

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.

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

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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 km² 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 questionnaire⁸ 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 B₁, B₂, B₆, and B₁₂; 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 \geq 2	Overall	KL = 0 or 1	KL \geq 2
No. of participants	270	114	156	449	96	353
Age (years)	72.1 \pm 6.3	70.4 \pm 5.9	73.4 \pm 6.3 [†]	72.0 \pm 7.0	68.8 \pm 6.1*	72.8 \pm 7.0 [†]
Height (cm)	160.2 \pm 6.2	160.1 \pm 6.8	159.9 \pm 5.8	146.9 \pm 6.3*	148.5 \pm 6.1*	146.8 \pm 6.3*
Weight (kg)	58.9 \pm 9.6	58.3 \pm 9.6	59.2 \pm 9.6	49.7 \pm 8.5*	48.7 \pm 6.7*	49.9 \pm 8.9*
BMI (kg/m ²)	22.8 \pm 2.9	22.5 \pm 2.8	23.1 \pm 3.0	22.9 \pm 3.4	22.1 \pm 2.6	23.2 \pm 3.5 [†]

Data are means \pm 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 \geq 2) and without (KL = 0 or 1) radiographic knee OA according to sex

Parameter	Men		Women	
	KL = 0 or 1	KL \geq 2	KL = 0 or 1	KL \geq 2
Total energy (MJ/day)	9.77 \pm 2.88	9.90 \pm 2.73	7.07 \pm 1.75	7.03 \pm 1.78
Dietary nutrients				
Animal protein (g/day)	46.3 \pm 20.7	48.4 \pm 20.9	36.8 \pm 12.9	37.4 \pm 16.2
Vegetable protein (g/day)	34.1 \pm 10.1	33.8 \pm 9.4	27.2 \pm 6.7	26.1 \pm 6.8
Animal fat (g/day)	27.6 \pm 13.3	28.7 \pm 12.2	21.9 \pm 7.8	22.1 \pm 10.1
Vegetable fat (g/day)	21.2 \pm 10.9	21.9 \pm 10.4	19.7 \pm 8.6	17.6 \pm 8.1*
Carbohydrate, (g/day)	352 \pm 116	356 \pm 114	259 \pm 72	261 \pm 75
Vitamin D (μ g/day)	22.0 \pm 11.5	23.7 \pm 13.0	16.7 \pm 7.4	18.5 \pm 9.9
Vitamin E (mg α -TE/day)	7.76 \pm 3.43	7.89 \pm 3.15	7.24 \pm 2.51	6.84 \pm 2.58
Vitamin K (μ g/day)	266 \pm 171	228 \pm 131*	253 \pm 125	213 \pm 115*
Vitamin B ₁ (mg/day)	0.81 \pm 0.27	0.80 \pm 0.24	0.71 \pm 0.16	0.67 \pm 0.19
Vitamin B ₂ (mg/day)	1.09 \pm 0.44	1.06 \pm 0.37	0.97 \pm 0.27	0.92 \pm 0.33
Niacin (mgNE/day)	18.1 \pm 6.9	18.0 \pm 6.6	14.1 \pm 4.1	13.6 \pm 5.1
Vitamin B ₆ (mg/day)	1.34 \pm 0.49	1.32 \pm 0.45	1.08 \pm 0.29	1.05 \pm 0.35
Vitamin B ₁₂ (μ g/day)	12.1 \pm 6.3	12.5 \pm 6.5	9.2 \pm 4.0	9.6 \pm 4.9
Vitamin C (mg/day)	103 \pm 43	96 \pm 39	117 \pm 45	113 \pm 42
Dietary fiber (g/day)	11.7 \pm 4.0	11.2 \pm 3.3	11.0 \pm 3.2	10.5 \pm 3.0
Salt (g/day)	13.0 \pm 4.1	12.5 \pm 3.7	10.4 \pm 2.6	10.4 \pm 3.1

Data are the mean \pm 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 \geq 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 \geq 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 \geq 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 \geq 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

Condition	Overall		Men		Women	
	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

* $P < 0.05$

[†] $P < 0.01$

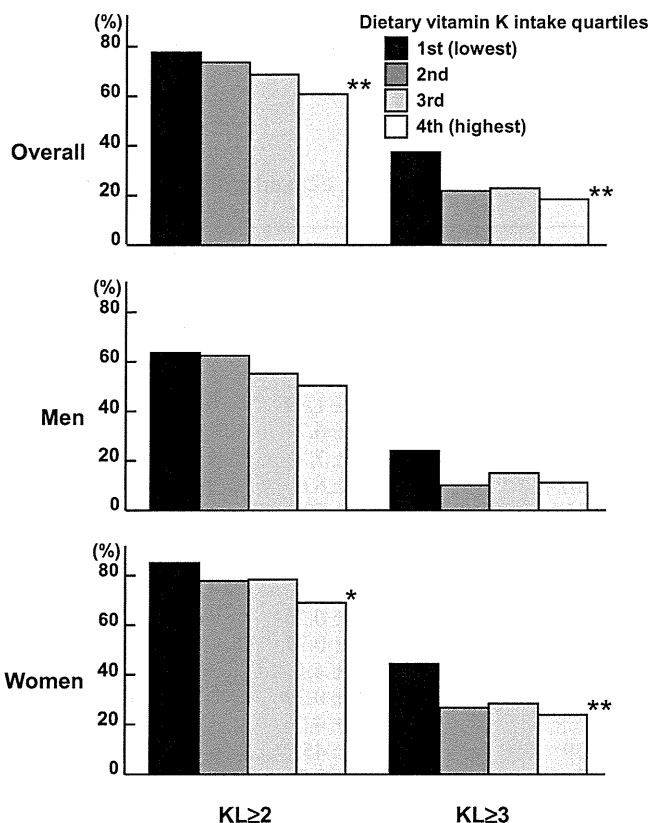


Fig. 1. Prevalence of KL ≥ 2 and KL ≥ 3 knee osteoarthritis per quartile of dietary vitamin K intake. The 25th, 50th, and 75th percentiles were, respectively, 141.4, 205.8, and 285.8 mg/day in the overall population; 145.0, 222.8, and 314.0 mg/day in men; and 137.4, 199.9, and 279.3 mg/day in women. * $P < 0.05$ 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 K₁ or phylloquinone, which is contained in green leafy vegetables, and vitamin K₂ 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 cofactor 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 previous 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.

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 edn. Philadelphia: Lippincott Williams & Wilkins; 2007. p. 3–26.
2. McAlindon TE, Felson DT, Zhang Y, Hannan MT, Aliabadi P, Weissman B, et al. Relation of dietary intake and serum levels of vitamin D to progression of osteoarthritis of the knee among participants in the Framingham Study. *Ann Intern Med* 1996;125: 353–9.
3. McAlindon TE, Jacques P, Zhang Y, Hannan MT, Aliabadi P, Weissman B, et al. Do antioxidant micronutrients protect against the development and progression of knee osteoarthritis? *Arthritis Rheum* 1996;39:648–56.
4. McAlindon TE, Biggee BA. Nutritional factors and osteoarthritis: recent developments. *Curr Opin Rheumatol* 2005;17:647–52.
5. Ameye LG, Chee WS. Osteoarthritis and nutrition: from nutraceuticals to functional foods: a systematic review of the scientific evidence. *Arthritis Res Ther* 2006;8:R127.

6. Neogi T, Booth SL, Zhang YQ, Jacques PF, Terkeltaub R, Aliabadi P, et al. Low vitamin K status is associated with osteoarthritis in the hand and knee. *Arthritis Rheum* 2006;54:1255–61.
7. Felson DT, Niu J, Clancy M, Aliabadi P, Sack B, Guermazi A, et al. Low levels of vitamin D and worsening of knee osteoarthritis: results of two longitudinal studies. *Arthritis Rheum* 2007;56:129–36.
8. Sasaki S, Yanagibori R, Amano K. Self-administered diet history questionnaire developed for health education: a relative validation of the test-version by comparison with 3-day diet record in women. *J Epidemiol* 1998;8:203–15.
9. 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* 2009;68:1401–6.
10. Otsuka R, Tamakoshi K, Yatsuya H, Murata C, Sekiya A, Wada K, et al. Eating fast leads to obesity: findings based on self-administered questionnaires among middle-aged Japanese men and women. *J Epidemiol* 2006;16:117–24.
11. Ichikawa Y, Hiramatsu F, Hamada H, Sakai A, Hara K, Kogirima M, et al. Effect of protein and energy intakes on body composition in non-diabetic maintenance-hemodialysis patients. *J Nutr Sci Vitaminol (Tokyo)* 2007;53:410–8.
12. Murakami K, Mizoue T, Sasaki S, Ohta M, Sato M, Matsushita Y, et al. Dietary intake of folate, other B vitamins, and omega-3 polyunsaturated fatty acids in relation to depressive symptoms in Japanese adults. *Nutrition* 2008;24:140–7.
13. Kellgren JH, Lawrence JS. Radiological assessment of osteoarthritis. *Ann Rheum Dis* 1957;16:494–502.
14. Kellgren JH, Lawrence JS, editors. *The epidemiology of chronic rheumatism: atlas of standard radiographs of arthritis*. Oxford: Blackwell Scientific; 1963.
15. Booth SL, Suttie JW. Dietary intake and adequacy of vitamin K. *J Nutr* 1998;128:785–8.
16. Kaneki M, Hodges SJ, Hosoi T, Fujiwara S, Lyons A, Crean SJ, et al. Japanese fermented soybean food as the major determinant of the large geographic difference in circulating levels of vitamin K2: possible implications for hip-fracture risk. *Nutrition* 2001;17:315–21.
17. Furie B, Bouchard BA, Furie BC. Vitamin K-dependent biosynthesis of gamma-carboxyglutamic acid. *Blood* 1999;93:1798–808.
18. Schneider C, King RM, Philipson L. Genes specifically expressed at growth arrest of mammalian cells. *Cell* 1988;54:787–93.
19. Loeser RF, Varnum BC, Carlson CS, Goldring MB, Liu ET, Sadiev S, et al. Human chondrocyte expression of growth-arrest-specific gene 6 and the tyrosine kinase receptor axl: potential role in autocrine signaling in cartilage. *Arthritis Rheum* 1997;40:1455–65.
20. Melaragno MG, Cavet ME, Yan C, Tai LK, Jin ZG, Haendeler J, et al. Gas6 inhibits apoptosis in vascular smooth muscle: role of Axl kinase and Akt. *J Mol Cell Cardiol* 2004;37:881–7.
21. Stenhoff J, Dahlbäck B, Hafzi S. Vitamin K-dependent Gas6 activates ERK kinase and stimulates growth of cardiac fibroblasts. *Biochem Biophys Res Commun* 2004;319:871–8.
22. Hafzi S, Dahlbäck B. Gas6 and protein S: vitamin K-dependent ligands for the Axl receptor tyrosine kinase subfamily. *FEBS J* 2006;273:5231–44.
23. Stheneur C, Dumontier MF, Guedes C, Fulchignoni-Lataud MC, Tahiri K, Karsenty G, et al. Basic fibroblast growth factor as a selective inducer of matrix Gla protein gene expression in proliferative chondrocytes. *Biochem J* 2003;369(Pt 1):63–70.
24. Luo G, D'Souza R, Hogue D, Karsenty G. The matrix Gla protein gene is a marker of the chondrogenesis cell lineage during mouse development. *J Bone Miner Res* 1995;10:325–34.
25. Munroe PB, Olgunturk RO, Fryns JP, Van Maldergem L, Ziereisen F, Yuksel B, et al. Mutations in the gene encoding the human matrix Gla protein cause Keutel syndrome. *Nat Genet* 1999;21:142–4.
26. Luo G, Ducy P, McKee MD, Pinero GJ, Loyer E, Behringer RR, et al. Spontaneous calcification of arteries and cartilage in mice lacking matrix GLA protein. *Nature* 1997;386:78–81.
27. Pauli RM, Lian JB, Mosher DF, Suttie JW. Association of congenital deficiency of multiple vitamin K-dependent coagulation factors and the phenotype of the warfarin embryopathy: clues to the mechanism of teratogenicity of coumarin derivatives. *Am J Hum Genet* 1987;41:566–83.
28. Howe AM, Lipson AH, de Silva M, Ouvrier R, Webster WS. Severe cervical dysplasia and nasal cartilage calcification following prenatal warfarin exposure. *Am J Med Genet* 1997;71:391–6.
29. Zhang W, Moskowitz RW, Nuki G, Abramson S, Altman RD, Arden N, et al. OARSI recommendations for the management of hip and knee osteoarthritis. Part I. Critical appraisal of existing treatment guidelines and systematic review of current research evidence. *Osteoarthritis Cartilage* 2007;15:981–1000.
30. Simon LS, Strand V. The pharmacologic treatment of osteoarthritis. In: Moskowitz RW, Altman RD, Hochberg MC, Buckwalter JA, Goldberg VM, editors. *Osteoarthritis: diagnosis and medical/surgical management*. 4th edn. Philadelphia: Lippincott Williams & Wilkins; 2007. p. 267–86.

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.

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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 OA²⁰. 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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KL ≥ 2 and KL ≥ 3 knee OA separately with the presence of knee pain according to gender and age stratum.

Subjects and methods

SUBJECTS

The ROAD study is a nationwide OA prospective study constituted of population-based cohorts established in several communities in Japan. To date, we have completed creation of a baseline database including clinical and genetic information of 3,040 inhabitants (1,061 men and 1,979 women) ranging in age from 23–95 years (mean 70.6 years), who were recruited from listings of resident registration in three communities. Itabashi-ku, an urban community located in the east of Tokyo, had a population of 529,400/32 km² with 0.1, 25, and 75% of jobs in the primary industry (agriculture, forestry, fishing and mining), the secondary industry (manufacturing and construction), and the tertiary industry (service industry), respectively, and residents ≥ 65 years constituted 19.1% of the population. Hidakagawa-cho, a rural mountainous community located in the center of Wakayama, had a population of 11,300/330 km² with 29, 24 and 47% of jobs in the three industries above, and 30.5% were ≥ 65 years. Taiji-cho, a rural seacoast community located south of Wakayama, had a population of 3,500/6 km² with 13, 18, and 69% of jobs in the three industries, and those ≥ 65 years accounted for 34.9% of the total. Participants in the urban region were recruited from a cohort study²⁴ in which the participants were randomly drawn from the Itabashi-ward residents register database and the response rate in the age groups of 60 years or older was 75.6%. Participants in the mountainous and seacoast regions were recruited from listings of resident registration and the response rates in the age groups of 60 years or older were 68.4% and 29.3%, respectively. All participants provided written informed consent, and the study was conducted with the approval of ethics committees of the University of Tokyo and the Tokyo Metropolitan Institute of Gerontology. Participants completed an interviewer-administered questionnaire of 400 items that included lifestyle information such as occupational career, smoking habits, alcohol consumption, family history, medical history, physical activity, reproductive variables, and health-related quality of life. Anthropometric measurements included height, weight, arm length, bilateral grip strength and body mass index (BMI; weight [kg]/height² [m²]). Medical information was taken by well-experienced orthopaedic surgeons (S.M. and H.O.) on systemic, local and mental status including information of knee, hip and low back pain, swelling and range of motion of the joints, and patellar and achilles tendon reflex. Knee pain was defined as that in and around the knee joint on most days during the past month. A self-recorded nutritional survey was also performed. Blood and urine samples were collected for biochemical and genetic examinations. Plain radiographs of knee, hip and lumbar spine were taken for all participants. Participants were confirmed to be comparable to the Japanese general population according to the national nutrition survey by the Ministry of Health, Labour and Welfare (Japan). Mean height was 162.5 and 149.7 cm in men and women, respectively, in the ROAD study vs 162.6 and 149.9 cm in the Japanese general population. Weight was 61.3 and 51.8 kg vs 61.6 and 53.8 kg. Percentage of the population with a smoking habit was 26.4 and 3.2% vs 29.4 and 4.0%. From the baseline data of the overall participants, the present study analyzed 2,282 (817 men and 1,465 women) aged 60 years or older, after excluding six subjects with total knee arthroplasty.

RADIOGRAPHIC ASSESSMENT

All participants had radiographic examination of both knees using an anterior–posterior view with weight-bearing and foot map positioning. Fluoroscopic guidance with a horizontal anterior–posterior X-ray beam was used to visualize the joint space properly. Knee radiographs were read without knowledge of participant clinical status by a single well-experienced

orthopaedist (S.M.), and KL grade was defined using the KL radiographic atlas for overall knee radiographic grades¹⁵. The higher KL grade in both knees was designated as that of a participant. The radiographic knee OA with pain was defined as: (1) a subject reporting knee pain lasting at least 1 month with pain having last occurred within the current or previous year; and (2) radiographic OA in that painful knee. To evaluate the 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. One hundred other radiographs were also scored by two experienced orthopaedic surgeons (S.M. & H.O.) using the same atlas for interobserver variability. The intra- and inter variabilities evaluated for KL grade (0–4) were confirmed by the kappa analysis to be sufficient for assessment (0.86 and 0.80, respectively). Further, to determine the prevalence of medial and lateral knee OA, knee radiographs were also read for JSN in the medial and lateral compartment separately according to the Osteoarthritis Research Society International (OARSI) atlas by a single well-experienced orthopaedist (S.M.)²⁵. Medial OA was defined as present when a knee had a KL grade ≥ 2 and medial JSN score of ≥ 1 on a 0–3 scale. Lateral OA was defined as being present when a knee had a KL grade ≥ 2 and lateral JSN score of ≥ 1 on a 0–3 scale.

STATISTICAL ANALYSIS

The differences of age and BMI between men and women were examined by non-paired *t*-test. Differences in age, height, weight and BMI among the urban, mountainous and seacoast communities were determined using one-way analysis of covariance and Scheffe's test. To compare the prevalence of radiographic knee OA between men and women, we performed logistic-regression analysis after adjustment for age and BMI. Association of prevalence with age was determined by logistic-regression analysis after adjustment for BMI. Association of the variables such as age, BMI, gender and community with radiographic knee OA was evaluated by multivariate logistic-regression analysis. Logistic-regression analyses were used to estimate odds ratio and the associated 95% confidence interval (CI) of KL = 2 and KL ≥ 3 knee OA for pain compared with KL = 0 or 1 after adjustment for age, BMI, and community. Data analyses were performed using SAS version 9.0 (SAS Institute Inc., Cary, NC).

Results

The characteristics of the 2,282 participants aged 60 years and older in the three cohorts of the ROAD study are shown in Table I. Men were significantly older than women in the overall population and in some communities. Although the seacoast residents tended to show higher body height and weight than the other two communities, BMI was comparable among the three communities and between genders.

Table II shows the prevalence of radiographic knee OA, knee pain and radiographic knee OA with pain in the overall population and subgroups classified by gender and community. In the overall population, prevalence of KL ≥ 2 and KL ≥ 3 OA was 61.9 and 20.6%, respectively, and that of knee pain was 32.8%. That of KL ≥ 2 and KL ≥ 3 OA with knee pain was 26.1% and 13.2%, respectively. The prevalence of unilateral and bilateral KL ≥ 2 knee OA was 12.3% and 49.5%, respectively, while the prevalence of unilateral and bilateral KL ≥ 2 knee OA with pain was 2.9% and 20.4%, respectively. We next analyzed the prevalence of

Table I
Characteristics of participants

	Men				Women			
	Overall	Urban	Mountainous	Seacoast	Overall	Urban	Mountainous	Seacoast
Number of subjects	817	396	266	155	1,465	740	433	292
Age, years	74.7 \pm 6.1	77.3 \pm 4.1	72.1 \pm 6.2†	72.7 \pm 7.4†	74.0 \pm 6.4*	76.4 \pm 4.8*	72.0 \pm 7.0†	70.9 \pm 6.8*†
Height, cm	161.3 \pm 6.3	161.3 \pm 5.9	160.3 \pm 6.6	163.0 \pm 6.1†	148.6 \pm 6.2	148.6 \pm 5.7	146.8 \pm 6.4†	151.1 \pm 5.9†
Weight, kg	60.1 \pm 9.9	59.8 \pm 8.3	59.3 \pm 11.4	62.2 \pm 10.6†	50.9 \pm 8.9	50.7 \pm 8.4	49.8 \pm 9.7	53.0 \pm 8.6†
BMI, kg/m ²	23.0 \pm 3.3	23.0 \pm 2.7	23.0 \pm 3.8	23.3 \pm 3.3	23.0 \pm 3.7	22.9 \pm 3.5	23.0 \pm 4.1	23.2 \pm 3.5

Data are means \pm SD.

**P* < 0.05 vs men in the corresponding group by non-paired *t*-test.

†*P* < 0.05 vs urban residents in the corresponding group by Scheffe's test.

Table II
Number (percentage) of participants with radiographic knee OA, knee pain, and their combination

	Overall	Men				Women			
		Overall	Urban	Mountainous	Seacoast	Overall	Urban	Mountainous	Seacoast
Radiographic knee OA									
KL ≥ 2	1,413 (61.9)	384 (47.0)	171 (43.2)	154 (57.9)	59 (38.1)	1,029 (70.2)*	521 (70.4)*	340 (78.5)*	168 (57.5)*
KL ≥ 3	470 (20.6)	110 (13.5)	27 (6.8)	45 (16.9)	38 (24.5)	360 (24.6)*	133 (18.0)*	139 (32.1)*	88 (30.1)*
Knee pain									
	748 (32.8)	197 (24.1)	100 (25.3)	76 (28.6)	21 (13.5)	551 (37.6)*	299 (40.4)*	176 (40.6)*	76 (26.0)*
Radiographic knee OA with pain									
KL ≥ 2	595 (26.1)	129 (15.8)	54 (13.6)	60 (22.6)	15 (9.7)	466 (31.8)*	237 (32.0)*	165 (38.1)*	64 (21.9)*
KL ≥ 3	301 (13.2)	63 (7.7)	21 (5.3)	29 (10.9)	13 (8.4)	238 (16.2)*	97 (13.1)*	93 (21.5)*	48 (16.4)*

*P < 0.01 vs men in the corresponding group by logistic-regression analysis after adjustment for age and BMI.

medial and lateral knee OA in the participants and found that they were 20.4 and 2.1% in men and 40.0 and 3.1% in women, respectively. Logistic-regression analysis after adjustment for age and BMI revealed that the prevalence of radiographic knee OA, knee pain, and their combination was significantly higher in women than in men. When the association of the prevalence with the age group (<65, 65–69, 70–74, 75–79 and ≥80) was examined, radiographic knee OA (KL ≥ 2 and KL ≥ 3) tended to increase with age in both genders [Fig. 1(A)]. Interestingly, the prevalence of knee pain was age-dependent in women, but not in men. Hence, that of radiographic OA with pain tended to be higher with age in women, but was affected little by age in men [Fig. 1(B)].

To examine the association of age, BMI, gender, and community with radiographic knee OA, knee pain, and their combination, we further performed logistic-regression analyses to estimate odds ratios and 95% CI (Table III). Age, BMI, and female sex were shown to be risk factors for all of them. Among the communities, mountainous area residents had a higher risk of KL ≥ 2 and KL ≥ 3 knee OA

than urban residents, and seacoast area residents had a higher risk for KL ≥ 3 knee OA than urban residents.

We then evaluated the association between radiographic knee OA and knee pain in the designated knee. Figure 2 shows the percentage of subjects with knee pain in sub-groups classified by radiographic OA severity: KL = 0/1, KL = 2, and KL ≥ 3. Although the percentage with pain was positively correlated with the radiographic severity, the difference between KL = 2 and KL ≥ 3 appeared to be greater than that between KL = 0/1 and KL = 2 in the overall population and all communities. When odds ratios of KL = 2 and KL ≥ 3 OA as compared to KL = 0/1 for the pain were estimated by logistic-regression analysis after adjustment for age, BMI, and community, KL = 2 OA was moderately but significantly associated with knee pain in both genders of the overall population (Table IV). However, KL ≥ 3 OA was much more strongly associated with knee pain not only in both genders of the overall population, but also in those of all age strata. Interestingly, although association of KL = 2 OA with pain was comparable between men and women, that of KL ≥ 3 OA with pain was stronger in

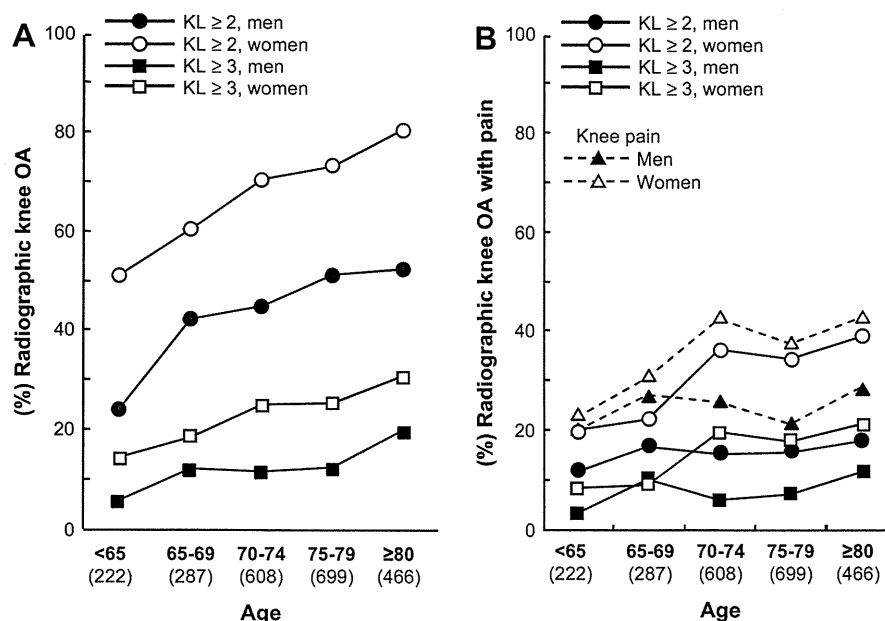


Fig. 1. (A) Percentage of subjects with radiographic knee OA (KL ≥ 2 or KL ≥ 3) in each age stratum (<65, 65–69, 70–74, 75–79 and ≥80). (B) Percentage of subjects with knee pain and radiographic knee OA (KL ≥ 2 or KL ≥ 3) with pain in each age stratum. The number of subjects in each age stratum is shown in parentheses.

Table III
Association of age, BMI, gender, and community with radiographic knee OA, knee pain and their combination

	Radiographic knee OA				Knee pain		Radiographic knee OA with pain			
	KL \geq 2		KL \geq 3		OR	95% CI	KL \geq 2		KL \geq 3	
	OR	95% CI	OR	95% CI			OR	95% CI	OR	95% CI
Age, years	1.09	1.07–1.11*	1.11	1.09–1.13*	1.04	1.02–1.06*	1.07	1.05–1.08*	1.09	1.07–1.12*
BMI, kg/m ²	1.14	1.11–1.18*	1.23	1.19–1.28*	1.18	1.14–1.21*	1.21	1.17–1.25*	1.24	1.20–1.29*
Women (vs Men)	3.28	2.71–3.97*	1.58	1.39–1.79*	2.05	1.68–2.51*	2.83	2.26–3.57*	2.59	1.92–3.53*
Community (vs Urban)										
Mountainous	2.64	2.08–3.35*	3.83	2.92–5.03*	1.27	1.02–1.58*	1.95	1.54–2.47*	2.84	2.09–3.85*
Seacoast	0.95	0.74–1.23	4.13	3.05–5.59*	0.56	0.42–0.73*	0.75	0.55–1.01	1.95	1.35–2.78*

The odds ratios were calculated by logistic-regression analysis after adjustment for all other variables.

* $P < 0.01$ OR = odds ratio, CI = confidential interval.

men. Considering that knee pain is more prevalent in women than in men (Tables II and III), we examined the association of gender with knee pain according to the KL grade. The odds ratio for knee pain of women compared with men estimated by a logistic-regression analysis after adjustment for age and BMI in the subgroup without radiographic knee OA (KL = 0/1) was comparable to or greater than that in those with radiographic knee OA (KL = 2 or KL \geq 3) (Supplementary Table S1), suggesting independent backgrounds of knee pain between genders.

Discussion

The present study initially estimated the prevalence of knee OA in the Japanese elderly (≥ 60 years) using the baseline data of population-based cohorts in the ROAD study. The prevalence of KL ≥ 2 OA, the conventional diagnostic criterion of radiographic OA determined by the anterior–posterior view with standing position, was 47.0% and 70.2% in men and women, respectively (Table II), which was much higher than that of previous epidemiologic studies in elderly Caucasians in the USA and Europe^{4–9}, although not greatly different from African Americans and Chinese^{10–12} (Supplementary Table S1). Caucasians seem to show a lower prevalence of radiographic OA than other races. In fact, the Johnston County study and the NHANES studies showed that African Americans had a higher prevalence of radiographic knee OA than Caucasians^{6,8–10}. A previous Japanese community-based study, although with a rather small sample size, also showed that the prevalence of KL ≥ 2 knee OA of elderly Japanese women living in a seacoast area, Hizen-Oshima, was higher than that of Caucasian women in the Framingham study¹³ (OR = 1.96, 95% CI = 1.50–2.56). Although the prevalence in the present study was higher than that in the Hizen-Oshima study, it was not much different from that of KL ≥ 2 knee OA of women in the seacoast area of the present study (46.4 vs 57.5%, Table II). Knee OA is a major public health issue causing impairment of activities of daily living and the number of patients with knee OA is suggested to be increasing with the advancing age of the population in Japan. According to the National Livelihood Survey of the Ministry of Health, Labour and Welfare in Japan, this disease is now ranked second among the diseases that cause disabilities requiring support with activities of daily living.

In the present study, the prevalence of unilateral and bilateral KL ≥ 2 knee OA was 12.3% and 49.5%, respectively,

while it was 12.5 and 34.1% in the Beijing study and 15.2 and 19.7% in the Framingham study, respectively¹¹. The high prevalence of bilateral OA in this study was comparable to that in the Beijing study, but higher than that in the Framingham study. The high prevalence of bilateral knee OA may indicate that environmental or ethnic factors have an important role in knee OA in Japan and China. Zhang *et al.* described that the higher prevalence of bilateral knee OA in China could be due to the much more physically active lifestyle of the Chinese compared with US whites, especially among those who are elderly¹¹. The higher prevalence of bilateral knee OA in Japan could also be due to lifestyle factors, because the Japanese traditional lifestyle includes sitting on the heels on a mat and using Japanese-style lavatories; these positions may cause mechanical stress to the knee joint and possibly lead to the acceleration of OA^{26,27}. On the other hand, the prevalence of medial and lateral knee OA in the present study was 20.4 and 2.1% in men and 34.0 and 3.1% in women, respectively. The ratio of lateral to medial knee OA was 0.10 and 0.09 in men and women, respectively, while it was 0.13 and 0.20 in the Framingham study and 0.80 and 0.64 in the Beijing study, respectively²⁸. In the present study, the prevalence of lateral knee OA was much lower than that of medial knee OA, which was comparable to that in the Framingham study, but lower than that in the Beijing study. There may be different etiologies of medial and lateral compartment OA in different ethnic populations. Further study is required to elucidate the underlying background of this disease.

Contrary to KL ≥ 2 OA, the prevalence of KL ≥ 3 OA was not much different in men from that in Caucasians, although it was still higher in women^{4,5,7} (Supplementary Table S1). This indicates that the prevalence of KL = 2 knee OA is particularly high in the present study, especially in men. Considering the definition of the KL grade, this may mean that osteophytosis is more prevalent in elderly Japanese men, while JSN is comparable between the two ethnic groups. There is accumulating evidence that osteophytosis and JSN have distinct etiologic mechanisms. A recent cross-sectional study has shown that osteophytosis was unrelated not only to JSN on plain radiographs, but also to cartilage loss measured by quantitative MRI¹⁷. Furthermore, our study on an experimental mouse model for OA has identified a cartilage specific molecule, carminerin, that regulates osteophytosis without affecting joint cartilage destruction during the OA progression^{18,19}. Hence, there may be some risk factors that are specific to osteophytosis in elderly Japanese men.

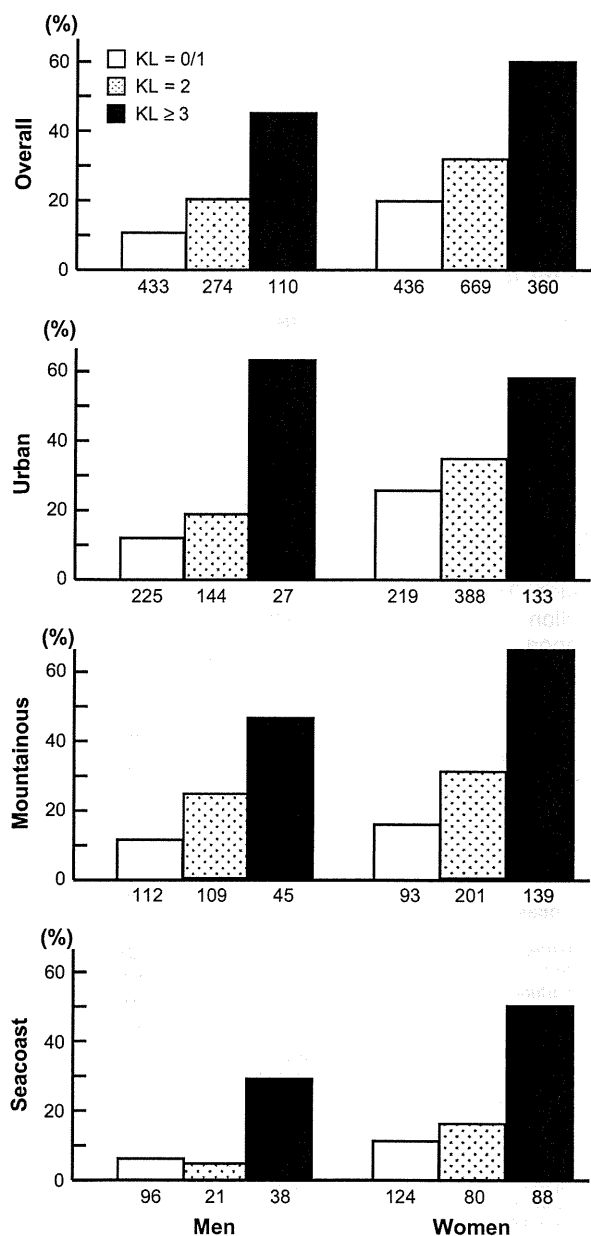


Fig. 2. Percentage of subjects with knee pain in each subgroup classified by the KL grade in the overall population and communities. The number of subjects in each subgroup is shown under the bars.

This study, the first analysis of the baseline data of the ROAD study, found that age and BMI were risk factors of radiographic knee OA (Table III), consistent with previous epidemiologic studies^{1,29,30}. These factors may be related to the accumulation of mechanical stress on the knee joint. Female sex was also shown to be a strong risk factor, as in previous studies⁴⁻⁸, possibly implicating an involvement of muscle strength to compensate the mechanical stress, as women are known to have less muscle strength than men in all decades³¹. Rural residency was also a risk factor of radiographic knee OA even after adjustment for age and BMI, indicating the involvement of other environmental factors like nutrition or occupation as well as genetic factors. In fact, the principle industries in the rural communities were

Table IV
Association of KL grade with knee pain according to age

	<65		65-69		70-74		75-79		≥80	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Men										
KL = 2	1.96	1.27-3.05†	1.31	0.37-4.49	2.51	1.12-5.74	2.87	1.29-6.82*	0.58	0.24-2.11
KL ≥ 3	8.55	5.00-14.84†	7.91	1.72-41.02†	5.44	1.77-17.02	13.49	4.91-39.86†	8.24	2.77-27.02†
Women										
KL = 2	1.55	1.15-2.09†	1.36	0.62-3.06	1.59	0.92-2.79	1.45	0.84-2.58	1.87	0.92-4.04
KL ≥ 3	4.37	3.09-6.21†	3.16	1.18-8.73*	5.60	2.93-10.97†	2.82	1.49-5.43†	7.36	3.25-17.66†

The odds ratio was calculated by logistic-regression analysis compared with subjects with KL grade 0 or 1 after adjustment for age, BMI and communities.
*P < 0.05; †P < 0.01.

farming, forestry and fishing, each of which demands physical activity and repetitive laborious use of the knee joints. Because the database of the ROAD study includes such detailed information of environmental factors including occupational career, lifestyle, and physical activity, as well as genetic information, further analyses will allow us to elucidate the risk factors and backgrounds of knee OA in more detail.

The present study also showed that the odds ratio for knee pain of KL \geq 3 OA was much higher than that of KL = 2 OA in both genders (Table IV), suggesting that JSN was more closely associated with the pain than osteophytosis. On the other hand, approximately 10% of men and 20% of women without radiographic knee OA (KL = 0/1) had knee pain. Although the prevalence of knee pain and radiographic OA with pain was approximately double in women what it was in men (Table II), the association of knee pain with radiographic knee OA, especially with KL \geq 3 OA, was stronger in men (Table IV). Furthermore, the odds ratio for knee pain of women compared with men in the subgroup without radiographic knee OA (KL = 0/1) was comparable to or greater than that in those with radiographic knee OA (Supplementary Table S1). This suggests the existence of a cause of pain that is independent of OA in women, while the pain in men may be more dependent on JSN by OA. Radiographic JSN represents not only joint cartilage destruction, but also meniscal loss or extrusion. In addition, knee pain may arise from a variety of structures other than joint cartilage, like menisci, synovium, ligaments, bursae, bone and the bone marrow^{32–36}. Hence, comprehensive mechanistic studies for the knee pain taking various tissues in and around the knee joint into consideration will be needed to elucidate the relationship between radiographic OA and symptomatic OA.

Although the prevalence of radiographic knee OA increased with age in both genders, that of knee pain was age-dependent only in women (Fig. 1). This might be due to the accumulated mechanical stress to the knee due to the Japanese traditional lifestyle and the decreased muscle strength as described above, both of which women may experience more than men. Alternatively, elderly men generally retire from their occupations around 60 to 70 years, while women must continue to do household chores even after the age of 70.

There are several limitations in this study. First, the radiographic investigators did not have readers calibrate themselves to readings from other studies. Although we reported higher prevalence of radiographic knee OA than in previous studies, radiographic acquisition, scoring techniques and methodology across studies limit strict comparisons between our results and previous reports. Differences across studies in the thresholds used by readers to define osteophytes may have a substantial impact on their prevalence. The high prevalence of knee OA in our study compared to that in other populations may be due to such differences. Second, our analysis did not include patellofemoral joint radiographs, which would likely increase the prevalence of radiographic outcomes and perhaps increase the concordance between radiographic knee OA and its pain. Third, because the KL system emphasizes osteophytosis, it is unclear how to handle knee OA with JSN but no osteophytosis. The investigation of the relationship among knee OA features including JSN and osteophytosis is the next task in the ROAD study.

In conclusion, the present cross-sectional study using a large-scale population from the ROAD study revealed a high prevalence of radiographic knee OA in the Japanese elderly. Knee pain was more strongly associated with

KL \geq 3 OA with JSN than with KL = 2 with osteophytosis, although it was distinctly associated with radiographic OA between genders. Further progress in developing an accurate method for surrogate measurement of the structural severity of knee OA, along with continued longitudinal survey in the ROAD study, will elucidate the environmental and genetic backgrounds of knee OA and its relation to knee pain.

Conflict of interest

There are no conflicts of interest.

Acknowledgements

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Supplementary material

Supplementary material for this article may be found, in the online version, at doi:10.1016/j.joca.2009.04.005.

References

- 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 ed. Philadelphia: Lippincott Williams & Wilkins; 2007:3–26.
- 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.
- 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.
- Kellgren JH, Lawrence JS. Osteo-arthrosis and disk degeneration in an urban population. *Ann Rheum Dis* 1958;17:388–97.
- Felson DT, Naimark A, Anderson J, Kazis L, Castelli W, Meenan RF. The prevalence of knee osteoarthritis in the elderly. The Framingham osteoarthritis study. *Arthritis Rheum* 1987;30:914–8.
- Anderson JJ, Felson DT. Factors associated with osteoarthritis of the knee in the first national Health and Nutrition Examination Survey (HANES I). Evidence for an association with overweight, race, and physical demands of work. *Am J Epidemiol* 1988;128:179–89.
- van Saase JL, van Romunde LK, Cats A, Vandenbroucke JP, Valkenburg HA. Epidemiology of osteoarthritis: Zoetermeer survey. Comparison of radiological osteoarthritis in a Dutch population with that in 10 other populations. *Ann Rheum Dis* 1989;48:271–80.
- Dillon CF, Rasch EK, Gu Q, Hirsch R. Prevalence of knee osteoarthritis in the United States: arthritis data from the third national health and nutrition examination survey 1991–94. *J Rheumatol* 2006;33:2271–9.
- Jordan JM, Helmick CG, Renner JB, Luta G, Dragomir AD, Woodard J, *et al.* Prevalence of knee symptoms and radiographic and symptomatic knee osteoarthritis in African Americans and Caucasians: the Johnston County Osteoarthritis project. *J Rheumatol* 2007;34:172–80.
- Hirsch R, Cheng X, Grigorian M, Stock A, Schaffler G, Zaim S, *et al.* Radiographic knee osteoarthritis prevalence in older adults in the United States (abstract). *Arthritis Rheum* 2001;44(Suppl 9):225.
- Zhang Y, Xu L, Nevitt MC, Aliabadi P, Yu W, Qin M, *et al.* Comparison of the prevalence of knee osteoarthritis between the elderly Chinese population in Beijing and whites in the United States: the Beijing osteoarthritis study. *Arthritis Rheum* 2001;44:2065–71.

12. Du H, Chen SL, Bao CD, Wang XD, Lu Y, Gu YY, *et al.* Prevalence and risk factors of knee osteoarthritis in Huang-Pu District, Shanghai, China. *Rheumatol Int* 2005;25:585–90.
13. Yoshida S, Aoyagi K, Felson DT, Aliabadi P, Shindo H, Takemoto T. Comparison of the prevalence of radiographic osteoarthritis of the knee and hand between Japan and the United States. *J Rheumatol* 2002;29:1454–8.
14. Hart DJ, Spector TD. The relationship of obesity, fat distribution and osteoarthritis in women in the general population: the Chingford Study. *J Rheumatol* 1993;20:331–5.
15. Kellgren JH, Lawrence JS, Eds. *The Epidemiology of Chronic Rheumatism: Atlas of Standard Radiographs of Arthritis*. Oxford: Blackwell Scientific; 1963.
16. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. *Ann Rheum Dis* 1957;16:494–502.
17. Jones G, Ding C, Scott F, Glisson M, Cicuttini F. Early radiographic osteoarthritis is associated with substantial changes in cartilage volume and tibial bone surface area in both males and females. *Osteoarthritis Cartilage* 2004;12:169–74.
18. Yamada T, Kawano H, Koshizuka Y, Fukuda T, Yoshimura K, Kamekura S, *et al.* Carminerin contributes to chondrocyte calcification during endochondral ossification. *Nat Med* 2006;12:665–70.
19. Kamekura S, Kawasaki Y, Hoshi K, Shimoaka T, Chikuda H, Maruyama Z, *et al.* Contribution of runt-related transcription factor 2 to the pathogenesis of osteoarthritis in mice after induction of knee joint instability. *Arthritis Rheum* 2006;54:2462–70.
20. Linaker CH, Walker-Bone K, Palmer K, Cooper C. Frequency and impact of regional musculoskeletal disorders. *Baillieres Clin Rheumatol* 1999;13:197–215.
21. Summers MN, Haley WE, Reveille JD, Alarcon GS. Radiographic assessment and psychologic variables as predictors of pain and functional impairment in osteoarthritis of the knee or hip. *Arthritis Rheum* 1988;31:204–9.
22. 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.
23. 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.
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. Altman RD, Gold GE. Atlas of individual radiographic features in osteoarthritis, revised. *Osteoarthritis Cartilage* 2007;15(Suppl A):A1–A56.
26. Kivimaki J, Riihimaki H, Hanninen K. Knee disorders in carpet and floor layers and painters. *Scand J Work Environ Health* 1992;18:310–6.
27. Cooper C, McAlindon T, Coggon D, Egger P, Dieppe P. Occupational activity and osteoarthritis of the knee. *Ann Rheum Dis* 1994;53:90–3.
28. Felson DT, Nevitt MC, Zhang Y, Aliabadi P, Baumer B, Gale D, *et al.* High prevalence of lateral knee osteoarthritis in Beijing Chinese compared with Framingham caucasian asubjects. *Arthritis Rheum* 2002;46:1217–22.
29. van Saase JL, Vandenbroucke JP, van Romunde LK, Valkenburg HA. Osteoarthritis and obesity in the general population. A relationship calling for an explanation. *J Rheumatol* 1988;15:1152–8.
30. Hartz AJ, Fischer ME, Brill G, Kelber S, Rupley Jr D, Oken B, *et al.* The association of obesity with joint pain and osteoarthritis in the HANES data. *J Chronic Dis* 1986;39:311–9.
31. 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.
32. Saito T, Koshino T. Distribution of neuropeptides in synovium of the knee with osteoarthritis. *Clin Orthop Relat Res* 2000;376:172–82.
33. Bollet AJ. Edema of the bone marrow can cause pain in osteoarthritis and other diseases of bone and joints. *Ann Intern Med* 2001;134:591–3.
34. Teichtahl AJ, Wluka AE, Morris ME, Davis SR, Cicuttini FM. The relationship between the knee adduction moment and knee pain in middle-aged women without radiographic osteoarthritis. *J Rheumatol* 2006;33:1845–8.
35. Thorp LE, Sumner DR, Wimmer MA, Block JA. Relationship between pain and medial knee joint loading in mild radiographic knee osteoarthritis. *Arthritis Rheum* 2007;57:1254–60.
36. Felson DT, Niu J, Guermazi A, Roemer F, Aliabadi P, Clancy M, *et al.* Correlation of the development of knee pain with enlarging bone marrow lesions on magnetic resonance imaging. *Arthritis Rheum* 2007;56:2986–92.

COHORT PROFILE

Cohort Profile: Research on Osteoarthritis/ Osteoporosis Against Disability study

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How did the study come about?

Since the proportion of the ageing population in Japan is increasing, a comprehensive and evidence-based strategy is urgently required for the prevention of musculoskeletal diseases, including osteoarthritis (OA) and osteoporosis (OP), both of which affect the activities of daily living (ADL) and quality of life (QOL) and increase morbidity and mortality.^{1–4} However, few prospective, longitudinal studies for the purpose of developing such a strategy have been conducted, and little information is available regarding the prevalence and incidence of musculoskeletal disorders, including OA and OP, as well as pain and disability in the Japanese population.^{5–10} 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 was established in 2005 by N.Y., T.A., H.O., S.M., H.K. and K.N. (principal investigators). The principal investigators are affiliated with the 22nd Century Medical and Research Center, University of Tokyo.

What does the ROAD study cover?

The ROAD study is a multi-centre prospective observational study that aims to elucidate the environmental and genetic background of bone and joint diseases (with OA and OP as the representative bone and joint diseases). It is designed to examine the extent to which risk factors for these diseases are related to

the clinical features of the diseases, laboratory and radiographic findings, bone mass, bone geometry, life-style, nutritional factors, anthropometric and neuromuscular measures and fall propensity. It also aims to determine how these diseases affect the ADL and QOL of Japanese men and women.

The study will provide the information required to develop clinical algorithms for the early identification of potential high-risk populations. It will also provide information required to develop policies for the detection and prevention of OA, OP and osteoporotic fractures. The immediate goal of this study is to establish a representative population of elderly people, principally for the study of bone and joint health. The establishment of this cohort will also facilitate the expansion of other studies in related areas of investigation. Moreover, the knowledge gained from the ROAD study will have major implications for understanding and managing several other common problems of ageing.

Who are in the sample?

The subjects were residents of any one of the 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 (Figure 1). The inclusion criteria, apart from residence in the communities mentioned above, were the ability to (i) walk to the survey site, (ii) report data and (iii) understand and sign an informed consent form. The age of the participants recruited from the urban region was ≥ 60 years, and that of the participants from the other

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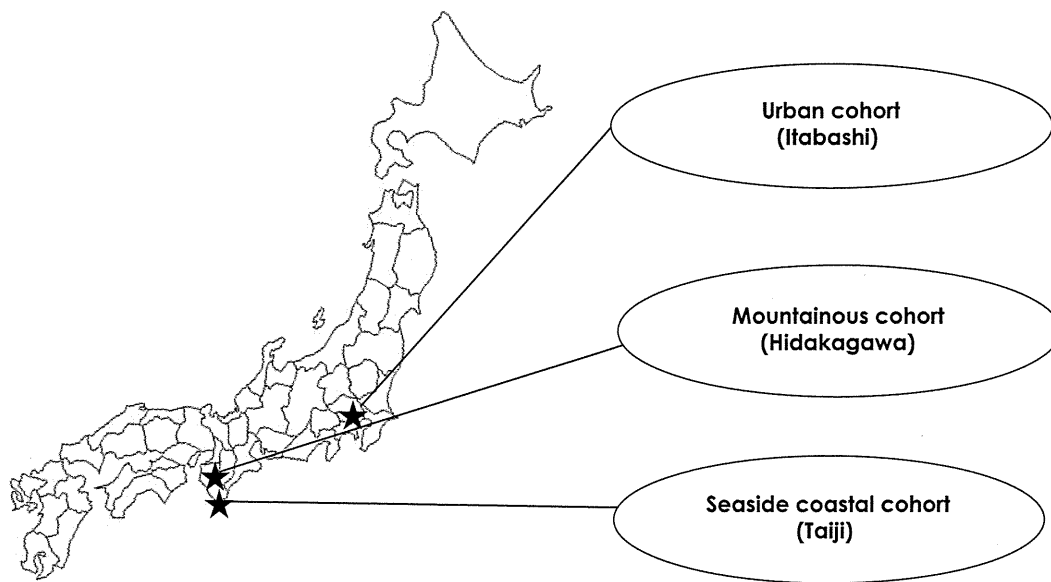


Figure 1 Locations of the three regions from which the study cohort was derived

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

Age strata (years)	Men				Women			
	Total	Urban	Mountainous	Coastal	Total	Urban	Mountainous	Coastal
≤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	1061	465	319	277	1979	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)
Current smoker (%)	25.9	19.0	28.9	31.1	3.5	2.9	4.7	2.9
Current drinker (%)	64.4	60.5	69.8	63.2	25.9	27.4	26.1	24.2

BMI = body mass index.

two regions was ≥40 years. In the urban region, invitation letters were distributed only to the inhabitants whose name was on a list of community-dwelling people that was prepared in 2002.¹¹

Subjects from each area who were willing to attend the study were invited to participate. Despite being younger (58 years) than the age limit defined in the inclusion criteria, 2 inhabitants from the urban area, 9 from the mountainous area and 36 from the coastal area were included in the study because they were very keen to participate. Over the 1.5-year

period from October 2005 to March 2007, 3040 of 5785 candidates were enrolled from the three regions (participation rate, 52.5%).

Selected characteristics of the study population, including age, height, weight, BMI and proportions of participants who smoked and consumed alcohol, are shown in Table 1. 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. No significant differences were observed in BMI values between the genders, but the proportions of both current smokers and alcohol consumers were significantly higher among men than among women.

All participants provided written informed consent, and 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 the participants during the examination and during any other study procedures.

How often have they been followed up?

We intend to follow-up the three population-based cohorts of the ROAD study for at least 10 years. In October 2008, after a follow-up period of 3 years, a second comprehensive clinical examination

was started and is ongoing. We will repeat the baseline measurements during the second examination. A third and fourth examination will be performed at 6 and 10 years, respectively, after the baseline examination.

What has been measured?

The baseline examination of the ROAD study consisted of the following: interviewer-administered questionnaire, dietary assessment, anthropometric measurements, visual and neuromuscular function assessment, biochemical measurements, medical history taking, radiographic assessment and bone mineral density (BMD) measurement (Table 2).

Interviewer-administered questionnaire

A questionnaire was prepared by modifying the questionnaire used in the Osteoporotic Fractures in Men Study (MrOS),¹² and adding some new items to the modified questionnaire. Knee symptoms were

Table 2 Summary of data collected in the ROAD study

Interviewer-administrated questionnaire	
Cigarette smoking, alcohol consumption	
Medical history, medications	
Reproductive variables, lactation	
Dietary history, history of falls and fractures	
Physical activity using PASE	
Family history	
Evaluation of knee symptoms using WOMAC	
Health-related QOL (EQ5D, SF-8)	
Dietary assessment	
Nutrient intake calculated using BDHQ	
Anthropometric measurements	
Height, weight, arm span, grip strengths	
Circumference of both wrists, circumference of waist	
Heart rate, systolic and diastolic blood pressure	
Visual and neuromuscular function	
Visual acuity	
Walking speed with tandem walking 6 m x 20 cm	
Rise from a chair	
Biochemical measurements	
Blood samples	Blood counts, haemoglobin, haemoglobin A1C, blood sugar
Sera	Total protein, AST, ALT, GGT, total cholesterol, HDL-cholesterol, triglyceride BUN, uric acid, creatinine
DNA samples extracted	
Urine samples	Urinary protein, occult blood, sugar, urobilinogen
Medical information	
Pain in back, lumbar, knee and hip	
Swelling and range of motion of the joints	
Tendon reflexes	
Cognitive function used by Mini-Mental Status Examination	
Radiographic assessment	
Anteroposterior and lateral views of lumbar spine	
Anteroposterior view of both knees	
Anteroposterior view of both hips	
BMD measurements	
Lumbar spine and proximal femur (mountainous and coastal areas)	

AST=aspartate aminotransferase; ALT=alanine aminotransferase; GGT= γ -glutamyltranspeptidase; HDL=high-density lipoprotein; BUN=blood urea nitrogen; BDHQ=Brief Diet History Questionnaire; PASE=Physical Activity Scale for the Elderly; WOMAC=Western Ontario and McMaster University Osteoarthritis Index; EQ5D=European QOL-5 dimensions instrument; SF-8=Medical Outcomes Study 8-item Short Form.

evaluated using the WOMAC.¹³ The health-related QOL was evaluated using the EuroQOL, EQ5D¹⁴ and the SF-8.¹⁵ The study staff recorded all the medications administered and their doses. Physical activity was quantified using the PASE.¹⁶

Dietary assessment

Dietary assessment was made using a BDHQ, and the dietary intakes of nutrients during the previous month were determined. Each participant received a questionnaire that included detailed explanations. Well-trained interviewers clarified any unclear sections in the questionnaire, which was to be completed by the participants at their leisure. The BDHQ is a four-page structured questionnaire that includes questions about the frequency of consumption of 80 principal foods. The serving sizes of the foods are described as normal portions, i.e. the standard weight and volume of servings commonly consumed by the general Japanese population. The BDHQ was modified from a comprehensive, 16-page version of a validated self-administered diet history questionnaire.¹⁷ A total of 141 components, including dietary energy and nutrient intakes, were calculated using an *ad hoc* computer algorithm for the BDHQ.

Anthropometric measurements

Anthropometric factors were measured by well-trained medical nurses. The height and weight of the participants at age 25 years were also noted. BMI [weight in kilograms/(height in metres)²] was calculated on the basis of the current height and weight.

Visual and neuromuscular function

Visual acuity was assessed by the Landolt ring test. Walking speed was determined by recording the time taken by a subject to walk 6 m at the fastest possible speed. The time required for tandem walking across a 6-m long and 20-cm wide path was used to determine balance. The ability to rise from a chair without using the arms (chair stand) and the ability to perform five chair stands was evaluated; the time required to complete the tasks was noted.

Biochemical measurements

Blood and urine samples were obtained from each participant for biochemical and genomic examinations. Urinary protein, occult blood, sugar and urobilinogen were tested using disposable reagent strips (uro-hema-combi sticks; Siemens Medical Solutions Diagnostics, Tokyo, Japan). Residual blood, plasma, serum and urine specimens were processed and stored in a deep freezer (−80°C). DNA was extracted from stored whole-blood specimens, and biochemical markers of bone turnover and cartilage will be measured using these stored serum and urine samples.

Medical history

Medical history was obtained by experienced orthopaedic surgeons (S.M. and H.O.). To quantify cognitive function, the participants were instructed to complete the modified Mini-Mental Status Examination—Japanese version.¹⁸ Physicians explained any unclear sections of this questionnaire to the participants and assessed the participants' cognitive status on the basis of the completed questionnaire.

Radiographic assessment

The severity of OA was radiographically determined according to the Kellgren–Lawrence (KL) grading system as follows¹⁹: KL0—normal joint; KL1—slight osteophytes; KL2—definite osteophytes; KL3—disc-space narrowing and large osteophytes; and KL4—bone sclerosis, disc-space narrowing and large osteophytes. In the ROAD study, joints that exhibited only disc-space narrowing and no large osteophytes were graded as KL3. The radiographs were examined by a single, experienced orthopaedic surgeon (S.M.), who was blinded to the clinical status of the participants. If at least one knee joint was graded as KL2 or higher, the participant was diagnosed with radiographic knee OA. Similarly, if at least one intervertebral joint of the lumbar spine was graded as KL2 or higher, the participant was diagnosed with radiographic lumbar spondylosis.

BMD measurement

In the mountainous and coastal areas, the BMD of the lumbar spine and proximal femur was measured using dual energy X-ray absorptiometry (DXA) (Hologic Discovery; Hologic, Waltham, MA, USA) during the baseline examination. Another BMD measurement was scheduled for the second examination.

To maintain the quality of measurement, the same DXA equipment was used, and the same spine phantom was scanned daily to monitor the machine's performance in study populations from different regions. The BMD of the phantom was adjusted to $1.032 \pm 0.016 \text{ g/cm}^2$ ($\pm 1.5\%$) during all examinations. In addition, to exclude inter-observer variability, the same physician (N.Y.) examined all participants. In another study, N.Y. had measured the intra-observer variability in both *in vitro* and *in vivo* experiments using Lunar DPX.²⁰ In the case of the *in vitro* experiment, the coefficient of variance (CV) for the BMD of the L2–L4 vertebrae was 0.35%. In the case of the *in vivo* experiments, which were performed on five male volunteers, the CVs for the BMDs of the L2–L4 vertebrae, the proximal femur, Ward's triangle and the trochanter were 0.61–0.90, 1.02–2.57, 1.97–5.45 and 1.77–4.17%, respectively.

OP was defined on the basis of the World Health Organization (WHO) criteria; specifically, it was diagnosed when the BMD T-scores were lower than the mean lumbar peak bone mass minus 2.5 SDs.²¹

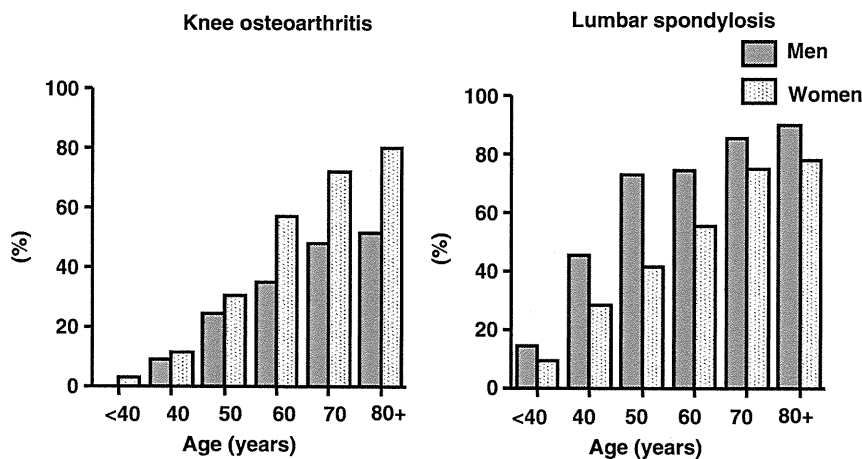


Figure 2 Prevalence of radiographic knee osteoarthritis and lumbar spondylosis, classified by age and gender

In Japan, the mean BMD of the L2–L4 vertebrae among both young male and female adults has been measured using Hologic DXA.²² These indices were used in the present study; lumbar spine BMD $<0.714 \text{ g/cm}^2$ (in case of both men and women), and femoral neck BMD $<0.546 \text{ g/cm}^2$ (men) or 0.515 g/cm^2 (women) were considered to indicate OP.

All assessments performed in the baseline study will be repeated at the first, second and third follow-ups.

What is attrition like?

The first follow-up (second examination) commenced on October 2008, 3 years from baseline assessment. By the end of 2008, follow-up was completed in Hidakagawa, the mountainous region. Of the 864 participants (319 men and 545 women) in the baseline study, 635 subjects (224 men and 411 women) attended the second examination. The response rate for the second examination in the mountainous area was 73.5%. The most common reasons for non-participation were illness and difficulty in visiting the clinic (43% of the dropouts). Further, 26 people (12% of the dropouts) who participated in the baseline study died during the 3-year period following the initial assessment. In other two areas, the follow-ups are on going. The total attrition will be determined at the end of March 2010.

What has the ROAD study found?

By analysing the data from the baseline study, we have determined the prevalence of OA and OP.

OA

The age–sex distribution of radiographic knee OA and lumbar spondylosis was calculated (Figure 2); both conditions were diagnosed at KL grades of ≥ 2 .

In the overall population, the prevalence of radiographic knee OA and lumbar spondylosis 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. Thus, both the overall and sex-specific prevalence of lumbar spondylosis were higher than those of knee OA.²³

OP

The prevalence of OP was calculated for the participants from mountainous and coastal regions in the ROAD study (Figure 3). The prevalence of OP of the lumbar spine and femoral neck in women was 6- and 5-fold, respectively, than in men. The differences were significant ($P < 0.001$).²³

What are the main strengths and weaknesses of the ROAD study?

Strengths

In Japan, little epidemiological information is available of musculoskeletal diseases such as OA and OP. The ROAD study is the first large population-based prospective study conducted on the Japanese population and is designed to supply essential information, chiefly of OA and OP.

We confirmed the high prevalence of OA and OP among the ROAD study participants, and we will conduct follow-up examinations for at least 10 years in order to clarify the relationships of OA, OP and osteoporotic fractures with the following parameters: lifestyle, anthropometric and neuromuscular measurements, bone mass, bone geometry and fall propensity. Further, we will determine how these impairments affect QOL and mortality. We also expect to assess the similarities and differences in the risk factors of OA and OP. In addition, we will clarify the incident morbidity of other lifestyle-related disorders,

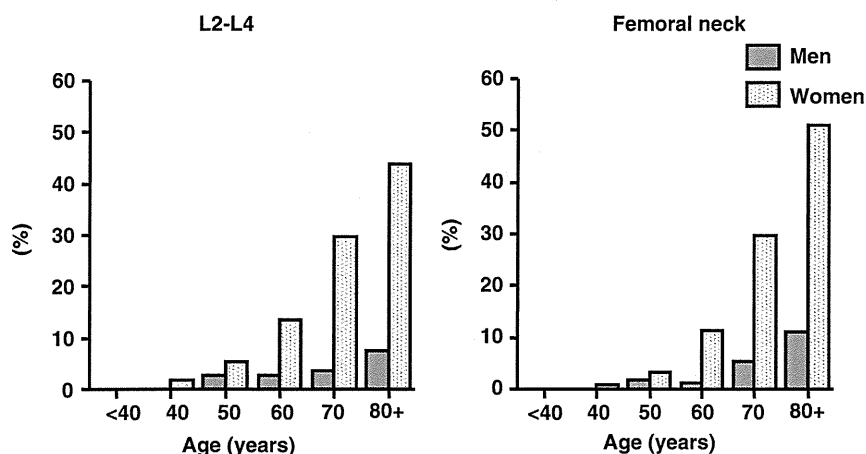


Figure 3 Prevalence of osteoporosis of the lumbar spine and femoral neck

such as obesity, hypertension, diabetes mellitus, cardiovascular and metabolic diseases and dementia.

The ROAD study data will facilitate the development of clinical guidelines for the detection and prevention of osteoporotic fractures in other countries. This study was designed such that it would be similar to the Study of Osteoporotic Fractures, a large observational study on the determinants of fractures in older women,²⁴ and to MrOS, a large observational study on the determinants of fractures in older men²⁵ in the USA.

Finally, the completion of the ROAD study will provide unique opportunities for the study of other conditions that are common among older men and women, such as obesity, diabetes, cardiovascular disease, cognitive disorders and frailty. The blood, plasma, serum and urine specimens stored during the ROAD study will enable the clarification of a variety of new biochemical and genetic factors associated with musculoskeletal disorders and the aforementioned diseases.

Weaknesses

Although the ROAD study includes a large number of subjects (more than 3000), these subjects are voluntary participants and have been recruited from only three areas; hence, they do not truly represent the general population. The 'healthy' and 'regional' selection biases should be confirmed.²⁶ We could not directly compare the baseline characteristics between the responders and non-responders owing to lack of data regarding the non-responders. Hence, to determine whether a selection bias existed in the ROAD study, we compared the anthropometric measurements and frequencies of smoking and alcohol drinking between the participants and the general Japanese population. The values for the general population were obtained from the 2005 National Health and Nutrition Survey conducted by the Ministry of Health, Labour and Welfare, Japan, which is an annual survey to clarify the health status of the Japanese population and is

conducted on approximately 18 000 inhabitants from 6000 randomly selected families.²⁷

The BMIs of ROAD study participants and the Japanese population were compared (Table 3). No significant differences were identified, except that the male participants aged 70–74 years were significantly smaller in build than men of this age group in the overall Japanese population ($P < 0.05$).

The proportion of current smokers and current drinkers (those who regularly smoked or drank more than once a month) in the general Japanese population was compared with that in the study population (Figure 4). Both proportions were significantly higher in the general Japanese population than in the study population (smokers: men, $P < 0.001$ and women, $P < 0.001$; drinkers: men, $P < 0.01$ and women, $P < 0.001$), suggesting that participants of the ROAD study had healthier lifestyles than the general Japanese population. This bias due to the selection of 'healthy' individuals should be taken into consideration while generalizing the results of the ROAD study.

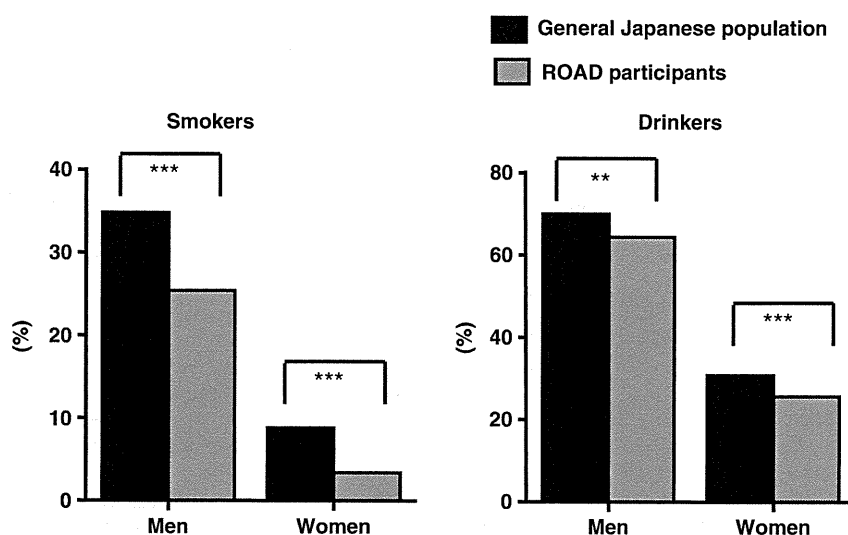
Further, BMD was measured only in the participants from the mountainous and coastal areas. The total number of participants from these two areas (1690) may be large enough to accurately estimate the incidence and evaluate risk factors. Nevertheless, regional bias should be taken into account while generalizing the results.

Can I get hold of the data? Where can I find out more?

The ROAD study group welcomes specific and detailed proposals for new collaborations. Initial enquiries should be addressed to N.Y. Some information about the ROAD study is available on the website of the Department of Joint Disease Research, 22nd Century Medical and Research Centre,

Table 3 Comparison of BMI (SD) (kg/m²) of the participants with general Japanese population

Age strata (years)	Men		Women	
	ROAD	Japanese	ROAD	Japanese
40–49	24.5 (4.4)	24.0 (3.3)	21.9 (4.1)	22.4 (3.5)
50–59	23.6 (2.9)	23.7 (3.1)	23.0 (3.3)	23.1 (3.4)
60–69	23.8 (3.2)	23.8 (2.9)	23.3 (3.2)	23.5 (3.7)
70–74	23.1 (2.8)	23.7 (3.2)	23.4 (3.5)	23.2 (3.4)
75–79	22.8(2.9)	23.3 (3.0)	23.0 (3.7)	23.4 (3.5)
≥80	22.6 (2.9)	22.3 (2.6)	22.2 (3.2)	22.5 (4.0)

**Figure 4** Comparison of the proportion of current smokers and drinkers between the participants of the ROAD study and the general Japanese population. ** $P < 0.01$, *** $P < 0.001$

University of Tokyo Hospital (<http://www.h.u-tokyo.ac.jp/center22/kansetu.html>).

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References

- Ministry of Health, Labour and Welfare. Outline of the results of National Livelihood Survey 2004. http://www.mhlw.go.jp/toukei/saikin/hw/k-tyosa/k-tyosa_04/4-2.html (5 August 2009, date last accessed).
- Yamamoto I. Estimation for the number of patients of Osteoporosis in Japan. *Osteoporosis Jpn* 1999;7:10–11 (in Japanese).
- Muraki S, Yamamoto S, Ishibashi H, Nakamura K. Factors associated with mortality following hip fracture in Japan. *J Bone Miner Metab* 2006;24:100–4.
- Jornell O, Kanis JA, Oden A *et al.* Mortality after osteoporotic fractures. *Osteoporosis Int* 2004;15:38–42.
- Yoshimura N, Dennison E, Wilman C, Hashimoto T, Cooper C. Epidemiology of chronic disc degeneration and osteoarthritis of the lumbar spine in Britain