6. Rizzoli R, Greenspan SL, Bone G 3rd, Schnitzer TJ, Watts NB, Adami S, et al. Alendronate Once-Weekly Study Group. Two-year results of once-weekly administration of alendronate 70 mg for the treatment of postmenopausal osteoporosis J Bone Miner Res 2002;17:1988–96.
7. Shiraki M, Kushida K. Fukunaga M for the Alendronate Phase III Osteoporosis Research Group. A double-masked multicenter comparative study between alendronate and alfacalcidol in Japanese patients with osteoporosis. Osteoporos Int. 1999;11: 183–92.
8. Morii H, Ohashi Y, Taketani Y, Fukunaga M, Nakamura T, Itabashi A, et al. Effect of raloxifene on bone mineral density and biochemical markers of bone turnover in Japanese postmenopausal women with osteoporosis: results from a randomized placebo-controlled trial. Osteoporos Int. 2003;14:793–800.
9. Garnero P, Sornay-Rendu E, Duboeuf F, Delmas PD. Markers of bone turnover predict postmenopausal forearm bone loss over 4 years: the OFELY study. J Bone Miner Res. 1999;4:1614–21.
10. Dresner-Pollak R, Parker RA, Poku M, Thompson J, Seibel MJ, Greenspan SL. Biochemical markers of bone turnover reflect femoral bone loss in elderly women. Calcif Tissue Int. 1996;59: 328–33.
11. Bauer DC, Sklarin PM, Stone KL, Black DM, Nevitt MC, Ensrud KE, et al. Biochemical markers of bone turnover and prediction of hip bone loss in older women. The study of osteoporotic fractures. J Bone Miner Res. 1999;14:1404–10.
12. Iki M, Morita A, Ikeda Y, Sato Y, Akiba T, Matsumoto T, et al. Biochemical markers of bone turnover predict bone loss in perimenopausal women but not in postmenopausal women—the Japanese Population-Based Osteoporosis (JPOS) cohort study. Osteoporos Int. 1966;17:1086–95.
13. Garnero P, Hausherr E, Chapuy MC, Marcelli C, Grandjean H, Muller C, et al. Markers of bone resorption predict hip fracture in elderly women: the EPIDOS prospective study. J Bone Miner Res. 1996;11:1531–8.
14. Garnero P, Cloos P, Sornay-Rendu E, Qvist P, Delmas PD. Type I collagen racemization and isomerization and the risk of fracture in postmenopausal women: the OFELY prospective study. J Bone Miner Res. 2002;17:826–33.
15. Garnero P, Sornay-Rendu E, Claustrar B, Delmas PD. Biochemical markers of bone turnover, endogenous hormones and the risk of fracture in postmenopausal women: the OFELY study. J Bone Miner Res. 2003;15:1526–36.
16. Yoshimura N, Hashimoto T, Kasamatsu T, Morioka S, Aoki N, Shiraki M. Bone metabolic marker levels in residents of a rural community in Japan. J Bone Miner Metab. 1996;14:39–42.
17. Yoshimura N, Hashimoto T, Sakata K, Morioka S, Kasamatsu T, Cooper C. Biochemical markers of bone turnover and bone loss at the lumbar spine and femoral neck. The Taiji study. Calcif Tissue Int. 1999;65:198–202.
18. Kasamatsu T, Yoshimura N, Morioka S, Sugita K, Hashimoto T. A population survey on bone mineral density in a fishing village in Wakayama Prefecture (Part 1). Distribution of bone mineral density by sex and age on a representative sample of the community. Jpn J Hyg. 1996;50:1084–92. (in Japanese).
19. Yoshimura N, Kasamatsu T, Morioka S, Hashimoto T. A population survey on bone mineral density in a fishing village in Wakayama Prefecture (Part 2). The analysis of the risk factors affecting the bone mineral density. Jpn J Hyg. 1996;51:677–84. (in Japanese).
20. Yoshimura N, Hashimoto T, Morioka S, Sakata K, Kasamatsu T, Cooper C. Determinants of bone loss in a rural Japanese community. The Taiji study. Osteoporos Int. 1998;8:604–10.
21. Yoshimura N, Kakimoto T, Nishioka M, Kishi T, Iwasaki H, Niwa T, et al. Evaluation of reproducibility of bone mineral density measured by dual energy X-ray absorptiometry (DPX-L). J Wakayama Med Soc. 1997;48:461–6.
22. World Health Organization. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. WHO technical report series 843. Geneva: WHO; 1994.
23. Orimo H, Hayashi Y, Fukunaga M, Sone T, Fujiwara S, Shiraki M, et al. Osteoporosis Diagnostic Criteria Review Committee: Japanese Society for Bone and Mineral Research. Diagnostic criteria for primary osteoporosis: year 2000 revision. J Bone Miner Metab. 2001;19:331–7.
24. Kawaguchi H, Matsumoto T, Kurokawa T, Orimo H, Mizunashi K, Takuwa Y, et al. Serum levels of BGP determined by two-site immunoradiometric assay (IRMA) using monoclonal antibodies (in Japanese). Clin Endocrinol. 1990;38:95–100.
25. Melkko J, Niemi S, Risteli L, Risteli J. Radioimmunoassay of the carboxyterminal propeptide of human type I procollagen. Clin Chem. 1990;36:1328–32.
26. Fujimoto D, Suzuki M, Uchiyama A, Miyamoto S, Inoue T. Analysis of pyridinoline, a crosslinking compound of collagen fibers, in human urine. J Biochem. 1983;94:1133–6.
27. Schmidt-Gayk H, Spanuth E, Kotting J, Bartl R, Felsenberg D, Pfeilshifter J, et al. Performance evaluation of automated assays for β-Crosslaps, N-MID osteocalcin and intact parathyroid hormone (BIROSE multicenter study). Clin Chem Lab Med. 2004;42:90–5.
28. Gomez B Jr, Ardakani S, Ju J, Jenkins D, Cerelli MJ, Daniloff GY, et al. Monoclonal antibody assay for measuring bone-specific alkaline phosphatase activity in serum. Clin Chem. 1995;41:1560–6.
29. Melkko J, Kauppila S, Niemi S, Risteli L, Haukipuro K, Jukkola A, et al. Immunoassay for intact amino-terminal propeptide of human type I procollagen. Clin Chem. 1996;42:947–54.
30. Hirota Y, Kurimoto F, Hata K, Miura M. Fundamental studies on the determination of serum intact PINP (amino-terminal propeptide of type I procollagen) with RIA method. Clin Endocrinol. 1997;4:431–5. (in Japanese).
31. Clemens JD, Herrick MV, Singer FR, Eyre DR. Evidence that serum NTx (collagen-type I N-telopeptides) can act as an immunochemical marker of bone resorption. Clin Chem. 1997;43:2058–63.
32. Gertz BJ, Clemens JD, Holland SD, Yuan W, Greenspan S. Application of a new serum assay for type I collagen cross-linked N-telopeptides: assessment of diurnal changes in bone turnover with and without alendronate treatment. Calcif Tissue Int. 1998;63:102–6.
33. Yoshimura N, Muraki S, Oka H, Mabuchi A, Kinoshita H, Yoshida M, et al. Epidemiology of lumbar osteoporosis and osteoarthritis and their causal relationship—is osteoarthritis a predictor for osteoporosis, or vice versa?: The Miyama study. Osteoporos Int. 2009;20:999–1008.
34. Yoshimura N, Hashimoto T. Differences of values of BMD between mountainous and fishing areas, Wakayama prefecture, Japan. Osteoporos Jpn. 1999;7:12–3. (in Japanese).
35. Yoshimura N, Sakata K, Morioka S, Yasuda Y, Hashimoto T, Kasamatsu T. The comparison of incidence of fast bone losers in mountainous and fishing areas. Osteoporos Jpn. 1997;5:231–4. (in Japanese).
36. Yoshimura N, Hashimoto T, Morioka S, Kasamatsu T, Aoki N, Shiraki M. The difference of distribution of bone metabolic marker levels between mountainous and fishing villages. Osteoporos Jpn. 1996;4:119–22. (in Japanese).
37. Wakayama Prefecture. The results of Nutrition Survey in Wakayama Prefecture 1993. (in Japanese).
38. Yoshimura N, Muraki S, Oka H, Kawaguchi H, Nakamura K, Akune T. Cohort profile: research on osteoarthritis/osteoporosis

against disability (ROAD) study. Int J Epidemiol. 2010;39: 988–95.
39. Yoshimura N, Kasamatsu T, Sakata K, Hashimoto T, Cooper C. The relationship between endogenous estrogen, sex hormone binding globulin and bone loss in female residents of a rural Japanese community: the Taiji study. J Bone Miner Metab. 2002;20:303–10.
40. Yoshimura N, Muraki S, Oka H, Kawaguchi H, Nakamura K, Akune T. Capacity of endogenous sex steroids to predict bone loss, osteoporosis and osteoporotic fracture in Japanese men: ten-year follow-up of the Taiji cohort study. J Bone Miner Metab 2011;29:96–102.
41. Yoshimura N, Takijiri T, Kinoshita H, Danjoh S, Kasamatsu T, Morioka S, et al. Characteristics and course of bone mineral densities among fast bone losers in a rural Japanese community: the Miyama study. Osteoporos Int. 2004;15:139–44.
42. Delmas PD, Eastell R, Garnero P, Seibel MJ, Stepan J, for the Committee of Scientific Advisors of the International Osteoporosis Foundation. The use of biochemical markers of bone turnover in osteoporosis, Osteoporos Int 11 Suppl 2000;6:S2–17.
43. Seibel MJ. Molecular markers of bone turnover: biochemical, technical and analytical aspects. Osteoporos Int. 2000;11(Suppl 6):S18–29.

Arthritis Care & Research
Vol. 63, No. 10, October 2011, pp 1425–1431
DOI 10.1002/acr.20562

ORIGINAL ARTICLE

Prevalence of Falls and the Association With Knee Osteoarthritis and Lumbar Spondylosis As Well As Knee and Lower Back Pain in Japanese Men and Women

SHIGEYUKI MURAKI,[1] TORU AKUNE,[1] HIROYUKI OKA,[1] YOSHIO EN-YO,[2] MUNEHITO YOSHIDA,[2] KOZO NAKAMURA,[1] HIROSHI KAWAGUCHI,[1] AND NORIKO YOSHIMURA[1]

Objective. There is little information on falls by sex and age strata in Japan, and few factors associated with falls have been established. However, the association between bone and joint diseases and falls remains unclear. We examined prevalence of falls by sex and age strata, determined its association with radiographic osteoarthritis (OA) of the knee and lumbar spine, and determined knee and lower back pain after single and multiple falls.

Methods. A questionnaire assessed the number of falls during 12 months preceding baseline. Knee and lumbar spine radiographs were read by Kellgren/Lawrence (K/L) grade; radiographic knee OA and lumbar spondylosis were defined as a K/L grade of 3 or 4. Knee and lower back pain were estimated by an interview.

Results. A total of 587 men and 1,088 women (mean ± SD age 65.3 ± 12.0 years) were analyzed. During 1 year, 79 (13.5%) men and 207 (19.0%) women reported at least 1 fall. With increasing age, the prevalence of multiple falls was higher in women, but lower in elderly men age >60 years. In men, few factors were significantly associated with falls. In women, radiographic knee OA and lumbar spondylosis, as well as knee and lower back pain, were significantly associated with multiple falls without adjustment. Lower back pain and knee pain were independently associated with multiple falls in women after adjustment.

Conclusion. Lower back pain and knee pain were significantly associated with multiple falls in women.

INTRODUCTION

Falls are one of the main causes of injury, disability, and death among the elderly (1,2). In Japan, according to the recent National Livelihood Survey of the Ministry of Health, Labour and Welfare, fall and fracture are ranked fifth among diseases that cause disabilities and subsequently require support with activities of daily living (3). However, there have been few population-based studies for prevalence of fall based on sex and age strata. Further, in terms of factors associated with falls, muscle strength, balance, vision, and functional capacities, there are traits that diminish with aging, and these factors have been suggested as predictive risk factors for falls and fractures (4). Cognitive impairment has also been established as a risk factor for falls (5), but the association of bone and joint diseases, especially osteoarthritis (OA), with falls remains unclear.

The representative sites of OA are the knee and lumbar spine. Knee OA and lumbar spondylosis (LS) are major public health issues since they cause chronic pain and disability (6–11). The prevalence of radiographic knee OA and LS is high in Japan (12,13), with 25,300,000 and 37,900,000 subjects ages ≥40 years estimated to experience radiographic knee OA and LS, respectively (14). The National Livelihood Survey ranked OA fourth among diseases that cause disabilities and subsequently require sup-

Supported by Grants-in-Aid for Scientific Research (grants B20390182, C20591737, and C20591774), for Young Scientists (grant A18689031), and for Exploratory Research (grant 19659305) from the Japanese Ministry of Education, Culture, Sports, Science and Technology; by the Ministry of Health, Labor and Welfare (grants H17-Men-eki-009, H18-Choujyu-037, and H20-Choujyu-009); by Research Aid from the Japanese Orthopaedic Association; and by the Japan Orthopaedics and Traumatology Foundation (grant 166).

[1]Shigeyuki Muraki, MD, PhD, Toru Akune, MD, PhD, Hiroyuki Oka, MD, Kozo Nakamura, MD, PhD, Hiroshi Kawaguchi, MD, PhD, Noriko Yoshimura, MD, PhD: University of Tokyo, Tokyo, Japan; [2]Yoshio En-yo, MD, Munehito Yoshida, MD, PhD: Wakayama Medical University, Wakayama, Japan.

Address correspondence to Shigeyuki Muraki, MD, PhD, Department of Clinical Motor System Medicine, 22nd Century Medical and Research Center, Faculty of Medicine, University of Tokyo, Hongo 7-3-1, Bunkyo-ku, Tokyo 113-8655, Japan. E-mail: murakis-ort@h.u-tokyo.ac.jp.

Submitted for publication December 13, 2010; accepted in revised form July 9, 2011.

Significance & Innovations

- During 1 year, 13.5% of men and 19.0% of women reported at least 1 fall.
- With increasing age, prevalence of multiple falls was higher in women, but lower in elderly men age >60 years.
- Lower back pain and knee pain were independently associated with multiple falls in women.

port with activities of daily living (3), but there have been few studies of the association between falls and OA (15,16). In previous studies, knee OA was assessed only by interview and not by radiography. The principal clinical symptom of knee OA is pain (17), but its correlation with the radiographic severity of knee OA is not as strong as expected (12,18–20). In fact, in a study in Japan, ~20% of the subjects without knee OA had knee pain, and 30% of the subjects with severe knee OA had no knee pain (12). Therefore, knee OA diagnosed by interview could be limited by variable accuracy. In addition, men and women were not examined separately in these previous studies, although sex differences have been found in the prevalence of knee OA (12). Furthermore, knee OA is conventionally defined according to Kellgren/Lawrence (K/L) grade (21), and our previous study showed that the association of a K/L grade of 2 (knee OA with pain) was weak, but that a K/L grade of 3 or 4 (knee OA with pain) was strong (12); therefore, the association of knee OA with falls may be different between a K/L grade of 2 for knee OA and a K/L grade of 3 or 4 for knee OA. However, there are no population-based studies on the association of severity of knee OA with falls. With regard to LS, to the best of our knowledge, there have been no population-based studies regarding its association with falls.

Previous studies have shown that associations between individual risk factors and a single fall are few in number and weak compared to risk factors for multiple falls (16), indicating that single and multiple falls may have different backgrounds. Therefore, to determine factors associated with falls, single and multiple falls should be analyzed separately.

The objectives of this study were to clarify prevalence of single and multiple falls by sex and age strata in Japan using a large-scale, population-based cohort study known as Research on Osteoarthritis/osteoporosis Against Disability (ROAD). Further, we examined the associations of radiographic knee OA and LS, as well as knee and lower back pain, with single and multiple falls in Japanese men and women.

PATIENTS AND METHODS

Patients. The ROAD study is a nationwide prospective study designed to establish epidemiologic indexes for evaluation of clinical evidence for the development of a disease-modifying treatment for bone and joint diseases (OA and osteoporosis are the representative bone and joint diseases, respectively). It consists of population-based cohorts in 3 communities in Japan. A detailed profile of the ROAD study has been described elsewhere (12–14,22); a brief summary is provided here. To date, we have completed the creation of a baseline database that includes clinical and genetic information for 3,040 subjects (1,061 men and 1,979 women) with a mean age of 70.6 years (range 23–95 years), who were recruited from resident registration listings in 3 communities: an urban region in Itabashi, Tokyo; a mountainous region in Hidakagawa, Wakayama; and a coastal region in Taiji, Wakayama.

Residents of these regions were recruited from the resident registration list of the relevant region. The participants in the urban region were recruited from a randomly selected cohort from the Itabashi-ward residents' registration database (22). The participation rate was 75.6%. The participants in mountainous and coastal regions were also recruited from the resident-registration lists, and the participation rates in these 2 areas were 56.7% and 31.7%, respectively. The inclusion criteria, apart from residence in the communities mentioned above, were the ability to 1) walk to the survey site, 2) report data, and 3) understand and sign an informed consent form. The baseline survey of the ROAD study was completed in 2006. All participants provided their written informed consent, and the study was conducted with the approval of the ethics committees of the University of Tokyo and the Tokyo Metropolitan Institute of Gerontology.

Falls assessment. All subjects were interviewed with regard to falls and fractures by experienced interviewers and were asked the following questions: "Have you experienced falls during the 12 months preceding baseline, and if yes, how many falls did you experience?" and "Have you experienced any fractures when you fell?" According to a previous study on falls (23), a fall is defined as a sudden, unintentional change in position causing an individual to land at a lower level on an object, the floor, or the ground, other than as a consequence of a sudden onset of paralysis, epileptic seizure, or overwhelming external force.

Pain assessment. All subjects were also interviewed by experienced orthopedists (SM and HO) with regard to knee pain and lower back pain and were asked the following questions: "Have you experienced knee pain on most days in the past year, in addition to now?" and "Have you experienced lower back pain on most days in the past year, in addition to now?" Those who answered yes were defined as having pain.

Radiographic assessment. All participants underwent radiographic examination of both knees using anteroposterior and lateral views with weight-bearing and foot map positioning; radiographic examination of the anteroposterior and lateral views of the lumbar spine, including intervertebral levels L1/2 to L5/S, was also performed. Knee and lumbar spine radiographs were read without the knowledge of participant clinical status by a single, experienced orthopedist (SM) using the K/L radiographic atlas

(21) to determine the severity of K/L grading. Radiographs were scored as grade 0 through 4, with higher grades being associated with more severe OA. We defined knee OA and LS as a K/L grade of ≥3 in at least 1 knee and 1 intervertebral level, respectively. To evaluate the intraobserver variability of K/L grading, 100 randomly selected radiographs of the knee and the lumbar spine were scored by the same observer more than 1 month after the first reading. One hundred other radiographs were also scored by 2 experienced orthopedic surgeons (SM and HO) using the same atlas for interobserver variability. The intra- and interobserver variabilities evaluated were confirmed by kappa analysis to be sufficient for assessment (0.86 and 0.80 for knee OA, and 0.84 and 0.76 for LS, respectively).

Covariates. Anthropometric measurements included height, weight, and body mass index (BMI; kg/m^2). Grip strength was measured on bilateral sides using a TOEI LIGHT handgrip dynamometer, and the best measurement was used to characterize maximum muscle strength. To measure physical performance, the time taken to walk 6 meters at normal walking speed in a hallway was recorded. Subjects were told to walk from a marked starting line to a 6-meter mark as if they were walking down their hallway at home. Time was measured in seconds with a stopwatch and rounded to the nearest hundredth of a second. The average of 2 trials was recorded. These gait-speed trial measurements are considered highly reliable in community-dwelling elderly subjects (24–27).

The time taken for 5 consecutive chair rises without the use of hands was also recorded. Hands were folded in front of the chest with feet flat on the floor, following the protocol described by Guralnik et al (28) and used by other researchers (25,29,30). Time was measured in seconds with a stopwatch and rounded to the nearest hundredth of a second. Timing began with the command "go" and ended when the buttocks contacted the chair on the fifth landing. The reliability of this protocol is adequate (25,28,29). Cognition was also evaluated for all subjects using a Mini-Mental State Examination, and a cutoff score of <24 was used to select participants with cognitive impairment (31).

Statistical analyses. The differences in age, anthropometric measurements, and physical performance measurements between men and women were examined by Student's unpaired *t*-test, and among groups of nonfallers, single fallers, and multiple fallers using one-way analysis of variance (ANOVA). The prevalence of cognitive impairment, radiographic knee OA and LS, and knee and lower back pain was compared between men and women, and among nonfallers, single fallers, and multiple fallers by using the chi-square test. The prevalence of single and multiple falls was also compared between men and women, among subjects with no knee OA (K/L grade 0 or 1), with K/L grade 2 for knee OA and K/L grade 3 or 4 for knee OA, and among subjects with no LS (K/L grade 0 or 1), with K/L grade 2 for LS, and K/L grade 3 or 4 for LS by using the chi-square test. The association of knee pain and lower back pain with physical performance was determined by logistic regression analysis. Multinomial logistic regression analysis was also used to determine the association of anthropometric measurements, physical performance, cognitive impairment, radiographic knee OA and LS defined as K/L grade 3 or 4, and knee and lower back pain, with single and multiple falls compared with nonfalls. Further, to determine the independent association of radiographic knee OA and LS, and knee and lower back pain with single and multiple falls compared with nonfalls, we first used multinomial logistic regression analysis with age, BMI, cognitive impairment, radiographic knee OA and LS, and knee and lower back pain as independent variables. In addition to the above independent variables, we additionally adjusted for grip strength, 6-meter walking time, and chair stand time. Data analyses were performed using SAS software, version 9.0.

RESULTS

Of the 1,690 subjects in the mountainous and seaside cohorts at baseline, 15 subjects provided incomplete fall questionnaires, leaving a total of 1,675 subjects (587 men, 1,088 women). Table 1 shows the age, anthropometric measurements, and physical performance of the participants in the present study. Regarding physical performance, grip strength, 6-meter walking time, and chair stand time were significantly better in men than in women. The prevalence of cognitive impairment was not significantly different between men and women. The prevalence of radiographic knee OA and knee pain was significantly higher in women than in men, while that of LS and lower back pain was not different between men and women.

During the 12 months preceding the baseline examination, 79 men (13.5%, 95% confidence interval [95% CI] 10.9–16.5%) and 207 women (19.0%, 95% CI 16.8–21.5%) reported at least 1 fall, and 48 men (8.2%, 95% CI 6.2–10.7%) and 80 women (7.4%, 95% CI 5.9–9.1%) reported multiple falls. Chi-square test showed that the prevalence of single and multiple falls were significantly different between men and women ($P < 0.0001$). Among 286 subjects with at least 1 fall, 6 subjects (2.1%) had a wrist fracture, 2 (0.7%) had a proximal humerus fracture, 1 (0.3%) had a vertebral fracture, and 12 (4.2%) had fractures at other sites. With increasing age, the prevalence of falls was lower in elderly men age >60 years; however, the prevalence of falls was higher in women with increasing age (Table 2). Moreover, with increasing age, the prevalence of multiple falls was also lower in elderly men age >60 years, but it was higher in women with increasing age (Table 2). The prevalence (95% CI) of a single fall (%) was similar among age strata in men and women (for men: 5.3% [1.8–14.4%], 6.8% [3.3–13.4%], 3.2% [1.4–7.3%], 5.5% [3.2–9.4%], and 7.4% [1.0–12.5%] in the age subgroups of <50 years, 50–59 years, 60–69 years, 70–79 years, and ≥80 years, respectively; for women: 11.9% [7.5–18.5%], 11.1% [7.5–16.1%], 12.0% [8.9–16.0%], 11.6% [8.6–15.6%], and 11.4% [6.7–18.9%] in the age subgroups of <50 years, 50–59 years, 60–69 years, 70–79 years, and ≥80 years, respectively).

Table 3 shows the age, anthropometric measurements,

Table 1. Characteristics of participants*

	Overall	Men	Women
Subjects, no.	1,675	587	1,088
Age, years	65.3 ± 12.0	66.3 ± 11.7	64.7 ± 12.1†
Height, cm	155.1 ± 9.3	163.4 ± 7.2	150.6 ± 6.9†
Weight, kg	55.6 ± 10.8	62.3 ± 10.9	52.0 ± 8.9†
BMI, kg/m^2	23.0 ± 3.4	23.3 ± 3.2	22.9 ± 3.5†
Grip strength, kg	27.4 ± 9.8	35.7 ± 9.3	22.9 ± 6.8†
6-meter walking time, seconds	5.5 ± 2.5	5.3 ± 2.2	5.6 ± 2.6†
Chair stand time, seconds	10.1 ± 4.4	9.7 ± 3.6	10.4 ± 4.8†
Cognitive impairment, %	4.5	5.2	4.2
Radiographic knee OA, %	20.3	15.0	23.0‡
Radiographic lumbar spondylosis, %	37.1	37.7	36.9
Knee pain, %	24.4	18.9	27.4‡
Lower back pain, %	20.1	21.7	21.2

* Values are the mean ± SD unless indicated otherwise. BMI = body mass index; OA = osteoarthritis.
† $P < 0.05$ vs. men by Student's unpaired *t*-test.
‡ $P < 0.05$ vs. men by chi-square test.

physical performance, and prevalence of cognitive impairment among nonfallers, single fallers, and multiple fallers. One-way ANOVA showed that there were no significant associations of age, anthropometric measurements, physical performance, and prevalence of cognitive impairment with falls in men, while age and BMI were higher in multiple fallers than in nonfallers in women. With regard to physical performance, grip strength was lower and 6-meter walking time and chair stand time were longer in multiple fallers than in nonfallers and single fallers in women. Further, prevalence of cognitive impairment was also different among nonfallers, single fallers, and multiple fallers in women. Further, to determine the association of anthropometric measurements, physical performance, and cognitive impairment with single and multiple falls, we also used multinomial logistic regression analysis and found that age (odds ratio [OR] 1.04, 95% CI 1.02–1.06), BMI (OR 1.10, 95% CI 1.03–1.17), grip strength (OR 0.92, 95% CI 0.89–0.96), 6-meter walking time (OR 1.10, 95% CI 1.02–1.17), chair stand time (OR 1.06, 95% CI 1.02–1.10), and cognitive impairment (OR 3.86, 95% CI 1.67–3.83) were significantly associated with multiple falls in women.

To determine the association of the severity of knee OA with falls, we classified subjects as those with no knee OA (K/L grade 0 or 1), with K/L grade 2 for knee OA, and with K/L grade 3 or 4 for knee OA. The prevalence of falls in subjects with no knee OA, K/L grade 2 for knee OA, and K/L grade 3 or 4 for knee OA was 11.8%, 17.1%, and 12.5%, and 17.7%, 17.6%, and 25.6% in men and women, respectively. There were no significant associations between falls and the severity of knee OA in men (chi-square test; $P = 0.27$), while prevalence of falls was higher in women with K/L grade 3 or 4 for knee OA than those with no knee OA and K/L grade 2 for knee OA ($P = 0.01$). Similar to knee OA, we classified subjects as those with no LS (K/L grade 0 or 1), those with K/L grade 2 for LS, and those with K/L grade 3 or 4 for LS. The prevalence of falls in subjects with no LS, K/L grade 2 for LS, and K/L grade 3 or 4 for LS was 16.3%, 11.3%, and 14.0%, and 17.0%, 20.5%, and 20.7% in men and women, respectively. There were no significant associations between falls and the severity of LS in men and women (chi-square test, $P = 0.38$ and 0.32, respectively). We next used the chi-square test to determine the association of single and multiple falls with knee OA and LS defined as K/L grade 3 or 4 (Table 4). A chi-square test showed that no significant factors were associated with falls in men, but radiographic knee OA, knee pain, and lower back pain were significantly associated with falls in women.

Multinomial logistic regression analysis also showed that radiographic knee OA, LS, and knee and lower back pain were significantly associated with multiple falls in women (Table 5). Because knee pain and lower back pain were also significantly associated with grip strength, 6-meter walking time, and chair stand time in men and women

Table 2. Prevalence of falls by age strata in men and women*

	Single fall		Multiple falls	
Age, years	Men	Women	Men	Women
<50	15.8 (8.5–27.4)	13.4 (8.7–20.2)	10.5 (4.9–21.1)	1.5 (0.4–5.3)
50–59	10.7 (6.1–18.1)	17.4 (12.8–23.1)	3.9 (1.5–9.6)	6.3 (3.7–10.4)
60–69	16.7 (11.6–23.3)	18.8 (14.9–23.4)	13.5 (9.0–19.7)	6.8 (4.5–10.1)
70–79	12.4 (8.7–17.5)	21.1 (16.9–25.9)	6.9 (4.2–11.1)	9.4 (6.7–13.1)
≥80	11.1 (5.2–22.2)	23.8 (16.7–32.8)	3.7 (1.0–12.5)	12.4 (7.4–20.0)

* Values are the percentage (95% confidence interval).

Table 3. Comparison of characteristics among nonfallers, single fallers, and multiple fallers in men and women*

	Men				Women			
	Nonfallers	Single fallers	Multiple fallers	*P*	Nonfallers	Single fallers	Multiple fallers	*P*
Subjects, no.	508	31	48		881	127	80	
Age, years	66.4 ± 11.7	67.6 ± 11.9	64.6 ± 11.3	0.50	64.4 ± 12.1	64.3 ± 12.2	69.1 ± 10.4	0.004
Height, cm	163.5 ± 7.4	162.3 ± 6.3	162.9 ± 5.9	0.56	150.9 ± 6.8	150.7 ± 7.7	148.5 ± 7.0	0.01
Weight, kg	62.6 ± 11.1	60.7 ± 10.4	60.3 ± 9.0	0.27	51.8 ± 8.8	53.3 ± 9.2	52.8 ± 8.9	0.15
BMI, kg/m^2	23.3 ± 3.2	23.0 ± 3.1	22.7 ± 2.8	0.27	22.7 ± 3.4	23.4 ± 3.6	23.9 ± 3.7	0.002
Grip strength, kg	35.8 ± 9.3	34.0 ± 9.6	35.5 ± 9.1	0.57	23.3 ± 6.8	22.6 ± 6.5	19.9 ± 5.3	< 0.001
6-meter walking time, seconds	5.2 ± 2.2	5.8 ± 2.5	5.6 ± 2.3	0.21	5.5 ± 2.6	5.7 ± 2.6	6.3 ± 2.7	0.03
Chair stand time, seconds	9.6 ± 3.6	10.3 ± 3.8	10.2 ± 3.3	0.30	10.2 ± 4.8	10.5 ± 4.6	11.9 ± 5.1	0.01
Cognitive impairment, %	4.6	6.5	10.6	0.26	3.3	5.6	11.7	0.008

* Values are the mean ± SD unless indicated otherwise. One-way analysis of variance was used to determine the differences in age, height, weight, body mass index (BMI), grip strength, 6-meter walking time, normal step length, and chair stand time among nonfallers, single fallers, and multiple fallers. Chi-square test was used to determine the differences in prevalence of cognitive impairment among nonfallers, single fallers, and multiple fallers.

(logistic regression analysis; $P < 0.05$); to examine the independent association between radiographic knee OA, knee pain, radiographic LS, and lower back pain in women, we first used multinomial logistic regression analysis with age, BMI, cognitive impairment, radiographic knee OA, knee pain, radiographic LS, and lower back pain as independent variables (Table 5). In this analysis, only lower back pain was independently associated with multiple falls in women. In addition to the above independent variables, we also adjusted for grip strength, 6-meter walking time, and chair stand time, and found that the significant association of lower back pain with multiple falls disappeared, while knee pain was independently associated with multiple falls in women (Table 5).

DISCUSSION

The present study is the first large-scale population-based cohort study of the prevalence of single and multiple falls and their association with radiographic knee OA and LS, as well as pain in Japanese men and women. We found that lower back pain and knee pain were independently associated with multiple falls in women.

There were distinct associations between age strata and single and multiple falls. We found that several factors were associated with multiple falls in women, but no factors were associated with a single fall in women. Previous studies have shown that associations between individual risk factors and a single fall are few in number and weak compared with risk factors for multiple falls (16). A single fall in a year could be accidental and occur due to individual as well as environmental factors, which may partly explain why there were no factors significantly associated with a single fall in our study. In contrast, several factors were associated with multiple falls in the present study, indicating that multiple falls may occur primarily due to individual factors.

In women, the prevalence of multiple falls was higher with increasing age, but in men, the prevalence of multiple falls was lower in subjects ages >60 years, although this could be a random error because of small prevalence, particularly in men. This may be partly explained by the

Table 4. Comparison of radiographic knee OA and LS, as well as knee and lower back pain, among nonfallers, single fallers, and multiple fallers in men and women*

	Men				Women			
	Nonfallers	Single fallers	Multiple fallers	*P*	Nonfallers	Single fallers	Multiple fallers	*P*
Subjects, no.	508	31	48		881	127	80	
Radiographic knee OA†	77/507 (15.2)	4/31 (12.9)	7/47 (14.9)	0.9417	186/875 (21.3)	31/127 (24.4)	33/79 (41.8)	0.0002
Knee pain‡	97/508 (19.1)	3/31 (9.7)	11/48 (22.9)	0.3268	224/880 (25.5)	37/127 (29.1)	37/80 (46.3)	0.0003
Radiographic LS	190/508 (37.4)	12/31 (38.7)	19/48 (39.6)	0.9490	318/881 (36.1)	45/127 (35.4)	38/80 (47.5)	0.1210
Lower back pain§	99/508 (19.5)	10/31 (32.3)	9/48 (18.8)	0.2203	177/880 (20.1)	31/127 (24.4)	28/80 (35.0)	0.0062

* Values are the number/total number (percentage) unless otherwise indicated. The chi-square test was used to determine the differences in radiographic findings and pain among nonfallers, single fallers, and multiple fallers. Radiographic knee OA and LS were defined as Kellgren/Lawrence grade 3 or 4. OA = osteoarthritis; LS = lumbar spondylosis.
† Nine subjects with total knee arthroplasty were excluded.
‡ One subject with incomplete information regarding knee pain was excluded.
§ One subject with incomplete information regarding lower back pain was excluded.

Table 5. Association of radiographic knee OA and LS, as well as knee and lower back pain, with single and multiple falls in women*

	Crude OR (95% CI)		Adjusted OR_1 (95% CI)†		Adjusted OR_2 (95% CI)‡	
	Single falls	Multiple falls	Single falls	Multiple falls	Single falls	Multiple falls
Radiographic knee OA	1.20 (0.76–1.83)	2.66 (1.64–4.26)	1.07 (0.63–1.82)	1.43 (0.78–2.61)	1.04 (0.60–1.77)	1.31 (0.70–2.43)
Knee pain	1.20 (0.79–1.81)	2.52 (1.58–4.02)	1.00 (0.62–1.61)	1.61 (0.92–2.79)	0.99 (0.60–1.61)	1.87 (1.06–3.28)
Radiographic LS	0.97 (0.65–1.43)	1.60 (1.01–2.54)	0.87 (0.57–1.32)	1.12 (0.68–1.85)	0.88 (0.57–1.33)	1.04 (0.61–1.74)
Lower back pain	1.28 (0.82–1.96)	2.14 (1.30–3.46)	1.34 (0.84–2.08)	1.72 (1.01–2.88)	1.33 (0.84–2.08)	1.58 (0.91–2.70)

* Radiographic knee osteoarthritis (OA) and lumbar spondylosis (LS) were defined as Kellgren/Lawrence grade 3 or 4. Multinomial logistic regression analysis was used to calculate the odds ratio (OR) and 95% confidence interval (95% CI) compared with nonfallers. Eight subjects with total knee arthroplasty or incomplete information regarding pain were excluded.
† Adjusted OR_1 was calculated using multinomial logistic regression analysis with age, body mass index, cognitive impairment, radiographic knee OA, knee pain, radiographic LS, and lower back pain as independent variables.
‡ Adjusted OR_2 was calculated using multinomial logistic regression analysis with grip strength, 6-meter walking time, and chair stand time in addition to the above independent variables.

fact that elderly men generally retire from their occupations at approximately ages 60–70 years; therefore, their environment may change and men may become more sedentary as they age, leading to lower risks of falls. Women, however, must often continue to do household chores even after age 60 years, and their environment may therefore change to a smaller extent than that of men, but their health or muscle strength continues to decline (32), leading to the higher risk of falls.

Our study is the first population-based study to examine the association between knee OA and LS diagnosed by radiography and falls in Japanese men and women. Radiographic knee OA and LS were significantly associated with multiple falls in women, but not in men, although no significant association of radiographic knee OA or LS with falls may be due to the small number of falls in men. The sex differences identified in the association between radiographic knee OA and falls may be partly explained by the weaker quadriceps muscles and increased postural sway associated with knee OA (33,34), both of which are known to be independent risk factors for falls (16,35). In men, muscle strength was higher than that in women in all decades (32), which may obscure the association between radiographic knee OA and falls. LS was also significantly associated with falls in this study, but the OR was lower than that for knee OA. Therefore, falls may be more strongly associated with problems of the lower extremities rather than the trunk.

After adjustment for age, BMI, and cognitive impairment, lower back pain was independently associated with multiple falls, and after adjustment for age, BMI, grip strength, cognitive impairment, 6-meter walking time, and chair stand time, knee pain was independently associated with multiple falls. Given that the significant association of radiographic knee OA and LS with multiple falls disappeared after adjustment, multiple falls may occur due to symptoms such as pain caused by radiographic knee OA or LS rather than radiographic changes in the knee or lumbar spine itself. A previous study also suggested that subjects with knee pain had an increased risk of falls (15). In other words, falls may be preventable when pain is relieved by medical care, even if subjects have radiographic knee OA or LS.

The present study has several limitations. First, this is a large-scale population-based study with a cross-sectional analysis of baseline data. Therefore, causal relationships could not be determined. The ROAD study is a longitudinal survey; therefore, further progress may help elucidate any causal relationships. Second, our subjects lived in the community, and therefore our findings may not apply to elderly persons residing in institutions. Third, we did not include other weight-bearing OA diseases, such as hip OA, in the analysis, although this disorder also affects falls (36). However, the prevalence of K/L grade 3 or 4 for hip OA is 1.4% and 3.5% in Japanese men and women (37), respectively, which is smaller than that of K/L grade 3 or 4 for knee OA in the present study. Therefore, it is possible that hip OA would not strongly affect the results of the present study. Fourth, the prevalence of fall was comparably small, particularly in men. Therefore, our results regarding the prevalence may include random error, but the present study is the first large-scale, population-based cohort study of the prevalence of falls in Japanese men and women.

In conclusion, the present cross-sectional analysis using a large-scale population from the ROAD study revealed the prevalence and factors associated with falls in men and women. In women, lower back pain and knee pain were significantly associated with multiple falls. Further studies, along with continued longitudinal surveys in the ROAD study, will help elucidate the background of knee OA and LS, and their relationship with falls.

ACKNOWLEDGMENTS

The authors wish to thank Mrs. Tomoko Takijiri and other members of the Public Office in Hidakagawa, as well as Mrs. Tamako Tsutsumi, Mrs. Kanami Maeda, and other members of the Public Office in Taiji for their assistance in the location and scheduling of participants for examinations.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Muraki had full access to all of the data in the study and takes

responsibility for the integrity of the data and the accuracy of the data analysis.
Study conception and design. Muraki, Akune, Oka, En-yo, Yoshida, Nakamura, Kawaguchi, Yoshimura.
Acquisition of data. Muraki, Akune, Oka, En-yo, Yoshimura.
Analysis and interpretation of data. Muraki, Akune, Oka, Yoshimura.

REFERENCES

1. Baker S, O'Neill B, Karpf RS. The injury fact book. Lexington (MA): Lexington Books; 1984.
2. Fife D, BarancikJI, Chatterjee MS. Northeastern Ohio Trauma Study, II: injury rates by age, sex and cause. Am J Public Health 1984;74:473–8.
3. Ministry of Health, Labour and Welfare. The outline of the results of National Livelihood Survey 2007. URL: http://www.mhlw.go.jp/toukei/list/20-19-1.html.
4. Dargent-Molina P, Favier F, Grandjean H, Baudoin C, Schott AM, Hausherr E, et al. Fall-related factors and risk of hip fracture: the EPIDOS prospective study. Lancet 1996;348:145–9.
5. Tinetti ME, Speechley M, Ginter SF. Risk factors for falls among elderly persons living in the community. N Engl J Med 1988;319:1701–7.
6. Jackson DW, Simon TM, Aberman HM. Symptomatic articular cartilage degeneration: the impact in the new millennium. Clin Orthop Relat Res 2001;391 Suppl:S14–25.
7. Reginster JY. The prevalence and burden of arthritis. Rheumatology (Oxford) 2002;41 Suppl:S3–6.
8. Buckwalter JA, Saltzman C, Brown T. The impact of osteoarthritis: implications for research. Clin Orthop Relat Res 2004;427 Suppl:S6–15.
9. Sharma L, Kapoor D. Epidemiology of osteoarthritis. In: Moskowitz RW, Altman RD, Hochberg MC, Buckwalter JA, Goldberg VM, editors. Osteoarthritis: diagnosis and medical/surgical management. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2007. p. 3–26.
10. Hadjipavlou AG, Simmons JW, Pope MH, Necessary JT, Goel VK. Pathomechanics and clinical relevance of disc degeneration and annular tear: a point-of-view review. Am J Orthop 1999;28:561–71.
11. Emery SE, Ringus VM. Osteoarthritis of the spine. In: Moskowitz RW, Altman RD, Hochberg MC, Buckwalter JA, Goldberg VM, editors. Osteoarthritis: diagnosis and medical/surgical management. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2007. p. 427–52.
12. Muraki S, Oka H, Akune T, Mabuchi A, En-yo Y, Yoshida M, et al. Prevalence of radiographic knee osteoarthritis and its association with knee pain in the elderly of Japanese population-based cohorts: the ROAD study. Osteoarthritis Cartilage 2009;17:1137–43.
13. Muraki S, Oka H, Akune T, Mabuchi A, En-Yo Y, Yoshida M, et al. Prevalence of radiographic lumbar spondylosis and its association with low back pain in the elderly of population-based cohorts: the ROAD study. Ann Rheum Dis 2008;68:1401–6.
14. Yoshimura N, Muraki S, Oka H, Mabuch A, En-yo Y, Yoshida M, et al. Prevalence of knee osteoarthritis, lumbar spondylosis and osteoporosis in Japanese men and women: the Research on Osteoarthritis/osteoporosis Against Disability (ROAD). J Bone Miner Metab 2009;27:620–8.
15. Arden NK, Crozier S, Smith H, Anderson F, Edwards C, Raphael H, et al. Knee pain, knee osteoarthritis, and the risk of fracture. Arthritis Rheum 2006;55:610–5.
16. Nevitt MC, Cummings SR, Kidd S, Black D. Risk factors for recurrent nonsyncopal falls: a prospective study. JAMA 1989;261:2663–8.
17. Linaker CH, Walker-Bone K, Palmer K, Cooper C. Frequency and impact of regional musculoskeletal disorders. Baillieres Clin Rheumatol 1999;13:197–215.
18. Summers MN, Haley WE, Reveille JD, Alarcon GS. Radiographic assessment and psychological variables as predictors of pain and functional impairment in osteoarthritis of the knee or hip. Arthritis Rheum 1988;31:204–9.
19. Cicuttini FM, Baker J, Hart DJ, Spector TD. Association of pain with radiological changes in different compartments and views of the knee joint. Osteoarthritis Cartilage 1996;4:143–7.
20. Wluka AE, Wolfe R, Stuckey S, Cicuttini FM. How does tibial cartilage volume relate to symptoms in subjects with knee osteoarthritis? Ann Rheum Dis 2004;63:264–8.
21. Kellgren JH, Lawrence JS, editors. The epidemiology of chronic rheumatism: atlas of standard radiographs of arthritis. Oxford: Blackwell Scientific; 1963.
22. Yoshimura N, Muraki S, Oka H, Kawaguchi H, Nakamura K, Akune T. Cohort profile: research on osteoarthritis/osteoporosis against disability (ROAD). Study Int J Epidemiol 2010;39:988–95.
23. Tinetti M, Baker D, Dutcher J, Vincent J, Rozett R. Reducing the risk of falls among older adults in the community. Berkeley (CA): Peaceable Kingdom Press; 1997.
24. Shimada H, Lord SR, Yoshida H, Kim H, Suzuki T. Predictors of cessation of regular leisure-time physical activity in community-dwelling elderly people. Gerontology 2007;53:293–7.
25. Judge JO, Davis RB III, Ounpuu S. Step length reductions in advanced age: the role of ankle and hip kinetics. J Gerontol A Biol Sci Med Sci 1996;51:M303–12.
26. Judge JO, Lindsey C, Underwood M, Winsemius D. Balance improvements in older women: effects of exercise training. Phys Ther 1993;73:254–64.
27. Steffan TM, Hacker TA, Mollinger L. Age- and gender-related test performance in community-dwelling older people: six-minute walk test, Berg balance scale, timed up and go test, and gait speeds. Phys Ther 2002;82:128–37.
28. Guralnik JM, Simonsick EM, Ferrucci L, Glynn RJ, Berkman LF, Blazer DG, et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. J Gerontol 1994;49:M85–94.
29. Bohannon RW. Comfortable and maximum walking speed of adults aged 20-79 years: reference values and determinants. Age Ageing 1997;26:15–9.
30. Bohannon RW. Sit-to-stand test for measuring performance of lower extremity muscles. Percept Motor Skills 1995;80:163–6.
31. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–98.
32. Sinaki M, Nwaogwugwu NC, Phillips BE, Mokri MP. Effect of gender, age, and anthropometry on axial and appendicular muscle strength. Am J Phys Med Rehabil 2001;80:330–8.
33. Jones G, Nguyen T, Sambrook PN, Lord SR, Kelly PJ, Eisman JA. Osteoarthritis, bone density, postural stability, and osteoporotic fractures: a population based study. J Rheumatol 1995;22:921–5.
34. Wegener L, Kisner C, Nichols D. Static and dynamic balance responses in persons with bilateral knee osteoarthritis. J Orthop Sports Phys Ther 1997;25:13–8.
35. Campbell AJ, Borrie MJ, Spears GF. Risk factors for falls in a community-based prospective study of people 70 years and older. J Gerontol 1989;44:Ml12–7.
36. Arden NK, Nevitt MC, Lane NE, Gore LR, Hochberg MC, Scott JC, et al, for the Study of Osteoporotic Fractures Research Group. Osteoarthritis and risk of falls, rates of bone loss, and osteoporotic fractures. Arthritis Rheum 1999;42:1378–85.
37. Inoue K, Wicart P, Kawasaki T, Huang J, Ushiyama T, Hukuda S, et al. Prevalence of hip osteoarthritis and acetabular dysplasia in French and Japanese adults. Rheumatology (Oxford) 2000;39:745–8.

ARTHRITIS & RHEUMATISM
Vol. 63, No. 12, December 2011, pp 3859–3864
DOI 10.1002/art.30641

Independent Association of Joint Space Narrowing and Osteophyte Formation at the Knee With Health-Related Quality of Life in Japan

A Cross-Sectional Study

Shigeyuki Muraki,[1] Hiroyuki Oka,[1] Toru Akune,[1] Yoshio En-yo,[2] Munehito Yoshida,[2] Takao Suzuki,[3] Hideyo Yoshida,[3] Hideaki Ishibashi,[3] Fumiaki Tokimura,[3] Seizo Yamamoto,[3] Kozo Nakamura,[1] Hiroshi Kawaguchi,[1] and Noriko Yoshimura[1]

Objective. **To clarify the individual associations of joint space narrowing (JSN) and osteophytosis at the knee with quality of life (QOL) in Japanese men and women using a large-scale population-based cohort from the Research on Osteoarthritis Against Disability (ROAD) study.**

Methods. **The associations of minimum joint space width (JSW) and osteophyte area in the medial compartment of the knee with QOL parameters, such as the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), were examined. Minimum JSW and osteophyte area in the medial compartment of the knee were measured using a computer-aided system for the diagnosis of knee osteoarthritis.**

Results. **Of the 3,040 participants in the ROAD study, the present study included 2,039 participants age 40 years or older who completed the questionnaires (741 men and 1,298 women with a mean ± SD age of 68.6 ± 10.9 years). Multiple regression analysis after adjustment for age and body mass index showed that minimum JSW was significantly associated with scores on the pain domains of the WOMAC in men and women, while osteophyte area was significantly associated with scores on the physical function domains of the WOMAC in men and women.**

Conclusion. **The findings of this cross-sectional study using a large-scale population from the ROAD study indicate that JSN and osteophytosis are independently associated with QOL.**

Knee osteoarthritis (OA) is a major public health issue that causes chronic pain and disability (1–3). The prevalence of radiographic knee OA is high in Japan (4), with 25,300,000 persons age 40 years and older estimated to have radiographic knee OA (5). According to the recent National Livelihood Survey of the Ministry of Health, Labor, and Welfare of Japan, OA is ranked fourth among diseases that cause disabilities that subsequently require support with activities of daily living (6).

Knee OA is characterized by the pathologic features of joint space narrowing (JSN) and osteophytosis, but there is some controversy regarding whether osteophytosis affects knee symptoms or quality of life

Supported by the Japanese Ministry of Education, Culture, Sports, Science, and Technology (Grants-in-Aid S19109007, B20390182, C20591737, and C20591774 for Scientific Research, A18689031 for Young Scientists, and 19659305 for Exploratory Research), the Japanese Ministry of Health, Labor, and Welfare (grants H17-Men-eki-009, H18-Choujyu-037, H20-Choujyu-009, and H21-Chouju-Wakate-011), the Japanese Orthopaedic Association (research funding through the JOA-Subsidized Science Project Research 2006-1), and the Japan Orthopaedics and Traumatology Foundation (grant 166).

[1]Shigeyuki Muraki, MD, PhD, Hiroyuki Oka, MD, Toru Akune, MD, PhD, Kozo Nakamura, MD, PhD, Hiroshi Kawaguchi, MD, PhD, Noriko Yoshimura, MD, PhD: University of Tokyo, Tokyo, Japan; [2]Yoshio En-yo, MD, Munehito Yoshida, MD, PhD: Wakayama Medical University, Wakayama, Japan; [3]Takao Suzuki, MD, PhD, Hideyo Yoshida, MD, PhD, Hideaki Ishibashi, MD, PhD, Fumiaki Tokimura, MD, PhD, Seizo Yamamoto, MD, PhD: Tokyo Metropolitan Institute of Gerontology, Tokyo, Japan.

Patents for the Knee Osteoarthritis Computer-Aided Diagnosis (KOACAD) system are held by the University of Tokyo.

Address correspondence to Shigeyuki Muraki, MD, PhD, Department of Clinical Motor System Medicine, 22nd Century Medical and Research Center, Faculty of Medicine, University of Tokyo, Hongo 7-3-1, Bunkyo-ku, Tokyo 113-8655, Japan. E-mail: murakis-ort@h.u-tokyo.ac.jp.

Submitted for publication August 24, 2010; accepted in revised form August 18, 2011.

(QOL). Nevertheless, researchers examining the hand and hip have argued that the separate radiographic features should be recorded and may be more meaningful than overall composite scores such as the Kellgren/Lawrence (K/L) scale (7). Furthermore, a previous study showed that osteophytes were well correlated with knee symptoms and performed better as a primary diagnostic feature than JSN in cross-sectional epidemiologic studies of knee OA (8). However, most conventional systems for grading radiographic severity have consisted of categorical grades, such as the K/L scale (9), which is unable to individually assess JSN and osteophytosis. Several studies have shown that knee OA had a strong effect on QOL (10–13), but in those studies, knee OA was defined by categorical grades such as the K/L grade or the American College of Rheumatology grade (14), total knee arthroplasty, and self-questionnaire.

A radiographic atlas of individual features published by the OA Research Society International in 1995 (15) and revised in 2007 (16) allows JSN and osteophyte formation to be evaluated separately. However, the grading is still limited in reproducibility and sensitivity due to the subjective judgment of individual observers and the categorical classification into 4 grades (0–3). To overcome this problem, joint space width (JSW) and osteophyte area should be evaluated using a fully automatic system. To the best of our knowledge, no population-based studies have been conducted to separately measure JSW or osteophyte area in order to clarify the associations of JSN with QOL and of osteophytosis with QOL, despite the fact that the associations between these major features of knee OA and QOL are likely to be different.

Differences between the sexes have also been observed in knee OA. The prevalence of knee OA is higher in women than in men (4), and the association of knee pain with knee OA also differs by sex (4). Thus, the impact of JSN on QOL and of osteophytosis on QOL may also differ between the sexes. However, to the best of our knowledge, no population-based studies have been conducted to assess the associations of JSN and osteophytosis with QOL in men and women separately.

The objective of this study was therefore to separately clarify the association between JSN and QOL and the association between osteophytosis and QOL in Japanese men and women in a large-scale, population-based cohort from the Research on Osteoarthritis Against Disability (ROAD) study. A fully automatic system was used to measure JSW and osteophyte area. QOL was measured using disease-specific scales for knee OA, such as the Western Ontario and McMaster Universities OA Index (WOMAC).

SUBJECTS AND METHODS

Participants. The ROAD study is a nationwide prospective study designed to establish epidemiologic indexes for the evaluation of clinical evidence for the development of a disease-modifying treatment for bone and joint diseases (with OA and osteoporosis as the representative bone and joint diseases). It consists of population-based cohorts in several communities in Japan. The ROAD study has been described in detail previously (4,5,17). To date, we have completed the creation of a baseline database including clinical and genetic information for 3,040 participants (1,061 men and 1,979 women) ranging in age from 23 to 95 years (mean 70.6 years), who were recruited from resident registration listings in 3 communities: an urban region in Itabashi, Tokyo; a mountainous region in Hidakagawa, Wakayama; and a seacoast region in Taiji, Wakayama. All participants provided written informed consent, and the study was conducted with the approval of the ethics committees of the University of Tokyo and the Tokyo Metropolitan Institute of Gerontology. Height, weight, and body mass index (BMI) (weight [kg]/height [m^2]) were measured. Among the 2,995 participants in the ROAD study who were age 40 years or older, 2,222 (74.2%) completed the WOMAC. The 2,222 participants who completed the WOMAC were younger than those who did not (mean age 68.9 years for those who completed the WOMAC versus 75.9 years for those who did not; $P < 0.0001$). These 2,222 participants were also less likely to be women (63.8% of those who completed the WOMAC versus 68.3% of those who did not; $P < 0.05$), and were less likely to have knee OA than the subjects who did not complete the WOMAC (54.1% versus 60.4%; $P < 0.01$). Of the 2,222 subjects, 183 subjects with lateral knee OA or total knee arthroplasty were excluded. Therefore, a total of 2,039 participants (741 men and 1,298 women) age 40 years or older (mean ± SD 68.6 ± 10.9 years) who had completed the WOMAC were included in the present study.

Radiographic assessment. Radiographic examinations of both knees of all participants, using an anteroposterior view with weight-bearing and foot map positioning, were performed by experienced radiologic technicians. The beam was positioned parallel to the floor with no angle and aimed at the joint space. To visualize the joint space properly and to center the patella over the lower end of the femur, we used fluoroscopic guidance with an anteroposterior x-ray beam, and the images were downloaded into Digital Imaging and Communication in Medicine (DICOM) format files. Knee radiographs were read by a single experienced orthopedist (SM), who was blinded with regard to participant clinical status, using the K/L radiographic atlas for overall knee radiographic grades (9), and knee OA was defined as a K/L grade of 2 or severe. Minimum JSW in the medial compartment and osteophyte area at the medial tibia were measured by the Knee Osteoarthritis Computer-Aided Diagnosis (KOACAD) system, and for each subject the knee with the lower minimum JSW was defined as the designated knee. The KOACAD system is a fully automatic system that can quantify the major features of knee OA

on standard radiographs and allows for objective, accurate, and simple assessment of the structural severity of knee OA in general clinical practice. This system was programmed to measure minimum JSW in the medial and lateral compartments and osteophyte area at the medial tibia using digitized knee radiographs. The KOACAD system has been described in detail previously (18). The KOACAD system was applied to the DICOM data by the experienced orthopedist who developed this system (HO), and the reliability of measurement is good (18). Lateral knee OA was defined as a K/L grade of ≥2 with lower lateral minimum JSW than medial minimum JSW.

QOL instrument. To carry out the QOL assessment, we used the WOMAC. The WOMAC, a 24-item OA-specific index, consists of 3 domains: pain, stiffness, and physical function. Each of these 24 items is graded on either a 5-point Likert scale (scores of 0–4) or a 100-mm visual analog scale (19,20). In the present study, we used the Likert scale (version LK 3.0). The domain score ranges from 0 to 20 for pain, 0 to 8 for stiffness, and 0 to 68 for physical function. Japanese versions of the WOMAC have been validated (21).

Statistical analysis. Differences in age, height, weight, BMI, minimum JSW, osteophyte area, and QOL measurements between men and women were examined using Student's unpaired *t*-test. Associations of minimum JSW and osteophyte area with scores on the pain and physical function domains of the WOMAC were determined using multiple regression analysis without adjustment. To assess independent associations of minimum JSW and osteophyte area with QOL, multiple regression analysis was used with age, BMI, minimum JSW, and osteophyte area as independent variables. Data analysis was performed using SAS, version 9.0.

RESULTS

The characteristics of the 2,039 participants in the present study are shown in Table 1. The minimum JSW was significantly lower and osteophyte area was significantly higher in women than in men. Scores on all domains of the WOMAC were significantly lower (indicating better status) in men than in women. Osteophyte area was only moderately associated with minimum JSW on linear regression analysis ($R^2 = 0.173$, $P < 0.05$).

Linear regression analysis without adjustment showed that minimum JSW and osteophyte area were significantly associated with scores on the pain and physical function domains of the WOMAC in the overall population as well as in men and women analyzed separately (Table 2). To determine the independent associations of minimum JSW and osteophyte area with scores on the pain and physical function domains of the WOMAC, we used multiple regression analysis with age, sex, BMI, minimum JSW, and osteophyte area as independent variables in the overall population (Table 2). Minimum JSW and osteophyte area were independently associated with scores on the pain and physical function domains of the WOMAC (β coefficients −0.16 and 0.11 for the association of pain domain score with minimum JSW and osteophyte area, respectively, and β coefficients −0.13 and 0.16 for the association of physical function domain score with minimum JSW and osteophyte area, respectively).

When men and women were analyzed separately (Table 2), in men, minimum JSW was independently associated with the pain domain scores (β coefficient −0.13), but not with the physical function domain scores (β coefficient 0.07) of the WOMAC, while osteophyte area was independently associated with the physical function domain scores (β coefficient 0.14), but not with the pain domain scores (β coefficient −0.07) of the WOMAC. In women, both minimum JSW and osteophyte area were independently associated with scores on the pain and physical function domains of the WOMAC, and the absolute values of the beta values for minimum JSW for scores on the pain domains of the WOMAC

Table 1. Characteristics of the subjects*

	Overall population (n = 2,039)	Men (n = 741)	Women (n = 1,298)
Age, years	68.6 ± 10.9	69.7 ± 10.5	67.9 ± 11.2†
Height, cm	154.7 ± 8.9	162.8 ± 6.5	150.1 ± 6.5†
Weight, kg	55.1 ± 10.4	61.4 ± 10.2	51.5 ± 8.6†
BMI, kg/m^2	22.9 ± 3.3	23.1 ± 3.1	22.8 ± 3.4†
Minimum JSW, mm	2.61 ± 0.98	2.97 ± 0.92	2.40 ± 0.96†
Osteophyte area, mm^2	2.99 ± 8.68	1.28 ± 4.46	3.98 ± 10.25†
Radiographic knee OA, %	50.2	39.0	56.8
WOMAC			
Pain	1.35 ± 2.42	1.10 ± 2.12	1.50 ± 2.57†
Stiffness	0.72 ± 1.25	0.63 ± 1.10	0.77 ± 1.33†
Function	3.99 ± 7.84	3.24 ± 6.69	4.42 ± 8.41†

* Except where indicated otherwise, values are the mean ± SD. BMI = body mass index; JSW = joint space width; OA = osteoarthritis; WOMAC = Western Ontario and McMaster Universities OA Index.
† $P < 0.05$ versus men, by Student's unpaired *t*-test.

Table 2. Associations of minimum JSW and osteophyte area with WOMAC domain scores*

	Pain				Physical function			
	Crude regression coefficient (95% CI)	*P*	Adjusted regression coefficient (95% CI)†	*P*	Crude regression coefficient (95% CI)	*P*	Adjusted regression coefficient (95% CI)†	*P*
Overall population								
Minimum JSW	−0.71 (−0.81, −0.60)	<0.0001	−0.37 (−0.48, −0.25)	<0.0001	−2.33 (−2.66, −1.99)	<0.0001	−0.97 (−1.34, −0.59)	<0.0001
Osteophyte area	0.07 (0.05, 0.08)	<0.0001	0.03 (0.02, 0.04)	<0.0001	0.25 (0.21, 0.29)	<0.0001	0.14 (0.10, 0.18)	<0.0001
Men								
Minimum JSW	−0.47 (−0.64, −0.31)	<0.0001	−0.29 (−0.47, −0.11)	0.002	−1.34 (−1.86, −0.82)	<0.0001	−0.48 (−1.04, 0.08)	0.10
Osteophyte area	0.07 (0.04, 0.11)	<0.0001	0.03 (−0.005, 0.07)	0.09	0.30 (0.19, 0.41)	<0.0001	0.20 (0.09, 0.32)	0.0005
Women								
Minimum JSW	−0.83 (−0.97, −0.69)	<0.0001	−0.41 (−0.57, −0.25)	<0.0001	−2.89 (−3.35, −2.43)	<0.0001	−1.22 (−1.72, −0.72)	<0.0001
Osteophyte area	0.06 (0.05, 0.08)	<0.0001	0.03 (0.01, 0.04)	0.0001	0.24 (0.20, 0.29)	<0.0001	0.12 (0.08, 0.17)	<0.0001

* WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; 95% CI = 95% confidence interval.
† Calculated by multiple regression analysis with age, sex, body mass index, minimum joint space width (JSW), and osteophyte area as the independent variables in the overall population and with age, body mass index, minimum JSW, and osteophyte area as the independent variables in the groups of men and women only.

were larger than those for osteophyte area (−0.15 and 0.11, respectively), while the absolute values of the beta values for minimum JSW for scores on the physical function domains of the WOMAC were smaller than those for osteophyte area (−0.14 and 0.15, respectively).

When the analysis was restricted to the partici-

Table 3. Associations of minimum JSW and osteophyte area with WOMAC domain scores in the subjects with knee OA*

	Pain				Physical function			
	Crude regression coefficient (95% CI)	*P*	Adjusted regression coefficient (95% CI)†	*P*	Crude regression coefficient (95% CI)	*P*	Adjusted regression coefficient (95% CI)†	*P*
Overall population								
Minimum JSW	−0.81 (−0.97, −0.65)	<0.0001	−0.51 (−0.69, −0.33)	<0.0001	−2.77 (−3.32, −2.22)	<0.0001	−1.46 (−2.05, −0.87)	<0.0001
Osteophyte area	0.06 (0.04, 0.07)	<0.0001	0.03 (0.01, 0.04)	0.0007	0.22 (0.18, 0.27)	<0.0001	0.12 (0.07, 0.17)	<0.0001
Men								
Minimum JSW	−0.59 (−0.86, −0.31)	<0.0001	−0.42 (−0.72, −0.11)	0.009	−1.95 (−2.81, −1.08)	<0.0001	−0.97 (−1.97, −0.01)	0.05
Osteophyte area	0.07 (0.02, 0.11)	0.003	0.02 (−0.02, 0.07)	0.40	0.34 (0.21, 0.48)	<0.0001	0.24 (0.10, 0.39)	0.001
Women								
Minimum JSW	−0.89 (−1.09, −0.68)	<0.0001	−0.56 (−0.78, −0.34)	<0.0001	−3.00 (−3.71, −2.29)	<0.0001	−1.61 (−2.35, −0.88)	<0.0001
Osteophyte area	0.05 (0.04, 0.07)	<0.0001	0.03 (0.01, 0.04)	0.002	0.20 (0.15, 0.26)	<0.0001	0.11 (0.05, 0.16)	0.0001

* Knee osteoarthritis (OA) was defined as a Kellgren/Lawrence grade of ≥2. WOMAC = Western Ontario and McMaster Universities OA Index; 95% CI = 95% confidence interval.
† Calculated by multiple regression analysis with age, sex, body mass index, minimum joint space width (JSW), and osteophyte area as the independent variables in the overall population and with age, body mass index, minimum JSW, and osteophyte area as the independent variables in the groups of men and women only.

pants with knee OA, the results were almost the same (Table 3). In men with knee OA, minimum JSW was independently associated with pain domain scores (β coefficient -0.17), but not with physical function domain scores (β coefficient 0.05). In women with knee OA, both minimum JSW and osteophyte area were independently associated with physical function domain scores, but the beta value for minimum JSW for physical function domain scores was smaller than that for osteophyte area (-0.12 and 0.20, respectively).

DISCUSSION

This is the first study to separately examine the associations of JSN and osteophytosis with QOL, measured by a disease-specific scale such as WOMAC, using a large-scale population-based Japanese cohort. In addition, JSN and osteophytosis were estimated not by categorical grade but by continuous values such as minimum JSW and osteophyte area at the knee. In the present study, JSN as well as osteophytosis was independently associated with QOL.

The present study showed that both JSN and osteophytosis reduce QOL. Osteophytosis appears to begin with the activation of periosteal layers, with initial generation of chondrophytes and subsequent calcification to real osteophytes. The process is probably an adaptive reaction of the joint in order to cope with joint instability, and thus osteophyte area may indicate the severity of joint instability (22), which might lead to loss of QOL. When men and women were analyzed separately, minimum JSW was significantly associated with scores on the WOMAC pain domain but not the WOMAC physical function domain in men, while osteophyte area was associated with scores on the physical function domain but not the pain domain. According to the methodology of the WOMAC, pain domains estimate the severity of pain, indicating that JSN may be strongly associated with pain. In contrast, physical function domains assess difficulties in activities of daily living, indicating that osteophytosis may be mainly associated with activities of daily living, particularly in men.

Our findings also indicated differences between the sexes in the associations of JSN and osteophytosis with QOL. Minimum JSW was significantly associated with scores on the physical function domains of the WOMAC in women, but not in men. Similarly, osteophyte area was associated with scores on the pain domains of the WOMAC in women, but not in men. These differences may indicate that JSN and osteophytosis were more strongly associated with loss of QOL in women than in men. Our previous study also showed that the odds ratio of knee pain for K/L grade 3 or 4 knee OA was approximately twice as high in women as in men (4). This may be partly explained by the lower muscle mass in women than in men. Previous reports have shown that muscle mass is also associated with QOL (23,24). In men, muscular strength may obscure the associations of JSN and osteophytosis with QOL loss; thus, these were not associated with some QOL parameters in men.

The present study has several limitations. First, this is a large-scale, population-based study, with a cross-sectional study of baseline data. Thus, causal relationships could not be determined. The ROAD study is a longitudinal survey, so further progress may help elucidate any causal relationships. Second, we did not include other weight-bearing forms of OA, such as hip OA, in the analysis, although this disorder may also affect QOL. However, the prevalence of K/L grade 3 or 4 hip OA is 1.4% and 3.5% in Japanese men and women (25), respectively, which is lower than the prevalence of K/L grade 3 or 4 knee OA (13.5% and 24.6% in Japanese men and women, respectively) (4). Thus, it is possible that including hip OA would not strongly affect the results of the present study. Third, the QOL questionnaire was completed by 74.2% of all participants age 40 years or older in the ROAD study. Participants who completed the questionnaire were younger and more likely to have knee OA than the participants who did not complete the questionnaire, and thus the participants included in this study may have had better QOL than those who did not complete the questionnaire, and our results may have overestimated QOL. Fourth, although osteophytes may be even more pronounced in the contralateral tibiofemoral compartment (26), at present the KOACAD system can only measure medial osteophytes at the tibia. We are now developing the KOACAD system to measure osteophytes at other sites; thus, we may be able to clarify the association between osteophytes at other sites and QOL in the near future.

In conclusion, the present cross-sectional study using a large-scale population from the ROAD study revealed that JSN and osteophytosis are independently associated with QOL. Further studies, along with continued longitudinal surveys in the ROAD study, will help clarify the mechanisms of JSN and osteophytosis at the knee, and their relationship with QOL.

ACKNOWLEDGMENTS

The authors wish to thank Dr. Anamizu and members of the Department of Orthopedics, Tokyo Metropolitan Geri-

atric Medical Center and Mr. Kutsuma and other members of the Department of Radiology, Tokyo Metropolitan Geriatric Medical Center. The authors thank Mrs. Tomoko Takijiri and other members of the Public Office in Hidakagawa Town and Mrs. Tamako Tsutsumi, Mrs. Kanami Maeda, and other members of the Public Office in Taiji Town for their assistance in locating and scheduling participants for examinations.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Muraki had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Muraki, Oka, Akune, En-yo, M. Yoshida, Suzuki, H. Yoshida, Ishibashi, Tokimura, Yamamoto, Nakamura, Kawaguchi, Yoshimura.

Acquisition of data. Muraki, Oka, Akune, En-yo, Yoshimura.

Analysis and interpretation of data. Muraki, Oka, Akune, Yoshimura.

REFERENCES

1. Sharma L, Kapoor D. Epidemiology of osteoarthritis. In: Moskowitz RW, Altman RD, Hochberg MC, Buckwalter JA, Goldberg VM, editors. Osteoarthritis: diagnosis and medical/surgical management. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2007. p. 3–26.
2. Guccione AA, Felson DT, Anderson JJ, Anthony JM, Zhang Y, Wilson PW, et al. The effects of specific medical conditions on the functional limitations of elders in the Framingham Study. Am J Public Health 1994;84:351–8.
3. Felson DT, Zhang Y. An update on the epidemiology of knee and hip osteoarthritis with a view to prevention [review]. Arthritis Rheum 1998;41:1343–55.
4. Muraki S, Oka H, Akune T, Mabuchi A, En-yo Y, Yoshida M, et al. Prevalence of radiographic knee osteoarthritis and its association with knee pain in the elderly of Japanese population-based cohorts: the ROAD study. Osteoarthritis Cartilage 2009;17: 1137–43.
5. Yoshimura N, Muraki S, Oka H, Mabuchi A, En-yo Y, Yoshida M, et al. Prevalence of knee osteoarthritis, lumbar spondylosis and osteoporosis in Japanese men and women: the Research on Osteoarthritis/Osteoporosis Against Disability (ROAD). J Bone Miner Metab 2009;27:620–8.
6. Ministry of Health, Labor, and Welfare, Japan. The outline of the results of National Livelihood Survey 2007. URL: http://www.mhlw.go.jp/toukei/list/20-19-1.html. In Japanese.
7. Croft P, Cooper C, Wickham C, Coggon D. Defining osteoarthritis of the hip for epidemiologic studies. Am J Epidemiol 1990;132: 514–22.
8. Spector TD, Hart DJ, Byrne J, Harris PA, Dacre JE, Doyle DV. Definition of osteoarthritis of the knee for epidemiologic studies. Ann Rheum Dis 1993;52:790–4.
9. Kellgren JH, Lawrence JS, editors. The epidemiology of chronic rheumatism: atlas of standard radiographs of arthritis. Oxford: Blackwell Scientific; 1963.
10. Woo J, Lau E, Lee P, Kwok T, Lau WC, Chan C, et al. Impact of osteoarthritis on quality of life in a Hong Kong Chinese population. J Rheumatol 2004;31:2433–8.
11. Brazier JE, Harper R, Munro J, Walters SJ, Snaith ML. Generic and condition-specific outcome measures for people with osteoarthritis of the knee. Rheumatology (Oxford) 1999;38:870–7.
12. Hill CL, Parsons J, Taylor A, Leach G. Health related quality of life in a population sample with arthritis. J Rheumatol 1999;26: 2029–35.
13. Muraki S, Akune T, Oka H, En-yo Y, Yoshida M, Saika A, et al. Association of radiographic and symptomatic knee osteoarthritis with health-related quality of life in a population-based cohort study in Japan: the ROAD study. Osteoarthritis Cartilage 2010; 18:1227–34.
14. Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K, et al. Development of criteria for the classification and reporting of osteoarthritis: classification of osteoarthritis of the knee. Arthritis Rheum 1986;29:1039–49.
15. Altman RD, Hochberg M, Murphy WA Jr, Wolfe F, Lequesne M. Atlas of individual radiographic features in osteoarthritis. Osteoarthritis Cartilage 1995;3:3–70.
16. Altman RD, Gold GE. Atlas of individual radiographic features in osteoarthritis, revised. Osteoarthritis Cartilage 2007;15:A1–56.
17. Yoshimura N, Muraki S, Oka H, Kawaguchi H, Nakamura K, Akune T. Cohort profile: Research on Osteoarthritis/Osteoporosis Against Disability study. Int J Epidemiol 2010;39:988–95.
18. Oka H, Muraki S, Akune T, Mabuchi A, Suzuki T, Yoshida H, et al. Fully automatic quantification of knee osteoarthritis severity on plain radiographs. Osteoarthritis Cartilage 2008;16:1300–6.
19. Barr S, Bellamy N, Buchanan WW, Chalmers A, Ford PM, Kean WF, et al. A comparative study of signal versus aggregate methods of outcome measurement based on the WOMAC Osteoarthritis Index. J Rheumatol 1994;21:2106–12.
20. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol 1988;15:1833–40.
21. Hashimoto H, Hanyu T, Sledge CB, Lingard EA. Validation of a Japanese patient-derived outcome scale for assessing total knee arthroplasty: comparison with Western Ontario and McMaster Universities osteoarthritis index (WOMAC). J Orthop Sci 2003;8: 288–93.
22. Van den Berg WB. Osteophyte formation in osteoarthritis. Osteoarthritis Cartilage 1999;7:333.
23. Iannuzzi-Sucich M, Prestwood KM, Kenny AM. Prevalence of sarcopenia and predictors of skeletal muscle mass in healthy, older men and women. J Gerontol A Biol Sci Med Sci 2002;57:M772–7.
24. Sayer AA, Syddall HE, Martin HJ, Dennison EM, Roberts HC, Cooper C. Is grip strength associated with health-related quality of life? Findings from the Hertfordshire Cohort Study. Age Ageing 2006;35:409–15.
25. Inoue K, Wicart P, Kawasaki T, Huang J, Ushiyama T, Hukuda S, et al. Prevalence of hip osteoarthritis and acetabular dysplasia in French and Japanese adults. Rheumatology (Oxford) 2000;39: 745–8.
26. Felson DT, Gale DR, Elon Gale M, Niu J, Hunter DJ, Goggins J, et al. Osteophytes and progression of knee osteoarthritis. Rheumatology (Oxford) 2005;44:100–4.

Osteoarthritis and Cartilage 19 (2011) 1301–1306

Osteoarthritis and Cartilage

Association of vitamin D status with knee pain and radiographic knee osteoarthritis

S. Muraki†*, E. Dennison‡, K. Jameson‡, B.J. Boucher§, T. Akune†, N. Yoshimura||, A. Judge‡¶, N.K. Arden‡¶, K. Javaid‡¶, C. Cooper‡¶

† Department of Clinical Motor System Medicine, 22nd Century Medical & Research Center, Faculty of Medicine, University of Tokyo, Tokyo, Japan
‡ MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton General Hospital, UK
§ Centre for Diabetes, Bart's & The London School of Medicine and Dentistry, Queen Mary University of London, UK
|| Department of Joint Disease Research, 22nd Century Medical & Research Center, Faculty of Medicine, University of Tokyo, Tokyo, Japan
¶ NIHR Oxford Biomedical Research Unit, University of Oxford, Nuffield Orthopaedic Centre, Oxford, UK

ARTICLE INFO

Article history:
Received 3 February 2011
Accepted 29 July 2011

Keywords:
Knee osteoarthritis
Gene polymorphism
Epidemiology

SUMMARY

Objective: The objective of the present study was to explore the association of serum vitamin D concentration and polymorphism in the vitamin D receptor (VDR), with knee pain and radiographic knee osteoarthritis (OA) among men and women in a large population-based UK cohort study.
Methods: Seven hundred and eighty-seven participants in the Hertfordshire Cohort Study (399 men, 388 women; mean age 65.6 ± 2.7 years) underwent a questionnaire on knee pain and radiographic knee examination. This study examined the association of Fok1, Cdx2 and Apa1 polymorphism in the gene for the VDR and serum 25(OH)D concentration with knee pain and radiographic knee OA by a generalized estimating equations population averaged logistic regression analysis in the Hertfordshire Cohort Study.
Results: There were no associations of Fok1, Cdx2 and Apa1 polymorphisms of the VDR with knee OA except for Aa for Apa1 compared with AA [Odds ratio (OR) 0.59, 95% confidence interval (CI) 0.36–0.95, $P = 0.031$]. While, ff for Fok1 (OR 1.60, 95% CI 1.07–2.39, $P = 0.022$) and AA for Cdx2 polymorphism (OR 2.21, 95% CI 1.07–4.56, $P = 0.032$) was significantly associated with higher prevalence of knee pain compared with FF for Fok1 and GG for Cdx2, respectively. None of these are statistically significant after adjusting for the three polymorphisms tested. 25(OH)D level was not significantly associated with radiographic knee OA, while, low tertile of 25(OH)D level tended to be associated with knee pain compared with high tertile of 25(OH)D level.
Conclusion: The present cross-sectional study using a large-scale population from the Hertfordshire Cohort study indicated that vitamin D may be associated with pain rather than radiographic change, but the evidence for an association between vitamin D genetic variation and pain in knee OA is very weak in the present study. Further replication of our results will be required to elucidate the association of vitamin D and knee OA.

Introduction

Knee osteoarthritis (OA) is a major public health issue that causes chronic pain and disability[1–3], although at present the pathogenesis of this condition remains largely unknown. Several environmental factors have been associated with OA, including obesity[4–6], previous injury[7], knee-bending occupations[8,9], and other metabolic factors[10,11]. A previous population-based UK study of twins has also demonstrated a clear genetic influence on radiologic knee OA in women, with up to 65% of the variance being explained by genetic factors[12].

Vitamin D has been shown to stimulate synthesis of proteoglycan by mature articular cartilage *in vitro*[13], and this suggests that vitamin D may directly affect articular cartilage metabolism. Vitamin D receptor (VDR) is found in many types of tissues, including chondrocytes[14,15]. A previous study showed that VDR gene polymorphism was associated with bone[16], although it is still controversial[17]. The relationship between osteoporosis and OA suggests that VDR gene polymorphisms may be associated with both diseases[18]. However, the association of VDR gene polymorphisms with knee OA is

* Address correspondence and reprint requests to: S. Muraki, Department of Clinical Motor System Medicine, 22nd Century Medical & Research Center, Faculty of Medicine, University of Tokyo, Hongo 7-3-1, Bunkyo-ku, Tokyo 113-8655, Japan. Tel: 81-3-5800-9178; Fax: 81-3-5800-9179.
E-mail address: murakis-ort@h.u-tokyo.ac.jp (S. Muraki).

1063-4584/$ – see front matter © 2011 Osteoarthritis Research Society International. Published by Elsevier Ltd. All rights reserved.
doi:10.1016/j.joca.2011.07.017

controversial[19–23]. This may be partly due to different races, differences in environmental factors related to vitamin D metabolism, or the presence of other genetic factors that influence VDR function.

The association of vitamin D level with knee OA is also controversial[24–28]. In previous studies, McAlindon suggested that low serum levels of vitamin D were associated with progression of knee OA[24]. A recent study has also shown that serum 25(OH)D levels were associated with decreased knee cartilage loss[28], but Hunter *et al.* found that there was no significant association between vitamin D levels and knee osteophytes after adjusting for age, body mass index (BMI) and relatedness[25]. The Framingham study also found no association of vitamin D levels with knee OA worsening[26]. This may be partly explained by VDR gene polymorphism, because vitamin D exerts its endocrine and autocrine/paracrine local effects upon binding to and activating its intracellular receptor VDR. In other words, the association of vitamin D level with knee OA may be different by VDR gene polymorphisms, but, to the best of our knowledge, there were no studies investigating the association of vitamin D level with knee OA by VDR gene polymorphisms.

The principal clinical symptom of knee OA is pain[29], but the correlation between pain and radiographic severity is inconsistent[4,30–32]. Fewer studies have addressed factors which might influence knee pain[32–35]; among these, older age, female gender, and physically demanding work, have all been proposed[30–33]. Previous studies, however, have not addressed the role of vitamin D status or fixed genetic variation in the VDR.

The objective of this study was to clarify the association of VDR gene polymorphism with knee pain and radiographic knee OA among men and women in the general population, as well as to examine the association between circulating vitamin D concentration and these indices of OA.

Subjects and methods

Subjects

The Hertfordshire Cohort Study is a population-based cohort study in the UK. Details of the study design have been published previously[36], thus, a brief summary is provided here. The selection procedure was as follows: using the National Health Service Central Registry at Southport, and Hertfordshire Family Health Service Association, we traced men and women who were born during 1931–1939 in Hertfordshire, and still lived there during the period 1998–2003. After obtaining written permission from each subject's general practitioner (GP), we approached each person by letter, asking him or her if they would be willing to be contacted by one of our research nurses. If subjects agreed, a research nurse performed a home visit and administered a structured questionnaire. This included information on socioeconomic status, medical history, drug history, cigarette smoking, alcohol consumption, and reproductive variables in women.

At a subsequent clinic, height was measured to the nearest 0.1 cm using a Harpenden pocket stadiometer (Chasmors Ltd, London, UK) and weight to the nearest 0.1 kg on a SECAfloor scale (Chasmors Ltd). Fasting venous whole-blood samples were taken at this clinic visit. Eligible subjects were then invited to book a return visit for knee radiography. Weightbearing anteroposterior and lateral semiflexed radiographs of both knees were taken at the same hospital using the same radiographic equipment; a standard tube to film distance of 100 cm was used. Radiographs were performed at a median duration of 6 months [interquartile range (IQR) 4.8–7.2] after the clinic visit. Radiographs were graded at the tibiofemoral joints using the Kellgren Lawrence (KL) grade[37]. One trained reader graded the radiographs; KL grade ≥ 2 was the threshold for a definition of knee OA. Subjects were also asked "Have you had any pain in or around your right knee on most days in the last month?" and "Have you had any pain in or around your left knee on most days in the last month?" Knee pain reported in this way was defined as having knee pain. A total of 498 men and 468 women completed a home questionnaire, attended clinic, and underwent knee radiography.

A fasting morning blood sample was obtained from all subjects at the first clinic visit, and the serum separated and stored at −70°C. 25(OH)vitamin D was assayed using a DiaSorin Liason automated chemiluminescent assay with equal specificity for both D2 and D3 (coefficient of variation for vitamin D across the assays was 10–12% for within batch and 10–15% between batch).

Genomic DNA was extracted from whole-blood samples according to standard procedures. VDR genotype was determined by the polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP) analysis, and three VDR polymorphic sites (Fok1, Cdx2 and Apa1) were analyzed.

Ethical permission for the study was granted by the East and North Hertfordshire Ethical Committees. All participants gave written informed consent.

Statistical analysis

To assess gene polymorphism effects on radiographic knee OA and knee pain, indicator variables were created for Fok1 (FF and ff), Cdx2 (GA and AA) and Apa1 (AA and aa) polymorphism. As both knees have a pain score and a radiographic grade, a generalized estimating equations (GEE) population averaged logistic regression model was used to adjust for clustering of knees within patients. To examine 25(OH)D levels and their association with knee OA and knee pain, we classified subjects into three categories; high tertile (>51.5 nmol/l), middle tertile (35.5–51.5 nmol/l) and low tertile (<35.5 nmol/l). A GEE population averaged logistic regression analysis was used to determine the association of vitamin D level with knee OA and knee pain with and without adjustment for age, gender, BMI, season of the clinic visit and KL grade. To decide whether statically significant associations between VDR polymorphisms and knee outcomes are noteworthy, we used Wacholder's method to calculate the False Positive Report Probability (FPRP) [Wacholder in JNCI 2004]. Data analyses were performed using SAS version 9.0 (SAS Institute, Cary, NC, USA) and Stata version 11.2 (Stata, College Station, TX, USA).

Results

Of 984 subjects, 170 (17.3%) provided incomplete pain questionnaires. A further 19 (1.9%) lacked genotypic information. We also excluded eight subjects with total knee arthroplasty, leaving 787 (399 males and 388 females) participants in this analysis. Comparison between the 787 subjects with complete information and those without complete information revealed no statistically significant differences in mean age (responders 65.6 years, nonresponders 65.7 years; $P = 0.66$), sex (responders 80.3% women, nonresponders 79.8% women; $P = 0.87$), BMI (responders 27.0, nonresponders 27.4; $P = 0.19$) or prevalence of knee OA (responders 15.2% women, nonresponders 16.3% women; $P = 0.74$). The characteristics of these participants are shown in Table I. The men were slightly younger than the women, and they had a lower mean BMI; serum vitamin D concentration was also significantly higher among men than women. There were no significant differences in mean values [IQR] of 25(OH)D concentration (nmol/l) among VDR gene polymorphisms of Fok1 [FF 45.5 (30.0–56.0), Ff 47.1 (31.5–56.8), ff 51.3 (31.0–69.0)], Cdx2 [GG 45.9 (30.6–56.0), AG 47.5 (31.2–60.2), AA 54.1 (36.7–68.0)] and Apa1 [AA 48.4 (32.9–61.3), Aa 47.5 (30.0–59.1), aa 42.7 (31.0–50.9)]. There were no significant

Table I
Characteristics of participants

	Overall	Men	Women	*P*-value
Number of subjects	787	399	388	
Age, years	65.6 (2.7)	64.8 (2.6)	66.4 (2.6)	<0.001
BMI, kg/m^2	27.0 (4.3)	26.8 (3.6)	27.2 (4.9)	0.22
25(OH)D level, nmol/l* means, (IQR)	42.5 (30.8, 57.3)	44.4 (34.7, 64.2)	41.0 (28.3, 54.1)	<0.001
Radiographic knee OA, *n*, (%)	120 (15.3)	70 (17.5)	50 (12.9)	0.069
Knee pain, *n*, (%)	309 (39.3)	147 (36.8)	162 (41.8)	0.16

Except where indicated otherwise, values represent means (standard deviation). The differences in age, BMI and 25(OH)D level between men and women were examined by the non-paired Student's *t*-test. The differences in prevalence of radiographic knee OA and knee pain between men and women were examined by chi square test.

* Of 787 subjects, 25(OH)D was measured in 683 subjects.

differences in the prevalence of radiographic knee OA and knee pain between genders. Of 120 subjects with radiographic knee OA, 79 (65.8%) had knee pain, while, of 667 subjects without radiographic knee OA, 230 (34.5%) had knee pain. Knee pain was significantly associated with radiographic knee OA after adjustment for age, gender and BMI [Odds ratio (OR); 3.03, 95% confidence interval (CI); 1.98–4.68].

We examined the association of VDR gene polymorphisms and radiographic knee OA (Table II). There were no associations of Fok1, Cdx2 and Apa1 polymorphisms of the VDR with knee OA except for Aa for Apa1 compared with AA after adjustment for age, gender and BMI, and FPRP values were low for association of Apa1 (Aa) on radiographic knee OA suggesting this association may be noteworthy. We also examined the associations of the alleles with knee OA. f for Fok1 tended to associate with higher prevalence of knee OA than F ($P = 0.06$). The alleles for Cdx2 and Apa1 were not significantly associated with knee OA ($P = 0.94$ and 0.64).

We also examined the association of VDR gene polymorphisms and knee pain (Table III). Unlike radiographic knee OA, Fok1 and Cdx2 polymorphism was significantly associated with prevalence of knee pain after adjustment for age, gender BMI and KL grade, and FPRP values were low for association of Fok1 (ff) for knee pain, suggesting this association may be noteworthy. There were no associations of Apa1 polymorphisms with knee pain. When analyzed in men and women separately, Fok1 polymorphism was significantly associated with knee pain after adjustment for age, BMI and KL grade in women (Ff: OR; 1.17, 95% CI; 0.75–1.81, $P = 0.486$, ff: OR; 2.46, 95% CI; 1.38–4.39, $P = 0.002$, compared with FF), while, not in men (Ff: OR; 1.10, 95% CI; 0.71–1.73, $P = 0.649$, ff: OR; 1.01, 95% CI; 0.58–1.76, $P = 0.98$, compared with FF). We also examined the associations of the alleles with knee pain. f for Fok1 had significantly associated with higher prevalence than F ($P = 0.01$). The alleles for Cdx2 and Apa1 were not significantly associated with knee pain ($P = 0.49$ and 0.64, respectively).

We next examined the association of 25(OH)D level and knee OA (Table IV). GEE logistic regression analysis showed that 25(OH)D level was not significantly associated with radiographic knee OA. For knee pain effect of vitamin D level was non-linear, so we classified subjects into three groups; high tertile (>51.5 nmol/l, $n = 225$), middle tertile (35.5–51.5 nmol/l, $n = 229$) and low tertile (<35.5 nmol/l, $n = 229$); low tertile of 25(OH)D level tended to be associated with knee pain compared with high tertile of 25(OH)D level after adjustment for age, gender, BMI, season of the clinic visit and KL grade (Table IV).

Discussion

This is the first study to examine the association of radiographic knee OA and knee pain with vitamin D level and VDR gene polymorphism at the same time. A Fok1 polymorphism of the VDR was significantly associated with radiographic knee OA and knee pain. There were no associations between radiographic knee OA and 25(OH)D level, while 25(OH)D level tended to be associated with knee pain.

The association of VDR gene polymorphism with OA is controversial[19–23]. In previous studies, a nested case-control study in Britain showed the 'T' allele was associated with knee OA in women[19]. The Rotterdam Study showed that the 'bAT' haplotype was associated with reduced prevalence of OA[20]. While, The Framingham study found no evidence for an association of the VDR gene with knee OA[23]. In a case-control study in Japan, there was also no significant association between VDR gene polymorphism and knee OA[21], although cases were sampled from hospital attenders in the study and controls did not undergo X-rays, causing the inevitable selection bias to occur. This inconsistency may also be due to differences in the relative importance of this gene in different races, differences in environmental factors related to vitamin D metabolism, or the presence of other genetic factors that influence VDR function. Further, the association of genetic factors with knee OA is diminishing later in life due to the effects of lifestyle factors, thus it may be difficult to find out their association in the elderly. In the present study, a Fok1 polymorphism of the VDR was significantly associated with radiographic knee OA. Vitamin D has been shown to stimulate synthesis of proteoglycan by mature

Table II
Association of VDR gene polymorphisms and radiographic knee OA

	Total	Number (%) with knee OA	Crude OR (95% CI)	*P*-value	Adjusted OR (95% CI)*	*P*-value	Power†	FPRP prior probability	
								0.1	0.01
Fok1									
FF	328	39 (11.9)	1.00		1.00				
Ff	333	60 (18.0)	1.50 (0.96, 2.34)	0.072	1.54 (0.96, 2.46)	0.071	0.47	0.58	0.94
ff	108	18 (16.7)	1.38 (0.75, 2.57)	0.301	1.56 (0.82, 2.94)	0.173	0.27	0.85	0.98
Cdx2									
GG	491	75 (15.3)	1.00		1.00				
AG	248	37 (14.9)	1.03 (0.66, 1.59)	0.903	0.94 (0.60, 1.48)	0.781	0.49	0.93	0.99
AA	29	5 (17.2)	1.30 (0.48, 3.57)	0.605	1.09 (0.43, 2.74)	0.858	0.11	0.99	1.00
Apa1									
AA	213	36 (16.9)	1.00		1.00				
Aa	388	51 (13.1)	0.64 (0.40, 1.03)	0.068	0.59 (0.36, 0.95)	0.031	0.39	0.42	0.89
aa	166	31 (18.7)	1.12 (0.65, 1.91)	0.687	1.04 (0.60, 1.81)	0.884	0.28	0.97	1.00

Of 787 subjects, genotyping was completed for 769, 768 and 767 with Fok1, Csk2 and Apa1 polymorphism of the VDR, respectively.

* As both knees have a radiographic grade, GEE population averaged logistic regression analysis after adjustment for age, gender and BMI was used to calculate adjusted OR.

† To detect an OR of 1.5, we are looking for a difference in proportions of 15.3% vs 21.3% for radiographic knee OA.

Table III
Association of VDR gene polymorphisms and knee pain

	Total	Number (%) with knee pain	Crude OR (95% CI)	*P*-value	Adjusted OR* (95% CI)	*P*-value	Power†	FPRP prior probability	
								0.1	0.01
Fok1									
FF	328	115 (35.1)	1.00		1.00				
Ff	333	139 (41.7)	1.19 (0.89, 1.61)	0.244	1.14 (0.84, 1.56)	0.398	0.71	0.83	0.98
ff	108	51 (47.2)	1.50 (1.00, 2.24)	0.052	1.60 (1.07, 2.39)	0.022	0.40	0.33	0.84
Cdx2									
GG	491	189 (38.5)	1.00		1.00				
AG	248	94 (37.9)	1.05 (0.78, 1.42)	0.733	0.99 (0.73, 1.34)	0.936	0.71	0.92	0.99
AA	29	15 (51.7)	2.20 (1.08, 4.47)	0.03	2.21 (1.07, 4.56)	0.032	0.14	0.67	0.96
Apa1									
AA	213	87 (40.8)	1.00		1.00				
Aa	388	151 (38.9)	0.90 (0.65, 1.23)	0.5	0.93 (0.67, 1.30)	0.678	0.62	0.91	0.99
aa	166	64 (38.6)	0.97 (0.65, 1.43)	0.864	0.92 (0.61, 1.40)	0.71	0.45	0.93	0.99

Of 787 subjects, genotyping was completed for 769, 768 and 767 with Fok1, Csk2 and Apa1 polymorphism of the VDR, respectively.
* As both knees have a pain score, GEE population averaged logistic regression analysis after adjustment for age, gender, BMI and KL grade was used to calculate adjusted OR.
† To detect an OR of 1.5, we are looking for a difference in proportions of 39.3% vs 49.3% for knee pain.

articular cartilage *in vitro*[13], and this suggests that vitamin D may directly affect articular cartilage metabolism. Further, *in vitro* experiments confirmed that loss of VDR in chondrocytes reduced osteoclastogenesis by inducing receptor activator of NF-κB ligand (RANKL) expression[38], indicating that polymorphism of the VDR may affect osteophyte formation. In addition, the VDR gene has a thymine to cytosine single nucleotide polymorphism (SNP) at the Fok1 restriction site in the first of two potential start (ATG) codons located in the 50 region, resulting in a VDR protein that is shorter by three amino acids[39]. The F allele lacks the first ATG; thus, translation starts at the second ATG, instead of the first ATG, where translation of the f allele starts[40]. Most data indicate that the F allele is more effective than the f allele in transactivation of the 1,25-dihydroxyvitamin D signal[41]. However, a meta-analysis studying the association between VDR polymorphisms and OA[42] found no associations between VDR variation and OA. The ongoing GWAS studies on OA did not also find the foci polymorphism[43,44]. In the present study, the best *P*-value is only 0.022 which would be at least 0.066 when adjusted. Given the lack of a replication cohort, the evidence for an association between vitamin D genetic variation and pain in knee OA is very weak. In addition, considering that the sample size is modest for association studies in general, and more specifically for genetic association studies, the significant association of VDR gene polymorphism with radiographic knee OA in the present study may be due to random error. Additional and larger studies will be required, and, longitudinal studies may also determine whether this locus has any influence on the progression of joint damage at the knee.

IOF Working Group suggests that 75 nmol/L is the appropriate target level of serum 25(OH)D for individuals[45]. Vitamin D insufficiency, defined as 25(OH)D levels <75 nmol/L is prevalent worldwide[46], and the present study also showed that 604/683 (88.4%) had vitamin D insufficiency defined as <75 nmol/L. While, the association of serum vitamin D level and radiographic knee OA is controversial[24–27], McAlindon suggested that subjects with low serum levels of vitamin D are approximately three times more likely to have progression of established knee OA than subjects with high serum levels[24], but the number of subjects with progressive knee OA were comparably small in the study. Hunter *et al.* found that there was evidence of decreased vitamin D levels in subjects with knee osteophytes compared to those without osteophyte, but after adjusting for age, BMI and relatedness, the significant differences disappeared[25]. While, the Framingham study also found no association of vitamin D levels with knee OA worsening, defined as joint space loss on radiography or as worsening cartilage score on magnetic resonance imaging (MRI)[26]. In the present study, contrary to VDR gene polymorphisms, there were no significant association between vitamin D level and radiographic knee OA. Further, there were no differences in association of vitamin D level with radiographic knee OA among VDR gene polymorphisms.

Like radiographic knee OA, a Fok1 polymorphism of the VDR was significantly associated with knee pain in the present study. Further, knee pain also tended to be associated with vitamin D level, although it was not associated with radiographic knee OA. The correlation with the radiographic severity of knee OA is controversial[4,30–32]. In our previous study, 10% of men and 20% of women without radiographic knee OA had knee pain, and approximately 50% of men and 40% of women with severe radiographic knee OA had no knee pain in the elderly[4]. This indicates

Table IV
Association of 25(OH)D level with radiographic knee OA and knee pain

	Radiographic knee OA					Knee pain				
	n (%)	Crude OR (95% CI)	*P*-value	Adjusted OR* (95% CI)	*P*-value	*n* (%)	Crude OR (95% CI)	*P*-value	Adjusted OR† (95% CI)	*P*-value
25(OH)D level		0.99 (0.90, 1.10)	0.889	1.03 (0.92, 1.16)	0.627		–	–	–	–
Tertile 3 (51.2–147)	30/225 (13.3)	–	–	–	–	79/225 (35.1)	1.00		1.00	
Tertile 2 (35.9–51)	41/229 (17.9)	–	–	–	–	89/229 (38.9)	1.10 (0.77, 1.58)	0.598	1.04 (0.70, 1.56)	0.832
Tertile 1 (17–35.8)	36/229 (15.7)	–	–	–	–	105/229 (45.9)	1.48 (1.04, 2.10)	0.031	1.47 (0.95, 2.25)	0.08

OR of continuous vitamin D is for a 10-unit increase. For knee pain effect of vitamin D level was non-linear, so stratified into tertiles. Of 787 subjects, 25(OH)D was measured in 683 subjects.
* As both knees have and a radiographic grade, GEE population averaged logistic regression analysis after adjustment for age, gender, BMI and season of the clinic visit was used to calculate adjusted OR.
† As both knees have a pain score, GEE population averaged logistic regression analysis after adjustment for age, gender, BMI, season of the clinic visit and KL grade was used to calculate adjusted OR.

that there may be other factors associated with knee pain rather than radiographic knee OA, but there were few studies regarding factors associated with knee pain. Previous studies have shown that age, female sex and physical demanding work were associated with knee pain[32–35], but these factors were also reported as those associated with radiographic knee OA[4,9]. In the present study, vitamin D level tended to be associated with knee pain without association with radiographic knee OA, indicating that the association of vitamin D level with knee pain may be independent of radiographic knee OA. In fact, the result was almost similar after adjustment for radiographic knee OA, although it did not reach significance. Previous study has shown that vitamin D deficiency was related to quadriceps weakness[47], which is strongly associated with knee pain and disability in the community, even when activation and psychological factors are taken into account[48]. This may partly explain the association of vitamin D level and knee pain.

There are several limitations in the present study. First, the sample size was modest for association studies in general, and more specifically for genetic association studies. Further, we did not make multiple testing adjustments in the present study. In addition, studies reporting biomarker associations and, even more so, genetic associations have suffered from the report of false positives and the best way of addressing this is by testing these associations in independent cohorts and replicating the results. Thus the association of VDR gene polymorphisms with knee pain may be due to random error. However, FPRP values were low for association of Apa1 (Aa) on radiographic knee OA, and Fok1 (ff) for knee pain, suggesting these associations may be noteworthy, thus, these may merit replication in further studies. Second, we did not analyze Bsm and Taq, although these SNP are near Apa1. Third, 25(OH)D should have different association with different feature of ROA such as joint space narrowing or osteophytosis, but we did not analyze the association of joint space narrowing or osteophytosis with 25(OH)D or VDR polymorphisms.

In conclusion, the present cross-sectional study using a large-scale population from the Hertfordshire Cohort study revealed that a Fok1 and Cdx2 polymorphism of the VDR were significantly associated with knee pain, but not with radiographic knee OA. There were no associations between radiographic knee OA and vitamin D level, but it tended to be associated with knee pain. Further replication of our results will be required to elucidate the association of vitamin D and knee OA.

Author contributions

All authors have made substantial contributions to all three of sections (1), (2) and (3) below:

(1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data,

(2) drafting the article or revising it critically for important intellectual content,

(3) final approval of the version to be submitted.

Conflict of interest

There are no conflicts of interest.

Acknowledgments

This study was supported by a project grant from Arthritis Research UK. The research was also supported by the NIHR Biomedical Research Unit in Nutrition, University of Southampton; and the NIHR Biomedical Research Unit in Musculoskeletal Science, University of Oxford. The MRC Lifecourse Epidemiology Unit is supported by the Medical Research Council of Great Britain. Twenty-five adults who had vitamin D assays were part-funded by a North-East Thames NHS R & D Directorate grant; we are grateful to Kate Noonan for 25(OH)D immunoassays and to Mrs Gill Strange who prepared the manuscript.

References

1. Sharma L, Kapoor D. Epidemiology of osteoarthritis. In: Moskowitz RW, Altman RD, Hochberg MC, Buckwalter JA, Goldberg VM, Eds. Osteoarthritis: Diagnosis and Medical/Surgical Management. 4th edn. Philadelphia: Lippincott Williams & Wilkins; 2007:3–26.
2. Guccione AA, Felson DT, Anderson JJ, Anthony JM, Zhang Y, Wilson PW, *et al.* The effects of specific medical conditions on the functional limitations of elders in the Framingham Study. Am J Public Health 1994;84:351–8.
3. Felson DT, Zhang Y. An update on the epidemiology of knee and hip osteoarthritis with a view to prevention. Arthritis Rheum 1998;41:1343–55.
4. Hochberg MC, Lethbridge-Cejku M, Scott WW, Reichle R, Plato CC, Tobin JD. The association of body weight, body fatness and body fat distribution with osteoarthritis of the knee: data from the Baltimore Longitudinal Study of Aging. J Rheumatol 1995;22:488–93.
5. Hart DJ, Spector TD. The relationship of obesity, fat distribution and osteoarthritis in the general population: the Chingford study. J Rheumatol 1993;20:331–5.
6. Muraki S, Oka H, Akune T, Mabuchi A, En-yo Y, Yoshida M, *et al.* Prevalence of radiographic knee osteoarthritis and its association with knee pain in the elderly of Japanese population-based cohorts: the ROAD study. Osteoarthritis Cartilage 2009;17:1137–43.
7. Roos H, Adalberth T, Dahlberg L, Lohmander LS. Osteoarthritis of the knee after injury to the anterior cruciate ligament or meniscus: the influence of time and age. Osteoarthritis Cartilage 1995;3:261–7.
8. Felson DT. Do occupation-related physical factors contribute to arthritis? Balliere's Clin Rheumatol 1994;8:63–77.
9. Muraki S, Akune T, Oka H, Mabuchi A, En-yo Y, Yoshida M, *et al.* Association of occupational activity with radiographic knee osteoarthritis and lumbar spondylosis in elderly patients of population-based cohorts: a large-scale population-based study. Arthritis Rheum 2009;61:779–86.
10. Hart DJ, Doyle DV, Spector TD. Association between metabolic factors and knee osteoarthritis in women: the Chingford Study. J Rheumatol 1995;22:1118–23.
11. Thompson PW, Spector TD, James IT, Henderson E, Hart DJ. Urinary collagen crosslinks reflect the radiographic severity of knee osteoarthritis. Br J Rheumatol 1992;31:759–61.
12. Spector TD, Cicuttini F, Baker J, Loughlin J, Hart D. Genetic influences on osteoarthritis in females: a study of twins. BMJ 1996;312:940–3.
13. Corvol MT, Dumontier MF, Tsagris L, Lang F, Bourguignon J. Cartilage and vitamin D in vitro. Ann Endocrinol (Paris) 1981;142:482–7.
14. Norman AW, Roth J, Orci L. The vitamin D endocrine system: steroid metabolism, hormone receptors and biological response (calcium binding proteins). Endocrine Rev 1982;3:31–6.
15. Tetlow LC, Smith SJ, Mawer EB, Woolley DE. Vitamin D receptors in the rheumatoid lesion: expression by chondrocytes, macrophages and synoviocytes. Ann Rheum Dis 1999;58:118–21.
16. Morrison NA, Qi JC, Tokita A, Kelly PJ, Crofts L, Nguyen TV, *et al.* Prediction of bone density from vitamin D receptor alleles. Nature 1994;367:284–7.