**Table 2** Number (%) of participants with radiographic lumbar spondylosis and low back pain according to gender and age

| | | Radiographic lumbar spondylosis | | |
|---|---|---|---|---|
| | | KL≥2 | KL≥3 | Low back pain |
| Overall | 2288 | 1728 (75.8) | 1149 (50.4) | 659 (28.8) |
| Men | 818 | 688 (84.1) | 383 (46.8) | 201 (24.6) |
| <70 | 154 | 114 (74.0) | 51 (33.1) | 35 (22.7) |
| 70–79 | 491 | 419 (85.3)* | 232 (47.3)* | 119 (24.2) |
| ≥80 | 173 | 155 (89.6)* | 100 (57.8)* | 47 (27.2) |
| Women | 1470 | 1040 (70.7)† | 766 (52.1)† | 458 (31.2)† |
| <70 | 356 | 196 (55.1) | 128 (36.0) | 80 (22.5) |
| 70–79 | 818 | 612 (74.8)* | 456 (55.7)* | 273 (33.4)* |
| ≥80 | 296 | 232 (78.3)* | 182 (61.5)* | 105 (35.5)* |

Radiographic spondylosis was determined at the severest level among L1/2–L5/S1.
*$p<0.05$ vs subjects aged <70 years by Scheffe's test after adjustment for body mass index.
There was no significant difference between ages 70–79 and ≤80 in both genders.
†$p<0.05$ vs men by logistic regression analysis after adjustment for age and body mass index.
K/L, Kellgren/Lawrence grading.

compared among the generations, radiographic spondylosis (KL≥2 and ≥3) and low back pain tended to increase with age. Interestingly, the difference was greater between ages <70 and 70–79 years than between 70–79 and ≥80 years.

To identify risk factors for the radiographic spondylosis and low back pain, we further performed the logistic regression analysis to estimate odds ratios and confidence intervals (table 3). Age and BMI were significantly associated with radiographic spondylosis. Male sex was confirmed to be a risk factor for KL≥2 spondylosis while female sex was a risk factor for KL≥3 and low back pain. Among the communities, residents of the mountainous area had a lower risk for KL≥3 spondylosis than urban residents.

We then examined the association between radiographic spondylosis and low back pain. Considering that intervertebral levels other than the severest level of radiographic spondylosis might possibly cause low back pain, spondylosis at all intervertebral levels from L1/2 to L5/S was evaluated: KL≥2 spondylosis was found to be comparably prevalent at L2/3, L3/4 and L4/5 while KL≥3 spondylosis was remarkably prevalent at L4/5 in both men and women (table 4). In fact, among the five levels L4/5 was most frequently determined to be the severest level in both genders (men: L1/2 49.4%, L2/3 59.5%, L3/4 58.0%, L4/5 64.5%, L5/S 48.3%; women: L1/2 49.5%, L2/3 58.0%, L3/4 58.6%, L4/5 65.5%, L5/S 44.3%). We then looked at the percentage of subjects with low back pain in three groups: KL = 0 or 1, KL = 2, and KL≥3, at each intervertebral level and the severest level in the overall population and the three communities (fig 1). When odds ratios of KL = 2 and KL≥3 spondylosis compared with KL = 0 or 1 for pain were estimated by logistic regression analysis after adjustment for age and BMI, KL = 2 spondylosis was not significantly associated with pain in either gender at any intervertebral level (table 5). However, KL≥3 spondylosis was related at all levels in women while in none of the levels in men. Furthermore, the number of intervertebral levels with KL≥3 spondylosis was significantly associated with low back pain in women ($p<0.01$) but not in men by multiple regression analysis after adjustment for age and BMI. The association between KL≥3 spondylosis at the severest level and low back pain in women was evident at younger ages (<70 and 70–79 years; see table 1 in online supplement) and in the urban community (see table 2 in online supplement).

## DISCUSSION

This study showed that the prevalence of radiographic lumbar spondylosis with KL≥2 and KL≥3 in elderly people (≥60 years) was 75.8% and 50.4%, respectively, and that of low back pain was 28.8% in the overall population. Although KL≥2 spondylosis was more prevalent in men (84.1%) than in women (70.7%), KL≥3 spondylosis and low back pain were more prevalent in women. This study also showed that KL = 2 spondylosis was not significantly associated with low back pain compared with KL = 0 or 1, while KL≥3 spondylosis was related to the pain only in women.

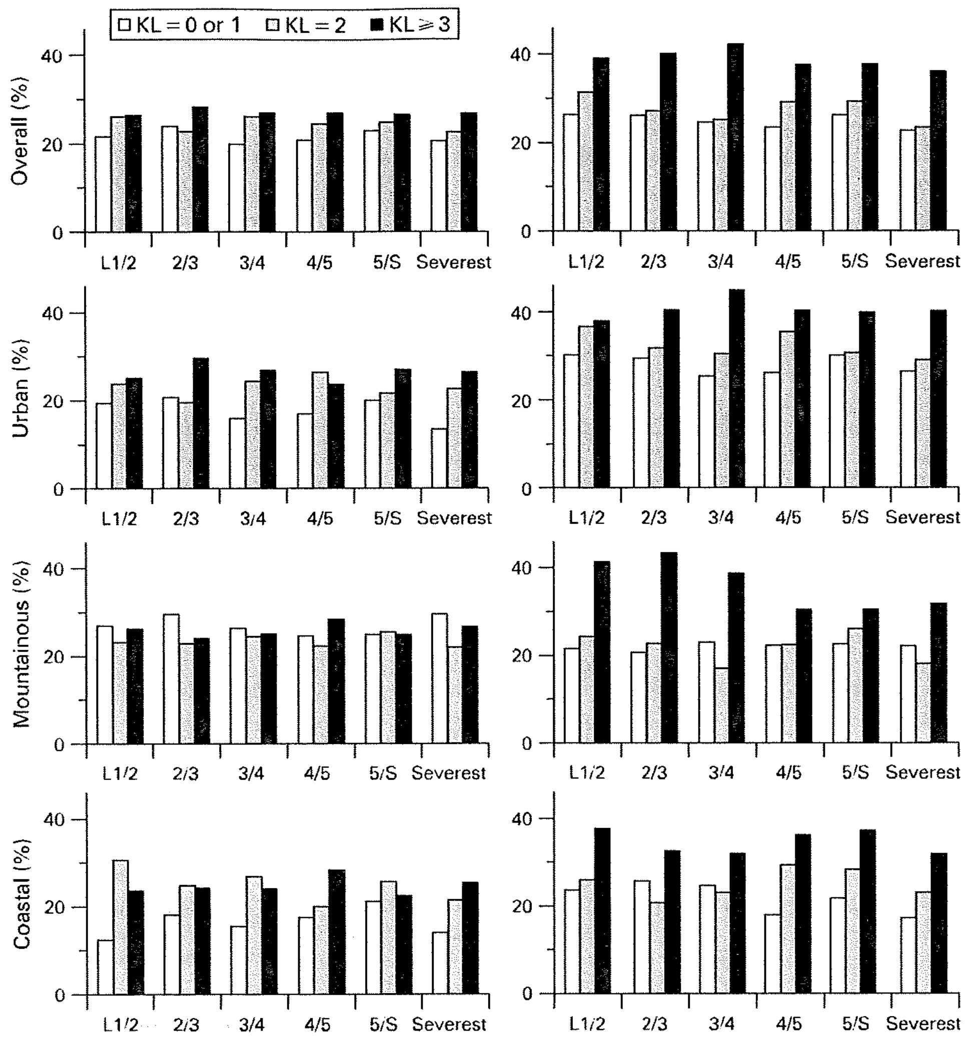
Most previous epidemiological studies on lumbar spondylosis focused on middle-aged or younger populations, reporting the prevalence to be 46.5–83.7%.[4 6–8 10 11] Our previous small-scale study on a younger population reported the prevalence to be 76.3% and 37.4%.[9] Interestingly, the subjects were living in a mountainous area in Japan, which was shown to have a lower risk for spondylosis in the present study. The variability may therefore be due to the differences in age, community, the sample size and ethnic variation. In fact, a study on elderly people (≥65 years) showed that the prevalence of KL≥2 spondylosis was 84.8% and 70.6%, similar to the present results, although in a relatively small number of subjects.[5] We have reported a different prevalence of lumbar spondylosis in Japan and the UK in a small-scale comparative study,[9] which may in part relate to ethnic variation. It should be noted that this is the first population-based study to investigate the age-related prevalence of lumbar spondylosis in elderly people. Although KL≥2 and KL≥3 spondylosis tended to increase with age, a significant difference was detected between the 60s and the 70s, but not thereafter. However, this cross-sectional

**Table 3** Association of gender and community with radiographic lumbar spondylosis and low back pain

| | Radiographic lumbar spondylosis | | |
|---|---|---|---|
| | KL≥2 | KL≥3 | Low back pain |
| | OR (95% CI) | OR (95% CI) | OR (95% CI) |
| Age (years) | 1.07 (1.06 to 1.09)† | 1.05 (1.04 to 1.07)† | 1.02 (1.00 to 1.04)* |
| BMI (kg/m²) | 1.06 (1.03 to 1.09)† | 1.04 (1.01 to 1.06)† | 1.02 (0.99 to 1.05) |
| Women (vs men) | 0.68 (0.61 to 0.76)† | 1.13 (1.03 to 1.23)† | 1.19 (1.08 to 1.31)† |
| Community (vs urban) | | | |
| Mountainous | 0.82 (0.65 to 1.04) | 0.56 (0.45 to 0.69)† | 0.87 (0.69 to 1.08) |
| Coastal | 1.24 (0.93 to 1.66) | 1.06 (0.84 to 1.34) | 0.86 (0.66 to 1.11) |

Radiographic spondylosis was determined at the severest level among L1/2–L5/S1.
The odds ratios were calculated by logistic regression analysis after adjustment for all other variables.
*$p<0.05$; †$p<0.01$.
BMI, body mass index; KL, Kellgren/Lawrence grading; OR, odds ratio; CI, confidence interval.

Figure 1 Percentage of subjects with low back pain according to the Kellgren/Lawrence (KL) grade in the overall population and in urban, mountainous and coastal communities.




analysis does not, of course, lead to the conclusion that individual lumbar spondylosis hardly progresses after 80 years. Since the ROAD study is a prospective cohort study of >10 years, the follow-up data will clarify the progression with ageing. Furthermore, there was a difference in prevalence between urban and mountainous communities. Considering that lumbar spondylosis is a common disease whose progression is governed by environmental and genetic factors, the regional difference is inevitable, as previously reported.[6] Although age and obesity are known to be representative risk factors for lumbar spondylosis,[7] the difference between communities in the present study was significant even after adjustment for age and BMI, indicating the involvement of other factors. Here again, a further longitudinal survey of the ROAD database including detailed environmental and genomic information will elucidate the underlying backgrounds.

Interestingly, KL≥2 spondylosis was more prevalent in men than in women, while KL≥3 spondylosis was more prevalent in women. We and others also have reported that osteophytosis of the lumbar spine is more common in men than in women,[8 9] while disc space narrowing is more prevalent in women.[9] Based on the definition of the KL grading,[12] the discrepancy may be due to distinct aetiological mechanisms between osteophyte formation and disc space narrowing. A cross-sectional study which investigated the extent, prevalence and distribution of spinal spondylosis in women also showed that osteophytosis and disc space narrowing were significantly correlated, but each predicted only 19% of the variation in the other.[11] A previous prospective study in knee joints in the Chingford Study cohort found no association between osteophyte formation and joint space narrowing.[14] A recent study using quantitative magnetic resonance imaging (MRI) in knee joints also reported that osteophyte formation was unrelated to cartilage loss.[15] Furthermore, in an experimental mouse knee osteoarthritis model, we have identified a cartilage-specific molecule, carminerin, that induces only osteophyte formation without affecting cartilage degeneration during the progression of osteoarthritis.[16 17] Further clinical and basic research will disclose the distinct backgrounds of these two representative features of osteoarthritis.

**Table 4** Number (%) of subjects with radiographic lumbar spondylosis at each intervertebral level in all cohorts

| | KL≥2 | | KL≥3 | |
|---|---|---|---|---|
| | Men | Women | Men | Women |
| L1/2 | 474 (57.9) | 609 (41.4) | 116 (14.2) | 254 (17.3) |
| L2/3 | 541 (66.1) | 749 (51.0) | 164 (20.1) | 355 (24.2) |
| L3/4 | 554 (67.7) | 735 (50.0) | 194 (23.7) | 419 (28.5) |
| L4/5 | 523 (63.9) | 736 (50.1) | 306 (37.5) | 605 (41.2) |
| L5/S | 400 (48.9) | 576 (39.2) | 197 (24.2) | 413 (28.1) |

KL, Kellgren/Lawrence grading.

**Table 5** Association of Kellgren/Lawrence (KL) grade at each intervertebral level with low back pain

| | L1/2 | L2/3 | L3/4 | L4/5 | L5/S | Severest |
|---|---|---|---|---|---|---|
| | OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) |
| Men | | | | | | |
| KL = 2 | 1.30 (0.92 to 1.84) | 0.94 (0.65 to 1.36) | 1.43 (0.98 to 2.11) | 1.24 (0.82 to 1.89) | 1.12 (0.75 to 1.65) | 1.15 (0.70 to 1.92) |
| KL≥3 | 1.30 (0.79 to 2.11) | 1.25 (0.80 to 1.94) | 1.49 (0.96 to 2.32) | 1.42 (0.97 to 2.08) | 1.22 (0.82 to 1.81) | 1.44 (0.89 to 2.38) |
| Women | | | | | | |
| KL = 2 | 1.20 (0.91 to 1.57) | 0.99 (0.75 to 1.31) | 0.96 (0.71 to 1.30) | 1.25 (0.82 to 1.88) | 1.07 (0.73 to 1.54) | 0.99 (0.69 to 1.42) |
| KL≥3 | 1.66 (1.23 to 2.24)* | 1.74 (1.32 to 2.30)* | 2.10 (1.62 to 2.72)* | 1.88 (1.48 to 2.38)* | 1.60 (1.25 to 2.06)* | 1.80 (1.38 to 2.37)* |

The odds ratio was calculated by logistic regression analysis compared with subjects with KL grade 0 or 1 after adjustment for age and body mass index.
*$p<0.01$.
OR, odds ratio; CI, confidence interval.

Symptomatic low back pain was associated with KL≥3 spondylosis in women but not in men, but not with KL≥2 spondylosis in either gender. Considering the definition of KL grading, this may suggest that disc space narrowing but not osteophytosis of the lumbar spine contributes to low back pain, which is consistent with previous reports.[18] Differences in the association between genders might be dependent on muscle strength to compensate for spinal instability due to disc space narrowing, since men are known to have greater muscle strength than women at all ages.[19] However, approximately 30% of participants without definite radiographic lumbar spondylosis (KL = 0 or 1) had low back pain, and the odds ratio of KL≥3 spondylosis for pain was 1.44 in men and 1.80 in women, which is much lower than the previously reported odds ratio of 8.5 for KL≥3 osteoarthritis in the knee joint for knee pain.[20] This may be because low back pain arises from a number of disorders other than disc space narrowing such as nociceptive stimuli, inflammation, muscle weakness and abnormal load on muscle, ligament or capsular tissues.[21] Indeed, disc degeneration was detected by MRI in at least one lumbar level in all but one asymptomatic volunteers aged 60–80 years.[22] Furthermore, pain is also influenced by psychological factors such as depression, since a significant association between low back pain and depression has been confirmed in many longitudinal studies.[23–25] A recent psychophysical study has shown that anxiety was linked to self-reported and induced low back pain in men but not in women.[26] This might be an alternative reason for the lower association between radiographic spondylosis and low back pain in men.

This study has several limitations. First, prevalence figures using a large-scale population-based sample of elderly people may be generalisable to the Japanese population. However, this study investigated elderly participants who lived independently rather than those who lived in institutional settings, so the calculated prevalence may be underestimated. Second, the definition of low back pain in the present study did not determine the severity. The association of lumbar spondylosis with the severity of low back pain could not be examined in this study. Third, the analyses did not include facet joint osteoarthritis or vertebral fracture, which would probably be associated with low back pain. This is the next factor to be investigated in the ROAD study. Fourth, since the KL system emphasises osteophytosis, it is unclear how to handle lumbar spondylosis with disc space narrowing but no osteophytosis. Since quantitative MRI is still too laborious and expensive to perform in general clinical practice, we are now developing a computer-aided diagnostic program which enables the fully automatic measurement of major features of lumbar spondylosis including disc space narrowing and osteophytosis on plain radiographs.

In conclusion, this cross-sectional study using a large-scale population from the ROAD study revealed a high prevalence of radiographic lumbar spondylosis in elderly people. The prevalence differed to some extent by age, gender and community. Gender seems to be distinctly associated with KL≥2 and KL≥3 lumbar spondylosis, and disc space narrowing with or without osteophytosis in women may be a risk factor for low back pain. Further progress, along with continued longitudinal survey in the ROAD study, will elucidate the environmental and genetic backgrounds of lumbar spondylosis and its relation with low back pain.

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**Competing interests:** None.

**Ethics approval:** All participants provided written informed consent, and the study was conducted with approval of the ethical committees of the University of Tokyo and the Tokyo Metropolitan Institute of Gerontology

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ORIGINAL ARTICLE

# Prevalence of knee osteoarthritis, lumbar spondylosis, and osteoporosis in Japanese men and women: the research on osteoarthritis/osteoporosis against disability study

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**Abstract** Musculoskeletal diseases, especially osteoarthritis (OA) and osteoporosis (OP), impair activities of daily life (ADL) and quality of life (QOL) in the elderly. Although preventive strategies for these diseases are urgently required in an aging society, epidemiological data on these diseases are scant. To clarify the prevalence of knee osteoarthritis (KOA), lumbar spondylosis (LS), and osteoporosis (OP) in Japan, and estimate the number of people with these diseases, we started a large-scale population-based cohort study entitled research on osteoarthritis/osteoporosis against disability (ROAD) in 2005. This study involved the collection of clinical information from three cohorts composed of participants located in urban, mountainous, and coastal areas. KOA and LS were radiographically defined as a grade of ≥2 by the Kellgren–Lawrence scale; OP was defined by the criteria of the Japanese Society for Bone and Mineral Research. The 3,040 participants in total were divided into six groups based on their age: ≤39, 40–49, 50–59, 60–69, 70–79, and ≥80 years. The prevalence of KOA in the age groups ≤39, 40–49, 50–59, 60–69, 70–79, and ≥80 years 0, 9.1, 24.3, 35.2, 48.2, and 51.6%, respectively, in men, and the prevalence in women of the same age groups was 3.2, 11.4, 30.3, 57.1, 71.9, and 80.7%, respectively. With respect to the age groups, the prevalence of LS was 14.3, 45.5, 72.9, 74.6, 85.3, and 90.1% in men, and 9.7, 28.6, 41.7, 55.4, 75.1, and 78.2% in women, respectively. Data of the prevalence of OP at the lumbar spine and femoral neck were also obtained. The estimated number of patients with KOA, LS, and L2–L4 and femoral neck OP in Japan was approximately 25, 38, 6.4, and 11 million, respectively. In summary, we estimated the prevalence of OA and OP, and the number of people affected with these diseases in Japan. The ROAD study will elucidate epidemiological evidence concerning determinants of bone and joint disease.

**Keywords** Epidemiology · Prevalence · Establishment of population-based cohort · Osteoarthritis · Osteoporosis

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## Introduction

Osteoarthritis (OA) and osteoporosis (OP) are major public health problems in the elderly that affect their activities of daily life (ADL) and quality of life (QOL), leading to increased morbidity and mortality. The number of patients with OA increases with the age of the population. According to the recent National Livelihood Survey of the Ministry of Health, Labour and Welfare in Japan, OA is ranked fourth, and falls and osteoporotic fractures are ranked fifth, among the diseases causing disabilities that subsequently require support for activities related to daily living [1]. The authors of the present study as well as other authors have reported increased mortality following osteoporotic fractures at the hip and other sites [2, 3].

Because of the increasing proportion of the aging population in Japan, there is an urgent need for a comprehensive and evidence-based prevention strategy for musculoskeletal diseases, including OA and OP. However, few prospective longitudinal studies have been undertaken, and little information is available regarding the prevalence and incidence of OA and lumbar spondylosis (LS), as well as pain and disability, in the Japanese population [4–7]. Only the estimated number of patients with knee osteoarthritis (KOA) and LS is not known.

More population-based prospective studies have been performed for OP than for OA [8–12]. Japanese guidelines for the prevention and treatment of OP, on the basis of evidence obtained from studies conducted with Japanese subjects, were published in 2006 [13]; however, many epidemiological indices of OP still remain to be clarified. For instance, there is insufficient evidence regarding the risks relating to the incidence of OP, osteoporotic vertebral fractures, and bone loss. Further, data on the number of patients with OP were last reported in 1999 [14], thus necessitating an analysis based on the current prevalence of OP. It is difficult to design rational clinical and public health approaches for the diagnosis, evaluation, and prevention of OA and OP without such epidemiological data.

The research on osteoarthritis/osteoporosis against disability (ROAD) study is a prospective cohort study that aims to elucidate the environmental and genetic background for bone and joint diseases, especially OA and OP; it is designed to examine the extent to which risk factors for these diseases are related to clinical features, laboratory and radiographic findings, bone mass and bone geometry, lifestyle, nutritional factors, anthropometric and neuromuscular measures, and fall propensity, as well as to determine how these diseases affect ADL and QOL in Japanese men and women.

Here, the prevalence of KOA, LS, and OP is clarified, and the number of patients with these diseases in Japan is estimated by analyzing the baseline data of the ROAD study.

## Participants and methods

### Study population

A complete baseline database was established that included the clinical and genomic information of 3,040 inhabitants (1,061 men and 1,979 women) with a mean age of 70.3 [standard deviation (SD), 11.0] years, 71.0 (SD, 10.7) years in men and 69.9 (SD, 11.2) years in women. These subjects were recruited from listings of resident registrations in three communities with different characteristics: an urban region in Itabashi, Tokyo; a mountainous region in Hidakagawa, Wakayama; and a coastal region in Taiji, Wakayama (Fig. 1).

Itabashi Ward, an urban community located in the eastern Tokyo (area, 32 km$^2$) has a population of 529,400, and the proportion of aged people in this region, defined as the number of residents who were 65 years old or older (≥65) divided by the total population, is 19.1%. The percentage of the population having jobs in primary industries (agriculture, forestry, fishing, or mining), secondary industries (manufacturing and construction), and in tertiary industries (service industries) is 0.1, 25, and 75%, respectively [15]. Hidakagawa Town, a rural mountainous community located in the center of Wakayama (area, 330 km$^2$), has a population of 11,300 and 30.5% of the inhabitants are ≥65 years old. The percentages of workers with jobs in the primary, secondary, and tertiary industries are 29, 24 and 47%, respectively [15]. Taiji Town, a rural coastal community located south of Wakayama (area, 6 km$^2$), has a population of 3,500, with 34.9% of inhabitants ≥65 years old; the percentages of workers with jobs in primary, secondary, and tertiary industries are 13, 18, and 69%, respectively [15].

Residents of these three urban, mountainous, and coastal regions were recruited from the resident-registration lists of the relevant regions. Participants in the urban region, aged ≥60 years, were recruited from among those of a randomly selected cohort study from the previously established Itabashi Ward resident registration database [16]. The

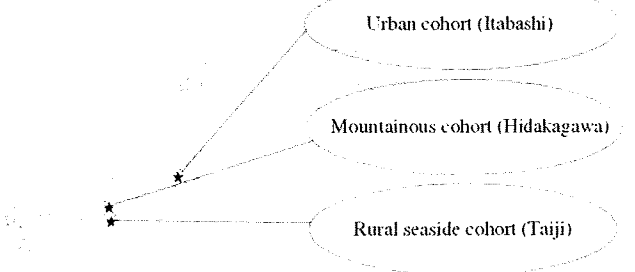


**Fig. 1** Location of the three cohorts with different characteristics in Japan

response rate was 75.6%. Participants in the mountainous and coastal regions, aged ≥40 years, were recruited from listings of resident registration. However, those inhabitants aged <60 years in the urban area and <40 years in the mountainous and coastal areas who were interested in participating in the study were invited to be examined.

In addition to residence in the communities as outlined above, the inclusion criteria were as follows: the patient had to (1) be able to walk to the clinic at which the survey was performed, (2) provide self-reported data, and (3) understand and sign an informed consent form. No other exclusion criteria were used.

Participants were enrolled and the initial baseline examinations were completed over a 1.5-year period from October 2005 through March 2007. All participants provided written informed consent. The study was conducted with the approval of the ethics committees of the University of Tokyo (nos. 1264 and 1326) and the Tokyo Metropolitan Institute of Gerontology (no. 5). Careful consideration was given to ensure a safe experience for participants during their examinations and any other study procedures.

### Radiographic assessment

Plain radiographs of the lumbar spine in the anteroposterior and lateral views and bilateral knees in the anteroposterior view with weight-bearing and foot map positioning were obtained. The severity of radiographic OA was determined according to Kellgren–Lawrence (KL) grading as follows [17]: KL0, normal; KL1, slight osteophytes; KL2, definite osteophytes; KL3, joint or intervertebral space narrowing with large osteophytes; KL4, bone sclerosis, joint or intervertebral space narrowing, and large osteophytes. In the ROAD study, participants were classified into KL3 if they had joint or intervertebral space narrowing without large osteophytes. Radiographs at each site, i.e., the knees, hips, and vertebrae, were examined by a single, experienced orthopaedic surgeon (S.M.), who was masked regarding participants' clinical status. If at least one knee joint was graded as KL2 or higher, the participant was diagnosed with radiographic KOA. Similarly, if at least one intervertebral level of the lumbar spine was graded as KL2 or higher, the participant was diagnosed with radiographic LS.

### Bone mineral density measurement

In the mountainous and coastal areas, bone mineral density (BMD) was measured at the lumbar spine (L2–L4) and the proximal femur using dual-energy X-ray absorptiometry (DXA) (Hologic Discovery; Hologic, Waltham, MA, USA) at baseline.

To control quality, the same DXA equipment was used and the same spine phantom was scanned daily to monitor the machine's performance in study populations at different regions. The BMD of the phantom was adjusted to $1.032 \pm 0.016$ g/cm$^2$ ($\pm1.5\%$) during all examinations. In addition, the same physician (N.Y.) examined all participants to prevent observer variability. Intraobserver variability using the Lunar DPX in vitro and in vivo had been measured by the same physician (N.Y.) for another study [18]. Coefficient of variance (CV) for L2–L4 in vitro was 0.35%, and CVs for L2–L4, the proximal femur, Ward's triangle, and the trochanter examined in vivo in five male volunteers were 0.61–0.90, 1.02–2.57, 1.97–5.45, and 1.77–4.17%, respectively.

OP was defined as a BMD of less than 70% of peak bone mass according to the criteria of the Japanese Society for Bone and Mineral Research [19]. OP was defined by BMD < 0.708 g/cm$^2$ at the lumbar spine in the case of both men and women, and by BMD < 0.604 g/cm$^2$ at the femoral neck for men and <0.551 g/cm$^2$ for women, respectively.

### Statistical analysis

All statistical analyses were performed using STATA statistical software (STATA, College Station, TX, USA). Differences in proportion were compared by the chi-square test. Differences of continuous values were tested for significance using analysis of variance (ANOVA) for comparisons among multiple groups and Scheffe's least significant difference (LSD) test for pairs of groups. Significant items were selected, and multiple regression and logistic regression analyses were performed by adjusting suitable variables.

## Results

Table 1 shows selected characteristics of the participants in the three regions including age, height, weight, body mass index (BMI), and BMD. The percentage of participants >60 years of age was 99.8, 84.3, and 54.7% in the urban, mountainous, and seacoast regions, respectively. Two-thirds of the 3,040 participants were women, and the mean age of female participants was 1 year less than that of the male participants.

Regarding the gender differences in the anthropometric measurements, height and weight were significantly lower in women than in men, but no significant difference in BMI was noted between the genders. All values of BMD at L2–L4, femoral neck, and total hip were significantly higher in men than in women ($P < 0.001$).

**Table 1** Age–sex distribution and mean values (standard deviation) of selected characteristics of the participants

| Age strata (years) | Men | | | | Women | | | |
|---|---|---|---|---|---|---|---|---|
| | Total | Urban | Mountainous | Seacoast | Total | Urban | Mountainous | Seacoast |
| –39 | 14 | 0 | 2 | 12 | 31 | 0 | 7 | 24 |
| 40–49 | 44 | 0 | 7 | 37 | 105 | 0 | 17 | 88 |
| 50–59 | 107 | 0 | 36 | 71 | 211 | 2 | 67 | 142 |
| 60–69 | 168 | 11 | 93 | 64 | 385 | 60 | 183 | 142 |
| 70–79 | 535 | 315 | 150 | 70 | 913 | 594 | 196 | 123 |
| 80– | 193 | 139 | 31 | 23 | 334 | 229 | 75 | 30 |
| Total | 1,061 | 465 | 319 | 277 | 1,979 | 885 | 545 | 549 |
| Age (years) | 71.0 (10.7) | 77.2 (4.3) | 69.5 (9.1) | 62.6 (13.2) | 69.9 (11.2) | 76.3 (5.0) | 68.6 (10.4) | 60.8 (12.5) |
| Height (cm) | 162.5 (6.7) | 161.3 (5.9) | 161.4 (6.9) | 165.8 (6.8) | 149.8 (6.5) | 148.5 (5.6) | 148.2 (6.7) | 153.2 (6.2) |
| Weight (kg) | 61.3 (10.0) | 60.0 (8.5) | 60.0 (10.2) | 64.8 (11.0) | 51.5 (8,6) | 50.8 (8.3) | 50.5 (8.6) | 53.5 (8.8) |
| BMI (kg/m$^2$) | 23.1 (3.0) | 23.0 (2.8) | 23.0 (3.0) | 23.5 (3.4) | 22.9 (3.5) | 23.0 (3.4) | 23.0 (3.4) | 22.8 (3.6) |
| BMD (g/cm$^2$) | | | | | | | | |
| L2–L4 | 1.05 (0.20) | – | 1.04 (0.20) | 1.06 (0.21) | 0.87 (0.18) | – | 0.83 (0.18) | 0.91 (0.18) |
| Femoral neck | 0.74 (0.13) | – | 0.73 (0.13) | 0.76 (0.13) | 0.63 (0.12) | – | 0.60 (0.12) | 0.66 (0.13) |
| Total hip | 0.88 (0.14) | – | 0.87 (0.14) | 0.90 (0.14) | 0.74 (0.14) | – | 0.72 (0.13) | 0.76 (0.14) |

*BMI* body mass index, *BMD* bone mineral density

Table 2 shows the age-sex distribution for prevalence of radiographic KOA and LS determined by a KL grade ≥2, classified by region. In the overall population, prevalence of radiographic KOA and LS was 54.6% (42.0% in men and 61.5% in women) and 70.2% (80.6% in men and 64.6% in women), respectively, indicating that the prevalence of LS was higher than that of KOA in the overall population, as well as in the respective genders. When the prevalence was compared among the age strata, radiographic KOA and LS tended to be higher with age in both genders (Table 2). Prevalence of radiographic KOA was 0% in men and 3.2% in women in the <40-year age group and 42.6% in men and 62.4% in women in the ≥40-year age group, and the differences were significant ($P < 0.001$). According to gender, the prevalence was significantly higher in women than in men in the overall population ($P < 0.001$). OA in both knees was observed in 43.1% (31.5% in men and 49.4% in women) of all participants. The overall prevalence of radiographic LS across all ages was 80.6% in men and 64.6% in women, which was considerably higher than that of KOA. In contrast to radiographic KOA, the prevalence of this condition was significantly higher in men than in women ($P < 0.001$). Similar to KOA, the prevalence of LS was lower in the <40-year age group than in the ≥40-year age group, with significant differences in both genders ($P < 0.001$). Among all the participants, 42.3% (37.1% in men and 45.1% in women) had both KOA and LS.

The prevalence of KOA and LS classified by region is also shown in Table 2. Regarding the regional differences, the prevalence of KOA was the highest in the mountainous area, followed by the urban area and the seacoast area in both men and women. By contrast, the prevalence of LS was the highest in the urban area, followed by the mountainous area and the seacoast area.

Logistic regression analysis was performed to determine the effect of region, gender, age, and body build on the prevalence of OA in participants ≥60 years of age, using the presence of KOA as an objective variable, and region (seacoast: 0, mountainous: 1), gender (men: 0, women: 1), age, and BMI as explanatory factors. The analysis revealed that the risk for KOA was significantly higher in the mountainous area [odds ratio (OR), 2.7; 95% confidence interval (CI), 2.1–3.6, $P < 0.001$], in women (OR, 3.4; 95% CI, 2.79–4.06; $P < 0.001$), in advanced age (+1 year: OR, 1.09; 95% CI, 1.07–1.11, $P < 0.001$), and in larger body build (+1 BMI: OR, 1.16; 95% CI, 1.13–1.20; $P < 0.001$). By contrast, the risk of LS was reduced in the mountainous area (OR, 0.63; 95% CI, 0.48–0.83; $P < 0.01$) and in women (OR, 0.47; 95% CI, 0.38–0.58; $P < 0.001$). Advanced age and higher BMI were associated with the presence of LS as well as KOA (+1 year: OR, 1.08; 95% CI, 1.06–1.10; $P < 0.001$; +1 BMI: OR, 1.09; 95% CI, 1.05–1.12; $P < 0.001$, respectively).

Table 3 shows the mean values of BMD among residents of mountainous and coastal regions in the ROAD study. Although the mean BMD values of the lumbar spine were no different between men and women in the age group of <40 years, those of the femoral neck and proximal total hip in the same age group were significantly

**Table 2** Prevalence (%) of knee osteoarthritis and lumbar spondylosis classified by age, gender, and region

| Age strata (years) | Knee osteoarthritis | | | | Lumbar spondylosis | | | |
|---|---|---|---|---|---|---|---|---|
| | Total | Urban | Mountainous | Seacoast | Total | Urban | Mountainous | Seacoast |
| Men | | | | | | | | |
| –39 | 0.0 | – | 0.0 | 0.0 | 14.3 | – | 0.0 | 16.7 |
| 40–49 | 9.1 | – | 42.9 | 2.7 | 45.5 | – | 28.6 | 48.7 |
| 50–59 | 24.3 | – | 55.6 | 8.5 | 72.9 | – | 75.0 | 71.8 |
| 60–69 | 35.2 | 37.5 | 44.1 | 21.9 | 74.6 | 75.0 | 69.9 | 81.3 |
| 70–79 | 48.2 | 41.3 | 63.5 | 45.7 | 85.3 | 83.8 | 85.3 | 91.4 |
| 80– | 51.6 | 45.6 | 74.2 | 56.5 | 90.1 | 89.9 | 90.3 | 91.3 |
| Total | 42.0 | 42.5 | 57.1 | 23.8 | 80.6 | 85.5 | 78.4 | 75.1 |
| Women | | | | | | | | |
| –39 | 3.2 | – | 0.0 | 4.2 | 9.7 | – | 0.0 | 12.5 |
| 40–49 | 11.4 | – | 29.4 | 8.0 | 28.6 | – | 29.4 | 28.4 |
| 50–59 | 30.3 | 50.0 | 46.3 | 22.5 | 41.7 | 100.0 | 29.9 | 46.5 |
| 60–69 | 57.1 | 49.1 | 68.3 | 45.8 | 55.4 | 64.3 | 50.3 | 58.5 |
| 70–79 | 71.9 | 69.3 | 83.2 | 66.1 | 75.1 | 76.1 | 70.4 | 32.0 |
| 80– | 80.7 | 77.3 | 91.9 | 76.9 | 78.2 | 79.6 | 69.3 | 90.0 |
| Total | 61.5*** | 70.0*** | 72.1*** | 37.8*** | 64.6*** | 76.3*** | 56.3*** | 54.6*** |

*** Significantly different ($P < 0.001$) from prevalence in men of the same region

higher in men than in women ($P < 0.001$). When the BMD values were compared among age strata, the prevalence of OP tended to be higher with age in both genders; however, the tendency was much greater in women than in men. Multiple regression analysis was performed to determine the effect of region, gender, age, and body build on BMD in the overall population of the mountainous and seacoast areas, using each value of BMD at lumbar spine, femoral neck, and total hip as an objective variable, and region (seacoast: 0, mountainous: 1), gender (men: 0, women: 1), age, and BMI as explanatory factors. The analysis revealed there was no regional difference in the BMD values at L2–L4, femoral neck, and total hip, whereas there were significant differences in gender (beta at L2–L4, femoral neck, and total hip, −0.41, −0.41, and −0.47, respectively, all $P < 0.001$), age (beta at L2–L4, femoral neck, and total hip, −0.28, −0.43, and −0.42, respectively, all $P < 0.001$), and BMI (beta at L2–L4, femoral neck, and total hip, 0.29, 0.33, and 0.37, respectively, all $P < 0.001$).

Table 4 reveals the prevalence of OP at the lumbar spine, the femoral neck, and the total hip among residents of mountainous and coastal regions in the ROAD study. The prevalence of OP in women was six, two, and three-fold higher, respectively, than in men, with a significant difference ($P < 0.001$). Although the prevalence of OP at the lumbar spine was higher for persons in the seacoast area than in the mountainous area, the prevalence at the femoral neck and total hip were higher in the mountainous area than in the seacoast area. In women, the prevalence of OP at the lumbar spine, femoral neck, and total hip were all higher in the mountainous area than in the seacoast area.

Logistic regression analysis was performed to determine the effect of region, gender, age, and body build on the prevalence of OP, using the presence of OP at L2–L4 as an objective variable, and region (seacoast: 0, mountainous: 1), gender (men: 0, women: 1), age, and BMI as explanatory factors. The analysis revealed that the risk for OP at L2–L4 was significantly higher in women (OR, 10.2; 95% CI, 6.07–17.1; $P < 0.001$), in advanced age (+1 year: OR, 1.10; 95% CI, 1.08–1.12; $P < 0.001$), whereas it was significantly lower in larger body build (+1 BMI: OR, 0.74; 95% CI, 0.69–0.79; $P < 0.001$). There was no significant difference in the prevalence of OP at L2–L4 between the mountainous and seacoast area. A similar tendency was shown in the prevalence of OP at the femoral neck and total hip (femoral neck: women versus men, OR, 3.82; 95% CI, 2.77–5.27; $P < 0.001$; +1 year: OR, 1.11; 95% CI, 1.09–1.13; $P < 0.001$; +1 BMI: OR, 0.75; 95% CI, 0.72–0.79; $P < 0.001$; total hip: women versus men, OR, 4.39; 95% CI, 2.88–6.70; $P < 0.001$; +1 year: OR, 1.11; 95% CI, 1.09–1.14; $P < 0.001$; +1 BMI: OR, 0.70; 95% CI, 0.65–0.75; $P < 0.001$).

## Discussion

Little epidemiological information is available for musculoskeletal diseases such as OA and OP in Japan. The

**Table 3** Mean values (standard deviation) of bone mineral density of participants classified by age, gender, and region

| Age strata (years) | L2–L4 (g/cm$^2$) | | | Femoral neck (g/cm$^2$) | | | Total hip (g/cm$^2$) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Total | Mountainous | Seacoast | Total | Mountainous | Seacoast | Total | Mountainous | Seacoast |
| Men | | | | | | | | | |
| –39 | 1.05 (0.13) | 0.97 (0.03) | 1.06 (0.13) | 0.83 (0.13) | 0.72 (0.02) | 0.84 (0.14) | 0.96 (0.15) | 0.87 (0.12) | 0.98 (0.15) |
| 40–49 | 1.06 (0.15) | 1.08 (0.15) | 1.06 (0.15) | 0.82 (0.13) | 0.77 (0.09) | 0.83 (0.14) | 0.96 (0.14) | 0.94 (0.08) | 0.96 (0.15) |
| 50–59 | 1.05 (0.20) | 1.03 (0.20) | 1.06 (0.19) | 0.80 (0.15) | 0.81 (0.17) | 0.79 (0.14) | 0.93 (0.15) | 0.93 (0.17) | 0.93 (0.14) |
| 60–69 | 1.04 (0.17) | 1.05 (0.16) | 1.03 (0.18) | 0.75 (0.10) | 0.76 (0.10) | 0.75 (0.12)b | 0.90 (0.12) | 0.90 (0.11) | 0.89 (0.14) |
| 70–79 | 1.05 (0.23) | 1.03 (0.22) | 1.08 (0.25) | 0.71 (0.12)abcd | 0.70 (0.13)cd | 0.73 (0.12)b | 0.85 (0.14)bc | 0.85 (0.14) | 0.86 (0.12)b |
| 80– | 1.04 (0.26) | 1.05 (0.25) | 1.01 (0.30) | 0.68 (0.12)abcd | 0.69 (0.13)c | 0.68 (0.12)abcd | 0.80 (0.15)abcd | 0.81 (0.13)c | 0.78 (0.16)abc |
| Total | 1.05 (0.20) | 1.04 (0.20) | 1.06 (0.21) | 0.74 (0.13) | 0.73 (0.13) | 0.76 (0.13) | 0.88 (0.14) | 0.87 (0.14) | 0.90 (0.14) |
| Women | | | | | | | | | |
| –39 | 1.08 (0.12) | 1.11 (0.15) | 1.07 (0.12) | 0.78 (0.13) | 0.76 (0.16) | 0.78 (0.12) | 0.86 (0.13)* | 0.86 (0.13) | 0.86 (0.13)* |
| 40–49 | 1.04 (0.13) | 1.06 (0.10) | 1.04 (0.14) | 0.74 (0.12)*** | 0.75 (0.09) | 0.74 (0.12)*** | 0.85 (0.13)*** | 0.86 (0.10) | 0.84 (0.13)*** |
| 50–59 | 0.94 (0.16)ab*** | 0.94 (0.16)** | 0.94 (0.16)ab*** | 0.71 (0.11)a*** | 0.70 (0.10)*** | 0.71 (0.12)*** | 0.81 (0.12)*** | 0.83 (0.12)*** | 0.80 (0.12)*** |
| 60–69 | 0.85 (0.15)abc*** | 0.85 (0.15)abc*** | 0.86 (0.16)abc*** | 0.63 (0.09)abc*** | 0.62 (0.10)abc*** | 0.63 (0.09)abc*** | 0.75 (0.11)abc*** | 0.75 (0.11)bc*** | 0.74 (0.11)abc*** |
| 70–79 | 0.80 (0.17)abcd*** | 0.79 (0.17)abcd*** | 0.82 (0.17)abc*** | 0.57 (0.10)abcd*** | 0.56 (0.10)abcd*** | 0.59 (0.10)abcd*** | 0.68 (0.11)abcd*** | 0.67 (0.11)abcd*** | 0.69 (0.11)abcd*** |
| 80– | 0.76 (0.16)abcd*** | 0.84 (0.16)abcd*** | 0.78 (0.16)abc*** | 0.52 (0.08)abcde*** | 0.52 (0.08)abcd*** | 0.52 (0.09)abcd*** | 0.60 (0.10)abcde*** | 0.61 (0.10)abcde*** | 0.59 (0.10)abcde*** |
| Total | 0.87 (0.18)*** | 0.83 (0.18)*** | 0.91 (0.18)*** | 0.63 (0.12)*** | 0.60 (0.11)*** | 0.66 (0.13)*** | 0.74 (0.13)*** | 0.72 (0.13)*** | 0.76 (0.14)*** |

[a] Significantly different ($P < 0.05$) from values of the age group in their thirties

[b] Significantly different ($P < 0.05$) from values of the age group in their forties

[c] Significantly different ($P < 0.05$) from values of the age group in their fifties

[d] Significantly different ($P < 0.05$) from values of the age group in their sixties

[e] Significantly different ($P < 0.05$) from values of the age group in their seventies

*, **, *** Significantly different (* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$) from values in men of the same age-strata and the same region

**Table 4** Prevalence (%) of osteoporosis according to the JSBMR criteria, classified by age, gender, and region

| Age strata (years) | L2–L4 | | | Femoral neck | | | Total hip | | |
|---|---|---|---|---|---|---|---|---|---|
| | Total | Mountainous | Seacoast | Total | Mountainous | Seacoast | Total | Mountainous | Seacoast |
| Men | | | | | | | | | |
| –39 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| 40–49 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| 50–59 | 2.8 | 5.6 | 1.4 | 6.5 | 8.3 | 5.6 | 2.8 | 2.8 | 2.8 |
| 60–69 | 2.6 | 0.0 | 6.3 | 7.0 | 4.3 | 10.9 | 3.2 | 1.1 | 6.3 |
| 70–79 | 3.6 | 3.3 | 4.3 | 22.3 | 23.3 | 20.0 | 8.2 | 10.0 | 4.3 |
| 80– | 7.4 | 6.5 | 8.7 | 13.0 | 16.1 | 8.7 | 18.5 | 16.1 | 21.7 |
| Total | 3.4 | 2.8 | 3.6 | 12.4 | 14.7 | 9.8 | 6.1 | 6.9 | 5.1 |
| Women | | | | | | | | | |
| –39 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| 40–49 | 1.9 | 0.0 | 2.3 | 2.9 | 0.0 | 3.4 | 3.8 | 0.0 | 4.6 |
| 50–59 | 5.3 | 3.0 | 6.3 | 4.8 | 1.5 | 6.4 | 3.9 | 1.5 | 5.0 |
| 60–69 | 13.5 | 15.3 | 11.4 | 22.2 | 23.0 | 21.3 | 10.8 | 10.9 | 10.6 |
| 70–79 | 29.8 | 31.8 | 26.0 | 42.9 | 44.6 | 40.2 | 25.9 | 25.6 | 26.2 |
| 80– | 43.8 | 47.3 | 36.7 | 65.1 | 64.4 | 66.7 | 46.6 | 43.8 | 53.3 |
| Total | 19.2*** | 23.4*** | 12.8*** | 26.5*** | 32.7*** | 20.3*** | 16.3*** | 19.0*** | 13.6*** |

*JSBMR* Japanese Society for Bone and Mineral Research

*** Significantly different ($P < 0.001$) from prevalence in men of the same region

ROAD study is the first large observational study that was conducted in the Japanese population, and it was designed to supply essential information mainly regarding OA and OP. Among the large-scale population-based epidemiological studies aimed at preventing OA, the present ROAD study, which includes 3,040 participants, ranks at the same level as the Framingham study with 1,805 participants [20] and the Chingford study with 1,353 participants [21].

The present study clarified the age-sex distribution of the prevalence of KOA and LS as radiographically diagnosed in Japanese populations. If the results obtained from the ROAD study were applicable to the total age-sex distribution derived from the Japanese census in 2005 [15], it would be assumed that 25,300,000 people (8,600,000 men and 16,700,000 women) aged 40 years and older would be affected by radiographic KOA and 37,900,000 people (18,900,000 men and 19,000,000 women) aged 40 years and older would be affected by radiographic LS. This estimation would include asymptomatic OA. However, because one-quarter of men with radiographic OA and one-third of women with radiographic OA were reported to have pain, which is considered symptomatic OA [22, 23], it was determined that approximately 7,800,000 people (2,200,000 men and 5,600,000 women) aged 40 years and older would be affected by symptomatic KOA. Further, 11,000,000 people (4,700,000 men and 6,300,000 women) would be affected by symptomatic LS, based on the same assumption of the proportions of symptomatic and asymptomatic OA.

In this study, the Japanese criteria were used to clarify the prevalence of OP at the lumbar spine and hip. If the results obtained from the ROAD study were again applied to the entire Japanese age–sex distribution, 6,400,000 people (800,000 men and 5,600,000 women) aged 40 years and older would be affected by OP at the lumbar spine, and 10,700,000 people (2,600,000 men and 8,100,000 women) and 6,600,000 people (1,300,000 men and 5,300,000 women) would be affected by OP at the femoral and total hip, respectively. Because there are huge estimated numbers of patients with KOA, LS, and OP in Japan, these bone and joint diseases may be called national diseases. The Japanese Orthopaedic Association has proposed that the term "locomotive syndrome" be adopted to designate the condition evident in the high-risk group with musculoskeletal disorders who are highly likely to need nursing care [24]. The present study estimated that a total of 47,000,000 people (21,000,000 men and 26,000,000 women) aged 40 years and older would be affected by either OA or OP and are candidates for developing locomotive syndrome. Considering that the population of Japan is aging very rapidly and that more than 20% of the population is aged 65 years and over, there is an urgent need to develop preventive strategies for addressing these diseases that cause disability in the elderly.

In addition, the various associated factors for KOA and LS were identified in this research. The prevalence of KOA was higher in women than in men, whereas that of LS was higher in men than in women. Further, the prevalence of

KOA was higher in the mountainous area than in the seacoast area, whereas the prevalence of LS was higher in the seacoast area than in the mountainous area. The difference in the presence of KOA and LS based on gender difference may in part relate to the etiological differences of these two diseases, including genetic factors; the differences based on regional differences could be affected by environmental factors. Further investigation of the ROAD study will elucidate the genetic and environmental background underlying these diseases, although these could not be determined by the present study. Regarding OP, a high prevalence of OP among the ROAD study participants was confirmed; female sex and advanced age were associated with the presence of OP; and it was confirmed that BMI was associated with BMD at any site. The ROAD study participants will be followed up for at least 10 years to clarify the relationships between musculoskeletal diseases and risk factors for the early prevention of the disabilities caused by them.

There are several limitations in the present study. First, although the ROAD study includes a large number of participants (>3,000), these participants do not truly represent the general population as they have been recruited from only three areas. To confirm whether the participants of the ROAD study are representative of the Japanese population, we compared anthropometric measurements and frequency of smoking and alcohol drinking between the participants and the general Japanese population. The values for the general population were obtained from the report on the 2005 National Health and Nutrition Survey conducted by the Ministry of Health, Labour and Welfare, Japan [25]. The mean BMI (standard deviation in parentheses) of men in the age groups of 40, 50, 60, 70–74, 75–79, and 80 years or older as reported in the National Health and Nutrition Survey was 23.99 (3.27), 23.74 (3.07), 23.75 (2.94), 23.68 (3.18), 23.31 (3.04), and 22.27 (2.64), respectively, and that of women was 22.44 (3.49), 23.06 (3.37), 23.54 (3.66), 23.16 (3.42), 23.42 (3.53), and 22.50 (3.97), respectively. In the ROAD study, the mean BMI for men in identical age strata was 24.50 (4.36), 23.58 (2.90), 23.78 (3.16), 23.08 (2.82), 22.81 (2.86), and 22.62 (2.90), and for women it was 21.92 (4.08), 23.04 (3.29), 23.31 (3.21), 23.44 (3.46), 22.96 (3.66), and 22.21 (3.16), respectively. No significant differences were identified between our participants and the total Japanese population, except that the male participants aged 70–74 years in the ROAD study were significantly smaller in terms of body structure than the overall Japanese population ($P < 0.05$). This difference should be taken into consideration when evaluating the potential risk factors in men aged 70–74 years; factors such as body build, particularly heavy weight, are known to be associated with the occurrence of KOA [26]. Thus, our results might represent an underestimation. Conversely, a small body build is frequently associated with occurrence of OP [27]; therefore, in this case, our results might represent an overestimation.

Although care should always be taken when generalizing results obtained from the ROAD study for all similarly aged men and women, the overall BMI of the participants was basically comparable to that of the broader Japanese population. In addition, the proportion of current smokers and current drinkers (those who regularly smoked or drank more than one drink/month) in the general Japanese population was compared with that in the study population. Both proportions were significantly higher in the general Japanese population than in the study population (smokers: men, 34.8% in Japanese population, 25.3% in ROAD subjects, $P < 0.001$; women, 8.8% in Japanese population, 3.4% in ROAD subjects, $P < 0.001$; drinkers: men, 69.8% in Japanese population, 64.4% in ROAD subjects, $P < 0.01$; women, 30.8% in Japanese population, 25.5% in ROAD subjects, $P < 0.001$), suggesting that participants of the ROAD study had healthier lifestyles than the general Japanese population. This "healthy" selection bias should be taken into consideration when generalizing the results obtained from the ROAD study. Second, the age distributions of the participants among the three cohorts were different. In the urban, mountainous, and coastal areas, 99.8, 84.3, and 54.7% of the participants, respectively, were more than 60 years old. This selection bias should be considered in the analysis of regional differences of frequencies and risk factors. Third, BMD values were not collected from the participants in Itabashi Ward because of lack of available apparatus. So, our estimation of the number of patients with osteoporosis was based on the data collected in the countryside. This selection bias should always be taken into consideration when generalizing the study data to the Japanese population.

In conclusion, the prevalence of KOA, LS, and OP was clarified, and the number of people affected with these diseases in Japan was estimated, using the baseline data of the ROAD study. This study will provide the information required to develop clinical algorithms for the early identification of potential high-risk populations, as well as essential information for the development of policies for the detection and prevention of OA, OP, or osteoporotic fractures. Furthermore, establishment of the cohort will also facilitate the expansion of other studies in related areas of investigation. The knowledge gained from the ROAD study will have major implications for the understanding and management of several additional common problems of aging.

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*Original article*

# Association of low dietary vitamin K intake with radiographic knee osteoarthritis in the Japanese elderly population: dietary survey in a population-based cohort of the ROAD study

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**Abstract**
***Background.*** The present study sought to identify dietary nutrients associated with the prevalence of radiographic knee osteoarthritis (OA) in the Japanese elderly of a population-based cohort of the Research on Osteoarthritis Against Disability (ROAD) study.
***Methods.*** From the baseline survey of the ROAD study, 719 participants ≥60 years of age (270 men, 449 women) of a rural cohort were analyzed. Dietary nutrient intakes for the previous 1 month were assessed by a self-administered brief diet history questionnaire. The radiographic severity at both knees was determined by the Kellgren/Lawrence (KL) system.
***Results.*** The prevalence of knee OA of KL ≥2 was 70.8%. Age, body mass index, and female sex were positively associated with the prevalence. Among the dietary factors, only vitamin K intake was shown to be inversely associated with the prevalence of radiographic knee OA by multivariate logistic regression analysis. The presence of joint space narrowing of the knee was also inversely associated with vitamin K intake. The prevalence of radiographic knee OA for each dietary vitamin K intake quartile decreased with the increased intake.
***Conclusions.*** The present cross-sectional study using a population-based cohort supports the hypothesis that low dietary vitamin K intake is a risk factor for knee OA. Vitamin K may have a protective role against knee OA and might lead to a disease-modifying treatment.

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## Introduction

Osteoarthritis (OA) is a major public health issue causing disability of the elderly in most developed countries.[1] There is an urgent need for safe, effective strategies for preventing and treating this disease. Such strategies could come from dietary nutrition as studies have indicated an association of nutritional factors with OA.[2-7] Diet and nutritional factors are important because they are modifiable. However, epidemiological data on the relation between nutritional factors and OA are insufficient. We thus set up a population-based prospective cohort study named Research on Osteoarthritis Against Disability (ROAD) in 2005. The present study investigated the association of the prevalence of radiographic knee OA with dietary nutritional factors assessed by a self-administered brief diet history questionnaire (BDHQ) in the Japanese elderly living in a rural community participating in the ROAD study.[8]

## Participants and methods

### *Participants*

The ROAD study is a population-based prospective cohort study designed to clarify the environmental and genetic risk factors for OA. The participants of the ROAD study were recruited from the residents of three communities that have different characteristics: an urban region in Itabashi, Tokyo; a mountainous region in Hidakagawa, Wakayama; and a coastal region in Taiji, Wakayama.[9] The inclusion criteria were as follows: The patient (1) had to be able to walk to the clinic at which the survey was performed, (2) provide self-reported data, and (3) understand and sign an informed consent form. Residents of the urban, mountainous, and coastal regions were recruited from the resident registration list of the relevant region.

The age of the participants recruited from the urban region was ≥60 years, and that of the participants from the two other regions was ≥40 years. In the urban, mountainous, and coastal areas, 99.8%, 84.3%, and 54.7% of the participants, respectively, were >60 years of age. Two-thirds of the participants were women, and their mean age was 1 year less than that of the male participants. The baseline survey of the Hidakagawa cohort was conducted from November 2005 to February 2006. The community has a population of 11 300/330 km$^2$ and residents ≥65 years constitute 30.5% of the population. All participants provided written informed consent, and the study was conducted with approval of ethics committees of the institution. From the baseline data of 723 participants who were ≥60 years in the cohort, we analyzed 719 participants (270 men, 449 women) after excluding four individuals who had undergone knee surgery.

*Dietary assessment*

For the dietary survey, we used the BDHQ and investigated dietary nutrient intakes for the previous 1 month. A questionnaire was given to each participant with detailed explanations to fill it out at home and was addressed by well-trained interviewers when the participant visited the clinic. The BDHQ is a 4-page, structured questionnaire that inquires about the consumption frequency of a total of 56 food and beverage items, with specified serving sizes described in terms of a natural portion or the standard weight and volume measurement of servings commonly consumed in general Japanese populations. The BDHQ was developed based on a comprehensive (16-page) version of a validated self-administered diet history questionnaire[8] and is now widely used for the dietary survey in Japan.[10–12] Estimates of dietary intake for the 56 food and beverage items, energy, and selected nutrients were calculated using an ad hoc computer algorithm for the BDHQ, which was based on the Standard Tables of Food Composition in Japan. Dietary intake levels of total energy and 16 nutrient factors (animal protein; vegetable protein; animal fat; vegetable fat; carbohydrate; vitamins $B_1$, $B_2$, $B_6$, and $B_{12}$; niacin; vitamins C, D, E, and K; dietary fiber; salt) were analyzed.

*Radiographic assessment*

All participants had plain radiographic examinations of both knees with an anteroposterior view with weight-bearing and foot map positioning. Knee radiographs were read, without knowledge of the participants' clinical status, by a single well-experienced orthopedist using the Kellgren/Lawrence (KL) radiographic atlas, and a KL grade (0–4) was determined.[13,14] The higher KL grade in both knees was designated as that of the participant. To evaluate intraobserver variability of the KL grading, 100 randomly selected radiographs of the knee were scored by the same observer more than 1 month after the first reading. Furthermore, 100 other radiographs were scored by two experienced orthopedic surgeons using the same atlas for interobserver variability. The intra- and interobserver variabilities were evaluated by kappa analysis and were confirmed to be sufficient for assessment (0.86 and 0.80, respectively).

*Statistical analysis*

Differences in crude mean values of dietary nutrient intakes were examined by a nonpaired *t*-test between the KL = 0 or 1 group and the KL ≥2 group for each sex, and those with significant differences were further evaluated by multivariate logistic regression analysis after adjustment for age, sex, body mass index (BMI), and total energy to estimate the odds ratio (OR) and its associated 95% confidence interval (95% CI). Association of the presence of joint space narrowing of the knee defined as KL ≥3 with nutrient intakes was also examined by logistic regression analysis. The Cochran-Mantel-Haenszel test was used to determine the association of the prevalence of knee OA for each dietary nutrient intake quartile for linear trend. Data analyses were performed using SAS version 9.0 (SAS Institute, Cary, NC, USA). $P < 0.05$ was considered significant.

## Results

Characteristics of the 719 participants are shown in Table 1. The prevalence of KL ≥2 knee OA was 70.8% (57.8% in men, 78.6% in women) and that of KL ≥ 3 was 25.9% (15.9% in men, 31.8% in women). Neither the age nor the BMI was significantly different between men and women in the overall population. Participants with KL ≥2 knee OA were older than those without it (KL = 0 or 1) in both sexes, and the BMI was higher in KL ≥2 than in KL = 0 or 1 in women.

We compared total energy and 16 dietary nutrient intakes between the groups with and without KL ≥2 knee OA (Table 2). Vegetable fat intake was significantly lower in the KL ≥2 group than in the KL = 0 or 1 group in women. Vitamin K intake was significantly lower in the KL ≥2 group than in the KL = 0 or 1 group in both sexes. Total energy and other nutrient intakes

**Table 1.** Characteristics of participants

| | Men | | | Women | | |
|---|---|---|---|---|---|---|
| | Overall | KL = 0 or 1 | KL ≥2 | Overall | KL = 0 or 1 | KL ≥ 2 |
| No. of participants | 270 | 114 | 156 | 449 | 96 | 353 |
| Age (years) | 72.1 ± 6.3 | 70.4 ± 5.9 | 73.4 ± 6.3† | 72.0 ± 7.0 | 68.8 ± 6.1* | 72.8 ± 7.0† |
| Height (cm) | 160.2 ± 6.2 | 160.1 ± 6.8 | 159.9 ± 5.8 | 146.9 ± 6.3* | 148.5 ± 6.1* | 146.8 ± 6.3* |
| Weight (kg) | 58.9 ± 9.6 | 58.3 ± 9.6 | 59.2 ± 9.6 | 49.7 ± 8.5* | 48.7 ± 6.7* | 49.9 ± 8.9* |
| BMI (kg/m$^2$) | 22.8 ± 2.9 | 22.5 ± 2.8 | 23.1 ± 3.0 | 22.9 ± 3.4 | 22.1 ± 2.6 | 23.2 ± 3.5† |

Data are means ± SD
KL, Kellgren/Lawrence system; BMI, body mass index
* $P < 0.05$ vs. men in the corresponding group by nonpaired *t*-test
† $P < 0.05$ vs. KL = 0 or 1 in the corresponding group by nonpaired *t*-test

**Table 2.** Comparison of total energy and dietary nutrient intakes between participants with (KL ≥2) and without (KL = 0 or 1) radiographic knee OA according to sex

| | Men | | Women | |
|---|---|---|---|---|
| Parameter | KL = 0 or 1 | KL ≥2 | KL = 0 or 1 | KL ≥2 |
| Total energy (MJ/day) | 9.77 ± 2.88 | 9.90 ± 2.73 | 7.07 ± 1.75 | 7.03 ± 1.78 |
| Dietary nutrients | | | | |
| Animal protein (g/day) | 46.3 ± 20.7 | 48.4 ± 20.9 | 36.8 ± 12.9 | 37.4 ± 16.2 |
| Vegetable protein (g/day) | 34.1 ± 10.1 | 33.8 ± 9.4 | 27.2 ± 6.7 | 26.1 ± 6.8 |
| Animal fat (g/day) | 27.6 ± 13.3 | 28.7 ± 12.2 | 21.9 ± 7.8 | 22.1 ± 10.1 |
| Vegetable fat (g/day) | 21.2 ± 10.9 | 21.9 ± 10.4 | 19.7 ± 8.6 | 17.6 ± 8.1* |
| Carbohydrate, (g/day) | 352 ± 116 | 356 ± 114 | 259 ± 72 | 261 ± 75 |
| Vitamin D (μg/day) | 22.0 ± 11.5 | 23.7 ± 13.0 | 16.7 ± 7.4 | 18.5 ± 9.9 |
| Vitamin E (mgα-TE/day) | 7.76 ± 3.43 | 7.89 ± 3.15 | 7.24 ± 2.51 | 6.84 ± 2.58 |
| Vitamin K (μg/day) | 266 ± 171 | 228 ± 131* | 253 ± 125 | 213 ± 115* |
| Vitamin $B_1$ (mg/day) | 0.81 ± 0.27 | 0.80 ± 0.24 | 0.71 ± 0.16 | 0.67 ± 0.19 |
| Vitamin $B_2$ (mg/day) | 1.09 ± 0.44 | 1.06 ± 0.37 | 0.97 ± 0.27 | 0.92 ± 0.33 |
| Niacin (mgNE/day) | 18.1 ± 6.9 | 18.0 ± 6.6 | 14.1 ± 4.1 | 13.6 ± 5.1 |
| Vitamin $B_6$ (mg/day) | 1.34 ± 0.49 | 1.32 ± 0.45 | 1.08 ± 0.29 | 1.05 ± 0.35 |
| Vitamin $B_{12}$ (μg/day) | 12.1 ± 6.3 | 12.5 ± 6.5 | 9.2 ± 4.0 | 9.6 ± 4.9 |
| Vitamin C (mg/day) | 103 ± 43 | 96 ± 39 | 117 ± 45 | 113 ± 42 |
| Dietary fiber (g/day) | 11.7 ± 4.0 | 11.2 ± 3.3 | 11.0 ± 3.2 | 10.5 ± 3.0 |
| Salt (g/day) | 13.0 ± 4.1 | 12.5 ± 3.7 | 10.4 ± 2.6 | 10.4 ± 3.1 |

Data are the mean ± SD
TE, tocopherol equivalent; NE, niacin equivalent
* $P < 0.05$ vs. KL = 0 or 1 in each group by nonpaired *t*-test

were not significantly different between the groups in either sex. Logistic regression analysis was performed using the presence of KL ≥2 knee OA (1, yes vs. 0, no) as an objective variable and age, BMI, sex, total energy, vegetable fat, and vitamin K intakes (vs. +1 SD) as explanatory variables (Table 3). Age, BMI, and sex were associated with the presence of radiographic knee OA (KL ≥2). Although vegetable fat intake had no significant association, dietary vitamin K intake (OR = 0.75, 95% CI = 0.63–0.89 vs. +1 SD) was shown to be inversely associated with the presence of radiographic knee OA in the overall population.

Table 4 shows the association between KL grade and dietary vitamin K intake according to sex. Logistic

**Table 3.** Association of age, BMI, sex, and nutrient intakes with radiographic knee OA (KL ≥ 2) in the overall population

| Parameter | OR | 95% CI |
|---|---|---|
| Age (years) | 1.11 | 1.07–1.14* |
| BMI (kg/m$^2$) | 1.15 | 1.08–1.22* |
| Women (vs. men) | 3.08 | 2.16–4.40* |
| Dietary nutrient intakes | | |
| Vegetable fat[a] (SD) | 0.93 | 0.78–1.10 |
| Vitamin K[a] (SD) | 0.75 | 0.63–0.89* |

The odds ratios for KL ≥ 2 (vs. KL = 0 or 1) were calculated by logistic regression analysis
OR, odds ratio; CI, confidence interval
* $P < 0.01$
[a]Adjusted for age, sex, BMI, and total energy

**Table 4.** Association between KL grade and dietary vitamin K intake according to sex

| | Overall | | Men | | Women | |
|---|---|---|---|---|---|---|
| Condition | OR | 95% CI | OR | 95% CI | OR | 95% CI |
| KL ≥2 (vs. KL = 0 or 1) | 0.75 | 0.63–0.89† | 0.76 | 0.59–0.95* | 0.74 | 0.58–0.96* |
| KL ≥3 (vs. KL ≤2) | 0.67 | 0.53–0.84† | 0.74 | 0.50–1.04 | 0.61 | 0.45–0.81† |

Odds ratios were calculated by logistic regression analysis after adjustment for age, sex, BMI, and total energy
* $P < 0.05$
† $P < 0.01$

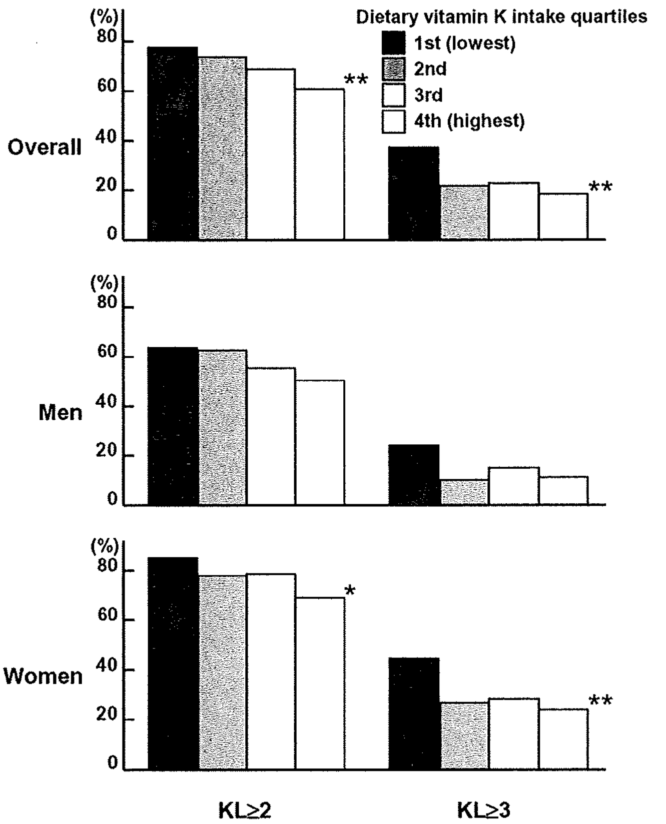


**Fig. 1.** Prevalence of KL ≥2 and KL ≥3 knee osteoarthritis per quartile of dietary vitamin K intake. The 25th, 50th, and 75th percentiles were, respectively, 141.4, 205.8, and 285.8 mg/day in the overall population; 145.0, 222.8, and 314.0 mg/day in men; and 137.4, 199.9, and 279.3 mg/day in women. *$P < 0.05$ and **$P < 0.01$ for linear trend

regression analysis using the presence of KL ≥2 knee OA as an objective variable showed that vitamin K intake was inversely associated with KL ≥2 knee OA in both sexes (OR = 0.76, 95% CI = 0.59–0.95 vs. +1 SD in men; OR = 0.74, 95% CI = 0.58–0.96 vs. +1 SD in women) as well as in the overall population. Furthermore, logistic regression analysis using the presence of KL ≥3 knees (vs. KL ≤2) as an objective variable revealed that KL ≥ 3 knees (vs. KL ≤2) were also inversely associated with vitamin K intake in the overall population (OR = 0.67, 95% CI = 0.53–0.84 vs. +1 SD) and in women (OR = 0.61, 95% CI = 0.45–0.81 vs. +1 SD), indicating that the presence of joint space narrowing of the knee was inversely associated with dietary vitamin K intake. Furthermore, we examined the prevalence of KL ≥2 and KL ≥3 knee OA for each dietary vitamin K intake quartile (Fig. 1), which decreased with ascending vitamin K intake. This tendency was significant in the overall population and in women.

## Discussion

The present study investigated the association of radiographic knee OA with nutritional factors in a population-based cohort of the ROAD study. Total energy, protein, fat, and carbohydrate had no significant association with knee OA. Among dietary vitamin intakes, vitamin K was inversely associated with the prevalence of radiographic knee OA. Previous published epidemiological studies have suggested a relation between OA and vitamins.[2–7] Vitamin K includes vitamin $K_1$ or phylloquinone, which is contained in green leafy vegetables, and vitamin $K_2$ or menaquinone, which is synthesized by bacteria and abundantly contained in a traditional Japanese fermented soybean food called *natto*.[15,16] Vitamin K belongs to the fat-soluble vitamins, which may be the reason why vegetable fat intake was lower in the knee OA group in women, although it was not significant in the multivariate analysis. Plasma levels of phylloquinone has been reported to be inversely associated with the prevalence of OA in the hand and knee,[6] which is consistent with the results of the present study.

Vitamin K serves as an essential cofacotor of γ-glutamyl carboxylase, an enzyme for the γ-carboxylation of vitamin K-dependent proteins including matrix Gla protein (MGP).[17] MGP is an extracellular matrix protein of the mineral-binding Gla protein family that includes osteocalcin, the growth arrest-specific protein 6 (Gas6). Gas6 is up-regulated in growth-arrested cells,[18] suggesting a role in protection from certain cellular stresses, such as apoptosis. In fact, many studies demonstrated the ability of Gas6 to promote cell survival and proliferation.[19–22] MGP is expressed by proliferative and late hypertrophic chondrocytes,[23,24] and mutations in MGP are responsible for Keutel syndrome in which patients are affected by aberrant cartilage calcification.[25] Studies of MGP-deficient mice suggest that MGP is an inhibitor of extracellular matrix calcification in the epiphyseal growth plate.[26] Warfarin, a vitamin K-antagonist anticoagulant, is known to cause warfarin embryopathy characterized by abnormal calcification and decreased growth of the cartilage.[27,28] These data demonstrate that vitamin K plays an important role in cartilage metabolism as a inhibitor of extracellular matrix calcification as well as a promotor of cell survival and proliferation. Habitual low dietary vitamin K intake may exert an inhibitory effect on the vitamin K-dependent MGP and Gas6 functions and modulate the pathogenesis of OA by influencing the process of osteophytosis and cartilage destruction.

The minimum amounts of vitamin K intake recommended by the Japanese Ministry of Health, Labor, and Welfare are 75 and 65 μg/day for men and women, respectively. The percentages of participants who did not meet the criteria in this study were 8.5% in men, 3.6% in women, and 5.4% in the overall population—all of whom belonged to the 1st quartile (lowest) in Fig. 1. However, even in the 2nd through 4th quartiles, the prevalence of radiographic OA decreased with ascending vitamin K intake, suggesting that the recommended amount of vitamin K intake may not be sufficient for the prevention of knee OA.

The management of knee OA is largely palliative, focusing on the alleviation of symptoms, although it is a major public health issue causing disabilities in the elderly. The Osteoarthritis Research Society International (OARSI) current recommendations include a combination of nonpharmacological interventions and pharmacological treatments.[29] Considering that nonsteroidal antiinflammatory drugs (NSAIDs) with serious adverse effects caused by their long-term use remain among the most widely prescribed drugs for OA,[30] there is a need for safe, effective alternative strategies for the prevention and treatment of this disease. Such strategies could come from dietary nutrition, and vitamin K might have a preventive role against OA.

There are limitations in the present study. This is a cross-sectional study of the baseline data, and a causal relation could not be determined. In addition, the dietary survey in this study investigated dietary habits only for the pevious month, which did not necessarily reflect a long habit of several years, despite the fact that OA is a slowly progressing chronic disease. This dietary survey also investigated whether participants had changed their dietary habits. Those who answered yes comprised 9.6%; and 90.4% of participants answered they had not changed their dietary habits. Although it is likely that dietary habits in middle-aged and elderly people are usually quite different from those in children and young adults, there is a possibility that most of participants in this study had not changed their dietary habits for several years or for a longer time, which may have affected the disease process of OA. Furthermore, the dietary survey in the present study was conducted from autumn to winter although there are four seasons in Japan and diets may vary with the season. Therefore, the present study could give some bias for the effect of season on the nutritional quality of diets. This is a limitation in this study because we could not follow participants during all seasons to get a measure of average diets during the year. We are planning a follow-up study during the same season to minimize the variation caused by seasonal differences. Longitudinal data are required to confirm the relation between vitamin K and OA.

## Conclusion

The present cross-sectional study using a population-based cohort supports the hypothesis that low dietary vitamin K intake is a risk factor for knee OA. Vitamin K may have a protective role against knee OA and might lead to disease-modifying treatment.

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We declare that we have no conflict of interest regarding the present manuscript.

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OA OSTEOARTHRITIS

# Prevalence of radiographic knee osteoarthritis and its association with knee pain in the elderly of Japanese population-based cohorts: The ROAD study

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## Summary

*Objective*: We investigated the prevalence of radiographic knee osteoarthritis (OA) and knee pain in the Japanese elderly using a large-scale population of a nationwide cohort study, Research on Osteoarthritis Against Disability (ROAD), and examined their association.

*Methods*: From the baseline survey of the ROAD study, 2,282 participants ≥60 years (817 men and 1,465 women) living in urban, mountainous and seacoast communities were analyzed. The radiographic severity at both knees was determined by the Kellgren/Lawrence (KL) grading system. KL ≥ 2 and KL ≥ 3 knee OA were examined separately to assess osteophytosis and joint space narrowing (JSN).

*Results*: The prevalence of KL ≥ 2 OA (47.0% and 70.2% in men and women, respectively) was much higher than that of previous studies in Caucasians, while that of KL ≥ 3 OA was not much different in men. Age, BMI, female sex and rural residency were risk factors for radiographic knee OA, knee pain and their combination. The prevalence of knee pain was age-dependent in women, but not in men. Knee pain was more strongly associated with KL ≥ 3 OA than with KL = 2, and the association was higher in men than in women. Female sex was a strong risk factor even in the subgroup without radiographic knee OA (KL = 0/1).

*Conclusion*: The present cross-sectional study revealed a high prevalence of radiographic knee OA in the Japanese elderly. Knee pain was strongly associated with JSN especially in men, while women tended to have knee pain even without radiographic OA.


*Key words*: Osteoarthritis, Knee, Prevalence, Pain, Cross-sectional.

## Introduction

Knee osteoarthritis (OA), characterized by pathological features including joint space narrowing (JSN) and osteophytosis, is a major public health issue causing chronic pain and disability of the elderly in most developed countries[1–3]. Despite the urgent need of strategies for the prevention and treatment of this condition, the prevalence overall and among demographic subgroups is not well characterized. The reported prevalence of radiographic knee OA differs considerably among previous population-based epidemiologic studies[4–14]. This may be due to a limitation of the sample size or a variability of age, ethnicity and radiological acquisition.

With the goal of establishing epidemiologic indexes to evaluate clinical evidence for the development of a disease-modifying treatment of OA, we set up a large-scale nationwide OA cohort study called Research on Osteoarthritis Against Disability (ROAD) in 2005. We have to date created a baseline database with detailed clinical and genetic information on three population-based cohorts in urban, mountainous and seacoast communities of Japan. The present study initially investigated the prevalence and distribution of knee OA according to age, gender and community using cohorts of 2,282 participants who were 60 years or older in the baseline survey of the ROAD study.

The most popular grading system for the radiographic severity of knee OA is the Kellgren/Lawrence (KL) system with classification into five-grade (0–4) scales. KL grade 2 is defined as osteophyte formation and grade 3 as JSN in addition to osteophyte formation; and KL ≥ 2 is generally thought to be the standard of the diagnostic criterion of knee OA[15,16]. However, accumulating evidence has shown that osteophytosis and JSN have distinct etiologic mechanisms and their progression is neither constant nor proportional[17–19]. Hence, to assess these two pathological features separately, the present study examined not only the prevalence of KL ≥ 2, but also that of KL ≥ 3 knee OA.

Arthritis is the most common cause of pain in the elderly, and knee pain is the principal clinical symptom of knee OA[20]. Although much effort has been devoted toward a definition of knee pain, the correlation with radiographic severity of the knee OA was not as strong as one would expect[21–23]. This study also examined the association of

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