NCGC National Clinical Guideline Centre

Osteoporosis: fragility fracture risk

Osteoporosis: assessing the risk of fragility fracture

Short clinical guideline - CG146

Evidence and recommendations

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February 2017: The guideline was updated to correct reference to the WHO in relation to the FRAX tool.

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August 2019: We updated the weekly alcohol intake for men in recommendation 1.1 in line with the UK chief medical officers' low risk drinking guidelines. See the amended recommendation at www.nice.org.uk/guidance/CG146

Osteoporosis: assessing the risk of fragility fracture
NICE short clinical guideline

This guideline was developed following the NICE short clinical guideline process. This document includes all the recommendations, details of how they were developed and summaries of the evidence they were based on.

For further information on writing clinical guidelines, see chapter 10 and appendix N of 'The guidelines manual' (available from www.nice.org.uk/GuidelinesManual).

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1 Introduction

Osteoporosis is a disease characterised by low bone mass and structural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture. Osteoporosis leads to nearly 9 million fractures annually worldwide[34], and over 300,000 patients with fragility fractures present to hospitals in the UK each year[6].

Fragility fractures are fractures that result from mechanical forces that would not ordinarily result in fracture, known as low-level (or 'low energy') trauma[40]. The World Health Organization (WHO) has quantified this as forces equivalent to a fall from a standing height or less. Reduced bone density is a major risk factor for fragility fracture. Other factors that may affect the risk of fragility fracture include the use of oral or systemic glucocorticoids, age, sex, previous fractures, and family history of osteoporosis. Because of increased bone loss after the menopause in women, and age-related bone loss in both women and men, the prevalence of osteoporosis increases markedly with age, from 2% at 50 years to more than 25% at 80 years[52] in women. As the longevity of the population increases, so will the incidence of osteoporosis and fragility fracture.

Fragility fractures occur most commonly in the spine (vertebrae), hip (proximal femur), and wrist (distal radius). They may also occur in the arm (humerus), pelvis, ribs, and other bones. Osteoporotic fractures are defined as fractures associated with low bone mineral density (BMD) and include clinical spine, forearm, hip and shoulder fractures. Osteoporotic fragility fractures can cause substantial pain and severe disability, often leading to a reduced quality of life, and hip and vertebral fractures are associated with decreased life expectancy. Hip fracture nearly always requires hospitalisation, is fatal in 20% of cases and permanently disables 50% of those affected; only 30% of patients fully recover[65]. Projections suggest that, in the UK, hip fracture incidence will rise from 70,000 per year in 2006 to 91,500 in 2015 and 101,000 in 2020[16].

Direct medical costs from fragility fractures to the UK healthcare economy were estimated at £1.8 billion in 2000, with the potential to increase to £2.2 billion by 2025 and with most of these costs relating to hip fracture care[7]. There are also indirect costs to the patient and their families such as productivity loss by patient and families who may need to care for patient.

There are a number of therapies and treatments available for the prevention of fragility fractures in people thought to be at risk, or to prevent further fractures in those who have already had one or more fragility fractures. However, identifying who will benefit from preventative treatment is imprecise. A number of risk assessment tools are available to predict fracture incidence over a period of time, and these may be used to aid decision making. These tools are limited in that they may not include all risk factors, or may lack details of some risk factors. Tools are dependent on the accuracy of the epidemiological data used to derive them and tools validated in other populations may not apply to the UK.. Two tools, FRAX and QFracture, are available for use in the UK. It is not clear whether these tools are equally accurate and whether choice of tool should depend on circumstances. This short clinical guideline aims to provide guidance on the selection and use of risk assessment tools in the care of people who may be at risk of fragility fractures in all settings in which NHS care is received.

1.1 Who this guideline is for

This document is for all healthcare professionals and other staff who care for people at risk of fragility fracture.

1.2 Patient-centred care

This guideline offers best practice advice on the assessment of fragility fracture risk in adults.

Assessment should take into account patients' needs and preferences. People at risk of fragility fracture should have the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare professionals. If patients do not have the capacity to make decisions, healthcare professionals should follow the Department of Health's advice on consent (available from www.dh.gov.uk/consent) and the code of practice that accompanies the Mental Capacity Act (summary available from www.publicguardian.gov.uk). In Wales, healthcare professionals should follow advice on consent from the Welsh Assembly Government (available from www.wales.nhs.uk/consent).

Good communication between healthcare professionals and patients is essential. It should be supported by evidence-based written information tailored to the patient's needs. Assessment and the information patients are given about it, should be culturally appropriate. It should also be accessible to people with additional needs such as physical, sensory or learning disabilities, and to people who do not speak or read English.

If the patient agrees, families and carers should have the opportunity to be involved in decisions about treatment and care.

Families and carers should also be given the information and support they need.

2 Guideline summary

For details of how this guideline was developed see appendix C.

2.1 Full list of recommendations

Targeting risk assessment

1. Consider assessment of fracture risk:
   - in all women aged 65 years and over and all men aged 75 years and over
   - in women aged under 65 years and men aged under 75 years in the presence of risk factors, for example:
     - previous fragility fracture
     - current use or frequent recent use of oral or systemic glucocorticoids
     - history of falls
     - family history of hip fracture
     - other causes of secondary osteoporosis[a]
     - low body mass index (BMI) (less than 18.5 kg/m2)
     - smoking
     - alcohol intake of more than 14 units per week for women and more than 21 units per week for men.
2. Do not routinely assess fracture risk in people aged under 50 years unless they have major risk factors (for example, current or frequent recent use of oral or systemic glucocorticoids, untreated premature menopause or previous fragility fracture), because they are unlikely to be at high risk.
3. Estimate absolute risk when assessing risk of fracture (for example, the predicted risk of major osteoporotic or hip fracture over 10 years, expressed as a percentage).
4. Use either FRAX[b] (without a bone mineral density [BMD] value, if a dual-energy X-ray absorptiometry [DXA] scan has not previously been undertaken) or QFracture[c], within their allowed age ranges, to estimate 10-year predicted absolute fracture risk when assessing risk of fracture. Above the upper age limits defined by the tools, consider people to be at high risk.
5. Interpret the estimated absolute risk of fracture in people aged over 80 years with caution, because predicted 10-year fracture risk may underestimate their short-term fracture risk.
6. Do not routinely measure BMD to assess fracture risk without prior assessment using FRAX (without a BMD value) or QFracture.

a Causes of secondary osteoporosis include endocrine (hypogonadism in either sex including untreated premature menopause and treatment with aromatase inhibitors or androgen deprivation therapy; hyperthyroidism; hyperparathyroidism; hyperprolactinaemia; Cushing's disease; diabetes), gastrointestinal (coeliac disease; inflammatory bowel disease; chronic liver disease; chronic pancreatitis; other causes of malabsorption), rheumatological (rheumatoid arthritis; other inflammatory arthropathies), haematological (multiple myeloma; haemoglobinopathies; systemic mastocytosis), respiratory (cystic fibrosis; chronic obstructive pulmonary disease), metabolic (homocystinuria), chronic renal disease and immobility(due for example to neurological injury or disease).

b FRAX, the WHO fracture risk assessment tool, is available from www.shef.ac.uk/FRAX. It can be used for people aged between 40 and 90 years, either with or without BMD values, as specified.

c QFracture is available from www.qfracture.org. It can be used for people aged between 30 and 84 years. BMD values cannot be incorporated into the risk algorithm.

7. Following risk assessment with FRAX (without a BMD value) or QFracture, consider measuring BMD with DXA in people whose fracture risk is in the region of an intervention threshold[d] for a proposed treatment, and recalculate absolute risk using FRAX with the BMD value.

8. Consider measuring BMD with DXA before starting treatments that may have a rapid adverse effect on bone density (for example, sex hormone deprivation for treatment for breast or prostate cancer).

9. Measure BMD to assess fracture risk in people aged under 40 years who have a major risk factor, such as history of multiple fragility fracture, major osteoporotic fracture, or current or recent use of high-dose oral or systemic glucocorticoids (more than 7.5 mg prednisolone or equivalent per day for 3 months or longer).

10. Consider recalculating fracture risk in the future:
    - if the original calculated risk was in the region of the intervention threshold[e] for a proposed treatment and only after a minimum of 2 years, or
    - when there has been a change in the person's risk factors.

11. Take into account that risk assessment tools may underestimate fracture risk in certain circumstances, for example if a person:
    - has a history of multiple fractures
    - has had previous vertebral fracture(s)
    - has a high alcohol intake
    - is taking high-dose oral or high-dose systemic glucocorticoids (more than 7.5 mg prednisolone or equivalent per day for 3 months or longer)
    - has other causes of secondary osteoporosis.[f]

12. Take into account that fracture risk can be affected by factors that may not be included in the risk tool, for example living in a care home or taking drugs that may impair bone metabolism (such as anti-convulsants, selective serotonin reuptake inhibitors, thiazolidinediones, proton pump inhibitors and anti-retroviral drugs).

d An intervention threshold is the level of risk at which an intervention is recommended. People whose risk is in the region from just below to just above the threshold may be reclassified if BMD is added to assessment. It is out of the scope of this guideline to recommend intervention thresholds. Healthcare professionals should follow local protocols or other national guidelines for advice on intervention thresholds.

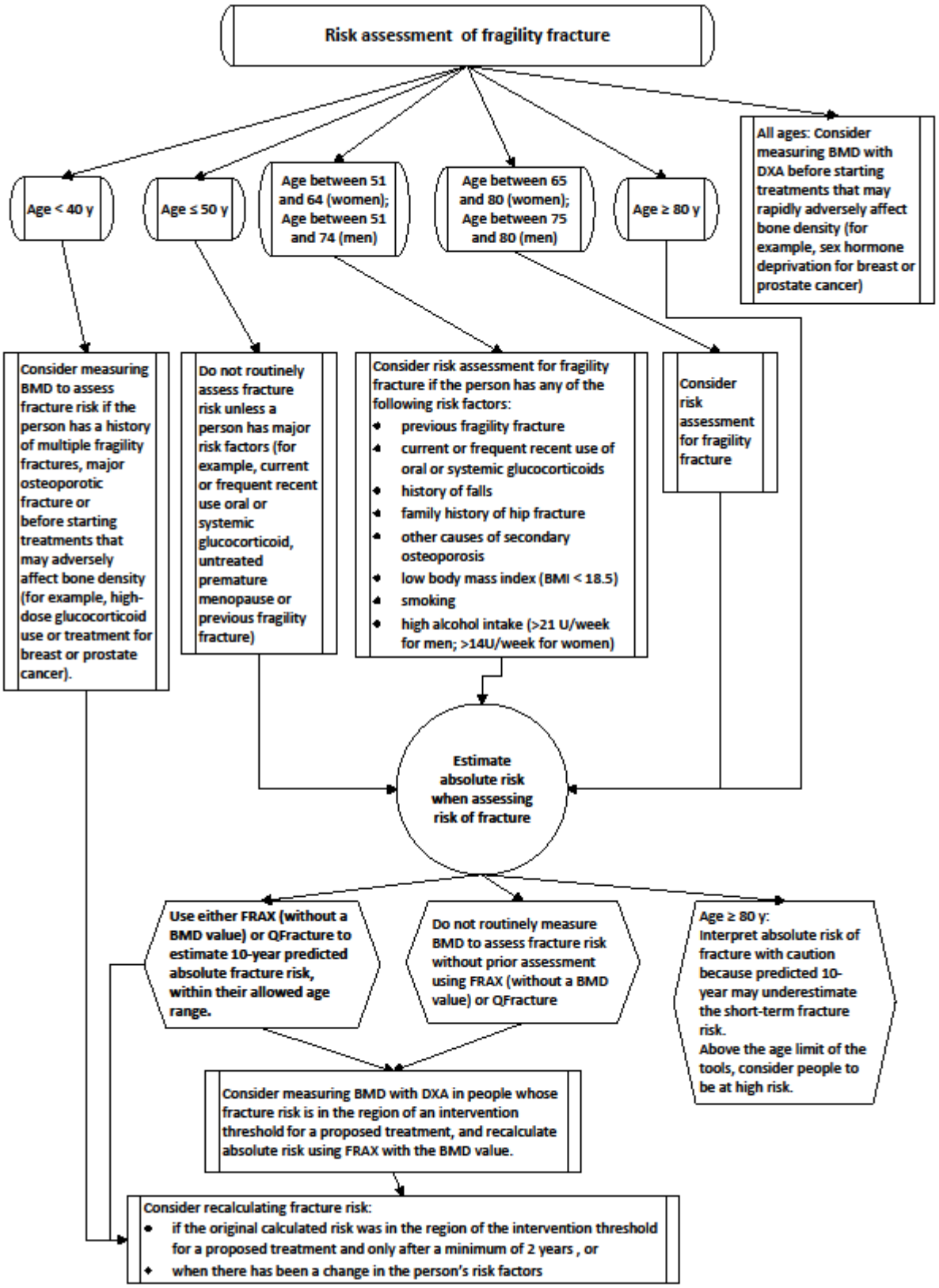
e An intervention threshold is the level of risk at which an intervention is recommended. It is out of the scope of this guideline to recommend intervention thresholds. Healthcare professionals should follow local protocols or other national guidelines for advice on intervention thresholds.

f Causes of secondary osteoporosis include: endocrine (hypogonadism in either sex including untreated premature menopause and treatment with aromatase inhibitors or androgen deprivation therapy; hyperthyroidism; hyperparathyroidism; hyperprolactinaemia; Cushing's disease; diabetes), gastrointestinal (coeliac disease; inflammatory bowel disease; chronic liver disease; chronic pancreatitis; other causes of malabsorption), rheumatological (rheumatoid arthritis; other inflammatory arthropathies), haematological (multiple myeloma; haemoglobinopathies; systemic mastocytosis), respiratory (cystic fibrosis; chronic obstructive pulmonary disease), metabolic (homocystinuria), chronic renal disease and immobility (due for example to neurological injury or disease).

2.2 Full list of research recommendations

1. 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?
2. What is the utility of FRAX and QFracture in adults receiving bone protective therapy?
3. What is the utility of FRAX and QFracture in detecting risk of fragility fracture in adults with causes of secondary osteoporosis?
4. What is the added prognostic value of BMD in the assessment of fracture risk with FRAX?
5. What is the utility of FRAX and QFracture in detecting risk of fragility fracture in adults living in residential care?
6. What is the accuracy of FRAX, QFracture and BMD in detecting risk of fragility fracture in adults of different ethnic origin in the UK population?

2.3 Algorithm



3 Who needs formal risk assessment?

3.1 Introduction

During the scoping phase of the guideline, stakeholders requested guidance on which individuals needed formal risk assessment. While risk assessment tools can be used for any person where they or a healthcare professional is concerned about risk of fragility fracture, it was recognised that advice on targeting of opportunistic risk assessment would be helpful. The final scope therefore included this issue. The GDG considered a pragmatic review to inform which individuals to target. The review was not intended to quantify the precise risk associated with individual risk factors, or to establish whether risk factors are independent, but to highlight common and important factors that should alert healthcare professionals to consider assessment of fragility fracture risk. The GDG therefore wished to see estimates of risk and prevalence for these factors. The GDG considered that calculation of absolute risk with a risk assessment tool is the preferred approach to estimate fragility fracture risk (see section 4).

3.2 Review question

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, 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

3.3 Clinical evidence review

The GDG agreed on a number of common risk factors that they wished to evaluate for potential use to target full assessment. These were BMI, glucocorticoid use, family history of fracture, previous fracture, smoking, alcohol and history of falls. The evidence review includes evidence from individual patient data (IPD) meta-analyses. IPD meta-analyses were found for the following prognostic factors: BMI, oral glucocorticoid use, family history of fracture, previous fracture, smoking and alcohol. The GDG considered these IPD analyses adequate for the purpose of estimating risk because they use original data from large cohorts and were assessed as acceptable quality (see appendix C for details on the methodology adopted; see appendix D for the complete evidence tables and quality assessment). These IPD meta-analyses were published in 2004/2005, so a literature search was performed from 2004 to 2011 to update the evidence, but no relevant studies were identified. For some prognostic factors, additional information (for example, level of smoking) was provided by the QFracture derivation study[28].

For 'history of falls', a comprehensive systematic review of the literature was carried out and 22 relevant prospective cohort studies were identified; data from the included studies were not pooled into a meta-analysis. It was deemed inappropriate to pool the studies because of methodological difficulties in combining aggregate level data: the studies themselves differed considerably in their design and analysis, and also in their definition of 'history of falls'. When the definition of history of falls was similar amongst two or more studies, forest plots (see appendix D) are used as a visual representation of the results.

Paragraph 3.3.1 contains a summary of results for the prognostic factors as listed in the protocol above; see appendix C for the methods used in this particular review and appendix D for the full evidence tables and quality assessment in detail.

3.3.1 Summary of results

Table 1: Study details and clinical summary of findings: BMI

Study	Population	Fracture	Result	Comments
De Laet 2005[15]	N = 59,644 men and women. 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 (Sweden).	Any	0.98 (0.97 to 0.99)‡ a	‡RR (relative risk) (95% CI) per unit increase BMI (gradient of risk) a) adjusted for age and time since start of follow-up.
		Osteoporotic	0.97 (0.97 to 0.98)‡ a	
		Hip	0.93 (0.91 to 0.94)‡ a	
		Any	1.66 (1.31 to 2.09)‡ a 1	‡RR (95% CI) a) adjusted for age and time since start of follow-up, BMI of 1) 15, 2) 20, 3) 30, 4) 35 kg/m^2 (BMI 25 = reference RR = 1). ‡RR (95% CI) b) adjusted for age, time since start of follow-up and BMD, BMI of 1) 15, 2) 20, 3) 30, 4) 35 (BMI 25 = reference RR = 1.00).
			1.21 (1.12 to 1.30)‡ a 2	
			0.92 (0.85 to 1.00)‡ a 3	
			0.85 (0.75 to 0.98)‡ a 4	
			1.00 (0.75 to 1.33)‡ b 1	
			0.98 (0.90 to 1.08)‡ b 2	
			1.01 (0.91 to 1.11)‡ b 3	
			0.99 (0.82 to 1.19)‡ b 4	
		Osteoporotic	1.79 (1.35 to 2.37)‡ a 1	‡RR (95% CI) a) adjusted for age and time since start of follow-up, BMI of 1) 15, 2) 20, 3) 30,
			1.27 (1.16 to 1.38)‡ a 2	
			0.89 (0.81 to 0.98)‡ a 3	
			0.74 (0.62 to 0.90)‡ a 4	
			1.07 (0.78 to 1.48)‡ b 1	
			1.02 (0.92 to 1.13)‡ b 2	

Study	Population	Fracture	Result	Comments
			0.96 (0.86 to 1.08)‡ b 3	4) 35 kg/m^2 (BMI 25 = reference RR = 1).
			0.91 (0.73 to 1.13)‡ b 4	‡RR (95% CI)
				b) adjusted for age, time since start of follow-up and BMD, BMI of
				1) 15,
				2) 20,
				3) 30,
				4) 35
				(BMI 25 = reference RR = 1.00).
		Hip	4.48 (3.11 to 6.45)‡ a 1	‡RR (95% CI)
			1.95 (1.71 to 2.22)‡ a 2	a) adjusted for age and time since start of follow-up, BMI of
			0.83 (0.69 to 0.99)‡ a 3	1) 15,
			0.75 (0.50 to 1.11)‡ a 4	2) 20,
			2.16 (1.42 to 3.28)‡ b 1	3) 30,
			1.42 (1.23 to 1.65)‡ b 2	4) 35 kg/m^2
			0.83 (0.69 to 0.99)‡ b 3	(BMI 25 = reference RR = 1).
			0.75 (0.50 to 1.11)‡ b 4	‡RR (95% CI)
				b) adjusted for age, time since start of follow-up and BMD, BMI of
				1) 15,
				2) 20,
				3) 30,
				4) 35
				(BMI 25 = reference RR = 1.00).

Table 2: Study details and clinical summary of findings: prior oral glucocorticoid use

Study	Population	Fracture	Result	Comments
Kanis 2004[37]	N = 42,542 men and women.	Any	1.57 (1.37 to 1.80) ‡ c	‡RR (95% CI) ever use versus no use,
	7 cohorts		1.67 (1.10 to 2.51)‡ Δ	c) BMD adjusted,

Study	Population	Fracture	Result	Comments
	EVOS/EPO (Europe), CaMos (Canada), Rotterdam (Netherlands), DOES (Australia), Sheffield (UK), Rochester (USA), Gothenburg (Sweden)		1.39 (1.18 to 1.64)‡◊	Δ) male, ◊) female.
		Osteoporotic	1.66 (1.42 to 1.92)‡c	
			2.16 (1.42 to 3.27)‡Δ	
			1.42 (1.18 to 1.70)‡◊	
		Hip	2.25 (1.60 to 3.15)‡c	
			2.62 (0.91 to 7.51)‡Δ	
			2.07 (1.38 to 3.10)‡◊	

Table 3: Study details and clinical summary of findings: family history of fracture

Study	Population	Fracture	Result	Comments
Kanis 2004[36]	N = 34,928 men and women. 7 cohorts EVOS/EPOS (Europe), CaMos (Canada), Rotterdam (Netherlands), DOES (Australia), Sheffield (UK), Rochester (USA), Gothenburg (Sweden).	Any	1.17 (1.07 to 1.28)‡5	‡RR (95%CI), 5) parental, 6) maternal, 7) paternal, 8) sibling, 9) all.
			1.17 (1.06 to 1.28)‡6	
			1.13 (1.00 to 1.27)‡7	
			1.21 (1.05 to 1.38)‡8	
			1.19 (1.09 to 1.34)‡9	
		Osteoporotic	1.18 (1.06 to 1.31)‡5	
			1.17 (1.05 to 1.31)‡6	
			1.13 (0.98 to 1.30)‡7	
			1.20 (1.02 to 1.42)‡8	
			1.10 (1.10 to 1.34)‡9	
		Hip	1.49 (1.17 to 1.89)‡5	
			1.43 (1.17 to 1.89)‡6	
			1.14 (0.83 to 1.57)‡7	
			1.39 (0.93 to 2.08)‡8	
			1.48 (1.18 to 1.85)‡9	

Table 4: Study details and clinical summary of findings: previous fracture

Study	Population	Fracture	Result	Comments
Kanis 2004A[38]	N = 60,161 men and women. 11 cohorts Rotterdam, EVOS/EPOS (Europe), CaMos (Canada), Rochester (USA), Sheffield (UK), DOES (Australia), EPIDOS (France), OFELY (France), Kuopio (Finland), Hiroshima (Japan), Gothenburg I and II (Sweden).	Any	1.86 (1.75 to 1.98)‡ d	‡RR (95% CI), d) without adjustment for BMD, c) with adjustment for BMD.
			1.77 (1.64 to 1.91)‡ c	
		Osteoporotic	1.86 (1.72 to 2.01)‡ d	
			1.76 (1.60 to 1.93)‡ c	
		Hip	1.85 (1.58 to 2.17)‡ d	
			1.62 (1.30 to 2.01)‡ c	

Table 5: Study details and clinical summary of findings: smoking

Study	Population	Fracture	Result	Comments
Kanis 2005A[39]	N = 59,232 10 cohorts EVOS/EPOS (Europe), CaMos (Canada), Rotterdam (Netherlands, DOES (Australia), Sheffield (UK), Rochester (USA), Gothenburg I and II (Sweden), Hiroshima (Japan), Kupio (Finland).	Any	1.13 (1.01 to 1.25)‡	‡RR (95%CI), adjusted for e) age, f) age and BMD, g) age and BMI, h) age and BMI and BMD.
			1.25 (1.15 to 1.36)‡ e	
			1.13 (1.01 to 1.25)‡ f	
			1.19 (1.09 to 1.30)‡ g	
			1.12 (1.01 to 1.25)‡ h	
		Osteoporotic	1.01 (0.87 to 1.17)‡	
			1.29 (1.17 to 1.43)‡ e	
			1.13 (1.00 to 1.28)‡ f	
			1.21 (1.08 to 1.34)‡ g	
			1.11 (0.98 to 1.26)‡ h	
		Hip	1.60 (1.27 to 2.02)‡	
			1.84 (1.52 to 2.22)‡ e	
			1.60 (1.27 to 2.02)‡ f	
			1.65 (1.34 to 2.03)‡ g	
			1.55 (1.23 to 1.98)‡ h	

Table 6: Study details and clinical summary of findings: alcohol

Study	Population	Fracture	Result	Comments

Study	Population	Fracture	Result	Comments
Kanis 2005B[35]	N = 5939 10 cohorts EVOS/EPOS (Europe), CaMos (Canada), Rotterdam (Netherlands, DOES (Australia), Sheffield (UK), Rochester (USA), Gothenburg I and II (Sweden), Hiroshima (Japan), Kupio (Finland).	All	1.23 (1.06 to 1.43)‡ d 10	‡ RR (95%CI) d) without adjustment for BMD, c) with adjustment for BMD according to alcohol intake; 10) more than 2, 11) more than 3, 12) more than 4 units daily (reference 1 unit alcohol – RR = 1.00). # RR (95% CI) per unit increase in alcohol.
			1.33 (1.10 to 1.60)‡ d 11	
			1.51 (1.20 to 1.91)‡ d 12	
			1.24 (1.06 to 1.45)‡ c 10	
			1.34 (1.11 to 1.62)‡ c 11	
			1.51 (1.19 to 1.93)‡ c 12	
		Osteoporotic	1.05 (1.02 to 1.08)#	
			1.38 (1.16 to 1.65)‡ d 10	
			1.55 (1.26 to 1.92)‡ d 11	
			1.70 (1.30 to 2.22)‡ d 12	
			1.36 (1.13 to 1.63)‡ c 10	
			1.53 (1.23 to 1.91)‡ c 11	
			1.64 (1.24 to 2.17)‡ c 12	
		Hip	1.07 (1.02 to 1.14)#	
			1.68 (1.19 to 2.36)‡ d 10	
			1.92 (1.28 to 2.88)‡ d 11	
			2.26 (1.35 to 3.79)‡ d 12	
			1.70 (1.35 to 3.79)‡ c 10	
			2.05 (1.35 to 3.11)‡ c 11	
			2.39 (1.39 to 4.09)‡ c 12	

Table 7: Study details and clinical summary of findings: history of falls – fall in past 12 months (versus no falls)

Study	Population	Fracture	Result	Comments
Chen 2009[9]	N = 1894, men and women aged 65 to 104 years from nursing care homes, Australia	Hip	0.95 (0.72 to 1.26)§	§HR (95% CI) univariate analysis. Follow-up mean (SD) 2.65 (1.38) years.
Wolinsky	N = 5511, men and women	Hip	1.35 ($p < 0.001$)¶ a	¶HR (95% CI)

Study	Population	Fracture	Result	Comments
2009[77]	aged ≥ 70 years, USA			a) adjusted for age, sex, race, residence type, BMI, smoking history, diabetes, psychological problems, heart disease, cognitive function. Follow-up mean 7.1 years per person.
Guessous 2008[23]	N = 6174, women aged ≥ 70 years, Switzerland	Osteoporotic*	1.40 (1.11 to 1.76)†	†HR (95% CI) multivariable analysis. *Hip, wrist or arm. Follow-up 2.8 years.
Hans 2008[24]	N = 12 958, women aged ≥ 70 years, Switzerland and France	Hip	1.36 (1.08 to 1.73)§ 1.29 (1.01 to 1.65)† b	§HR (95% CI) univariate analysis, †HR (95% CI) multivariable analysis b) adjusted for age, BMI, history of fracture after age 50 years, results of chair test, current cigarette smoking, diabetes mellitus, stiffness index. Follow-up mean (SD) 3.2 (0.9) years.
Lewis 2007[49]	N = 5995, men aged ≥ 65 years, USA	Non-spine	1.82 (1.42 to 2.35)† c 1.82 (1.42 to 2.35)† d 1.58 (1.22 to 2.04)† e	†HR (95% CI) c) age adjusted, d) age and BMD adjusted, multivariable analysis e) 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. Follow-up mean (SD) 4.1 (0.9) years.
Díez-Pérez 2007[17]	N = 5201 women aged ≥ 65 years, Spain	Overall non-spinal Main non-spinal* Hip Wrist/forearm Humerus	1.70 (1.35 to 2.15)† 1.66 (1.28 to 2.15)† 1.23 (0.68 to 2.22)† 2.05 (1.39 to 3.01)† 1.53 (0.86 to 2.27)†	*Hip, forearm/wrist, humerus, pelvis, clavicle, leg. Follow-up mean (SD) 2.83 (0.72) years. †HR (95% CI) multivariable analysis.
Nguyen 2005[54]	N = 1469, men and women aged ≥ 60 years, Australia	Hip	2.0 (1.3 to 3.2)§ ◊ 2.0 (1.0 to 4.4)§ Δ 2.0 (1.4 to 2.9)† c 2.0 (1.6 to 2.4)† d 1.4 (0.9 to 2.1)† f	§HR (95% CI) univariate analysis for ◊) women, Δ) men, †HR (95% CI) c) age adjusted, d) age and BMD adjusted,

Study	Population	Fracture	Result	Comments
				f) age, BMD and gender adjusted. Follow-up median (IQR) 12 (6 to 13) years.
Porthouse 2004[58]	N = 4292, women aged > 70 years, UK	Any non-vertebral	2.06 (1.63 to 2.59)¥	¥OR (95%CI) univariate analysis. Follow-up 24 months.
		Hip	2.92 (1.70 to 5.01)¥	
		Wrist	1.60 (1.10–2.31)¥	
Seeley 1996[64]	N = women aged ≥ 65 years, USA	Ankle	1.76 (1.26 to 2.46)‡ c	‡RR (95% CI) c) age adjusted, g) adjusted for age, bone mass, weight gain since 25 years, vigorous activity ≤ 1 trip 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). Follow-up mean (SD) 5.9 (1.2) years.
			1.53 (1.14 to 2.06)‡ g	

Table 8: Study details and clinical summary of findings: history of falls – fall(s) in past 12 month

Study	Population	Fracture	Result	Comments
Vogt 2002[76]	N = 9704 women aged ≥ 65 years, USA	Distal radius fracture	1.2 (1.0 to 1.2)‡ c 1	‡RR (95% CI) c) age adjusted 1) fell once, ‡RR (95% CI); 2) fell twice or more. Follow-up mean 9.8 years.
			1.6 (1.2 to 2.0)‡ c 2	

Table 9: Study details and clinical summary of findings: history of falls – fall in past 6 months

Study	Population	Fracture	Result	Comments
van Staa 2005[74]	N = 191,752 men and women aged ≥ 40 years, UK	Osteoporotic	2.57 (2.30 to 2.86)‡ h	‡RR (95% CI) h) age and gender adjusted. Follow-up mean 2.5 years per person.
		Femur/hip	2.52 (2.12 to 3.00)‡ h	
		Vertebral	2.24 (1.71 to 2.92)‡ h	
Dargent-Molina	N = 6933 women ≥ 75 years, France	Hip	1.4 (0.9 to 2.0)‡ j	‡RR (95% CI) j) adjusted for age, tandem walk (able after several trials, unable, not

Study	Population	Fracture	Result	Comments
2002[14]				performed), gait speed, visual acuity. Follow-up mean (SD) 3.7 (0.8) years.
Lee 2002[42]	N = 6901 women aged ≥ 75 years, France	Humeral	3.0 (1.5 to 6.1)‡ k	‡RR (95% CI) k) adjusted for femoral neck BMD, calcaneal speed of sound (SOS), maternal history of hip fracture, number of physical activities, closed-eye static balance score, ankle or foot pain. Follow up mean (SD) 3.6 (0.8) years.

Table 10: Study details and clinical summary of findings: history of falls – fall in past 90 days

Study	Population	Fracture	Result	Comments
Stolee 2009[69]	N = 40,279, men and women aged ≥ 60 years residential care Canada	Hip	1.44 (1.27 to 1.64)‡ h 1.28 (1.12 to 1.46)# h	‡RR (95% CI) h) age and gender adjusted, #RR (95% CI) multivariable h) age and gender adjusted. Follow-up 180 to 1440 days.

Table 11: Study details and clinical summary of findings: history of falls – fall in past month

Study	Population	Fracture	Result	Comments
Papaioannou 2005[55]	N = 5143 postmenopausal women aged > 25 years, Canada	Main non-vertebral	0.970 (0.562 to 1.675)†	†HR (95%CI) multivariable analysis. Follow-up 3 years.
		Any non-vertebral	1.028 (0.689 to 1.532)†	

Table 12: Study details and clinical summary of findings: history of falls

Study	Population	Fracture	Result	Comments
Hippisley-Cox 2009[28]	N = 2,357,865, primary care, England and Wales, men and women aged 30 to 85 years	*Osteoporotic	1.82 (1.66 to 1.99)† ◊ m	†HR (95%CI) multivariable analysis, ◊) women and Δ) men, m) adjusted for smoking, alcohol consumption, rheumatoid arthritis, cardiovascular disease, Type 2 diabetes, asthma, liver disease, current tricyclic antidepressants, current glucocorticoids, fractional polynomial terms for age
		*Osteoporotic	2.23 (1.80 to 2.75)† Δ m	
		Hip	2.03 (1.80 to 2.29)† ◊ m	
		Hip	2.66 (2.03 to 3.49)† Δ m	

Study	Population	Fracture	Result	Comments
				and BMI. Imputed data to replace missing values for smoking status, alcohol, BMI. *Distal radius, or vertebral fracture. Follow-up 15 years.
van Staa 2006[73]	N = 366 104 women aged ≥ 50 years, UK	Femur/hip	1.96 (1.79 to 2.15)‡ h	‡RR (95%CI) adjusted for h) age and gender. Follow-up mean 5.8 years.
		Clinical vertebral	1.82 (1.47 to 2.25)‡ h	
		Other clinical osteoporotic	1.74 (1.60 to 1.89)‡ h	
Sambrook 2007[60]	N = 2005 men and women in residential care aged 65 to 104 years, Australia	All*	1.14 (0.90 to 1.43)⊥	⊥IRR (95% CI) univariate analysis. *Hip, vertebral, pelvic, wrist, humeral, rib, femoral shaft, miscellaneous. Follow-up median 705 days.

Table 13: Study details and clinical summary of findings: history of falls – more than two falls in last year of follow-up (versus two or less falls)

Study	Population	Fracture	Result	Comments
Cauley 2007A[8]	N = 159,579 postmenopausal women aged 50 to 79 years USA	Any*	1.27 (1.22 to 1.32)† ⅄	†HR (95%CI) multivariable analysis, ⅄Caucasian, ⌖Black, ⌗Hispanic, ✧Asian/Pacific Islander, ⌑American Indian. *except those of fingers, toes, skull, face or sternum. Follow-up mean (SD) 9.8 (2.6) years.
			1.67 (1.38 to 2.02)† ⌖	
			1.80 (1.40 to 2.32) † ⌗	
			1.41 (1.04 to 1.91)† ✧	
			1.38 (0.75 to 2.55)† ⌑	

Table 14: Study details and clinical summary of findings: history of falls – fall rate during follow-up

Study	Population	Fracture	Result	Comments
Sambrook 2007[60]	N = 2005 men and women in residential care aged 65 to 104 years, Australia	Any	3.02 (2.21 to 4.20)⊥ 3	⊥IRR (95% CI) univariate analysis, 3) fall rate per person year ≥ 3.08, 4) fall rate per person year 1.05 to 3.08,
			2.22 (1.59 to 3.09)⊥ 4	
			1.67 (1.19 to 2.34)⊥ 5	

Study	Population	Fracture	Result	Comments
			3.35 (2.28 to 4.72)∏ 3	5) fall rate per person year 0.05 to 1.00.
			2.42 (1.71 to 3.42)∏ 4	∏IRR (95%CI) multivariable analysis, 3) fall rate per person year ≥ 3.08,
			1.65 (1.17 to 2.34)∏ 5	4) fall rate per person year 1.05 to 3.08,
				5) fall rate per person year 0.05 to 1.00.
				Follow-up median 705 days.

Table 15: Study details and clinical summary of findings: history of falls – fall rate during follow-up

Study	Population	Fracture	Result	Comments
Schwartz 2005[63]	N = 9845 women subjects aged ≥ 65 years, USA	Hip	1.30 (1.03 to 1.64)ϕ c 6	ϕRate ratio (95% CI)
			1.48 (1.07 to 2.03) ϕ c 7	c) age adjusted, fall rate/year;
			1.85 (1.24 to 2.74) ϕ c 8	6) 0.01 to 0.75,
			1.01 (0.67 to 1.51) ϕ n 9	7) 0.76 to 1.75,
			0.99 (0.65 to 1.49) ϕ n 10	8) > 1.75.
			1.44 (1.02 to 2.04) ϕ n 11	ϕRate ratio (95% CI)
			1.57 (1.10 to 2.23) ϕ n 12	n) adjusted for age and rate of falls in first 4 years; change in rate of falls in first 4 years (number of falls/year/year)
			1.16 (0.88 to 1.52) ϕ p 6	9) 0.001 to 1.13,
			1.25 (0.88 to 1.79) ϕ p 7	10) 0.14 to 0.27,
			1.38 (0.86 to 2.22) ϕ p 8	11) 0.28 to 0.44,
			1.04 (0.69 to 1.55) ϕ q 9	12) 0.44.
			0.97 (0.64 to 1.47) ϕ q 10	ϕ Rate ratio (95% CI)
			1.33 (0.93 to 1.91) ϕ q 11	p) adjusted for change in rate of falls in first four years (number of falls/year/year), 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 BMD, fall rate/year;
			1.42 (0.99 to 2.04) ϕ q 12	6) 0.01 to 0.75,
		Proximal humerus	1.06 (0.79 to 1.43) ϕ c 6	7) 0.76 to 1.75,
			0.99 (0.62 to 1.58) ϕ c 7	8) > 1.75.
			1.85 (0.62 to 2.20) ϕ c 8	
			0.84 (0.47 to 1.50) ϕ n 9	
			0.85 (0.47 to 1.54) ϕ n 10	
			0.92 (0.53 to 1.59) ϕ n 11	

Study	Population	Fracture	Result	Comments
			1.65 (1.00 to 2.72) ϕ n 12	ϕ Rate ratio (95% CI) q) adjusted for rate of falls in first 4 years (no. falls/year), age, current use of thyroid hormone replacement, 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 BMD. Follow-up median 6.3 years.
			1.00 (0.70 to 1.41) ϕ p 6	
			0.83 (0.49 to 1.39) ϕ p 7	
			0.75 (0.36 to 1.56) ϕ p 8	
			0.89 (0.50 to 1.60) ϕ q 9	
			0.87 (0.48 to 1.60) ϕ q 10	
			0.97 (0.56 to 1.69) ϕ q 11	
			1.79 (1.08 to 2.95) ϕ q 12	

Table 16: Study details and clinical summary of findings: history of falls – incidence of falls during follow-up (versus one fall)

Study	Population	Fracture	Result	Comments
Kaptoge 2005[41]	N = 5370 men and women, ≥ 65 years, Europe	Any non-spine	0.09 (0.06 to 0.13)‡ ◊ 13	‡RR (95% CI) (modelling with 'all falls'), ◊ women, 13) 0 versus 1 fall, 14) 2 versus 1 fall, 15) 3+ versus 1 fall. Follow-up median 3 years.
			0.81 (0.54 to 1.21)‡ ◊ 14	
			0.60 (0.40 to 0.91)‡ ◊ 15	
		Upper limb	0.09 (0.05 to 0.15)‡ ◊ 13	
			0.64 (0.35 to 1.18)‡ ◊ 14	
			0.54 (0.30 to 0.97)‡ ◊ 15	
		Lower limb	0.09 (0.04 to 0.18)‡ ◊ 13	
			0.68 (0.33 to 1.40)‡ ◊ 14	
			0.64 (0.32 to 1.31)‡ ◊ 15	

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3.3.2 Regression coefficients from the QFracture development cohort study

The development of QFracture was based on a large UK primary care population: QResearch database (please see chapter 4 for more information on the QFracture risk assessment tool) .The coefficients and hazard ratios (HR) associated with each potential fracture risk factor for osteoporotic and hip fracture in men and women were estimated as one of the first steps during the model derivation/development phase and they were used as weights for the QFracture scores.

These data have been captured and included in this review question in addition to the IPD meta-analyses. Because of high percentage of imputation of missing data for alcohol intake in men, HRs calculated in the complete case analysis are presented here (Table 17). Multiply imputed data are not greatly different from those reported in the complete case analysis.

In men, statistically significant associations with risk of osteoporotic fracture (distal radius, hip and vertebral) and hip fracture were found for the following risk factors: smoking status (moderate and heavy smoking), very heavy alcohol intake, current corticosteroids, history of falls and other causes of secondary osteoporosis (including rheumatoid arthritis, type 2 diabetes, asthma, current tricyclic antidepressants and liver disease).

In women, statistically significant associations with risk of osteoporotic fracture and hip fracture were found for the following risk factors: smoking status (moderate and heavy smoking), alcohol intake (heavy and very heavy), current corticosteroids (osteoporotic fracture risk only), history of falls and other causes of secondary osteoporosis (including rheumatoid arthritis, type 2 diabetes, asthma, cardiovascular disease (hip fracture risk only), current tricyclic antidepressants and liver disease). Additional risk factors were explored in women (Table 18) and data showed statistically significant associations with osteoporotic fracture risk but not with hip fracture risk for the following risk factors: menopausal symptoms, parental history of osteoporosis and malabsorption.

Fractional polynomials were used to model non-linear associations for age and BMI as continuous variables in the QFracture development cohort. The fractional polynomial curves showed that the risk of osteoporotic and hip fractures increased with age (compared with age 30) in both men and women. BMI (compared with BMI=25kg/m^2) was shown to be inversely associated with fracture (both osteoporotic and hip) risk in both men and women.

At present, regression coefficients for FRAX are not publicly available (please see chapter 4 for more information on the FRAX risk assessment tool).

Table 17: Regression coefficients (or adjusted hazard ratios*) reported in the QFracture derivation study for osteoporotic and hip fracture in men and women (complete case analysis) (Reproduced from BMJ 2009;339:b4229, http://www.bmj.com/highwire/filestream/396994/field_highwire_article_pdf/0.pdf open access article)[28]

Risk factor	Osteoporotic fracture Men	Hip fracture Men	Osteoporotic fracture Women	Hip fracture Women
Non-smoker	1.00	1.00	1.00	1.00
Ex-smoker	0.98 (0.91 to 1.05)	0.99 (0.87 to 1.11)	1.02 (0.97 to 1.06)	1.05 (0.97 to 1.14)
Current smoker:				
Light	1.06 (0.95 to 1.17)	1.23 (1.03 to 1.46)	1.02 (0.95 to 1.10)	1.21 (1.06 to 1.37)
Moderate	1.24 (1.13 to 1.36)	1.61 (1.37 to 1.91)	1.14 (1.07 to 1.20)	1.42 (1.28 to 1.58)
Heavy	1.4 (1.27 to 1.55)	2.18 (1.82 to 2.62)	1.21 (1.12 to 1.31)	1.87 (1.62 to 2.16)
Alcohol:				

Risk factor	Osteoporotic fracture Men	Hip fracture Men	Osteoporotic fracture Women	Hip fracture Women
Non-drinker	1.00	1.00	1.00	1.00
Trivial < 1 unit/day	0.91 (0.84 to 0.99)	0.81 (0.71 to 0.92)	1.00 (0.97 to 1.04)	0.92 (0.86 to 0.97)
Light 1–2 units/day	0.95 (0.88 to 1.03)	0.84 (0.74 to 0.97)	1.04 (0.99 to 1.09)	0.91 (0.84 to 0.99)
Moderate 3–6 units/day	1.08 (0.98 to 1.19)	0.91 (0.76 to 1.09)	1.08 (0.96 to 1.21)	1.10 (0.89 to 1.35)
Heavy 7–9 units/day	1.06 (0.83 to 1.35)	0.85 (0.52 to 1.38)	1.58 (1.06 to 2.36)	1.60 (0.76 to 3.35)
Very heavy > 9 units/day	1.84 (1.47 to 2.29)	2.56 (1.78 to 3.67)	2.40 (1.66 to 3.46)	2.93 (1.57 to 5.47)
Current corticosteroids†	1.65 (1.39 to 1.97)	1.61 (1.23 to 2.10)	1.17 (1.07 to 1.28)	1.13 (0.97 to 1.31)
History of falls†	2.17 (1.60 to 2.93)	2.29 (1.46 to 3.61)	1.65 (1.45 to 1.87)	1.69 (1.40 to 2.05)
Other causes of secondary osteoporosis				
Rheumatoid arthritis†	1.41 (1.01 to 1.97)	1.81 (1.15 to 2.85)	1.26 (1.11 to 1.43)	1.82 (1.52 to 2.18)
Cardiovascular disease†	1.11 (0.89 to 1.39)	1.15 (0.84 to 1.58)	1.12 (0.99 to 1.28)	1.26 (1.04 to 1.52)
Type 2 diabetes†	1.18 (1.02 to 1.37)	1.42 (1.15 to 1.74)	1.27 (1.17 to 1.39)	1.79 (1.59 to 2.02)
Asthma†	1.24 (1.10 to 1.39)	1.24 (1.01 to 1.52)	1.28 (1.20 to 1.36)	1.39 (1.24 to 1.55)
Current tricyclic antidepressants†	1.40 (1.18 to 1.67)	1.77 (1.37 to 2.28)	1.29 (1.21 to 1.37)	1.31 (1.18 to 1.46)
Liver disease†	3.59 (2.45 to 5.24)	3.75 (2.01 to 6.99)	1.79 (1.30 to 2.46)	1.75 (1.02 to 3.02)

†*Compared with patients without condition/medication at baseline. *Hazard ratios simultaneously adjusted for all other variables shown in table as well as fractional polynomial terms for age and BMI. Fractional polynomial terms for age and BMI were: (age/10) and age (age/10)^2 and (BMI/10)$^{-2}$ for osteoporotic fracture; and (age/10)^2 and log (BMI/10) and (log[BMI/10])^2 for hip fracture.*

Table 18: Regression coefficients (or adjusted hazard ratios*) reported in the QFracture derivation study for osteoporotic and hip fracture, in women only (complete case analysis) (Reproduced from BMJ 2009;339:b4229, http://www.bmj.com/highwire/filestream/396994/field_highwire_article_pdf/0.pdf open access article)[28]

Risk factor	Osteoporotic fracture Women	Hip fracture Women
Menopausal symptoms†	1.13 (1.03 to 1.23)	1.16 (0.99 to 1.36)
Gastrointestinal malabsorption†	1.32 (1.11 to 1.57)	1.29 (0.94 to 1.76)
Other endocrine disorder†	1.10 (0.95 to 1.26)	1.09 (0.69 to 1.71)
Parental history osteoporosis†	1.63 (1.38 to 1.92)	1.09 (0.69 to 1.71)
No use of hormone replacement therapy (HRT)	1.00	1.00
Type of HRT†:		
Low-dose unopposed equine oestrogen	0.91 (0.81 to 1.02)	0.84 (0.66 to 1.06)
Low dose unopposed non-equine	0.90 (0.82 to 0.99)	0.96 (0.79 to 1.17)

Risk factor	Osteoporotic fracture Women	Hip fracture Women
oestrogen		
High-dose unopposed equine oestrogen	0.72 (0.57 to 0.90)	0.66 (0.37 to 1.16)
High-dose unopposed non-equine oestrogen	0.73 (0.57 to 0.94)	0.74 (0.40 to 1.38)
Cyclical low-dose equine	0.90 (0.81 to 1.01)	0.91 (0.68 to 1.21)
Cyclical low-dose non-equine	0.88 (0.78 to 0.99)	0.78 (0.56 to 1.08)
Cyclical high-dose equine	1.14 (0.81 to 1.60)	1.06 (0.44 to 2.56)
Cyclical high-dose non-equine	0.79 (0.67 to 0.93)	0.93 (0.61 to 1.42)
Continuous low-dose equine	1.16 (0.96 to 1.39)	1.20 (0.82 to 1.77)
Continuous low-dose non-equine	0.97 (0.83 to 1.14)	0.87 (0.59 to 1.30)
Continuous high-dose non-equine	0.82 (0.72 to 0.93)	0.73 (0.54 to 1.00)
Tibolone	0.86 (0.67 to 1.10)	0.41 (0.19 to 0.86)

*†Compared with patients without condition/ medication at baseline. *Hazard ratios simultaneously adjusted for all other variables shown in table as well as fractional polynomial terms for age and BMI. Fractional polynomial terms for age and BMI were: (age/10) and age (age/10)^2 and (BMI/10)$^{-2}$ for osteoporotic fracture; and (age/10)^2 and log(BMI/10) and (log[BMI/10])^2 for hip fracture.*

3.4 Clinical evidence review on age

There is an association between increasing age and fragility fracture[28 10 66 31]. In considering opportunistic risk assessment, the GDG considered that there was an age below which fragility fracture was unlikely and where the risk generated by a risk assessment tool would be very low if the person did not have any other risk factors. The GDG wished to provide some guidance to the non-specialists who would be using the risk assessment tools and doing opportunistic risk assessment. The GDG was therefore interested in epidemiological data to establish at what age the fragility fracture rate starts increasing. The GDG's aim was to establish a cut-off age below which assessment of fragility fracture in people without risk factors would be unlikely to be necessary. The GDG used information collected for the assessment of risk assessment tools to inform these recommendations. The data extracted by the technical team for the GDG are described below.

The GDG considered epidemiological data from three UK studies: Hippisley-Cox 2009[28] (incidence of fracture vs age), Collins 2011[10] (risk of fracture vs age), and Singer 1998[66] (incidence of fractures vs age).

The aim of the Hippisley-Cox 2009[28] study was to develop and internally validate the QFracture risk assessment tool; it analysed data collected in the QResearch database, which is a large primary care electronic database for England and Wales. About 2 million patients were included in the analysis (aged between 30 and 85 years, with no previous recorded fracture) and assigned to either the derivation dataset (67%) or the validation dataset (33%). Results are shown in Figure 1, Figure 2, Figure 3 and Figure 4 below.

Figure 1: Number of incident cases of major osteoporotic fracture (number of fractures) by age in men (from Hippisley-Cox 2009[28])

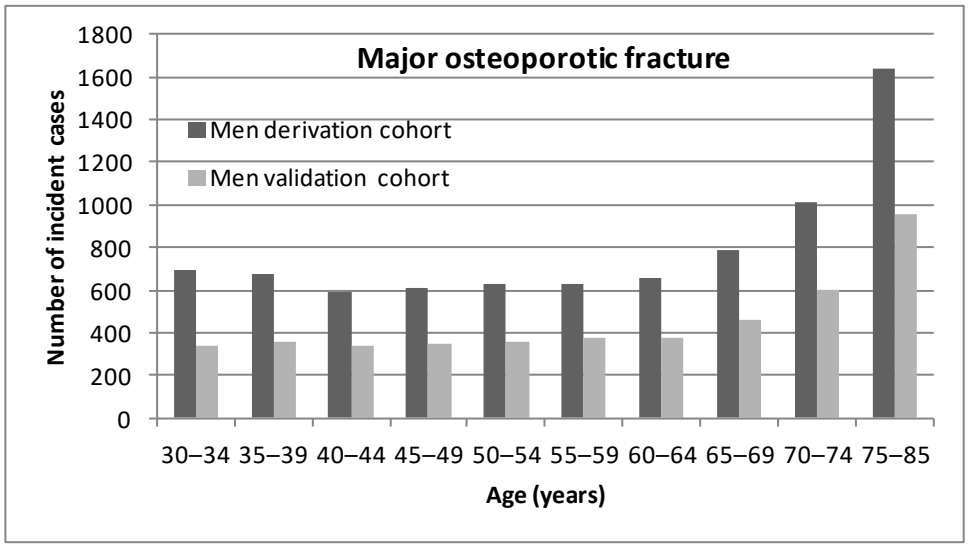


Figure 2: Number of incident cases of hip fracture (number of fractures) by age in men (from Hippisley-Cox 2009[28])

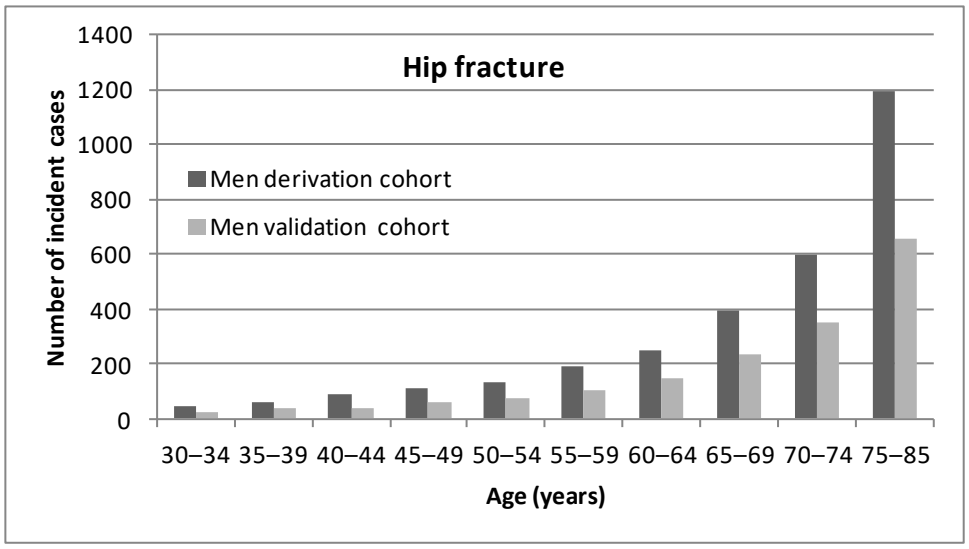


Figure 3: Number of incident cases of major osteoporotic fracture (number of fractures) by age in women (from Hippisley-Cox 2009[28])

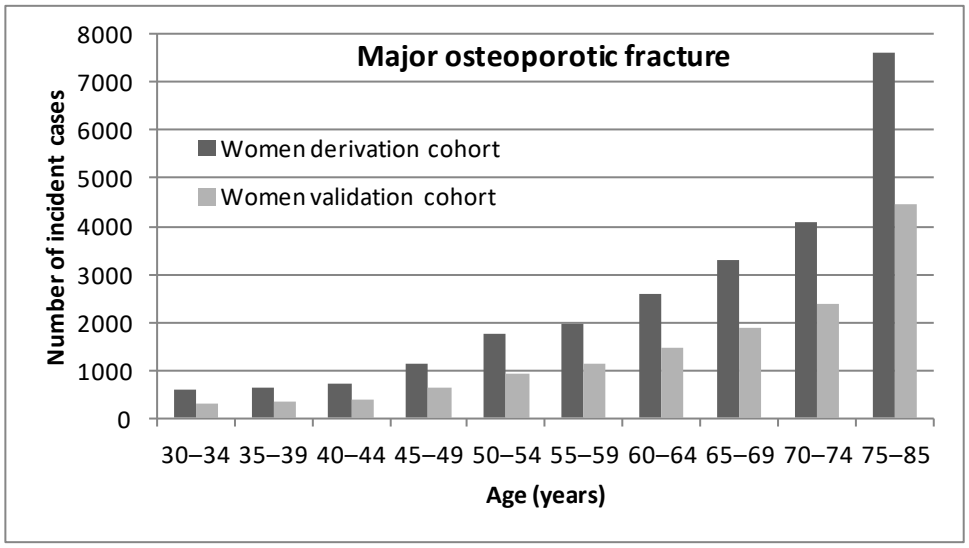
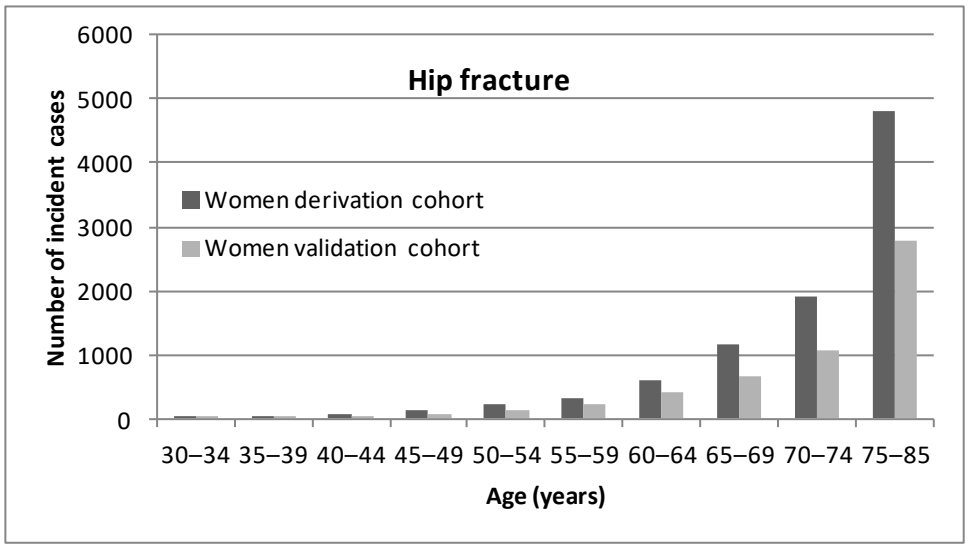


Figure 4: Number of incident cases of hip fracture (number of fractures) by age in women (from Hippisley-Cox 2009[28])



The Collins 2011[10] study analysed data collected in the THIN (The Health Improvement Network) database, which comprises the records of about 20% of UK general practices. The aim of the study is to externally validate the QFracture risk assessment tool. More than 2 million patients were included in the analysis (aged between 30 and 85 years, with no previous recorded fracture). Results are shown in Figure 5 and Figure 6 below.

Figure 5: 10-year observed risk of hip and major osteoporotic fracture by age, in women (from Collins 2011[10])

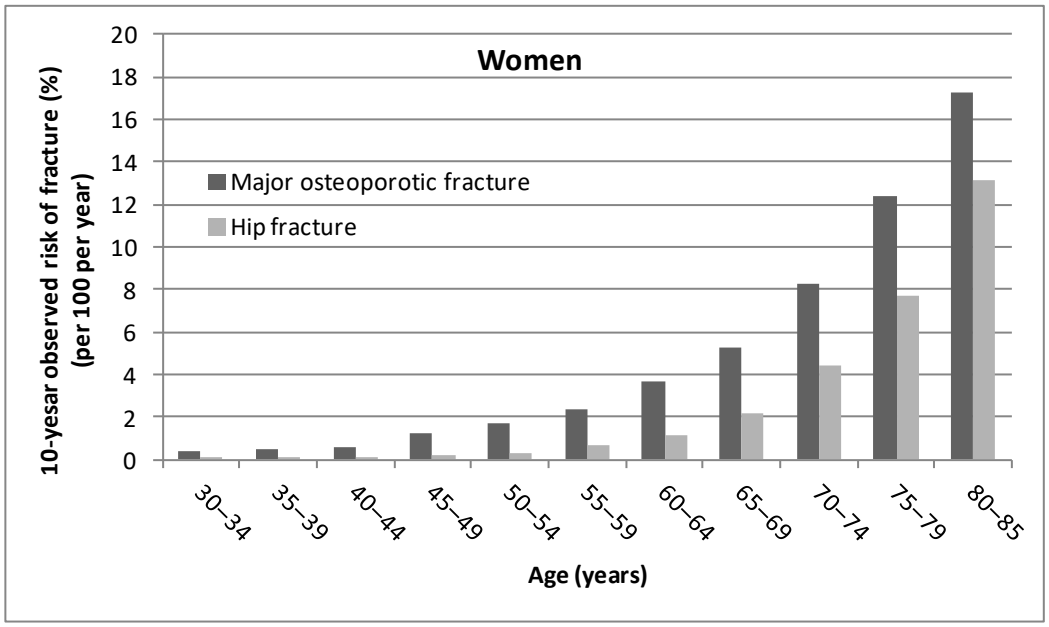
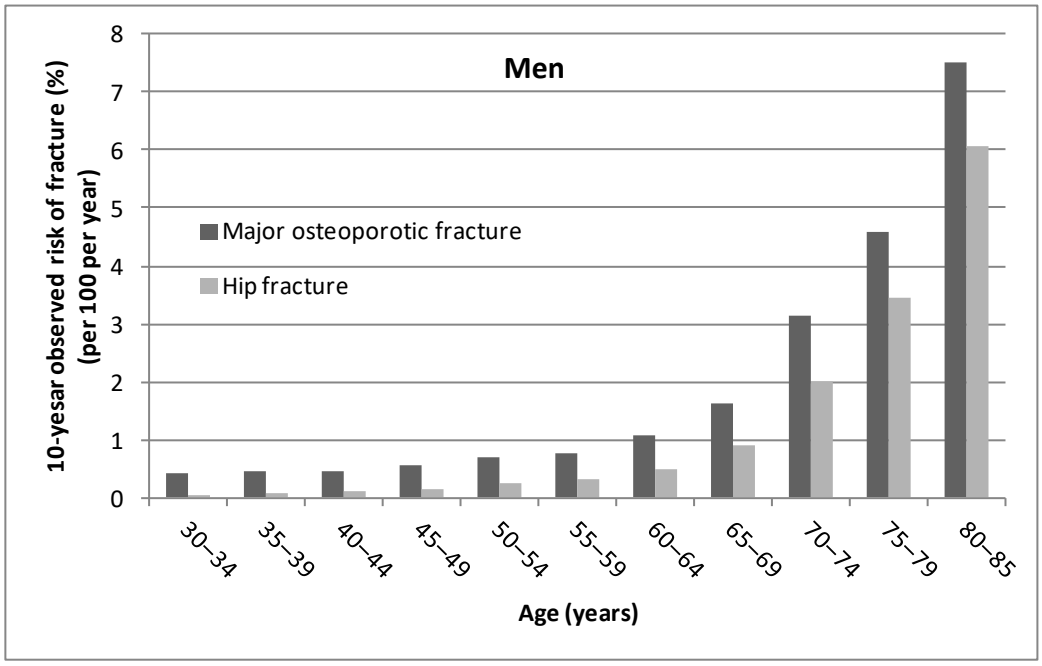


Figure 6: 10-year observed risk of hip and major osteoporotic fracture by age, in men (from Collins 2011[10])



The Singer 1998[66]study is a report of the incidence of fractures in the adult population of Edinburgh, UK related to age and gender (more than 15,000 patients). This is the epidemiological study upon which the development of the UK FRAX tool is based. Results are shown in Figure 7 and Figure 8 below.

Figure 7: Incidence of all fractures (per 10,000 population per annum) vs age, in men and women (from Singer 1998[66], reproduced with permission of the author and copyright © of the British Editorial Society of Bone and Joint Surgery)

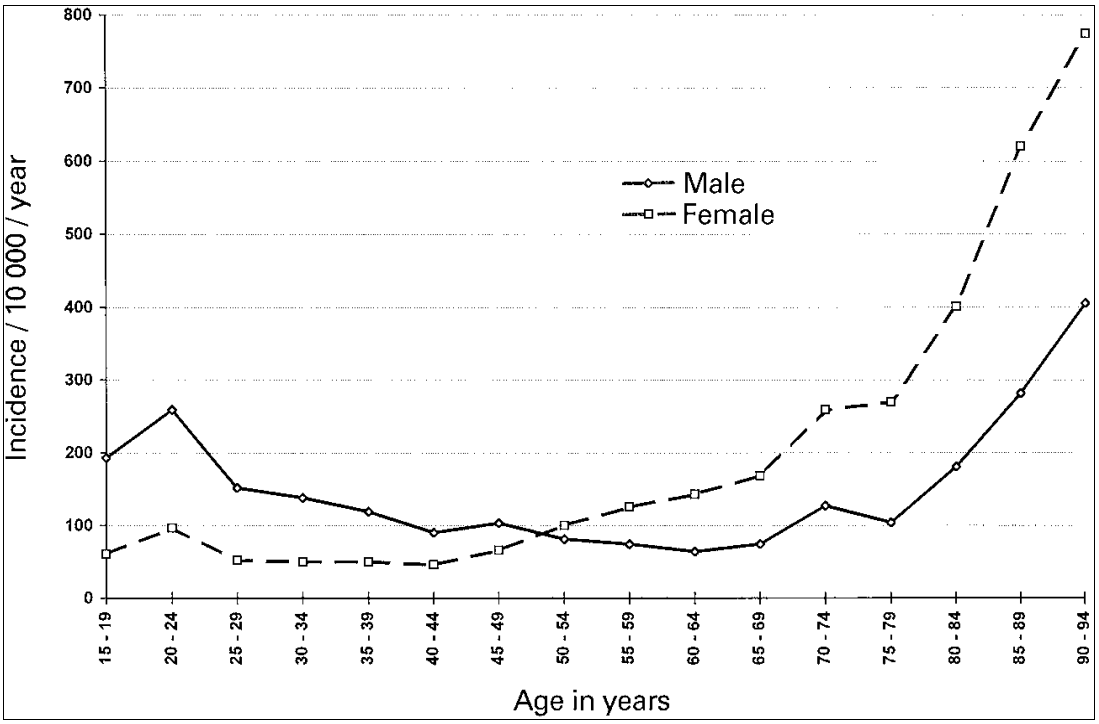
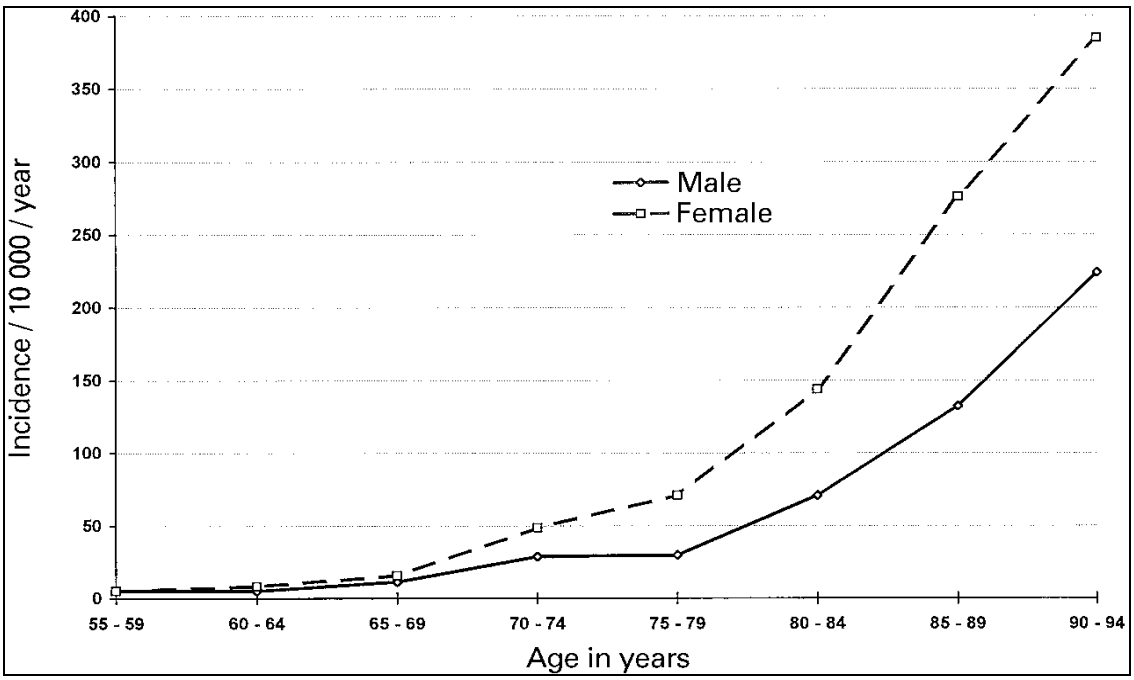


Figure 8: Incidence of hip fractures (per 10,000 population per annum) vs age, in men and women (from Singer 1998[66], reproduced with permission of the author and copyright © of the British Editorial Society of Bone and Joint Surgery)



The graphs above (Figures 1 to 8) clearly suggest that there is a relationship between increasing age and incidence of fragility fracture, and that the incidence of fracture in women starts rising about 10 years earlier than in men.

3.5 Health economic evidence review

No economic studies were identified on the cost effectiveness of simple clinical measures for targeting people for risk assessment of fragility fracture.

3.6 Evidence statements

For details of how the evidence is graded, see 'The guidelines manual' (available from www.nice.org.uk/GuidelinesManual); see appendix D for the quality of evidence.

3.6.1 Clinical evidence statement

BMI

One IPD meta-analysis of 59,644 men and women that included data from 12 cohort studies suggests that the risk of any, osteoporotic and hip fractures increased with decreasing BMI; risk appeared greater for hip fracture. Increased risk of fracture at low BMI was largely independent of age and sex, but dependent upon BMD.

Prior oral glucocorticoid use

One IPD meta-analysis of 42,542 men and women that included data from seven cohort studies suggests that ever prior oral glucocorticoid use versus no use is associated an increased risk of any, osteoporotic and hip fractures.

Family history of fracture

One IPD meta-analysis of 34,928 men and women that included data from seven cohort studies suggests that a maternal, paternal and sibling history of fracture may be associated with an increased risk of any, osteoporotic and hip fractures. There was no appreciable difference between men versus women for family history of fracture as a prognostic factor for risk of fracture.

Previous history of fracture

One IPD meta-analysis of 60,161 men and women that included data from 11 cohort studies suggests that a previous history of fracture is associated with an increased risk of any, osteoporotic and hip fractures. There was no appreciable difference between men versus women for history of previous fracture as a prognostic factor for risk of fracture.

Smoking

One IPD meta-analysis of 59,232 men and women that included data from 10 cohort studies suggests that current smoking is associated with an increased risk of any, osteoporotic and hip fractures.

Alcohol

One IPD meta-analysis of 5939 men and women that included data from three cohort studies suggests that an intake of greater than 2 units of alcohol per day is associated with an increased risk of any, osteoporotic and hip fractures.

History of falls in past 12 months

One Australian study of 1894 men and women in nursing care facilities suggests that a history of falls in the past 12 months is not associated with an increased risk of hip fracture.

One cohort study conducted in the USA of 5511 men and women suggests that a history of falls in the past 12 months is associated with an increased risk of hip fracture.

One Swiss cohort study of 6714 women suggests that a history of falls in the past 12 months is associated with an increased risk of hip, wrist or arm fractures.

One study of 12,958 women derived from a French cohort and a Swiss cohort suggests that a history of falls in the past 12 months is associated with an increased risk of hip fracture.

One cohort study conducted in the USA of 5995 men suggests that history of falls in the past 12 months is associated with an increased risk of non-spinal fracture.

One Spanish cohort study of 5201 women suggests that history of falls in the past 12 months is associated with an increased risk of hip fracture.

One Spanish cohort study of 5201 women suggests that history of falls in the past 12 months is associated with an increased risk of non-vertebral fracture.

One Australian cohort study of 1669 men and women suggests that a history of falls in the past 12 months is associated with an increased risk of hip fracture.

One UK cohort study of 4292 women suggests that a history of falls in the past 12 months is associated with an increased risk of any non-vertebral, hip and wrist fractures.

History of falls in past 6 months

One UK cohort study of 191,752 men and women and one French cohort study of 6933 women suggest that history of falls in the past 6 months is associated with an increased risk of hip fracture.

History of falls

Two cohort studies in UK populations found that a history of falls was associated with an increased the risk of osteoporotic and hip fractures.

One Canadian study of 2005 men and women suggests that that a history of falls was associated with an increased risk of all fractures.

Fall rate

One cohort study of 159,579 women conducted in the USA found that greater than two falls in the last year of follow-up was associated with an increased risk of any fractures.

One cohort study of 2005 men and women in Australia found that an increased fall rate during study follow-up of median 705 days was associated with an increased risk of any fractures.

One cohort study of 9,485 women in the USA found that women with an increased fall rate during the study follow-up of approximately 4 years had an increased risk of subsequent fracture of the hip and of the proximal humerus, compared with women without an increase in falls, after adjustment for age, average rate of falls over 4 years and other known risk factors for fracture.

Incidence of falls during follow-up

One European cohort study of 5370 men and women found that increased falling during study follow-up was associated with an increased risk of any non-spine, upper-limb and lower-limb fractures.

3.6.2 Economic evidence statement

No economic evidence was found on this question.

3.7 Recommendations and link to evidence

Recommendations	**1. Consider assessment of fracture risk:** • **in all women aged 65 years and over and all men aged 75 years and over** • **in women aged under 65 years and men aged under 75 years in the presence of risk factors, for example:** ○ **previous fragility fracture** ○ **current use or frequent recent use of oral or systemic glucocorticoids** ○ **history of falls** ○ **family history of hip fracture** ○ **other causes of secondary osteoporosis[g]** ○ **low body mass index (BMI) (less than 18.5 kg/m2)** ○ **smoking** ○ **alcohol intake of more than 14 units per week for women and more than 21 units per week for men.** **2. Do not routinely assess fracture risk in people aged under 50 years unless they have major risk factors (for example, current or frequent recent use of oral or systemic glucocorticoids, untreated premature menopause or previous fragility fracture), because they are unlikely to be at high risk.**
Relative values of different outcomes	The GDG wished to target opportunistic risk assessment to those individuals who are likely to be at increased risk. Hip fracture and osteoporotic fractures were considered clinically important.
Trade-off between clinical benefits and harms	The GDG considered there were unlikely to be harms in recommending that healthcare professionals consider risk assessment in groups whose risk is higher than the general population.. Appropriate risk assessment may allow individuals to avail of preventative treatment and some factors such as alcohol and smoking can be modified using lifestyle interventions. The GDG considered that there it was unlikely to be clinically harmful to assess people at low risk and understood that both they and healthcare professionals may gain reassurance if risk is assessed as low.
Economic considerations	The GDG considered that absolute risk of fragility fracture differs within the general population; in particular, fracture rates for patients below 50 years are very low. Thus, risk assessment for everyone would incur unnecessary costs and may not provide any additional benefit to patients. Targeting risk assessment for all women from age 65 and all men from age 75, and for women less than 65 years and men less than 75 years with risk factors, was considered an efficient use of resources because the risk of fracture is likely to be highest in this population. The recommendations aim at promoting better use of resources by targeting

g Causes of secondary osteoporosis include endocrine (hypogonadism in either sex including untreated premature menopause and treatment with aromatase inhibitors or androgen deprivation therapy; hyperthyroidism; hyperparathyroidism; hyperprolactinaemia; Cushing's disease; diabetes), gastrointestinal (coeliac disease; inflammatory bowel disease; chronic liver disease; chronic pancreatitis; other causes of malabsorption), rheumatological (rheumatoid arthritis; other inflammatory arthropathies), haematological (multiple myeloma; haemoglobinopathies; systemic mastocytosis), respiratory (cystic fibrosis; chronic obstructive pulmonary disease), metabolic (homocystinuria), chronic renal disease and immobility (due for example to neurological injury or disease).

	risk assessment to patients more likely to require treatment.
Quality of evidence	**Age:**, the GDG reviewed the incidence and rates of fracture as reported in both the internal and external validation of QFracture and also a paper reporting fracture rates from Edinburgh, which was used in development of FRAX score for the UK. The GDG considered that hip fractures were likely to be well recorded in GP databases but that vertebral fractures were less likely to be comprehensively diagnosed and recorded. **Previous fracture:** The IPD analysis of 11 cohorts (N = 60,161; mean age = 62.9 years) indicated that previous fracture is associated with increased risk of fracture, mostly independent of BMD. The GDG considered that site of fracture and the occurrence of multiple fractures are important when considering fracture risk but these are not reported in the review. The identified data in all IPD analyses were on author-selected studies, no details on literature searching were reported, therefore there is potential for study-inclusion bias. Statistical analysis was appropriate for all the IPD analyses, limiting the potential for presentation of invalid results. The measurement of the outcome of fracture was adequately valid and reliable to limit misclassification in all the IPD analyses. **Oral or systemic glucocorticoid use**: The IPD analysis of 7 cohorts (N = 42,542; mean age ranged from 55 to 70 years in men and 58 to 72 years in women, across cohorts) indicated that ever use of oral glucocorticoid is associated with an increased risk of osteoporotic fracture. The IPD analysis does not make a distinction between past and current use of glucocorticoid, the duration of treatment (continuous/intermittent use) or dose. The IPD analysis included oral glucocorticoid use only and follow up search did not find more up to date analyses that included inhaled glucocorticoids. Oral glucocorticoid use is defined in QFracture as use in the previous 6 months and was associated with increased risk of osteoporotic fracture in women and men. This finding of increased risk is further supported by data reported in the QFracture derivation study. **Smoking:** In the IPD analysis of 10 cohorts (N = 59,232; mean age = 63 years), **c**urrent smoking was associated with a significantly increased risk of any osteoporotic fracture and hip fracture (when relative risk [RR] adjusted for age, age and BMD, age and BMI, age and BMI and BMD). Past smoking was associated with an increased risk compared with no smoking history, but lower than for current smoking. The QFracture studies indicated increased risk with increasing cigarette consumption with people smoking more than 10 cigarettes a day. **Alcohol intake:** The IPD analysis of three cohorts (N = 16,971; mean age = 65 years), indicated that alcohol intake of ≥ 2 units/day is associated with an increased risk of fracture. The magnitude of association did not change when BMD was adjusted in the model. In the QFracture derivation study, moderate to very heavy alcohol intake is associated with increasing fracture risk. The GDG had some concerns about the accuracy of alcohol consumption reported both in IPD analyses (only three cohorts included alcohol consumption and none of these were in the UK) and QFracture cohorts because the prevalence of heavy drinking was very low. **Family history of fracture:** The IPD analysis of seven cohorts (N = 34,928; mean age = 65 years) indicated that family history of fracture is associated with increased risk of fracture, independent of BMD. Family history of any fractures and family history of hip fractures are both associated with increased fracture risk, but the effect of family history of hip fracture is stronger. This finding of increased risk is further supported by data reported in the QFracture derivation study. **BMI:** The IPD analysis of 12 cohorts (N = 59,644; mean age = 63 years) indicated that relative risk for any fracture was 0.98 per unit increase in BMI.

	However, the proportion of individuals in the high BMI category was small (3.4% in ≥ 35 kg/m^2 category), therefore the data may not be robust enough to detect any association. This finding of increased risk is supported by data reported in the QFracture derivation study. **History of falls:** 21 studies included in the clinical evidence review indicated that a history of falls is associated with an increased risk of fracture. Eight of the 21 cohort studies that were identified were of high quality, hence they were of sufficient quality to limit bias to the results because of the following: the study population was appropriate, loss to follow-up was adequately addressed, the measurement of falls and the outcome of fracture was appropriate, confounders were accounted for and the appropriate statistical methods were used. Four cohorts were of moderate quality because the only identified bias was that it was unclear if the self-reporting of falls had been validated. One cohort was of moderate quality because loss to follow-up was not addressed. The remaining seven cohort studies were of poor quality because there was potential for bias in two or more of the following: loss to follow-up, measurement of falls, measurement of fracture, measurement of confounding factors. Definitions of history of falls were heterogeneous across studies: a fall in the past 12 months (five studies), a fall in the past 6 months or 90 days (three studies), a fall in the past 1 month (one study), history of falls (yes vs no) (three studies), greater than two falls in the last year of follow up (one study), fall rate (two studies), and incident falls (≥ 3 vs one fall) during follow up (one study). Many studies were of large sample size and were representative of the population of interest. Most of them were non-UK studies. This finding of increased risk is further supported by data reported in the QFracture derivation study. The GDG considered that falls were likely to be poorly recorded in GP databases and the prevalence reported in GP datasets is low compared with epidemiological data. **Causes of secondary osteoporosis:** The decision to include people with secondary osteoporosis in this recommendation and which groups to consider was based on GDG consensus. No economic evidence was found on risk factors.
Other considerations	Fracture rates, particularly fractures associated with osteoporosis, increase with age. The GDG was aware that the recommendations would be used by healthcare professionals without extensive knowledge of fragility fracture risk, and wished to guide practitioners both on who to target and when the use of tool was not necessary. The GDG used the available data on age and fracture incidence, knowledge of the available risk tools and consensus to develop the recommendations. The review indicated that hip fracture rates begin to increase at age 65 in women and age 75 in men. Risk prediction should occur at around the time that intervention will be needed, so the GDG agreed that risk assessment should be considered from age 65 for women without any risk factors and from age 75 for men without any risk factors because fracture rates increase from these ages. The GDG considered whether these ages might appear as relatively high but this recommendation applies to people who do not have any clinical risk factors and is unlikely to miss those at risk as most people at risk will have additional clinical risk factors. The GDG wanted to make a recommendation specific for the younger population (below 50 years of age), because they were aware that, without clinical risk factors, the result of the risk assessment would be low. The GDG also wanted to highlight the importance of carrying out a risk assessment in this younger population if they have a major risk factor, and the risk tools can be used within their specified age range (see recommendation 4 for further details).

The GDG considered that the aim of the recommendations was to trigger assessment and recognised that each factor identified might not be represented in the algorithm or may be expressed in the algorithm in a different way.

Previous fracture: The GDG clarified that both the site of fracture and a history of multiple fractures are important but these are not reported in the IPD review. Previous fragility fracture includes asymptomatic vertebral fractures detected on X-ray or DXA imaging. The GDG considered that height loss of 4 cm or more and/or kyphosis are possible signs of vertebral fracture, and these signs should prompt the healthcare professional to carry out further investigations, such as imaging, to correctly diagnose a vertebral fracture. This should then lead to appropriate risk assessment.

Oral or systemic glucocorticoid use: The GDG considered that there are multiple variations in how glucocorticoids are used (for example, lower doses over longer time periods for polymyalgia or short high doses for exacerbations of asthma). Individuals may also have had one-off treatment courses (for example, for Bell's palsy). The GDG considered that the risk is associated with current and/or frequent past use of oral glucocorticoids and the GDG was aware that there is a dose–effect relationship between steroid use and fracture risk[75]. Clinical judgement is required in assessing patients receiving glucocorticoid doses exceeding for example 7.5 mg per day for prolonged periods.

The GDG considered it was not possible or desirable to develop precise estimates of risk for all scenarios because risk is also influenced by other characteristics of the patient.

Alcohol intake: The trend in the QFracture dataset was for increased fracture risk in people as alcohol intake increased. Because these factors are not intended to be precise indicators of fracture risk but prompts to risk assessment, the GDG decided to use standard hazardous alcohol levels as a trigger to assessment. These levels are more than 21 units per week in men and more than 14 units per week in women and are consistent with the evidence on fracture risk.

Family history of fracture: The GDG noted that for younger people their parents may not yet be old enough to have sustained a hip or osteoporotic fracture, or may have died before they sustained one. Both FRAX and QFracture consider parental history of hip fracture as risk factor. In QFracture, the risk factor is either parental history of hip fracture or parental history of osteoporosis. Parental history of hip fracture is generally more clearly remembered and/or recorded, however, patients who report clear history of family vertebral or other osteoporotic fracture should also have opportunistic risk assessment performed.

BMI: Low BMI is a risk factor for osteoporosis and high BMI has been considered to be protective. The GDG was aware of increasing evidence that fragility fractures occur in women with high BMI, questioning the presumption that these women are not at risk. As a guide, the GDG agreed BMI lower than 18.5kg/m^2 should definitely prompt assessment.

History of falls: The GDG considered that falls and/or a history of falling should prompt the assessment of fracture risk, with falls becoming increasingly important for older, frailer people.

Causes of secondary osteoporosis: Bone metabolism and BMD are affected by other diseases: these effects can include a direct effect on bone, effects on absorption and the effect of treatments (for example, steroids). The GDG did not consider it possible to offer an exhaustive list but suggested that the following list includes the most common causes that need consideration:

- Endocrine: hypogonadism in either sex, including untreated premature menopause and treatment with aromatase inhibitors or androgen

	deprivation therapy; hyperthyroidism; hyperparathyroidism; hyperprolactinaemia; Cushing's disease; diabetes. • Gastrointestinal: coeliac disease; inflammatory bowel disease; chronic liver disease; chronic pancreatitis; other causes of malabsorption. • Rheumatological: rheumatoid arthritis; other inflammatory arthropathies. • Haematological: multiple myeloma; haemoglobinopathies; systemic mastocytosis. • Respiratory: cystic fibrosis[13,72]; chronic obstructive pulmonary disease. • Metabolic: homocystinuria. • Chronic renal disease. • Immobility (due for example to neurological injury or disease).

3.8 Research recommendation

1. 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: Fracture risk is currently assessed 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 needed 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.

4 Risk assessment tools (FRAX, QFracture, BMD)

4.1 Clinical introduction

The risk assessment tools considered in this review are FRAX (with or without BMD), QFracture and BMD (measured by DXA). There are other tools available to assess the risk of fragility fracture, however, during the scoping phase of this short guideline, the stakeholders advised the developers that these three tools are the only validated tools routinely used in the UK. The GDG has therefore agreed to consider the evidence only for FRAX, QFracture and BMD.

FRAX

The FRAX tool was developed in 2008 to calculate the risk of fractures in women and men from several clinical risk factors (CRF), with or without the measurement of femoral neck BMD. The clinical risk factors included in the FRAX algorithm are: age, sex, weight, height, previous fracture, parental hip fracture, current smoking, glucocorticoids, rheumatoid arthritis, secondary osteoporosis and alcohol intake (≥ 3units/day). It is applicable to people aged 40–90 years.

The outputs are a 10-year probability of hip fracture and the 10-year probability of a major osteoporotic fracture (clinical spine, forearm, hip or humerus fracture).

FRAX was developed using baseline and follow up data from nine prospective population-based cohorts (including Europe, Australia, Canada and Japan) and validated in 11 prospective population-based cohorts (> 1 million patient years). A UK version of FRAX calibrated to fracture epidemiology in the UK is available. The FRAX tool can be used either with or without BMD results. For clarity, in this guideline we have used the terms 'FRAX with BMD' and 'FRAX without BMD'.

QFracture

QFracture was developed in 2009, and has been internally and externally validated based on large primary care populations in the UK (QResearch and THIN clinical databases). The algorithm is based on variables that are readily available in electronic healthcare records. It estimates an individual's 10-year risk of developing both hip and major osteoporotic fractures (including hip, spine and wrist), without BMD measurement. It is applicable to people aged 30–85 years.

The clinical risk factors included in the QFracture algorithm in men and women are: age, sex, BMI, smoking, alcohol intake, glucocorticoids, asthma, cardiovascular disease, history of falls, chronic liver disease, rheumatoid arthritis, type 2 diabetes and tricyclic antidepressants. Additional factors used in women only are: hormone replacement therapy, parental history of hip fracture, menopausal symptoms, gastrointestinal malabsorption and other endocrine disorders.

Table 19 explains which risk factors are included in the two risk assessment algorithms:

Table 19: Risk factors included in FRAX and QFracture algorithms (as of April 2012)

	QFracture	FRAX
Age	30-84y	40-90y
Sex	Yes	Yes
BMI	Yes	Yes
Weight	Yes	Yes
Height	Yes	Yes
Previous fracture	No	Yes
Parental history of hip fracture	Yes	Yes

	QFracture	FRAX
Smoking	Yes	Yes
Alcohol	Yes	Yes
Hormone replacement therapy	Yes	No
Menopausal symptoms	Yes	No
Endocrine disorders	Yes	No
Glucocorticoid use	Yes	Yes
Secondary osteoporosis (e.g. type I diabetes, chronic hyperthyroidism, premature menopause, chronic liver disease, chronic malnutrition, chronic liver disease)	No	Yes
Asthma	Yes	No
Cardiovascular disease	Yes	No
History of falls	Yes	No
GI Malabsorption	Yes	No
Chronic liver disease	Yes	No
Rheumatoid arthritis	Yes	Yes
Type 2 diabetes	Yes	No
Tricyclic anti-depressants	Yes	No
Bone mineral density (femoral neck T-score/ absolute value)	No	Yes (Optional)

BMD

BMD is the major criterion used for the diagnosis and monitoring of osteoporosis. BMD gives a quantitative assessment of bone mass per unit area, expressed in g/cm^2. Many techniques are available to measure BMD, but the most widely used are based on X-ray absorptiometry in bone, particularly dual-energy X-ray absorptiometry (DXA). DXA may be used to assess bone mineral content at different sites of the skeleton, including those most vulnerable to fracture. The most commonly measured sites are the lumbar spine and the proximal femur. However, the accuracy of lumbar spine measurements may be impaired by scoliosis and vertebral deformity, and so the proximal femur is the preferred site for fragility fracture risk prediction.

The WHO defines osteoporosis as a BMD of 2.5 or more standard deviations below that of a normal young healthy female (a T score of ≤ –2.5 SD) for postmenopausal women and men over 50 years as measured by DXA at the femoral neck. Low BMD is a major risk factor for fragility fracture and other risk factors may act via their effect on BMD. Drugs that target BMD are the most common intervention for people at risk of fragility fracture. The place of BMD measurement in assessment of fragility fracture risk is therefore important.

An estimate of BMD may also be used in the FRAX tool, by either entering the type of DXA scanning equipment used and then the actual femoral neck BMD (in g/cm^2) or, in women, entering the T-score based on the NHANES III female reference data and measured at the femoral neck. The FRAX tool can also be used in patients without a BMD test.

4.1.1 Review question

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)

4.2 Clinical evidence review on discrimination

Discrimination is the ability to distinguish people at high risk from people at low risk. The most common way of measuring discrimination is by plotting the sensitivity versus one minus specificity for all possible thresholds. The result is the receiver operating characteristic (ROC) curve and the area under the curve (AUC) is the model's discriminatory power.

The AUC is a measure of performance across all risk values, and not necessarily those that may be clinically relevant. Sensitivity and specificity at risk threshold specified by the GDG (10%, 20% and 30% for major osteoporotic fractures, 3% and 5% for hip fracture) were requested from authors of papers.

Below we have presented a summary of the characteristics of included studies and a summary of quality assessment of studies, followed by results of AUC and sensitivities and specificities where available.

The studies were quality assessed by a modified version of QUADAS II. See appendix C, section C.2.1.2, for full details of the QUADAS II methodology used. See appendix D for detailed tables of characteristics of included studies and QUADAS II.

Table 20: FRAX – summary of included studies

Author, year (cohort)	Study design	Country	Sex	Mean age	Population (N)	Hip fractures (n)	Major osteoporotic fractures (n)
Bolland 2010[4] (from	Prospective	New	F	74	1422	57	229

Author, year (cohort)	Study design	Country	Sex	Mean age	Population (N)	Hip fractures (n)	Major osteoporotic fractures (n)
RCT: calcium supplement vs placebo)	cohort	Zealand					
Fraser 2011[21] (CaMos [FRAX primary cohort])	Prospective cohort	Canada	F+M	66	6697 F:4778 M:1919	696 F:573 M:123	175 F:129 M:46
Sornay-Rendu 2010A[67] (OFELY)	Prospective cohort	France	F	59	867	N/A	95
Ensrud 2009[20] (SOF [FRAX validation cohort])	Prospective cohort	USA	F	71	6252	389	1037
Hippisley-Cox 2009[28] (subgroup analysis; QFracture validation)	Prospective cohort	UK	F+M separately	F:49 M:46	424336	1738	N/A
Leslie 2010A[45] (Manitoba)	Retrospective cohort	Canada	F+M	67	39,603 F:36,730 M:2873	549 F:506 M:43	2543 F:2380 M:163
Tanaka 2010[70](Miyama + Taiji) [Miyama: FRAX validation cohort]	Prospective cohort	Japan	F	59.5	400	N/A	60
Tremollieres 2010A[71] (MENOS)	Prospective cohort	France	F	54	2651	N/A	145
Donaldson 2009[18] (placebo group of RCT study)	Prospective cohort	USA	F	54	3223	N/A	253
Pluskiewicz 2010[56]	Cross-sectional	Poland	F	69	2012		728
Sandhu 2010[62]	Case-control	Australia	F+M separately	F:71 M:72	F:144 M:56	N/A	F:69 M:31
Sambrook 2011[61]	Prospective cohort	10 countries including UK	F		19,586	67	468

Table 21: FRAX – QUADAS II: Quality assessment of included studies

Author, year	Risk of selection Bias	Risk of index test bias	Risk of reference standard bias	Risk of other bias	Risk of multiple test bias	Overall risk of bias	Applicability
Bolland 2010[4]	Low	Low	Low	High	Low	High	Indirect
Fraser 2011[21]	High	Low	Low	Low	Low	High	Indirect
Sornay-Rendu	Low	Low	Low	High	Low	High	Indirect

Author, year	Risk of selection Bias	Risk of index test bias	Risk of reference standard bias	Risk of other bias	Risk of multiple test bias	Overall risk of bias	Applicability
2010A[67]							
Ensrud 2009[20]	High	Low	Low	Low	Low	High	Indirect
Hippisley-Cox 2009[28] (subgroup analysis; QFracture validation)	Low	Low	Low	Very High	Low	Very high	Direct
Leslie 2010A[45]	High	High	Very high	High	Low	Very high	Indirect
Tanaka 2010[70](Miyama + Taiji)	Low	High	Low	High	Low	High	Indirect
Tremolliers 2010A[71]	High	Low	Low	High	Low	High	Indirect
Donaldson 2009[18]	Very High	High	Low	Low	Low	Very high	Indirect
Pluskiewicz 2010[56]	Very High	Low	Low	High	Low	Very high	Indirect
Sandhu 2010[62]	Very High	Very High	High	High	Low	Very high	Indirect
Sambrook 2011[61]	Low	Low	Low	High	Low	High	Direct

Table 22: QFracture – summary of included studies

Author, Year (cohort)	Study design	Country	Sex	Mean age	Population (N)	Hip fractures (n)	Major osteoporotic fractures (n)
Collins 2011[(a) 10]	Prospective cohort	UK	F+M separately	F:48 M:47	2,244,636 F:1,136,417 M:1,108,219	F: 9165 M: 3023	F: 19,055 M: 6153
Hippisley-Cox 2009[(b) 28]	Prospective cohort	UK	F+M separately	F:49 M:46	1,275,917 F: 642,153 M:633,764	F: 5424 M: 1738	F: 13952 M: 4519

(a) External validation of QFracture
(b)Internal independent validation of QFracture

Table 23: QFracture – QUADAS II: quality assessment of included studies

Author, year	Risk of selection Bias	Risk of index test bias	Risk of reference standard bias	Risk of other bias	Risk of multiple test bias	Overall risk of bias	Applicability
Collins	Low	Low[(a)]	Low	High	N/A	High	Direct

Author, year	Risk of selection Bias	Risk of index test bias	Risk of reference standard bias	Risk of other bias	Risk of multiple test bias	Overall risk of bias	Applicability
2011[10]							
Hippisley-Cox 2009[28]	Low	Low	Low	High	N/A	High	Direct

(a)Risk of index test bias was high for men - there was >50% imputation for one of the risk factors.

Table 24: BMD – summary of included studies

Author, year (cohort)	Study design	Country	Sex	Mean age	Population (N)	Hip fracture (n)	Major osteoporotic fracture (n)	Vertebral fracture (n)
Stewart 2006 (APOSS)[68]	Prospective cohort	UK	F	49	3883	2	325	5
Tremollieres 2010A (MENOS)[71]	Prospective cohort	France	F	54	2651	N/A	145	N/A
Hans 2004 (EPIDOS)[25]	Prospective cohort	France	F	82	5898	227	N/A	N/A
Popp 2009 (SEMOF)[57]	Prospective cohort	Switzerland	F	76	637	N/A	68	N/A
Hollaeder 2009 (BOS)[29]	Prospective cohort	Switzerland	F	70	432	N/A	N/A	24
Leslie 2007D (Manitoba)[43,47]	Prospective cohort	Canada	F	65	16,505	189	765	149
Nguyen 2008 (Dubbo)[53]	Prospective cohort	Australia	M+F	71	1358	N/A	F:426 M:149	N/A
Tanaka 2010 (Miyama/Taiji)[70]	Prospective cohort	Japan	F	60	400	N/A	60	N/A
Bauer 2007 (MrOS)[2]	Prospective cohort	USA	M	76	5581	49	239	N/A
Cummings 1994 (SOF)[11]	Prospective cohort	USA	F	73	7963	83	N/A	N/A
Hillier 2007 (SOF)[27]	Prospective cohort	USA	F	72	4124	275	877	340
Robbins 2007 (WHI)[59]	Prospective cohort	USA	F	63	10750	80	N/A	N/A

Table 25: BMD – QUADAS II: quality assessment of included studies

Author, year	Risk of selection bias	Risk of index test bias	Risk of reference standard bias	Risk of other bias	Risk of multiple test bias	Overall risk of bias	Applicability
Stewart 2006[68]	Low	Low	Low	High	Low	High	Direct
Tremolieres 2010A[71]	High	Low	Low	High	Low	High	Indirect
Hans 2004[25]	Low	Low	Low	Low	Low	Low	Indirect

Author, year	Risk of selection bias	Risk of index test bias	Risk of reference standard bias	Risk of other bias	Risk of multiple test bias	Overall risk of bias	Applicability
Popp 2009[57]	Low	Low	Low	High	N/A	High	Indirect
Hollaeder 2009[29]	Low	Low	Low	Very High	N/A	Very high	Indirect
Leslie 2007D[47]	High	Low	Low	High	N/A	High	Indirect
Nguyen 2008[53]	Low	Low	Low	Low	N/A	Low	Indirect
Tanaka 2010[70]	Low	High	Low	High	Low	High	Indirect
Bauer 2007[2]	Low	Low	Low	High	Low	High	Indirect
Cummings 1994[11]	Low	Low	Low	High	N/A	High	Indirect
Hillier 2007[27]	Low	Low	Low	Low	N/A	Low	Indirect
Robbins 2007[59]	Low	Low	Low	High	High	High	Indirect

Table 26: FRAX – clinical summary of findings: AUC ranges [95% CI] (see appendix D for forest plots)

Outcome	FRAX with BMD	FRAX without BMD
Hip fracture, F	70–75 [64–77]%[4,12,20,56]	65–85%[4,20,28,61]
Hip fracture, M	-	82%[28]
Hip fracture, F+M	80–83 [77–85]%[21,45]	77–79 [73–81]%[21,45]
Major osteoporotic fracture, F	64–83 [60–85]%[4,12,20,56,62,67,70]	61–75 [56–79]%[4,20,61,67,71]
Major osteoporotic fracture, M	57 [41–73]%[62]	-
Major osteoporotic fracture, F+M	69 [67–71]%[21,45]	66%[21,45]

Table 27: QFracture– clinical summary of findings: AUC ranges [95% CI] (see appendix D for forest plots)

Outcome	QFracture
Hip fracture, F	89% [no 95% CI reported] [10,28]
Hip fracture, M	85–86% [no 95% CI reported] [10,28]
Major osteoporotic fracture, F	79–82% [no 95% CI reported] [10,28]
Major osteoporotic fracture, M	69–74% [no 95% CI reported] [10,28]

Table 28: BMD – clinical summary of findings: AUC ranges [95% CI] (see appendix D for forest plots)

Outcome	BMD
Hip fracture, M	85% [no 95% CI reported][2]
Hip fracture, F	64–82 [61–85]%[11,25,27,43,59]
Major osteoporotic fracture, M	66–68 [61-71]%[2,53]
Major osteoporotic fracture, F	63–71 [56-73]%[27,43,53,57,68,70,71]
Vertebral fracture, F	66–70[54-78]%[27,29,43]

4.2.1 Discrimination of the tools in adults receiving osteoporosis therapy

One study[48] reported discrimination data for FRAX (with and without BMD) and BMD alone in the sub-population of women receiving osteoporosis therapy. Patients in this study were classified into four groups, depending on their medication use as follows:

- Untreated: no use in the year before or after BMD testing, and less than 6 months lifetime use for earlier years;
- High adherence current user: MPR (medication possession ratio)≥0.80 in the year after BMD testing;
- Low adherence current user: MPR<0.80 in the year after BMD testing;
- Past user: any use in the year prior to BMD testing or at least 6 months lifetime use for earlier years, with no use in the year after BMD testing.

See appendix D for full details of characteristics of included studies and QUADAS II quality assessment.

Table 29: Summary of included studies

Author, year (cohort)	Study design	Country	Sex	Mean age	Population (N)	Hip fractures (n)	Major osteoporotic fractures (n)
Leslie 2012[48]	Retrospective cohort	Canada	F	65	35,764	474	2276

Table 30: QUADAS II – Quality assessment of included studies

Author, year	Risk of selection bias	Risk of index test bias	Risk of reference standard bias	Risk of other bias	Risk of multiple test bias	Overall risk of bias	Applicability
Leslie 2012[48]	High	High	Low	Low	Low	High	Indirect

Table 31: Clinical summary of findings: AUC ranges [95% CI] (see appendix D for forest plots)

	Untreated	High adherence current treatment	Low adherence current treatment	Past treatment
FRAX without BMD, Major osteoporotic fracture	0.63 [0.61-0.65]	0.67 [0.65-0.69]	0.69 [0.67-0.71]	0.67 [0.62-0.72]
FRAX with BMD, Major osteoporotic fracture	0.66 [0.64-0.68]	0.64 [0.62-0.66]	0.71 [0.70-0.73]	0.69 [0.64-0.74]
BMD alone, Major osteoporotic fracture	0.65 [0.62-0.67]	0.65 [0.63-0.67]	0.69 [0.67-0.71]	0.66 [0.61-0.71]
FRAX without BMD, Hip fracture	0.78 [0.74-0.82]	0.76 [0.72-0.79]	0.83 [0.80-0.86]	0.83 [0.80-0.86]
FRAX with BMD, Hip fracture	0.82 [0.79-0.85]	0.80 [0.77-0.83]	0.85 [0.83-0.88]	0.85 [0.83-0.88]
BMD alone, Hip fracture	0.78 [0.74-0.83]	0.77 [0.73-0.80]	0.82 [0.79-0.85]	0.79 [0.70-0.88]

4.2.2 Sensitivities and specificities at pre-specified thresholds

Data were received for the following studies: Bolland 2011[4], Ensrud 2009[19], Fraser 2011[21], Hippisley-Cox 2009[28], Leslie 2010A[45], and the results are shown in the tables below (see appendix D for the forest plots).

Table 32: Clinical summary of findings for hip fractures: sensitivity and specificity ranges [95% CI]

Outcome	Sensitivity	Specificity
FRAX with BMD (3% threshold)[4,21,46]	46–77 [39–81]%	72–80 [69–81]%
FRAX without BMD (3% threshold)[4,21,28,46]	59–79 [51–82]%	39–-86 [36–86]%
QFracture (3% threshold)[28]	55 [54–56]%	88 [88–88]%
FRAX with BMD (5% threshold)[4,20,21,45]	29–76 [23–80]%	63–89 [61–90]%
FRAX without BMD (5% threshold)[4,20,21,28,45]	39–78 [31–82]%	50–92 [49–92]%
QFracture (5% threshold)[28]	39 [38–40]%	93 [93–93]%

Table 33: Clinical summary of findings for major osteoporotic fractures: sensitivity and specificity ranges [95% CI]

Outcome	Sensitivity	Specificity
FRAX with BMD (10% threshold) [4,20,21,45]	42–97 [35–98]%	15–76 [14–78]%
FRAX without BMD (10% threshold) [4,20,21,45]	50–100 [46–100]%	0–72 [0–73]%
QFracture (10% threshold)[28]	22 [22–23]%	94 [94–95]%
FRAX with BMD (20% threshold) [4,20,21,45]	9–28 [6–30]%	81–96 [80–97]%
FRAX without BMD (20% threshold) [4,20,21,45]	16–29 [13–31]%	81–93 [80–94]%
QFracture (20% threshold)[28]	2 [2–2]%	100 [100–100]%
FRAX with BMD (30% threshold) [4,20,21,45]	0–18 [0–21]%	94–99 [93–99]%
FRAX without BMD (30% threshold) [4,20,21,45]	4–10 [3–11]%	96-99 [95–99]%
QFracture (30% threshold)[28]	0 [0–0]%	100 [100–100]%

4.3 Clinical evidence review on calibration

Calibration refers to how well the predicted risk corresponds to the observed risk in a population. It does not provide information as to whether the correct people are predicted to be at high risk.

Calibration results for FRAX and QFracture tools are reported below, by study.

4.3.1 Leslie 2010A[45]: calibration of the Canadian FRAX tool

The two tables below (Table 34 and Table 35) report the predicted risk for hip and osteoporotic fracture, for the population divided by gender.

To evaluate calibration of the FRAX tool, patients were stratified by fifth of predicted risk. A graphical representation is given in Figure 9 below, for hip and osteoporotic fracture, divided for men and women.

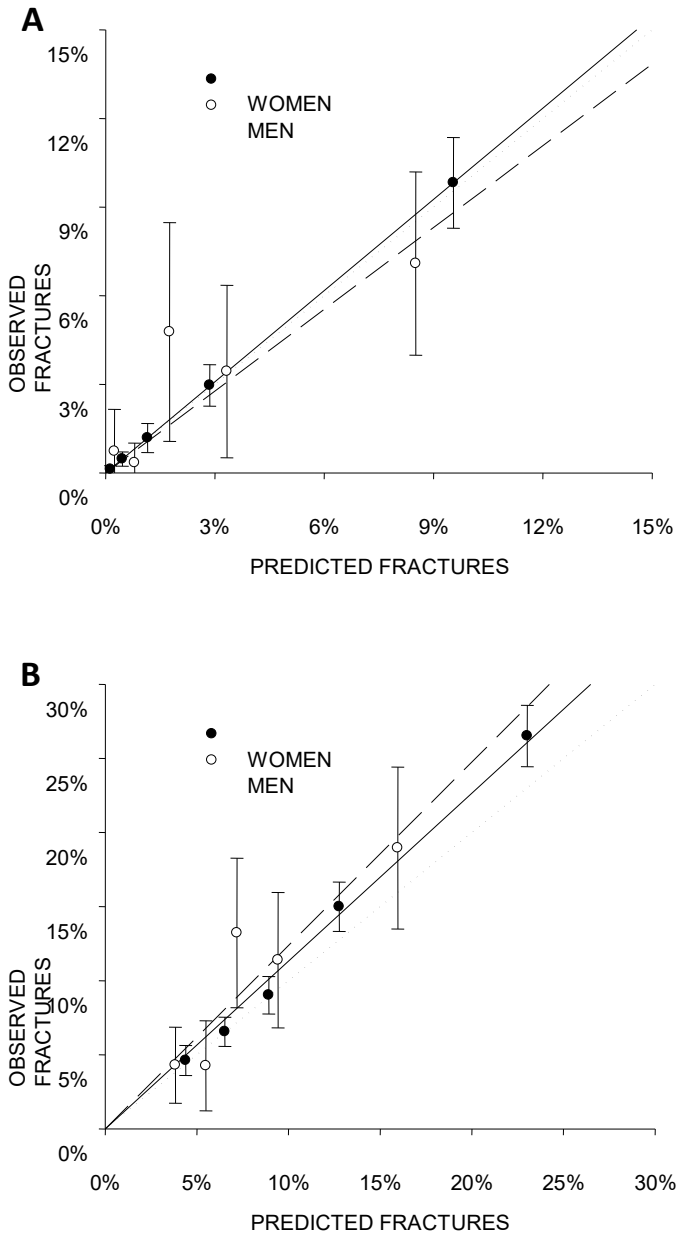
Table 34: Predicted risk for hip fracture

Hip fractures	Women	Men
10-year Kaplan-Meier estimate (%) [95% CI]	2.7 [2.1–3.4]	3.5 [0.8–6.2]
Mean predicted risk (%)	2.8 (FRAX with BMD)	2.9 (FRAX with BMD)

Table 35: Predicted risk for major osteoporotic fracture

Major osteoporotic fractures	Women	Men
10-year Kaplan-Meier estimate (%) [95% CI]	12.1 [10.8–13.4]	10.7 [6.6–17.9]
Mean predicted risk (%)	11.3 (FRAX with BMD)	8.4 (FRAX with BMD)

Figure 9: Predicted 10-year fracture risk from Canadian FRAX tool with BMD (x axis) versus observed Kaplan-Meier 10-year fracture rates (y axis) by fifth of predicted risk for women (solid line) and men (dashed line). The dotted line depicts the line of identity (perfect agreement). (A) Hip fractures. (B) Osteoporotic fractures. 95% error bars are shown. (Reproduced from Leslie 2010 A[45], with permission of the corresponding author and copyright © of the American Society for Bone and Mineral Research)



The regression slopes for hip fracture are:

- Women: 1.03 [1.02–1.04]
- Men: 0.92 [0.57–1.27]

For women, there is reasonable agreement between observed and predicted risk of hip fracture, with a slight underestimation of predicted 10-year hip fracture risk. For men, the agreement between observed and predicted risk of hip fracture is reasonable but with some noticeable differences in the last three fifths of predicted risk.

The regression slopes for major osteoporotic fracture are:

- Women: 1.13 [1.08–1.19]
- Men: 1.24 [1.00–1.48]

For women, there is an under-prediction for the two highest fifths of predicted 10-year fracture risk. For men, there is an underestimation of predicted 10-year fracture risk in the last three fifths of predicted 10-year fracture risks.

4.3.2 Leslie 2012[48]: calibration of the Canadian FRAX in women receiving osteoporosis treatment

In Leslie 2012[48], a stepwise gradient in observed 10-year major osteoporotic and hip fracture incidence was plotted as a function of the predicted probability tertile in untreated women (reference subgroup) and each treated subgroup. The authors found that in the untreated group there was good agreement between the predicted and observed 10-year fracture incidence, with the 95% CI containing the line of identity, for both FRAX with and without BMD. Regression slopes were not reported for any of the subgroups, however, none of the 95% CI for the treated subgroups fell below the line of identity (Figure 10 and Figure 11).

Treatment effects were also assessed in 3047 women with high adherence to at least 5 years of bisphosphonate use (MPR≥0.80). The only subgroup where incidence fractures were significantly less than predicted was for hip fractures in the highest risk tertile (observed/predicted ration 0.61, 95% CI 0.40-0.83, p-value<0.001), thought there were good concordance between observed and predicted major osteoporotic fractures (observed/predicted ration 0.92, 95% CI 0.78-1.06, p-value=0.280).

Figure 10: Predicted 10-year major osteoporotic fracture probability from FRAX versus observed fracture incidence estimated to 10-years, according to risk tertile. Results are stratified by osteoporosis treatment status with the reference group being untreated women (heavy solid line with 95% CI shaded area). 95% CI bars are shown for the treated subgroups. The dotted line indicates the line of identity (perfect concordance between observed and predicted fracture incidence). (Reproduced from Leslie 2012[48], with permission of the author and copyright © of the American Society for Bone and Mineral Research)

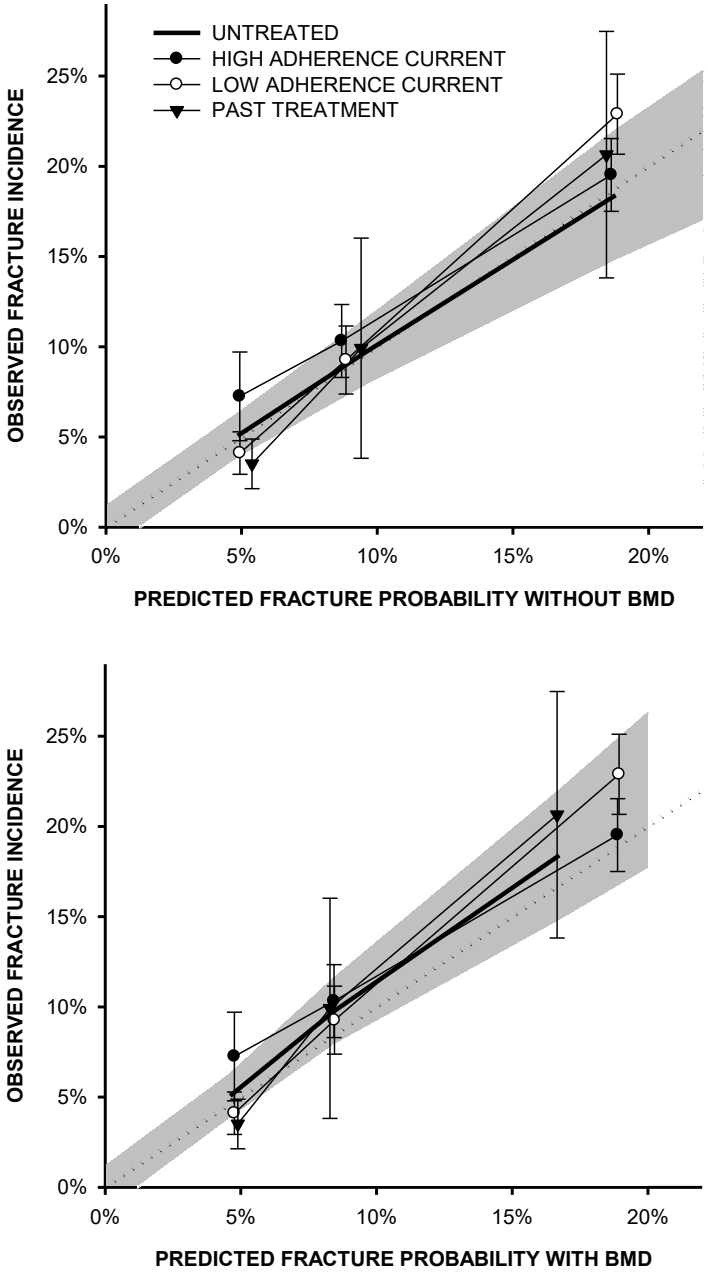
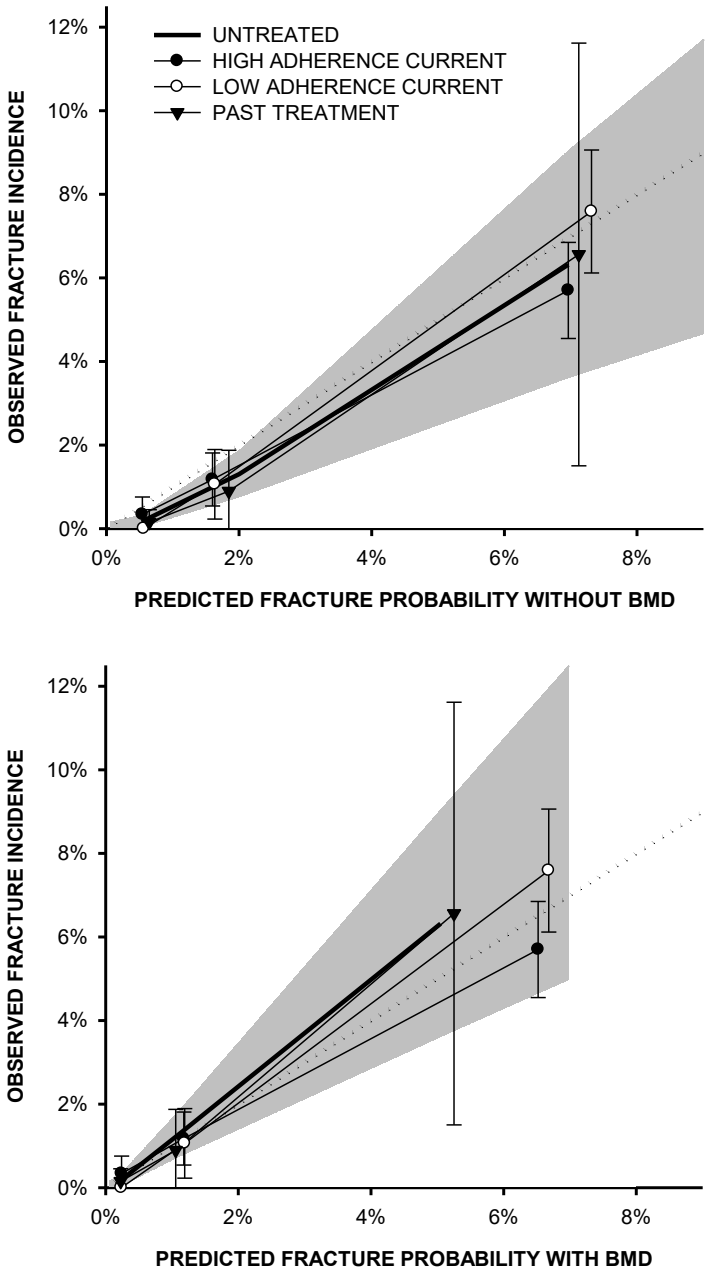


Figure 11: Predicted 10-year hip fracture probability from FRAX versus observed fracture incidence estimated to 10-years, according to risk tertile. Results are stratified by osteoporosis treatment status with the reference group being untreated women (heavy solid line with 95% CI shaded area). 95% CI bars are shown for the treated subgroups. The dotted line indicates the line of identity (perfect concordance between observed and predicted fracture incidence). (Reproduced from Leslie 2012[48], with permission of the author and copyright © of the American Society for Bone and Mineral Research)



4.3.3 Fraser 2011[21]: calibration of the Canadian FRAX with BMD tool

In Fraser 2011[21], patients were stratified by fifth of predicted risk and the study compared the mean 10-year fracture probabilities from the Canadian FRAX tool with BMD by quintile subgroups versus the Kaplan-Meier estimates of observed 10-year fracture outcome, divided by men and women. They found that, for major osteoporotic fracture, the predicted probabilities are within the 95% CI for the observed probability in all fifths of predicted risk, except for the middle one for women (in which the observed probability is slightly higher than the predicted) and the second lowest for men (in which the observed probability is slightly lower than the predicted probability). The regression slopes of the 10-year fracture probability predicted by the FRAX tool with BMD (x-axis) vs the Kaplan-Meier estimates of observed 10-year fracture outcome (y-axis) indicate noticeable under-prediction, for both women and men:

- Women: 1.07
- Men: 1.26

For hip fractures, the regression slopes of the 10-year fracture probability predicted by the FRAX tool with BMD (x-axis) vs the Kaplan-Meier estimates of observed 10-year fracture outcome (y-axis) are:

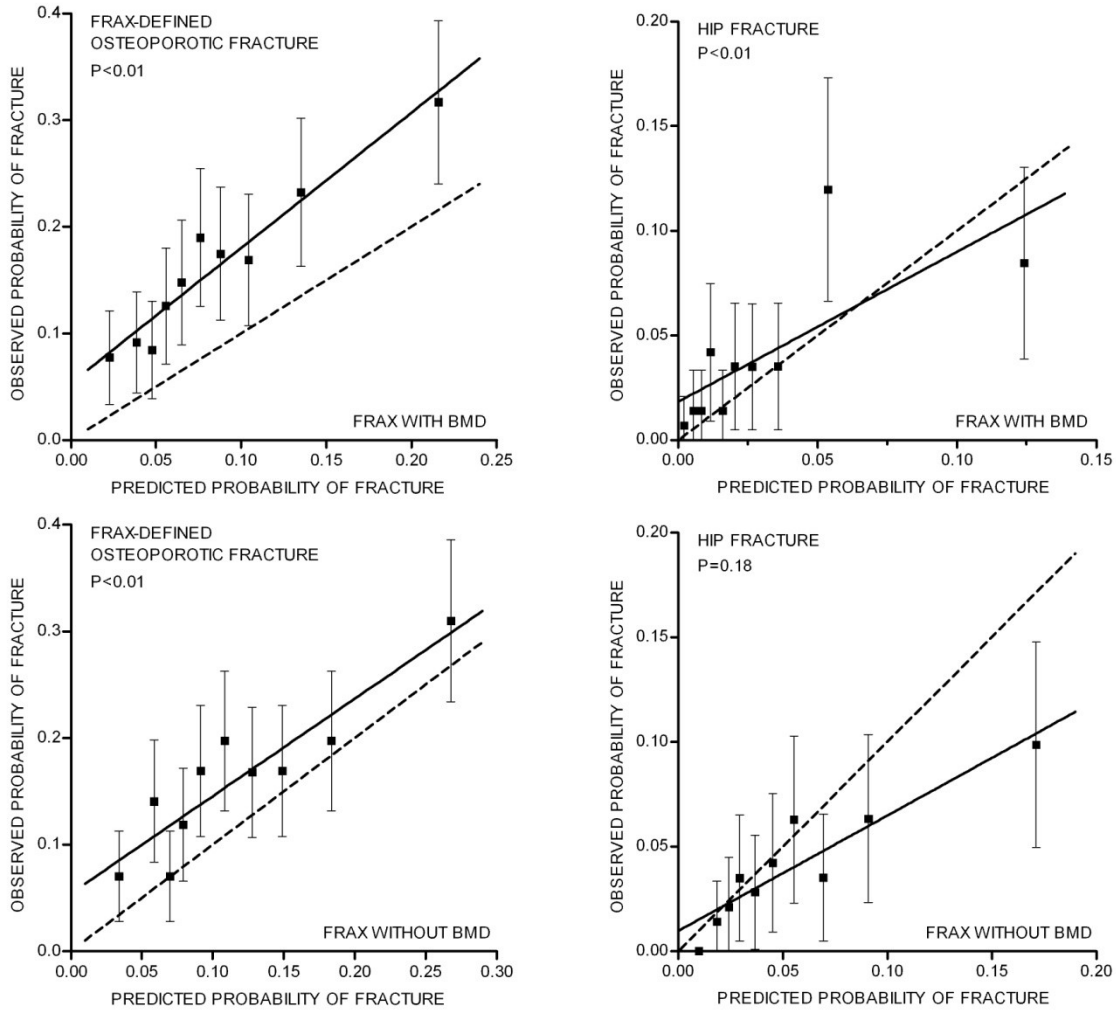
- Women: 0.93
- Men: 1.83

The probability predictions are within the 95% CI for the observed probability in three fifths of predicted risk (probably because of the small number of patients and small numbers of events), while in the highest two fifths of predicted risk for men the model noticeably underestimated the 10-year risk of hip fracture.

4.3.4 Bolland 2011[4]: calibration of the UK FRAX tool in a New Zealand population

In Bolland 2011[4], patients were stratified by risk deciles; results are shown in Figure 12.

Figure 12: Calibration of the calculators. Each panel shows a plot of the observed 10-year probability (expressed as decimals on a scale 0 to 1) of fracture (error bars indicate the 95% CI) versus the mean estimated fracture probability for the cohort divided by decile of estimated probability. The dotted line represents a perfectly calibrated model, and the solid line the line of best fit. The p values indicate the goodness of fit using the Hosmer-Lemeshow test (P< 0.05 indicates a significant difference from the perfectly calibrated model).
(Reproduced from Bolland 2011[4], with permission of the author and copyright © of the American Society for Bone and Mineral Research)



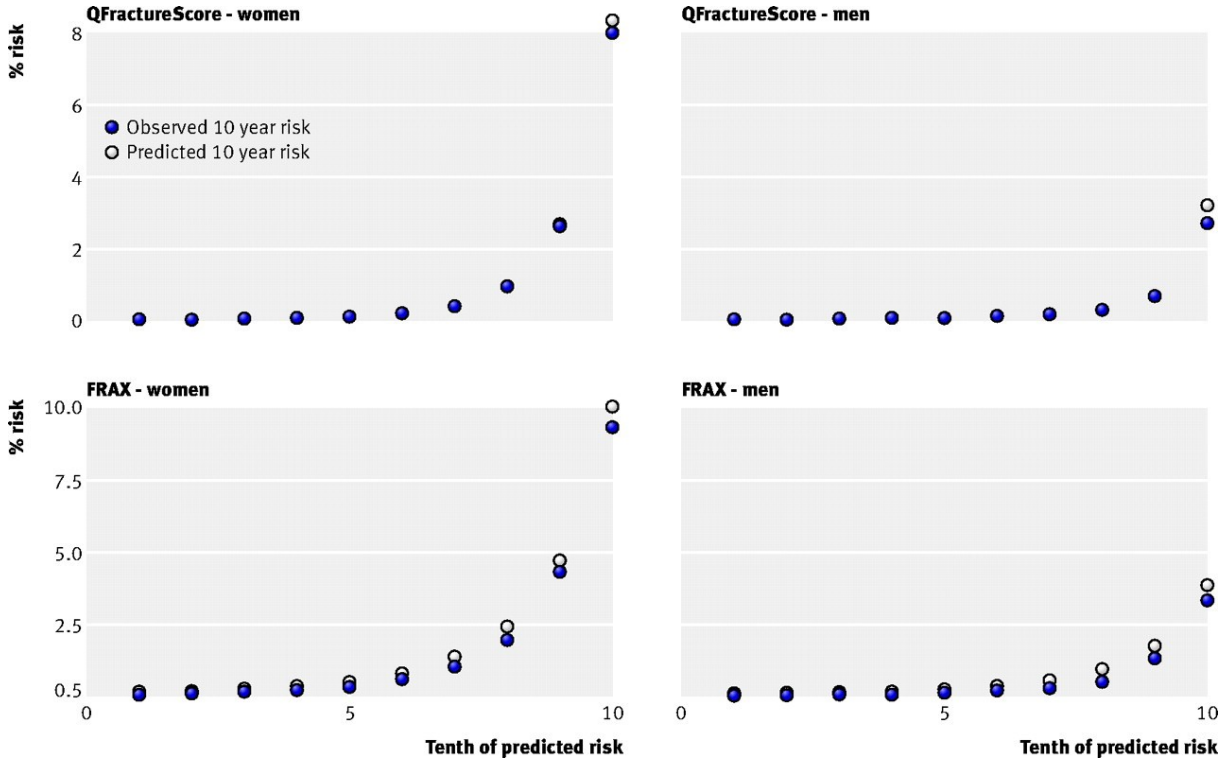
For osteoporotic fractures, FRAX (with and without BMD) is poorly calibrated (P< 0.01). For hip fracture, the number of events is low (n = 57), therefore, although P = 0.18 for FRAX without BMD, there is a limitation in interpreting the analysis of calibration.

4.3.5 Hippisley-Cox 2009 [28]: calibration of QFracture in the internal validation study and comparison with FRAX

The population was stratified into tenths of predicted risk (10 categories). For osteoporotic fractures, it showed good calibration overall (ratio predicted vs observed risk ranged from 0.92 to 1.11). For hip fracture, similar results were found, except for over-prediction in the lowest tenth of risk (ratio predicted vs observed risk 1.86 and 2.32 in men and women), and the top tenth risk in men (ratio predicted vs observed risk 1.19).

The study performed a subgroup analysis to directly compare calibration of FRAX and QFracture in the same population. Results in Figure 13 show that FRAX tended to over-predict the risk of hip fracture within each tenth of predicted risk.

Figure 13: Predicted and observed 10-year risk of hip fracture with QFracture and FRAX (Reproduced from BMJ 2009;339:b4229, open access article, with permission of the author)[28]



4.3.6 Collins 2011[10]: calibration of QFracture in the external validation study

Figure 14: Observed versus predicted 10-year fracture risks for women. (Reproduced from BMJ 2011;342:d3651, open access article, with permission of the author)[10]

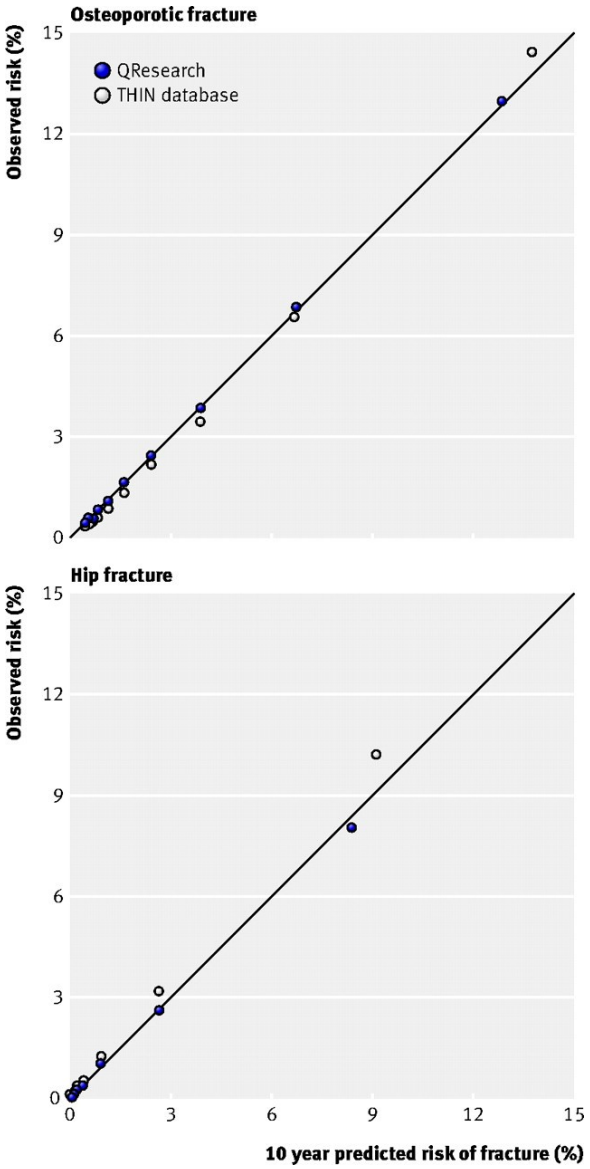
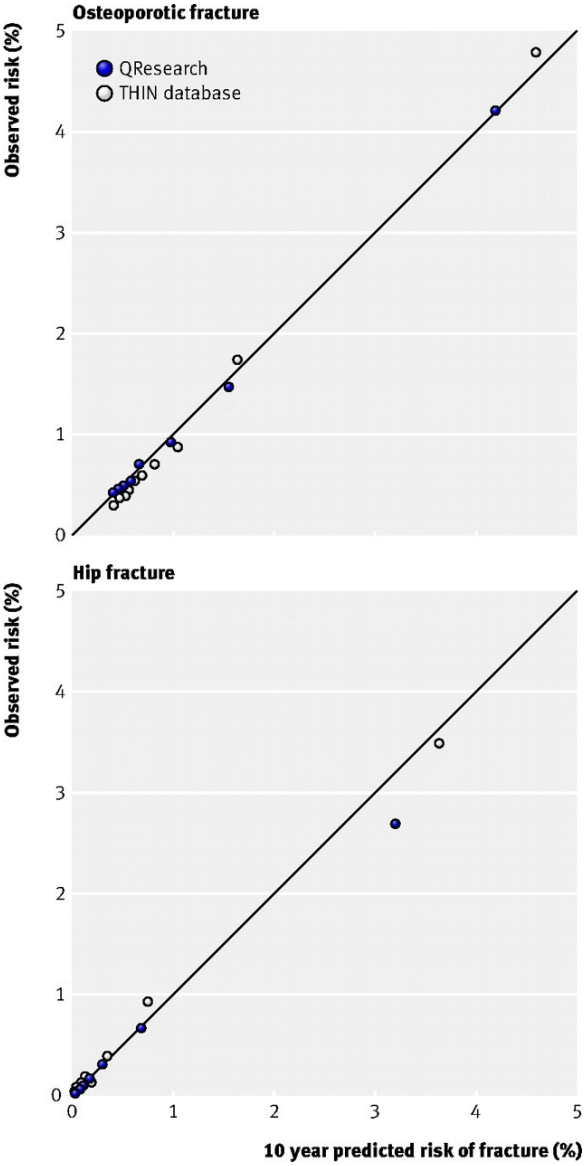


Figure 15: Observed versus predicted 10-year fracture risks for men.
(Reproduced from BMJ 2011;342:d3651, open access article, with permission of the author)[10]



Overall, there is good calibration: there is close agreement between predicted and observed risk of osteoporotic and hip fractures across all deciles of risk; there is no over- or under-prediction. There was also close agreement between predicted and observed fracture risks across all age groups.

No relevant studies were identified for calibration of BMD.

4.4 Clinical evidence review on reclassification

Reclassification is the extent to which a model is superior to another model in terms of correct categorisation of individuals, usually at thresholds that are considered to be important for treatment (for example, using clinical- and cost-effectiveness analysis). The proportion of individuals reclassified largely depends on the threshold selected and the population studied. Reclassification data became available during the development of the guideline showing how people were reclassified between FRAX and QFracture (data prepared by Hippisley-Cox and colleagues, 2011) and with the addition of BMD to FRAX. One other study that examined reclassification when BMD is added to clinical risk factors was available and this is also reported for completeness.

See appendix D for full details of characteristics of included studies and QUADAS II quality assessment.

Table 36: Summary of included studies

Author, year (cohort)	Study design	Comparison	Country	Sex	Min. age	Population (N)	Fractures (n)	Selected threshold
Johansson 2004[33]	Prospective cohort (placebo arm of a RCT)	Clinical risk factors ± BMD	UK	F	75	2,113	282	35%
Leslie 2011[44]	Retrospective cohort	FRAX ± BMD	Canada	F + M	50	39,630 F: 36,730 M:2,873	890	20%

Table 37: QUADAS II – Quality assessment of included studies

Author, year	Risk of selection bias	Risk of index test bias	Risk of reference standard bias	Risk of other bias	Risk of multiple test bias	Overall risk of bias	Applicability
Johansson 2004[33]	Low	High	Low	Low	Low	High	Indirect
Leslie 2011[44]	High	High	Very high	High	Low	Very high	Indirect

The study by Johansson et al.[33] looked at reclassification using clinical risk factors (CRFs) alone versus CRFs with the addition of BMD. An arbitrary intervention threshold of 35% was selected. Of 2113 women, 17% (n = 354) were classified as high risk and 83% (n = 1759) were classified as low risk based on CRFs alone. After a subsequent recalculation based on CRFs plus BMD, 31% (109/354) of those initially classified as high risk would be reclassified as low risk; 12% (210/1759) of those initially classified as low risk would be reclassified as high risk. In addition, misclassifications were most frequent close to the pre-specified threshold of 35%. Results are summarised in Table 38 below.

Table 38: Risk reclassification data for clinical risk factors (CRFs) alone versus CRFs with the addition of BMD – major osteoporotic fracture probability[33]

	Initial calculation CRFs without BMD Number classified (% total)	Subsequent calculation (reclassification) CRFs + BMD		Post-reclassification Number classified (% total)
		Number remained high/low risk	Number reclassified (change from high to low or low to high risk)	
High risk (≥ 35%)	354/2113 (16.8%)	245	109	455*/2113 (21.5%)
Low risk (< 35%)	1759/2113 (83.2%)	1549	210	1658*/2113 (78.5%)

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

The study by Leslie at al.[44] conducted an analysis on reclassification, comparing FRAX alone with FRAX plus BMD. An intervention threshold of major osteoporotic fracture of 20% was chosen (from the National Osteoporosis Foundation [NOF] guideline). A total of 22.2% of the population (total N = 39,603) were reclassified. Most reclassification occurred around moderate risk (10–20%) and almost all reclassifications were to the adjacent risk category. Of 39,603 participants, 29% (N = 11,630) were classified as moderate risk based on FRAX alone, respectively. After subsequent recalculation based on FRAX plus BMD, a total of 10.2% (4027/11630) of those that were initially classified as moderate risk (based on FRAX alone) got reclassified as either low (N = 2957) or high (N = 1070) risk. Results are summarised in Table 39 below.

Table 39: Risk reclassification data for FRAX alone versus FRAX with the addition of BMD – major osteoporotic fracture probability[44]

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	22,599	20,108	2460	31
	Fractures (n)	890	681	206	3
	% fracture probability 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	11,630	2957	7603	1070
	Fractures (n)	909	131	624	154
	% fracture probability 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
	Fractures (n)	744	3	191	550
	% fracture probability 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 Fractures (n) % fracture probability at 10 years % overall reclassified	39,603 2543 12 (0.3) 22.2%	23,137 815 6.7 (0.3) 7.6%	12,246 1021 16.4 (0.7) 11.7%	4220 707 31 (1.4) 2.8%

Hippisley-Cox and colleagues have supplied further information, including an additional analysis of reclassification. They defined high risk a 10-year risk of hip fracture in the top tenth for each risk score. The key finding was that patients who were categorised as low risk on FRAX and high on QFracture had higher 10-year observed risks than those who were high on FRAX and low on QFracture and this is consistent in both men and women.

For women, 88.9% are classified as low risk by both scores and 8.8% are classified as high risk by both scores. 1.2% of women would be classified as high risk on FRAX but low risk on QFracture and 1.1% of women would be classified as low risk on FRAX but high risk on QFracture. Their analysis included the 10-year observed risk; however, it is not possible to draw an accurate conclusion.

Similar findings were found in men. Results are summarised in Table 40 below.

Table 40: Reclassification statistics – QFracture versus FRAX (data prepared by Hippisley-Cox and colleagues, 2011). Reallocation of subjects based on using the top decile of risk for each score (using Kaplan-Meier plots)

	Number of patients	% of total	10-year observed risk
Women			
Low on both tools	404,105	88.9	0.88
Low on FRAX and high on QFracture	5624	1.2	7.69
High on FRAX and low on QFracture	4946	1.1	7.15
High on both tools	39,824	8.8	9.66
Total	454,499		
Men			
Low on both tools	377,954	89.1	0.09
Low on FRAX and high on QFracture	6330	1.5	2.24
High on FRAX and low on QFracture	3950	0.9	1.45
High on both tools	36,102	8.5	3.63
Total	424,336		

4.5 Health economic evidence review

Five studies [3,26,30,51] [32]were found comparing screening strategies; however they were all excluded. Three studies[3,26,30] were excluded because they compared risk assessment strategies irrelevant to the current comparison and compared screening strategies for the diagnosis of osteoporosis. One study [30]was excluded because it incorporated a treatment pathway in the economic model where treatment criteria were not applicable to the UK. The final study [32] was excluded because its did not conduct an incremental analysis and as such was not applicable for our purposes. See exclusion list in appendix E for further details of excluded studies.

An original cost analysis of performing risk assessment tools was performed. Comparators include QFracture, FRAX, BMD and FRAX plus BMD. Costs were calculated for a hypothetical cohort of patients presenting to the GP. Details of methods and results are presented in Appendix E.

Our cost analysis showed that risk assessment tools that do not include BMD measurement are less costly than those that include this measurement. Moreover, the cost difference between risk assessment tools that do not include BMD, namely FRAX and QFracture, is negligible.

In a comparison of risk assessment tools that entail assessment with DXA scan, the FRAX plus BMD strategy is less costly than the 'BMD for all' strategy if fewer than 68% of people are referred for a DXA scan after a FRAX in the 'FRAX plus BMD' strategy. After performing a series of one-way sensitivity analyses on some parameters, results were found to be sensitive to the cost of GP consultation: where the GP consultation cost is smaller than the base case estimate, the FRAX plus BMD strategy is less costly than the BMD-for-all strategy, even at higher patient referral rates for BMD in the FRAX plus BMD strategy.

4.6 Evidence statements

4.6.1 Clinical evidence statements

23 studies (total N ranged from 200 to 2,244,636) reported considerable uncertainty as to whether there was any difference in discrimination amongst FRAX, QFracture and BMD (low to very high risk of bias).

12 studies (total N ranged from 200 to 424,336) reported an AUC between 57% and 85% for FRAX; 2 studies (total N ranged from 1,275,917 to 2,244,636) reported an AUC between 69% and 89% for QFracture; 12 studies (total N ranged from 400 to 16,505) reported an AUC between 63% and 82% for BMD (low to very high risk of bias).

Four studies (total N ranged from 1422 to 39,603) reported (high risk of bias):

- sensitivity between 46% and 77% and specificity between 72% and 80% for FRAX with BMD (3% threshold for hip fracture)
- sensitivity between 29% and 76% and specificity between 63% and 89% for FRAX with BMD (5% threshold for hip fracture)
- sensitivity between 42% and 97% and specificity between 15% and 76% for FRAX with BMD (10% threshold for major osteoporotic fracture)
- sensitivity between 50% and 100% and specificity between 0% and 72% for FRAX without BMD (10% threshold for major osteoporotic fracture)
- sensitivity between 9% and 28% and specificity between 81% and 96% for FRAX with BMD (20% threshold for major osteoporotic fracture)
- sensitivity between 16% and 29% and specificity between 81% and 93% for FRAX without BMD (20% threshold for major osteoporotic fracture)
- sensitivity between 0% and 18% and specificity between 94% and 99% for FRAX with BMD (30% threshold for major osteoporotic fracture)
- sensitivity between 4% and 10% and specificity between 96% and 99% for FRAX without BMD (30% threshold for major osteoporotic fracture).

Five studies (total N ranged from 1422 to 424,336) reported (high risk of bias):

- sensitivity between 59% and 79% and specificity between 39% and 86% for FRAX without BMD (3% threshold for hip fracture)
- sensitivity between 39% and 78% and specificity between 50% and 92% for FRAX without BMD (5% threshold for hip fracture).

A subgroup analysis of one study (total N 424,336) reported (high risk of bias):

- sensitivity of 55% and specificity of 88% for QFracture (3% threshold for hip fracture)

- sensitivity of 39% and specificity of 93% for QFracture (5% threshold for hip fracture)
- sensitivity of 22% and specificity of 94% for QFracture (10% threshold for major osteoporotic fracture)
- sensitivity of 2% and specificity of 100% for QFracture (20% threshold for major osteoporotic fracture)
- sensitivity of 0% and specificity of 100% for QFracture (30% threshold for major osteoporotic fracture).

Three studies for FRAX (total N ranged from 1422 to 39,603) and two for QFracture (total N ranged from 1,275,917 to 2,244,636) suggested that the two tools are overall well calibrated (high risk of bias).

4.6.2 Economic evidence statements

- The cost difference between FRAX and QFracture risk stratification tools is negligible.
- If fewer than 68% of individuals in the FRAX+BMD strategy are referred for a DXA scan, then this strategy is less costly than performing BMD for all.

4.7 Recommendations and link to evidence

Recommendation	**3. Estimate absolute risk when assessing risk of fracture (for example, the predicted risk of major osteoporotic or hip fracture over 10 years, expressed as a percentage).**
Relative values of different outcomes	The clinical outcomes that the GDG wished to predict were hip fractures and all osteoporotic fractures. Although hip fractures are particularly associated with significant morbidity and mortality, other osteoporotic fractures, particularly vertebral fractures, are a cause of significant morbidity.
Trade-off between clinical benefits and harms	The GDG agreed that the output of the risk assessment should be an absolute risk. The GDG considered that the presence of one risk factor (for example, current use of glucocorticoid) is not sufficient to establish whether a patient is at high risk of fragility fracture; a formal assessment tool should be used to make the transition from RR, based on one risk factor, to absolute risk. The GDG considered that individuals are more likely to be given unnecessary treatment if treatment is based on one known risk factor. Similarly, people who might benefit from interventions might be assumed to be at low risk if an assessment that includes multiple risk factors is not carried out. The GDG considered the distinction between the 10-year fracture probability as output from risk assessment tools and the actual incidence of fractures of an individual over 10 years. Therefore, clinical judgement is needed when interpreting individual risks to patients.
Economic considerations	There were no published economic evaluations on the use of risk factor tools. The GDG considered that providing treatment based on RR of one known risk factor may increase costs unnecessarily and may not provide any additional health benefit to the patient. The GDG also considered that even if a patient has a substantial number of risk factors, their absolute risk may still be low and as such the patient would be unlikely to benefit from treatment.
Quality of evidence	The recommendation is based on review of risk tools and GDG expert opinion and consensus.
Other considerations	The GDG recognised that individual healthcare professionals conducting an assessment might have the expertise to recognise that the risk factors present are enough to classify the patient as high risk (for example, older people with previous fracture). However, given that the outcome of assessment might be long-term pharmacological treatment, the GDG considered that the

	assessment of absolute risk was preferred and is particularly important for a non-expert in the assessment of fragility fracture risk. Validated assessment tools (FRAX, QFracture) are web-based and freely available for people to use (a person can either carry out self-assessment or a healthcare professional can complete it for them). In cases when internet access and/or a computer are not available (for example, a GP on a home visit in a rural area), a simplified paper version of FRAX is also available, as well as iPhone and iPad applications for both tools. There is no conclusive evidence that providing treatment on the basis of risk assessment will result in better clinical and cost effective care but the GDG is aware of an ongoing trial in which the efficacy of treatment in individuals identified by FRAX as being at high risk of fracture is being investigated (SCOOP study [see www.scoopstudy.ac.uk]). The GDG considered it important to differentiate between risk and intervention thresholds. Absolute risk provides a numerical risk estimation in a given time period. The description of this risk (as, for example, low or high) is potentially influenced by a number of factors such as individual patient characteristics and type of risk being predicted. An intervention threshold will be influenced by the absolute risk, the effect of the intervention on that risk, adverse events and costs – these can be summarised as the cost effectiveness of the intervention. Different interventions can therefore have different intervention thresholds. Different drug therapy intervention thresholds have been proposed, comprising fixed thresholds (for example, 20% 10-year fracture risk of major fracture, 3% 10-year fracture risk of hip fracture as used in the USA), and thresholds that increase with age (as proposed by National Osteoporosis Guideline Group (NOGG) and currently linked to the UK version of the FRAX website). The GDG had some concerns that they were unable to recommend thresholds for treatment as this guideline did not include clinical and cost effectiveness of treatments. The GDG recognised that until NICE develops further guidance on treatment, the default position for many healthcare practitioners would be to follow guidance set by other organisations or that decisions about which threshold to use will be taken at a local level, in light of characteristics of the high-risk population identified.

Recommendation	**4. Use either FRAX[h] (without a bone mineral density [BMD] value, if a dual-energy X-ray absorptiometry [DXA] scan has not previously been undertaken) or QFracture[i], within their allowed age ranges, to estimate 10-year predicted absolute fracture risk when assessing risk of fracture. Above the upper age limits defined by the tools, consider people to be at high risk.**
Relative values of different outcomes	The clinical outcomes that the GDG wished to predict were hip fractures and all osteoporotic fractures. Although hip fractures are particularly associated with significant morbidity and mortality, other osteoporotic fractures, particularly vertebral fractures, are a cause of significant morbidity. The GDG was interested in both calibration and discrimination of risk assessment tools. The available tools have been shown to predict hip, spine, humerus and wrist (FRAX) or hip, wrist and spine (Q-fracture), but not other fractures.

h FRAX, the WHO fracture risk assessment tool, is available from www.shef.ac.uk/FRAX. It can be used for people aged between 40 and 90 years, either with or without BMD values, as specified.

i QFracture is available from www.qfracture.org. It can be used for people aged between 30 and 84 years (as of May 2012). BMD values cannot be incorporated into the risk algorithm.

Trade-off between clinical benefits and harms	One purpose of risk assessment is to decide on suitability for treatment. Over-prediction will result in unnecessary treatment and anxiety, whereas under-prediction means a person would not be offered potentially preventative treatment. The GDG agreed that as a general rule an assessment tool is better than clinical judgement alone. They acknowledge that practitioners experienced in assessment of fragility risk may find an assessment tool unnecessary but that for the generalist an assessment tool is the preferred way of assessing risk. The evidence indicated that all the tools considered are better than chance at predicting risk and use of an appropriate assessment tool is unlikely to cause harm to a patient.
Economic considerations	The original cost analysis developed for this guideline showed that FRAX (without BMD) and QFracture risk assessment tools had similar costs and are less costly than risk assessment tools that include BMD measurement. The clinical review indicated that both FRAX and QFracture are better than chance at predicting risk of fracture.
Quality of evidence	All the studies included in the review were classified as being at high or very high risk of bias. The GDG was interested in validation studies of risk assessment tools in the UK. The studies on QFracture were conducted in the UK, while for FRAX only limited evidence for the UK population is available, therefore their applicability is indirect. Two validation studies (one internal and one external validation) were available for QFracture. The authors of QFracture have published a comparison of FRAX with QFracture with their internal validation of QFracture. There are no other validation studies available in the UK for FRAX. The most common outcome reported was AUC. The evidence available to judge between FRAX and QFracture was limited. Based on the AUC alone, the tools appear to be poor to moderately predictive; however, the GDG recognised that discrimination data based on the AUC alone are not an adequate way of establishing whether one tool performs better than another due to a number of reasons, for example, the AUC is based on the ranks of the predicted probabilities and compares these ranks in people with and without the disease; but the ROC curve does not use the actual predicted probabilities Therefore it is not very sensitive to differences in probabilities between risk scores. In addition, studies included in the review contained individuals of different age ranges which may affect the AUC. Calibration data on FRAX is limited to analysis by Hippisley-Cox and colleagues. In the direct comparison between FRAX and QFracture using the same population the results are similar. QFracture shows better performance data on all measures reported but this is the database in which QFracture was developed and the difference in risk is small in absolute terms. The authors of QFracture provided information on reclassification between QFracture and FRAX and although these data favour QFracture the magnitude of the difference is small. The economic evidence was based on an original cost analysis with potentially serious limitations and partial applicability.
Other considerations	The only tools reviewed for the guideline were FRAX and QFracture. These were the tools identified during the scoping phase as appropriate for consideration as they are either already used in the UK and/or they are the tools where evidence of their validity in a UK population might be available. The GDG considered that the information available to assess tools was suboptimal. The method of development and coefficients used in the FRAX equation are not publicly available, how FRAX treats risk factors and interactions between risk factors (for example, causes of secondary osteoporosis and BMD) are not known. The majority of studies provided AUC data only. The GDG made a research recommendation outlining the evidence they would

	like to see in the assessment of risk prediction tools. QFracture is developed and validated in GP databases but this is the setting where most risk assessment will take place. The GDG recognised that FRAX is known to the health community and that the ability to incorporate BMD can be seen as an advantage. However given the lack of evidence for added value of BMD, the GDG did not consider this facility made FRAX the tool of choice. Both tools are available as stand-alone web-based tools that people can use independently of healthcare professionals. There is no strong evidence to suggest that one tool performs better than the other in people with a specific risk factor; for example, even if QFracture contains data for history of falls, there is no evidence it actually works better than FRAX in predicting risk of fracture in people who fall.

Recommendation	**5. Interpret the estimated absolute risk of fracture in people aged over 80 years with caution, because predicted 10-year fracture risk may underestimate their short-term fracture risk.**
Relative values of different outcomes	The clinical outcomes that the GDG wished to predict were hip fractures and all osteoporotic fractures. Although hip fractures are particularly associated with significant morbidity and mortality, other osteoporotic fractures, particularly vertebral fractures, are a cause of significant morbidity
Trade-off between clinical benefits and harms	Risk assessment tools provide absolute risk over 10 years. In older age groups, death is a competing risk, which means that in the 10-year timeframe, people are more likely to die from any cause than to experience a fragility fracture. People at risk may however benefit from interventions to prevent fracture because their absolute fracture risk over shorter time periods will be high.
Economic considerations	Given the lack of clinical evidence for this age group, assessing the cost-effectiveness of different strategies was not feasible. The GDG thought it best to leave decision making to the clinician on a case-by-case basis.
Quality of evidence	This recommendation is based on knowledge of risk assessment tools.
Other considerations	QFracture includes people up to 85 years and FRAX can include people up to 90 years. The available risk tools generate absolute risk over 10 years but the GDG considered that a shorter time period can be of value in informing decisions for people with short life expectancy at the time of assessment. QFracture can currently be adapted to provide risk estimation for a shorter period of time. The GDG agreed a recommendation using age 80 years as they considered the likelihood of co-morbidities or reduced life expectancy is greatest in this group. Clinical judgement is always required when interpreting risk scores but the GDG considered it particularly important in this group.

Recommendation	**6. Do not routinely measure BMD to assess fracture risk without prior assessment using FRAX (without a BMD value) or QFracture.**
Relative values of different outcomes	The clinical outcomes that the GDG wished to predict were hip fractures and all osteoporotic fractures. Although hip fractures are particularly associated with significant morbidity and mortality, other osteoporotic fractures, particularly vertebral fractures, are a cause of significant morbidity.
Trade-off between clinical benefits and harms	Measuring BMD requires radiation exposure but the amount of exposure is very low (less than natural daily background radiation). More accurate prediction would increase benefits and reduce harms for individual patients and the population.
Economic considerations	The original cost analysis developed for this guideline showed that risk assessment tools without BMD were less costly than risk assessment tools that

	incorporated BMD assessment. The threshold analysis conducted for this guideline showed that performing FRAX (without BMD) prior to BMD assessment was less costly than performing BMD assessment for all patients when referral for BMD after FRAX was less than 68%. One study[32] identified in the literature review reported that the highest referral rate for BMD after FRAX assessment in women aged 50-85 without prior fracture was 14%. The GDG judged that referral rates for BMD assessment in practice would differ according to patient groups.
Quality of evidence	All the studies included in the review were classified as being at high or very high risk of bias. The GDG was interested in studies of BMD alone and the comparison between FRAX without BMD and FRAX including BMD in the UK. 13 cohort studies on BMD alone reported AUC as an overall outcome for predictive accuracy. AUC ranges reported by the studies were found to be very similar to those reported in the studies on FRAX and QFracture. Of the 13 studies, three were at low risk of bias, eight were at high risk of bias and one was at very high risk of bias. Reasons for bias assessment include low event rate(< 100 fractures); relatively large percentage loss to follow up and no information on fracture history. Two studies (high risk of bias, indirect applicability) that directly compared FRAX and BMD alone (lumbar spine and femoral neck or hip BMD) found similar AUC ranges. The majority of the included studies were not based on the UK population, which led to indirect applicability. Only one study investigated the addition of BMD to FRAX and this study was in a Canadian population. An additional study investigated the addition of BMD to clinical risk factors. The overall risk of bias for both studies was high or very high, with indirect applicability. Both studies presented a cross-tabulation table of risk categories (10-year fracture probability) based on the models, which indicates the number of people who move to another risk category or remain in the same category. Reclassification occurred mostly around the set threshold. The studies did not report whether those who were reclassified were reclassified correctly. One study selected arbitrary thresholds. Results on sensitivity and specificity of the tools at selected thresholds were not sufficient to conclude whether the addition of BMD to FRAX improves the performance of the tool. QFracture showed higher specificity, but also lower sensitivity, for hip fracture compared with FRAX, but there was not enough evidence to decide whether the difference was clinically important. The economic evidence was based on an original cost analysis with potentially serious limitations and partial applicability.
Other considerations	The GDG was aware that risk assessment tools had developed from the recognition that addition of clinical risk factors to BMD improves fracture risk prediction and that measurement of BMD can be costly and difficult to access even in relatively resource-rich countries like the UK. The main outcome from the studies was AUC and the GDG recognised that AUC is typically insensitive in assessing the impact of adding a new predictor (BMD) to a risk score. The reclassification studies examining addition of BMD to clinical risk factors or FRAX did not report whether the reclassification correctly identified people who did sustain a fracture. Reclassification was rarely from high to low categories or low to high categories and was clustered around the thresholds pre-specified in studies. The rationale for the thresholds chosen was not clear. The GDG agreed that measurement of BMD alone should not be a routine method of assessment for fracture risk but developed further recommendations for when it would be helpful.

Recommendation	**7. Following risk assessment with FRAX (without a BMD value) or QFracture, consider measuring BMD with DXA in people whose fracture risk is in the region of an intervention threshold[j] for a proposed treatment, and recalculate absolute risk using FRAX with the BMD value.**
Relative values of different outcomes	The clinical outcomes that the GDG wished to predict were hip fractures and all osteoporotic fractures. Although hip fractures are particularly associated with significant morbidity and mortality, other osteoporotic fractures, particularly vertebral fractures, are a cause of significant morbidity
Trade-off between clinical benefits and harms	The aim of assessment is to identify those at high risk and consider appropriate interventions. Measuring BMD requires radiation exposure but the amount of exposure is very low (less than natural daily background radiation). More accurate prediction would increase benefits and reduce harms for individual patients and the population.
Economic considerations	The original cost analysis developed for this guideline showed that risk assessment tools without BMD were less costly than risk assessment tools that incorporated BMD assessment. When the benefit of treatment is unclear, the GDG considered risk assessment using BMD is a good use of resources. Risk assessment using BMD can help reduce costs associated with unnecessary treatment and can increase health benefits for those appropriately treated.
Quality of evidence	The GDG used the evidence for use of BMD with and without FRAX and consensus to develop this recommendation. The economic evidence was based on an original cost analysis with potentially serious limitations and partial applicability.
Other considerations	The evidence for the reclassification with the addition of BMD indicated that reclassification was most likely around the threshold for treatment. The GDG therefore concluded the BMD measurement could be considered in people whose fracture risk is in the region of an intervention threshold and risk score recalculated. People well above the threshold can be treated without measurement of BMD to assess their risk although the GDG were aware that BMD may be used to monitor treatment. People well below the threshold can be reassured that they do not need treatment, preventing people from receiving investigations and treatment they did not require No evidence was found specifically relating to risk assessment of people who have taken or are already taking pharmacological treatment for low bone density or osteoporosis.

Recommendation	8. **Consider measuring BMD with DXA before starting treatments that may have a rapid adverse effect on bone density (for example, sex hormone deprivation for treatment for breast or prostate cancer).**
Relative values of different outcomes	The clinical outcomes that the GDG wished to predict were hip fractures and all osteoporotic fractures
Trade-off between clinical	The aim of assessment is to identify those at high risk and consider appropriate

j An intervention threshold is the level of risk at which an intervention is recommended. People whose risk is in the region from just below to just above the threshold may be reclassified if BMD is added to assessment. It is out of the scope of this guideline to recommend intervention thresholds. Healthcare professionals should follow local protocols or other national guidelines for advice on intervention thresholds.

benefits and harms	interventions. Measuring BMD requires radiation exposure but the amount of exposure is very low (less than natural daily background radiation). More accurate prediction would increase benefits and reduce harms for individual patients and the population.
Economic considerations	The original cost analysis developed for this guideline identified that fracture risk assessment without BMD is less costly than risk assessment with BMD. However, the GDG considered risk assessment without BMD inappropriate for this patient group. The initial extra cost of BMD assessment is justified because it can help reduce down stream costs associated with fractures resulting from undetected reduction in bone density and can increase health benefit for patients who avoid fractures because of timely and appropriate treatment.
Quality of evidence	The GDG used the evidence for use of BMD with and without FRAX and consensus to develop this recommendation.
Other considerations	The GDG considered that there are some people who are at risk of dramatic bone loss which will not be captured by FRAX or QFracture. The GDG were particularly concerned about people who are about to start sex hormone deprivation treatments for breast or prostate cancer. Their change in risk as a result of their cancer treatment will not be reflected in clinical risk factors. BMD measurement before and during treatment can be used as a means of quantifying fracture risk. The GDG agreed therefore to make a recommendation that BMD should be considered for this group. The GDG considered that effect on bone density is not sustained once cancer treatment is completed.

Recommendation	**9. Measure BMD to assess fracture risk in people aged under 40 years who have a major risk factor, such as history of multiple fragility fracture, major osteoporotic fracture, or current or recent use of high-dose oral or systemic glucocorticoids (more than 7.5 mg prednisolone or equivalent per day for 3 months or longer).**
Relative values of different outcomes	The clinical outcomes that the GDG wished to predict were hip fractures and all osteoporotic fractures. Although hip fractures are particularly associated with significant morbidity and mortality, other osteoporotic fractures, particularly vertebral fractures, are a cause of significant morbidity.
Trade-off between clinical benefits and harms	Younger people who have already sustained fragility fractures, particularly at major sites and/or multiple fractures, may be at high risk of future fracture. Exposure to low-dose radiation associated with measurement of BMD is outweighed by the benefit of potentially preventing future fractures in this group.
Economic considerations	Both FRAX and QFracture are not applicable to younger patients. However, the GDG believe that even if a person has a substantial number of risk factors, their absolute risk may still be low and as such they would be unlikely to benefit from treatment. While BMD incurs additional cost, this initial cost can reduce additional costs associated with unnecessary treatment.
Quality of evidence	This recommendation was informed by the GDG knowledge of risk tools and GDG consensus.
Other considerations	FRAX does not include people less than 40 years. Although QFracture includes people between 30 and 40 years, the number of fractures in the dataset for this age group is small. BMD is therefore the only tool available to assess fracture risk in this age group. Multiple fragility fractures or major osteoporotic fractures should be a trigger to consider assessment. People with other factors known to increase fragility fracture incidence (for example, high-dose oral or systemic glucocorticoids, untreated premature menopause) may also be assessed using BMD measurement. The GDG was aware that it is not possible

	to translate BMD into absolute fracture risk and how to proceed on the basis of results of BMD is unclear.

Recommendation	**10. Consider recalculating fracture risk in the future:** • **if the original calculated risk was in the region of the intervention threshold[k] for a proposed treatment and only after a minimum of 2 years, or** • **when there has been a change in the person's risk factors.**
Relative values of different outcomes	The clinical outcomes that the GDG wished to predict were hip fractures and all osteoporotic fractures. Although hip fractures are particularly associated with significant morbidity and mortality, other osteoporotic fractures, particularly vertebral fractures, are a cause of significant morbidity.
Trade-off between clinical benefits and harms	Unnecessary repeated assessment will potentially expose people to anxiety about their risk.
Economic considerations	The GDG believed that recalculating the risk of fragility fracture any more frequently would increase costs and be unlikely to provide any additional health benefit. Recalculating risk of fracture when there is a change in risk factors will incur additional costs but can reduce long-term costs associated with fractures that have been prevented and can also increase health benefit through appropriate treatment.
Quality of evidence	The recommendation is based on GDG knowledge of risk assessment tools and consensus.
Other considerations	Absolute risk and BMD usually change slowly. The GDG considered that repeating risk assessment is unnecessary for the majority of people unless there has been a change in risk factors. If an initial assessment indicates people are near a treatment threshold than repeating the assessment after a minimum of 2 years is appropriate. The GDG also considered that if BMD was part of the original assessment, then BMD should be re-measured as part of the repeated risk assessment; however, if BMD was not part of the original assessment, then the decision of measuring BMD will be based on the result of the repeated risk assessment (see recommendation 7).

Recommendation	**11. Take into account that risk assessment tools may underestimate fracture risk in certain circumstances, for example if a person:** • **has a history of multiple fractures** • **has had previous vertebral fracture(s)** • **has a high alcohol intake** • **is taking high-dose oral or high-dose systemic glucocorticoids (more than 7.5 mg prednisolone or equivalent per day for 3 months or longer)** • **has other causes of secondary osteoporosis[l].**

k An intervention threshold is the level of risk at which an intervention is recommended. It is out of the scope of this guideline to recommend intervention thresholds. Healthcare professionals should follow local protocols or other national guidelines for advice on intervention thresholds.

l Causes of secondary osteoporosis include endocrine (hypogonadism in either sex including untreated premature menopause and treatment with aromatase inhibitors or androgen deprivation therapy; hyperthyroidism; hyperparathyroidism; hyperprolactinaemia; Cushing's disease; diabetes), gastrointestinal (coeliac disease; inflammatory bowel disease; chronic liver disease; chronic pancreatitis; other causes of malabsorption), rheumatologival (rheumatoid arthritis; other inflammatory arthropathies), haematological

Relative values of different outcomes	The clinical outcomes that the GDG wished to predict were hip fractures and all osteoporotic fractures. Although hip fractures are particularly associated with significant morbidity and mortality, other osteoporotic fractures, particularly vertebral fractures, are a cause of significant morbidity.
Trade-off between clinical benefits and harms	Underestimation of actual risk using risk score could result in people being falsely reassured about their risk and not receiving appropriate interventions.
Economic considerations	Underestimation of actual risk would increase long-term costs and reduce health benefits.
Quality of evidence	This recommendation was informed by the evidence review of individual risk factors and the review of risk tools.
Other considerations	The GDG used their knowledge of how the risk tools work in practice to inform this recommendation. FRAX allows a binary response (yes/no) to history of fracture, smoking, oral or systemic glucocorticoid use, alcohol use and causes of secondary osteoporosis. The GDG considered that the binary response to previous fracture would potentially result in an underestimation of fracture risk if an individual has had multiple fractures. The reviews suggested a dose–response relationship with alcohol and smoking. The FRAX equations are not publicly available but the GDG considered the effect seen with heavy alcohol consumption in UK datasets would be unlikely to be captured in the binary response. The IPD analysis included only three cohorts with alcohol data, none of which was from the UK. Adjustment to the risk score may therefore be required. The GDG considered the dose effect with smoking to be of lesser magnitude. The FRAX website advises that glucocorticoid use is defined as ≥5 mg/day prednisolone or equivalent for at least 3 months. The GDG was aware of evidence of a dose–response relationship between glucocorticoids and fracture risk. Glucocorticoids can be used at different doses for differing periods of time and FRAX would underestimate the effect of higher doses on fracture risk. The GDG considered that risk scores are likely to underestimate risk attributed to causes of secondary osteoporosis. The GDG understands FRAX assumes that all the effect of causes of secondary osteoporosis (other than those which are covered by other questions, for example oral glucocorticoids and rheumatoid arthritis) is mediated through BMD and that by ticking this box an undefined BMD correction is used in the assessment. The GDG considered it likely that at least some causes of secondary osteoporosis affect fracture risk by mechanisms that are partially independent of BMD and fracture risk may therefore be underestimated in such patients. The GDG was also concerned that coding in routine general practices' databases may not be sufficiently accurate to identify many secondary causes such as hypogonadism and chronic liver disease. QFracture allows a more detailed quantification of both smoking and alcohol consumption but allows only a yes/no response to oral glucocorticoid use.

(multiple myeloma; haemoglobinopathies; systemic mastocytosis), respiratory (cystic fibrosis; COPD), metabolic (homocystinuria), chronic renal disease, immobility (due for example to neurological injury or disease).

Recommendation	**12. Take into account that fracture risk can be affected by factors that may not be included in the risk tool, for example living in a care home or taking drugs that may impair bone metabolism (such as anti-convulsants, selective serotonin reuptake inhibitors, thiazolidinediones, proton pump inhibitors and anti-retroviral drugs).**
Relative values of different outcomes	The clinical outcomes that the GDG wished to predict were hip fractures and all osteoporotic fractures. Although hip fractures are particularly associated with significant morbidity and mortality, other osteoporotic fractures, particularly vertebral fractures, are a cause of significant morbidity.
Trade-off between clinical benefits and harms	Underestimation of actual risk using risk scores may result in patients being falsely reassured about their risk and/or not receiving appropriate interventions from which they might benefit.
Economic considerations	There were no published economic evaluations. Underestimation of risk would increase long-term costs and reduce health benefits.
Quality of evidence	This recommendation was informed by the GDG knowledge of risk tools and GDG consensus.
Other considerations	Risk estimation tools do not include all factors that can influence fracture risk. Factors that are a significant risk factor for an individual may not be well recorded, not easily measured or not important for much of the population. Some anti-epileptic drugs (for example carbamazepine, primidone, phenobarbital, phenytoin, and sodium valproate) interfere with vitamin D metabolism and aromatase inhibitors are associated with reduced BMD. Immobility for physical or mental reasons is not included in risk scores but will affect bone density and fracture risk. Residents of care homes are likely to have many risk factors already included in risk scores (for example, older age, previous fracture, low BMI) but also factors not included such as poor mobility. There is some evidence that their BMD is lower than expected by age, they have a high risk of falls and high fracture rates. The GDG have developed a research recommendation to examine risk prediction for residents of care homes but considered that healthcare professionals should be aware of the combination of risks carried by this population, their high fracture risk and their low median survival. The median survival in a care home is < 600 days) which means 10-year risk is not appropriate. [5,22 1 50]

4.8 Research recommendations

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

Why this is important

Because of concerns about rare but serious side-effects of long-term anti-resorptive therapy, many physicians prescribe these drugs for a finite period of time, usually 3–5 years. Reassessment of fracture risk at the end of this treatment period is important, since some people remain at high risk of fracture and require continued treatment whereas others may benefit from a 'drug holiday' for 1 or more years. Neither FRAX nor QFracture has been examined in treated patients, and it is not known whether the ability of clinical risk factors with or without measurement of BMD to predict fracture risk is similar in untreated and treated patients. There is therefore a need for prospective studies to investigate the predictive power of these tools to assess fracture risk in patients after a period of bone protective therapy.

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

Why this is important

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

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

Why this is important

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

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

5. What is the utility of FRAX and QFracture in detecting risk of fragility fracture in adults living in residential care?

Why this is important

Care home residents are at high risk of fragility fracture[5,22]. This is probably related to increased age and frailty with multiple comorbidities, which increase fracture risk. There is also evidence that care home residents have lower BMD, with 70% assessed as having osteoporosis using densitometry criteria alone[1]. However, tools such as FRAX and QFracture, which only estimate fracture risk up to the ninth decade and use 10-year fracture risk, may under-estimate short-term risk in care home residents, who currently have a mean age of approximately 85 years and a life expectancy of less than 5 years[50].

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

6. What is the accuracy of FRAX, QFracture and BMD in detecting risk of fragility fracture in adults of different ethnic origin in the UK population?

Why this is important

The total population of the UK is around 60 million, with the ethnic minority population making up 7.9 per cent of that total in the 2001 census. The largest category was people of South Asian family origin, who accounted for 2 million people or 3.5% of the population. According to recent research, minority ethnic groups will increase and make up a fifth of Britain's population by 2051. Fragility fracture risk assessment tools such as FRAX and QFracture were derived from populations that may not reflect this ethnic diversity, and also make assumptions across different racial and ethnic groups that may not be valid. There is concern that these tools will not reliably predict which individuals from minority ethnic groups will or will not sustain a fracture. Further work is therefore needed to determine if these risk assessment tools are accurate and reliable in predicting fracture risk in different ethnic groups in England and Wales.

5 Glossary

5.1 Abbreviations

AUC	Area under the ROC curve
BMD	Bone mineral density
BMI	Body mass index
CI	Confidence interval
CRF	Clinical risk factor
DXA	Dual-energy X-ray absorptiometry
FN	False negative
FP	False positive
GDG	Guideline Development Group
GRADE	Grading of recommendations assessment, development and evaluation
HR	Hazard ratio
INB	Incremental net benefit
NCGC	National Clinical Guideline Centre
NHS	National Health Service
NICE	National Institute for health and Clinical Excellence
NOGG	National Osteoporosis Guideline Group
NPV	Negative predictive value
PPV	Positive predictive value
QUADAS	Quality assessment of diagnostic accuracy studies
QALY	Quality-adjusted life year
RF	Risk factor
RCT	Randomised controlled trial
ROC	Receiver operating characteristic
RR	Relative risk
THIN	The Health Improvement Network
TN	True negative
TP	True positive
vs	Versus
WHO	World Health Organization

5.2 Definitions of terms

Abstract	Summary of a study, which may be published alone or as an introduction to a full scientific paper.
Algorithm (in guidelines)	A flow chart of the clinical decision pathway described in the guideline, where decision points are represented with boxes, linked with arrows.
Allocation concealment	The process used to prevent advance knowledge of group assignment in a RCT. The allocation process should be impervious to any influence by the individual making the allocation, by being administered by someone who is not responsible for recruiting participants.
Anti-resorptive therapy	Therapy that tends to slow or block the resorption of bone, including drugs such as biphosphonates, oestrogen analogs, Raloxifene.
Applicability	The degree to which the results of an observation, study or review are likely to hold true in a particular clinical practice setting.
Area under the curve	Area under the ROC curve, or c statistics, ranges from 0.5 (no discrimination) to a theoretical maximum of 1 (perfect discrimination).
Arm (of a clinical study)	Sub-section of individuals within a study who receive one particular intervention (for example, placebo arm).
Association	Statistical relationship between two or more events, characteristics or other variables. The relationship may or may not be causal.
Baseline	The initial set of measurements at the beginning of a study (after run-in period where applicable), with which subsequent results are compared.
Before-and-after study	A study that investigates the effects of an intervention by measuring particular characteristics of a population both before and after receiving the intervention, and assessing any change that occurs.
Bias	Systematic (as opposed to random) deviation of the results of a study from the 'true' results, which is caused by the way the study is designed or conducted.
Blinding	Keeping the study participants, caregivers, researchers and outcome assessors unaware of the interventions to which the participants have been allocated in a study.
Body mass index (BMI)	An index of weight-for-height that is commonly used to classify underweight, overweight and obesity in adults. It is defined as the weight in kilograms divided by the square of the height in metres (kg/m^2).
Bone mineral density (BMD)	Refers to the amount of mineral per square centimetre of bone, usually assessed using a special X-ray such as DXA. It can also identify osteoporosis and help determine risk of fracture.
Calibration	A comparison between measurements. In the context of risk stratification, it indicates how well predicted risk (calculated using a risk score) agrees with observed risk in a population. A perfectly calibrated model is when the predicted risk equals the observed risk for all subgroups.

Carer (caregiver)	Someone other than a healthcare professional who is involved in caring for a person with a medical condition.
Case-control study	Comparative observational study in which the investigator selects individuals who have experienced an event (for example, developed a disease) and others who have not (controls), and then collects data to determine previous exposure to a possible cause.
Clinical efficacy	The extent to which an intervention is active when studied under controlled research conditions.
Clinical effectiveness	The extent to which an intervention produces an overall health benefit in routine clinical practice.
Clinician	A healthcare professional providing direct patient care (for example doctor, nurse or physiotherapist).
Cochrane Review	The Cochrane Library consists of a regularly updated collection of evidence-based medicine databases including the Cochrane Database of Systematic Reviews (reviews of RCTs prepared by the Cochrane Collaboration).
Cohort study	A retrospective or prospective follow-up study. Groups of individuals to be followed up are defined on the basis of presence or absence of exposure to a suspected risk factor or intervention. A cohort study can be comparative, in which case two or more groups are selected on the basis of differences in their exposure to the agent of interest.
Comorbidity	Co-existence of more than one disease or an additional disease (other than that being studied or treated) in an individual.
Comparability	Similarity of the groups in terms of characteristics likely to affect the study results (such as health status or age).
Complete case analysis	An analysis based on individuals with complete data only. Individuals with missing/unavailable data are excluded.
Concordance	This is a recent term whose meaning has changed. It was initially applied to the consultation process in which doctor and patient agree therapeutic decisions that incorporate their respective views, but now includes patient support in medicine taking as well as prescribing communication. Concordance reflects social values but does not address medicine-taking and may not lead to improved adherence.
Confidence interval (CI)	A range of values for an unknown population parameter with a stated ‘confidence’ (conventionally 95%) that it contains the true value. The interval is calculated from sample data, and generally straddles the sample estimate. The ‘confidence’ value means that if the method used to calculate the interval is repeated many times, then that proportion of intervals will actually contain the true value.
Confounding	In a study, confounding occurs when the effect of an intervention on an outcome is distorted as a result of an association between the population or intervention or outcome and another factor (the ‘confounding variable’) that can influence the outcome independently of the intervention under study.

Consensus methods	Techniques that aim to reach an agreement on a particular issue. Consensus methods may be used when there is a lack of strong evidence on a particular topic.
Control group	A group of patients recruited into a study that receives no treatment, a treatment of known effect or a placebo (dummy treatment) in order to provide a comparison for a group receiving an experimental treatment, such as a new drug.
Cost–benefit analysis	A type of economic evaluation where both costs and benefits of healthcare treatment are measured in the same monetary units. If benefits exceed costs, the evaluation would recommend providing the treatment.
Cost–consequence analysis	A type of economic evaluation where various health outcomes are reported in addition to cost for each intervention, but there is no overall measure of health gain.
Cost-effectiveness analysis	An economic study design in which consequences of different interventions are measured using a single outcome, usually in 'natural' units (for example, life-years gained, deaths avoided, heart attacks avoided, cases detected). Alternative interventions are then compared in terms of cost per unit of effectiveness.
Cost-effectiveness model	An explicit mathematical framework, which is used to represent clinical decision problems and incorporate evidence from a variety of sources in order to estimate the costs and health outcomes.
Cost–utility analysis	A form of cost-effectiveness analysis in which the units of effectiveness are QALYs.
Credible interval	The Bayesian equivalent of a confidence interval.
Cross-sectional study	A descriptive study in which disease and exposure status are measured simultaneously in a given population. It is thought to provide a snapshot of the frequency and characteristics of a disease in a population at a specific point in time. It is also used to assess prevalence in a population.
Decision analysis	An explicit quantitative approach to decision-making under uncertainty, based on evidence from research. This evidence is translated into probabilities, and then into diagrams or decision trees, which direct the clinician through a succession of possible scenarios, actions and outcomes.
Derivation	The development of a risk stratification tool (risk score). Derivation cohort refers to the population used to derive the risk score.
Discounting	Costs and perhaps benefits incurred today have a higher value than costs and benefits occurring in the future. Discounting health benefits reflects individual preference for benefits to be experienced in the present rather than the future. Discounting costs reflects individual preference for costs to be experienced in the future rather than the present.
Discrimination	Ability of differentiating between those who will develop a health condition and those who will not develop a health condition. Perfect discrimination corresponds to a c statistic of 1 and is achieved if the

	scores for all the cases are higher than those for all the non-cases, with no overlap.
Dominance	An intervention is said to be dominated if there is an alternative intervention that is both less costly and more effective.
Drop-out	A participant who withdraws from a trial before the end.
Dual-energy X-ray absorptiometry (DXA)	A test that measures BMD using low energy X-rays. It is typically used to diagnose osteoporosis.
Economic evaluation	Comparative analysis of alternative health strategies (interventions or programmes) in terms of both their costs and consequences.
Effect (as in effect measure, treatment effect, estimate of effect, effect size)	The observed association between interventions and outcomes or a statistic to summarise the strength of the observed association.
Effectiveness	See 'Clinical effectiveness'.
Efficacy	See 'Clinical efficacy'.
Epidemiological study	The study of a disease within a population, defining its incidence and prevalence and examining the roles of external influences (for example, infection, diet) and interventions.
EQ-5D (EuroQol-5D)	A standardised instrument used to measure a health outcome. It provides a single index value for health status.
Evidence	Information on which a decision or guidance is based. Evidence is obtained from a range of sources including RCTs, observational studies and expert opinion (of clinical professionals and/or patients).
Exclusion criteria (literature review)	Explicit standards used to decide which studies should be excluded from consideration as potential sources of evidence.
Exclusion criteria (clinical study)	Criteria that define who is not eligible to participate in a clinical study.
Extended dominance	If Option A is more clinically effective than Option B and has a lower cost per unit of effect when both are compared with a do-nothing alternative, then Option A is said to have extended dominance over Option B. Option A is therefore more efficient and should be preferred, other things remaining equal.
External validation	A process of validating a test/risk score to predict an individual's risk of developing a health condition, using an external population (different to the population used for the derivation of the risk score).
Extrapolation	In data analysis, predicting the value of a parameter outside the range of observed values.
False negative	Individuals who test negative for a condition and are in fact positive (that is, have the condition).
False positive	Individuals who test positive for a condition and are in fact negative (that is, do not have the condition).

Femoral neck	A flattened pyramidal process of bone, connecting the femoral head with the femoral shaft.
Follow-up	Observation over a period of time of an individual, group or initially defined population whose appropriate characteristics have been assessed in order to observe changes in health status or health-related variables.
Fragility fracture	A fracture occurring spontaneously or following a minor trauma, such a fall from standing height or less.
FRAX	A tool developed to evaluate risk of fracture in patients. It integrates the risks associated with clinical risk factors as well as BMD at the femoral neck. It gives the 10-year probability of hip fracture and 10-year probability of major osteoporotic fracture (clinical spine, forearm, hip or shoulder fracture). FRAX can be calculated with and without BMD and in this guideline we have specifically described tools as 'FRAX with BMD' or 'FRAX without BMD' for clarity.
Generalisability	The extent to which the results of a study based on measurement in a particular patient population and/or a specific context hold true for another population and/or in a different context. In this instance, this is the degree to which the guideline recommendation is applicable across both geographical and contextual settings. For instance, guidelines that suggest substituting one form of labour for another should acknowledge that these costs might vary across the country.
Gold standard	**See 'Reference standard'.**
GRADE/GRADE profile	A system developed by the GRADE Working Group to address the shortcomings of present grading systems in healthcare. The GRADE system uses a common, sensible and transparent approach to grading the quality of evidence. The results of applying the GRADE system to clinical trial data are displayed in a table known as a GRADE profile.
Harms	Adverse effects of an intervention.
Health economics	The study of the allocation of scarce resources among alternative healthcare treatments. Health economists are concerned with both increasing the average level of health in the population and improving the distribution of health.
Health-related quality of life (HRQoL)	A combination of an individual's physical, mental and social well-being; not merely the absence of disease.
Heterogeneity (or lack of homogeneity)	The term is used in meta-analyses and systematic reviews when the results or estimates of effects of treatment from separate studies seem to be very different – in terms of the size of treatment effects or even to the extent that some indicate beneficial and others suggest adverse treatment effects. Such results may occur as a result of differences between studies in terms of the patient populations, outcome measures, definition of variables or duration of follow-up.
Imprecision	Results are imprecise when studies include relatively few patients and

	few events and thus have wide CIs around the estimate of effect.
Imputation	A procedure of handling datasets with missing values (due to lost to follow up, etc.). Once all missing values have been imputed, the dataset can be analysed using standard techniques for complete data.
Incidence	The number of new cases that develop the event of interest within a specific time period.
Inclusion criteria (literature review)	Explicit criteria used to decide which studies should be considered as potential sources of evidence.
Incremental analysis	The analysis of additional costs and additional clinical outcomes with different interventions.
Incremental cost	The mean cost per patient associated with an intervention minus the mean cost per patient associated with a comparator intervention.
Incremental net benefit (INB)	The value (usually in monetary terms) of an intervention net of its cost compared with a comparator intervention. The INB can be calculated for a given cost-effectiveness (willingness to pay) threshold. If the threshold is £20,000 per QALY gained then the INB is calculated as: (£20,000 x QALYs gained) – incremental cost.
Index test	Test under evaluation
Indirectness	The available evidence is different to the review question being addressed, in terms of PICO (population, intervention, comparison and outcome).
Individual patient data meta-analysis	A specific type of systematic review. Rather than extracting data from study publications, the original research data are sought directly from the researchers responsible for each study. These data can then be re-analysed centrally and combined, if appropriate, in meta-analyses. IPD reviews offer benefits related to the quality of data and the type of analyses that can be done. For this reason they are considered to be a 'gold standard' of systematic review.
Intention to treat analysis (ITT)	A strategy for analysing data from a RCT. All participants are included in the arm to which they were allocated, whether or not they received (or completed) the intervention given to that arm. Intention-to-treat analysis prevents bias caused by the loss of participants, which may disrupt the baseline equivalence established by randomisation and which may reflect non-adherence to the protocol.
Internal validation	A process of validating a test/risk score to predict an individual's risk of developing a health condition, using the same population in which the risk score is derived.
Intervention	Healthcare action intended to benefit the patient (for example, drug treatment, surgical procedure or psychological therapy).
Intraoperative	The period of time during a surgical procedure.
Kappa statistic	A statistical measure of inter-rater agreement that takes into account the agreement occurring by chance.
Length of stay	The total number of days a participant stays in hospital.

Licence See 'Product licence'.

Life-years gained Mean average years of life gained per person as a result of the intervention compared with an alternative intervention.

Likelihood ratio The likelihood ratio combines information about the sensitivity and specificity. It tells you how much a positive or negative result changes the likelihood that a patient would have the disease. The likelihood ratio of a positive test result (LR+) is sensitivity divided by 1 − specificity.

Long-term care Residential care in a home that may include skilled nursing care and help with everyday activities. This includes nursing homes and residential homes.

Loss to follow-up Individuals who actively participated in a study and became lost during the follow up phase of the study due to various reasons such as moving out of the study area. This usually leads to unavailability of data for these individuals.

Lumbar spine The lumbar vertebrae are the largest segments of the movable part of the vertebral column. They are designated L1 to L5, starting at the top.

Major osteoporotic fracture Fracture associated with low BMD and includes clinical spine, forearm, hip or shoulder fractures.

Markov model A method for estimating long-term costs and effects for recurrent or chronic conditions, based on health states and the probability of transition between them within a given time period (cycle).

Meta-analysis A statistical technique for combining (pooling) the results of a number of studies that address the same question and report on the same outcomes to produce a summary result. The aim is to derive more precise and clear information from a large data pool. It is generally more reliably likely to confirm or refute a hypothesis than the individual trials.

Multivariate model A statistical model for analysis of the relationship between two or more predictor (independent) variables and the outcome (dependent) variable.

Negative predictive value (NPV) (in screening/diagnostic tests) A measure of the usefulness of a screening/diagnostic test. It is the proportion of those with a negative test result who do not have the disease, and can be interpreted as the probability that a negative test result is correct. It is calculated as follows:

$$NPV = \frac{\mathrm{TN}}{\mathrm{TN} + \mathrm{FN}}$$

Number needed to treat (NNT) The number of patients that on average must be treated to prevent a single occurrence of the outcome of interest.

Observational study Retrospective or prospective study in which the investigator observes the natural course of events with or without control groups (for example, cohort studies and case–control studies).

Observed risk The observed probability of a health condition or event occurring within a specified population.

Odds ratio A measure of treatment effectiveness. The odds of an event happening in the treatment group, expressed as a proportion of the odds of it happening in the control group. The 'odds' is the ratio of events to non-events.

Opportunistic screening Opportunistic screening or case-finding occurs when a test is offered to an individual without symptoms of the disease when they present to a healthcare practitioner for reasons unrelated to that disease.

Opportunity cost The loss of other healthcare programmes displaced by investment in or introduction of another intervention. This may be best measured by the health benefits that could have been achieved had the money been spent on the next best alternative healthcare intervention.

Osteoporosis A systemic skeletal disease characterised by low bone mass and structural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture. According to the WHO criteria, osteoporosis is defined as a BMD that lies ≥2.5 standard deviations below the average value for young healthy adults (a T-score of <2.5 SD).

Outcome Measure of the possible results that may stem from exposure to a preventive or therapeutic intervention. Outcome measures may be intermediate endpoints or they can be final endpoints. See 'Intermediate outcome'.

p value The probability that an observed difference could have occurred by chance, assuming that there is in fact no underlying difference between the means of the observations. If the probability is less than 1 in 20, the p value is less than 0.05; a result with a p value of less than 0.05 is conventionally considered to be 'statistically significant'.

Placebo An inactive and physically identical medication or procedure used as a comparator in controlled clinical trials.

Polypharmacy The use or prescription of multiple medications.

Positive predictive value (PPV) (in screening/diagnostic tests) A measure of the usefulness of a screening/diagnostic test. It is the proportion of those with a positive test result who have the disease, and can be interpreted as the probability that a positive test result is correct. It is calculated as follows:

$$PPV = \frac{\mathrm{TP}}{\mathrm{TP} + \mathrm{FP}}$$

Postoperative Pertaining to the period after patients leave the operating theatre, following surgery.

Post-test probability The positive post-test probability is the post-test probability of a target condition given a positive test result, and is calculated as:

Positive post-test probability = True positives / (True positives + False positives)

The post-test probability of disease given a negative result is calculated as:

	Negative post-test probability = False negatives / (False negatives + True negatives)
Power (statistical)	The ability to demonstrate an association when one exists. Power is related to sample size; the larger the sample size, the greater the power and the lower the risk that a possible association could be missed.
Predicted risk	The predicted probability of a health condition or event occurring, using an algorithm or risk equation.
Preoperative	The period before surgery commences.
Pre-test probability	For diagnostic tests. The proportion of people with the target disorder in the population at risk at a specific time point or time interval. Prevalence may depend on how a disorder is diagnosed.
Primary care	Healthcare delivered to patients outside hospitals. Primary care covers a range of services provided by GPs, nurses, dentists, pharmacists, opticians and other healthcare professionals.
Primary outcome	The outcome of greatest importance, usually the one in a study that the power calculation is based on.
Probability	A measure of the likeliness that a (random) event will occur. It is a numerical measure that ranges between 0 and 1. The higher the probability of an event, the more certain we are that the event will occur. A 10-year fracture probability refers to an individual's risk of developing a fracture over the next 10 years.
Product licence	An authorisation from the Medicines and Healthcare products Regulatory Agency (MHRA) to market a medicinal product.
Prognosis	A probable course or outcome of a disease. Prognostic factors are patient or disease characteristics that influence the course of a disease. Good prognosis is associated with low rate of undesirable outcomes; poor prognosis is associated with a high rate of undesirable outcomes.
Prospective study	A study in which people are entered into the research and then followed up over a period of time with future events recorded as they happen. This contrasts with studies that are retrospective.
Publication bias	Also known as reporting bias. A bias caused by only a subset of all the relevant data being available. The publication of research can depend on the nature and direction of the study results. Studies in which an intervention is not found to be effective are sometimes not published. Because of this, systematic reviews that fail to include unpublished studies may overestimate the true effect of an intervention. In addition, a published report might present a biased set of results (for example, only outcomes or sub-groups where a statistically significant difference was found).
QFracture	A risk assessment tool to evaluate an individual's 10-year probability of osteoporotic (hip, vertebral or distal radius) and hip fracture risk. The algorithm was developed and validated in the UK.
Quality of life	See 'Health-related quality of life'.

QUADAS II	A revised tool for the quality assessment of diagnostic accuracy studies. The tool comprises domains that assess risk of bias and takes into account concerns regarding applicability.
Quality-adjusted life year (QALY)	An index of survival that is adjusted to account for the patient's quality of life during this time. QALYs have the advantage of incorporating changes in both quantity (longevity/mortality) and quality (morbidity, psychological, functional, social and other factors) of life. Used to measure benefits in cost–utility analysis. The QALYs gained are the mean QALYs associated with one treatment minus the mean QALYs associated with an alternative treatment.
Randomisation	Allocation of participants in a research study to two or more alternative groups using a chance procedure, such as computer-generated random numbers. This approach is used in an attempt to ensure there is an even distribution of participants with different characteristics between groups and thus reduced sources of bias.
Randomised controlled trial (RCT)	A comparative study in which participants are randomly allocated to intervention and control groups and followed up to examine differences in outcomes between the groups.
Receiver operating characteristic (ROC) curve	A graphical method of assessing the accuracy of a diagnostic test. Sensitivity is plotted against 1 – specificity. A perfect test will have a positive, vertical linear slope starting at the origin. A good test will be somewhere close to this ideal.
Reference standard	The test that is considered to be the best available method to establish the presence or absence of the outcome – this may not be the one that is routinely used in practice.
Relative risk (RR)	The number of times more likely or less likely an event is to happen in one group compared with another (calculated as the risk of the event in group A/the risk of the event in group B).
Reporting bias	See 'Publication bias'.
Resource implication	The likely impact in terms of finance, workforce or other NHS resources.
Retrospective study	A retrospective study deals with the present/past and does not involve studying future events. This contrasts with studies that are prospective.
Review question	In guideline development, this term refers to the questions about treatment and care that are formulated to guide the development of evidence-based recommendations.
Risk	The likelihood that an undesirable event will occur. Risk is often expressed as absolute risk and relative risk. Absolute risk is the probability of a person developing a particular event over a specified time period, in contrast with RR. See 'relative risk'.
Secondary outcome	An outcome used to evaluate additional effects of the intervention deemed a priori as being less important than the primary outcomes.
Selection bias	A systematic bias in selecting participants for study groups, so that the groups have differences in prognosis and/or therapeutic sensitivities at

	baseline. Randomisation (with concealed allocation) of patients protects against this bias.
Sensitivity	Sensitivity or recall rate is the proportion of true positives that are correctly identified as such. For example, in diagnostic testing it is the proportion of true cases that the test detects. See the related term 'Specificity'
Sensitivity analysis	A means of representing uncertainty in the results of economic evaluations. Uncertainty may arise from missing data, imprecise estimates or methodological controversy. Sensitivity analysis also allows for exploring the generalisability of results to other settings. The analysis is repeated using different assumptions to examine the effect on the results. One-way simple sensitivity analysis (univariate analysis): each parameter is varied individually in order to isolate the consequences of each parameter on the results of the study. Multi-way simple sensitivity analysis (scenario analysis): two or more parameters are varied at the same time and the overall effect on the results is evaluated. Threshold sensitivity analysis: the critical value of parameters above or below which the conclusions of the study will change are identified. Probabilistic sensitivity analysis: probability distributions are assigned to the uncertain parameters and are incorporated into evaluation models based on decision analytical techniques (for example, Monte Carlo simulation).
Significance (statistical)	A result is deemed statistically significant if the probability of the result occurring by chance is less than 1 in 20 ($p < 0.05$).
Specificity	The proportion of true negatives that are correctly identified as such. For example, in diagnostic testing the specificity is the proportion of non-cases incorrectly diagnosed as cases. See related term 'Sensitivity'. In terms of literature searching a highly specific search is generally narrow and aimed at picking up the key papers in a field and avoiding a wide range of papers.
Stakeholder	Those with an interest in the use of the guideline. Stakeholders include manufacturers, sponsors, healthcare professionals, and patient and carer groups.
Standard deviation	A measure of variability that shows the amount of spread from the mean. A low standard deviation indicates that the data points tend to be close to the mean and high standard deviation indicates that the data points are spread out over a large range of values.
Systematic review	Research that summarises the evidence on a clearly formulated question according to a pre-defined protocol using systematic and explicit methods to identify, select and appraise relevant studies, and to extract,

	collate and report their findings. It may or may not use statistical meta-analysis.
Threshold	The level that must be reached for an effect to be produced. In the context of intervention threshold for osteoporosis, it is defined as the threshold of fracture probability at which interventions become cost-effective.
Time horizon	The time span over which costs and health outcomes are considered in a decision analysis or economic evaluation.
Time to event	Time to event or survival analysis takes into account censoring and non-normality. The non-normality aspect of the data violates the normality assumption of most commonly used statistical model such as regression or ANOVA. A censored observed is defined as an observation with incomplete data. The purpose of survival analysis is to follow subjects over time and observe at what point in time they experience the event of interest.
Treatment allocation	Assigning a participant to a particular arm of the trial.
True negative	Individuals who test negative for a condition and are negative (that is,. do not have the condition).
True positive	Individuals who test positive for a condition and are positive (that is, have the condition).
T-score	Test result (for example, BMD) of an individual compared with a healthy young adult in a defined population. Differences between the individual's BMD and that of the healthy young adult average are measured in units called standard deviations. The more standard deviations below 0, indicated as negative numbers, the lower the BMD and the higher the risk of fracture.
Univariate	Analysis that separately explores each variable in a data set.
Utility	A measure of the strength of an individual's preference for a specific health state in relation to alternative health states. The utility scale assigns numerical values on a scale from 0 (death) to 1 (optimal or 'perfect' health). Health states can be considered worse than death and thus have a negative value.
Validation	A process of validating a test/risk score to predict an individual's risk of developing a health condition.
Z-score	Test result (for example, BMD) of an individual compared with a typical individual of the same age.

Appendices (see separate files)

Appendix A: Declarations of interests

Appendix B: Research recommendations

Appendix C: How this guideline was developed

Appendix D: Evidence tables and forest plots

Appendix E: Full health economic report

6 Reference list

1 Aspray TJ, Stevenson P, Abdy SE, Rawlings DJ, Holland T, Francis RM. Low bone mineral density measurements in care home residents--a treatable cause of fractures. Age and Ageing. 2006; 35(1):37-41

2 Bauer DC, Ewing SK, Cauley JA, Ensrud KE, Cummings SR, Orwoll ES et al. Quantitative ultrasound predicts hip and non-spine fracture in men: the MrOS study. Osteoporosis International. 2007; 18(6):771-777

3 Ben Sedrine W, Broers P, Devogelaer JPD, Kaufman JM, Goemaere S, Reginster J. Interest of a prescreening questionnaire to reduce the cost of bone densitometry. Osteoporosis International. 2002; 13(5):434-442

4 Bolland MJ, Siu AT, Mason BH, Horne AM, Ames RW, Grey AB et al. Evaluation of the FRAX and Garvan fracture risk calculators in older women. Journal of Bone and Mineral Research. 2011; 26(2):420-427

5 Brennan J, Johansen A, Butler J, Stone M, Richmond P, Jones S et al. Place of residence and risk of fracture in older people: a population-based study of over 65-year-olds in Cardiff. Osteoporosis International : a Journal Established As Result of Cooperation Between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2003; 14(6):515-519

6 British Orthopaedic Association. The care of patients with fragility fracture. British Orthopaedic Association, 2007

7 Burge RT, Worley D, Johansen A, Bhattacharyya S, Bose U. The cost of osteoporotic fractures in the UK: projections for 2000-2020. Journal of Medical Economics. 2001; 4(1-4):51-62

8 Cauley JA, Wu L, Wampler NS, Barnhart JM, Allison M, Chen Z et al. Clinical risk factors for fractures in multi-ethnic women: the Women's Health Initiative. Journal of Bone & Mineral Research. 2007; 22(11):1816-1826

9 Chen JS, Sambrook PN, Simpson JM, Cameron ID, Cumming RG, Seibel MJ et al. Risk factors for hip fracture among institutionalised older people. Age & Ageing. 2009; 38(4):429-434

10 Collins GS, Mallett S, Altman DG. Predicting risk of osteoporotic and hip fracture in the United Kingdom: prospective independent and external validation of QFractureScores. BMJ. 2011; 342:d3651

11 Cummings SR, Marcus R, Palermo L, Ensrud KE, Genant HK. Does estimating volumetric bone density of the femoral neck improve the prediction of hip fracture? A prospective study. Journal of Bone and Mineral Research. 1994; 9(9):1429-1432

12 Cummins NM, Poku EK, Towler MR, O'Driscoll OM, Ralston SH. Clinical Risk Factors for Osteoporosis in Ireland and the UK: A Comparison of FRAX and QFractureScores. Calcified Tissue International. 2011; 89(2):172-177

13 Cystic Fibrosis Trust. Cystic fibrosis and bone health (factsheet). Bromley: Cystic Fibrosis Trust, 2011 Available from: www.cftrust.org.uk

14 Dargent-Molina P, Douchin MN, Cormier C, Meunier PJ, Breart G, EPIDOS study group. 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. Osteoporosis International. 2002; 13(7):593-599

15 DeLaet C, Kanis JA, Oden A, Johanson H, Johnell O, Delmas P et al. Body mass index as a predictor of fracture risk: a meta-analysis. Osteoporosis International. 2005; 16(11):1330-1338

16 Department of Health. Hospital Episode Statistics. 2006. Available from: http://www.hesonline.org.uk/Ease/servlet/ContentServer?siteID=1937&categoryID=192

17 Diez-Perez A, Gonzalez-Macias J, Marin F, Abizanda M, Alvarez R, Gimeno A et al. Prediction of absolute risk of non-spinal fractures using clinical risk factors and heel quantitative ultrasound. Osteoporosis International. 2007; 18(5):629-639

18 Donaldson MG, Palermo L, Schousboe JT, Ensrud KE, Hochberg MC, Cummings SR. FRAX and risk of vertebral fractures: the fracture intervention trial. Journal of Bone and Mineral Research. 2009; 24(11):1793-1799

19 Ensrud KE, Ewing SK, Cawthon PM, Fink HA, Taylor BC, Cauley JA et al. A comparison of frailty indexes for the prediction of falls, disability, fractures, and mortality in older men. Journal of the American Geriatrics Society. 2009; 57(3):492-498

20 Ensrud KE, Lui LY, Taylor BC, Schousboe JT, Donaldson MG, Fink HA et al. A comparison of prediction models for fractures in older women: is more better? Archives of Internal Medicine. 2009; 169(22):2087-2094

21 Fraser LA, Langsetmo L, Berger C, Ioannidis G, Goltzman D, Adachi JD et al. Fracture prediction and calibration of a Canadian FRAX[REGISTERED] tool: a population-based report from CaMos. Osteoporosis International. 2011; 22(3):829-837

22 Godden S, Pollock AM. The use of acute hospital services by elderly residents of nursing and residential care homes. Health and Social Care in the Community. 2001; 9(6):367-374

23 Guessous I, Cornuz J, Ruffieux C, Burckhardt P, Krieg MA. Osteoporotic fracture risk in elderly women: estimation with quantitative heel US and clinical risk factors. Radiology. 2008; 248(1):179-184

24 Hans D, Durosier C, Kanis JA, Johansson H, Schott-Pethelaz AM, Krieg MA. 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. Journal of Bone & Mineral Research. 2008; 23(7):1045-1051

25 Hans D, Schott AM, Duboeuf F, Durosier C, Meunier PJ, EPIDOS Group. Does follow-up duration influence the ultrasound and DXA prediction of hip fracture? The EPIDOS prospective study. Bone. 2004; 35(2):357-363

26 Harrison EJ, Adams JE. Application of a triage approach to peripheral bone densitometry reduces the requirement for central DXA but is not cost effective. Calcified Tissue International. 2006; 79(4):199-206

27 Hillier TA, Stone KL, Bauer DC, Rizzo JH, Pedula KL, Cauley JA et al. Evaluating the value of repeat bone mineral density measurement and prediction of fractures in older women: the study of osteoporotic fractures. Archives of Internal Medicine. 2007; 167(2):155-160

28 Hippisley-Cox J, Coupland C. Predicting risk of osteoporotic fracture in men and women in England and Wales: prospective derivation and validation of QFractureScores. BMJ. 2009; 339:1291-1295

29 Hollaender R, Hartl F, Krieg MA, Tyndall A, Geuckel C, Buitrago-Tellez C et al. Prospective evaluation of risk of vertebral fractures using quantitative ultrasound measurements and bone mineral density in a population-based sample of postmenopausal women: results of the Basel Osteoporosis Study. Annals of the Rheumatic Diseases. 2009; 68(3):391-396

30 Ito K, Hollenberg JP, Charlson ME. Using the osteoporosis self-assessment tool for referring older men for bone densitometry: a decision analysis. Journal of the American Geriatrics Society. 2009; 57(2):218-224

31 Johansen A, Evans RJ, Stone MD, Richmond PW, Lo SV, Woodhouse KW. Fracture incidence in England and Wales: a study based on the population of Cardiff. Injury. 1997; 28(9-10):655-660

32 Johansson H, Kanis JA, Oden A, Compston J, McCloskey E. A comparison of case-finding strategies in the UK for the management of hip fractures. Osteoporosis International : a Journal Established As Result of Cooperation Between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2012; 23(3):907-915

33 Johansson H, Oden A, Johnell O, Jonsson B, de Laet C, Oglesby A et al. Optimization of BMD measurements to identify high risk groups for treatmentGÇöA test analysis. Journal of Bone and Mineral Research. 2004; 19(6):906-913

34 Johnell O, Kanis JA. An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. Osteoporos Int. 2006; 17(12):1726-1733

35 Kanis JA, Johansson H, Johnell O, Oden A, De LC, Eisman JA et al. Alcohol intake as a risk factor for fracture. Osteoporosis International. 2005; 16(7):737-742

36 Kanis JA, Johansson H, Oden A, Johnell O, De LC, Eisman JA et al. A family history of fracture and fracture risk: a meta-analysis. Bone. 2004; 35(5):1029-1037

37 Kanis JA, Johansson H, Oden A, Johnell O, De LC, Melton III LJ et al. A meta-analysis of prior corticosteroid use and fracture risk. Journal of Bone & Mineral Research. 2004; 19(6):893-899

38 Kanis JA, Johnell O, De LC, Johansson H, Oden A, Delmas P et al. A meta-analysis of previous fracture and subsequent fracture risk. Bone. 2004; 35(2):375-382

39 Kanis JA, Johnell O, Oden A, Johansson H, De LC, Eisman JA et al. Smoking and fracture risk: a meta-analysis. Osteoporosis International. 2005; 16(2):155-162

40 Kanis JA, Oden A, Johnell O, Jonsson B, De LC, Dawson A. The burden of osteoporotic fractures: a method for setting intervention thresholds. Osteoporos Int. 2001; 12(5):417-427

41 Kaptoge S, Benevolenskaya LI, Bhalla AK, Cannata JB, Boonen S, Falch JA 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

42 Lee SH, Dargent-Molina P, Breart G, EPIDOS Group, Epidemiologie de lS. Risk factors for fractures of the proximal humerus: results from the EPIDOS prospective study. Journal of Bone & Mineral Research. 2002; 17(5):817-825

43 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. 2007; 40(4):991-996

44 Leslie WD, Berger C, Langsetmo L, Lix LM, Adachi JD, Hanley DA et al. Construction and validation of a simplified fracture risk assessment tool for Canadian women and men: results from the CaMos and Manitoba cohorts. Osteoporosis International. 2011; 22(6):1873-1883

45 Leslie WD, Lix LM, Johansson H, Oden A, McCloskey E, Kanis JA et al. Independent clinical validation of a Canadian FRAX tool: fracture prediction and model calibration. Journal of Bone & Mineral Research. 2010; 25(11):2350-2358

46 Leslie WD, Lix LM, Langsetmo L, Berger C, Goltzman D, Hanley DA et al. Construction of a FRAX[REGISTERED] model for the assessment of fracture probability in Canada and implications for treatment. Osteoporosis International. 2011; 22(3):817-827

47 Leslie WD, Tsang JF, Caetano PA, Lix LM, Manitoba Bone Density Program. Effectiveness of bone density measurement for predicting osteoporotic fractures in clinical practice. Journal of Clinical Endocrinology & Metabolism. 2007; 92(1):77-81

48 Leslie WD, Lix LM, Johansson H, Oden A, McCloskey E, Kanis J. Does osteoporosis therapy invalidate FRAX for fracture prediction? Journal of Bone and Mineral Research. 2012; [EPUB]:n/a

49 Lewis CE, Ewing SK, Taylor BC, Shikany JM, Fink HA, Ensrud KE et al. Predictors of non-spine fracture in elderly men: the MrOS study. Journal of Bone & Mineral Research. 2007; 22(2):211-219

50 McCann M, O'Reilly D, Cardwell C. A Census-based longitudinal study of variations in survival amongst residents of nursing and residential homes in Northern Ireland. Age and Ageing. 2009; 38(6):711-717

51 Mueller D, Econ H, Gandjour A. Cost-effectiveness of using clinical risk factors with and without DXA for osteoporosis screening in postmenopausal women. Value in Health. 2009; 12(8):1106-1117

52 National Institute for Health and Clinical Excellence. Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women (amended). (TA160). National Institute for Health and Clinical Excellence, 2011

53 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. 2008; 19(10):1431-1444

54 Nguyen ND, Pongchaiyakul C, Center JR, Eisman JA, Nguyen TV. Identification of high-risk individuals for hip fracture: a 14-year prospective study. Journal of Bone & Mineral Research. 2005; 20(11):1921-1928

55 Papaioannou A, Joseph L, Ioannidis G, Berger C, Anastassiades T, Brown JP et al. Risk factors associated with incident clinical vertebral and nonvertebral fractures in postmenopausal women: the Canadian Multicentre Osteoporosis Study (CaMos). Osteoporosis International. 2005; 16(5):568-578

56 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. 2010; 46(6):1661-1667

57 Popp AW, Senn C, Franta O, Krieg MA, Perrelet R, Lippuner K. Tibial or hip BMD predict clinical fracture risk equally well: results from a prospective study in 700 elderly Swiss women. Osteoporosis International. 2009; 20(8):1393-1399

58 Porthouse J, Birks YF, Torgerson DJ, Cockayne S, Puffer S, Watt I. Risk factors for fracture in a UK population: a prospective cohort study. Quarterly Journal of Medicine. 2004; 97(9):569-574

59 Robbins J, Aragaki AK, Kooperberg C, Watts N, Wactawski-Wende J, Jackson RD et al. Factors associated with 5-year risk of hip fracture in postmenopausal women. JAMA. 2007; 298(20):2389-2398

60 Sambrook PN, Cameron ID, Chen JS, Cumming RG, Lord SR, March LM et al. Influence of fall related factors and bone strength on fracture risk in the frail elderly. Osteoporosis International. 2007; 18(5):603-610

61 Sambrook PN, Flahive J, Hooven FH, Boonen S, Chapurlat R, Lindsay R et al. Predicting fractures in an international cohort using risk factor algorithms, without bone mineral density. Journal of Bone & Mineral Research. 2011;

62 Sandhu SK, Nguyen ND, Center JR, Pocock NA, Eisman JA, Nguyen TV. Prognosis of fracture: evaluation of predictive accuracy of the FRAX algorithm and Garvan nomogram. Osteoporosis International. 2010; 21(5):863-871

63 Schwartz AV, Nevitt MC, Brown BW, Jr., Kelsey JL. Increased falling as a risk factor for fracture among older women: the study of osteoporotic fractures. American Journal of Epidemiology. 2005; 161(2):180-185

64 Seeley DG, Kelsey J, Jergas M, Nevitt MC. 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

65 Sernbo I, Johnell O. Consequences of a hip fracture: a prospective study over 1 year. Osteoporos Int. 1993; 3(3):148-153

66 Singer BR, McLauchlan GJ, Robinson CM, Christie J. Epidemiology of fractures in 15,000 adults: the influence of age and gender. Journal of Bone and Joint Surgery British Volume. 1998; 80(2):243-248

67 Sornay-Rendu E, Munoz F, Delmas PD, Chapurlat RD. The FRAX tool in French women: How well does it describe the real incidence of fracture in the OFELY cohort. Journal of Bone and Mineral Research. 2010; 25(10):2101-2107

68 Stewart A, Kumar V, Reid DM. Long-term fracture prediction by DXA and QUS: a 10-year prospective study. Journal of Bone & Mineral Research. 2006; 21(3):413-418

69 Stolee P, Poss J, Cook RJ, Byrne K, Hirdes JP. Risk factors for hip fracture in older home care clients. Journals of Gerontology Series A-Biological Sciences & Medical Sciences. 2009; 64(3):403-410

70 Tanaka S, Yoshimura N, Kuroda T, Hosoi T, Saito M, Shiraki M. The Fracture and Immobilization Score (FRISC) for risk assessment of osteoporotic fracture and immobilization in postmenopausal women--A joint analysis of the Nagano, Miyama, and Taiji Cohorts. Bone. 2010; 47(6):1064-1070

71 Tremollieres FA, Pouilles JM, Drewniak N, Laparra J, Ribot CA, Dargent-Molina P. Fracture risk prediction using BMD and clinical risk factors in early postmenopausal women: sensitivity of the WHO FRAX tool. Journal of Bone and Mineral Research. 2010; 25(5):1002-1009

72 UK Cystic Fibrosis Trust Bone Mineralisation Working Group. Bone mineralisation in cystic fibrosis. Cystic Fibrosis Trust, 2007

73 van Staa TP, Geusens P, Kanis JA, Leufkens HG, Gehlbach S, Cooper C. A simple clinical score for estimating the long-term risk of fracture in post-menopausal women. QJM. 2006; 99(10):673-682

74 van Staa TP, Geusens P, Pols HA, De LC, Leufkens HG, Cooper C. A simple score for estimating the long-term risk of fracture in patients using oral glucocorticoids. QJM. 2005; 98(3):191-198

75 van Staa TP, Leufkens HG, Abenhaim L, Zhang B, Cooper C. Oral corticosteroids and fracture risk: relationship to daily and cumulative doses. Rheumatology (Oxford, England). 2000; 39(12):1383-1389

76 Vogt MT, Cauley JA, Tomaino MM, Stone K, Williams JR, Herndon JH. Distal radius fractures in older women: a 10-year follow-up study of descriptive characteristics and risk factors. The study of osteoporotic fractures. Journal of the American Geriatrics Society. 2002; 50(1):97-103

77 Wolinsky FD, Bentler SE, Liu L, Obrizan M, Cook EA, Wright KB et al. Recent hospitalization and the risk of hip fracture among older Americans. Journals of Gerontology Series A-Biological Sciences & Medical Sciences. 2009; 64(2):249-255