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RISK FACTORS FOR LOW BMD IN HEALTHY MEN AGE 50 YEARS OR OLDER: A SYSTEMATIC REVIEW

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RISK FACTORS FOR LOW BMD IN HEALTHY MEN AGE 50 YEARS OR OLDER: A SYSTEMATIC REVIEW

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MINI ABSTRACT

In this systematic review, we summarize risk factors for low bone mineral density and bone loss in healthy men age 50 years or older. Consistent risk factors were: age, smoking, low weight, physical/functional limitations and previous fracture. Data specific to men has clinical and policy implications.

ABSTRACT

Introduction: Osteoporosis is a significant healthcare problem in men as well as women, yet the majority of evidence on diagnosis and management of osteoporosis is focused on postmenopausal women. The objective of this systematic review is to examine risk factors for low bone mineral density (BMD) and bone loss in healthy men age 50 years or older.

Methods: A systematic search for observational studies was conducted in MEDLINE, Cochrane Database of Systematic Reviews, DARE, CENTRAL, CINAHL and Embase, Health STAR. The three main search concepts were bone density, densitometry and risk factors. Trained reviewers assessed articles using a priori criteria.

Results: Of 642 screened abstracts, 299 articles required a full review, and 25 remained in the final assessment. Consistent risk factors for low BMD/bone loss were: Advancing age, smoking, and low weight/weight loss. Although less evidence was available, physical/functional limitations and prevalent fracture (after age 50) were also associated with low BMD/bone loss. The evidence was inconsistent or weak for: physical activity, alcohol consumption, calcium intake, muscle strength, family history of fracture/osteoporosis, and height/height loss.

Conclusion: In this systematic review, we identified several risk factors for low BMD/bone loss in men that are measurable in primary practice.

KEY WORDS

bone density; DXA; men; osteoporosis; risk factors; systematic review

INTRODUCTION

Osteoporosis is a disease characterized by low bone mineral density (BMD) and structural deterioration of bone tissue leading to bone fragility and increased susceptibility to fractures, particularly of the hip, spine and wrist [1]. Although not as common as in women, osteoporosis remains a significant healthcare problem in men. In the Canadian Multicentre Osteoporosis Study (CaMos), the estimated prevalence of osteoporosis (BMD T-score ≤ -2.5) at the femoral neck and/or lumbar spine in men 50 years or older is 6.6% (in women the comparable estimate is 15.8%) [2].

Although BMD should not be used in isolation to predict fractures, BMD predicts osteoporotic fractures in men independently of age, body weight, and prevalent fractures and regardless of the site of measurement [3]. In a meta-analysis, the risk ratio for hip fractures increased by 2.94-fold per SD decrease in femoral neck BMD for men age 65 or older [4]. The prospective Mr. OS study of older men also confirmed that hip BMD is strongly associated with risk of non-vertebral fractures, particularly those of the hip (3.2-fold increased risk per SD decrease) [5]. Although it was a weaker predictor, spine BMD also predicted fractures in men. When results were compared with the related study in women (SOF: Study of Osteoporotic Fractures), women were more likely to fracture than men until age 80, after which the difference between the sexes was no longer significant. The association between BMD and fracture risk is at least as strong in men as in women [5].

Clearly, fractures are the most serious consequence of osteoporosis. One quarter of all hip fractures occur in men [6;7], and the prevalence of a radiographic vertebral deformity (Grade 1 or Grade 2) in men 50 years or older is comparable to women (21.5% versus 23.5%) [8].

Furthermore, fracture-related excess mortality, morbidity and institutionalization may be greater for men than for women [6;9-11].

Research to date has largely focused on the diagnosis and management of osteoporosis in postmenopausal women. Previous guidelines have not adequately addressed the diagnosis and management of osteoporosis in men. The objective of this systematic review was to evaluate the evidence regarding risk factors for low BMD and bone loss in healthy men age 50 years or older.

METHODS

Target Population

This systematic literature review represents a synthesis of the evidence on risk factors for low BMD and bone loss in healthy men age 50 years or older. We were interested in factors that could be assessed in primary practice via clinical history. The underlying assumption is that men with co-morbidities and/or taking medications that are known to be associated with low BMD or fracture should be referred for BMD testing. Medical conditions and medications associated with an increased risk of osteoporosis are outlined elsewhere [12].

Search Strategy and Eligibility

A research librarian drafted the final search protocol and conducted the literature review. The search was carried out on the following databases via the OVID search interface: MEDLINE, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects (DARE), Cochrane Central Register of Controlled Trials (CENTRAL), CINAHL and Embase, Health STAR between January 1, 1990 and January 2006. The search was divided into 3 main concepts which were bone density, densitometry and risk factors. The search terms used in the database search for the bone density concept were “Bone density” OR “bone mineral content” OR “bone loss” OR “BMD” and these were combined with the densitometry concept “bone density testing”; “Densitometry” OR “x-ray densitometry” OR “x-ray absorptiometry” and then combined with the risk concept “Exp risk” OR “relative and risk” OR “causation” OR “odds and ratio”. Limits for age criteria were limited to 45 years or older (our population of interest was men age 50 or older, however the MEDLINE limit is age 45 or older), and English abstracts.

Only observational studies including prospective cohort, retrospective cohort, cross-sectional and case-control studies were included in the search. Randomized controlled trials, case series, case reports, letters, editorials, and narrative reviews were excluded from the search.

BMD measurement sites were the lumbar spine, proximal femur (total hip, femoral neck, or greater trochanter), or total body. Only studies with dual energy x-ray absorptiometry (DXA) measurements were considered. Studies with variables that could not be easily assessed in primary practice (e.g., genetic markers), or with inadequate description of risk factor measurement were excluded. Articles evaluating clinical risk assessment tools were also considered. Studies investigating osteoporosis associated with diseases or medications known to affect bone metabolism were excluded.

Quality Assessment

Titles and abstracts were screened for eligibility. When eligibility was uncertain, the full-text article was retrieved. Trained reviewers assessed the methodological quality of the studies using a quality assessment checklist. The internal validity of each study was assessed using the following criteria: appropriate study design, standardized bone densitometry technique, BMD assessment blinded to exposure (risk factor) status, valid risk factor measurement, minimization of bias (selection bias; recall bias), duration of follow-up, loss to follow-up, appropriate statistical analysis, and control for confounding variables.

An individual grade was assigned to each study based on the rating system of the United States Preventive Services Task Force (USPSTF) [13]. In brief, the USPSTF has a three-category rating of the internal validity of each study: 'Good', 'Fair', and 'Poor' (Table 1). Studies graded 'Good' or 'Fair' were further abstracted into evidence tables; studies assigned a grade of 'Poor'

were excluded and not considered further. The majority of studies were reviewed in duplicate; where disagreement arose, the lead investigator was consulted for a final rating.

Data abstracted included a description of the patient population (inclusion and exclusion criteria, mean age, ethnicity, country, sample size), study design, duration of follow-up, risk factors assessed, precision of DXA technique, BMD measurement site(s), and results (odds ratios, regression beta-coefficients and/or R^2 values) reported as values after adjustment for confounding. Unless otherwise specified, osteoporosis was defined as a T-score $\leq$ - 2.5.

Data Synthesis

Due to the heterogeneity of outcomes, a meta-analysis was not carried out. In summarizing the evidence for each risk factor, we took into account the study design (prospective versus cross-sectional), quality and quantity of individual studies (i.e., number of 'good' versus 'fair'), and consistency of findings (i.e., Did all studies find a significant association? Was the direction of the effect the same?). Where evidence was insufficient (i.e., few studies available) this was also noted.

RESULTS

A flowchart of the selection process is provided in Figure 1. The search strategy identified 642 relevant abstracts. In total, 25 articles from 18 different studies (summarized in Table 2**)** met both the inclusion and quality criteria. Some of the studies classified as cross-sectional were actually from prospective cohort studies, but were cross-sectional analyses of the cohorts at baseline. Male sample sizes in the final group of studies ranged from 137 to 5995 with a median of 458. Study cohorts were mainly Caucasian participants, with the exception of the following studies: Japanese - Yoshimura 1998 [14] and 2002 [15]; Chinese - Cheung 2005 [16]; Kung 2005 [17]; Lau 2006 [18]; and Lynn 2005 [19]. In the Mr. Os study in the United States [20], approximately 11% of participants were non-Caucasian including 4.1% African American, 3.2% Asian, 2.1% Hispanic/Latino, and <3% other ethnicities.

For each risk factor below, the evidence is presented for cross-sectional BMD, and if longitudinal studies were available, for bone loss. Hip and lumbar spine results are presented separately only if the association varied between sites. Results reported below are based on multivariable analyses unless otherwise mentioned. The majority are based on large cohort studies that examined the independent contribution of several potential osteoporosis risk factors simultaneously. The evidence for each risk factor (including quantity, quality, consistency, and direction of association) is summarized in Table 3 and Figure 2.

Advancing Age

Eleven studies (6 longitudinal, 5 cross-sectional) were included in the assessment of BMD and age. At the hip, there was consistent evidence that BMD declines with age [20-28]. In men age 50 to 80 years or older (age range varied by study), in multivariable analyses hip BMD decreased

linearly with age at a rate of approximately 1.5 - 2.5% per decade [20;26] and decreased by up to 5% per decade in univariate analyses [20;25;28]. In longitudinal studies, the crude rate of bone loss (expressed as a percentage of baseline BMD/year) at the hip was approximately 0.3 - 0.5% per year [21-24].

At the lumbar spine, on the other hand, several studies reported that BMD increased with age [15;20;22;29]. The overall increase was approximately 1.5 – 3.5% per decade (unadjusted and adjusted) for men age 60 years and older [20;22]. In a 10-year longitudinal analysis (unadjusted), Yoshimura et al. [15] reported that men in their fifties increased by 0.55%/year, no change in the sixties and decreased by 0.16%/year in the seventies. The increases seen at the lumbar spine may be explained by age-related degenerative changes (e.g., osteophytes) that may falsely elevate spine BMD. This was evidenced by one study [25] in which a non-significant increase (unadjusted) in BMD occurred after age 55, however when men with severe arthritis were excluded, lumbar spine BMD decreased significantly with age. Two other studies [21;27] (age range 50 to 80+ years) reported that lumbar spine BMD decreased with age. In the longitudinal study [21], the bone loss was approximately 0.37% over four years.

In longitudinal studies, whether the annual rate of bone loss is accelerated in older age strata was somewhat inconsistent at the hip. In three studies [15;23;24], the crude rate of loss at the hip was accelerated at later age strata (up to age 80); three other studies [21;22;29] did not find accelerated loss. At the spine, three studies [21;22;29] did not find accelerated rates with age; however one study found an accelerated gain during the fifties [15].

Smoking

Eleven studies (3 longitudinal, 8 cross-sectional) were included in the assessment of BMD and smoking. In four studies [18;28;30;31] both current and former smokers were at greater risk for low BMD compared with non-smokers, except in one study [20] where the risk was not significant and was attenuated particularly by adjusting for weight. In these studies, current smokers had greater risk than former smokers at the hip. At the lumbar spine, the risk was similar for current and former smokers [18;28;30-32].

A dose response relationship with lifetime tobacco exposure (pack-years of smoking) was present in three studies [18;31;32], particularly in those who smoked in early adulthood [31], but was not present in two others [33;34]. Certain smoking sub-groups may also be at increased risk: men with >20 pack years [32], and current smokers with low body weight (<75 kg) [32]. In former smokers, those who quit more than 10 years ago may have substantially higher BMD than those who have quit more recently (within 10 years) [31].

In two longitudinal studies, current smoking was predictive of bone loss at the hip [21;23] occurring at approximately double the rate compared with never smokers [21;23] and even former smokers [21]. In a third study, after adjustment for age and rate of change in body mass index (BMI), current smoking was associated with a greater rate of bone loss at the trochanter [29].

Weight/Weight Loss

Seventeen studies (7 longitudinal, 10 cross-sectional) were included in the assessment of BMD and weight/weight loss. In nine studies [16-20;27;28;35;36] weight or BMI were positively associated with BMD at both sites, and in one study at the lumbar spine only [34]. The magnitude

of this relationship was consistent across studies in different geographic regions [China [18], United States [20], Europe [26;36]]: BMD was approximately 3-7% higher at the hip and lumbar spine for every 10 kg increase in weight.

In six longitudinal studies [14;21-24;35] low baseline weight or BMI predicted subsequent bone loss at the hip. Furthermore, weight loss was associated with an increased rate of bone loss at the hip [14;21;22;24], and at the lumbar spine [[21] adjusted; [29] unadjusted]. In particular, a weight loss of >1% per year may substantially elevate the risk of lower BMD [24]. In one large cohort study [21], men who lost ≥5% of their baseline weight had approximately double the rate of bone loss than men whose weight remained stable. In another study [22], those who gained weight had very little or no bone loss.

Physical/Functional Limitations

Four studies (3 longitudinal, 1 cross-sectional) were included in the assessment of BMD and physical/functional limitations. These included measures of 1) lower limb disability: impairments in arising, walking, bending, getting out of a car [23]; 2) physical functioning rated on a 5-point scale [24]; 3) being chair or bed bound [21]; and 4) rising from a chair without using the arms ['Get Up and Go' test [20]]. All of these measures of physical/functional limitations predicted bone loss at the hip [21;23;24] or were independently associated with BMD [20]. Men with lower limb disability [23] or who spent most of the day in bed or in a chair [21] had approximately double the rate of hip bone loss than men without these limitations. Men who could rise from a chair without using arms had 2-4% higher hip BMD than those who could not [20].

Prevalent Fracture (after age 50)

Five studies (1 longitudinal, 4 cross-sectional) were included in the assessment of BMD and prevalent fracture. In four cross-sectional studies [17;18;20;28] that examined this risk factor, a negative association was found between prevalent fracture and BMD. Only one longitudinal study [29] examined the relationship between prevalent fracture and rate of bone loss. In univariate analysis, this demonstrated an association with bone loss at the lumbar spine, but may have lacked power to detect an association at the hip.

Alcohol

Fifteen studies (5 longitudinal, 10 cross-sectional) were included in the assessment of BMD and moderate alcohol consumption. There was inconsistent evidence from the cross-sectional studies: five studies found a positive association between moderate alcohol consumption and BMD at the hip [20;36;37] and/or lumbar spine [20;28;34], while five others did not find an independent association at either BMD site [16-18;27;30].

Moderate alcohol intake was not predictive of the rate of bone loss in several longitudinal studies [21-24].

Physical Activity

Twelve studies were included in the assessment of BMD and physical activity (4 longitudinal, 8 cross-sectional). In the cross-sectional studies, there was inconsistent evidence: five studies found a positive association between BMD and physical activity (regular activity or lifetime activity) at both sites [16;17;20;27;36], however the association was weak i.e., <1% change in BMD per SD of physical activity score or accounted for a small proportion of the variance. In three other studies, physical activity was not independently associated with BMD [35] [18;28]. In

longitudinal studies, physical activity was not predictive of bone loss [21;22;24]. It is difficult to compare studies, as study duration varied as well as the accuracy and method of measuring the exercise variable.

Calcium Intake

Fourteen studies were included in the assessment of BMD and calcium (5 longitudinal, 9 cross-sectional). There was inconsistent evidence from the cross-sectional studies: five studies found a positive association between calcium intake (dietary and/or supplements) and BMD at the lumbar spine and hip [17;20;34-36]. In two studies [20;35], the association was weak i.e., <1% change in BMD per SD of calcium intake or accounted for a small proportion of the variance. Four other studies did not find an independent association at either BMD sites [16;18;27;28].

In five longitudinal studies, the evidence was also inconsistent. In two studies [[23] adjusted; [29] unadjusted], dietary calcium intake was predictive of bone loss. In particular [23], men in the lower quartiles of calcium intake (<1100 mg/day) had approximately double the rate of bone loss. In the other three studies [21;22;24], calcium intake (dietary or supplements) was not predictive of bone loss.

Muscle Strength

Six studies (1 longitudinal, 5 cross-sectional) were included in the assessment of BMD and muscle strength. Of five cross-sectional studies that examined this factor, three reported an association between BMD and muscle strength [grip strength: [18;20]; quadriceps strength: [35]], however the effect was weak i.e., <1% change in BMD per SD of muscle strength, measured in kg. A fourth study [34] reported a stronger positive association between triceps and abdominal

strengths and hip BMD. In a fifth study [16], muscle strength was not an independent associate of BMD.

In a longitudinal study [14], greater baseline grip strength predicted decreased bone loss at the hip.

Family History of Fracture/Osteoporosis

Four studies (all cross-sectional) were included in the assessment of BMD and family history of fracture/osteoporosis. In two studies [28;36], an association was not found between family history of fracture [36] or osteoporosis [28] and low BMD, however maternal history was not recorded separately. Few parental fractures were reported in the one study (possibly lacked power to detect an association), and the other study only examined family history of osteoporosis. Recall bias is likely an important factor with this variable. In the two studies that examined maternal and paternal history separately [20;38], moderate declines in BMD were found for maternal [20;38] and paternal [20] history of fracture and/or osteoporosis. There were no longitudinal studies that evaluated this risk variable.

Height/Height Loss

Eight studies were included in the assessment of BMD and height/height loss (1 longitudinal, 7 cross-sectional). In five of eight cross-sectional studies, height was not independently associated with BMD [16;26;28;30;34]. In the remaining three studies [17;20;30], there were inconsistencies regarding the sites and direction of the association. Only one longitudinal study [14] examined height loss and the effect was modest: for each 1 cm of height lost annually, BMD decreased by 0.17%/year at the hip.

Summary

As summarized in Table 3 and Figure 2, there was consistent evidence that advancing age, smoking (current and/or former), and low weight/weight loss each had a negative impact on BMD and bone loss in men age 50 years or older. Physical/functional limitations and prior fragility fracture also each had a negative impact on BMD and bone loss, however fewer studies examined these factors. In longitudinal studies, physical activity and alcohol were not predictive of bone loss; in cross-sectional studies, there was inconsistent evidence regarding an association with BMD. The evidence was inconsistent or weak for: calcium, muscle strength, family history of fracture/osteoporosis, and height/height loss.

DISCUSSION

This systematic review reinforces that the primary risk factors, advancing age and prior fragility fracture, are markers of low BMD in men. In addition, smoking, low body weight, and weight loss were consistent risk factors and should be given consideration in assessing the need for densitometry. Furthermore, men with poor physical functioning, lower limb disability, and/or confined to a chair or bed may also be at increased risk. Although men with co-morbidities and/or taking medications were excluded from this review, treatments such as glucocorticoids and androgen deprivation therapy have also been associated with bone loss [39;40] and increased risk of fractures [40-42].

There are many similarities in risk factors between men and women. In a systematic review of osteoporosis in postmenopausal women [43], increasing age, white race, low weight or weight loss, history of previous fracture, family history of fracture, history of falls, and low scores on one or more measures of physical activity or function were consistently associated with increased risks of low bone density and fractures. Factors that were less consistent across studies, but had some significant association were: smoking, alcohol use, caffeine use, low calcium and vitamin D intake, and use of certain drugs.

This review should be taken in the context of previous recommendations. The National Osteoporosis Foundation recommends testing men age 70 years and older, regardless of clinical risk factors, and men age 50-70 years based on their clinical risk profile [12]. The 2002 Osteoporosis Canada clinical practice guidelines for the diagnosis and management of osteoporosis recommend BMD testing for individuals age 65 years and over [44]. Recently, Khan et al. [45] updated the 2002 guidelines with additional information specific to men. Younger men should undergo bone densitometry in the presence of secondary causes of bone loss [45],

and if other key risk factors for fracture are present, including a fragility fracture (after age 40, especially vertebral compression fractures), and systemic glucocorticoids (≥7.5 mg prednisone/day for a duration of 3 or more months).

The relationship between BMD and fracture risk in men has been well documented [3;4], and the predictive power of BMD remains fairly constant over time (i.e., years since baseline measure). However, further research is needed since a large percentage of fractures occur in men with BMD T-scores above the osteoporotic range [3].

The Canadian Association of Radiologists (CAR) and Osteoporosis Canada [46] have developed an integrated model to assist clinicians in utilizing bone densitometry reports and assessing a patient's 10-year fracture risk. This integrated model incorporates both BMD scores and other primary clinical risk factors. A patient is classified into a 'risk category' (low, moderate, high) according to gender, age, and lowest BMD T-score. If the patient also has 1) a fragility fracture after age 40, or 2) taken glucocorticoid therapy for >3 months, then they are elevated to the next category of risk. If both of these factors are present, they are considered 'high risk' irrespective of BMD.

In general, our results regarding risk factors for BMD are consistent with a series of meta-analyses which examined risk factors for osteoporotic fracture [47-53]. The World Health Organization (WHO) has developed a tool (FRAX) that integrates both clinical risk factors and BMD (femoral neck T-score) in order to predict fracture risk [54;55]. Population-based cohorts in Europe, North America, Asia and Australia were utilized to develop the model. Both paper-based and computer-driven tool are available, and by entering the requested information on clinical risk factors, 10-year probabilities for hip fracture and major osteoporotic fracture (clinical spine, hip,

forearm, or shoulder) are generated. The clinical risk factors examined are: BMD (if not available, BMI can be used); age (between 40 and 90 years); BMI; prior fracture history, parental hip fracture (patient's mother or father), use of oral glucocorticoids, rheumatoid arthritis, secondary osteoporosis (including type I diabetes, osteogenesis imperfecta in adults, untreated long-standing hyperthyroidism, hypogonadism, premature menopause (<45 years), chronic malnutrition, or malabsorption and chronic liver disease), current smoking, and alcohol (3 or more units/day). Although our goal was to examine risk factors for low BMD, our results are consistent with these clinical risk factors for fracture, with three caveats: 1) We did not examine use of glucocorticoids or any disease states as our goal was to examine healthy men. 2) We did not find a negative association with alcohol; however the majority of the studies we examined did not look at excessive alcohol use. 3) Only four cross-sectional studies were available for parental history; two studies found a moderate association with BMD and parental history of fracture and/or osteoporosis, and two studies did not find an association (few parental cases were reported and they may have lacked power; additionally one study only examined history of osteoporosis and not fracture).

The present study has some limitations that should be mentioned. Due to the heterogeneity of outcomes in the observational studies we examined, a meta-analysis was not carried out. It was difficult to provide single summary statements; for many risk factors the quality and strength and/or direction of association was varied amongst studies. However, we attempted to standardize our approach as best as we could by summarizing the association, quality and quantity for each risk factor. Furthermore, despite several large cohort studies, no single study included all risk factors and outcomes of interest. The quantity of studies available for some risk

factors was lacking, particularly for muscle strength, family history of fracture/osteoporosis, height loss, physical/functional limitations, and prevalent fracture (after age 50).

Study cohorts were mainly Caucasian participants, however several studies were Asian cohorts (Japanese and Chinese) [14-19], and the Mr. OS study in the United States [20] included some non-Caucasian participants (approximately 11%). There did not appear to be major differences in risk factors between these studies, however it is recognized that not all ethnicities were represented in our review of the literature.

Conclusion

Previous guidelines have not adequately addressed the management of osteoporosis in men. Risk assessment has been primarily based on data from post-menopausal women, and does not incorporate available research regarding younger individuals and men. In this systematic review, we evaluated the evidence from 25 articles meeting quality criteria and identified several consistent risk factors for low BMD in healthy men aged 50 years or older.

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Table 1: Quality Grading Of Individual Studies

Grade	Definition
Good	A study that meets all the criteria for that specific design
Fair	A study that meets most of the criteria but does not contain any fatal flaws[a] that invalidate its results
Poor	A study that contains one or more fatal flaws[a]

[a]A fatal flaw in our systematic review included no description of selection criteria and lack of adjustment for any confounders, especially weight. If selection criteria were not described, but there was adequate adjustment for confounders, especially weight, then the study was included.

Adapted from: Harris et al., Current methods of the U.S. Preventive Services Task Force: a review of the process [13].

Table 2: Studies Included in the Final Assessment

Author/Year Rating	Study Design Country	Description of Male Cohort[a]
Burger 1998 [23] Good	Longitudinal (2-year) Netherlands	- N = 1856 - Population-based cohort (entire district invited);74% follow-up - Mean age = 66.7 (SD 7.2) - Age strata (% of participants): 55-59 (21%); 60-69 (48%); 70-79 (27%); 80+ (4%)
Dennison 1999 [22] Good	Longitudinal (4-year) United Kingdom	- N = 173 - Population-based cohort (entire district invited);77% follow-up - Mean age = 66.1 (SD 3.2) - Age range: 60-75
Hannan 2000 [21] Good	Longitudinal (4-year) United States	- N = 278 - Osteoporosis sub-study: surviving participants from the Framingham population-based cohort; 63% follow-up - Mean age = 74.5 (SD 4.5) - Age range: 67-90

Author/Year Rating	Study Design Country	Description of Male Cohort[a]
Knoke 2003 [24] Fair	Longitudinal (4-year) United States	- N = 469 - Osteoporosis sub-study: surviving participants from the Rancho Bernardo population-based cohort; 60% follow-up - Mean age = 70.6 (SD 8.3) - Age range: 54-87
Naves 2005 [29] Fair	Longitudinal (4-year) Spain	- N = 150 - Population-based cohort (random selection);79% follow-up - Mean age = 63.4 (SD 8.4) - Age range: 50-80+
Yoshimura 1998 [14] Good	Longitudinal (3-year) Japan (Taiji)	- N = 181 - Population-based cohort (random selection for DXA sub-study); 91% follow-up - Age strata: 50 recruited for each decade, 40-49, 50-59, 60-69, 70-79

Author/Year Rating	Study Design Country	Description of Male Cohort[a]
Yoshimura 2002 [15] Good	Longitudinal (10-year) Japan (Miyama)	- N = 137 - Population-based cohort (random selection for DXA sub-study); 69% follow-up - Age strata: 50 recruited for each decade, 40-49, 50-59, 60-69, 70-79
Bendavid 1996 [27] Fair	Cross-sectional United States	- N = 218 - Osteoporosis sub-study: surviving participants from the Rancho Bernardo population-based cohort - Mean age = 58.0 (SD 3.7) - Age range: 50-64
Cauley 2005 [20] Good	Cross-sectional United States (Mr. OS)	- N = 5995 - Population-based cohort (multiple recruitment strategies including mass mail-out to population registries) - Mean age = 73.7 (SD 5.9) - Age strata (% of participants): 65-69 (30%); 70-74 (29%); 75-79 (24%); 80+ (18%)[56]

Author/Year Rating	Study Design Country	Description of Male Cohort[a]
Cheung 2005 [16] Fair	Cross-Sectional Hong Kong	- N = 407 - Volunteers recruited from health talks/fairs - Mean age= 68.4 (SD 10.4) - Age range: 50-96
Huuskonen 2000 [34] Fair	Cross-sectional Finland	- N = 140 - Population-based cohort (random selection) - Mean age = 58.1 (SD 2.9) - Age range: 54-63
Kiel 1996 [31] Fair	Cross-sectional United States	- N = 448 - Osteoporosis sub-study: surviving participants from the Framingham population-based cohort; 40 years of smoking data included - Mean age = 75 - Age range: 68-98

Author/Year Rating	Study Design Country	Description of Male Cohort[a]
Kung 2005 [17] Fair	Cross-Sectional Hong Kong	- N = 420 - Volunteers recruited from health talks/fairs - Mean age = 65 - Age range: 50-93
Lau 2006 [18] Fair	Cross-sectional Hong Kong (Mr. OS)	- N = 2000 - Volunteers recruited from housing estates, community centers - Age range: 65-92 - Age strata (% of participants): 65-69 (33%); 70-79 (35%); 75+ (31%)
Looker 2004 [38] Fair	Cross-Sectional United States (NHANES III)	- N = 2613 - Population-based cohort (random, multistage probability design) - Mean age = 52.3 (with maternal OP history); 44.9 (No maternal OP history) - Age range: 20-80+[b]

Author/Year Rating	Study Design Country	Description of Male Cohort[a]
Lunt 1997 [26] Fair Lunt 2001 [36] Good	Cross-sectional Europe (EVOS)	- N = 2228 - Population-based cohort (random selection) - Mean age = 65 (SD 8) - Age range: 50-80
Lynn 2005 [19] Fair	Cross-Sectional Hong Kong	- N = 1970 - Volunteers recruited from housing estates, community centers, nursing homes - Mean age = 73 (SD 5)
May 1994 [33] May 1995 [37] Fair	Cross-sectional United Kingdom	- N = 453 [33] and N=458 [37] - Volunteers from selected general medical practices (all eligible men) - Mean age = 69 (SD 3) - Age range: 64-76

Author/Year Rating	Study Design Country	Description of Male Cohort[a]
Nguyen 1994 [30] Nguyen 2000 [35] Good	Cross-sectional Australia (Dubbo)	- N= 690 [35] and N = 709 [30] - Population-based cohort (entire district invited) - Mean age: 69.5 (SD 6.5) - Age strata (% of participants): 60-69 (58%); 70-79 (33%); 80+ (9%)
Orwoll 2000 [28] Fair	Cross-sectional United States	- N = 355 - Volunteers recruited from 3 rural communities (local advertising) - Mean age = 71.5 (SD 7.4) - Age range: 60-92
Szulc 2000 [25] Szulc 2002 [32] Fair	Cross-sectional France (MINOS)	- N = 719 [32] and N = 777 [25] - Population-based cohort (random sample from health insurance company) - Age range: 51-85 - Age strata (% of participants): 51-60 (25%); 61-70 (52%); 71+ (23%)

[a]Sample sizes for longitudinal studies are participants who completed both baseline and follow-up measures. [b]The cohort included men 20 years and older, however a separate analysis was conducted for men 50+.

Table 3: Risk factors for Low BMD in Men Age 50 or Older: Summary of Evidence

	Studies in Final Assessment: Study Design, Quantity, Quality[a]	Consistent Evidence?[b]		Direction of Association with BMD
		BMD	Bone Loss	
Advancing Age	Longitudinal: 4 good/2 fair Cross-sectional: 5 fair	Hip: Yes Spine: No	Yes	Hip: Negative[c] Spine: Positive/Negative
Smoking (current and/or former)	Longitudinal: 2 good/1 fair Cross-sectional: 2 good/6 fair	Yes[d]	Yes	Negative
Baseline Weight/Weight Loss	Longitudinal: 5 good/2 fair Cross-sectional: 2 good/8 fair	Yes	Yes	Baseline Weight: Positive Weight Loss: Negative
Physical/Functional Limitations	Longitudinal: 2 good/1 fair Cross-sectional: 1 good	Only 1 study	Yes	Negative (except for the Get up and Go test)[e]
Prevalent Fracture (after age 50)	Longitudinal: 1 fair Cross-sectional: 1 good/3 fair	Yes	Only 1 study	Negative
Alcohol	Longitudinal: 3 good/1 fair Cross-sectional: 2 good/8 fair	No	Yes	No association/Positive[f]

Physical Activity	Longitudinal: 2 good/1 fair Cross-sectional: 3 good/5 fair	No	Yes	No association/Positive[f]
Calcium	Longitudinal: 3 good/2 fair Cross-sectional: 2 good/9 fair	No	No	No association/Positive
Muscle Strength	Longitudinal: 1 good Cross-sectional: 2 good/3 fair	No	Only 1 study	Positive
Family History of fracture/osteoporosis	Cross-sectional: 1 good/3 fair	No	No studies available	Negative
Height/Height Loss	Longitudinal: 1 fair Cross-sectional: 2 good/5 fair	No	Only 1 study	No association/Inconsistent[g]

[a]Individual quality rating for each study. [b] Any conflicting results for or against an association (or in the direction of the association) between the risk factor and BMD/bone loss?; [c]The rate of loss at the hip may be accelerated in older age strata; [d]In one study the decrease in BMD for smokers was non-significant [20]; [e]Get up and Go test was positively associated. [f]Either positive or no association in cross-sectional studies. No association with bone loss in any longitudinal study. [g]The majority of studies did not find an association; in other studies the direction of effect was inconsistent.

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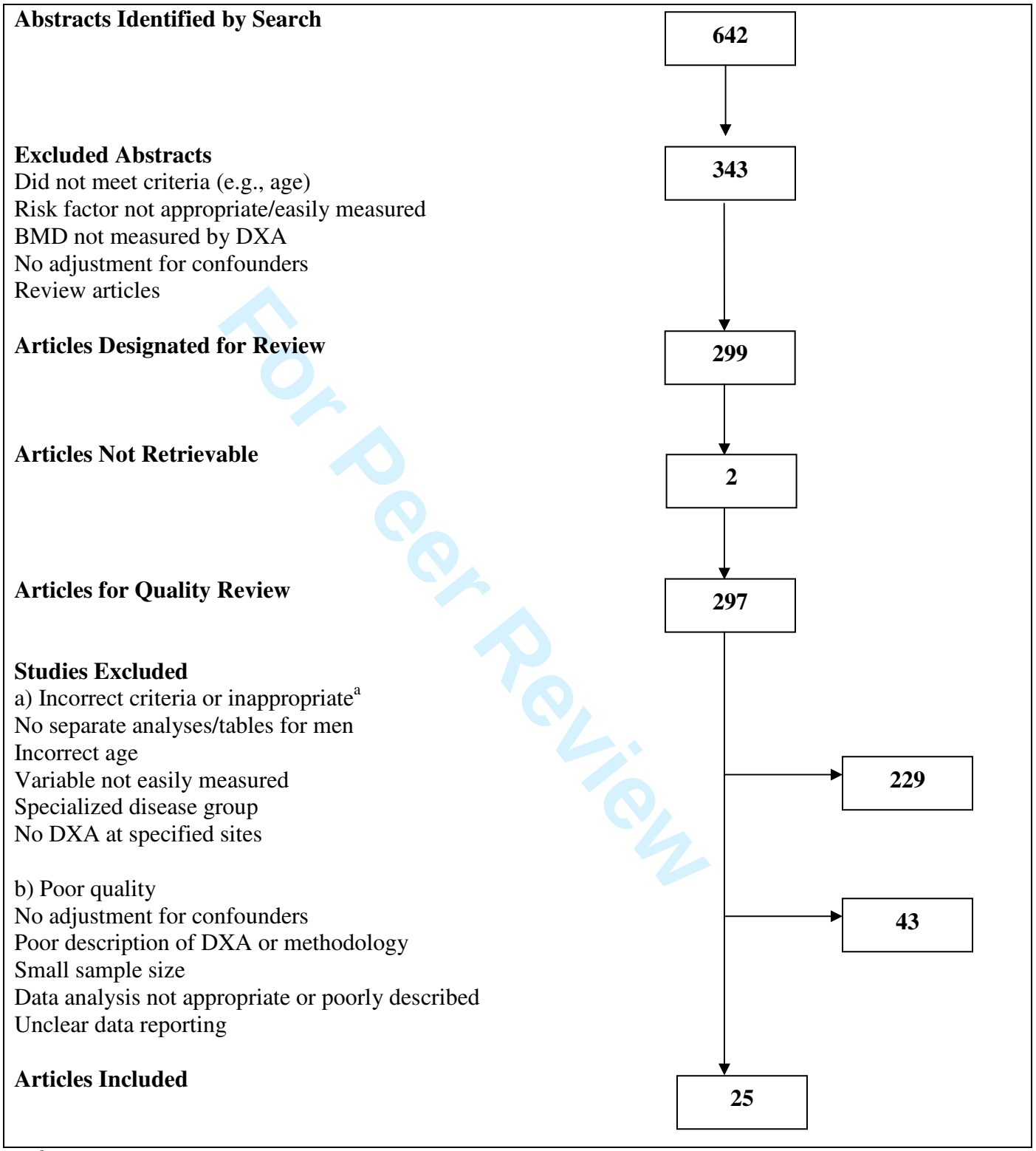
Figure 1: Systematic Review Flowchart



[a]May also have been of poor quality.

Figure 2: Summary of risk factors for low BMD and bone loss in men age 50 years and older

Consistent Evidence:

- Advancing age
- Smoking (current or former)
- Low weight & weight loss
- Physical/functional limitations*
- Prevalent fracture (after age 50)

*Examples: impairments in rising, walking, bending; being chair or bed-bound

Inconsistent or More Evidence Required

- Physical activity
- Alcohol
- Calcium intake
- Muscle strength
- Family history of fracture/osteoporosis
- Height/height loss