Published in final edited form as:
Ann Rheum Dis. 2010 January ; 69(1): 163–168. doi:10.1136/ard.2008.099531.

High systemic bone mineral density increases the risk of incident knee OA and joint space narrowing, but not radiographic progression of existing knee OA: The MOST study

Michael C. Nevitt, PhD[1], **Yuqing Zhang, DSc**[2], **M. Kassim Javaid, MD, PhD**[3], **Tuhina Neogi, MD**[2], **Jeffrey R. Curtis, MD, MPH**[4], **Jingbo Niu, DSc**[2], **Charles E. McCulloch, PhD**[1], **Neil A. Segal, MD**[5], and **David T. Felson, MD, MPH**[2]

[1]University of California, San Francisco, CA, U.S.A

[2]Boston University Medical Center, Boston, MA, U.S.A

[3]University of Oxford, Oxford, U.K.

[4]University of Alabama at Birmingham, Birmingham, AL, U.S.A.

[5]University of Iowa, Iowa City, IA, U.S.A.

Abstract

Objectives—Previous studies suggest that high systemic bone mineral density (BMD) is associated with incident knee OA defined by osteophytes, but not with joint space narrowing (JSN), and are inconsistent regarding BMD and progression of existing OA. We tested the association of BMD with incident and progressive tibiofemoral OA in a large, prospective study of men and women ages 50–79 with, or at risk for, knee OA.

Methods—Baseline and 30-month weight-bearing PA and lateral knee x-rays were scored for K–L grade, JSN and osteophytes. Incident OA was defined as the development of K–L grade ≥2 at follow-up. All knees were classified for increases in grade of JSN and osteophytes from baseline. The association of gender-specific quartiles of baseline BMD with risk of incident and progressive OA was analyzed using logistic regression, adjusting for covariates.

Results—The mean age of 1,754 subjects was 63.2 (SD, 7.8) and BMI 29.9 (SD, 5.4). In knees without baseline OA, higher femoral neck and whole body BMD were associated with an increased risk of incident OA and increases in grade of JSN and osteophytes ($p < 0.01$ for trends); adjusted odds were 2.3 to 2.9-fold greater in the highest vs. the lowest BMD quartiles. In knees with existing OA, progression was not significantly related to BMD.

Conclusions—In knees without OA, higher systemic BMD was associated with a greater risk of the onset of JSN and K–L grade ≥2. The role of systemic BMD in early knee OA pathogenesis warrants further investigation.

Corresponding author and address for reprints: Prof. Michael C. Nevitt, PhD, UCSF Department of Epidemiology and Biostatistics, 185 Berry Street, Lobby 4, Suite 5700, San Francisco, CA, 94107-1762, U.S., Telephone: (415)514-8048, Fax: (415)514-8150; mnevitt@psg.ucsf.edu.

COMPETING INTERESTS
None.

Keywords

Bone mineral density; knee osteoarthritis; incidence; progression

INTRODUCTION

Osteoarthritis (OA) has long been known to be more common in persons with high bone mineral density (BMD)(1). Recent longitudinal studies in Caucasians have found that higher axial BMD is associated with an increased risk of incident radiographic OA (ROA) of the knee, defined by osteophytes and Kellgren-Lawrence (K–L) grade(2⁻6), but have not found a relationship with the onset of joint space narrowing (JSN)(3, 4, 6). Findings on the relationship of BMD to radiographic progression of existing knee OA are inconsistent, with some studies suggesting paradoxically that higher BMD is protective(3, 4) and that the role of BMD in knee OA differs by stage of disease(7, 8).

Previous longitudinal studies of BMD and knee ROA have several limitations. They have not had sufficient numbers of both incident, and especially progressive, OA(3, 4, 6) to adequately assess the relationship of BMD to each endpoint. Prior studies used standing radiographs taken with the knee fully extended, a protocol that is both insensitive and inaccurate for assessment of JSN(9). No studies have taken into account knee malalignment, a strong determinant of OA progression in the more loaded compartment(10) that may modify the effects of other risk factors on progression(11, 12).

We used data from the Multicenter Osteoarthritis Study (MOST) to examine the relationship of baseline hip and whole body BMD and history of fracture, a marker for osteoporosis, with the incidence and progression of tibiofemoral knee ROA assessed using sensitive radiographic methods(13⁻15). MOST includes a large prospective study of both incidence and progression and was designed, in part, to evaluate whether bone density and other risk factors affect OA risk at different disease stages.

METHODS

Subjects

Subjects in MOST were ages 50 to 79 years at baseline with knee OA, or at high risk of developing it. Persons at high risk included include those who were overweight (defined as greater than the Framingham Study age- and gender-specific median weight(16)), had knee pain, aching or stiffness on most of the last 30 days, had previous knee surgery or a history of knee injury that made it difficult to walk for at least one week. Exclusions included screening positive for rheumatoid arthritis(17), ankylosing spondylitis, psoriatic arthritis, Reiter's syndrome, conditions that made continued participation unlikely, bilateral knee replacement surgery and unable to walk without help or a walker. Subjects were recruited from Birmingham, Alabama and Iowa City, Iowa through mass mailing, supplemented by media and community outreach. The study protocol was approved by the Human Subjects Review Boards at each of the four institutions collaborating on MOST.

Baseline measurements

Right hip and whole body BMD were measured using Hologic QDR 4500A DXA scanners (Hologic Inc., Bedford, MA). Subjects completed questionnaires about fractures since age 45, frequent hip pain, physical activity (Physical Activity in the Elderly Scale(18)), smoking and medication use. Participants were weighed (balance beam scale) and had height measured (stadiometer) without shoes or heavy clothes (BMI computed as kg/m^2) and had knee height

(19) and hip pain on internal rotation of the hip assessed(20). Concentric knee extensor (quadriceps) strength was measured with a Cybex 350 isokinetic dynamometer (Avocent, Huntsville, AL).

Radiographic methods

At baseline and a 30 month follow-up visit, subjects underwent weight-bearing PA fixed flexion knee radiographs(14, 21) using a plexiglass positioning frame (SynaFlexer, TM) and lateral weight bearing films of each knee using the Framingham OA Study protocol(15). A musculoskeletal radiologist and a rheumatologist experienced in reading study films, assessed PA films for K–L grades and individual radiographic feature scores including medial and lateral JSN and osteophyte (0–3)(22). Lateral films were scored for medial and lateral tibiofemoral JSN (0–3) (15). Weighted kappas for agreement between the two readers were as follows: K–L grade = 0.79; medial compartment JSN = 0.81; lateral compartment JSN = 0.86; and osteophytes = 0.65. In previous studies(10) we found that knees often showed a worsening of JSN longitudinally but did not show enough additional narrowing to move one full OARSI grade (e.g. 1 to 2). When this occurred in knees with JSN at baseline, readers were instructed to use ½ grades(13). Paired films were read by both readers working independently, with time sequence known and blinded to clinical data. If readers disagreed on the presence of incident OA or worsening of JSN, using the definitions below, an adjudication panel of three readers decided whether incidence or progression had occurred.

For knees without tibiofemoral ROA (K–L grade = 0 or 1) at baseline, we defined incident ROA as new onset K–L grade ≥ 2 at 30 month follow-up. In knees with, and without, ROA at baseline we defined progression of JSN as an increase in medial or lateral JSN by ≥ ½ grade based on either the PA or lateral view(13, 15). Knees with a K–L grade of 4 or a JSN grade of 3 both medially and laterally were not eligible for progression. We used data on osteophytes (scored 0–3 at each of 4 sites on the PA view) from the radiologist as this feature was not adjudicated. Progression of osteophytes was defined as an increase of ≥1 grade in any location.

We measured the hip-knee-ankle (HKA) mechanical axis from baseline bilateral full limb radiographs(23) acquired using the method of Sharma et al.(24). In a reliability study of full-limb films (60 limbs) assessed by two different readers, the interobserver ICC for HKA angle was 0.95. Neutral alignment was defined as an angle of 179° to 181° and severe malalignment was defined as an angle <173° or >187°.

Analysis

Given the higher BMD of nonwhites(25), it was necessary to examine this group separately but the number of nonwhites was too small to evaluate race differences in the association of BMD with knee OA, so nonwhites were excluded. We included subjects with radiographic endpoint data available as of August, 2007. These subjects were more likely to be female and had a lower BMI and BMD than those without radiographic data ($p<.05$), while other characteristics were similar. We excluded 194 individuals who reported hip pain by both questionnaire and examination in the same hip as the DXA measurement since higher BMD in hips with prevalent OA (20, 26) could bias results.

We analyzed the association of gender-specific quartiles of femoral neck and whole body BMD and history of fracture with incident and progressive knee ROA. All of our results were essentially the same using BMD from other DXA scan regions (e.g. total hip, leg). Analyses were knee-based, so a subject could contribute knees to either one, or both, of the incidence and progression analyses, with some subjects having only one knee and other subjects both knees in the analysis. The association of BMD and fracture with knee ROA outcomes was analyzed using logistic regression, using GEE methods to account for the correlation between

two knees in a person. Odds ratios (ORs) were calculated for each BMD quartile compared to the lowest BMD group as referent category. We performed tests for trend using continuous BMD measures in logistic regression models, added quadratic terms to models to examine potential nonlinear relationships and used spline regression models to evaluate threshold effects. We analyzed men and women combined after determining that the relationships were similar based on gender by BMD interaction terms in logistic models. Analyses were adjusted for BMI, age, gender (in the combined analyses), smoking, physical activity, knee injury, knee height (a stable indicator of skeletal size(27) to account for the latter's effect on apparent areal BMD(28)), and current estrogen and bisphosphonate use. Separate models adjusted additionally for quadriceps strength(29), but this did not change any of our results.

We performed several sensitivity analyses. Because prevalent knee OA may result in faster bone loss in the hip(30), we repeated incidence analyses excluding subjects with ROA in one knee at baseline. We examined the effect of malalignment on results for JSN progression first by excluding severely malaligned knees and then analyzing only neutrally aligned knees. Analyses of JSN progression in knees with OA at baseline were repeated using alternative outcome definitions: 1) using JSN data from the PA film only; and 2) requiring an increase in JSN of a full grade or greater. Finally, we repeated main analyses excluding users of hormone replacement therapy and bisphonsphonates, with no change in results.

RESULTS

Among 1,754 white subjects (63% women) (Table 1), both genders were, on average, obese and had relatively high BMD. Based on femoral neck BMD, the proportion of men and women who were osteopenic or osteoporotic was much lower(25, 31), while the proportion with a BMI of 30.0 or greater was higher(32), than in the same age U.S. population. The median follow-up time was 31.1 (range 27.1 to 41.3) months.

BMD and Incident ROA

In knees without ROA at baseline, incident ROA occurred in 126 (5.5%; 4.1% in men, 6.5% in women). The risk of incident ROA increased with higher BMD in both men and women (Table 2) with no difference by gender ($p > 0.55$ for interactions of BMD with gender). In men and women combined, those with BMD in the three highest quartiles at the femoral neck or in the highest quartile for whole body had a 2-fold increase in the adjusted odds of incident ROA compared to the lowest quartile of BMD.

In knees without ROA at baseline, an increase in JSN grade occurred in 184 (8.1%; 5.9% in men and 9.5% in women) at follow-up. Higher femoral neck (Table 3) and whole body (data not shown) BMD were associated with increased risks of JSN in men and women, with no difference by gender ($p > 0.24$ for gender by BMD interactions). Among men and women combined, those in the highest femoral neck BMD quartile had a 2.7-fold increase in the odds of JSN compared to the lowest BMD quartile. The corresponding odds ratio for whole body BMD was 2.9 (95% CI: 1.7, 4.8; p-value for trend <0.001). In knees without ROA at baseline, higher femoral neck (table 3) and whole body (data not shown) BMD were also associated with an increase in osteophytes, with no differences by gender ($p > 0.43$). Higher BMD was strongly associated with increase in JSN grade both in knees with a baseline K–L grade of 0 and in those with a K–L grade of 1 (Figure 1).

In sensitivity analyses, excluding subjects who had ROA in one knee at baseline did not change any of our results. In men, we found no significant nonlinear relationships of BMD with incident OA or JSN, and smoothed curves from spline regression models suggested that risk continued to increase with higher values of BMD.

BMD and Progression

Progression of JSN occurred in 491 (52.7%; 51.8% in men and 53.2% in women) knees with ROA at baseline. Neither progression of JSN nor progression of osteophytes were associated with BMD in either gender (data by gender are not shown). In genders combined, adjusted odds ratios for JSN progression ranged from 0.7 to 1.0 by femoral neck BMD quartile and from 1.0 to 1.3 by whole body BMD quartiles (Figure 2). There was a nonsignificant trend for greater osteophyte progression with higher femoral neck BMD.

In sensitivity analyses excluding 140 knees with severe baseline malalignment or restricted to 216 knees with neutral alignment, femoral neck BMD was not associated with JSN progression (p-values for trend = 0.43 and 0.72). Results were similar for whole body BMD. Also in sensitivity analyses, BMD was not associated with JSN progression based on the reading of the PA film alone. Similarly, JSN increases of a full grade or more were not related to femoral neck BMD (p for trend = 0.48), but there was a trend (p= 0.07) for an association with whole body BMD

Fracture history and use of antiresorptive drugs

A history of any fracture since age 45 was not associated with incident ROA (OR in combined genders: 1.2; 95% CI: 0.7, 2.1), nor with an increase in JSN in normal knees (1.2; 0.7, 2.0)) nor with progressive JSN in knees with ROA at baseline. In sensitivity analyses excluding users of ERT and bisphosphonates, our results for both incidence and progression outcomes were unchanged.

DISCUSSION

In this large prospective study of persons with, and at high risk for, knee osteoarthritis we confirmed that higher systemic BMD is associated with an increased risk of incident ROA of the knee(3, 4, 6) and report for the first time that high BMD is strongly associated with an increased risk of developing JSN in knees without ROA, including those with a baseline K–L grade of 0. In contrast to some previous studies(3, 4), higher BMD was not associated with a reduced risk of structural progression of existing disease.

There are several possible explanations for the association of high BMD with the risk of developing knee ROA and JSN. First, they may share common causes that are not accounted for in our analyses, including genetic factors linked to high bone mass that also have a role in OA pathogenesis(26). For example, the Wnt/*B*-catenin signaling pathway is involved in regulating the development and functioning of both osteoblasts(33) and chondrocytes(34), and polymorphisms of genes encoding Wnt antogonists have been associated with OA of the hip (35, 36) and knee(37) as well as with a high bone density phenotype(38, 39). Excess lower extremity loading from physical activities not well-captured by our survey instrument could also confound the association of hip BMD with the risk of knee OA.

Second, factors related to a high BMD, such as elevated levels of skeletal growth factors, even if they do not affect the risk of OA, per se, could stimulate the development of osteophytes in early OA(40) and these are detected on radiographs as incident disease. Although consistent with previous findings that high BMD was related to the initial development of osteophytes but not JSN(3, 4, 6), this explanation it is at odds with our finding that high BMD was related to development of JSN in knees without OA.

Third, larger bones have greater apparent areal BMD(28) and our findings may reflect, in part, larger skeletal dimensions in persons more likely to develop knee OA(41, 42). Although we adjusted for a measure of lower limb bone size that is related to the risk of knee OA(41) and BMI, there may be residual effects of bone size on areal BMD. Studies using MRI and CT may

further elucidate the relationship of skeletal geometry and true volumetric BMD to the risk of knee OA(43).

On the other hand, high bone mass or its determinants may be directly involved in the pathogenesis of knee OA, for example by influencing the subchondral calcified tissue response to joint loading in a positive feedback loop that further increases stress on joint tissues(44–48). Human joints with OA evidence a broad spectrum of subchondral calcified tissue changes (40, 49–56). Some of these changes may precede the initiation of OA while others are part of the joint's response to abnormal loading conditions resulting from OA. In several animal models, subchondral bone changes occur contemporaneously with early cartilage loss(49–53), but there are few such data on early knee OA in humans(54).

In knees with prevalent ROA, BMD was not associated with progression of JSN. Our findings contrast with those of two prior studies that suggested that higher hip BMD protects from JSN progression(3, 4) and with a third that found greater progression in persons with high spine BMD(6). Our results do suggest that the relationship of BMD to OA may change once a knee has developed disease equivalent to K–L grade 2 or higher. What could account for this? Many knees that develop OA become malaligned and this is known to modify the relationship of some risk factors with JSN progression(11, 12). However, our results were unchanged when excluding malaligned knees. The relationship of BMD with progression may be modified by more rapid bone loss related to the presence of knee OA(30). Studies similar to ours with data on bone loss are needed to evaluate this. Our findings for BMD and progression are consistent with the fact that few risk factors for incident knee ROA have been found to also predict more rapid progression(8, 57). Persons with existing knee OA who do not have high BMD are likely to have other risk factors for knee OA, which increase the rate of progression in these subjects with knee ROA and low BMD. Finally, our study assessed the risk of a dichotomous progression outcome which may be less sensitive for detecting risk factors than if a measure of the rate of progression is the outcome.

A history of any fracture after age 45 was not associated with the risk of either incident or progressive knee ROA. However, these findings do not rule out a possible association of skeletal fragility with knee ROA since the occurrence of fractures at all sites combined is only moderately associated with low BMD(58) and is a marker for falls in addition to skeletal fragility. Also, we did not assess radiographic vertebral fractures, which have been linked to a reduced risk of incident knee OA(4, 6), and few or our subjects had osteoporosis. Use of antiresorptive drugs by persons with osteoporosis or prior fractures may modify the relationship of skeletal status to knee OA. However, our results were unchanged in analyses excluding those using antiresorptive agents.

Our study has several strengths. We had larger number of subjects with disease at baseline and used radiography methods more sensitive to JSN(14, 15) compared to previous studies that used the fully extended knee view(9). We had much larger numbers of knees with progressive JSN (more than 100 in each quartile of BMD) compared to these prior studies (e.g. one had only 25 progressor knees in the entire cohort(6)), permitting us to evaluate more robustly the relation of BMD with progression and, by extension, to compare the relation of BMD to disease incidence and progression. Sensitivity analyses using alternative definitions of JSN progression did not change our results, confirming the robustness of our primary measure of progression. We studied both men and women, while some previous large cohort studies of this issue have focused on women. In agreement with one other study we found that the relationship of BMD to the risk of knee ROA was similar by gender(6). No previous study has analyzed BMD and JSN progression within strata of knee mechanical alignment, the extremes of which may obscure the effect of other risk factors on progression(12).

Our study also has several limitations. We studied only whites and our findings may not apply to other racial groups. We did not assess spine BMD. However, bone hypertrophy in OA of the spine increases apparent areal spine BMD(59), which may bias its association with knee OA. Prevalent hip OA may have a similar effect on areal hip BMD, but we excluded subjects with hip pain consistent with OA. We could not control for the possible effects of ROA in other joints on whole body BMD. We may have had too few subjects with osteoporosis to observe a possible association of very low BMD with progression; however, since obesity is such a strong risk factor for knee OA persons with knee OA tend to have high BMD. Several associations in subgroups (men and K–L grade 1 knees) suggested nonlinearity, but these may be chance findings.

In conclusion, high systemic BMD in white men and women is associated with an increased risk of early radiographic changes of knee OA, including the onset of JSN in knees without osteophytes at baseline, but is not associated with progression of JSN in later stages of disease. These differences by stage of disease warrant further consideration. Because high BMD increases the risk of developing knee OA independently of obesity, a potent risk factor for disease, our findings have potential importance for identifying those most at risk for knee OA. These results should spur investigation of common genetic links between high bone mass and the risk of knee OA as well as the relationship between skeletal phenotype and the pathophysiology of early disease.

Acknowledgments

The authors gratefully acknowledge Dr. Leena Sharma whose ancillary study to MOST funded the measurements of knee alignment. We also thank Dr. Piran Aliabadi, MD, and Burt Sack, MD, who were the radiograph readers and Michael Peterson for assistance in preparation of the manuscript.

FUNDING

This study was supported by NIH Grants U01 AG18820; U01 AG18832; U01 AG18947; U01 AG19069 and R01HD043502.

REFERENCES

1. Dequeker J, Boonen S, Aerssens J, Westhovens R. Inverse relationship osteoarthritis-osteoporosis: what is the evidence? What are the consequences? Br J Rheumatol 1996;35(9):813–818. [PubMed: 8810662]
2. Sowers M, Lachance L, Jamadar D, Hochberg MC, Hollis B, Crutchfield M, et al. The associations of bone mineral density and bone turnover markers with osteoarthritis of the hand and knee in pre-and perimenopausal women. Arthritis Rheum 1999;42(3):483–489. [PubMed: 10088771]
3. Zhang Y, Hannan MT, Chaisson CE, McAlindon TE, Evans SR, Aliabadi P, et al. Bone mineral density and risk of incident and progressive radiographic knee osteoarthritis in women: the Framingham Study. J Rheumatol 2000;27(4):1032–1037. [PubMed: 10782833]
4. Hart DJ, Cronin C, Daniels M, Worthy T, Doyle DV, Spector TD. The relationship of bone density and fracture to incident and progressive radiographic osteoarthritis of the knee: the Chingford Study. Arthritis Rheum 2002;46(1):92–99. [PubMed: 11817613]
5. Hochberg MC, Lethbridge-Cejku M, Tobin JD. Bone mineral density and osteoarthritis: data from the Baltimore Longitudinal Study of Aging. Osteoarthritis Cartilage 2004;12A:S45–S48. [PubMed: 14698641]
6. Bergink AP, Uitterlinden AG, Van Leeuwen JP, Hofman A, Verhaar JA, Pols HA. Bone mineral density and vertebral fracture history are associated with incident and progressive radiographic knee osteoarthritis in elderly men and women: the Rotterdam Study. Bone 2005;37(4):446–456. [PubMed: 16027057]
7. Felson DT, Nevitt MC. Epidemiologic studies for osteoarthritis: new versus conventional study design approaches. Rheum Dis Clin North Am 2004;30(4):783–797. [PubMed: 15488693]

8. Cooper C, Snow S, McAlindon TE, Kellingray S, Stuart B, Coggon D, et al. Risk factors for the incidence and progression of radiographic knee osteoarthritis. Arthritis Rheum 2000;43(5):995–1000. [PubMed: 10817551]
9. Brandt K, Mazzuca S, Conrozier T, Dacre J, Peterfy C, Provvedini D, et al. Which is the best radiographic protocol for a clinical trial of a structure modifying drug in patients with knee osteoarthritis? J Rheumatol 2002;29(6):1308–1320. 29(6):1308-20. [PubMed: 12064851]
10. Felson DT, McLaughlin S, Goggins J, LaValley MP, Gale ME, Totterman S, et al. Bone marrow edema and its relation to progression of knee osteoarthritis. Ann Intern Med 2003;139((5 Pt 1)):330–336. [PubMed: 12965941]
11. Sharma L, Dunlop DD, Cahue S, Song J, Hayes KW. Quadriceps strength and osteoarthritis progression in malaligned and lax knees. Ann Intern Med 2003;138(8):613–619. [PubMed: 12693882]
12. Felson DT, Goggins J, Niu J, Zhang Y, Hunter DJ. The effect of body weight on progression of knee osteoarthritis is dependent on alignment. Arthritis Rheum 2004;50(12):3904–3909. [PubMed: 15593215]
13. Felson DT, Nevitt MC, Yang M, Niu J, Torner JC, Lewis CE, et al. A New Approach Yields High Rates of X-Ray Progression in Knee Osteoarthritis (OA). J Rheumatol 2008;35(10):2047–2054. [PubMed: 18793000]
14. Nevitt MC, Peterfy C, Guermazi A, Felson DT, Duryea J, Woodworth T, et al. Longitudinal performance evaluation and validation of fixed-flexion radiography of the knee for detection of joint space loss. Arthritis Rheum 2007;56(5):1512–1520. [PubMed: 17469126]
15. LaValley MP, McLaughlin S, Goggins J, Gale D, Nevitt MC, Felson DT. The lateral view radiograph for assessment of the tibiofemoral joint space in knee osteoarthritis: its reliability, sensitivity to change, and longitudinal validity. Arthritis Rheum 2005;52(11):3542–3547. [PubMed: 16255043]
16. Felson DT, Anderson JJ, Mainmark A, Walker AM, Meenen RF. Obesity and knee osteoarthritis: The Framingham Study. Ann Intern Med 1988;109:18–24. [PubMed: 3377350]
17. Karlson EW, Sanchez-Guerrero J, Wright EA, Lew RA, Katz JN, Liang MH. A connective tissue disease screening questionnaire (CSQ) for population studies. Ann Epidemiol 1995;5(4):294–302.
18. Martin KA, Rejeski WJ, Miller ME, James MK, Ettinger WH Jr, Messier SP. Validation of the PASE in older adults with knee pain and physical disability. Med Sci Sport Exerc 1999;31(5):627–633.
19. Chumlea WC. Accuracy and reliability of a new sliding caliper. Am J Phys Anth 1985;68:425–427.
20. Nevitt MC, Lane NE, Scott JC, Hochberg MC, Pressman AR, Genant HK, et al. Radiographic osteoarthritis of the hip and bone mineral density. Arthritis Rheum 1995;38:907–916. [PubMed: 7612040]
21. Peterfy C, Li J, Zaim S, Duryea J, Lynch J, Miaux Y, et al. Comparison of fixed-flexion positioning with fluoroscopic semi-flexed positioning for quantifying radiographic joint-space width in the knee: test-retest reproducibility. Skeletal Radiology 2003;32(3):128–132. [PubMed: 12605275]
22. Altman R, Hochberg M, Murphy W, Wolfe F, Lequesne M. Atlas of individual radiographic features in osteoarthritis. Osteoarthritis and Cartilage 1995;3(A):3–70. [PubMed: 8581752]
23. Cooke TD, Harrison L, Khan B, Scudamore A, Chaudhary MA. Analysis of limb alignment in the pathogenesis of osteoarthritis: a comparison of Saudi Arabian and Canadian cases. Rheumatol Int 2002;22(4):160–164. [PubMed: 12172956]
24. Sharma L, Song J, Felson DT, Cahue S, Shamiyeh E, Dunlop DD. The role of knee alignment in disease progression and functional decline in knee osteoarthritis. JA 2001;286(2):188–195.
25. Looker AC, Wahner HW, Dunn WL, Calvo MS, Harris TB, Heyse SP, et al. Updated data on proximal femur bone mineral levels of US adults. Osteoporos Int 1998;8(5):468–489. [PubMed: 9850356]
26. Antoniades L, MacGregor AJ, Matson M, Spector TD. A cotwin control study of the relationship between hip osteoarthritis and bone mineral density. Arthritis Rheum 2000;43:1450–1455. [PubMed: 10902745]
27. Chumlea WCRA, Steinbaugh ML. Estimating stature from knee height for persons 60 to 90 years of age. J Am Geriatr Soc 1985;33:116–120. [PubMed: 3968366]
28. Looker AC, Beck TJ, Orwoll ES. Does body size account for gender differences in femur bone density and geometry? J Bone Miner Res 2001;16(7):1291–1299. [PubMed: 11450705]

29. Slemenda C, Heilman DK, Brandt KD, Katz BP, Mazzuca SA, Braunstein EM, et al. Reduced quadriceps strength relative to body weight: a risk factor for knee osteoarthritis in women? Arthritis Rheum 1998;41(11):1951–1959. [PubMed: 9811049]
30. Burger H, van Daele PL, Odding E, Valkenburg HA, Hofman A, Grobbee DE, et al. The Rotterdam Study. Association of radiographically evident osteoarthritis with higher bone mineral density and increased bone loss with age. Arthritis Rheum 1996;39(1):81–86. [PubMed: 8546742]
31. Looker AC, Orwoll ES, Johnston CC Jr, Lindsay RL, Wahner HW, Dunn WL, et al. Prevalence of low femoral bone density in older U.S. adults from NHANES III. J Bone Miner Res 1997;12(11): 1761–1768. [PubMed: 9383679]
32. Ogden CL, Carroll MD, Curtin LR, McDowell MA, Tabak CJ, Flegal KM. Prevalence of overweight and obesity in the United States, 1999–2004. Jama 2006;295(13):1549–1555. [PubMed: 16595758]
33. Krishnan V, Bryant HU, Macdougald OA. Regulation of bone mass by Wnt signaling. J Clin Invest 2006;116(5):1202–1209. [PubMed: 16670761]
34. Tamamura Y, Otani T, Kanatani N, Koyama E, Kitagaki J, Komori T, et al. Developmental regulation of Wnt/beta-catenin signals is required for growth plate assembly, cartilage integrity, and endochondral ossification. J Biol Chem 2005;280(19):19185–19195. [PubMed: 15760903]
35. Loughlin J, Dowling B, Chapman K, Marcelline L, Mustafa Z, Southam L, et al. Functional variants within the secreted frizzled-related protein 3 gene are associated with hip osteoarthritis in females. Proc Natl Acad Sci U S A 2004;101(26):9757–9762. [PubMed: 15210948]
36. Lane NE, Lian K, Nevitt MC, Zmuda JM, Lui L, Li J, et al. Frizzled-related protein variants are risk factors for hip osteoarthritis. Arthritis Rheum 2006;54(4):1246–1254. [PubMed: 16572458]
37. Valdes AM, Loughlin J, Oene MV, Chapman K, Surdulescu GL, Doherty M, et al. Sex and ethnic differences in the association of ASPN, CALM1, COL2A1, COMP, and FRZB with genetic susceptibility to osteoarthritis of the knee. Arthritis Rheum 2007;56(1):137–146. [PubMed: 17195216]
38. Boyden LM, Mao J, Belsky J, Mitzner L, Farhi A, Mitnick MA, et al. High bone density due to a mutation in LDL-receptor-related protein 5. N Engl J Med 2002;346(20):1513–1521. [PubMed: 12015390]
39. Ai M, Holmen SL, Van Hul W, Williams BO, Warman ML. Reduced affinity to and inhibition by DKK1 form a common mechanism by which high bone mass-associated missense mutations in LRP5 affect canonical Wnt signaling. Mol Cell Biol 2005;25(12):4946–4955. [PubMed: 15923613]
40. Hunter DJ, Spector TD. The role of bone metabolism in osteoarthritis. Curr Rheumatol Rep 2003;5 (1):15–19. [PubMed: 12590880]
41. Hunter DJ, Niu J, Zhang Y, Nevitt MC, Xu L, Lui LY, et al. Knee height, knee pain, and knee osteoarthritis: the Beijing Osteoarthritis Study. Arthritis Rheum 2005;52(5):1418–1423. [PubMed: 15880346]
42. Wang Y, Wluka AE, Davis S, Cicuttini FM. Factors affecting tibial plateau expansion in healthy women over 2.5 years: a longitudinal study. Osteoarthritis Cartilage 2006;14(12):1258–1264. [PubMed: 16784878]
43. Bennell KL, Creaby MW, Wrigley TV, Hunter DJ. Tibial subchondral trabecular volumetric bone density in medial knee joint osteoarthritis using peripheral quantitative computed tomography technology. Arthritis Rheum 2008;58(9):2776–2785. [PubMed: 18759296]
44. Radin EL, Paul IL, Rose RM. Role of mechanical factors in pathogenesis of primary osteoarthritis. Lancet 1972;299(7749):519–521. [PubMed: 4110024]
45. Dequeker J, Mohan S, Finkelman RD, Aerssens J, Baylink DJ. Generalized osteoarthritis associated with increased insulin-like growth factor types I and II and transforming growth factor β in cortical bone from the iliac crest. Arthritis Rheum 1993;36:1702–1708. [PubMed: 8250990]
46. Burr DB. Anatomy and physiology of the mineralized tissues: role in the pathogenesis of osteoarthrosis. Osteoarthritis Cartilage 2004;12 Suppl A:S20–S30. [PubMed: 14698637]
47. Robinson JA, Chatterjee-Kishore M, Yaworsky PJ, Cullen DM, Zhao W, Li C, et al. Wnt/beta-catenin signaling is a normal physiological response to mechanical loading in bone. J Biol Chem 2006;281 (42):31720–31728. [PubMed: 16908522]
48. Diarra D, Stolina M, Polzer K, Zwerina J, Ominsky MS, Dwyer D, et al. Dickkopf-1 is a master regulator of joint remodeling. Nat Med 2007;13(2):156–163. [PubMed: 17237793]

49. Carlson CS, Loeser RF, Purser CB, Gardin JF, Jerome CP. Osteoarthritis in cynomolgus macaques. III: Effects of age, gender, and subchondral bone thickness on the severity of disease. J Bone Miner Res 1996;11(9):1209–1217. [PubMed: 8864894]
50. Boyd SK, Muller R, Matyas JR, Wohl GR, Zernicke RF. Early morphometric and anisotropic change in periarticular cancellous bone in a model of experimental knee osteoarthritis quantified using microcomputed tomography. Clin Biomech 2000;15(8):624–631.
51. Anderson-MacKenzie JM, Quasnichka HL, Starr RL, Lewis EJ, Billingham ME, Bailey AJ. Fundamental subchondral bone changes in spontaneous knee osteoarthritis. Int J Biochem Cell Biol 2005;37(1):224–236. [PubMed: 15381164]
52. Bailey AJ, Mansell JP, Sims TJ, Banse X. Biochemical and mechanical properties of subchondral bone in osteoarthritis. Biorheology 2004;41(3–4):349–358. [PubMed: 15299267]
53. Day JS, Van Der Linden JC, Bank RA, Ding M, Hvid I, Sumner DR, et al. Adaptation of subchondral bone in osteoarthritis. Biorheology 2004;41(3–4):359–368. [PubMed: 15299268]
54. Ding M, Odgaard A, Hvid I. Changes in the three-dimensional microstructure of human tibial cancellous bone in early osteoarthritis. J Bone Joint Surg Br 2003;85(6):906–912. [PubMed: 12931817]
55. Lo GH, Hunter DJ, Zhang Y, McLennan CE, Lavalley MP, Kiel DP, et al. Bone marrow lesions in the knee are associated with increased local bone density. Arthritis Rheum 2005;52(9):2814–2821. [PubMed: 16145676]
56. Hulet C, Sabatier JP, Souquet D, Locker B, Marcelli C, Vielpeau C. Distribution of bone mineral density at the proximal tibia in knee osteoarthritis. Calcif Tissue Int 2002;71(4):315–322. [PubMed: 12202957]
57. Belo JN, Berger MY, Reijman M, Koes BW, Bierma-Zeinstra SM. Prognostic factors of progression of osteoarthritis of the knee: a systematic review of observational studies. Arthritis Rheum 2007;57 (1):13–26. [PubMed: 17266080]
58. Stone KL, Seeley DG, Lui LY, Cauley JA, Ensrud K, Browner WS, et al. BMD at multiple sites and risk of fracture of multiple types: long-term results from the Study of Osteoporotic Fractures. J Bone Miner Res 2003;18(11):1947–1954. [PubMed: 14606506]
59. Orwoll ES, Oviatt SK, Mann T. The impact of osteophytic and vascular calcifications on vertebral mineral density measurements in men. J Clin Endocrinol Metab 1990;70(4):1202–1207. [PubMed: 2318940]

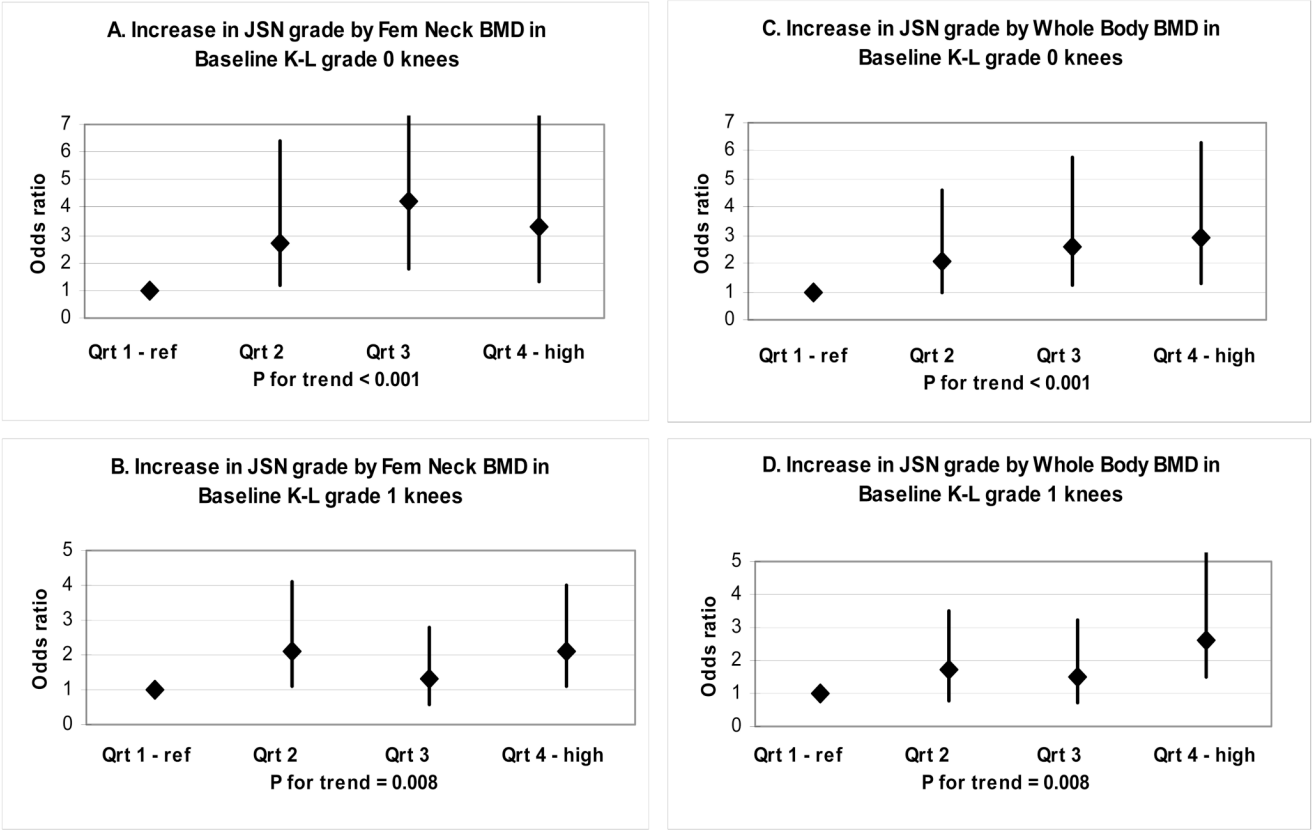

Figure 1.

Increase in grade of T-F joint space narrowing (JSN) in knees without T-F OA (K–L grade 0 or 1) at baseline. The figure shows odds ratios (95% CI) for increase in grade of joint space narrowing in knees with a baseline K–L grade of 0 (n= 1,670) and knees with a baseline K–L grade of 1 (n= 605), by gender specific quartile of femoral neck BMD and whole body BMD (men and women combined). Odds ratios and p-values for trend are adjusted for age, BMI, knee height, smoking, PASE activity score, knee injury, bisphosphonate use, estrogen use in women and gender. For BMD quartile cutpoints, see table 2.

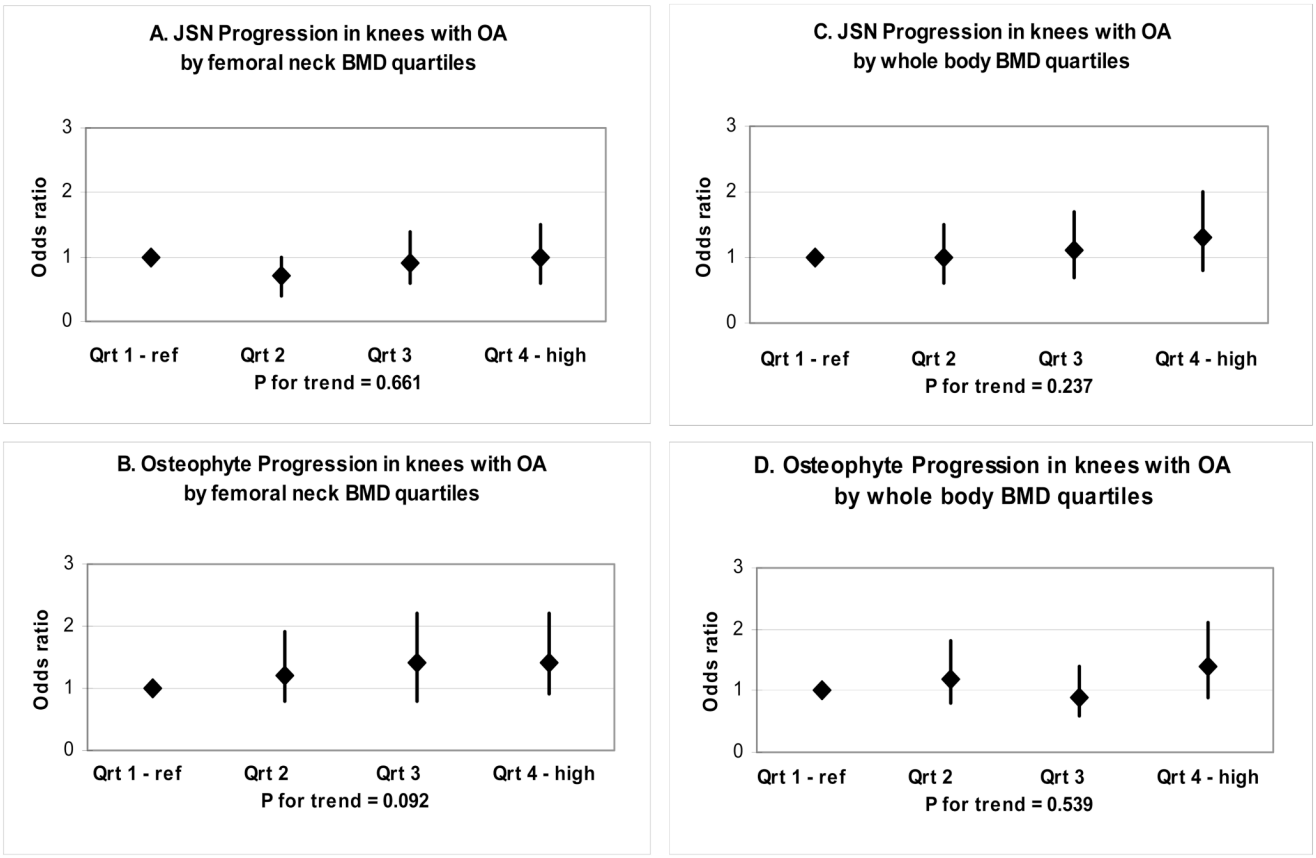

Figure 2.

Progression of joint space narrowing (JSN) and osteophytes in knees with ROA at baseline (K–L grade ≥ 2) for men and women combined. The figures shows odds ratios (95% CI) for increases in grade of JSN and osteophytes, by gender specific quartile of femoral neck BMD and whole body BMD. Odds ratios and p-values for trend adjusted for age, BMI, knee height, smoking, PASE activity score, knee injury, bisphosphonate use, estrogen use in women and gender. For BMD quartile cutpoints, see table 2.

Table 1

Baseline characteristics of participants

	Men (n= 667)	**Women (n=1,087)**
Age, mean (SD)	62.9 (8.1)	63.1 (7.7)
BMI, mean (SD)	30.1 (4.7)	29.9 (5.9)
BMI ≥ 30.0 n (%)	296 (44.4%)	481 (44.3%)
Current smoker, n (%)	31 (4.6%)	52 (4.8%)
Femoral neck BMD g/cm^2, mean (SD)	0.84 (0.13)	0.77 (0.12)
Whole body BMD g/cm^2, mean (SD)	1.11 (0.11)	0.94 (0.09)
Femoral neck BMD classification*		
Osteopenia	235 (35.2%)	472 (43.4%)
Osteoporosis	15 (2.2%)	24 (2.3%)
History of fracture after age 45, n (%)	103 (15.4 %)	264 (24.4%)
Current bisphosphonate user, n (%)	3 (0.4%)	128 (11.8%)
Current estrogen use in women, n (%)	- -	223 (20.5%)
Radiographic knee OA		
K–L grade <2 both knees	366 (54.9%)	594 (54.7%)
K–L grade >=2 in one knee	163 (24.4%)	237 (21.8%)
K–L grade >=2 in both knees	138 (20.7%)	256 (23.6%)

*Based on femoral neck BMD distribution in U.S. for nonhispanic whites ages 20–29 (31). Osteopenia (BMD 1 to 2.5 SDs below mean reference of group) men, 0.59–0.79 g/cm^2; women 0.56–0.74 g/cm^2. Osteoporosis (BMD more than 2.5 SDs below mean of reference group) men, <0.59 g/cm^2; women <0.56 g/cm^2.

Table 2

Incidence of tibiofemoral ROA (baseline K–L grade <2, follow-up ≥2), by gender-specific quartile of baseline BMD

Gender-specific quartile of baseline femoral neck BMD[1]	Men n of knees	Men Incident OA (%)	Men Adj. OR[3] (95% CI)	Women n of knees	Women Incident OA (%)	Women Adj. OR[3] (95% CI)	All subjects n of knees	All subjects Incident OA (%)	All subjects Adj. OR[3] (95% CI)
Q1 (low)	235	**1.3**	**1.0** ref	365	**4.1**	**1.0** ref	600	**3.0**	**1.0** ref
Q2	220	**5.9**	**3.8** (1.1, 13.7)	340	**6.2**	**1.6** (0.8, 3.4)	560	**6.1**	**2.1** (1.1. 3.8)
Q3	222	**3.2**	**2.0** (0.5, 8.6)	347	**6.6**	**1.7** (0.8, 3.7)	569	**5.3**	**1.7** (0.9. 3.4)
Q4 (high)	204	**6.4**	**3.3** (0.9, 12.7)	342	**9.1**	**2.2** (1.0, 4.8)	546	**8.1**	**2.3** (1.2, 4.5)
P-value for trend[3]			**0.11**			**0.005**			**0.001**
Gender-specific quartile of baseline whole body BMD[2]	Men			Women			All subjects		
Q1 (low)	237	**1.7**	**1.0** ref	341	**4.4**	**1.0** ref	578	**3.3**	**1.0** ref
Q2	230	**4.8**	**2.5** (0.8, 7.9)	368	**6.0**	**1.4** (0.7, 3.0)	598	**5.5**	**1.7** (0.9, 3.1)
Q3	220	**2.7**	**1.3** (0.4, 4.7)	356	**7.3**	**1.7** (0.8, 3.7)	576	**5.6**	**1.6** (0.8, 3.1)
Q4 (high)	192	**7.8**	**3.4** (1.2, 9.8)	328	**8.3**	**2.0** (0.9, 4.1)	520	**8.1**	**2.3** (1.3, 4.3)
P-value for trend[3]			**0.02**			**0.06**			**0.008**

[1]Femoral neck BMD cutpoints in g/cm^2 Men Q1 (<0.743), Q2 (0.743 – <0.840), Q3 (0.840 – <0.924), Q4 (≥0.924); Women Q1 (<0.679), Q2 (0.679 – <0.750), Q3 (0.750 – <0.832), Q4 (≥0.832).

[2]Whole body BMD cutpoints in g/cm^{2}Men Q1 (<1.035), Q2 (1.035 – <1.106), Q3 (1.06 – <1.180), Q4 (≥1.180); : Women Q1 (<0.875), Q2 (0.875 – <0.929), Q3 (0.929 – <0.989), Q4 (≥0.989).

[3]Adjusted for age, BMI, knee height, smoking, PASE activity score, knee injury, bisphosphonate use. Analyses including women additionally adjusted for estrogen use and analyses of men and women combined additionally adjusted for gender.

Table 3

Increase in grade of tibiofemoral joint space narrowing (JSN) and osteophytes in knees without OA at baseline (K–L grade <2), by gender-specific quartile of baseline femoral neck BMD

	Joint space narrowing								
	Men			**Women**			**All subjects**		
Gender-specific quartile of baseline femoral neck BMD[1]	**n of knees**	**Increase JSN (%)**	**Adj. OR**[2] **(95% CI)**	**n of knees**	**Increase JSN (%)**	**Adj. OR**[2] **(95% CI)**	**n of knees**	**Increase JSN (%)**	**Adj. OR**[2] **(95% CI)**
Q1 (low)	235	**1.3**	**1.0** ref	365	**6.3**	**1.0** ref	600	**4.3**	**1.0** ref
Q2	220	**7.3**	**4.5** (1.3, 16.0)	339	**9.7**	**2.0** (1.0, 3.8)	559	**8.8**	**2.3** (1.3. 4.0)
Q3	222	**5.4**	**3.5** (0.9, 13.1)	347	**10.9**	**2.3** (1.2, 4.4)	569	**8.8**	**2.3** (1.3. 4.2)
Q4 (high)	204	**10.3**	**5.6** (1.5, 20.3)	342	**11.1**	**2.4** (1.2, 4.6)	546	**10.8**	**2.7** (1.6, 4.8)
P-value for trend[2]			**0.002**			**<0.001**			**<0.001**
	Osteophytes								
	Men			Women			All subjects		
Gender-specific quartile of baseline **femoral neck BMD**[1]	n of knees	Increase Ost (%)	Adj. OR[3] (95% CI)	n of knees	Increase Ost (%)	Adj. OR[3] (95% CI)	n of knees	Increase Ost (%)	Adj. OR[3] (95% CI)
Q1 (low)	235	**6.0**	**1.0** ref	365	**6.0**	**1.0** ref	600	**6.0**	**1.0** ref
Q2	220	**6.8**	**1.0** (0.5, 2.4)	340	**9.7**	**1.8** (1.0, 3.2)	559	**8.6**	**1.5** (0.9. 2.4)
Q3	222	**5.9**	**0.9** (0.4, 2.2)	347	**10.9**	**1.9** (1.0, 3.6)	569	**9.0**	**1.5** (0.9. 2.4)
Q4 (high)	204	**9.8**	**1.4** (0.6, 3.2)	342	**14.6**	**2.4** (1.2, 4.5)	546	**12.8**	**1.9** (1.1, 3.1)
P-value for trend[2]			**0.173**			**0.002**			**0.002**

[1] Femoral neck BMD quartile cutpoints – See table 2.

[2] Adjusted for age, BMI, knee height, smoking, PASE activity score, knee injury, bisphosphonate use. Analyses including women additionally adjusted for estrogen use and analyses of men and women combined additionally adjusted for gender.