶	
0.01-0.75	1.16	0.88 to 1.52	1.00	0.70 to 1.41
0.76-1.75	1.25	0.88 to 1.79	0.83	0.49 to 1.39
>1.75	1.38	0.86 to 2.21	0.75	0.36 to 1.56

* Rate ratios were calculated by means of the Cox proportional hazards model, using backwards regression first and then adding variables for falls.

† Adjusted for the other variables in the table and for age, current use of thyroid hormone pills, current smoking, alcohol consumption in the past year, fracture after age 50 years, history of maternal hip fracture, being on one's feet for less than 4 hours per day, gait speed, using arms for chair standing, contrast sensitivity, height at age 25 years, weight, and calcaneal bone mineral density (n = 8,864; 242 women had missing values for one or more variables).

‡ Adjusted for the other variables in the table and for height loss since age 25 years, gait speed, waist:hip ratio, and distal radius bone mineral density (n = 8,990; 116 women had missing values for one or more variables).

§ RR, rate ratio; CI confidence interval

¶ Reference category

Table 52: Quality assessment, Schwartz 2005 (Am J Epidemiol. 2005 Jan 15;161(2):180-5. Increased falling as a risk factor for fracture among older women: the study of osteoporotic fractures. Schwartz AV, Nevitt MC, Brown BW Jr, Kelsey JL.)

	Items To Be Considered for Assessment of Potential Opportunity for Bias	Overall
1.1	The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results	Yes
1.2	Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias	Yes
1.3	The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias	Yes
1.4	The outcome of interest is adequately measured in study participants, sufficient to limit bias	Yes

	Items To Be Considered for Assessment of Potential Opportunity for Bias	Overall
1.5	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest	Yes
1.6	The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results	Yes

Incidence of falls

Table 53: Evidence table, Kaptoge 2005

Bibliographic reference	Study type	Number of patients	Patient characteristics	Prognostic factor	Length of follow-up	Outcome measures	Source of funding	Study quality / additional comments
Bone. 2005 Mar;36(3):387-98. Low BMD is less predictive than reported falls for future limb fractures in women across Europe: results from the European Prospective Osteoporosis Study. Kaptoge S, Benevolenskaya LI, Bhalla AK, Cannata JB, Boonen S, Falch JA, Felsenberg D, Finn JD, Nuti R, Hoszowski K, Lorenc R, Miazgowski T, Jajic I, Lyritis G, Masaryk P, Naves-	Prognostic cohort study	5370 men and women	European Prospective Osteoporosis Study (EPOS). 2451 men and 2919 women aged ≥ 50 years from 31 centres in Europe. **Men baseline characteristics (N = 2451)** 	Characteristic	Value
Mean age(SD)	63.7(8.0)
Mean(SD) height (cm)	172(0.07)
Mean(SD) weight (kg)	79.5(11.0)
Mean(SD) BMI (kg/m2)	26.9(3.3)
Prior history of fracture (%)	15 | **Women baseline characteristics (N = 22919)** | Characteristic	Value		Incidence of falls during 3 year follow-up	Median 3.0 years, range 0.5 to 5.4 years	Any non-spine fracture Upper limb fracture Lower limb fracture	European Union Concerted Action Grant under Biomed-1. UK Arthritis Research Campaign, Medical Research Council, European Foundation for Osteoporosis and Bone Disease.	Self reported fractures confirmed by radiology reports. Incidence of falls determined by dividing the total number of falls reported by subjects in an individual centre by the person-years risk. Subjects were followed by annual questionnaire and were asked to record the occurrence of any incident fractures

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.						and the occurrence and number of falls since the baseline survey or previous postal contact. Self reported fractures were confirmed where possible by radiology report or subject interview.
			Mean age(SD)	62.8(7.7)		
			Mean(SD) height (cm)	159(0.07)		
			Mean(SD) weight (kg)	68.6(11.0)		
			Mean(SD) BMI (kg/m2)	27.1(4.5)		
			Prior history of fracture (%)	21		

Results

Fractures in men: Upper limb; 24, lower limb; 25, any non-spine (includes limb fractures unassigned ICD codes and rib fractures); 83.

Fractures in women: Upper limb; 102, lower limb; 70, any non-spine (includes limb fractures unassigned ICD codes and rib fractures); 221.

Average 'all falls' reported during 3 year follow-up				
	Men		Women	
	N	%	N	%
0 fall	1852	77	1952	68
1 fall	233	10	441	15
2 fall	143	6	206	7
3+ falls	192	8	251	9
Total	2420	100	2850	100

Average 'fracture free falls' reported during 3 year follow-up				
	Men		Women	
	N	%	N	%
0 fall	1895	78	2052	72

1 fall	200	8	375	13
2 fall	135	6	185	6
3+ falls	190	8	238	8
Total	2420	100	2850	100

Model 1 (modelling with 'all falls')

RR(95%CI) of any non-spine fracture in women with outcome predictor in women; average falls reported during 3 year follow-up

0 versus 1; 0.09(0.06 to 0.13), P < 0.0001

2 versus 1; 0.81(0.54 to 1.21), P = 0.308

3+ versus 1; 0.60(0.40 to 0.91), P = 0.016

Compared with subjects who did not fall, subjects who fell once had greater risk of non-spine fracture. Subjects with multiple falls (3+) had greater risk of non-spine fracture compared with subjects who fell once.

RR(95%CI) of upper limb fracture in women with outcome predictor; average falls reported during 3 year follow-up

0 versus 1; 0.09(0.05 to 0.15), P < 0.0001

2 versus 1; 0.64 (0.35 to 1.18), P = 0.152

3+ versus 1; 0.54(0.30 to 0.97), P = 0.039

Compared with subjects who did not fall, subjects who fell once had greater risk of upper limb fracture. Subjects with multiple falls (3+) had greater risk of upper limb fracture compared with subjects who fell once.

RR(95%CI) of lower limb fracture in women with outcome predictor; average falls reported during 3 year follow-up

0 versus 1; 0.09(0.04 to 0.18), P < 0.0001

2 versus 1; 0.68(0.33 to 1.40), P = 0.299

3+ versus 1; 0.64(0.32 to 1.31), P = 0.222

Compared with subjects who did not fall, subjects who fell once had greater risk of lower limb fracture

Model 1 (modelling with 'fracture free falls')

RR(95%CI) of any non-spine fracture in women with outcome predictor; average falls reported during 3 year follow-up

0 versus 1; 0.80(0.51 to 1.23), P = 0.308

2 versus 1; 0.82(0.46 to 1.46), P = 0.504

3+ versus 1; 0.95(0.59 to 1.55), P = 0.852

RR(95%CI) of upper limb fracture in women with outcome predictor; average falls reported during 3 year follow-up

0 versus 1; 1.60(1.22 to 2.09), P = 0.001

2 versus 1; 2.30 (1.34 to 3.95), P = 0.002

3+ versus 1; 1.90(1.23 to 2.95), P = 0.004

Compared with subjects who did not fall, subjects who fell once had greater risk of upper limb fracture. Subjects who fell twice had greater risk of upper limb fracture compared with subjects who fell once. Subjects with multiple falls (3+) had greater risk of upper limb fracture compared with subjects who fell once.

RR(95%CI) of lower limb fracture in women with outcome predictor; average falls reported during 3 year follow-up

0 versus 1; 0.69(0.03 to 1.55), P = 0.365

2 versus 1; 0.96(0.38 to 2.45), P = 0.940

3+ versus 1; 0.94(0.39 to 2.23), P = 0.883

Table 54: **Quality assessment Kaptoge 2005 (reference: Bone. 2005 Mar;36(3):387-98. Low BMD is less predictive than reported falls for future limb fractures in women across Europe: results from the European Prospective Osteoporosis Study. Kaptoge S, Benevolenskaya LI, Bhalla AK, Cannata JB, Boonen S, Falch JA, Felsenberg D, Finn JD, Nuti R, Hoszowski K, Lorenc R, Miazgowski T, Jajic I, Lyritis G, Masaryk P, Naves-Diaz M, Poor G, Reid DM, Scheidt-Nave C, Stepan JJ, Todd CJ, Weber K, Woolf AD, Roy DK, Lunt M, Pye SR, O'neill TW, Silman AJ, Reeve J.)**

	Items To Be Considered for Assessment of Potential Opportunity for Bias	Overall
1.1	The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results	Yes
1.2	Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias	Yes
1.3	The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias	Unclear
1.4	The outcome of interest is adequately measured in study participants, sufficient to limit bias	Yes
1.5	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest	Yes
1.6	The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results	Yes

D.2 Evidence tables and QUADAS II tables for review question 2

In alphabetical order

Table 55: Bauer 2007, study characteristics

Tool, outcome	Study	Participants	Risk stratification tools
BMD, Any fragility fracture	Bauer 2007 prospective cohort study; internal validation - bootstrap. Study held in USA. Setting: community. 6 centres; MrOS study. Funding :National Institutes of Health funding.	• Population: men; ---. • Inclusion criteria: aged >=65y; ability to walk without assistance; no bilateral hip replacement; ability to provide self-reported data; residence near clinical site; no medical condition that would result in imminent death. • Exclusion criteria: . • Patient characteristics: age: fracture 77y (SD6.6); no fracture 74y (SD5.8); sex: male; no patients had a prior test. History of fracture: fracture history • Comorbidities: none. Other details: Men with fracture: mean BMI, 27.1kg/m2 (SD4); men with no fracture, mean BMI, 27.4 kg/m2 (SD3.8) • Other study comments: 99% complete follow up	• Type of diagnostic tool: Replacement • Index test: BMD was measured at femoral neck using DXA (on same visit when QUS was measured); time: (n=) • Reference standard: x-rays or radiographic reports; time mean 4.2y (SD 1y) (n=5581) • Other comparator tests: Calcaneal quantitative ultrasound(QUS). • for Target Condition/Outcome: 239 had non-spine fracture
BMD, hip fracture	Bauer 2007 prospective cohort study; internal validation - bootstrap. Study held in USA. Setting: community. 6 centres; MrOS study. Funding :Nationl Institutes of Health funding.	• Population: men; ---. • Inclusion criteria: aged >=65y; ability to walk without assistance; no bilateral hip replacement; ability to provide self-reported data; residence near clinical site; no medical condition that would result in imminent death. • Exclusion criteria: . • Patient characteristics: age: fracture	• Type of diagnostic tool: Replacement • Index test: BMD was measured at femoral neck using DXA (on same visit when QUS was measured); time: (n=5607) • Reference standard: x-rays or radiographic reports; time mean 4.2y (SD 1y) (n=5506) • Other comparator tests: Calcaneal

Tool, outcome	Study	Participants	Risk stratification tools
		81y (SD5.8); no fracture 74y (SD5.8); sex: male; no patients had a prior test. History of fracture: fracture history • Comorbidities: none. Other details: Men with fracture: mean BMI, 26.5kg/m2 (SD3.8); men with no fracture, mean BMI, 27.4 kg/m2 (SD3.8) • Other study comments: 99% complete follow up	quantitative ultrasound(QUS). • for Target Condition/Outcome: 49 hip fracture

Table 56:   Bauer 2007, QUADAS II

Tool, outcome	Selection bias	Index test bias	Reference standard bias	Multiple tests bias and other bias	Applicability	Overall risk of bias
BMD, Any fragility fracture	Patient enrolment: consecutive. Study design: not case control; prospective. Validation: adequate validation Selection bias overall: low	Imputation: no imputation. Threshold selected: unclear Index test bias overall: low	Analysis method: time to event analysis: length of follow up: appropriate. Missing outcome data: some patients not analysed. Reference standard measurement: acceptable Reference standard bias overall: low	No. of events: >=100 events Comments: No info on fracture history; 99% follow up rate Other bias overall: high Multiple index tests: all patients underwent all index tests; Randomisation ot applicable. Interaction between tests: results un-affected when undertaken together on the same patient;	Population: population different from UK Index test: appropriate to review question Reference standard: appropriate follow up time; ref standard measurement: acceptable Comments: USA Overall applicability: indirect	High

Tool, outcome	Selection bias	Index test bias	Reference standard bias	Multiple tests bias and other bias	Applicability	Overall risk of bias
				excusions not applicable Multiple tests bias overall: low		
BMD, hip fracture	Patient enrolment: consecutive. Study design: not case control; prospective. Validation: adequate validation Selection bias overall: low	Imputation: no imputation. Threshold selected: unclear Index test bias overall: low	Analysis method: time to event analysis: length of follow up: appropriate. Missing outcome data: some patients not analysed. Reference standard measurement: acceptable Reference standard bias overall: low	No. of events: <100 events Comments: No info on fracture history; 99% follow up rate Other bias overall: very high Single test	Population: population different from UK Index test: appropriate to review question Reference standard: follow up time too short; ref standard measurement: acceptable Comments: USA 49 hip fractures only Overall applicability: indirect	Very high

Table 57:   Bolland 2010, study characteristics

Tool, outcome	Study	Participants	Risk stratification tools
FRAX with BMD, any fragility fracture FRAX without BMD, any fragility fracture FRAX with BMD, hip fracture FRAX without BMD, hip fracture	Bolland 2010 prospective cohort study; ---. Study held in New Zealand. Setting: community. . Funding: One author received a scholarship from the HOPE Foundation for Research on Ageing. All authors	Population: all women; not higher risk. group of healthy older women with normal BMD for age who volunteered to take part in a clinical trial study of calcium supplement Inclusion criteria: women older than 55 years. Free from major medical	Type of diagnostic tool: --- Index test: Medical history was obtained by questionnaire, weight measured by electronic scales, height measured by Harpenden stadiometer, and BMD of the femoral neck was determined using Lunar Expert dual-

Tool, outcome	Study	Participants	Risk stratification tools
	state that they have no conflicts of interest.	conditions	energy X-ray abs

Table 58:   Bolland 2010, QUADAS II

Tool, outcome	Selection bias	Index test bias	Reference standard bias	Multiple tests bias and other bias	Applicability	Overall risk of bias
FRAX with BMD, any fragility fracture FRAX without BMD, any fragility fracture	Patient enrolment: random sample. Study design: not case control; prospective. Validation: ---. Comments: the cohort was a group of healthy older women with normal BMD for age who volunteered to take part in a clinical study. Selection bias overall: low	Imputation: no imputation. Threshold selected: ---. Comments: women included only if baseline data available. Index test bias overall: low	Analysis method: incidence data only: length of follow up: ---. Missing outcome data: some patients lost to follow up. Reference standard measurement: partially acceptable. Comments: In years 0 to 5 all fractures were verified independently; in years 6 to 11, fracture events were self-reported. Loss to follow up: 21%. 229 osteop. fractures; 57 hip fractures.	No. of events: >=100 events Comments: Discrepancy in the number of fracture between the original RCT study and this observational study. Other bias overall: high Multiple index tests: all patients underwent all index tests; Randomisation not applicable. Interaction between tests: results un-affected when undertaken together on the same patient; exclusions not applicable Multiple tests bias overall: low.	Population: population different from UK Index test: appropriate to review question Reference standard: appropriate follow up time; ref standard measurement: partially acceptable Comments: Country: New Zealand. Overall applicability: indirect	high
FRAX with BMD, hip	Patient enrolment:	Imputation: no	Analysis method:	No. of events: >=100	Population:	high

Tool, outcome	Selection bias	Index test bias	Reference standard bias	Multiple tests bias and other bias	Applicability	Overall risk of bias
fracture FRAX without BMD, hip fracture	random sample. Study design: not case control; prospective. Validation: ---. Comments: the cohort was a group of healthy older women with normal BMD for age who volunteered to take part in a clinical study Selection bias overall: low	imputation. Threshold selected: ---. Comments: women included only if baseline data available Index test bias overall: low	incidence data only: length of follow up: ---. Missing outcome data: some patients lost to follow up. Reference standard measurement: partially acceptable. Comments: n years 0 to 5 all fractures were verified independently; in years 6 to	events Comments: Discrepancy in the number of fracture between the original RCT study and this observational study. I Other bias overall: high Multiple index tests: all patients underwent all index tests; Randomisation not applicable. Interaction between tests: results un-affected when undertaken together on the same patient; exclusions not applicable Multiple tests bias overall: low.	population different from UK Index test: appropriate to review question Reference standard: appropriate follow up time; ref standard measurement: partially acceptable Comments: Country: New Zealand. Overall applicability: indirect	

Table 59:   Collins 2011, study characteristics

Tool, outcome	Study	Participants	Risk stratification tools
QFracture, hip fracture (women) QFracture, any fragility fracture (women)	Collins 2011 prospective cohort study; external validation - different researchers. Study held in UK, 364 general practices.	• Population: all women; not higher risk. Patients registered between June 1994 and June 2008 with records on the THIN database. The database comprises	• Type of diagnostic tool: Replacement • Index test: Primary care clinical database; time: (n= 1136417) • Reference standard for hip fracture: First incident diagnosis of hip fracture;

Tool, outcome	Study	Participants	Risk stratification tools
	Setting: GP surgery. 364 general practices, THIN database. Funding :No funding.	the records of GPs that use the INPS Vision system (currently 20% of UK GPs) • Inclusion criteria: age 30-85 years, had no previously recorded fracture (hip, distal radius, or vertebra), permanent residents in the UK, no interrupted periods of registration with a practice. • Exclusion criteria: 5202 (M+F) had a recorded hip fracture before June 1994 and were excluded from the analysis for hip fracture. 27,551 (M+F) had a recorded fracture before June 1994 and were excluded from the analysis for osteoporotic fracture. • Patient characteristics: age: median (IQR): women 48 (37-62); sex: female; no patients had a prior test. History of fracture: fracture history not recorded in study • Comorbidities: none stated. Other details: Women: mean BMI 26.15 (SD5); heavy smoker 6.9%; asthma 8.6%; current corticosteroids 3.2%; history of falls 2.6%; menopausal conditions 5.2% • Other study comments: Method of imputing missing values: multiple imputation using sensible values randomly selected from their predicted distribution. Five imputed datasets were generated and combined the	time median 6.03 (IQR2.62-8.5) years (n= 1136417) • Reference standard for osteoporotic fracture: First incident diagnosis of osteoporotic fracture (hip, distal radius, or vertebra); time median 5.98(IQR2.61-8.5 years (n=1136417) • for Target Condition/Outcome: 9165 incident cases of hip fractures (6,673,972 person years); 19055 incident cases of osteoporotic fractures (6,493,740 person years)

Tool, outcome	Study	Participants	Risk stratification tools
		results from analyses on each of the imputed datasets to produce estimates and CIs that incorporate the uncertainty of imputed values	
QFracture, hip fracture (men) QFracture, any fragility fracture (men)	Collins 2011 prospective cohort study; external validation - different researchers. Study held in UK, 364 general practices. Setting: GP surgery. 364 general practices, THIN database. Funding : No funding.	• Population: men; not higher risk. Patients registered between June 1994 and June 2008 with records on the THIN database. The database comprises the records of GPs that use the INPS Vision system (currently 20% of UK GPs)_ • Inclusion criteria: age 30-85 years, had no previously recorded fracture (hip, distal radius, or vertebra), permanent residents in the UK, no interrupted periods of registration with a practice. • Exclusion criteria: 5202 (M+F) had a recorded hip fracture before June 1994 and were excluded from the analysis for hip fracture. 27,551 (M+F) had a recorded fracture before June 1994 and were excluded from the analysis for osteoporotic fracture. • Patient characteristics: age: median (IQR): men 47(37-59); sex: male; no patients had a prior test. History of fracture: fracture history not recorded in study • Comorbidities: none stated. Other details: Men: mean BMI 26.63 (SD4.1); heavy smoker 10.6%; asthma 7.1%;	• Type of diagnostic tool: Replacement • Index test: Primary care clinical database; time: (n= 1108219) • Reference standard for hip fracture: First incident diagnosis of hip fracture; time median 6.03 (IQR2.62-8.5) years (n= 1108219) • Reference standard for osteoporotic fracture: First incident diagnosis of osteoporotic fracture (hip, distal radius, or vertebra); time median 5.98(IQR2.61-8.5 years (n=1108219) • for Target Condition/Outcome: 3023 incident cases of hip fractures (6,379,919 person years); 6153 incident cases of osteoporotic fractures (6,290,586 person years)

Tool, outcome	Study	Participants	Risk stratification tools
		current corticosteroids 2.1%; history of falls 1.4% • Other study comments: Method of imputing missing values: multiple imputation using sensible values randomly selected from their predicted distribution. Five imputed datasets were generated and combined the results from analyses on each of the imputed datasets to produce estimates and CIs that incorporate the uncertainty of imputed values	

Table 60:   Collins 2011, QUADAS II

Tool, outcome	Selection bias	Index test bias	Reference standard bias	Multiple tests bias and other bias	Applicability	Overall risk of bias
QFracture, Hip fracture Any fragility fracture (women)	Patient enrolment: consecutive. Study design: not case control; prospective. Validation: adequate validation Selection bias overall: low	Imputation: less than 50% imputation for 2-3 factors. Threshold selected: not stated. Comments: amount of missing data for alcohol intake for women 45% Index test bias overall: low	Analysis method: time to event analysis Length of follow up: uncertain if appropriate . Missing outcome data: some patients not analysed. Reference standard measurement: acceptable . Comments: Data from national	No. of events: >=100 events Comments: 5202 (M+F) had a recorded hip fracture before June 1994 and were excluded from the analysis; 27551 (M+F) had a recorded fracture (any) before June 1994 and were excluded from the	Population: appropriate to review question Index test: appropriate to review question Reference standard: appropriate follow up time; Ref standard measurement: acceptable Comments: country: uk Overall applicability:	High

Tool, outcome	Selection bias	Index test bias	Reference standard bias	Multiple tests bias and other bias	Applicability	Overall risk of bias
			primary care database Reference standard bias overall: low	analysis; data quality poor (GP database) Other bias overall: high	direct	
Qfracture Hip fracture Any fragility fracture (men)	Patient enrolment: consecutive. Study design: not case control; prospective. Validation: adequate validation Selection bias overall: low	Imputation: more than 50% imputation for 1 factor. Threshold selected: not stated. Comments: amount of missing data for alcohol intake for men 60.7% Index test bias overall: high	Analysis method: time to event analysis Length of follow up: uncertain if appropriate . Missing outcome data: some patients not analysed. Reference standard measurement: acceptable . Comments: Data from national primary care database Reference standard bias overall: low	No. of events: >=100 events Comments: 5202 (M+F) had a recorded hip fracture before June 1994 and were excluded from the analysis; 27551 (M+F) had a recorded fracture (any) before June 1994 and were excluded from the analysis; data quality poor (GP database) Other bias overall: high	Population: appropriate to review question Index test: appropriate to review question Reference standard: appropriate follow up time; Ref standard measurement: acceptable Comments: country: uk Overall applicability: direct	High

Table 61: Cummings 1994B, study characteristics

Tool, outcome	Study	Participants	Risk stratification tools
BMD, Hip fracture	Cummings 1994B prospective cohort study; ---. Study held in USA. Setting: community. Women living in 4 cities of the USA. Funding :.	• Population: postmenopausal women; not higher risk. Study of Osteoporotic Fractures (SOF cohort: one of the FRAX validation cohorts)_ •Inclusion criteria: Age≥65y. • Exclusion criteria: Previous hip fracture. • Patient characteristics: age: 73.2; sex: F; ---. History of fracture: fracture history • Comorbidities: none stated. Other details: Height (m): 1.59±0.06 Race, white: 7941 (99.7%) BMD (g/cm2): 0.65±0.11 • Other study comments: It is not clear wether the AUC for BMD is age-adjusted	• Type of diagnostic tool: --- • Index test: Hip BMD by DXA; time: at baseline (n= 7963) • Reference standard: BMD measured by QDR 1000 densitometer (Hologic, Inc., Waltham, MA); time Follou up time: 2.1 y (n= 7963) • for Target Condition/Outcome: 83 hip fractures

Table 62: Cummings 1994B, QUADAS II

Tool, outcome	Selection bias	Index test bias	Reference standard bias	Multiple tests bias and other bias	Applicability	Overall risk of bias
BMD, Hip fracture	Patient enrolment: selected group. Study design: not case control; prospective. Validation: adequate validation. Comments: SOF cohort (one of the	Imputation: no imputation. Threshold selected: --- Index test bias overall: low	Analysis method: incidence data only: length of follow up: uncertain if appropriate . Missing outcome data: no loss to follow up.	No. of events: <100 events Comments: 83 hip fractures Other bias overall: high Single test	Population: appropriate to review question Index test: appropriate to review question Reference standard: follow up time too	High

Tool, outcome	Selection bias	Index test bias	Reference standard bias	Multiple tests bias and other bias	Applicability	Overall risk of bias
	FRAX validation cohorts) Selection bias overall: low		Reference standard measurement: acceptable . Comments: Fractures confirmed by radiographic reports. Loss to follow up <1% Follow up time: 2.1y Reference standard bias overall: low		short; ref standard measurement: acceptable Comments: Country: USA Overall applicability: indirect	

Table 63: Donaldson 2009, study characteristics

Tool, outcome	Study	Participants	Risk stratification tools
FRAX with BMD, vertebral fracture FRAX without BMD, vertebral fracture	Donaldson 2009 prospective cohort study; external validation -different researchers. Study held in USA, 11 centres. Setting: ---. Clinical centres. Funding: Merck.	• Population: postmenopausal women; not higher risk. The study population was made up of the participants from the placebo groups of the trial study arms. Details about components of risk stratification tool, e.g. 15% had a maternal history of hip fracture; 2% had >2units alcohol/day; 4% had rheumatoid arthritis; 11% current smokers; mean BMI was 25.2 (SD4)• Inclusion criteria: A proportion of the participants must have had at least one prevalent VF in order to enrol in the vertebral fracture arm (placebo). The rest with no prevalent VF were enrolled in the clinical fracture arm (placebo). • Exclusion criteria: people with	• Type of diagnostic tool: Replacement • Index test: BMD measured at the hip, posterior-anterior spine, lateral spine by DXA (Hologic). Radiographic vertebral fracture with morphometry.; time: on presentation (n=3223) • Reference standard: Clinical vertebral fractures were defined as those that came to medical attention and were reported to the clinical centres by the participants, confirmed by radiographs from the patient's physician. Incident VF was defined by semi-quantative reading.; time mean follow up = 3.8 (SD0.8) years (n=3043) • Other comparator tests: FRAX with/ without BMD prevalent vertebral

Tool, outcome	Study	Participants	Risk stratification tools
		exposure to systemic glucocorticoids at baseline. • Patient characteristics: age: mean age 68.2 (SD=6.1); sex: female; --- (From a trial received placebo). History of fracture: 1005 had at least 1 prevalent certebral fracture; 43% (n=1391) had history of prior fragility fracture • Comorbidities: none stated. Other details: 55-81 years of age who had been postmenopausal for at least 2 years and had low femoral neck BMD (<=0.68 g/cm2) • Other study comments: Trial flow chart: Group 1- women with >=1 prevalent VF (vertebral fracture arm) Alendronate arm vs. placebo arm Group 2 - women with no prevalent VF (clinical fracture arm) Alendronate arm vs. placebo arm. The AUC was sig. greater for FRAX with BMD compared with FRAX without BMD (p=0.002). Additional results in paper: observed risk of new radiographic fracture in quartile 4 (highest risk) was compared to quartil 1 (lowest risk) of the predicted probabilities of FRAX with or without BMD. Results suggested that the observed risk of morphometric VF (7.3%) is slightly lower than the predicted risk (11.3%) based one FRAX (adjusted to reflect an ave. 3.8 years of F/U compared to 10 years).	fracture + age + femoral neck BMD (not extracted). • for Target Condition/Outcome: 7.3% (n=223) had >=1 new radiographic vertebral fracture, and 7.8% (n=253) had a major osteoporotic fracture at the end of follow up.

Table 64:   Donaldson 2009, QUADAS II

Tool, outcome	Selection bias	Index test bias	Reference standard bias	Multiple tests bias and other bias	Applicability	Overall risk of bias
FRAX with BMD, vertebral fracture FRAX without BMD, vertebral fracture	Patient enrolment: selected group. Study design: not case control; prospective. Validation: ---. Comments: participants were recruited based primarily on low BMD and they also had to meet other entry criteria for the trial; they are not a random sample of the population Selection bias overall: very high	Imputation: no imputation. Threshold selected: not applicable. Comments: Maternal history of fracture used instead of parental history Index test bias overall: high	Analysis method: incidence data only: length of follow up: too short. Missing outcome data: some patients lost to follow up. Reference standard measurement: acceptable Reference standard bias overall: low	No. of events: >=100 events Comments: 5.6% (n=180) did not have follow up radiograph. Follow up = 3.8 years. Loss to follow up: 6% N. vertebral fractures: 223 Other bias overall: low Multiple index tests: all patients underwent all index tests; Randomisation not applicable. Interaction between tests: results un-affected when undertaken together on the same patient; exclusions not applicable Multiple tests bias overall: low	Population: selected: Other Index test: appropriate to review question Reference standard: follow up time too short; ref standard measurement: acceptable Comments: Country: USA This study population has a higher prevalence of osteoporosis and fractures than the general pop. Overall applicability: indirect	Very high

Table 65:   Ensrud 2009, study characteristics

Tool, outcome	Study	Participants	Risk stratification tools
FRAX with BMD, any fragility fracture FRAX without BMD, any fragility fracture FRAX with BMD, hip fracture FRAX without BMD, hip fracture	Ensrud 2009 prospective cohort study; ---. Study held in USA. Setting: community. Women were recruited from population-based listing in 4 areas of the USA. Funding :National Institutes of Health funding (no direct role in the conduct of the study).	• Population: all women; not higher risk. SOF cohort (one of the FRAX validation cohorts)_ • Inclusion criteria: at least 65 years old. • Exclusion criteria: age <65y; black women; women unable to walk without assistance; women with a history of bilateral hip replacement. • Patient characteristics: age: 71.3 (5.1); sex: F; no patients had a prior test. History of fracture: fracture history • Comorbidities: none stated. Other details: Previous fracture, No(%): 2155(34.5) Oral glucocortiroid therapy, No(%): 741(11.9) Rheumatoid arthritis, No(%): 429(6.9) Parental history of hip fracture, No(%): 925(14.8) Current smoker, No(%): 583 (9.3) Alcohol intake, >=3 drinks per day, No(%): 184(2.9) BMI, Mean(SD): 26.4(4.6) Femoral neck BMD, mean(SD), g/cm2: 0.65(0.11) Women with hip fracture, No(%): 389(6.2) Women with major osteoporotic	• Type of diagnostic tool: --- • Index test: BMD of proximal femur measured by DXA; time: at baseline examination (n=6252) • Reference standard: Fracture confirmed by review of radiographic reports; time 9.2(1.8)y (n= 2652) • Other comparator tests: FRAX with/without BMD BMD+age; age+previous fracture. • for Target Condition/Outcome: Hip fracture (n=389, 6.2%) Major osteoporotic fracture (n=1037, 16.6%)

Tool, outcome	Study	Participants	Risk stratification tools
		fracture, No(%): 1037(16.6) Women with any clinical fracture, No(%): 1907(30.5)	

Table 66:   Ensrud 2009, QUADAS II

Tool, outcome	Selection bias	Index test bias	Reference standard bias	Multiple tests bias and other bias	Applicability	Overall risk of bias
FRAX with BMD, any fragility fracture FRAX without BMD, any fragility fracture FRAX with BMD, hip fracture FRAX without BMD, hip fracture	Patient enrolment: selected group. Study design: not case control; prospective. Validation: ---. Comments: SOF cohort: one of the FRAX validation cohorts Selection bias overall: high	Imputation: no imputation. Threshold selected: --- . Comments: women included if baseline data available Index test bias overall: low	Analysis method: incidence data only. length of follow up: appropriate. Missing outcome data: some patients lost to follow up. Reference Standard measurement: acceptable Reference standard bias overall: low	No. of events: >=100 events Comments: 2% loss to follow up. 1037 osteoporotic fractures; 389 hip fractures Other bias overall: low Multiple index tests: all patients underwent all index tests; Randomisation not applicable. Interaction between tests: results un-affected when undertaken together on the same patient; exclusions not applicable Multiple tests bias overall: low	different from UK Index test: appropriate to review question Reference standard: appropriate follow up time; ref standard measurement: acceptable Comments: Country: USA Overall applicability: indirect	High

Table 67: Fraser 2011, study characteristics

Tool, outcome	Study	Participants	Risk stratification tools
FRAX with BMD, any fragility fracture FRAX without BMD, any fragility fracture FRAX with BMD, hip fracture FRAX without BMD, hip fracture	Fraser 2011 prospective cohort study; ---. Study held in Canada. Setting: community. Funding :Dr Fraser is supported by the University of Western Ontario Resident Research Career Development Program. The Canadian Multicentre Osteoporosis Study was funded by the Canadian Institutes of Health Research (CIHR); and other pharma industries.	• Population: unselected patients; not higher risk. Prospective, population-based cohort, the Canadian Multicentre Osteoporosis Study (CaMos). One of the primary cohorts for FRAX. 4778 Women and 1919 Men (N=6697) • Inclusion criteria: Age ≥ 50 (at study entry). • Exclusion criteria: N/A. • Patient characteristics: age: F:65.8±8.8; M:65.3±9.1; sex: F (4778) + M (1919); unclear or not stated. History of fracture: fracture history Comorbidities: none stated. Other details: BMI: F 27.1±4.9; M 27.3±3.8 Prior fragility fracture: F 540(11.3%); M 94(4.9%) Parental hip fracture: F 397(8.3%); M 111(5.8%) Rheumatoid arthritis: F 43(0.9%); M6(0.3%) Current or recent corticosteroid use: F 67(1.4%); M 27(1.4%) Current smoking: 635(13.3%); M 342(17.8%) Alcohol >2U/day: F 43(0.9%); M 130(6.8%) Femoral neck T-score (white female): F -1.5±1.1; M -0.5±1.2 Minimum T-score (white female): F	• Type of diagnostic tool: --- • Index test: Participants completed a standardized interviewer administered questionnaire at baseline (detailed information on RFs) and baseline clinical assessment that included measurement of height, weight and BDM (measured at the lumbar spine and proximal femur).; time: (n=6697) • Reference standard: Incidence of fracture was self reported and identified by yearly postal questionnaire. Further information was gathered by interview. Consent to contact the treating physician was sought.; time (n=6697) • Other comparator tests: FRAX without BMD. • for Target Condition/Outcome: 10-year observed risk Major osteoporotic fractures: F 12.0%(95%CI 11.0-12.9%) M 6.4%(95%CI 5.2-7.5%); Hip fracture: F 2.7%(95%CI 2.2-3.2%); M 2.4%(95%CI 1.7-3.1%)

Tool, outcome	Study	Participants	Risk stratification tools
		-1.8±1.1; -0.8±1.1 • Other study comments: CaMos was one for the nine prospective population-based cohort studies used to identify CRFs for the original FRAX tool development. CaMos consists of community-dwelling ambulatory subjects; therefore results cannot be extrapolated to individuals living in long-term care facilities. Major osteoporotic fracture rates were imputed using major osteoporotic-to-hip fracture ratios from the USA FRAX tool.	

Table 68:   Fraser 2011, QUADAS II

Tool, outcome	Selection bias	Index test bias	Reference standard bias	Multiple tests bias and other bias	Applicability	Overall risk of bias
FRAX with BMD, any fragility fracture FRAX without BMD, any fragility fracture FRAX with BMD, hip fracture FRAX without BMD, hip fracture	Patient enrolment: random sample. Study design: not case control; prospective. Validation: ---. Comments: Participants were randomly selected using a standard protocol. CaMos is one of the FRAX primary cohorts. Selection bias	Imputation: imputation applied, but % data imputed not stated. Threshold selected: --- . Comments: Rheumatoid arthritis derived on self-report diagnosis plus treatment. Where parental hip fracture not available, any parental	Analysis method: incidence data only: length of follow up: appropriate. Missing outcome data: some patients lost to follow up. Reference standard measurement: acceptable . Comments: Major osteoporotic fracture rates imputed using major	No. of events: >=100 events Comments: Incomplete follow up: 18.7%. 696 osteporotic fractures. 175 hip fractures Other bias overall: low Multiple index tests: all patients underwent all index tests; Randomisation not	Population: population different from UK Index test: appropriate to review question Reference standard: appropriate follow up time; ref standard measurement: acceptable Comments: The study is for calibration of the	high

Tool, outcome	Selection bias	Index test bias	Reference standard bias	Multiple tests bias and other bias	Applicability	Overall risk of bias
	overall: high	osteoporotic fracture was used. Index test bias overall: low	osteoporotic-to hip fracture ratios from the USA FRAX tool Reference standard bias overall: low	applicable. Interaction between tests: results un-affected when undertaken together on the same patient; exclusions not applicable Multiple tests bias overall: low	Canadian FRAX tool. Overall applicability: indirect	

Table 69:   Hans 2004, study characteristics

Tool, outcome	Study	Participants	Risk stratification tools
BMD, hip fracture	Hans 2004 prospective cohort study; ---. Study held in France. Setting: community. Subjects recruited using the voting lists and health insurance company registers. Funding :INSERM/MSDChibret contract..	• Population: postmenopausal women; not higher risk. EPIDOS cohort (one of the FRAX validation cohorts). Caucasian healthy women. Most women were living independently at home; 10% lived in nursing homes._ • Inclusion criteria: Causasian; Age≥75y. • Exclusion criteria: Undergone bilateral hip replacement; previous hip fracture. • Patient characteristics: age: Fracture: 82.65±4.53; non-fracture: 80.35±3.71; sex: F; ---. History of fracture: fracture history • Comorbidities: none stated. Other details: Weight (kg): Fracture:	• Type of diagnostic tool: --- • Index test: BMD of the proximal femour *femoral neck and BMD) measured by DXA using the Lunar DPX Plus (GE-Lunar Corp., Madison, WI, USA).; time: at baseline (n= 5898) • Reference standard: Hip fracture were self reported then confirmed by radiographs and surgical reports.; time 3.5 (n= 5898) • Other comparator tests: Ultrasound (not extracted). • for Target Condition/Outcome: Hip fracture (3.5 y FU): 227

Tool, outcome	Study	Participants	Risk stratification tools
		57.89±9.20; nonfracture: 59.82±10.27 Height (cm): Fracture: 153.30±6.20; non-fracture: 153.57±5.87 BMI (kg/m2): Fracture: 24.64±3.70; non-fracture: 25.36±4.20 FN BMD (g/cm2): Fracture: 0.644±0.09; non-fracture: 0.717±0.107 • Other study comments: The study compared AUC for BMD at different follow up times: 1.5, 2.5 and 3.5 years.	

Table 70: Hans 2004, QUADAS II

Tool, outcome	Selection bias	Index test bias	Reference standard bias	Multiple tests bias and other bias	Applicability	Overall risk of bias
BMD, hip fracture	Patient enrolment: not stated. Study design: not case control; prospective. Validation: adequate validation. Comments: Elderly women Selection bias overall: low	Imputation: no imputation. Threshold selected: not stated Index test bias overall: low	Analysis method: incidence data only: length of follow up: uncertain if appropriate . Missing outcome data: ---. Reference standard measurement: acceptable . Comments: Loss to follow up: 7.2% Reference standard bias overall: low	No. of events: <100 events Comments: n. fractures: 227 Other bias overall: low Multiple index tests: --; Randomisation method unclear. Interaction between tests: --; -- Multiple tests bias overall: --	Population: appropriate to review question Index test: appropriate to review question Reference standard: follow up time too short; ref standard measurement: acceptable Comments: Country: France Elderly women Overall applicability: indirect	Low

Table 71: Hillier 2007, study characteristics

Tool, outcome	Study	Participants	Risk stratification tools
BMD, Hip fracture BMD, Any fragility fracture BMD, Vertebral fracture	Hillier 2007 prospective cohort study; ---. Study held in USA. Setting: community. Community dwelling in 4 USA regions. Funding :National Institute of Arthritis and Muscoloskeletal and Skin Disease; Public Health Service; various pharma companies..	• Population: postmenopausal women; not higher risk. Study of Osteoporotic Fractures, SOF cohort, one of the FRAX validation cohorts_ •Inclusion criteria: Age≥65y (>99% non-Hispanic whites). • Exclusion criteria: Women unable to walk without assistance; bilateral hip replacement.. • Patient characteristics: age: 72(4); sex: F; ---. History of fracture: fracture history • Comorbidities: none stated. Other details: Weight, Kg: 67(12) Hip BMD, g/cm2: 0.76(0.13) • Other study comments: Study compared overall sensitivity and specificity of 2 BMD measurements (at baseline and after 8 years) in predicting incident fracture. Therefore, it is necessary to compare the same fracture outcomes (ie, only incident fractures after the second repeat measurement). Therefore, they excluded the 513 incident non-spine and the 72 hip fractures that occurred between the initial and repeat BMD, and compared the prediction of incident non-spine and hip fractures after the second BMD measurement in all models.	• Type of diagnostic tool: --- • Index test: BMD of the proximal femour and subregions (intertrochanter, trochanter, fenoral neck, and Ward triangle by DXA (Hologic QDR 1000; Hologic inc, Waltham, Mass); time: 8y after baseline assessment (n= 4124) • Reference standard: Self reported, then then confirmed by radiology reports; time 5y after second mesurement (n= 4124) • Other comparator tests: BMD at baseline. • for Target Condition/Outcome: 877 non-spine fractures (follow up: 5y) 275 hip fractures (follow up: 5y) 340 spine fractures (follow up: 11.4y)

Table 72: Hillier 2007, QUADAS II

Tool, outcome	Selection bias	Index test bias	Reference standard bias	Multiple tests bias and other bias	Applicability	Overall risk of bias
BMD, Hip fracture BMD, Any fragility fracture BMD, Vertebral fracture	Patient enrolment: selected group. Study design: not case control; prospective. Validation: ---. Comments: Postmenopausal women Selection bias overall: low	Imputation: no imputation. Threshold selected: --- Index test bias overall: low	Analysis method: incidence data only: length of follow up: appropriate. Missing outcome data: some patients lost to follow up. Reference standard measurement: acceptable . Comments: total hip BMD Reference standard bias overall: low	No. of events: >=100 events Comments: loss to follow up: <5% Other bias overall: low Single test	Population: population different from UK Index test: appropriate to review question Reference standard: appropriate follow up time; ref standard measurement: acceptable Comments: Country: USA Overall applicability: indirect	Low

Table 73: Hippisley-Cox 2009, study characteristics

Tool, outcome	Study	Participants	Risk stratification tools
QFracture, hip fracture (women) QFracture, any fragility fracture (women)	Hippisley-Cox 2009 prospective cohort study; internal validation - independent sample. Study held in UK, 178 general practices. Setting: GP surgery. 178 general practices, Qresearch database. England and Wales Funding: Funded by David Stables as	• Population: all women; not higher risk. • Inclusion criteria: aged 30-85 at study entry date, drawn from patients registered with eligible practices during the 15 years between Jan 1993 and June 2008. Included patients in the analysis only once they had a min. of one year's complete data in their medical records.	• Type of diagnostic tool: Replacement • Index test: All the fracture risk factors are recorded within the Patients' electronic records as part of routine clinical practice; time: (n=653789) • Reference standard: First incident diagnosis of hip fracture (recorded on the general practice computer records);

Tool, outcome	Study	Participants	Risk stratification tools
	part of a larger study examining risks and benefits of HRT.	• Exclusion criteria: patients with a previous recorded fracture , temporary residents, with interrupted periods of registration with the practice, and with no valid Townsend deprivation score related to the postcode. 11636 excluded due to recorded fracture before study entry.	time (n=642153)
		• Patient characteristics: age: 49 (IQR 37-63) years; sex: female; no patients had a prior test. History of fracture: fracture history not recorded in study	• Other comparator tests: Subgroup analysis (compare against FRAX).
		• Comorbidities: none stated. Other details: Heavy drinker 0.1%; mean(SD) BMI 25.82 (4.85); heavy smoker 4.7%; Type II diabetes 1.86%; current corticosteroids 1.64%; menopausal symptoms 1.84%; parental history of osteoporosis 0.34%	• for Target Condition/Outcome: 5424 (0.8%) incident cases of hip fractures; 13952 (2.2%) incident cases of osteoporotic fractures
		• Other study comments: Randomly allocated two thirds of practices to the derivation dataset and the remaining third to the validation dataset	
		Follow up time not specified, presented as person years.	
		Open cohort design	
		Assumption: If there was no recorded value of a diagnosis, prescription, or family history then the patient did not have that exposure	
		Multiple imputation was conducted to replace missing values for alcohol, smoking status and BMI	

Tool, outcome	Study	Participants	Risk stratification tools
QFracture, hip fracture (women) FRAX without BMD (women) (*subgroup analysis*)	Hippisley-Cox 2009 prospective cohort study; internal validation - independent sample. Study held in UK, 178 general practices. Setting: GP surgery. Subgroup analysis restricting the population to patients aged 40- 85, in the validation cohort. 178 general practices, Qresearch database. Funding :Funded by David Stables as part of a larger study examining risks and benefits of HRT.	• Population: all women; not higher risk. • Inclusion criteria: aged 30-85 at study entry date, drawn from patients registered with eligible practices during the 15 years between Jan 1993 and June 2008. Included patients in the analysis only once they had a min. of one year's complete data in their medical records. • Exclusion criteria: patients with a previous recorded fracture , temporary residents, with interrupted periods of registration with the practice, and with no valid Townsend deprivation score related to the postcode. 11636 excluded due to recorded fracture before study entry. • Patient characteristics: age: 49 (IQR 37-63) years; sex: female; no patients had a prior test. History of fracture: fracture history not recorded in study • Comorbidities: none stated. Other details: Heavy drinker 0.1%; mean(SD) BMI 25.82 (4.85); heavy smoker 4.7%; Type II diabetes 1.86%; current corticosteroids 1.64%; menopausal symptoms 1.84%; parental history of osteoporosis 0.34% • Other study comments: Randomly allocated two thirds of practices to the derivation dataset and the remaining third to the validation dataset Follow up time not specified, presented	• Type of diagnostic tool: Replacement • Index test: All the fracture risk factors are recorded within the patients' electronic records as part of routine clinical practice. Qfracture score for this subgroup (40-85y) has been recalculated.; time: (n= 45499) • Reference standard: First incident diagnosis of hip fracture (recorded on the general practice computer records); time (n= 45499) • Other comparator tests: QFracture recalculated in the subgroup analysis; FRAX. Hip fracture score was calculated using the FRAX algorithm. • for Target Condition/Outcome: 5424 incident (overall) cases of hip fractures

Tool, outcome	Study	Participants	Risk stratification tools
		as person years. Open cohort design Assumption: If there was no recorded value of a diagnosis, prescription, or family history then the patient did not have that exposure Multiple imputation was conducted to replace missing values for alcohol, smoking status and BMI	
QFracture, hip fracture (men) QFracture, any fragility fracture (men)	Hippisley-Cox 2009 prospective cohort study; internal validation - independent sample. Study held in UK, 178 general practices. Setting: GP surgery. 178 general practices, Qresearch database. England and Wales. Funding :Funded by David Stables as part of a larger study examining risks and benefits of HRT.	• Population: men; not higher risk. • Inclusion criteria: aged 30-85 at study entry date, drawn from patients registered with eligible practices during the 15 years between Jan 1993 and June 2008. Included patients in the analysis only once they had a min. of one year's complete data in their medical records. • Exclusion criteria: patients with a previous recorded fracture , temporary residents, with interrupted periods of registration with the practice, and with no valid Townsend deprivation score related to the postcode. 7179 excluded due to recorded fracture before study entry. • Patient characteristics: age: 46 (IQR37-69) years; sex: male; no patients had a prior test. History of fracture: fracture history not recorded in study • Comorbidities: none stated. Other details: Heavy drinker 0.95%; mean(SD) BMI 26.41 (4.02); heavy smoker 6.62%;	• Index test: All the fracture risk factors are recorded within the patients electronic records as part of routine clinical practice; time: (n=640943) • Reference standard: First incident diagnosis of hip fracture (recorded on the general practice computer records); time (n=633764) • Other comparator tests: Subgroup analysis (compare against FRAX). • for Target Condition/Outcome: 1738 (0.27%) incident cases of hip fractures, 4519 (0.007%) incident cases of osteoporotic fractures

Tool, outcome	Study	Participants	Risk stratification tools
		Type II diabetes 2.25%; current corticosteroids 0.91%; parental history of osteoporosis 0.02% • Other study comments: Randomly allocated two thirds of practices to the derivation dataset and the remaining third to the validation dataset Follow up time not specified, presented as person years. Open cohort design Assumption: If there was no recorded value of a diagnosis, prescription, or family history then the patient did not have that exposure Multiple imputation was conducted to replace missing values for alcohol, smoking status and BMI	
QFracture, hip fracture (men) FRAX without BMD (men) (*subgroup analysis*)	Hippisley-Cox 2009 prospective cohort study; internal validation - independent sample. Study held in UK, 178 general practices. Setting: GP surgery. Subgroup analysis restricting the population to patients aged 40- 85, in the validation cohort. 178 general practices, Qresearch database. England and Wales. Funding :Funded by David Stables as part of a larger study examining risks and benefits of HRT.	• Population: men; not higher risk. • Inclusion criteria: aged 30-85 at study entry date, drawn from patients registered with eligible practices during the 15 years between Jan 1993 and June 2008. Included patients in the analysis only once they had a min. of one year's complete data in their medical records. • Exclusion criteria: patients with a previous recorded fracture , temporary residents, with interrupted periods of registration with the practice, and with no valid Townsend deprivation score related to the postcode. 7179 excluded due to recorded fracture before study entry. • Patient characteristics: age: 46	• Type of diagnostic tool: Replacement • Index test: All the fracture risk factors are recorded within the patients⬚ electronic records as part of routine clinical practice. Qfracture score for this subgroup (40-85y) has been recalculated.; time: (n=424336) • Reference standard: First incident diagnosis of hip fracture (recorded on the general practice computer records); time (n=424336) • Other comparator tests: QFracture recalculated in the subgroup analysis; FRAX. Hip fracture score was calculated using the FRAX algorithm. • for Target Condition/Outcome: 1738 incident (overall) cases of hip fractures

Tool, outcome	Study	Participants	Risk stratification tools
		(IQR37-69) years; sex: male; no patients had a prior test. History of fracture: fracture history not recorded in study • Comorbidities: none stated. Other details: Heavy drinker 0.95%; mean(SD) BMI 26.41 (4.02); heavy smoker 6.62%; Type II diabetes 2.25%; current corticosteroids 0.91%; parental history of osteoporosis 0.02% • Other study comments: Randomly allocated two thirds of practices to the derivation dataset and the remaining third to the validation dataset Follow up time not specified, presented as person years. Open cohort design Assumption: If there was no recorded value of a diagnosis, prescription, or family history then the patient did not have that exposure Multiple imputation was conducted to replace missing values for alcohol, smoking status and BMI	

Table 74: Hippisley-Cox 2009, QUADAS II

Tool, outcome	Selection bias	Index test bias	Reference standard bias	Multiple tests bias and other bias	Applicability	Overall risk of bias
QFracture, hip fracture QFracture, any	Patient enrolment: random sample. Study design: not case control; prospective.	Imputation: imputation applied, but % data imputed not stated. Threshold selected:	Analysis method: time to event analysis: length of follow up: unclear. Missing outcome	No. of events: >=100 events Comments: 11636 excluded due to recorded fracture	Population: appropriate to review question Index test: appropriate to	

Tool, outcome	Selection bias	Index test bias	Reference standard bias	Multiple tests bias and other bias	Applicability	Overall risk of bias
fragility fracture	Validation: adequate validation. Comments: internal validation using independent sample, randomly allocated to the validation dataset Selection bias overall: low	not stated. Comments: Data from a national GP database Index test bias overall: low	data: some patients not analysed. Reference standard measurement: acceptable Reference standard bias overall: low	before study entry; data quality poor (from GP database) Other bias overall: high Multiple index tests: Some patients underwent all index tests; Not randomised. Interaction between tests: results un-affected when undertaken together on the same patient; some patients appropriately excluded from having multiple index tests Multiple tests bias overall: low	review question Reference standard: follow up time unclear; ref standard measurement: acceptable Comments: Country: UK Overall applicability: direct	
QFracture, hip fracture FRAX without BMD (*subgroup analysis*)	Patient enrolment: random sample. Study design: not case control; prospective. Validation: adequate validation. Comments: internal validation using independent sample, randomly allocated to the validation	Imputation: imputation applied, but % data imputed not stated. Threshold selected: not stated. Comments: Data from a national GP database Index test bias overall: low	Analysis method: time to event analysis: length of follow up: unclear. Missing outcome data: some patients not analysed. Reference standard measurement: acceptable Reference standard	No. of events: >=100 events Comments: No. people developed fracture in subgroup not reported; data quality poor (from GP database) Other bias overall: very high Multiple index tests:	Population: appropriate to review question Index test: appropriate to review question Reference standard: follow up time unclear; ref standard measurement:	

Tool, outcome	Selection bias	Index test bias	Reference standard bias	Multiple tests bias and other bias	Applicability	Overall risk of bias
	dataset Selection bias overall: low		bias overall: low	Some patients underwent all index tests;Not randomised. Interaction between tests: results un-affected when undertaken together on the same patient; some patients appropriately excluded from having multiple index tests Multiple tests bias overall: low	acceptable Comments: Country: UK Subgroup analysis (number no. of participants not mentioned) Overall applicability: direct	

Table 75: Hollaeder 2009, study characteristics

Tool, outcome	Study	Participants	Risk stratification tools
BMD, vertebral fracture	Hollaeder 2009 prospective cohort study; ---. Study held in Switzerland. Setting: community. random selection of the population registry of elderly women living in Basel, Switzerland (Basel Osteoporosis Study). Funding :The Swiss Federal Research Commission for Rheumatology and Merck, Sharp & Dohme provided a research grant.	• Population: postmenopausal women; ---. Healthy Caucasian women 60-80y_• Inclusion criteria: . • Exclusion criteria: use of HRT for >5 years, current or previous fluoride treatment, current or previous cancer disease, chronic renal insufficiency, dementia, and immobility. Fractured vertebrae were excluded from the DXA analysis. 11% were not available for F/U. • Patient characteristics: age: 69.9 (SD3.1) years; sex: female; ---. History	• Type of diagnostic tool: --- • Index test: Femoral neck, Total hip and Lumbar spine (L1-4) BMD was measured using DXA (with quality control); time: (n= 432) • Reference standard: Two experienced radiologists, blinded for the results of all other bone measurements examined the radiographs independently for incident vertebral fracture (using Genant semi-quantitative method); time mean 3.4 years (n=432) • Other comparator tests: QUS measurements (not extracted).

Tool, outcome	Study	Participants	Risk stratification tools
		of fracture: 47% women with incident vertebral fracture (VF) had already had a VF at baseline. 17% women with no incident fracture had a prevalent VF • Comorbidities: none stated. Other details: Mean age, 69.9 (SD 3.1); BMI, 27.5kg/m2 (SD 4.9) • Other study comments: Logistic regression	• for Target Condition/Outcome: 24 women sustained one or more incident vertebral fracture (5.6% per 1000 women years)

Table 76: Hollaeder 2009, QUADAS II

Tool, outcome	Selection bias	Index test bias	Reference standard bias	Multiple tests bias and other bias	Applicability	Overall risk of bias
BMD, vertebral fracture	Patient enrolment: random sample. Study design: not case control; prospective. Validation: --- Selection bias overall: low	Imputation: no imputation. Threshold selected: not applicable Index test bias overall: low	Analysis method: incidence data only: length of follow up: too short. Missing outcome data: some patients lost to follow up. Reference standard measurement: acceptable . Comments: 11% were no available for F/U (reasons: not contactable by phone, did not respond to questionnaire, immobility, death Reference standard	No. of events: <100 events Comments: 24 events Other bias overall: very high Single test	Population: population different from UK Index test: appropriate to review question Reference standard: follow up time too short; ref standard measurement: acceptable Comments: Country: Switzerland Overall applicability: indirect	Very high

Tool, outcome	Selection bias	Index test bias	Reference standard bias	Multiple tests bias and other bias	Applicability	Overall risk of bias
			bias overall: low			

Table 77:   Leslie 2007A, study characteristics

Tool, outcome	Study	Participants	Risk stratification tools
BMD, vertebral fracture BMD, hip fracture BMD, any fragility fracture	Leslie 2007a prospective cohort study; ---. Study held in Canada. Setting: ---. Population-based database (Mannitoba bone density programme). Funding :CHAR/GE Healthcare Development Awards Programme.	• Population: postmenopausal women; ---. 50 years or older; 98.2% were of white ethnicity • Inclusion criteria: Had baseline results for lumbar spine and proximal femur BMD measured using DPX/Prodigy; GE Lunar); medical coverage from Manitoba Health during observation period. • Exclusion criteria: . • Patient characteristics: age: 65 (SD9)years; sex: Female; ---. History of fracture: fracture history unclear • Comorbidities: none stated. Other details: Height, 160 (SD7)cm; weight, 68 (SD14)kg; mean lumbar spine BMD, 1.03 (SD0.19) g/cm2; mean femur neck BMD, 0.82 (SD0.13)g/cm2; mean total hip BMD, 0.87 (SD.15)g/cm2 • Other study comments: Historical cohort	• Type of diagnostic tool: --- • Index test:Femoral neck, Total hip and Spine (L1-4) BMD using DXA; time: (n=16505) • Reference standard: Major osteoporotic fractures (hip, clinical spine, forearm, proximal humerus) from longitudinal health service record; time mean 3.2 (SD1.5) years (n=16505) • Other comparator tests: Humerus fracture (not extracted). • for Target Condition/Outcome: 149 sustained at least one first incident vertebral fracture (overall incidence rate = 18 per 1000 person years) 765 sustained at least one incident osteoporotic fracture (189 hip, 209 spine, 230 forearm and 191 proximal humerus fractures)

Table 78: Leslie 2007A, QUADAS II

Tool, outcome	Selection bias	Index test bias	Reference standard bias	Multiple tests bias and other bias	Applicability	Overall risk of bias
BMD, vertebral fracture BMD, hip fracture BMD, any fragility fracture	Patient enrolment: selected group. Study design: not case control; prospective. Validation: ---. Comments: Patients were selected on the basis of the availability of BMD results on the clinical database Selection bias overall: high	Imputation: no imputation. Threshold selected: not applicable Index test bias overall: low	Analysis method: time to event analysis: length of follow up: appropriate. Missing outcome data: ---. Reference standard measurement: acceptable . Comments: missing data - not applicable Reference standard bias overall: low	No. of events: >=100 events Comments: Previous fracture data not reported Other bias overall: high Single test	Population: population different from UK Index test: appropriate to review question Reference standard: appropriate follow up time; ref standard measurement: acceptable Comments: Country: Canada Overall applicability: indirect	High

Table 79: Leslie 2010A, study characteristics

Tool, outcome	Study	Participants	Risk stratification tools
FRAX with BMD, any fragility fracture FRAX without BMD, any fragility fracture FRAX with BMD, hip fracture FRAX without BMD, hip fracture	Leslie2010A Retrospective cohort study; ---. Study held in Canada. Setting: community. This report describes construction of the Canadian FRAX tool, with direct assessment of its calibration and fracture discrimination in a large clinical cohort from the Manitoba Bone Density Program database. Funding :The authors received speakers	• Population: unselected patients; not higher risk. 36730 women and 2873 men (combined 39603) aged 50 years or older at the time of baseline femoral neck DXA between Jan 1990 and March 2007. • Inclusion criteria: All women and men in the Province of Manitoba, Canada, aged 50 years or older at the time of baseline femoral neck dual-energy X-ray absorptiometry (DXA) between	• Type of diagnostic tool: --- • Index test: Femoral neck by DXA; time: (n= 39603) • Reference standard: Fractures assessed through a combination of hospital discharge abstracts and physicians billing claims.; time 10y (n= 39603) • Other comparator tests: FRAX with/without BMD, T-scores. • for Target Condition/Outcome: Hip

Tool, outcome	Study	Participants	Risk stratification tools
	fees, research grants, consultancies fees for pharma companies.	January 1990 and March 2007. • Exclusion criteria: Subjects without medical coverage from Manitoba Health during the observation period ending March 2008. • Patient characteristics: age: F: 65.7±9.8 M: 68.2±10.1; sex: F:36730; M:2873; no patients had a prior test. History of fracture: fracture history • Comorbidities: none stated. Other details: BMI, W:26.8±5.2, M:27.1±4.4 Prior Fragility fracture, W:4984(13.6), M:431(15) Parental hip fracture, W:1110(13.2), M:86(10.6) Rheumatoid arthritis, W:1311(3.6), M:219(7.6) Current or recent corticosteroid use, W:1542(4.2), M:634(22.1) COPD (smoking proxy), W:2928(8.0), M:521(18.1) Substance abuse (alcohol use proxy), W:874(2.4), M:122(4.2) Femoral neck T-score (white female), W:-1.5±1.0, M:-1.2±1.1 Minimum T-score (white female), W:-1.9±1.1, M:-1.5±1.2 Osteoporotic BMD (minimum T-score≤-2.5), W:11335(30.9), M:555(19.3) • Other study comments: The study	fracture: 549 (F:506, M:43) Osteoporotic fracture: 2543 (F:2380, M:163). Non-hip fractures (clinical spine, forearm, proximal humerus) that contribute to the osteoporotic FRAX model were imputed, based on an untested assumption that hip to non-hip fracture ratios in the USA and Canada would be similar.

Tool, outcome	Study	Participants	Risk stratification tools
		does not follow up a cohort of people over a period of time, but it is designed to construct the Canadian FRAX tool. Limitations: 1) Reliance on administrative data for fracture ascertainment is less reliable than direct radiographic review. 2) Incomplete parental hip fracture information and use of proxy variables for smoking and high alcohol intake. 3) non-hip fractures were imputed, based on an untested assumption that hip to non-hip fracture ratios in the USA and Canada would be similar.	

Table 80: Leslie 2010A, QUADAS II

Tool, outcome	Selection bias	Index test bias	Reference standard bias	Multiple tests bias and other bias	Applicability	Overall risk of bias
FRAX with BMD, any fragility fracture FRAX without BMD, any fragility fracture FRAX with BMD, hip fracture FRAX without BMD, hip fracture	Patient enrolment: selected group. Study design: not case control; retrospective. Validation: --- Selection bias overall: high	Imputation: imputation applied, but % data imputed not stated. Threshold selected: --- . Comments: Missing parental hip fracture information prior to 2005. Imputed using age- and sex-specific estimates of the effect of a positive response.	Analysis method: incidence data only: length of follow up: appropriate. Missing outcome data: ---. Reference standard measurement: partially acceptable Reference standard bias overall: low	No. of events: >=100 events Comments: 2543 osteoporotic fractutres; 549 hip fractures Other bias overall: low Multiple index tests: all patients underwent all index tests; Randomisation not applicable.	Population: population different from UK Index test: appropriate to review question Reference standard: appropriate follow up time; ref standard measurement: partially acceptable Comments: Country: Canada Overall applicability:	High

Tool, outcome	Selection bias	Index test bias	Reference standard bias	Multiple tests bias and other bias	Applicability	Overall risk of bias
		Index test bias overall: high		Interaction between tests: not applicable; exclusions not applicable Multiple tests bias overall: low	indirect	

Table 81:   Nguygen 2008, study characteristics

Tool, outcome	Study	Participants	Risk stratification tools
BMD, any fragility fracture (women)	Nguygen 2008 prospective cohort study; ---. Study held in Australia. Setting: community. residents (Dubbo study). Funding :National Health and Medical Research Council of Australia, educational grants from GE-Lunar, Merck Australia, Eli Lilly International, Sanofi-aventis.	• Population: postmenopausal women; ---. >=60years; 98.6% Caucasian (men + women) • Inclusion criteria: . • Exclusion criteria: Fractures due to major trauma and those due to underlying disease (e.g. cancer, bone-related disease) were excluded. • Patient characteristics: age: 71 (SD8) years; sex: female; ---. History of fracture: Any fracture group: one fracture from age 50y, 24.4%; no fracture group: one fracture from age 50y, 6.9% • Comorbidities: none stated. Other details: Any fracture: mean BMI, 25(SD4); current/ex smoking, 29.6%); one fall in last 12 mo, 22.8%; maternal history of osteoporosis, 18.8% No fracture: mean 26(SD5); current/ex smoking,28.8%); one fall in last 12 mo, 14.2%; maternal history of	• Type of diagnostic tool: --- • Index test: Femoral neck BMD measured by DXA (GE-Lunar); time: (n=1358) • Reference standard: radiologists' reports from two centres providing xray services; time median 13 (IQR8- 14) years (n=1358) • Other comparator tests: Age and BMD; Age, BMD, prior fracture and fall; age, weight, prior fracture and fall. • for Target Condition/Outcome: 426 sustained at least one first incident fracture (overall incidence rate = 35 per 1000 person years)

Tool, outcome	Study	Participants	Risk stratification tools
		osteoporosis, 15.3% • Other study comments: During follow up, ~5% women were on anti-osteoporosis treatment, 4.5% being prescribed calcium and vit D	
BMD, any fragility fracture (men)	Nguygen 2008 prospective cohort study; ---. Study held in Australia. Setting: community. residents (Dubbo study). Funding :National Health and Medical Research Council of Australia, educational grants from GE-Lunar, Merck Australia, Eli Lilly International, Sanofi-aventis.	• Population: men; ---. >=60years; 98.6% Caucasian (men + women)_ • Inclusion criteria: . • Exclusion criteria: Fractures due to major trauma and those due to underlying disease (e.g. cancer, bone-related disease) were excluded. • Patient characteristics: age: 70 (SD6) years; sex: men; ---. History of fracture: Any fracture group: one fracture from age 50y, 22.2%; no fracture group: one fracture from age 50y, 3.8% • Comorbidities: none stated. Other details: Any fracture: mean BMI, 25(SD4); current/ex smoking, 63.1%); one fall in last 12 mo, 18.1%; maternal history of osteoporosis, 14.1% No fracture: mean 26(SD4); current/ex smoking,61.5%); one fall in last 12 mo, 9.7%; maternal history of osteoporosis, 12.9%	• Type of diagnostic tool: --- • Index test: Femoral neck BMD measured by DXA (GE-Lunar); time: (n=858) • Reference standard: radiologists' reports from two centres providing xray services; time median 12 (IQR7- 14) years (n=858) • Other comparator tests: Age and BMD; Age, BMD, prior fracture and fall; age, weight, prior fracture and fall. • for Target Condition/Outcome: 149 sustained at least one first incident fracture (overall incidence rate = 18 per 1000 person years)

Table 82: Nguygen 2008, QUADAS II

Tool, outcome	Selection bias	Index test bias	Reference standard bias	Multiple tests bias and other bias	Applicability	Overall risk of bias

Tool, outcome	Selection bias	Index test bias	Reference standard bias	Multiple tests bias and other bias	Applicability	Overall risk of bias
BMD, any fragility fracture	Patient enrolment: consecutive. Study design: not case control; prospective. Validation: --- Selection bias overall: low	Imputation: no imputation. Threshold selected: not applicable Index test bias overall: low	Analysis method: time to event analysis: length of follow up: appropriate. Missing outcome data: unclear. Reference standard measurement: acceptable Reference standard bias overall: low	No. of events: >=100 events Comments: During follow up, ~5% women were on antiosteoporosis treatment, 4.5% being prescribed calcium and vit D Other bias overall: low Single test	Population: population different from UK Index test: appropriate to review question Reference standard: appropriate follow up time; ref standard measurement: acceptable Comments: Country: Australia Overall applicability: indirect	Low

Table 83: Pluskiewicz 2010, study characteristics

Tool, outcome	Study	Participants	Risk stratification tools
FRAX with BMD, any fragility fracture FRAX with BMD, hip fracture	Pluskiewicz 2010 cross sectional study Study held in Poland, Multi centre. Setting: secondary care. Bone densitometry centres in 4 Polish towns. Funding :Not stated.	• Population: postmenopausal women; not higher risk. • Inclusion criteria: postmenopausal women, 55 years and older. • Exclusion criteria: not stated. • Patient characteristics: age: 68.5 (SD7.9) years, range 55-90 years; sex: female; no patients had a prior test. History of fracture: 692 (34%) women had fracture history (one or more cases) at the age of 50 or later. 250 (12%) women had a history of multiple	• Type of diagnostic tool: --- • Index test: FRAX US Caucasian was used; BMD was measured using three Lunar devices and one Norland device; time: (n=2012) • Reference standard: ; time (n=) • Other comparator tests: Nguyen's nomogram (not extracted). • for Target Condition/Outcome: 728 (36%) women had at least one lowtrauma fractures (including distal forearm, vertebrae, proximal femur,

Tool, outcome	Study	Participants	Risk stratification tools
		fractures (max.9) • Comorbidities: none stated. Other details: mean BMI 28 (SD4.8) kg/m2; 23.5% with T-score for femoral neck BMD below -2.5; 10% had steroid use; 10.3% had secondary causes of osteoporosis; 9.4% were current smokers • Other study comments: The paper did not give % women with hip fracture	humerus, ribs and tibia and fibula) at age>45years

Table 84:   Pluskiewicz 2010, QUADAS II

Tool, outcome	Selection bias	Index test bias	Reference standard bias	Multiple tests bias and other bias	Applicability	Overall risk of bias
FRAX with BMD, any fragility fracture FRAX with BMD, hip fracture	Patient enrolment: unclear . Study design: not case control; ---. Validation: inadequate validation. Comments: cross-sectional study; exclusion criteria not stated Selection bias overall: very high	Imputation: no imputation. Threshold selected: not applicable. Comments: patients had BMD measured using different devices Index test bias overall: low	Analysis method: analysis method not stated: length of follow up: not stated. Missing outcome data: no loss to follow up. Reference Standard measurement: not stated Reference standard bias overall: low	No. of events: >=100 events Comments: Cross-sectional study. 728 fractures. Other bias overall: high Multiple index tests: all patients underwent all index tests; Randomisation not applicable. Interaction between tests: results un-affected when undertaken together on the same patient; exclusions not	Population: selected: different setting Index test: inappropriate to UK Reference standard: not stated; ref standard measurement: not stated Comments: country: Poland FRAX US Caucasian; no follow up time; ascertainment of fractures not stated; index test - devices not standardised across centres	Very high

Tool, outcome	Selection bias	Index test bias	Reference standard bias	Multiple tests bias and other bias	Applicability	Overall risk of bias
				applicable Multiple tests bias overall: low	Overall applicability: very indirect	

Table 85:   Popp 2009, study characteristics

Tool, outcome	Study	Participants	Risk stratification tools
BMD, Any fragility fracture	Popp 2009 prospective cohort study; ---. Study held in Switzerland. Setting: community. multicentre; Randomly recruited from official state registries (SEMOF study). Funding :Not stated.	• Population: postmenopausal women; ---. community-dwelling elderly women aged 70-80 years_• Inclusion criteria: Able to walk and being independent for their daily activities. • Exclusion criteria: history of hip fracture or bilateral hip replacement; women had no baseline DXA measurement and 7.1% loss to follow up. • Patient characteristics: age: 76.1 (SD3) years; sex: Female; ---. History of fracture: 52% had previous fracture • Comorbidities: none stated. Other details: mean age at menopause, 49 (SD4.5) years; mean BMI, 25.8 (SD4.3); mean lumbar spine (L1-4), 0.89 (SD0.178)g/cm2; mean femoral neck , 0.65(SD0.11)g/cm2; mean total hip, 0.77 (SD0.12)	• Type of diagnostic tool: --- • Index test: BMD measured at lumbar spine (L1-4), femoral neck and total hip by DXA; scans were performed according to manufacturer's guidelines with quality control; time: (n=637) • Reference standard: Self-reported clinical fracture (forearm, vertebral, hip/pelvis, ankle, proximal humerus, rib, elbow), confirmed by questionnaire either to the family practitioner or to the hospital in charge of the participants; time 2.8 (SD0.6) years (n=637) • Other comparator tests: BMD also measured at total hip, femoral neck, tibia. • for Target Condition/Outcome: 61 women sustained one or more clinical fragility fracture (total fracture=68)

Table 86: Popp 2009, QUADAS II

Tool, outcome	Selection bias	Index test bias	Reference standard bias	Multiple tests bias and other bias	Applicability	Overall risk of bias
BMD, Any fragility fracture	Patient enrolment: random sample. Study design: not case control; prospective. Validation: ---. Comments: Elderly population: over 50% had previous fracture Selection bias overall: low	Imputation: no imputation. Threshold selected: not applicable Index test bias overall: low	Analysis method: time to event analysis: length of follow up: too short. Missing outcome data: some patients lost to follow up. Reference standard measurement: acceptable . Comments: follow up time: 2.8 years 7.1% loss to follow up Reference standard bias overall: low	No. of events: <100 events Comments: 68 fractures Other bias overall: high Single test	Population: population different from UK Index test: appropriate to review question Reference standard: follow up time too short; ref standard measurement: acceptable Comments: Country: Switzerland Overall applicability: indirect	High

Table 87: Robbins 2007, study characteristics

Tool, outcome	Study	Participants	Risk stratification tools
BMD, Hip fracture	Robbins 2007 prospective cohort study; ---. Study held in USA. Setting: community. Women's Health Initiative (WHI) cohort. Funding :.	• Population: postmenopausal women; Postmenopausal women aged 50-79 from 40 clinical centres and assigned to multiple clinical trials and an observational study. A subset from 3 clinical centres underwent DXA scan. • Inclusion criteria: Age: 50-79 Post-menopausal. • Exclusion criteria: Women who did not undergo DXA scan. • Patient characteristics: age: 62.7; sex: F; ---. History of fracture: fracture	• Type of diagnostic tool: --- • Index test: ; time: at baseline (n= 10750) • Reference standard: Hip fractures self-reported then confirmed by x-ray and surgical report.; time Follow up: 8.7(1.2)y (n= 10750) • Other comparator tests: WHI algorithm; WHI algorithm + BMD (not extracted). • for Target Condition/Outcome: 80 hip fractures

Tool, outcome	Study	Participants	Risk stratification tools
		history • Comorbidities: none stated. Other details: • Other study comments: A prediction model was developed from the WHI observational study dataset and validated by the WHI clinical trial dataset. A subset of the WHI underwent DXA scan.	

Table 88:   Robbins 2007, QUADAS II

Tool, outcome	Selection bias	Index test bias	Reference standard bias	Multiple tests bias and other bias	Applicability	Overall risk of bias
BMD, Hip fracture	Patient enrolment: not stated. Study design: not case control; prospective. Validation: ---. Comments: Only a subset of the WHI cohort included (underwent DXA scan) Selection bias overall: low	Imputation: no imputation. Threshold selected: --- Index test bias overall: low	Analysis method: incidence data only: length of follow up: appropriate. Missing outcome data: ---. Reference standard measurement: acceptable . Comments: follow up time: 8.7 (1.2)y; Loss to follow up not stated Reference standard bias overall: low	No. of events: <100 events Comments: 80 hip fractures Other bias overall: high Multiple index tests: Some patients underwent all index tests; Randomisation method unclear. Interaction between tests: results un-affected when undertaken together on the same patient; some patients appropriately	Population: population different from UK Index test: appropriate to review question Reference standard: appropriate follow up time; ref standard measurement: acceptable Comments: Country: USA Overall applicability: indirect	High

Tool, outcome	Selection bias	Index test bias	Reference standard bias	Multiple tests bias and other bias	Applicability	Overall risk of bias
				excluded from having multiple index tests Multiple tests bias overall: high		

Table 89: Sambrook 2011, study characteristics

Tool, outcome	Study	Participants	Risk stratification tools
FRAX without BMD, any fragility fracture FRAX without BMD, hip fracture	Sambrook 2011 prospective cohort study; ---. Study held in 10 countries. (Australia, Belgium, Canada, France, Germany, Italy, The Netherlands, Spain, UK, USA) Setting: GP surgery. . Funding :Warner Chilcott Company, LLC and Sanofi Aventis.	• Population: peri- and post-menopausal women; not higher risk. Global Longitudinal Study of Osteoporosis in Women (GLOW)_ • Inclusion criteria: Age≥60y. • Exclusion criteria: Unable to complete the study survey due to cognitive impairment, language barrier, institionalization, or illness. Women on anti-osteoporosis medication.. • Patient characteristics: age: ; sex: F; ---. History of fracture: fracture history • Comorbidities: none stated. Other details: • Other study comments: Study conducted in physicians practices in Australia, Belgium, Canada, France, Germany, Italy, The Netherlands, Spain, UK, USA	• Type of diagnostic tool: --- • Index test: Self-administered questionnaires; time: at baseline (n= 19586) • Reference standard: ; time 2 years (n= 19586) • Other comparator tests: FRC and Age+previous fracture (not extracted). • for Target Condition/Outcome: 67 hip fractures 468 major osteoporotic fracture

Table 90: Sambrook 2011, QUADAS II

Tool, outcome	Selection bias	Index test bias	Reference standard bias	Multiple tests bias and other bias	Applicability	Overall risk of bias
FRAX without BMD, hip fracture	Patient enrolment: unclear . Study design: not case control; prospective. Validation: --- Selection bias overall: low	Imputation: no imputation. Threshold selected: not stated Index test bias overall: low	Analysis method: incidence data only: length of follow up: appropriate. Missing outcome data: some patients lost to follow up. Reference standard measurement: acceptable . Comments: Follow up:2 years Loss to follow up: <10% Reference standard bias overall: low	No. of events: <100 events Other bias overall: high Multiple index tests: --; --. Interaction between tests: --; -- Multiple tests bias overall: --	Population: appropriate to review question Index test: appropriate to review question Reference standard: appropriate follow up time; ref standard measurement: acceptable Comments: 10 countries in 3 continents (incl. UK) Overall applicability: direct	High
FRAX without BMD, any fragility fracture	Patient enrolment: unclear . Study design: not case control; prospective. Validation: --- Selection bias overall: low	Imputation: no imputation. Threshold selected: not stated Index test bias overall: low	Analysis method: incidence data only: length of follow up: appropriate. Missing outcome data: some patients lost to follow up. Reference standard measurement: acceptable . Comments: Follow up:2 years Loss to follow up: <10% Reference standard bias overall: low	No. of events: >=100 events Other bias overall: low Multiple index tests: --; --. Interaction between tests: --; -- Multiple tests bias overall: --	Population: appropriate to review question Index test: appropriate to review question Reference standard: appropriate follow up time; ref standard measurement: acceptable Comments: 10 countries in 3 continents (incl. UK) Overall applicability:	Low

Tool, outcome	Selection bias	Index test bias	Reference standard bias	Multiple tests bias and other bias	Applicability	Overall risk of bias
					direct	

Table 91: Sandhu 2010, study characteristics

Tool, outcome	Study	Participants	Risk stratification tools
FRAX with BMD, any fragility fracture (women)	Sandhu 2010 case control study; external validation - different researchers. Study held in Australia. Setting: secondary care. Hospital. Funding :Educational grants from Merck Sharp and Dohme, Sanofi-Aventis, Procter& Gamble Australia, Novartis and St. Vincent's Hospital Dept. of Nuclear Medicine.	• Population: postmenopausal women; not higher risk. Cases (n=69) are defined as individuals with a first osteoporotic fracture; controls (n=75) are defined as individuals without a fracture history (referred to clinic for further investigation and management of CRFs for fractures)• Inclusion criteria: Caucasian origin, aged between 60 and 90 years old. Cases were included if they had a major osteoporotic fracture defined in FRAX. • Exclusion criteria: On bone-specific treatment for >3 months or had other metabolic bone disorders such as Paget's disease or skeletal metastases. 330 records were excluded as a result. • Patient characteristics: age: Cases mean 73 (SD8) years; control mean 68 (SD8) years; sex: female; unclear or not stated. History of fracture: 48% of the cases (fractured) had prior fractures • Comorbidities: none stated. Other details: 15% had falls in the last 12 months; 62% had secondary causes of osteoporosis; 3% with family history of hip fracture; 6% were on corticisteroid;	• Type of diagnostic tool: Replacement • Index test: FRAX-UK; DXA scan had to be performed before or within 3 months of the incident fracture in the fracture group.; time: Average duration of time from BMD scan to study entry = 1.7 years in those with fractures and 3.7 years in those without fractures (n=144) • Reference standard: Obtained by medical records from outpatient Fracture and Bone and Calcium clinics; time N/A (n= 144) • Other comparator tests: Garvan. • for Target Condition/Outcome: 69 women with fracture(s) (69 fractures at the hip, spine, wrist or humerus)

Tool, outcome	Study	Participants	Risk stratification tools
		1% consumed >3 units of alcohol; 5% were current smokers • Other study comments: retrospective validation	
FRAX with BMD, any fragility fracture (men)	Sandhu 2010 case control study; external validation - different researchers. Study held in Australia. Setting: secondary care. Hospital. Funding :Educational grants from Merck Sharp and Dohme, Sanofi-Aventis, Procter& Gamble Australia, Novartis and St. Vincent's Hospital Dept. of Nuclear Medicine.	• Population: men; not higher risk. Cases (n=31) are defined as individuals with a first osteoporotic fracture; controls (n=25) are defined as individuals without a fracture history (referred to clinic for further investigation and management of CRFs for fractures) • Inclusion criteria: Caucasian origin, aged between 60 and 90 years old. Cases were included if they had a major osteoporotic fracture defined in FRAX. • Exclusion criteria: On bone-specific treatment for >3 months or had other metablic bone disorders such as Paget☐s disease or skeletal metastases. 330 records were excluded as a result. • Patient characteristics: age: Cases mean 75 (SD10) years; control mean 68 (SD8) years; sex: male; unclear or not stated. History of fracture: 16% of the cases (fractured) had prior fractures • Comorbidities: none stated. Other details: 10.8% had falls in the last 12 months; 68% had secondary causes of osteoporosis; 0% with family history of hip fracture; 25% were on corticisteroid; 0% consumed >3 units of alcohol; 5% were current smokers	• Type of diagnostic tool: Replacement • Index test: FRAX-UK; DXA scan had to be performed before or within 3 months of the incident fracture in the fracture group.; time: Average duration of time from BMD scan to study entry = 1.7 years in those with fractures and 3.7 years in those without fractures (n=56) • Reference standard: Obtained by medical records from outpatient Fracture and Bone and Calcium clinics; time N/A (n= 56) • Other comparator tests: Garvan. • for Target Condition/Outcome: 31 men with fracture(s) (32 fractures at the hip, spine, wrist or humerus)

Tool, outcome	Study	Participants	Risk stratification tools
		• Other study comments: retrospective validation	

Table 92: Sandhu 2010, QUADAS II

Tool, outcome	Selection bias	Index test bias	Reference standard bias	Multiple tests bias and other bias	Applicability	Overall risk of bias
FRAX with BMD, any fragility fracture	Patient enrolment: selected group. Study design: case control; retrospective. Validation: inadequate validation Selection bias overall: very high	Imputation: no imputation. Threshold selected: not stated. Comments: The process of selecting patients involved reviewing medical records to ensure that the inclusion and exclusion criteria were met, the person abstracting the data could not be blinded to case-control status of each participants Index test bias overall: very high	Analysis method: ---: length of follow up: --- . Missing outcome data: ---. Reference standard measurement: partially acceptable Reference standard bias overall: high	No. of events: <100 events Comments: no follow up time, case-control study 100 osteoporotic fractures Other bias overall: high Multiple index tests: N/A	Population: population different from UK Index test: appropriate to review question Reference standard: ---; ref standard measurement: partially acceptable Comments: Country: Australia Setting: outpatients attending fracture clinic; fracture confirmed by medical records; small sample size Overall applicability: indirect	Very high

Table 93: Sornay-Rendu 2010A, study characteristics

Tool, outcome	Study	Participants	Risk stratification tools
FRAX with BMD, any fragility fracture FRAX without BMD, any fragility fracture	Sornay-Rendu 2010 prospective cohort study; external validation - different researchers. Study held in France. Setting: ---. Health insurance company in France. Funding: Grant from AMGEN to INSERM.	• Population: all women; not higher risk. 680 post-menopausal women and 187 pre-menopausal women; randomly selected from a health insurance company in Lyon • Inclusion criteria: Aged 40 years or over. • Exclusion criteria: 16 women were excluded due to no information about incident fractures obtained; 50 non-fractured women died during the 10 year follow up. • Patient characteristics: age: mean 59 years; sex: female; no patients had a prior test. History of fracture: 10.3% had prior fracture • Comorbidities: none stated. Other details: Mean BMI 23.8kg/m2; mean femoral neck BMD 0.717 (SD0.12); 11.8% had a parental history of fracture; 10.6% current smokers; 3.1% on long term use of oral corticosteroids; 5.2% had daily intake of alcohol>2units • Other study comments: Additional results: the predicted fracture probability was substantially lower than the observed incidence of fracture in women aged >=65 years with low BMD values.	• Type of diagnostic tool: Replacement • Index test: ; time: At initial screening visit (n=867) • Reference standard: Major osteoporotic fracture (hip, vertebrae, shoulder and forearm). Incident cases were reported during annual follow up. All fractures were confirmed by radiographs or a surgical report. VF were identified using Genant method by trained physicians.; time 10 years (n= 851) • Other comparator tests: FRAX with BMD, BMD + age (not extracted), BMD alone (not extracted). • for Target Condition/Outcome: 116 women (13.6%) sustained 151 incident clinical fragility fracture at all sites (excluding fingers, toes, skull and face). 82 women (9.6%) reported 95 major osteoporotic fractures

Tool, outcome	Study	Participants	Risk stratification tools
		Statistical analysis: chi-squared test, unpaired T test, ROC curve	

Table 94: Sornay-Rendu 2010A, QUADAS II

Tool, outcome	Selection bias	Index test bias	Reference standard bias	Multiple tests bias and other bias	Applicability	Overall risk of bias
FRAX with BMD, any fragility fracture FRAX without BMD, any fragility fracture	Patient enrolment: random sample. Study design: not case control; prospective. Validation: adequate validation Selection bias overall: low	Imputation: no imputation. Threshold selected: not stated. Comments: Women included if baseline data available Index test bias overall: low	Analysis method: incidence data only: length of follow up: appropriate. Missing outcome data: some patients not analysed. Reference standard measurement: acceptable . Comments: Not time to- event Reference standard bias overall: low	No. of events: <100 events Comments: 16 women (1.8%) were excluded from analysis due to no information about incident fractures obtained Other bias overall: high Multiple index tests: all patients underwent all index tests; Randomisation not applicable. Interaction between tests: results un-affected when undertaken together on the same patient; exclusion not applicable Multiple tests bias overall: low	Population: selected: different setting Index test: appropriate to review question Reference standard: appropriate follow up time; ref standard measurement: acceptable Comments: Country: France Overall applicability: indirect	High

Table 95: Stewart 2006, study characteristics

Tool, outcome	Study	Participants	Risk stratification tools
BMD, any fragility fracture	Stewart 2006 prospective cohort study; ---. Study held in UK. Setting: community. randomly selected from a community based register, invited for scanning (APOSS study). Funding :An educational grant from SmithKlime Beecham and Grampian Osteoporosis Trust.	• Population: all women; ---. 45-54years• Inclusion criteria: Subjects that had subsequently been treated for osteoporosis were included in the analysis. • Exclusion criteria: self-reported fracture with no x-ray reports/confirmation by physician (n=68). • Patient characteristics: age: 48.6 (44-56); sex: female; ---. History of fracture: • Comorbidities: none stated. Other details: mean BMI=25.5 (SD4.5); mean spine BMD (g/cm2)=1.05 (SD0.161); mean femoral neck BMD=0.88 (SD0.125) • Other study comments: (n=741) 119 moved away, 35 died, 548 no response, 35 returned blank questionnaire, 4 unwilling/unable to participate	• Type of diagnostic tool: --- • Index test: Femoral neck and lumbar spine BMD measured by DXA (Norland); time: (n=3883) • Reference standard: any osteoporotic fracture (hip, vertebral, wrist and humeral); new fracture(s) were self-reported and validated by examination of X-ray reports by radiologists; time 9.7 (SD1.1) years (n= 3142) • Other comparator tests: QUS (not extracted). • for Target Condition/Outcome: 325 new fractures (2 hip, 88 wrist, 5 vertebral; 50 ankle)

Table 96: Stewart 2006, QUADAS II

Tool, outcome	Selection bias	Index test bias	Reference standard bias	Multiple tests bias and other bias	Applicability	Overall risk of bias
BMD, any fragility fracture	Patient enrolment: random sample. Study design: not case control; prospective.	Imputation: no imputation. Threshold selected: not applicable Index test bias overall: low	Analysis method: time to event analysis: length of follow up: appropriate. Missing outcome data: some	No. of events: >=100 events Comments: Prior fracture at baseline not reported	Population: appropriate to review question Index test: appropriate to review question	High

Tool, outcome	Selection bias	Index test bias	Reference standard bias	Multiple tests bias and other bias	Applicability	Overall risk of bias
	Validation: --- Selection bias overall: low		patients lost to follow up. Reference standard measurement: acceptable . Comments: ~20% loss to follow up overall Reference standard bias overall: low	Other bias overall: high Single test	Reference standard: appropriate follow up time; ref standard measurement: acceptable Comments: Country: UK Overall applicability: direct	

Table 97: Tanaka 2010, study characteristics

Tool, outcome	Study	Participants	Risk stratification tools
FRAX with BMD, any fragility fracture BMD, any fragility fracture	Tanaka 2010 prospective cohort study; ---. Study held in Japan. Setting: community. Community, Miyama village and Taiji cohort. Funding :.not stated	• Population: all women; not higher risk. Miyama Cohort (200 women) and Taiji cohort (200 women). Randomly selected. •Inclusion criteria: Age between 40-79y. • Exclusion criteria: . • Patient characteristics: age: 59.5±11.3; sex: F; ---. History of fracture: fracture history • Comorbidities: none stated. Other details: Height (cm): 150.2±6.2 Weight (kg): 51.2±9.3 • Other study comments: This study is designed to develop (in a different cohort) the FRISC tool, then validated in	• Type of diagnostic tool: --- • Index test: BMD of L2-4 and BMD at femoral neck, Ward's triangle and the trochanteric region measured by DXA (Lunar DPX, Lunar corporation, Madison, WI in the Myiama cohort; Hologic QDR-1000; Hologic Inc., Crosby Drive Bedford, MA in the Taiji cohort).; time: at baseline (n=.400) • Reference standard: The incidence of clinical fracture was evaluated in both cohorts; time (n= 400) • Other comparator tests: BMD alone (extracted) FRISC (not extracted). • for Target Condition/Outcome: 60 major osteoporotic fractures

Tool, outcome	Study	Participants	Risk stratification tools
		the Miyiama and Taiji cohort and compared to FRAX and BMD.	

Table 98:   Tanaka 2010, QUADAS II

Tool, outcome	Selection bias	Index test bias	Reference standard bias	Multiple tests bias and other bias	Applicability	Overall risk of bias
FRAX with BMD, any fragility fracture	Patient enrolment: random sample. Study design: not case control; prospective. Validation: adequate validation Selection bias overall: low	Imputation: more than 50% imputation for 2-3 factors. Threshold selected: --- . Comments: BMD measured by 2 different devices in the 2 cohorts. 50% missing data for parental history or previous fracture, it was assumed the answer was NO. Index test bias overall: high	Analysis method: incidence data only: length of follow up: appropriate. Missing outcome data: some patients lost to follow up. Reference standard measurement: acceptable . Comments: 16% loss to follow up follow up time: 10y Reference standard bias overall: low	No. of events: <100 events Comments: 60 major osteoporotic fractures Other bias overall: high Multiple index tests: all patients underwent all index tests; Randomisation method unclear. Interaction between tests: results un-affected when undertaken together on the same patient; no patients excluded from having multiple index tests Multiple tests bias overall: low	Population: population different from UK Index test: modified version Reference standard: appropriate follow up time; ref standard measurement: acceptable Comments: Country: Japan Overall applicability: indirect	High
BMD, any fragility fracture	Patient enrolment: random sample.	Imputation: no imputation.	Analysis method: incidence data only:	No. of events: <100 events	Population: population different	

Tool, outcome	Selection bias	Index test bias	Reference standard bias	Multiple tests bias and other bias	Applicability	Overall risk of bias
	Study design: not case control; prospective. Validation: adequate validation Selection bias overall: low	Threshold selected: --- . Comments: BMD measured by 2 different devices in the 2 cohorts Index test bias overall: low	length of follow up: appropriate. Missing outcome data: some patients lost to follow up. Reference standard measurement: acceptable . Comments: 16% loss to follow up follow up time: 10y Reference standard bias overall: low	Comments: 60 major osteoporotic fractures Other bias overall: high Multiple index tests: all patients underwent all index tests; Randomisation method unclear. Interaction between tests: results un-affected when undertaken together on the same patient; no patients excluded from having multiple index tests Multiple tests bias overall: low	from UK Index test: modified version Reference standard: appropriate follow up time; ref standard measurement: acceptable Comments: Country: Japan Overall applicability: indirect	

Table 99:   Tremollieres 2010A, study characteristics

Tool, outcome	Study	Participants	Risk stratification tools
FRAX without BMD, any fragility fracture BMD, any fragility fracture	Tremollieres 2009 prospective cohort study; ---. Study held in France. Setting: community. Menopause centre of the Toulouse	• Population: peri- and post-menopausal women; not higher risk. details about components of risk stratification tool, e.g. 15.2% cases and	• Type of diagnostic tool: Replacement • Index test: computer-assisted standardised questionnaire, recorded by the same research nurse; time: on presentation (n=2651)

Tool, outcome	Study	Participants	Risk stratification tools
	University Hospital. Funding: Institutional grant from Lilly France and Pierre Fabre Sante laboratories.	10% controls had a family history of hip fracture; mean femoral neck BMD in cases and controls are 0.77 and 0.84g/cm2; 8.3% cases and 2.1% controls had previous history of fracture •Inclusion criteria: age>45 years that were referred to the menopausal centre; all women who completed a computer-assisted standardised questionnaire. • Exclusion criteria: past/current osteoporosis treatment for more than 3 months. • Patient characteristics: age: 54(SD=4) years; sex: female; all patients had a prior test (systematic menopause check up). History of fracture: 2.1% women with incident fracture and 8.3% women without incident fracture had a previous fracture history (after 45years) • Comorbidities: none stated. Other details: • Other study comments: 2651 attended follow up visit. Of 1373 nonresponders, 109 had died, 424 refused to participate and 840 lost to follow up. 455 were excluded from the analysis due to past/current osteoporosis treatment for more than 3 months Additional results in paper (also presented in table): If the cut off for	• Reference standard: self-reported fracture incidence (including spine, hip, distal forearm and proximal humerus), confirmed by radiographs or by medical surgical reports; Radiographs of the spine were not performed, and only clinical spine fractures were considered.; time mean follow up 13.4 (SD=1.4) years (n=2196) • Other comparator tests: FRAX + parity; age, hip BMD, fracture history + parity (not extracted). • for Target Condition/Outcome: 415 sustained a first low-energy fracture, including 145 major osteoporotic fractures (108 wrist, 44 spine, 20 proximal humerus, 13 hip)

Tool, outcome	Study	Participants	Risk stratification tools
		high risk is set at 30% (30% women with the highest FRAX values or with the lowest BMD are classified as high risk), the sensitivity is 49% and 55% for FRAX and hip BMD, respectively. If set at 60%, the sensitivity is 80.3% for both FRAX and hip BMD.	

Table 100: Tremollieres 2010A, QUADAS II

Tool, outcome	Selection bias	Index test bias	Reference standard bias	Multiple tests bias and other bias	Applicability	Overall risk of bias
FRAX without BMD, any fragility fracture BMD, any fragility fracture	Patient enrolment: consecutive. Study design: not case control; prospective. Validation: ---. Comments: Subjects were referred for a menopause checkup. Reasons for referral are not known but may include a higher risk of osteoporosis Selection bias overall: high	Imputation: no imputation. Threshold selected: --- Index test bias overall: low	Analysis method: analysis method unclear: length of follow up: appropriate. Missing outcome data: significant loss to follow up. Reference standard measurement: acceptable Reference standard bias overall: low	No. of events: >=100 events Comments: 840/4024 (20.9%) lost to follow up; 424/4024 (10.5%) refused to participate in the follow up visit; 109/4024 died. 455/2196 excluded from analysis (osteoporosis treatment) Asymptomatic radiographic vertebral fractures were not considered. Other bias overall: high Multiple index tests: Unclear/not stated;	Population: selected: different setting Index test: appropriate to review question Reference standard: appropriate follow up time; ref standard measurement: acceptable Comments: Country: France all women were referred to the menopause centre Overall applicability: indirect	High

Tool, outcome	Selection bias	Index test bias	Reference standard bias	Multiple tests bias and other bias	Applicability	Overall risk of bias
				Not randomised. Interaction between tests: results un-affected when undertaken together on the same patient; no patients excluded from having multiple index tests		

D.3 Evidence tables and QUADAS II tables for reclassification studies

D.3.1 Evidence tables

Reference	Study type	Number of patients	Patient characteristics	Baseline and outcome variables	Statistical Methods	Source of funding
Johansson H, Oden A et al. Optimisation of BMD measurements to identify high risk groups for treatment – a test analysis. Journal of Bone and Mineral Research. 2004; 19(6): 906-913	Prospective cohort (from a RCT) Sheffield UK	N=2113 women	Women ≥75years Recruitment and eligibility criteria: selected randomly from the population of Sheffield. The population was identified from GP listings and the women were contacted by letter and invited to attend for assessment of skeletal status. Exclusion criteria: taking of bone active agents, known malabsorption states, lack of compliance due to poor mental state or concurrent illnesses. Randomisation: SAS/PLAN procedure for one site, two treatments, and a block size of 10. Treatment arms: bisphosphonate, clodronate, or placebo This is a follow up study of patients that were enrolled into the placebo arm. 		Mean (SD)
---	---
Height (cm)	156 (6)
Weight (kg)	64.8 (11.9)
BMI (kg/m2)	26.6 (4.5)
Previous fracture (%)	51
Maternal history of	19		Baseline factors measured: age, height, weight, BMI, personal and family history of fracture, smoking, milk intake, oral corticosteroids, and self-reported disorders associated with osteoporosis or fracture. BMD was assessed by DXA (Hologic 4500) at total hip and its regions. Outcomes Fractures according to site and death from any cause. Deaths were verified by death certificates. Fractures were asked about at 6 monthly home visits by study nurses. All self-reported fractures were independently verified from radiographic	Poisson model was used to identify sig. risk factors for all fractures and for +/- BMD. Hazard functions for mortality and fracture were used to compute 10y fracture probability. 10y fracture probabilities were calculated +/- BMD according to set intervention threshold of 35%. Logistic regression, to determine the prob. That an individual at low risk without BMD would be reclassified to be at high risk with the addition of BMD measurement (false –ve). Threshold	The Alliance for Better Bone Health, GE Lunar, Hologic, Lilly, Novartis, Pfizer, Roche, Wyeth, the IOF and the International Society for Clinical Densitometry

fracture (%)		inspection, radiographic reports, or operation and hospital summaries.
Sibling history of fracture (%)	21	
Current smoking (%)	7	Length of follow up: 6723 patient years
Milk intake (score 0-5)	3.1 (0.7)	
Corticosteroid use (%)	9.3	No. of fractures/deaths obtained: 208 deaths and 282 fractures (53 at the hip, 26 clinical vertebral fractures, 36 axial nonvertebral fractures and 117 appendicular fractures.)
Rheumatoid arthritis (%)	2.4	
Stroke (%)	2.5	
Diabetes (%)	0.6	
Hyperparathyroidism (%)	1.2	
Osteoarthritis (%)	70	
Age at menopause (years)	47.7 (5.5)	
Use of HRT (%)	1.4	

probabilities were used to determine the % of the population in whom BMD assessment would be required to optimise a case finding strategy:

P1 was the probability of reclassifying a high-risk patient to low-risk; base case was set at 0.8. If P1 is exceeded, a BMD measurement would be required.

P2 was the probability of reclassifying a low - risk patient to high-risk; base case was set at 0.2. If P2 is exceeded, a BMD measurement would be required.

Results

The 10 year fracture probability ranged from 11% to 55% (28±7%).

Table 1. Risk reclassification when major fracture probability initially calculated without BMD is recalculated using BMD

Total N = 2113	Initial calculation Clinical risk factors (CRFs)	Subsequent calculation CRFs + BMD	Post-recalculation with BMD,

	without BMD N reclassified	Number remained high/low risk	Number reclassified (change from high to low or low to high risk)	N reclassified
High risk	354	245	109	455*
Low risk	1759	1549	210	1658*

*Total = 455 women categorised at high risk [(354-109) + 210].
    1658 women categorised at low risk [(1759-210) + 109].

If intervention threshold was set at 35%:

- Based on CRFs alone, 354 (16.8%) women were classified as high risk and 1759 women were classified as low risk.
- With the addition of BMD to CRFs, 109 women that were initially classified as high risk would be reclassified as low risk and 210 women that were initially classified as low risk would be reclassified high risk.

Table 2. Distribution (%) of 10y fracture probabilities in women assessed with BMD and without BMD measurements

% fracture probability in 10 years	CRFs alone (number of women)	CRFs with BMD (number of women)	No. misclassified (%)	BMD (g/cm2), mean (95% CI)	T-score (SD units)	Mean age (years)
0-5						
5-10		9				
10-15	15	76		0.93 (0.86-1.00)	-0.13	77.8
15-20	302	349	1 (0.04)	0.85 (0.84-0.86)	-0.75	78.5
20-25	621	502	9 (0.42)	0.76 (0.75-0.77)	-1.50	80.3
25-30	312	399	36 (1.7)	0.78 (0.76-0.80)	-1.33	79.5
30-35	509	323	164 (7.76)	0.74 (0.73-0.75)	-1.67	79.6
Subtotal (0-35%)	1759	1658	210			
35-40	245	218	99 (4.68)	0.66 (0.64-0.68)	-2.33	82.1
40-45	55	126	8 (0.38)	0.69 (0.64-0.74)	-2.08	80.6
45-50	45	59	2 (0.09)	0.67 (0.64-0.70)	-2.25	80.6
50-55	9	35		0.57 (0.45-0.69)	-3.08	82.1

55-60		10				
60-65		6				
65-70		1				
70-75						
Subtotal (≥35%)	354	455	109			

Mean age and BMD (95% CI) given without the use of BMD.

Misclassifications were most frequent close to the threshold value chosen (35%).

Table 3. % of women required a BMD test in order to classify fracture risk, according to different probabilities of misclassification accepted (threshold between high and low risk was set at 35% 10y fracture probability)
P1 = probability of reclassifying at high to low risk with a BMD test;
P2 = probability of reclassifying at low to high risk with a BMD test

Under the assumption pre-specified in methods section (P1 >0.8 and P2 >0.2), BMD measurement would be required in 21.4% of the population.
If P1 = 0 and P2 = 0, all 354 patients classified as high risk without BMD would require a BMD test and 1759 patients classified as low risk would require a BMD test.

	P2					
P1	0	0.1	0.2	0.3	0.4	≥0.5
0	100	47.8	38.1	30.6	22.9	16.8
0.1	96.3	44.2	34.5	27	19.2	13.1
0.2	94.9	42.7	33.1	25.6	17.8	11.7
0.3	92.7	40.5	30.9	23.3	15.6	9.5
0.4	89.9	37.7	28	20.5	12.7	6.6
0.5	86	33.8	24.2	16.7	8.9	2.8
≥0.6	83.2	31.0	21.4	13.9	6.1	0

If the assumption was applied to the population (P1 >0.8 and P2 >0.2):

Total N = 2113	Initial calculation	Subsequent recalculation with addition of BMD	

	FRAX without BMD, N	No. reclassified to low risk	No. reclassified to high risk	
High risk	564	--	--	No. women selected for treatment = 564 109 false positives
Intermediate risk	452	452	0	
Low risk	1097	--	--	No. women not selected for treatment = 1549* 59 false negatives

No individuals considered to be at high risk would need a BMD because the probability of reclassification was consistently <0.8. 452 women classified initially at low risk would require a BMD test (21% population). This strategy implied that 59 of 455 high risk women were not detected, and the proportion of reclassified women of the whole population was 8% (59+109 of 2113).

Additional result(s) reported by the study:

Changing the intervention threshold such that 10% or 50% of the population would be selected would require that BMD tests be undertaken in 19% and 12% of the population, respectively (data not shown).

Reference	Study type	Number of patients	Patient characteristics	Baseline and outcome variables	Statistical Methods	Source of funding
Leslie WD and Morin S et al. Fracture risk assessment without bone density measurement in routine clinical practice. 2011.	Historical cohort Setting: Canada	N= 39,603 (36,730 women and 2,873 men)	Women and men ≥50years Recruitment and eligibility criteria: patients drawn from the Manitoba Bone Density Program database, which contains clinical BMD results for the Province of Manitoba. The DXA database can be linked with other population-based computerised health databases through an anonymous personal identifier. Patients with medical coverage and valid DXA measurements from the lumber spine and femoral neck.	Data from clinical databases. Height and weight were recorded at the time pf the BMD test. Prolonged glucocorticoid use was obtained from a provincial pharmacy database. Proxies were used for smoking (COPD diagnosis) and high alcohol intake	Survival curves were compared using the log-rank statistic. Cox-proportional hazards model were used. Fracture probability derived without BMD was included as a covariate in the model. Fracture probability was entered as a continuous	Not stated.

Exclusion criteria: Vertebral levels affected by artefact were excluded by experienced physicians using conventional criteria.

	Women (N=36,730)	Men (N=2,873)
Age (years) (SD)	65.7 (9.8)	68.2 (10.1)
Femoral neck T-score (SD)	-1.5 (1)	-1.2 (1.1)
Femoral neck ≤2.5 SD, n (%)	5258 (14.3)	269 (9.4)
Major osteoporotic fracture probability without BMD	11.6 (8%)	7.6 (4%)
Major osteoporotic fracture probability with BMD	11.1 (7.4%)	8.4 (5%)
Hip fracture probability without BMD	3.6 (5.1%)	2.8 (3.3%)
Hip fracture probability with BMD	2.8 (4.4%)	2.9 (3.9%)

(alcohol or substance abuse diagnosis) over the same time frame.

10 year probability of a major osteoporotic fracture was calculated using the Canadian FRAX tool by the WHO Collaborating Centre with and without femoral neck BMD for each case without knowledge of the fracture outcomes.

Length of follow up: mean 5.4 years of observation

Outcomes
Incident fractures were defined as fractures that occurred after the index BMD measurement with site-specific fracture codes (hospitalisation or physician visit).
Fractures were assessed through a combination of hospital discharge abstracts and physician billing claims.

No. of fractures obtained: 890

variable (log-transformed).
Observations were censored for migration out of the province (3% of cohort) but not for death (8.3% of cohort), which was treated as a competing hazard.
Reclassification of 10-year major osteoporotic fracture probability (low <10%, moderate 10-19%, or high ≥20%) and hip fracture probability (low 0-1.4%, moderate 1.5-2.9, high ≥3%), in accordance with Canadian practice guidelines and intervention threshold of 20% for major fracture and 3% for hip fracture from the US National Osteoporosis Foundation), initially derived without BMD and subsequently recalculated with BMD.
Fracture outcomes to 10 years within each table subgroup were estimated using the Kaplan-Meier method.

Results

Table 1. Area under the curve (95% CI) for fracture risk prediction

	Major osteoporotic fracture		Hip fracture	
	Women	Men	Women	Men
FN BMD alone	0.682 (0.67-0.693)	0.645 (0.601-0.689)	0.802 (0.783-0.82)	0.798 (0.726-0.870)
FRAX without BMD (CRFs alone)	0.666 (0.655-0.678)	0.609 (0.564-0.654)	0.789 (0.772-0.807)	0.733 (0.659-0.807)
FRAX with BMD	0.698 (0.687-0.708)	0.661 (0.619-0.703)	0.822 (0.805-0.838	0.789 (0.722-0.855)

Fracture probability derived with BMD gave higher AUC measures than probability derived without BMD or than BMD alone.

Table 2. Risk reclassification when major fracture probability initially calculated without BMD is recalculated using BMD

Fracture probability (FRAX without BMD)		Fracture probability (FRAX with BMD)			
		Overall	Low risk (<10%)	Moderate risk (10-19%)	High risk (≥20%)
Low risk (<10%)	N	22599	20108	2460	31
	N Fractures	890	681	206	3
	% fracture prob at 10 years	7.5 (0.3)	6.3 (0.3)	15.8 (1.3)	10 (5.5)
	% overall reclassified	6.3%	--	6.2%	0.1%
Moderate risk (10-19%)	N	11630	2957	7603	1070
	N Fractures	909	131	624	154
	% fracture prob at 10 years	15.2 (0.7)	9.3 (1.1)	15.5 (0.8)	27.5 (2.9)
	% overall reclassified	10.2%	7.5%	--	2.7%
High risk (≥20%)	N	5374	72	2183	3119
	N Fractures	744	3	191	550
	% fracture prob at 10 years	27.5 (1.4)	11.5 (6.4)	20.6 (2.5)	32.4 (1.6)
	% overall reclassified	5.7%	0.2%	5.5%	--
Overall	N	39603	23137	12246	4220
	N Fractures	2543	815	1021	707

| | % fracture prob at 10 years | 12 (0.3) | 6.7 (0.3) | 16.4 (0.7) | 31 (1.4) |
| | % overall reclassified | 22.2% | 7.6% | 11.7% | 2.8% |

FRAX without BMD

6.3% classified as low risk; 10.2% as moderate risk and 5.7% as high risk.

Adding BMD to FRAX to derive fracture probability led to reclassification of 22.2% of the entire population.

Almost all reclassiications were to the adjacent risk category, with very few people reclassified from low to high risk (0.1%) or high to low risk (0.2%).

Table 3. Effect of fracture probability initially calculated without BMD on change in intervention (reclassification) when fracture probability is recalculated using BMD (5% increment)

% fracture probability in 10 years	CRFs alone N (% total)	CRFs with BMD N (% total)	No. reclassified (major ≥20%) N (% total)	Reclassified (any criteria) N (% total)	Mean femoral T-score	Mean age (years)
<5	7240 (18.3)	6179 (15.6)	0 (0)	754 (1.9)	-0.9	54.1
5-9	15359 (38.8)	16958 (42.8)	31 (0.1)	3659 (9.2)	-1.3	62.5
Subtotal low (0-9%)	22,599 (57.1)	23137 (58.4)	31 (0.1)	4413 (11.1)	-1.1	71.4
10-14	7592 (19.2)	8186 (20.7)	309 (0.8)	3896 (9.8)	-1.7	70.1
15-19	4038 (10.2)	4060 (10.3)	761 (1.9)	2970 (7.5)	-1.9	74
Subtotal moderate (10-19%)	11630 (29.4)	12246 (30.9)	1070 (2.7)	6866 (17.3)	-1.7	79.6
20-24	2549 (6.4)	2092 (5.3)	1550 (3.9)	303 (0.8)	-2.1	77.7
25-29	1489 (3.8)	1081 (2.7)	591 (1.5)	69 (0.2)	-2.3	80.9
30-34	562 (1.4)	542 (1.4)	73 (0.2)	13 (0)	-2.3	79.5
35-39	447 (1.1)	247 (0.6)	30 (0.1)	1 (0)	-2.6	83.3
40-44	228 (0.6)	131 (0.3)	11 (0)	1 (0)	-2.7	84.2
45-49	57 (0.1)	65 (0.2)	0(0)	0 (0)	-2.5	80.6
≥50	42 (0.1)	62 (0.2)	0(0)	0 (0)	-2.9	81.6
Subtotal high (≥20%)	5374 (13.6)	4220 (10.7)	2255 (5.7)	387 (1.0)	-2.2	79.6
Total	39603 (100)	39603 (100)	3356 (8.5)	11666 (29.5)	-1.5	65.9

When reclassification was evaluated using a single cut off (<20% vs. ≥20%), only 8.5% of the cohort had their risk category changed with the addition of BMD to FRAX (2.8% moved to higher risk category and 5.7% moved to the lower risk category).

Table 4. Risk categorisation for major fracture probability calculated without BMD according to various intervention criteria

All subjects

Risk category without BMD	N (% total)	Various intervention criteria					
		Lowest T-score ≤2.5 (A)	Major fracture probability with BMD ≥20 % (B)	Hip fracture probability with BMD ≥3% (C)	Prior spine or hip fracture (D)	Any of the previous without hip probability (A, B or D)	Any of the previous with hip probability (A, B, C, or D)
Low (0-9%)	22602 (57.1)	3916 (17.3)	31 (0.1)	1091 (4.8)	228 (1.0)	4105 (18.2)	4413 (19.5)
Moderate (10-19%)	11627 (29.4)	4654 (40.0)	1070 (9.2)	5352 (46.0)	679 (5.8)	5096 (43.8)	6866 (59.1)
High (≥20%)	5374 (13.6)	3320 (61.8)	3119 (58.0)	4816 (89.6)	911 (17.0)	4037 (75.1)	4987 (92.8)
Total	39603 (100)	11890 (30.0)	4220 (10.7)	11259 (28.4)	1818 (4.6)	13238 (33.4)	16266 (41.1)

Among the 22602 subjects categorised at low risk without BMD (57.1% of entire cohort), 19.5% met any of the intervention criteria, with the most frequent criterion (17.3%) being a BMD T-score ≤2.5 SD.

By gender

Risk category without BMD	N (% total)	Various intervention criteria					
		Lowest T-score ≤2.5 (A)	Major fracture probability with BMD ≥20 % (B)	Hip fracture probability with BMD ≥3% (C)	Prior spine or hip fracture (D)	Any of the previous without hip probability (A, B or D)	Any of the previous with hip probability (A, B, C, or D)
Women							
Low (0-9%)	20376 (55.5)	3578 (17.6)	20 (0.1)	641 (3.1)	128 (0.6)	3683 (18.1)	3750 (18.4)
Moderate (10-19%)	11012 (30.0)	4448 (40.4)	1016 (9.2)	4876 (44.3)	506 (4.6)	4784 (43.4)	6344 (57.6)
High (≥20%)	5342 (14.5)	3309 (61.9)	3101 (58.0)	4785 (89.6)	897 (16.8)	4013 (75.1)	4955 (92.8)
Total	36730 (100)	11335 (30.9)	4137 (11.3)	10302 (28.0)	1531 (4.2)	12480 (34.0)	15049 (41.0)

Men							
Low (0-9%)	2223 (77.4)	337 (15.2)	11 (0.5)	450 (20.2)	100 (4.5)	422 (19.0)	663 (29.8)
Moderate (10-19%)	618 (21.5)	207 (33.5)	54 (8.7)	476 (77.0)	173 (28.0)	312 (50.5)	522 (84.5)
High (≥20%)	32 (1.1)	11 (34.4)	18 (56.3)	31 (96.9)	14 (43.8)	24 (75.0)	32 (100)
Total	2873 (100)	555 (19.3)	83 (2.9)	957 (33.3)	287 (10.0)	758 (26.4)	1217 (42.4)

Results were similar for women and men.

By age

Risk category without BMD	N (% total)	Various intervention criteria					
		Lowest T-score ≤2.5 (A)	Major fracture probability with BMD ≥20 % (B)	Hip fracture probability with BMD ≥3% (C)	Prior spine or hip fracture (D)	Any of the previous without hip probability (A, B or D)	Any of the previous with hip probability (A, B, C, or D)
<65 years							
Low (0-9%)	17554 (90.3)	2909 (16.6)	20 (0.1)	419 (2.4)	207 (1.2)	3080 (17.5)	3118 (17.8)
Moderate (10-19%)	1801 (9.3)	662 (36.8)	180 (10.0)	397 (22.0)	327 (18.2)	856 (47.5)	896 (49.8)
High (≥20%)	79 (0.4)	43 (54.4)	59 (74.7)	48 (60.8)	18 (22.8)	66 (83.5)	67 (84.8)
Total	19434 (100)	3614 (18.6)	259 (1.3)	864 (434)	552 (2.8)	4002 (20.6)	4081 (21.0)
≥65 years							
Low (0-9%)	5045 (25.0)	1006 (19.9)	11 (0.2)	672 (13.3)	21 (0.4)	1025 (20.3)	1295 (25.7)
Moderate (10-19%)	9829 (48.7)	3993 (40.6)	890 (9.1)	4955 (50.4)	352 (3.6)	4240 (43.1)	5970 (60.7)
High (≥20%)	5295 (26.3)	3277 (61.9)	3060 (57.8)	4768 (90.0)	893 (16.9)	3971 (75.0)	4920 (92.9)
Total	20169 (100)	8276 (41.0)	3961 (19.6)	10395 (51.5)	1266 (6.3)	9236 (45.8)	12185 (60.4)

Age strongly affected the number of individuals falling in the various risk categories, with 90.5% categorised at low risk <65 years vs. 25% for ≥65 years.

Table 5. Risk categorisation for hip fracture probability calculated without BMD according to various intervention criteria

All subjects

Risk category without BMD	N (% total)	Various intervention criteria					
		Lowest T-score ≤2.5 (A)	Major fracture probability with BMD ≥20 % (B)	Hip fracture probability with BMD ≥3% (C)	Prior spine or hip fracture (D)	Any of the previous without hip probability (A, B or D)	Any of the previous with hip probability (A, B, C, or D)
Low (0-1.4%)	20512 (51.8)	3325 (16.2)	51 (0.2)	514 (2.5)	298 (1.5)	3567 (17.4)	3612 (17.6)
Moderate (1.5-2.9%)	5706 (14.4)	1817 (31.8)	174 (3.0)	1163 (20.4)	266 (4.7)	1997 (35.0)	2268 (39.7)
High (≥3%)	13385 (33.8)	6748 (50.4)	3995 (29.8)	9582 (71.6)	1254 (9.4)	7674 (57.3)	10386 (77.6)
Total	39603 (100)	11890 (30.0)	4220 (10.7)	11259 (28.4)	1818 (4.6)	13238 (33.4)	16266 (41.1)

By gender

Risk category without BMD	N (% total)	Various intervention criteria					
		Lowest T-score ≤2.5 (A)	Major fracture probability with BMD ≥20 % (B)	Hip fracture probability with BMD ≥3% (C)	Prior spine or hip fracture (D)	Any of the previous without hip probability (A, B or D)	Any of the previous with hip probability (A, B, C, or D)
Women							
Low (0-1.4%)	19087 (52.0)	3137 (16.4)	43 (0.2)	413 (2.2)	215 (1.1)	3309 (17.3)	3323 (17.4)
Moderate (1.5-2.9%)	5210 (14.2)	1729 (33.2)	165 (3.2)	987 (18.9)	221 (4.2)	1875 (36.0)	2055 (39.4)
High (≥3%)	12433 (33.8)	6469 (52.0)	3929 (31.6)	8902 (71.6)	1095 (8.8)	7296 (58.7)	9671 (77.8)
Total	36730 (100)	11335 (30.9)	4137 (11.3)	10302 (28.0)	1531 (4.2)	12480 (34.0)	15049 (41.0)
Men							
Low (0-1.4%)	1425 (49.6)	188 (13.2)	8 (0.6)	101 (7.1)	83 (5.8)	258 (18.1)	289 (20.3)
Moderate (1.5-2.9%)	496 (17.3)	77 (17.7)	9 (1.8)	176 (35.5)	45 (9.1)	122 (24.6)	213 (42.9)
High (≥3%)	952 (33.1)	279 (29.3)	66 (6.9)	680 (71.4)	159 (16.7)	378 (39.7)	715 (75.1)
Total	2873 (100)	555 (19.3)	83 (2.9)	957 (33.3)	287 (10.0)	758 (26.4)	1217 (42.4)

By age

Risk category without BMD	N (% total)	Various intervention criteria					
		Lowest T-score ≤2.5 (A)	Major fracture probability with BMD ≥20 % (B)	Hip fracture probability with BMD ≥3% (C)	Prior spine or hip fracture (D)	Any of the previous without hip probability (A, B or D)	Any of the previous with hip probability (A, B, C, or D)
<65 years							
Low (0-1.4%)	17841 (91.8)	2858 (16.0)	46 (0.3)	381 (2.1)	295 (1.7)	3098 (17.4)	3122 (17.5)
Moderate (1.5-2.9%)	1270 (6.5)	549 (43.2)	106 (8.3)	307 (24.2)	185 (14.6)	667 (52.5)	710 (55.9)
High (≥3%)	323 (1.7)	207 (64.1)	107 (33.1)	176 (54.5)	72 (22.3)	237 (73.4)	249 (77.1)
Total	19434 (100)	3614 (18.6)	259 (1.3)	864 (4.4)	4002 (20.6)	4002 (20.6)	4081 (21.0)
≥65 years							
Low (0-1.4%)	2671 (13.2)	467 (17.5)	5 (0.2)	133 (5.0)	3 (0.1)	469 (17.6)	490 (18.3)
Moderate (1.5-2.9%)	4436 (22.0)	1268 (28.6)	68 (1.5)	856 (19.3)	81 (1.8)	1330 (30.0)	1558 (35.1)
High (≥3%)	13062 (64.8)	6541 (50.1)	3888 (29.8)	9406 (72.0)	1182 (9.0)	7437 (56.9)	10137 (77.6)
Total	20169 (100)	8276 (41.0)	3961 (19.6)	10395 (51.5)	1266 (6.3)	9236 (45.8)	12185 (60.4)

Similar results were found when risk categorisation was based upon hip fracture probability, without BMD.

Table 6. AUC (95% CI) for identification of individuals meeting various intervention criteria using major osteoporotic fracture/hip fracture probability, calculated without BMD (data presented graphically)

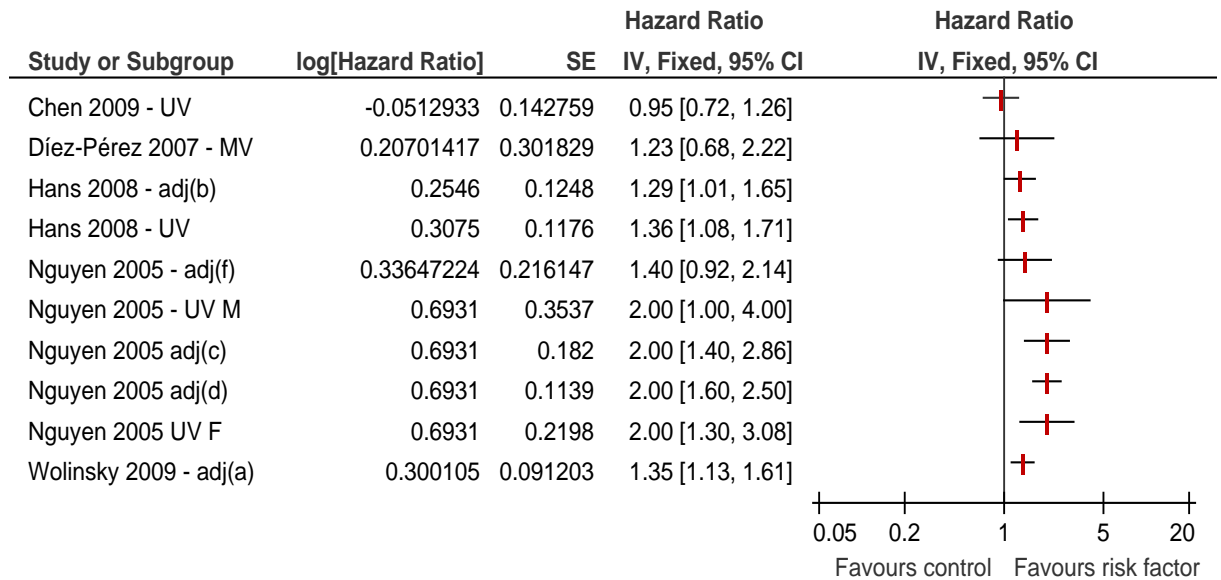|	AUC (95% CI)	
	Major fracture	Hip fracture
Lowest T-score ≤-2.5	0.73 (0.725-0.736)	0.735 (0.73-0.74)
Major probability with BMD ≥20%	0.951 (0.948-0.953)	0.931 (0.928-0.934)
Hip probability with BMD ≥3%	0.915 (0.912-0.918)	0.935 (0.933-0.938)
Prior spine or hip fracture	0.826 (0.818-0.835)	0.77 (0.76-0.78)
Any of the above (without hip ≥3%)	0.765 (0.76-0.77)	0.761 (0.756-0.766)
Any of the above (with hip ≥3%)	0.829 (0.825-0.833)	.832-0.841)

D.3.2   QUADAS II quality assessment of studies

Risk of overall selection bias	Risk of overall index test bias	Risk of reference standard bias	Risk of other bias	Overall applicability	Overall risk of bias
- Study type - Population - Inclusion/exclusion criteria	- BMD assessment - Collection of data on risk factors included in the risk assessment tool - Imputation - Is selected threshold appropriate?	- How incidence of fracture was obtained - Length of follow up	- Loss to follow up - Missing data - No. of fractures		
Johansson, 2011					
- A follow up study from a RCT (placebo arm) in which patients were randomly selected. Patients were identified from GP listings and contacted by letter and invited to attend for bone assessment. - This cohort is a relatively healthy population – patients were selected according to pre-specified eligibility criteria (in previous RCT), i.e. exclusion of the sickiest patients. - Women ≥75y from Sheffield, with 51% previous fracture. - Clearly defined inclusion/exclusion criteria.	- BMD was assessed by Hologic DXA. - Factors included in the risk assessment tools were largely self-reported. - Data that were made anonymous were provided to an independent statistician, and the investigators remained fully blinded. - No imputation. Only patients with information were included in the analysis. - Arbitrary threshold of 35% 10 year fracture probability chosen.	- Self-reported fractures verified by radiographic reports/hospital records independently. - Data that were made anonymous were provided to an independent statistician, and the investigators remained fully blinded. - Length of F/U: 6723 patient years	2796 enrolled into placebo arm of a previous RCT. Follow up data were available in 2175. Full baseline assessment was available in 2113 women (97%). - Number of fractures = 282 3% subjects with no baseline data were excluded from the analysis. ~20% lost to follow up - Analysis: current time (time since assessment) was included in the Poisson model as a covariate (describes change in risk with time from entry into the	Setting: UK Women ≥75y from Sheffield, with 51% previous fracture.	

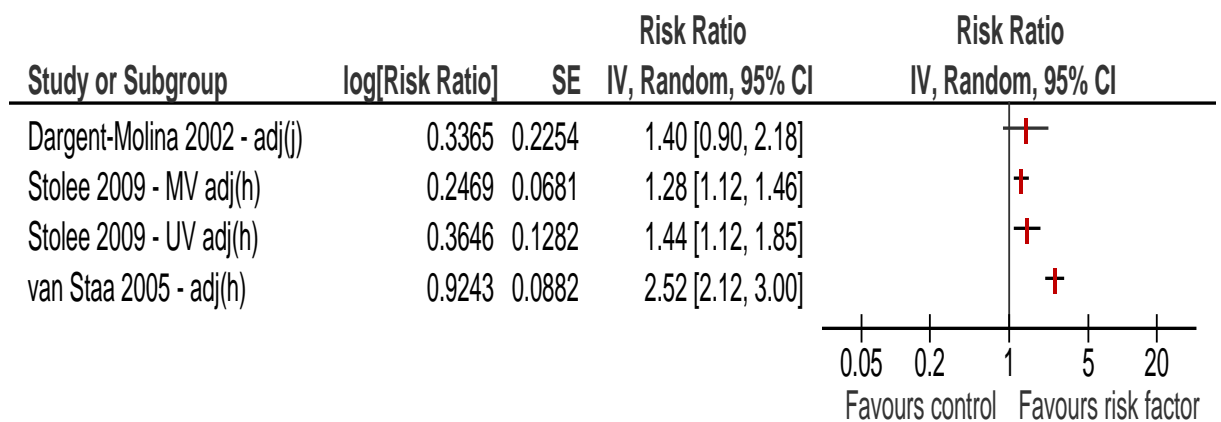|			study).		
LOW	HIGH	LOW	LOW	INDIRECT	HIGH
Leslie, 2011					
- Retrospective cohort - Patients drawn from the Manitoba Bone Density Program database, which contains clinical BMD results for the Province of Manitoba, Canada. - Men and women ≥50years. - Inclusion/exclusion criteria adequately described. - Baseline factors such as previous fracture, family history of fracture, current smoking, alcohol etc. not reported.	- BMD data recorded in the clinical database. For subjects with more than one set of BMD measurement on the database, only the first record was included. - Proxies were used for smoking (COPD) diagnosis) and high alcohol intake (alcohol or substance abuse diagnosis). - Incomplete data on family history of hip fracture (% not reported). 10-year fracture probability was calculated by the WHO Collaborating Centre for each case without knowledge of the fracture outcomes. - An intervention threshold of 20% was selected (according to the Canadian NOF guideline)	- Fractures were assessed through a combination of hospital discharge abstracts and physician billing claims. - Data from clinical database – less reliable than direct radiographic review, especially for vertebral fracture (majority not clinically diagnosed). - Non-hip fractures were imputed (untested assumption that hip:non hip fracture ratios in the USA and Canada would be similar (Leslie 2010A) - Length of F/U: 5 years	- Data from clinical database – information on risk factors likely to be of poor quality; records f hip fracture more accurate. - Incomplete data on family history of hip fracture (% not reported). - Number of fractures = 890. - Analysis: survival analysis using Kaplan-Meier curve.	Setting: Canada Canada FRAX was used. Calibration differences between Canada FRAX and UK FRAX.	
HIGH	HIGH	VERY HIGH	HIGH	INDIRECT	VERY HIGH

1   # D.4   Forest plots

2   **Figure 1:   Fall in past 12 months; hip fracture**

Study or Subgroup	log[Hazard Ratio]	SE	Hazard Ratio IV, Fixed, 95% CI	Hazard Ratio IV, Fixed, 95% CI
Chen 2009 - UV	-0.0512933	0.142759	0.95 [0.72, 1.26]	
Díez-Pérez 2007 - MV	0.20701417	0.301829	1.23 [0.68, 2.22]	
Hans 2008 - adj(b)	0.2546	0.1248	1.29 [1.01, 1.65]	
Hans 2008 - UV	0.3075	0.1176	1.36 [1.08, 1.71]	
Nguyen 2005 - adj(f)	0.33647224	0.216147	1.40 [0.92, 2.14]	
Nguyen 2005 - UV M	0.6931	0.3537	2.00 [1.00, 4.00]	
Nguyen 2005 adj(c)	0.6931	0.182	2.00 [1.40, 2.86]	
Nguyen 2005 adj(d)	0.6931	0.1139	2.00 [1.60, 2.50]	
Nguyen 2005 UV F	0.6931	0.2198	2.00 [1.30, 3.08]	
Wolinsky 2009 - adj(a)	0.300105	0.091203	1.35 [1.13, 1.61]	

0.05   0.2   1   5   20
Favours control   Favours risk factor

3

4   **Figure 2:   Fall in past 6 months / 90 days; hip fracture, osteoporotic, humeral**

Study or Subgroup	log[Risk Ratio]	SE	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Dargent-Molina 2002 - adj(j)	0.3365	0.2254	1.40 [0.90, 2.18]	
Stolee 2009 - MV adj(h)	0.2469	0.0681	1.28 [1.12, 1.46]	
Stolee 2009 - UV adj(h)	0.3646	0.1282	1.44 [1.12, 1.85]	
van Staa 2005 - adj(h)	0.9243	0.0882	2.52 [2.12, 3.00]	

0.05   0.2   1   5   20
Favours control   Favours risk factor

5

1

Figure 3:   'History of falls'; various fractures

Study or Subgroup	log[HR/RR/OR]	SE	HR/RR/OR IV, Fixed, 95% CI	HR/RR/OR IV, Fixed, 95% CI
1.1.2 History of falls - HR for hip fracture				
Hippisley-Cox2009b adj F	0.708	0.0614	2.03 [1.80, 2.29]	
Hippisley-Cox2009b adj M	0.9783	0.1379	2.66 [2.03, 3.49]	
1.1.3 History of falls - RR for hip fracture				
van Staa 2006a adj(h)	0.6729	0.0463	1.96 [1.79, 2.15]	
1.1.4 History of falls - HR for osteoporotic fracture				
Hippisley-Cox2009a - adj M	0.802	0.1093	2.23 [1.80, 2.76]	
Hippisley-Cox2009a adj F	0.5988	0.0469	1.82 [1.66, 2.00]	
1.1.5 History of falls - RR for osteoporotic				
van Staa 2006b adj(h)	0.5539	0.0428	1.74 [1.60, 1.89]	
1.1.6 History of falls - IRR for all fracture				
Sambrook 2007	0.131	0.1206	1.14 [0.90, 1.44]	

```
        0.1 0.2      0.5    1      2       5   10
        Protective factor    risk factor
```
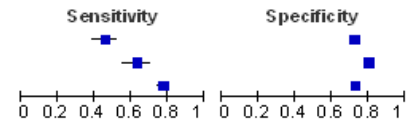
2

3

1   **Figure 4:   Sensitivity and specificity for hip fracture, at different thresholds (3% and 5%)**

FRAX with BMD (3%)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Bolland 2010	105	334	124	859	0.46 [0.39, 0.53]	0.72 [0.69, 0.75]
Fraser 2011	99	1316	58	5224	0.63 [0.55, 0.71]	0.80 [0.79, 0.81]
Leslie 2010A	425	10818	124	28236	0.77 [0.74, 0.81]	0.72 [0.72, 0.73]

FRAX without BMD (3%)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Bolland 2010	176	728	53	465	0.77 [0.71, 0.82]	0.39 [0.36, 0.42]
Fraser 2011	93	1533	64	5007	0.59 [0.51, 0.67]	0.77 [0.76, 0.78]
Hippisleay-Cox 2009	4249	123396	2818	748372	0.60 [0.59, 0.61]	0.86 [0.86, 0.86]
Leslie 2010A	426	12940	123	23114	0.78 [0.74, 0.81]	0.64 [0.64, 0.65]
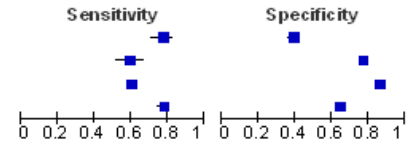
QFracture (3%)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Hippisleay-Cox 2009	3889	106250	3179	765557	0.55 [0.54, 0.56]	0.88 [0.88, 0.88]
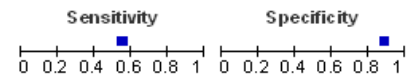
FRAX with BMD (5%)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Bolland 2010	66	167	163	1026	0.29 [0.23, 0.35]	0.86 [0.84, 0.88]
Ensrud 2009	297	2184	92	3660	0.76 [0.72, 0.80]	0.63 [0.61, 0.64]
Fraser 2011	68	732	89	5808	0.43 [0.35, 0.51]	0.89 [0.88, 0.90]
Leslie 2010A	362	6654	187	32400	0.66 [0.62, 0.70]	0.83 [0.83, 0.83]
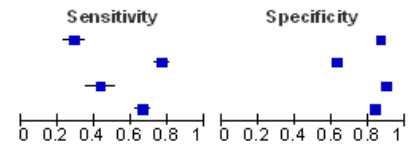
FRAX without BMD (5%)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Bolland 2010	117	453	112	740	0.51 [0.44, 0.58]	0.62 [0.59, 0.65]
Ensrud 2009	304	2924	85	2920	0.78 [0.74, 0.82]	0.50 [0.49, 0.51]
Fraser 2011	61	828	96	5712	0.39 [0.31, 0.47]	0.87 [0.87, 0.88]
Hippisleay-Cox 2009	2957	66739	4110	805029	0.42 [0.41, 0.43]	0.92 [0.92, 0.92]
Leslie 2010A	359	8940	190	30114	0.65 [0.61, 0.69]	0.77 [0.77, 0.78]
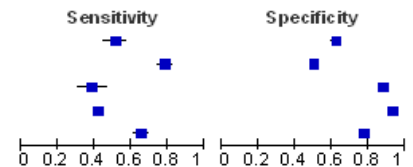
QFracture (5%)

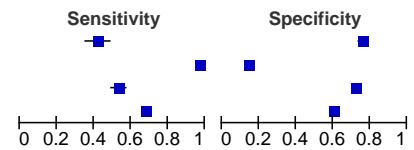| Study	TP	FP	FN	TN	Sensitivity	Specificity
Hippisleay-Cox 2009	2746	62259	4322	809548	0.39 [0.38, 0.40]	0.93 [0.93, 0.93]

2
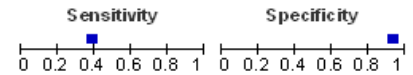
1   **Figure 5:   Sensitivity and specificity for major osteoporotic fracture, at different thresholds (10%,**
2   **20% and 30%)**

FRAX with BMD (10%)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Bolland 2010	96	286	133	907	0.42 [0.35, 0.49]	0.76 [0.73, 0.78]
Ensrud 2009	1005	4264	32	734	0.97 [0.96, 0.98]	0.15 [0.14, 0.16]
Fraser 2011	338	1705	297	4357	0.53 [0.49, 0.57]	0.72 [0.71, 0.73]
Leslie 2010A	1728	14733	815	22327	0.68 [0.66, 0.70]	0.60 [0.60, 0.61]

FRAX without BMD (10%)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Bolland 2010	147	561	82	632	0.64 [0.58, 0.70]	0.53 [0.50, 0.56]
Ensrud 2009	1037	4998	0	0	1.00 [1.00, 1.00]	0.00 [0.00, 0.00]
Fraser 2011	316	1724	319	4338	0.50 [0.46, 0.54]	0.72 [0.70, 0.73]
Leslie 2010A	1653	15348	890	21712	0.65 [0.63, 0.67]	0.59 [0.58, 0.59]
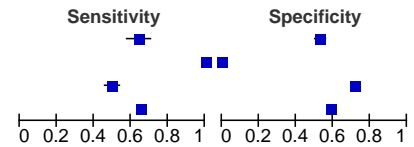
QFracture (10%)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Hippisleay-Cox 2009	3816	47012	13279	801959	0.22 [0.22, 0.23]	0.94 [0.94, 0.95]
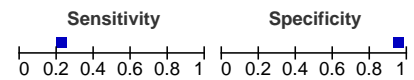
FRAX with BMD (20%)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Bolland 2010	21	48	208	1145	0.09 [0.06, 0.14]	0.96 [0.95, 0.97]
Ensrud 2009	422	946	615	4052	0.41 [0.38, 0.44]	0.81 [0.80, 0.82]
Fraser 2011	113	382	522	5680	0.18 [0.15, 0.21]	0.94 [0.93, 0.94]
Leslie 2010A	707	3512	1836	33548	0.28 [0.26, 0.30]	0.91 [0.90, 0.91]
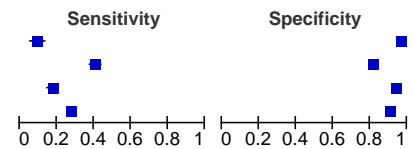
FRAX without BMD (20%)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Bolland 2010	46	107	183	1086	0.20 [0.15, 0.26]	0.91 [0.89, 0.93]
Ensrud 2009	370	966	667	4032	0.36 [0.33, 0.39]	0.81 [0.80, 0.82]
Fraser 2011	102	398	533	5664	0.16 [0.13, 0.19]	0.93 [0.93, 0.94]
Leslie 2010A	744	4628	1799	32432	0.29 [0.27, 0.31]	0.88 [0.87, 0.88]
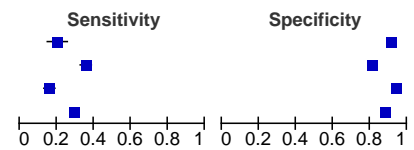
QFracture (20%)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Hippisleay-Cox 2009	316	3117	16779	845854	0.02 [0.02, 0.02]	1.00 [1.00, 1.00]
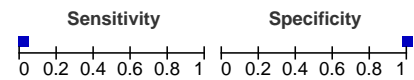
FRAX with BMD (30%)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Bolland 2010	0	12	229	1181	0.00 [0.00, 0.02]	0.99 [0.98, 0.99]
Ensrud 2009	187	313	850	4685	0.18 [0.16, 0.21]	0.94 [0.93, 0.94]
Fraser 2011	37	102	598	5960	0.06 [0.04, 0.08]	0.98 [0.98, 0.99]
Leslie 2010A	240	806	2303	36254	0.09 [0.08, 0.11]	0.98 [0.98, 0.98]
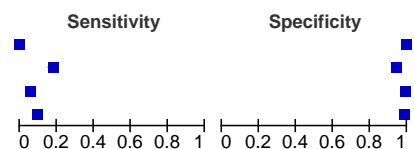
FRAX without BMD (30%)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Bolland 2010	11	24	218	1169	0.05 [0.02, 0.08]	0.98 [0.97, 0.99]
Ensrud 2009	86	197	951	4801	0.08 [0.07, 0.10]	0.96 [0.95, 0.97]
Fraser 2011	28	76	607	5986	0.04 [0.03, 0.06]	0.99 [0.98, 0.99]
Leslie 2010A	255	1080	2288	35980	0.10 [0.09, 0.11]	0.97 [0.97, 0.97]
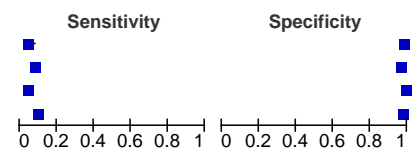
QFracture (30%)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Hippisleay-Cox 2009	37	329	17058	848642	0.00 [0.00, 0.00]	1.00 [1.00, 1.00]

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4

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Figure 6: **FRAX with BMD – Hip fracture**

Figure 7:   FRAX with BMD - Major osteoporotic fracture

FRAX with BMD - Major osteoporotic fracture

MEN AND WOMEN

Fraser 2011: 69% (67, 71); n= 6697 — 69%

Leslie 2010A: 69% (68, 71); n= 39603 — 69%

MEN

Sandhu 2010: 57% (41, 73); n= 56 — 57%

WOMEN

Bolland 2010: 64% (60, 68); n= 1422 — 64%

Sornay-Rendu 2010: 78% (72, 82); n= 851 — 78%

Ensrud 2009: 64% (62, 65); n= 6252 — 64%

Tanaka 2010: 70% (63, 77); n= 400 — 70%

Sandhu 2010: 78% (70, 86); n= 144 — 78%

Pluskiewicz 2010: 83% (82, 85); n= 2012 — 83%

Cummins 2011: 67% (0, 0); n= 584 — 67%

AUC (95% confidence intervals)

1

Figure 8:   FRAX without BMD - Hip fracture

FRAX without BMD - Hip fracture

MEN AND WOMEN

Fraser 2011: 77% (73, 79); n= 6697 — 77%

Leslie 2010A: 79% (78, 81); n= 39603 — 79%

MEN

Hippisley-Cox 2009: 82% (0, 0); n= 424336 — 82%

WOMEN

Bolland 2010: 69% (63, 76); n= 1422 — 69%

Ensrud 2009: 71% (68, 73); n= 6252 — 71%

Sambrook 2011: 65% (0, 0); n= 19586 — 65%

Hippisley-Cox 2009: 85% (0, 0); n= 454499 — 85%

0%   50%   100%

AUC (95% confidence intervals)

1

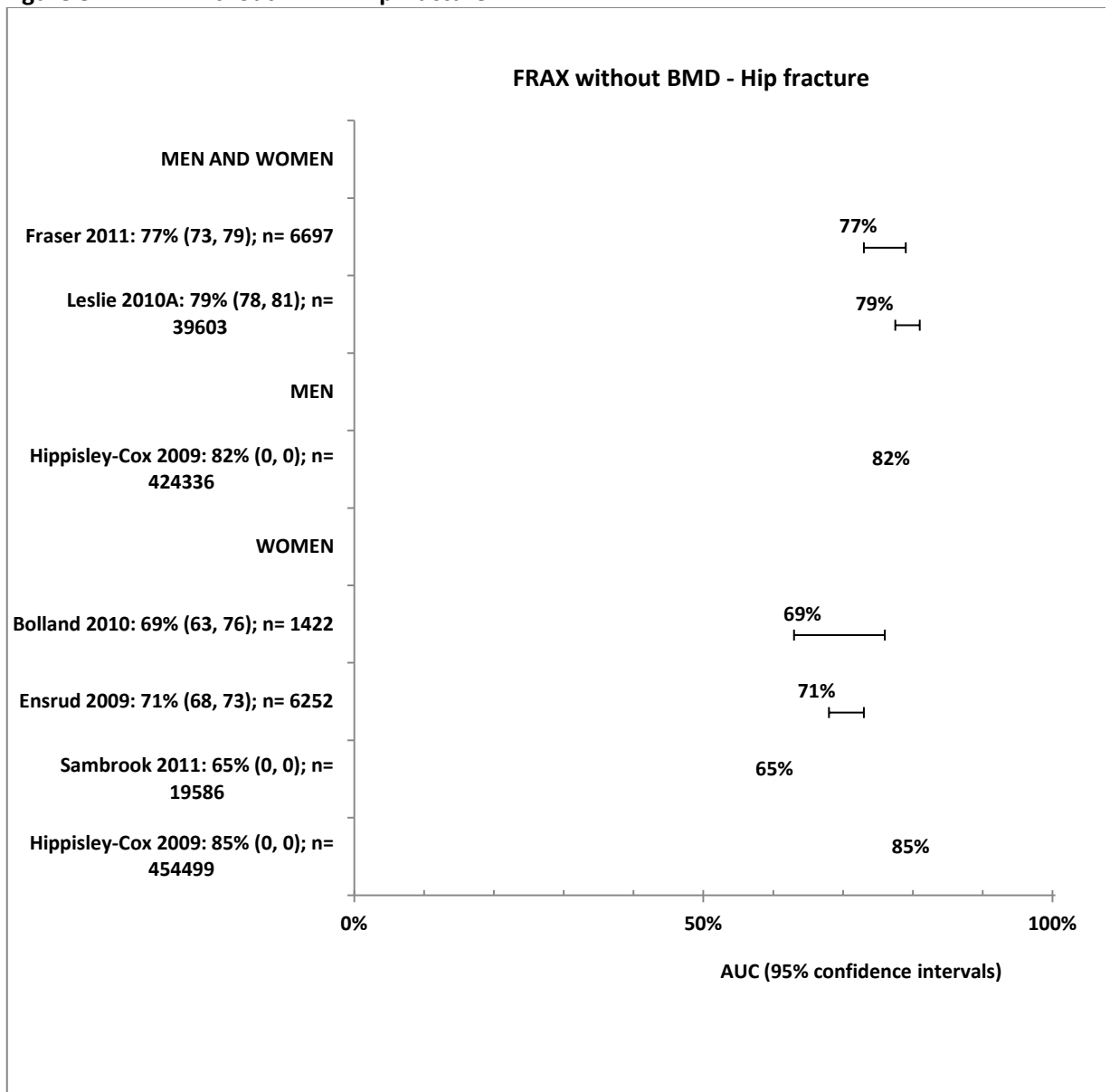**Figure 9:   FRAX without BMD - major osteoporotic fracture**

FRAX without BMD - major osteoporotic fracture

MEN AND WOMEN

Fraser 2011: 66% (64, 68); n= 6697 — 66%

Leslie 2010A: 66% (65, 67); n= 39603 — 66%

WOMEN

Bolland 2010: 62% (58, 66); n= 1422 — 62%

Sornay-Rendu 2010: 75% (71, 79); n= 851 — 75%

Ensrud 2009: 61% (59, 62); n= 6252 — 61%

Sambrook 2011: 60% (0, 0); n= 19586 — 60%

Tremollieres 2009: 63% (56, 69); n= 2196 — 63%

AUC (95% confidence intervals)

1

Figure 10: QFracture - Hip fracture

QFracture - Hip fracture

Women

Collins 2011 (Imputed): 89% (0, 0); n= 1136417 — 89.0%

Hippisley-Cox 2009 (Internal): 89% (89, 89); n= 642153 — 89.0%

Men

Collins 2011 (Imputed): 86% (0, 0); n= 1108219 — 85.5%

Hippisley-Cox 2009 (Internal): 86% (85, 86); n= 633764 — 85.6%

0.0%   50.0%   100.0%

AUC (95% confidence intervals)
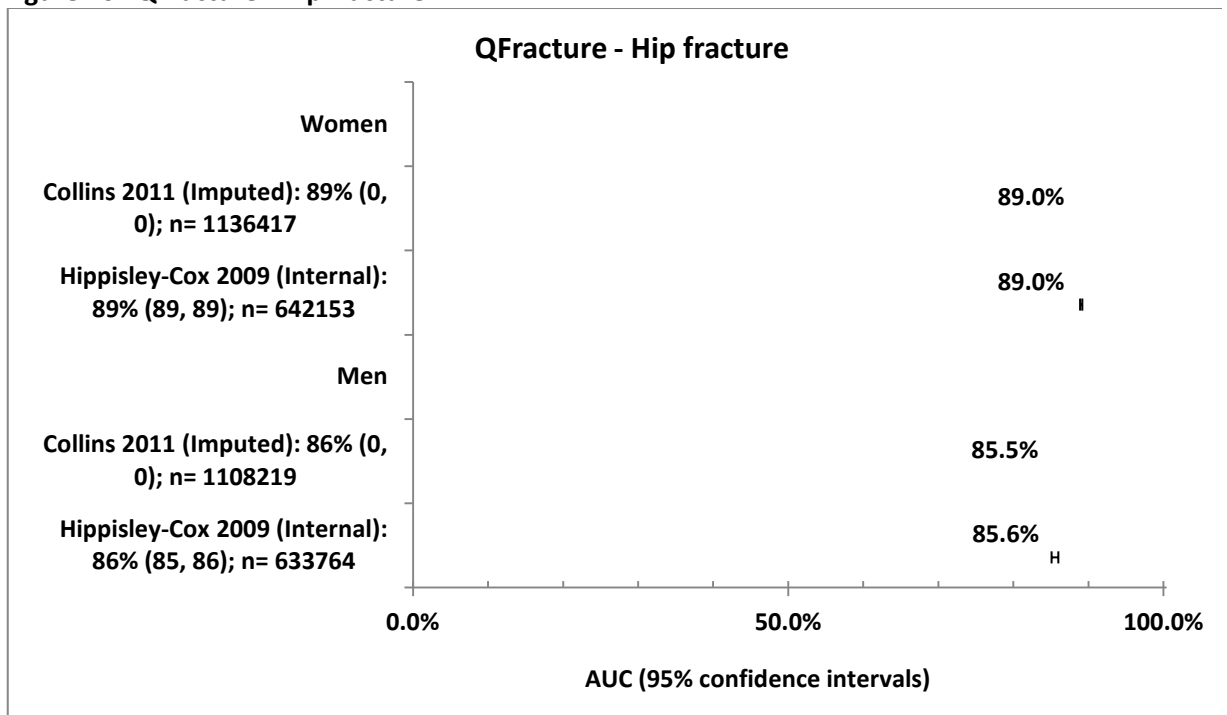
1

Figure 11: QFracture - major osteoporotic fracture

QFracture - major osteoporotic fracture

Women

Collins 2011 (Imputed): 82% (0, 0); n= 1136417 — 81.6%

Hippisley-Cox 2009 (Internal): 79% (79, 79); n= 642153 — 78.8%

Men

Collins 2011 (Imputed): 74% (0, 0); n= 1108219 — 73.9%

Hippisley-Cox 2009 (Internal): 69% (68, 69); n= 633764 — 68.8%

0.0%   50.0%   100.0%

AUC (95% confidence intervals)
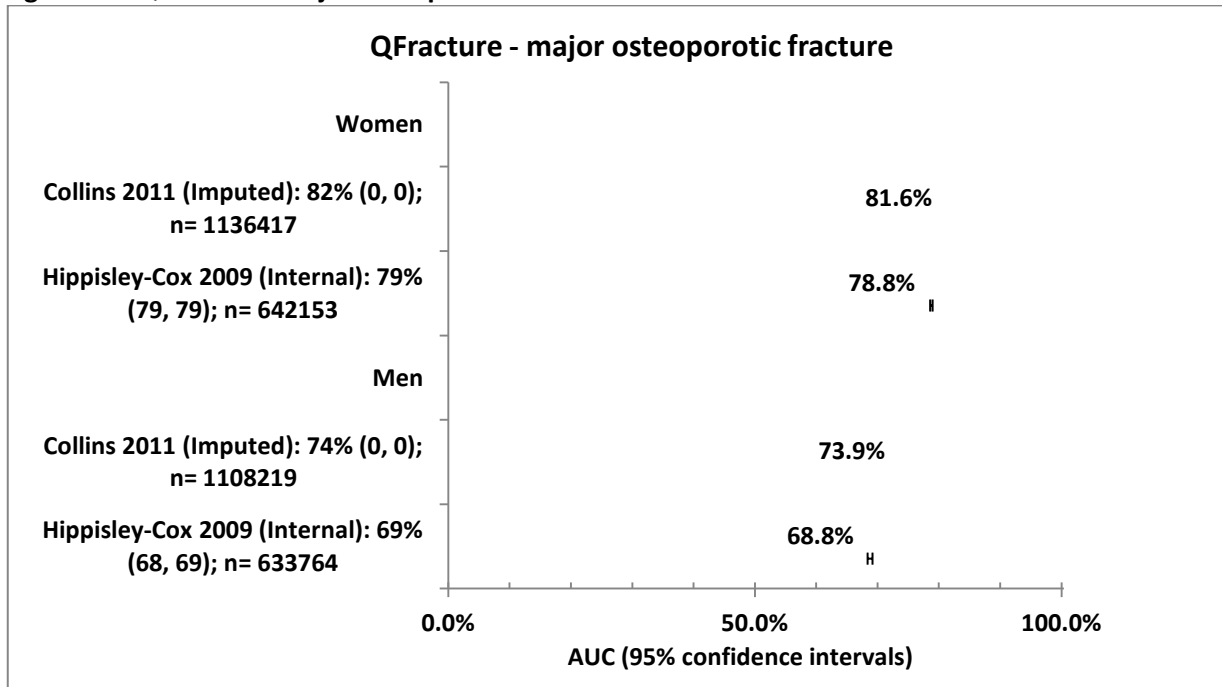
2

Figure 12: BMD - Hip fracture

BMD - Hip fracture

MEN	
Bauer 2007 (FN BMD): 85% (0, 0); n= 5606	85%
WOMEN	
Robbins 2007 (unclear): 79% (73, 85); n= 10750	79%
Leslie 2007a (Total hip BMD): 82% (79, 85); n= 16505	82%
Leslie 2007a (FN BMD): 79% (76, 83); n= 16505	79%
Leslie 2007a (Lumbar spine BMD): 66% (62, 70); n= 16505	66%
Hillier 2007 (Total hip BMD): 74% (0, 0); n= 4124	74%
Hans 2004 (Total femur BMD): 64% (61, 68); n= 5898	64%
Hans 2004 (FN BMD): 69% (66, 73); n= 5898	69%
Cummings 1994B (Intertrochanteric BMD): 78%…	78%
Cummings 1994B (Total hip BMD): 76% (0, 0); n= 7963	76%
Cummings 1994B (FN BMD): 73% (0, 0); n= 7963	73%

0%   50%   100%

AUC (95% confidence intervals)

1

Figure 13: BMD - Major osteoporotic fracture (Any, non-vertebral, forearm)

BMD - Major osteoporotic fracture (Any, non-vertebral, forearm)

MEN	
Nguygen 2008 (FN BMD): 66% (61, 71); n= 858	66%
Bauer 2007 (FN BMD): 68% (0, 0); n= 5581	68%
WOMEN	
Tremollieres 2009 (Hip BMD): 66% (60, 73); n= 2196	66%
Tanaka 2010 (unclear): 65% (58, 73); n= 400	65%
Stewart 2006 (FN BMD): 64% (63, 66); n= 3142	64%
Stewart 2006 (Lumbar spine BMD): 66% (64, 68); n= 3142	66%
Popp 2009 (FN BMD): 65% (58, 72); n= 637	65%
Popp 2009 (Total hip BMD): 64% (56, 71); n= 637	64%
Popp 2009 (Lumbar spine BMD): 63% (56, 70); n= 637	63%
Nguygen 2008 (FN BMD): 67% (64, 70); n= 1358	67%
Leslie 2007a (Total hip BMD; forearm fracture): 65% (61, 68); n= 16205	65%
Leslie 2007a (FN BMD; forearm fracture): 65% (61, 68); n= 16505	65%
Leslie 2007a (Lumbar spine BMD; forearm fracture): 63% (59, 67); n=…	63%
Leslie 2007a (Total hip BMD): 71% (69, 73); n= 16505	71%
Leslie 2007a (FN BMD): 69% (68, 71); n= 16505	69%
Leslie 2007a (Lumbar spine BMD): 65% (63, 67); n= 16505	65%
Hillier 2007 (Total hip BMD): 65% (0, 0); n= 4124	65%

0% 50% 100%

AUC (95% confidence intervals)

1

Figure 14: BMD - Vertebral fracture

2
3

4

Appendix E: Economic report on evaluation of fracture risk assessment tools

1   **Review question**: Which risk assessment tools are the most accurate for predicting the risk of
2   fragility fracture in adults, including those without known osteoporosis or previous fragility fracture?

3   # E.1 Health economic evidence review

4   Four studies were identified that assessed the cost-effectiveness of risk assessment tools but they
5   were all excluded. Details are reported in Table 101.

6   **Table 101 - List of excluded studies**

First author	Title	Journal	Publication year	Notes
Ben Sedrine [44]	Interest of a prescreening questionnaire to reduce the cost of bone densitometry.	*Osteoporosis International,* 13, 434-442.	(2002)	Outcomes measured (diagnosis of osteoporosis) not applicable to current study (risk assessment of fragility fracture)
Harrison [45]	Application of a triage approach to peripheral bone densitometry reduces the requirement for central DXA but is not cost effective.	*Calcified Tissue International,* 79, 199-206.	(2006)	Risk Assessment comparisons included peripheral bone densitometry and is not applicable to current study
Ito [46]	Using the Osteoporosis Self-Assessment Tool for Referring Oldwer Men for Bone Densitometry: A Decision Analysis	*The American Geriatrics Society*	(2009)	OST strategy excluded in our review, treatment based on osteoporosis risk and costs from the US.
Mueller [47]	Cost-effectiveness of using clincial risk factors with and without DXA for osteoporosisi screening in postmenopausal women	*Value in Health 12, 1106-1117.*	(2009)	Treatment pathway included in model. Treatment criteria not applicable to current practice in the UK.

7   # E.2 Original economic analysis

8   ### E.2.1 Overview: economic considerations

9   Using tools to estimate the future risk of fragility fracture in patients has important economic
10   implications. The use of risk assessment tools for fragility fracture is associated with the use of
11   resources (e.g. GP time). There may be considerable benefits when a risk assessment tool facilitates
12   early intervention and prevention of fragility fracture. However, a risk assessment tool that
13   overestimates the risk of fracture would lead to an increase of resource use. In this case, patients
14   may receive unnecessary treatment and may not benefit from that treatment. On the other hand, a
15   risk assessment tool that underestimates the risk of fracture would lead to under provision of
16   prevention treatment. This would see an increase in hospitalisation costs and a reduction in Quality
17   Adjusted Life Years (QALYs).

18   Although this is an area with significant economic implications, since prevention and treatment are
19   outside the scope of this guideline, a full and formal cost-effectiveness analysis including long-term

1 consequences of strategies was not conducted. Instead a simple cost analysis of performing the
2 assessment tools and/or DXA scan was performed.

3 **E.2.2 Methods of cost analysis**

4 We performed a cost analysis for a hypothetical cohort of patients presenting at the GP. We assumed
5 that an initial GP assessment prior to risk assessment would be required for all patients and as such
6 the cost of this was not incorporated in the following analysis.

7 Comparators included in the analysis were:
8 1. WHO Fracture Risk Assessment Tool (FRAX)
9 2. QFracture
10 3. BMD for all patients with no FRAX pre-screening
11 4. FRAX or QFracture followed by BMD when required

12 We estimated the cost of these strategies for performing risk assessment using GDG assumptions on
13 time necessary to perform the assessment and cost data from national sources (Table 102).

14 The GDG estimate of the additional time required to perform FRAX or QFracture within the first GP
15 consultation was on the range of 10 minutes. Therefore we decided it was reasonable to use the
16 average consultation time (11 minutes) as reported in the PSSRU publication[48]. We acknowledge this
17 is likely to be an overestimate since the GP consultation for a patient in the BMD strategy might take
18 the same time even if the patient does not have a FRAX or QFracture. This is because patient slots for
19 GP consultation tend to be fixed. In this case the cost estimated for FRAX and QFracture could be an
20 overestimate.

21 **Table 102 - Cost of risk Assessment Tools for Fragility Fracture**

Item	Breakdown of cost	Units required	Cost per component	Total Cost	Notes
QFracture	Additional time required at GP consultation	11.7 mins[a]	£36	£36	Unit Costs of Health and Social Care 2010. £3.1 per minute.[48]
FRAX	Additional time required at GP consultation	11.7 mins[a]	£36	£36	Unit Costs of Health and Social Care 2010. £3.1 per minute.[48]
BMD	DXA scan	1	£77	£113	NHS Reference Costs 2009-2010 for NHS Trusts and PCTs combined; Diagnostic imaging, direct access of DXA scan[49]
	Additional GP consultation	1	£36		Unit Costs of Health and Social Care 2010. £3.1 per minute; average consultation time 11.7 minutes[48]
Risk Score [b] +BMD	Additional time required at GP consultation	11.7	£36	_ [c]	Unit Costs of Health and Social Care 2010. £3.1 per minute; average consultation time 11.7 minutes[48]
	Additional GP consultation	0 to 1 [d]	£36		Unit Costs of Health and Social Care 2010. £3.1 per minute; average consultation time 11.7 minutes[48]
	DXA scan	0 to 1[d]	£77		NHS Reference Costs 2009-2010 for NHS Trusts and PCTs combined[49]

22 *(a) Experts from the GDG estimated a similar time for the GP consultation in patients undergoing QFracture and FRAX.*

(b) *Risk Score refers to Risk Assessment Tools without BMD, specifically FRAX or QFracture. The initial risk assessment before BMD can either be FRAX or QFracture. However the subsequent risk assessment following BMD refers to FRAX as QFracture does not incorporate a BMD component.*

(c) *It is not possible to estimate the total cost of the Risk Score + BMD strategy as it depends on the proportion of patients requiring a DXA scan.*

(d) *The units required varied according to the proportion of patients requiring a DXA scan*

Both the FRAX and QFracture risk stratification tools do not attract any access costs and can be completed within the same amount of time during the initial GP consultation. Hence, the GDG thought it unnecessary to compare the cost of QFracture versus FRAX.

The total cost of Risk Score + BMD is difficult to estimate as it is dependent on the proportion of patients receiving a BMD assessment. This proportion is represented by the variable p_BMD_ref (Figure 15).

Given this uncertainty, it was not possible to estimate a precise cost difference between the strategies 'BMD' and 'Risk Score + BMD'. However, this comparison was deemed very important from an economic point of view. While the addition of a Risk Score to a BMD assessment accrues additional costs in terms of GP time, the Risk Score may facilitate a selective referral of patients which would spare some patients from having a DXA scan unnecessarily.

E.2.3 Threshold Analysis

We conducted a threshold analysis to identify the proportion of patients referred for a BMD assessment after a Risk Score (the p_BMD_ref parameter) at which performing a Risk Score followed by BMD is cost neutral in comparison to BMD for all patients (Figure 15). Calculations are presented in section E.2.4.

Figure 15: Cost Analysis of BMD for all vs FRAX + BMD when required. Costs associated with each strategy are reported in the terminal node (the red triangles) while the probability of being referred for a BMD in the Risk Score +BMD strategy corresponds to the variable = p_BMD_ref.
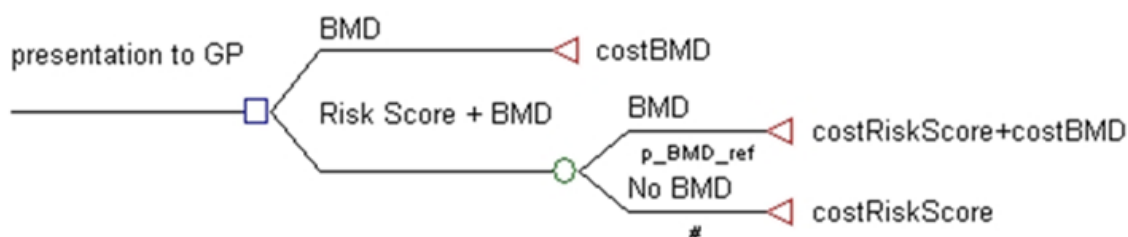
Estimates of resource use (Table 102) assumed the starting point of patients presenting in primary care to a GP. Cost components of the strategy 'BMD' (BMD for all patients) are a DXA scan and a follow up GP consultation for discussion of DXA scan results. Cost components of the strategy 'Risk Score + BMD' (risk score followed by BMD when required) are an increased time of the initial GP consultation for all patients and then a DXA scan and a follow up GP consultation for those patients referred for BMD assessment . As explained in E.2.2, the estimate of the additional GP consultation time for the calculation of the risk score might be an overestimate. The uncertainty around this estimate is addressed in section E.2.5.

E.2.4 Calculations

The following equation was used to estimate the threshold value of p_BMD_ref:

1   **I**   costBMD = costRiskScore + p_BMD_ref * cost BMD

2 where, as reported in Table 102

3 costBMD is given by the sum of the cost of DXA and the cost of a time required at a GP consultation

4 and costRiskScore is the cost time required at a GP consultation.

5 In this equation the variable p_BMD_ref was varied from 0 to 1 until the two sides of the equation

6 became equivalent.

E.2.5   Results

8 To solve equation I, we substituted the known quantities using the costs reported in Table 102:

9   **II**   113 = 36 + p_BMD_ref * 113

10 Equation II rearranged to estimate p_BMD_ref becomes:

11   **III**   P_BMD_ref = (£113 - £36)/113 = 0.68

12 The result shows that at a 68% referral rate for BMD in the strategy 'Risk score + BMD', the two
13 strategies would be cost neutral. At any referral rate below this value (<68%), the strategy 'Risk Score
14 + BMD' is less costly than the strategy 'BMD' (Figure 16).

15 We calculated the total cost of both strategies and identified the least costly strategy at different
16 levels of referral rate for a hypothetical cohort of 100 patients (Table 103). In this cohort, 'Risk Score+
17 BMD' is the least costly strategy if referrals for BMD are fewer than 68 patients. However, when
18 more than 68 patients are referred for BMD assessment, 'BMD' becomes the least costly strategy.

19 **Table 103: Cost Comparison of Risk Assessment Tools for a population of 100**

Total cost BMD	Total cost Risk Score + BMD		Least Costly Strategy
	Proportion of patients referred for BMD		
£11300	0	£3600	Risk Score + BMD
£11300	10%	£4730	Risk Score + BMD
£11300	20%	£5860	Risk Score + BMD
£11300	30%	£6990	Risk Score + BMD
£11300	40%	£8120	Risk Score + BMD
£11300	50%	£9250	Risk Score + BMD
£11300	60%	£10380	Risk Score + BMD
£11300	70%	£11510	BMD
£11300	80%	£12640	BMD
£11300	90%	£13770	BMD
£11300	100%	£14900	BMD

20 These results are also represented graphically as in Figure 16. The colour of the areas within specific
21 ranges of the parameter on the x-axis (p_BMD_ref) indicates the optimal strategy (least costly) when
22 the parameter takes any value within the range. The y-axis (expected value) indicates pounds spent
23 for performing the optimal strategy at the given x-axis parameter. These values are negative because
24 our analysis did not consider health benefits. Figure 16 illustrates that at 50% patient referral for

1 BMD, the optimal strategy is 'Risk Score+BMD' at £90 spent. However at 75% patient referral for
2 BMD, the 'BMD' strategy is optimal at £113 spent.

3 **Figure 16: Threshold analysis of proportion of patients referred for BMD in the FRAX+BMD**
4 **strategy. The colour of the areas within specific ranges of the x-axis (p_BMD_ref)**
5 **indicates the optimal strategy (least costly) when the parameter takes any value within**
6 **the range.**
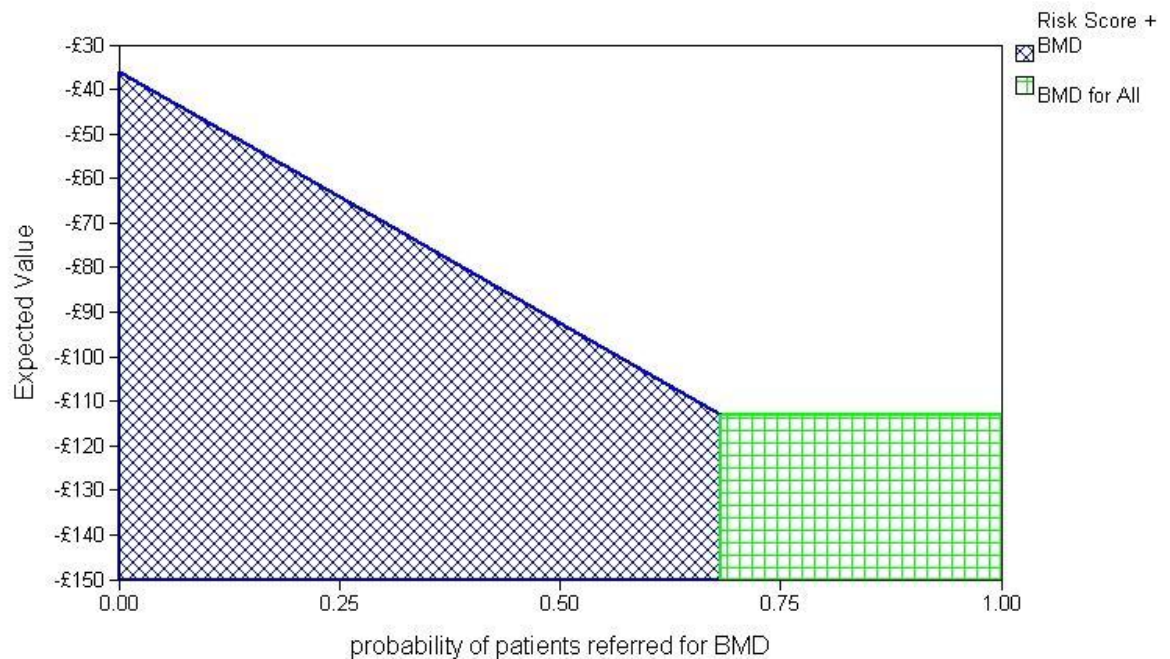
7

8   The likely overestimation of the cost of risk score calculation due to overestimation of GP time
9   required suggests that the referral rate at which the two strategies are cost-neutral may be higher
10 than what was found in our threshold analysis. We did a one-way sensitivity analysis to explore the
11 impact of this parameter on the results. We found that results are sensitive to the estimate of GP
12 time. For example, if the GP time required for performing a risk score is 8 minutes instead of the
13 estimated 11.7 minutes, the' Risk Score +BMD' strategy will be less costly than the 'BMD' strategy
14 even at a patient referral rate for BMD of 80%. In other words, reduction in the cost estimate for GP
15 time suggests that the 'Risk Score+ BMD' strategy will be the optimal strategy at even a higher
16 proportion of referrals for BMD than indicated in the base case analysis.

17 **E.2.6 Discussion**

18 FRAX and QFracture have similar costs and since the clinical evidence did not show any of them to be
19 superior we cannot say one is more cost-effective than the other.

20 The cost of FRAX or QFracture is lower compared to other strategies involving DXA scan (BMD for all
21 or Risk Score+BMD).

22 When we compared a strategy of using a Risk Score to select patients that require a BMD assessment
23 with a strategy of providing BMD measurement to everyone, we found that using first a risk score is
24 less costly if less than 68% of the patients assessed are then referred for BDM assessment. Whether
25 the actual referral rate is above or below 68% was not confirmed in our literature review. The GDG
26 judged that referral rates for BMD assessment in practice would differ according to patient groups.
27 Also, we might have overestimated the cost of FRAX and QFracture and therefore using a risk score

before referring patients for BMD might be less costly even at higher referral rates. Our analysis is limited by the absence of estimation of future consequences of the strategies compared. For example, untreated patients resulting from a false negative FRAX assessment could give rise to additional future costs and reduction in QALYs should a fracture occur. Therefore our analysis should be considered alongside the results of the clinical review. Reclassification studies could help us determine whether adding BMD to a risk score would lead to a change in management and therefore a potential increase in QALYs. A reclassification study[50] that was reviewed for this guideline presented the number of people who move to another risk category or remain in the same category subsequent to the addition of BMD to FRAX. However it was concluded that there is no data to show that adding BMD to FRAX improves calibration or discrimination. Therefore the GDG concluded that offering BMD assessment is a good use of NHS resources only when the benefit of treatment is unclear (for example for people who are in the region of an intervention threshold for a proposed treatment).

E.2.7   Conclusions

The cost difference between FRAX and QFracture Risk Stratification Tools is negligible.

If less than 68% of patients in the FRAX+BMD strategy are referred for a DXA scan, then this strategy is less costly than performing BMD for all.

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