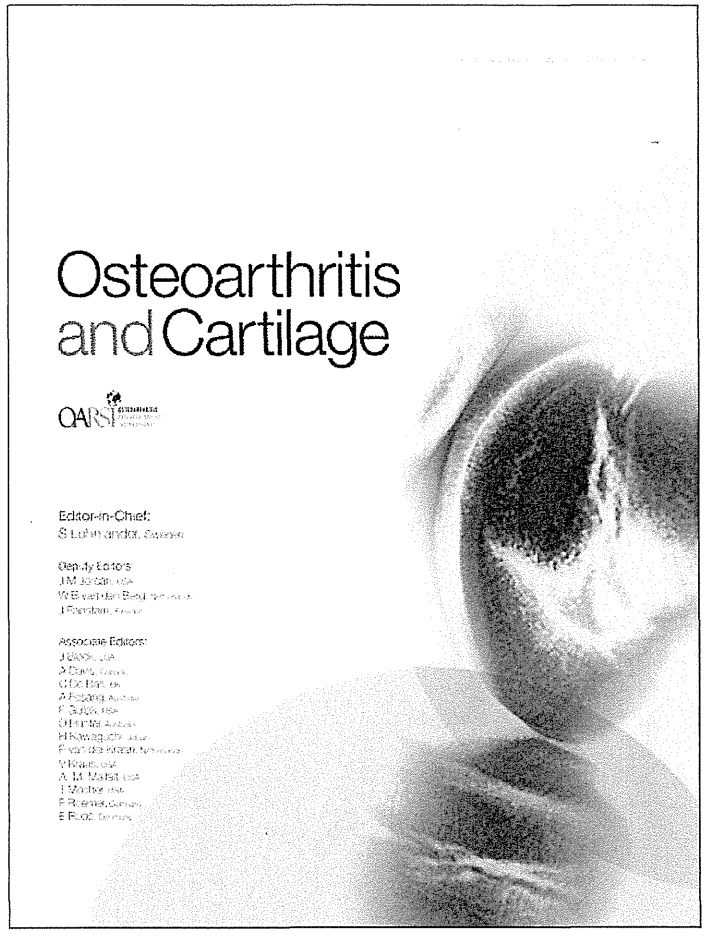

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Incidence and risk factors for radiographic lumbar spondylosis and lower back pain in japanese men and women: the ROAD study

S. Muraki †*, T. Akune †, H. Oka ‡, Y. Ishimoto §, K. Nagata §, M. Yoshida §, F. Tokimura ||, K. Nakamura ¶, H. Kawaguchi #, N. Yoshimura ‡

† *Department of Clinical Motor System Medicine, 22nd Century Medical & Research Center, Faculty of Medicine, the University of Tokyo, Tokyo, Japan*
‡ *Department of Joint Disease Research, 22nd Century Medical & Research Center, Faculty of Medicine, the University of Tokyo, Tokyo, Japan*
§ *Department of Orthopaedic Surgery, Wakayama Medical University, Wakayama, Japan*
|| *Department of Orthopaedic Surgery, Tokyo Geriatric Medical Center, Tokyo, Japan*
¶ *Rehabilitation Services Bureau, National Rehabilitation Center for Persons with Disabilities, Saitama, Japan*
# *Department of Sensory & Motor System Medicine, Faculty of Medicine, the University of Tokyo, Tokyo, Japan*

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SUMMARY

Objective: To determine the incidence of radiographic lumbar spondylosis (LS)and lower back pain, and their risk factors in Japan using a large-scale population from the nationwide cohort Research on Osteoarthritis/osteoporosis Against Disability (ROAD) Study.
Methods: Participants in the ROAD study who had been recruited between 2005 and 2007 were followed up with lumbar spine radiography for 3 years. A total of 2,282 paired radiographs (75% of the original sample) were scored using Kellgren and Lawrence (KL) grades, and the incidence and progression rate of radiographic LS was analyzed. The incidence of lower back pain was also examined. In addition, associations between risk factors and incident and progressive radiographic LS as well as incident lower back pain were tested.
Results: Given a 3.3-year follow-up, the incidence of KL $\geq$ 2 radiographic LS was 50.0% and 34.4% (15.3% and 10.5% per year), while that of KL $\geq$ 3 LS was 15.3% and 23.7% (4.6% and 7.2% per year) in men and women, respectively. The progression rate of LS was 20.5% and 27.4% (6.2% and 8.3% per year) in men and in women, respectively. In addition, the incidence of lower back pain was 28.3% and 31.2% (8.6% and 9.5% per year) in men and women. Lower back pain was not significantly associated with incident radiographic LS, while a more severe KL grade at baseline was associated with incident lower back pain.
Conclusion: The present longitudinal study revealed a high incidence of radiographic LS in Japan.

Introduction

Lumbar spondylosis (LS) and lower back pain are considered a major public health issue causing chronic disability of the elderly in most developed countries[1,2,3–8]. The prevalence of radiographic LS is high in Japan[3], with an estimated 37,900,000 individuals aged $\geq$40 years being affected by radiographic LS[9]. According to the recent National Livelihood Survey of the Ministry of Health, Labour and Welfare in Japan, lower back pain is rated first among symptoms that send men to the hospital[10]. Despite the urgent need for strategies to prevent and treat this condition, several cross sectional studies have investigated the prevalence of radiographic LS[3,9,11–16], but only a few have examined the incidence and progression of radiographic LS or their risk factors[17–21]. In addition, although lower back pain is believed to be the principal clinical symptom of LS, the correlation is not as close as would be expected, and the findings of cross sectional studies have often indicated a disconnect between them[3,11]. However, the incidences of radiographic LS and lower back pain have never been simultaneously analyzed in a longitudinal study.

The objective of the present study was to clarify the incidence and progression rate of radiographic LS as well as the incidence rate of lower back pain in Japanese men and women using the large-scale, population-based cohort study known as Research on Osteoarthritis/osteoporosis Against Disability (ROAD). In addition, we examined risk factors for the incidence and progression of LS as well as the incidence of lower back pain.

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

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Subjects and methods

Subjects

The ROAD study was a nationwide prospective study of bone and joint diseases (with osteoarthritis and osteoporosis as representative bone and joint diseases) in population-based cohorts established in several communities in Japan. A detailed profile of the ROAD study has already been described elsewhere[3,10,22,23], and thus a brief summary is provided here. Between 2005 and 2007, we created a baseline database that included clinical and genetic information about 3,040 inhabitants (1,061 men; 1,979 women) in the age range of 23–95 years (mean, 70.6 years), recruited from listings of resident registrations in three communities: an urban region in Itabashi, Tokyo; a mountainous region in Hidakagawa, Wakayama; and a coastal region in Taiji, Wakayama. All participants provided written informed consent, and the study proceeded 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 smoking habits, alcohol consumption, family history, and medical history. Anthropometric measurements included height and weight, from which the body mass index (BMI) (weight [kg]/height^2 [m^2]) was calculated. . Experienced orthopaedists also asked all participants the question regarding lower back pain: "Have you experienced lower back pain on most days during the past month, in addition to now?" Those who answered "yes" were defined as having lower back pain based on previous studies[3].

Between 2008 and 2010, we attempted to trace and review all 3,040 participants by inviting them to attend a follow-up interview and undergo repeat radiography. The interviews included questions about current lower back pain and were conducted by the same trained orthopaedists who undertook the baseline study between 2005 and 2007. Anthropometric data including height and weight, were also obtained at follow-up.

Radiographic assessment

Plain radiographs of the lumbar spine at baseline and follow-up were taken in anteroposterior and lateral positions, and the images were downloaded into Digital Imaging and Communication in Medicine (DICOM) files to assess radiographic spondylosis. We used contrast-adjusted images to detect osteophytes and intervertebral spaces when the original images were obscure. Osteophytes were analyzed at endplates. LS at baseline and follow-up was read in pairs according to the Kellgren and Lawrence (KL) grading[24] (without blinding to baseline and follow-up status) at each intervertebral level from L1/2 to L5/S by a single experienced orthopaedist (S.M.), who was blinded to the background of each patient. The KL scale defines radiographic OA in 5 categories: KL grade 0, no radiographic features of OA; KL grade 1, minimal osteophytosis only; KL grade 2, definite osteophytosis with some sclerosis of the anterior part of the vertebral plate; KL grade 3, marked osteophytosis and sclerosis of the vertebral plates with slight narrowing of the disc space; and KL grade 4, large osteophytes, marked sclerosis of the vertebral plates, and marked narrowing of the disc space. To evaluate the intraobserver variability of the KL grading, 100 randomly selected radiographs of the lumbar spine were scored by the same observer more than 1 month after the first reading. Furthermore, 100 other radiographs were scored by two experienced orthopaedic surgeons (S.M. and H.O.) using the same radiographic atlas to determine interobserver variability. Intra- and interobserver variability was evaluated by kappa analysis. These variabilities in the KL grading on lumbar radiographs were sufficient for assessment (0.84 and 0.76, respectively).

For the purposes of this study, we defined three LS outcomes. Incident KL ≥ 2 radiographic LS was defined if all vertebral interspaces had less than grade 2 disease at baseline, and if at least one vertebral interspace had grade ≥ 2 disease at follow-up. Incident KL ≥ 3 radiographic LS was defined if all vertebral interspaces had less than grade 3 disease at baseline, and if at least one vertebral interspace had $\geq$ grade 3 disease at follow-up. Progressive LS was defined as KL ≥ 2 LS at baseline, excluding subjects with KL $= 4$ LS at all vertebral interspaces because it cannot progress, and an increase of at least one grade in the affected vertebral interspace at follow-up.

Statistical analysis

Differences in age, height, weight, and BMI between men and women were examined using a non-paired Student's *t*-test. The prevalence of radiographic LS and lower back pain between men and women was compared the chi-squared test. We determined risk factors for incident and progressive LS and incident lower back pain using a univariate logistic regression analysis. Independent risk factors were determined by multiple logistic regression analysis with significant risk factors in a univariate logistic regression analysis with age, gender and BMI, as independent variables. Incident lower back pain was defined as no lower back pain at baseline and lower back pain at follow-up. Associations between the number of affected vertebral interspaces and incident lower back pain were assessed using the Cochran-Armitage test for trends. The odds ratio (OR) and 95% confidence interval (CI) of the number of affected vertebral interspaces with incident lower back pain compared with no affected vertebral interspaces was determined using a logistic regression analysis with adjustment for age and BMI. Data were analyzed using SAS version 9.0 software (SAS Institute Inc., Cary, NC).

Results

Of the 3,040 participants in the baseline study between 2005 and 2007, 125 (4.1%) had died by the time of the review 3 years later, 123 (4.0%) did not participate in the follow-up study due to bad health, 69 (2.3%) had moved, 83 (2.7%) declined the invitation to attend the follow-up study and 155 (5.1%) did not participate for other reasons. Among the 2,485 individuals who participated in the follow-up study, we excluded 186 (6.1%) who did not undergo plain radiography and 17 (0.6%) who provided incomplete pain questionnaires, leaving a total of 2,282 (74.4%; 758 men; 1,524 women) from whom paired radiographs and complete pain histories were obtained. Their median age at follow-up was 72.1 ± 11.5 years. The duration of follow-up between the initial and second radiographs was 3.3 ± 0.6 (mean $\pm$ SD) years. Those participating in the follow-up study were younger than those who did not survive or who did not participate for other reasons (responders 68.8 years, nonresponders 74.8 years; $P < 0.0001$). The follow-up study participants were also more likely to be women (responders 66.8% women, nonresponders 60.0% women; $P = 0.0007$) and were less likely to have LS at the baseline examination than either those who did not survive to follow-up or those who did not participate for other reasons (responders 68.1%, nonresponders 77.5%; $P < 0.0001$). The prevalence of lower back pain was similar between responders and nonresponders (responders 19.0%, nonresponders 18.7%; $P = 0.91$).

Table I shows the characteristics of the 2,282 participants at baseline in the ROAD study. Men were significantly older than women, and the BMI was higher in men than women. The prevalence of KL ≥ 2 LS was significantly higher in men than women at

Table I
Characteristics of participants at baseline

	Men	Women	*P*-values
Number of subjects	758	1,524	
Age at baseline, years	69.8 ± 11.0	68.3 ± 11.3	0.003
Height at baseline, cm	163.0 ± 6.6	150.4 ± 6.4	<0.0001
Weight at baseline, kg	62.0 ± 9.7	52.1 ± 8.6	<0.0001
BMI at baseline, kg/m^2	23.3 ± 3.0	23.0 ± 3.4	0.054
Grip strength at baseline, kg	34.3 ± 8.7	22.2 ± 6.1	<0.0001
Prevalence at baseline			
KL ≥ 2 (%)	79.9	62.3	<0.0001
KL ≥ 3 (%)	43.1	44.6	0.531
Lower back pain (%)	16.9	20.0	0.073
Smoking (%)	21.5	3.2	<0.0001
Alcohol (%)	63.2	23.0†	<0.0001

Except where indicated otherwise, values represent mean ± SD.
*$P < 0.05$ vs. men by non-paired Student's *t*-test; †$P < 0.05$ vs men by chi squared test.

baseline, while that of KL ≥ 3 LS and lower back pain was similar between men and women.

Table II shows the rates of incident and progressive radiographic LS as well as that of incident lower back pain. Given the 3.3-year follow-up, the rates of incident KL ≥ 2 and ≥3 LS and progressive LS, and incident lower back pain were 38%, 21%, 25%, and 30%, respectively. The incidence of KL ≥ 2 LS was significantly lower, but that of KL ≥ 3 LS was significantly higher in women than in men. The rate of progressive LS was also significantly higher in women than men. The rate of incident and progressive LS increased with age in men and women ($P < 0.05$) (Fig. 1). The rate of incident lower back pain was not age-dependent in either men or women ($P = 0.44$ and 0.85, respectively) (Fig. 1). We also showed incidence and progression of LS at each vertebral interspace in Supplementary Table. Among the vertebral interspaces, the incident rate of KL ≥ 2 LS was highest at the L2/3 interspace. While, the incident rate of KL ≥ 3 LS was highest at the L4/5 interspace.

Table III shows baseline risk factors for radiographic LS. Multiple logistic regression analysis showed that age was a risk factor for KL ≥ 2 and KL ≥ 3 LS and that higher BMI was a risk factor for KL ≥ 2, but not for KL ≥ 3. Female gender was a protective factor against the incidence of KL ≥ 2 LS but was a risk factor for the incidence of KL ≥ 3 LS. A higher KL grade at baseline was a risk factor for KL ≥ 3 LS. Lower back pain at baseline, smoking and alcohol consumption were not associated with incident KL ≥ 2 or KL ≥ 3 LS. We further examined the risk factors for progressive LS in individuals with KL ≥ 2 LS, excluding those with KL = 4 LS at all vertebral interspaces (Table IV). Age and female gender were also risk factors for progressive LS, whereas BMI, lower back pain at baseline, smoking and alcohol consumption were not associated with progressive LS. A grade of KL ≥ 3 at baseline was a risk factor for progressive LS compared with KL = 2.

We next examined the risk factors for incident lower back pain (Table IV). KL ≥ 3 LS was associated with incident lower back pain compared with KL = 0 or 1, whereas age, BMI, gender, smoking and alcohol consumption were not associated with incident lower back pain. We next examined the association between KL grade at each vertebral interspace and incident lower back pain (Table V). In women, KL ≥ 3 LS at L2/3, 3/4, 4/5, and 5/S and the most severely affected interspaces were significantly associated with incident lower back pain compared with KL < 3 at the corresponding interspaces. KL ≥ 3 LS at L2/3, 3/4, 4/5 and 5/S in men tended to be associated with incident lower back pain compared with KL < 3 at the corresponding interspaces, but these findings did not reach statistical significance except for the L3/4 and L5/S interspaces. KL ≥ 3 LS at the L1/2 interspace was not associated with incident lower back pain in men or women. Thus, we further examined the number of KL ≥ 3 vertebral interspaces among L2/3, 3/4, 4/5 and 5/S interspaces (Supplementary Fig. 1). The Cochran-Armitage test for trends showed that the incidence rate of lower back pain significantly increased as the number of affected vertebral interspaces increased in women ($P < 0.001$), but not in men ($P = 0.09$). In addition, multiple logistic regression analysis after adjustment for age and BMI showed that having three or more KL ≥ 3 vertebral interspaces was significantly associated with incident lower back pain in men (OR 1.69 95% CI 1.03–2.76) and in women (OR 1.77, 95% CI 1.34–2.34).

Discussion

This is the first population-based study to examine the rates of incident and progressive radiographic LS as well as incident lower back pain, and their risk factors in Japanese men and women. We found high rates of incident and progressive LS and incident lower back pain in Japanese men and women.

Few population-based studies have examined incident radiographic LS [17,18]. Symmons *et al.* examined radiographic changes in the lumbar spines of Dutch women (mean age, 54 years) using KL grade[17] and found that 4.2% per year of individuals with no disc degeneration (KL grade 0/1) but with recurrent back pain, and 3.2% per year of those with no disc degeneration and no back pain at baseline, had disc degeneration at follow-up. The present study found a 27.6% incidence rate of KL ≥ 2 LS in women aged in their 50s over a period of 3.3 years (9.0% per year), and thus the incidence of KL ≥ 2 LS is apparently considerably higher in Japanese than Caucasian women, although a strict comparison may be limited because of differences in definition of the incidence of LS. Considering the definition of the KL grade, this may suggests that the incidence of osteophytosis is higher in Japanese women than in Caucasian women.

Regarding progression of radiographic LS, Symmons *et al.* reported that 63.1% (7.0% per year) of individuals with disc degeneration and with recurrent back pain, and 55.4% (6.2% per year) of those with disc degeneration but without back pain at baseline, had worse disc degeneration at follow-up[17]. The present

Table II
Incidence of radiographic LS and progressive LS as well as incidence of lower back pain

	KL ≥ 2 LS		KL ≥ 3 LS		Progressive LS		Lower back pain	
	No. at risk	Incidence (%)	No. at risk	Incidence (%)	No. at risk	Incidence (%)	No. at risk	Incidence (%)
Overall	727	274 (37.7)	1,276	266 (20.8)	1,530	378 (24.7)	1,849	558 (30.2)
Men	152	76 (50.0)	431	66 (15.3)	599	123 (20.5)	630	178 (28.3)
Women	575	198 (34.4)*	845	200 (23.7)*	931	255 (27.4)*	1,219	380 (31.2)

Incident KL ≥ 2 and ≥3 radiographic LS at the overall vertebral interspace was defined as all vertebral interspaces having less than grade 2 or 3 disease at baseline, and if at least one vertebral interspace was grade 2 or higher or grade 3 or higher at follow-up, respectively.
Progressive LS in the overall inter spaces was defined as KL ≥ 2 LS at baseline, excluding subjects with KL = 4 LS at all vertebral interspaces because it cannot progress, and an increase by at least 1 grade in the affected vertebral interspace at follow-up.
Incident lower back pain was defined as no lower back pain at baseline and lower back pain at follow-up.
*$P < 0.05$ vs men by chi square test.

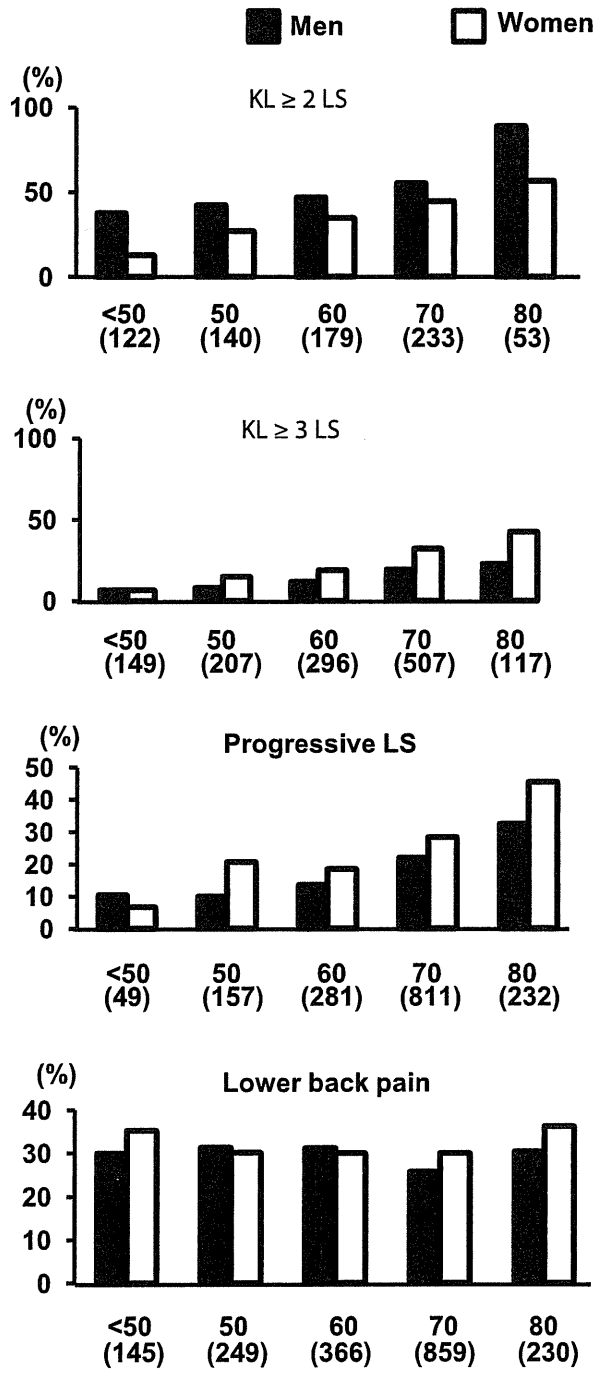

Fig. 1. Ratios (%) of individuals with incident radiographic LS (KL ≥ 2 and KL ≥ 3), progressive LS and incident lower back pain in each age stratum (<50, 50–59, 60–69, 70–79 and ≥80 years). Data in brackets are the number of individuals in each group.

study found that the progression rate of LS in women aged in their 50s was 20.9% over a period of 3.3 years (6.3% per year) and thus the progression rate of LS appears similar between Japanese and Caucasian women. In the present study, progression of radiographic LS was defined as KL ≥ 2 LS at baseline and an increase of at least one grade in the affected vertebral interspace at follow-up. Considering the definition of the KL grade, progression of radiographic LS may mean incidence or progression of disc space narrowing in subjects with osteophytosis, thus, our results may indicate that the incidence or progression of disc space narrowing is similar between Japanese and Caucasian women.

Furthermore, the present study included an investigation of KL ≥ 3 LS. To the best of our knowledge, incident KL ≥ 3 LS has never been investigated in a population-based study. LS was not defined according to KL grade but according to osteophytosis and disk space narrowing in the Chingford study[18]. That study showed that the progression of disk space narrowing was 3.2% per year in women whose mean age was 54 years at baseline. Our results regarding incident KL ≥ 3 LS might be comparable to these, considering the definition of KL grade, although a detailed comparison provides only limited accuracy. The incidence rate of KL ≥ 3 LS was 15.0% (4.5% per year) in Japanese women aged in their 50s at baseline in the present study, which was also higher than that in Caucasian women. This might in part be related to ethnic variations.

The incidence of KL ≥ 2 spondylosis was notably higher in men than in women, while that of KL ≥ 3 spondylosis was higher in women in the present study. Considering the definition of KL grade, this might mean that the incidence of osteophytosis is higher in men, whereas the incidence of disk space narrowing is higher in women. In fact, osteophytosis of the lumbar spine is more common in men than in women[11,12], whereas disc space narrowing is more prevalent in women[12]. A cross-sectional study that investigated the extent, prevalence and distribution of spinal spondylosis in women also showed that osteophytosis and disc space narrowing significantly correlated, but each predicted only 19% of the variation in the other[13]. This discordance suggests that different mechanisms influence the initiation of osteophytosis (the principal abnormality in KL grade 2 disease) and disk space narrowing (a principal abnormality in KL grade 3 disease). Our findings have implications for understanding of the pathogenesis of LS, as well as for designing preventive strategies.

In the present study, age, BMI, gender and KL grade at baseline were significantly associated with incident LS; this result differed from the findings of previous studies[19–21]. The UK twin spine study[19] using magnetic resonance imaging (MRI) showed that age, BMI and gender had no detectable effect on the progression of lumbar disc degeneration. The Finnish twin spine study also showed that body weight was not associated with progression of lumbar disc degeneration[20]. These differences may be explained not only by the differences in the definition of progressive LS, but also the ages of the subjects between these previous studies and the present study. The subjects in the UK twin study and Finnish twin study were quite younger at baseline than those in the present study (55 years, 49 years and 69 years, respectively). The association of these factors with LS may change among the age strata. In addition, racial differences may exist in the association of these factors with LS, because the prevalence or incidence of LS is different among races[3]. Age, BMI and female gender were not risk factors for lower back pain in the present study. Lower back pain occurrence might be mainly due to environmental, rather than to individual factors. Elderly men in particular generally retire at around age 60–70 years, and thus the load on the lower back might be greater in men aged below 60 years compared with those over 60 years, which might partly explain the lack of a significant association between age and the incidence of lower back pain. KL ≥ 3 LS was significantly associated with incident lower back pain compared with the absence of LS. Cross sectional studies have shown that the correlation between LS and lower back pain is not as strong as would be expected, and they are often disconnected[3,11]. However, this longitudinal study discovered that severe radiographic LS is a risk factor for lower back pain. We further found that the association between the number of KL ≥ 3 vertebral interspaces and the incidence of lower back pain differed between men and

Table III
Baseline risk factors for incident radiographic LS.

		KL ≥ 2					KL ≥ 3				
		No (%)	Crude OR	95% CI	Adjusted OR	95% CI	No (%)	Crude OR	95% CI	Adjusted OR	95% CI
Age, years			1.05	1.03–1.06	1.05	1.03–1.06		1.05	1.04–1.07	1.05	1.03–1.06
BMI, kg/m^2			1.07	1.02–1.12	1.07	1.02–1.13		1.01	0.97–1.06		
Gender											
Men		76/152 (50.0)	1.00	Reference	1.00	Reference	66/431 (15.3)	1.00	Reference	1.00	Reference
Women		198/575 (34.4)	0.53	0.37–0.76	0.50	0.34-0.72	200/845 (23.7)	1.71	1.27–2.34	2.19	1.54–3.17
Low back pain	No	223/607 (36.7)	1.00	Reference			219/1078 (20.3)	1.00	Reference		
	Yes	51/120 (42.5)	1.27	0.85–1.89			47/198 (23.7)	1.22	0.85–1.74		
Smoking	No	244/661 (36.9)	1.00	Reference			246/1136 (21.7)	1.00	Reference	1.00	Reference
	Yes	30/66 (45.5)	1.42	0.85–2.37			20/140 (14.3)	0.60	0.36–0.97	1.01	0.58–1.69
Alcohol	No	184/476 (38.7)	1.00	Reference			185/774 (23.9)	1.00	Reference	1.00	Reference
	Yes	90/251 (35.9)	0.89	0.64–1.22			81/502 (16.1)	0.61	0.46–0.82	0.87	0.63–1.20
KL grade											
KL = 0 or 1								1.00	Reference	1.00	Reference
KL = 2								1.66	1.27–2.19	1.67	1.24–2.25

The adjusted ORs were calculated by multiple logistic regression analysis after adjustment for all other significant variables without adjustment. We did not include KL grade in the analysis of incident KL ≥ 2 LS, because all subjects had KL = 0 or 1.

women. The incidence of lower back pain increased as the number of KL ≥ 3 vertebral interspaces increased in women, whereas the incidence was similar in men with 0, 1 and 2 KL ≥ 3 vertebral interspaces, and having 3 or more KL ≥ 3 vertebral interspaces suddenly increased the incidence of lower back pain.

There were several limitations in this study. First, we did not read the X-rays for osteophytes and joint space narrowing scored separately. Furthermore, in the KL classification, atrophic and degenerative features of LS, which likely have different aetiology, were combined; thus, the differences in associations with pain between these features may have been obscured. We are developing a computer-aided diagnostic program to enable fully automated measurements of the major features of LS, including disc space narrowing and osteophytosis on plain radiographs. The second limitation of our study was that a single orthopaedist read both films in pairs without being blinded to baseline and follow-up status. This may likely have caused the reader to over-read progression (i.e., inflate sensitivity) and therefore confer bias. This may be one reason for the higher incidence of LS in the present study compared with other studies. Third, we used only plain radiography to assess LS, although computed tomography (CT)/MRI is standard practice for evaluating nonspecific lower back pain in many countries. In addition, plain films can be affected by scoliosis, positioning and multiple other factors, which may have affected our results. Fourth, although experienced orthopaedists asked all participants the question regarding lower back pain based on previous studies[3,8], we defined lower back pain as present or absent, rather than as a continuous validated measure of pain, such as assessed by the Oswestry Disability Index[25]. Categorical methods are statistically less powerful than continuous methods. In addition, severity of lower back pain was not assessed in the present study. The association between lower back pain and other variables might have been underestimated in the present study. Furthermore, although the psychosocial dimension is an important factor for lower back pain[26], we did not include this in our analysis. Fifth, in the follow-up study, the responders was younger, more likely to be women and less likely to have LS at baseline compared with the nonresponders, which may have affected the results in the present study, because age, gender and KL grade were found to be associated with incident LS in the present study.

In conclusion, the present longitudinal study using a large-scale population from the ROAD study revealed a high incidence of radiographic LS in Japan. Gender seems to be distinctly associated with incident KL ≥ 2 and KL ≥ 3 LS, indicating that different

Table IV
Baseline risk factors for progressive LS and incident lower back pain

		Progressive LS					Lower back pain				
		No (%)	Crude OR	95% CI	Adjusted OR	95% CI	No (%)	Crude OR	95% CI	Adjusted OR	95% CI
Age, years			1.05	1.04–1.07	1.05	1.04–1.07		1.00	0.99–1.01	1.00	0.99–1.01
BMI, kg/m^2			1.01	0.98–1.05				1.01	0.98–1.04	1.01	0.98–1.04
Gender											
Men		123/599 (20.5)	1.00	Reference	1.00	Reference	178/630 (28.3)	1.00	Reference	1.00	Reference
Women		255/931 (27.4)	1.46	1.14–1.87	1.44	1.10–1.91	380/1219 (31.2)	1.15	0.93–1.42	1.12	0.90–1.39
Low back pain	No	302/1225 (24.7)	1.00	Reference							
	Yes	76/305 (24.9)	1.01	0.76–1.35							
Smoking	No	348/1385 (25.1)	1.00	Reference			503/1677 (30.0)	1.00	Reference		
	Yes	30/145 (20.7)	0.78	0.50–1.17			55/172 (32.0)	1.10	0.78–1.53		
Alcohol	No	253/958 (26.4)	1.00	Reference			360/1162 (31.0)	1.00	Reference		
	Yes	125/572 (21.9)	0.78	0.61–0.99			198/687 (28.8)	0.90	0.73–1.11		
KL grade											
KL = 0 or 1							177/607 (29.2)	1.00	Reference	1.00	Reference
KL = 2		103/549 (18.8)	1.00	Reference			118/471 (25.1)	0.81	0.62–1.06	0.86	0.64–1.14
KL ≥ 3		275/981 (28.0)	1.69	1.31–2.18			263/771 (34.1)	1.26	1.00–1.58	1.32	1.03–1.69

The adjusted ORs were calculated by multiple logistic regression analysis after adjustment for all other significant variables without adjustment. We did not include KL grade in the analysis of incident KL ≥ 2 LS, because all subjects had KL = 0 or 1.

Table V
Association of KL ≥ 3 LS at baseline with incident lower back pain by each vertebral interspace and the severest space in 1,849 subjects with no lower back pain at baseline

		L1/2		L2/3		L3/4		L4/5		L5/S		The severest	
		No. (%)	OR (95% CI)	No.(%)	OR (95% CI)	No. (%)	OR (95% CI)	No. (%)	OR (95% CI)	No. (%)	OR (95% CI)	No. (%)	OR (95% CI)
Men	KL < 3	154/552 (27.9)	1.00	142/528 (26.9)	1.00	136/512 (26.6)	1.00	117/424 (27.6)	1.00	130/496 (26.2)	1.00	98/368 (26.6)	1.00
N = 630	KL ≥ 3	24/78 (30.8)	1.20 (0.70–2.01)	36/102 (35.3)	1.57 (0.98–2.48)	42/118 (35.6)	1.62 (1.04–2.50)	61/206 (29.6)	1.15 (0.79–1.67)	48/134 (35.8)	1.65 (1.09–2.49)	80/262 (30.5)	1.26 (0.88–1.81)
Women	KL < 3	331/1,083 (30.6)	1.00	298/1,007 (29.6)	1.00	284/960(29.6)	1.00	236/828 (28.5)	1.00	284/971 (29.3)	1.00	197/710 (27.8)	1.00
N = 1,219	KL ≥ 3	49/136 (36.0)	1.28 (0.87–1.87)	82/212 (38.7)	1.52 (1.11–2.10)	96/259 (37.1)	1.43 (1.06–1.92)	144/391 (36.8)	1.50 (1.15–1.97)	96/248 (38.7)	1.56 (1.15–2.10)	183/509 (36.0)	1.51 (1.16–1.95)

Multiple logistic regression analysis after adjustment for age was used to calculate OR and 95% CI.

mechanisms might influence the initiation of osteophytosis and joint space narrowing. Lower back pain was not significantly associated with incident radiographic LS, whereas radiographic severe LS was a risk factor for incident lower back pain. Further progress, along with continued longitudinal surveys of the ROAD study, will elucidate the environmental and genetic background of LS.

Author contributions

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

(1) The conception and design of the study, or acquisition of data, or analysis and interpretation of data
(2) Drafting the article or revising it critically for important intellectual content
(3) Final approval of the version to be submitted

Conflicts of interest

There are no conflicts of interest.

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Supplementary material

Supplementary data related to this article can be found online at doi:10.1016/j.joca.2012.03.009

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CERVICAL SPINE

Prevalence of Cervical Cord Compression and Its Association With Physical Performance in a Population-Based Cohort in Japan

The Wakayama Spine Study

Keiji Nagata, MD, PhD,* Noriko Yoshimura, MD, PhD,† Shigeyuki Muraki, MD, PhD,‡ Hiroshi Hashizume, MD, PhD,* Yuyu Ishimoto, MD,* Hiroshi Yamada, MD, PhD,* Noboru Takiguchi, MD,* Yukihiro Nakagawa, MD, PhD,* Hiroyuki Oka, MD,† Hiroshi Kawaguchi, MD, PhD,§ Kozo Nakamura, MD, PhD,¶ Toru Akune, MD, PhD,‡ and Munehito Yoshida, MD, PhD*

Study Design. A population-based magnetic resonance imaging (MRI) study of the cervical spine.

Objective. This study was undertaken in order to investigate the prevalence of cervical cord compression (CCC) and to examine the association between CCC and physical performance measures in a population-based cohort established in Japan.

Summary of Background Data. Population-based cohort studies of the prevalence of CCC, although essential for clarification of the prevalence of slowly progressive disease and specification of the time of incidence of CCC, are not available.

Methods. This cross-sectional study was performed as a part of the Research on Osteoarthritis/osteoporosis Against Disability study, a large-scale population-based cohort study in Japan. From 1011 inhabitants who underwent MRI examinations, images of the cervical spine of 977 subjects (324 men and 653 women, mean age of 66.4 yr) were evaluated. CCC was assessed by sagittal T2-weighted MRI and was defined as spinal cord compression. The prevalence of CCC and its association with myelopathic signs (hyper-reflexia of the patellar tendon and Hoffmann and Babinski reflexes) were examined. In addition, physical performance measures (grip and release test, grip strength, 6-m walking time, step length, chair-stand time, and one-leg standing time) were tested.

Results. The prevalence of CCC was 24.4% and was significantly higher in men (29.3% in men and 21.9% in women, $P = 0.011$). The prevalence of CCC was higher with increasing age in both sexes. CCC was not significantly associated with any myelopathic signs but was significantly associated with grip and release test, 6-m walking time, step length, and chair-stand time.

Conclusion. In this MRI study, the prevalence of CCC was examined. The present results indicate that CCC correlates with physical performance measures from an early stage of the disease before myelopathic signs appear.

Key words: cervical cord compression, population-based study, MRI, physical performance. **Spine 2012;37:1892–1898**

Cervical cord compression (CCC) is a regressive and degenerative disorder. Symptoms of spinal cord compression are regarded as cervical myelopathy (CM).[1] CM sometimes can become irreversible and lead to a decrease in the performance of activities of daily living.[2–4]

Considering the regressive nature of CM, and the contemporary unprecedented rapid increase in the number of elderly people in the general population, an urgent need for the development of strategies for prevention of CM has emerged in most developed countries. Nonetheless, the prevalence of CCC, which is basic information needed for the prevention of CM, has not been well characterized. The prevalence of CCC cannot be estimated with hospital surveys, because most patients who visit hospitals have already developed a myelopathic condition. Therefore, a population-based study is essential for clarification of the prevalence of CCC. Magnetic resonance imaging (MRI) is an essential tool for diagnosis of CCC,[5,6] but no previous population-based studies of CCC using MRI have been performed. Previous studies concerning prevalence of CCC were performed with asymptomatic subjects and were not population-based studies.[7–9]

From the *Department of Orthopedic Surgery, Wakayama Medical University, Wakayama, Japan; †Departments of Joint Disease Research; ‡Clinical Motor System Medicine, 22nd Century Medical and Research Center, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan; §Department of Orthopaedic Surgery, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan; and ¶Rehabilitation Services Bureau, National Rehabilitation Center for Persons with Disabilities, Saitama, Japan.

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Address correspondence and reprint requests to Munehito Yoshida, MD, PhD, Department of Orthopedic Surgery, Wakayama Medical University, 811-1 Kimidera, Wakayama City, Wakayama 641-8509, Japan; E-mail: myoshida@wakayama-med.ac.jp

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TABLE 1. Characteristics of Men and Women Participating in This Study

	Men	Women
N	324	653
Age (yr)	67.2 ± 13.9	66.0 ± 13.4
Height (cm)	164.6 ± 7.2*	151.5 ± 7.2
Weight (kg)	64.5 ± 11.6*	53.0 ± 9.4
Body mass index (kg/m²)	23.7 ± 3.4†	23.1 ± 3.6
Physical performance measures		
Grip strength (kg)	38.0 ± 9.1*	23.9 ± 5.8
Grip and release test, number of times	24.9 ± 5.8*	22.5 ± 5.3
6-m walking time at a usual pace (s)	5.4 ± 1.5	5.8 ± 2.4
Step length at a usual pace (cm)	58.6 ± 9.2*	54.6 ± 10.1
6-m walking time at a maximal pace (s)	3.6 ± 1.1*	4.0 ± 1.6
Step length at a maximal pace (cm)	70.7 ± 10.7*	61.1 ± 11.2
Chair-stand time (s)	8.8 ± 3.4	9.0 ± 4.2
One-leg standing time (s)	35.9 ± 24.1	35.9 ± 23.6

*Significantly different from women by Student t test (*P < 0.001, †P < 0.01).*

Values are mean ± SD.

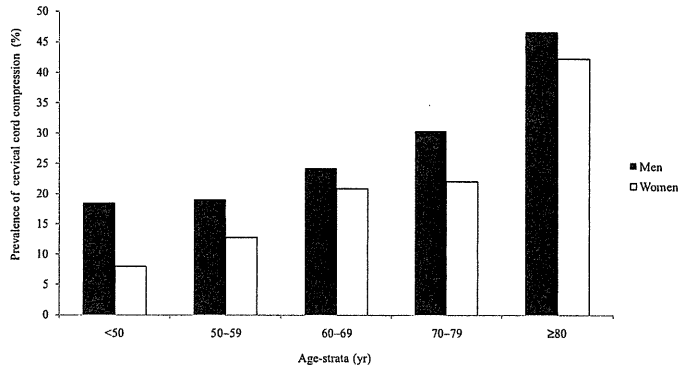

Figure 1. Prevalence of Cervical Cord Compression (≥grade 2) in sexes by age strata.

Decreases in physical performance are symptoms of CM[10,11] and can lead to a lower quality of life, especially in elderly patients.[12,13] Although CCC is commonly seen in asymptomatic subjects, it has not been clarified whether decreases in physical performance are seen in the early stages of CCC before the signs of myelopathy appear.

In this population-based study, CCC was evaluated using MRI, and the association of CCC with physical performance was examined.

MATERIALS AND METHODS

Participants

This study, was performed in a subcohort of the large-scale population-based cohort study entitled the Research on Osteoarthritis/osteoporosis Against Disability (ROAD). ROAD is a nationwide, prospective study of bone and joint diseases in population-based cohorts established in several communities in Japan. As a detailed profile of the ROAD study has already been described elsewhere,[14,15] only a brief summary is provided here. To date, a database has been created which includes baseline clinical and genetic information for 3040 inhabitants (1061 men and 1979 women) with an age range of 23 to 95 years (mean, 70.6 yr), recruited from listings of resident registrations in 3 communities: an urban region in Itabashi, Tokyo; a mountainous region in Hidakagawa, Wakayama; and a coastal region in Taiji, Wakayama. Participants completed an interviewer-administered questionnaire of 400 items that included lifestyle information, and anthropometric and physical performance measurements were taken. All study participants provided informed consent, and the study design was approved by the appropriate ethics review boards.

The second visit of the ROAD study to Hidakagawa and Taiji was performed between 2008 and 2010. From inhabitants participating in the second visit of the ROAD study, 1063 inhabitants were recruited for MRI examinations. Among those 1063 inhabitants, 52 declined the examination; therefore, 1011 inhabitants were registered in this study. Among those 1011 participants, those who had MRI-sensitive implanted devices (such as a pacemaker) and other disqualifiers were excluded. The cervical spine was scanned with MRI in 985 participants. Furthermore, 4 participants who had undergone a previous cervical operation were excluded from the analysis, and another 4 participants whose MRI interpretation was difficult because of poor image quality were also excluded. In total, MRI results were available for 977 participants (324 men and 653 women), with an age range of 21 to 97 years (mean, 67.2 yr for men and 66.0 yr for women). Anthropometric measurements included height (m), weight (kg), and body mass index (BMI) (weight [kg]/height² [m²]).

EVALUATION OF MYELOPATHIC SIGNS AND PHYSICAL PERFORMANCE

Medical information concerning neck pain, sensory disturbances, the Hoffmann reflex, the Babinski reflex, and the deep tendon reflex of the patellar tendon were gathered by an experienced orthopedic surgeon. The Hoffmann reflex was elicited with the hand in a neutral position by flicking the distal phalanx of the middle finger and observing flexion of the distal phalanx of the thumb.[16,17] The Babinski reflex was elicited by firmly sweeping from the lateral part of the sole to the base of the toes with a pointed end of a reflex hammer and observing the hallux extensor response.[18,19] Hyper-reflexia of

TABLE 2. Prevalence of Cervical Cord Compression (≥Grade 2) at Each Intervertebral Disc Level by Sex and Age

Age Strata	C2–C3	C3–C4	C4–C5	C5–C6	C6–C7	C7–Th1
Men						
Overall (N = 324)	0	5.3	12.7	18.5	11.4	0.9
<50 yr (N = 38)	0	5.3	2.6	13.2	2.6	0
50–59 yr (N = 58)	0	3.5	10.3	15.5	3.5	0
60–69 yr (N = 66)	0	1.5	9.1	15.2	15.2	1.5
70–79 yr (N = 89)	0	2.3	12.4	18.0	13.5	1.1
≥80 yr (N = 73)	0	13.7	23.3	27.4	16.4	1.4
Women						
Overall (N = 653)	0	3.5	8.1	14.9	6.0	0.2
<50 yr (N = 88)	0	0	1.1	8.0	2.3	0
50–59 yr (N = 117)	0	0	4.3	8.6	5.1	0
60–69 yr (N = 158)	0	0.6	7.0	13.9	7.6	0
70–79 yr (N = 172)	0	3.5	8.7	15.7	5.2	0.6
≥80 yr (N = 118)	0	13.6	17.8	26.3	8.5	0

Values are percentages for each intervertebral disc level.

the patellar tendon, a positive Hoffmann reflex, and a positive Babinski reflex were defined as aggravation on both sides. A myelopathic sign was defined as the presence of hyper-reflexia of the patellar tendon, the Hoffmann reflex, or the Babinski reflex.

For evaluation of physical performance, the following tests were conducted: a 10-s grip and release test (GRT), grip strength, 6-m walking time, step length, chair-stand time (CST), and one-leg standing (OLS) time. Grip strength was measured for each hand using a Toei Light handgrip dynamometer (Toei Light Co., Ltd., Saitama, Japan). To measure walking speed, the time taken to walk 6 m at a usual pace in a hallway was recorded. Similarly, the 6-m walking time at a maximal pace was measured. The time taken for 5 consecutive chair rises without the use of hands was also recorded. OLS time with each leg was measured using a stopwatch (upper limit, 60 s) and the time adopted was the mean of the times for both legs.[20–25] The participants were given a full explanation of each test but were not given any training.

Magnetic Resonance Imaging

MRI was performed on the cervical spine of each participant using a 1.5-T Excelart imaging system (Toshiba, Tokyo, Japan). All participants lay supine during the MRI, with exceptions for those participants with a rounded back, who used a triangular pillow under their heads and knees. The imaging protocol included a sagittal T2-weighted fast spin-echo pulse sequence (repetition time: 4000 ms, echo time: 120 ms, and field of view: 300 × 320 mm) and an axial T2-weighted fast spin-echo pulse sequence (repetition time: 4000 ms, echo time: 120 ms, and field of view: 180 × 180 mm).

MRI Assessment

Sagittal T2-weighted images were assessed from C2–C3 to C7–Th1. Grading of CCC was performed at each intervertebral level from C2–C3 to C7–Th1 by an orthopedic surgeon (K.N.) with experience of interpreting spinal MRI. Grading was defined as follows: grade 0 = no compression of the spinal cord but subarachnoid space remains; grade 1 = no compression of the spinal cord with subarachnoid space absent; grade 2 = compression of less than one-third of the spinal cord; grade 3 = compression of more than one-third but less than two-thirds of the spinal cord; and grade 4 = compression of more than two-thirds of the spinal cord. CCC was defined as grade 2 or more severe at the most severely affected intervertebral disc level.

To evaluate intraobserver variability, 100 randomly selected MRIs of the cervical spine were rescored by the same observer (K.N.) more than 1 month after the first reading. Furthermore, in order to evaluate interobserver variabilities, another 100 MRIs were examined and scored by a different orthopedic surgeon (H.H.) with experience interpreting spinal MRI. The intraobserver and interobserver variabilities for CCC evaluated by κ analysis were 0.78 and 0.72, respectively, and were deemed sufficient for assessment.

Statistical Analysis

Comparisons of baseline characteristics between sexes were made using the nonpaired Student *t* test for numerical

TABLE 3. Age, Body Mass Index, Myelopathic Signs, and Physical Performance Measures With and Without Cervical Cord Compression in the Overall Study Population

	No Compression (<Grade 2)	Compression (≥Grade 2)
Overall		
N	739	238
Age (yr)	64.7 ± 13.7	71.7 ± 11.7*
Body mass index (kg/m²)	23.2 ± 3.7	23.5 ± 3.3
Myelopathic signs and physical performance measures		
Hyper-reflexia of patellar tendon reflex, N (%)	49 (6.6)	20 (8.4)
Hoffmann reflex positive, N (%)	11 (1.5)	6 (2.5)
Babinski reflex positive, N (%)	10 (1.4)	8 (3.4)†
Grip and release test, number of times	23.7 ± 5.6	21.9 ± 5.3*
Grip strength (kg)	29.0 ± 9.6	27.2 ± 9.7†
6-m walking time at a usual pace (s)	5.5 ± 2.1	6.3 ± 2.3*
Step length at a usual pace (cm)	57.0 ± 9.0	52.8 ± 12.0*
6-m walking time at a maximal pace (s)	3.7 ± 1.3	4.4 ± 1.7*
Step length at a maximal pace (cm)	65.4 ± 11.4	60.7 ± 12.9*
Chair-stand time (s)	8.4 ± 3.4	10.3 ± 5.1*
One-leg standing time (s)	38.3 ± 23.2	28.4 ± 24.0*

Values are mean ± SD except where otherwise indicated.

Significantly different from values of the no compression group ($P < 0.001$, †$P < 0.01$).*

For continuous outcomes, comparison was by the Student t test. For categorical outcomes, comparison was by the χ^2 test.

variables. To evaluate the association and prevalence of CCC with age, a χ^2 test was used for each sex. Prevalence of myelopathic signs was compared between participants with and without CCC, using the χ^2 test. Measurements of physical performance, such as 6-m walking time, step length, CST, and OLS, were compared between participants with and without CCC, using the nonpaired Student *t* test. In addition, to determine the association of each physical performance with CCC, logistic regression analysis was used after overall adjustment for age, sex, and BMI. All statistical tests were performed at a significance level of 0.05 (2-sided) and were not adjusted for multiple testing. Data analyses were performed using JMP version 8 (SAS Institute Inc., Cary, NC).

RESULTS

Baseline characteristics of the 977 participants including anthropometric measurements and physical performance are shown in Table 1. There was no significant difference in age between sexes. Height, weight, and BMI were significantly higher in men than in women. Among physical performances, grip strength, GRT, 6-m walking time, and step length were significantly different between sexes ($P < 0.05$), whereas CST and OLS were not.

The prevalence of CCC in all participants was 24.4% (29.3% in men and 21.9% in women) and was significantly higher in men than in women ($P = 0.011$). As seen in Figure 1, the prevalence of CCC in men by age group for subjects aged 49 years and younger, 50–59, 60–69, 70–79, and 80 years and older was 18.4%, 19.0%, 24.2%, 30.3%, and 46.6%, respectively. Meanwhile, in women, the prevalence of CCC by age group for subjects aged 49 years and younger, 50–59, 60–69, 70–79, and 80 years and older was 8.0%, 12.8%, 20.9%, 22.1%, and 42.4%, respectively. A χ^2 test showed that the prevalence of CCC was higher with age in men and women ($P = 0.0024$ in men and $P < 0.0001$ in women). Furthermore, the prevalence of CCC of grade 3 or more was 5.9% in men and 2.6% in women. No participants had a CCC of grade 4 or more.

Table 2 shows the prevalence of CCC at each intervertebral disc level in men and women. CCC was most frequently recognized in both sexes at C5–C6, followed by C4–C5 and C6–C7. The prevalence of CCC was already higher than 10% at 50 to 59 years of age in C5–C6 in men and was higher than 10% in subjects 80 years and older at every intervertebral disc level (except for C2–C3 and C7–Th1).

Association of CCC with myelopathic signs and physical performance measures is shown in Tables 3 and 4. The prevalence of myelopathic signs, which was defined as having at least 1 myelopathic sign (including patellar tendon hyperreflexia, Hoffmann reflex, and Babinski reflex), was 3.2% in men and 16.1% in women with CCC. In men, none of the myelopathic signs were significantly different between the participants with and without CCC. Regarding physical performance measures, significant differences between the participants with and without CCC were found in GRT ($P = 0.0001$), grip strength ($P = 0.001$), 6-m walking time at a maximal pace ($P = 0.0038$), step length at a usual pace ($P = 0.0004$), step length at a maximal pace ($P = 0.001$), and OLS ($P = 0.0003$). Significant differences were not seen in the 6-m walking time at a usual pace ($P = 0.058$) or CST ($P = 0.067$). In women, the prevalence of Babinski reflex was significantly higher in participants with CCC than in those without CCC ($P = 0.019$), whereas the prevalence of hyper-reflexia of patellar tendon and Hoffman reflex was not significantly different ($P = 0.11$ and $P = 0.28$, respectively). There were significant differences between participants with and without CCC in all physical performance measures.

TABLE 4. Age, Body Mass Index, Myelopathic Signs, and Physical Performance Measures With and Without Cervical Cord Compression in Men and Women

	No Compression (<Grade 2)	Compression (≥Grade 2)
Men		
N	229	95
Age (yr)	65.5 ± 14.2	71.4 ± 12.1*
Body mass index (kg/m²)	23.8 ± 3.6	23.5 ± 3.0
Myelopathic signs and physical performance measures		
Hyper-reflexia of patellar tendon reflex, N (%)	7 (3.1)	2 (2.1)
Hoffmann reflex positive, N (%)	1 (0.4)	1 (1.1)
Babinski reflex positive, N (%)	2 (0.9)	1 (1.1)
Grip and release test, number of times	25.7 ± 6.0	22.9 ± 5.0*
Grip strength (kg)	39.1 ± 9.1	35.4 ± 8.7†
6-m walking time at a usual pace (s)	5.4 ± 1.5	5.7 ± 1.5
Step length at a usual pace (cm)	59.8 ± 8.9	55.8 ± 9.3*
6-m walking time at a maximal pace (s)	3.5 ± 1.0	3.9 ± 1.2†
Step length at a maximal pace (cm)	71.9 ± 10.1	67.6 ± 11.6†
Chair-stand time (s)	8.5 ± 3.3	9.3 ± 3.5
One-leg standing time (s)	39.0 ± 23.2	28.5 ± 24.6*
Women		
N	510	143
Age (yr)	64.3 ± 13.4	71.9 ± 11.5*
Body mass index (kg/m²)	22.9 ± 3.7	23.6 ± 3.5‡
Myelopathic signs and physical performance measures		
Hyper-reflexia of patellar tendon reflex, N (%)	42 (8.2)	18 (12.6)
Hoffmann reflex positive, N (%)	10 (2.0)	5 (3.5)
Babinski reflex positive, N (%)	8 (1.6)	7 (4.9)‡
Grip and release test, number of times	22.8 ± 5.3	21.3 ± 5.4†
Grip strength (kg)	24.5 ± 5.7	21.9 ± 5.8*
6-m walking time at a usual pace (s)	5.5 ± 2.3	6.7 ± 2.7*
Step length at a usual pace (cm)	55.7 ± 8.8	50.8 ± 13.2*
6-m walking time at a maximal pace (s)	3.8 ± 1.4	4.8 ± 1.9*
Step length at a maximal pace (cm)	62.5 ± 10.7	56.0 ± 11.7*
Chair-stand time (s)	8.4 ± 3.5	11.0 ± 5.8*

Values are mean ± SD except where otherwise indicated.

Significantly different from values of the group of no compression ($P < 0.001$, †$P < 0.01$, ‡$P < 0.05$).*

For continuous outcomes, comparison was by the Student t test. For categorical outcomes, comparison was by the χ^2 test.

In addition, multiple logistic regression analysis was performed to estimate the association of physical performance with CCC after adjustment for age, sex, and BMI (Table 5). As an overall result, GRT, step length at a usual and a maximal pace, 6-m walking time at a maximal pace, and CST were found to be significantly associated with CCC. The same logistic regression analysis was performed in participants older than 50 years, and the results remained the same.

TABLE 5. Association Between Cervical Cord Compression (≥Grade 2) and Physical Performance Measures

	OR	95% CI	*P*
*Overall**			
Grip and release test, N (+1SD)	0.26	0.08–0.79	0.02
Grip strength, kg (+1 SD)	0.22	0.03–1.37	0.11
6-m walking time at a usual pace, s (+1 SD)	4.88	0.81–31.1	0.09
Step length at a usual pace, cm (+1 SD)	0.04	0.03–0.45	0.01
6-m walking time at a maximal pace, s (+1 SD)	14.1	2.51–85.0	0.003
Step length at a maximal pace, cm (+1 SD)	0.13	0.03–0.46	0.002
Chair-stand time, s (+1 SD)	11.1	2.00–64.5	0.006
One-leg standing time, s (+1 SD)	0.87	0.51–1.50	0.62

**OR was calculated by multiple logistic regression analysis after adjustment for age, sex, and body mass index in the overall study population.*

OR indicates odds ratio; CI, confidence interval.

DISCUSSION

This study is the first population-based study to use MRI to clarify the prevalence of CCC and its association with myelopathic signs and physical performance measures in Japanese men and women. The prevalence of CCC was higher with increasing age in both sexes. There was no significant association between CCC and myelopathic signs. Regarding physical performance measures, GRT, step length at a usual and a maximal pace, 6-m walking time at a maximal pace, and CST were significantly associated with CCC.

Regarding the prevalence of CCC, Matsumoto *et al*[8] reported that CCC caused by disc protrusion beyond the vertebral body was found in 7.6% of all intervertebral discs using MRI in asymptomatic subjects. This study was the first to clarify the prevalence of CCC, age, and sex differences using MRI in a population-based cohort study.

Previous studies have shown that the prevalence of cervical spondylotic myelopathy was higher in men than in women.[2,26] However, as has been described earlier, and to the best of our knowledge, there have been no previous population-based studies regarding sex differences with CCC. Irvine *et al*[27] reported that the prevalence of cervical spondylosis was higher in men than in women, but the study was not population-based and diagnosis was made with x-ray films. This study is the first to clarify that the prevalence of CCC is more frequent in men than in women.

This study also used multiple logistic regression to examine the association of CCC with myelopathic signs and found that there was no significant association between CCC and hyper-reflexia of patellar tendon, Hoffman reflex, and the Babinski reflex. It is well recognized that, among the elderly, exaggerated reflexes are uncommon, whether they be caused by peripheral neuropathy or other causes. Therefore, diagnosis of early-stage CM using myelopathic signs is often difficult, especially among the elderly. In addition, the prevalence of severe CCC (> grade 3) was only 5.9% in men and 2.6% in women, and most of the participants with CCC had slight to moderate spinal compression. These findings may affect the results of this study, which found no significant association between CCC and myelopathic signs. With regard to physical performance measures, many were significantly associated with CCC in this study. The GRT, 6-m walking time at a maximal pace, and CST, all of which required agility, were significantly associated with CCC. This indicates that a decrease in agility may be observed early in the course of CM, and these kinds of physical performance measures may be useful indices for diagnosis of early-stage CM.

Limitations of the Study

There are several limitations in this study. First, although this study included more than 1000 participants, these participants may not represent the general population because they were recruited from only 2 areas of Japan. However, anthropometric measurements were compared between the participants of this study and the general Japanese population,[28] and no significant differences in BMI were found between participants in this study and the Japanese population at large in both sexes (BMI [SD] in men: 23.71 [3.41] and 23.95 [2.64], $P = 0.33$, respectively, and in women: 23.06 [3.42] and 23.50 [3.69], $P = 0.07$, respectively). In addition, the proportion of current smokers and current drinkers (those who regularly smoked or drank more than 1 drink per mo) in the general Japanese population was compared with the study population. Proportions of current smokers and drinkers in men and that of current drinkers in women were significantly higher in the general Japanese population than in the study population, and there was no significant difference in current smokers in women (male smokers, 32.6% in the Japanese population and 25.2% in study participants, $P = 0.015$; female smokers, 4.9% in the Japanese population and 4.1% in study participants, $P = 0.50$; male drinkers, 73.9% in the Japanese population and 56.8% in study participants, $P < 0.0001$; female drinkers,

28.1% in the Japanese population and 18.8% in study participants, $P < 0.0001$). These results suggest that it is likely that in this study, participants had healthier lifestyles than the general Japanese population. Second, the prevalence only applies to a portion of the Japanese population and cannot be extrapolated beyond that. Third, ossification of the posterior longitudinal ligament (OPLL) and spondylotic changes were included in CCC. There were a total of 21 participants with OPLL, which was examined by x-ray in the same population. Associations of physical performance between spondylotic changes and OPLL may be different; however, only 14 (1.4% in total) OPLL participants had CCC and therefore would not strongly affect the results of this study.

CONCLUSION

This cross-sectional population-based study revealed a high prevalence of CCC in the elderly. The prevalence of CCC was more frequent in men than in women. The highest prevalence of intervertebral lesions was at the C5–C6 level. The GRT, 6-m walking time at a maximal pace, and CST may be useful tools for diagnosis of the early stages of CM.

➢ Key Points

- ❑ This is the first study to reveal the prevalence of CCC, using a population-based study.
- ❑ The prevalence of CCC was 24.4% in this cohort.
- ❑ CCC was associated with physical performance both from an early stage of the disease and before signs of myelopathy.

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Accumulation of metabolic risk factors such as overweight, hypertension, dyslipidaemia, and impaired glucose tolerance raises the risk of occurrence and progression of knee osteoarthritis: a 3-year follow-up of the ROAD study

N. Yoshimura †*, S. Muraki ‡, H. Oka †, S. Tanaka §, H. Kawaguchi §, K. Nakamura ||, T. Akune ‡

† *Department of Joint Disease Research, 22nd Century Medical and Research Center, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan*
‡ *Department of Clinical Motor System Medicine, 22nd Century Medical and Research Center, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan*
§ *Department of Orthopaedic Surgery, Faculty of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan*
|| *Rehabilitation Services Bureau, National Rehabilitation Center for Persons with Disabilities, 1, Namiki 4-chome, Tokorozawa City, Saitama Prefecture 359-8555, Japan*

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SUMMARY

Objective: To clarify the association between the occurrence and progression of knee osteoarthritis (KOA) with components of metabolic syndrome (MS), including overweight (OW), hypertension (HT), dyslipidaemia (DL), and impaired glucose tolerance (IGT), in a general population.
Design: From the large-scale population-based cohort study entitled Research on Osteoarthritis/Osteoporosis Against Disability (ROAD) initiated in 2005, 1,690 participants (596 men, 1,094 women) residing in mountainous and coastal areas were enrolled. Of these, 1,384 individuals (81.9%; 466 men, 918 women) completed the second survey, including knee radiography, 3 years later. KOA was defined as Kellgren–Lawrence (KL) grade ≥ 2 using paired X-ray films. Based on changes in KL grades between the baseline and second surveys, cumulative incidence and progression of KOA were determined. OW, HT, DL, and IGT at baseline were assessed using standard criteria.
Results: The cumulative incidence of KOA among 1,384 completers over 3 years was 3.3%/year, and progression in KL grades for either knee, 8.0%/year. Logistic regression analyses after adjusting for potential risk factors revealed that the odds ratio (OR) for the occurrence of KOA significantly increased according to the number of MS components present (OR vs no component: one component, 2.33; two components, 2.82; ≥three components, 9.83). Similarly, progression of KOA significantly increased according to the number of MS components present (OR vs no component: one component, 1.38; two components, 2.29; ≥three components: 2.80).
Conclusion: Accumulation of MS components is significantly related to both occurrence and progression of KOA. MS prevention may be useful in reducing future KOA risk.

Introduction

Osteoarthritis (OA), which causes cartilage and disc degeneration and osteophyte formation at joints in the limbs and spine, is a major public health problem in the elderly and affects activities of daily living and quality of life, leading to increased morbidity and mortality[1–3]. According to the recent National Livelihood Survey by the Ministry of Health, Labour and Welfare in Japan, OA is ranked fourth among diseases that cause disabilities requiring support and long-term care[4]. The National Livelihood Survey also shows that cardiovascular disease (CVD) is ranked first in causing disabilities in the elderly[4]. Most CVD patients have multiple risk factors[5]. The presence of these risk factors in a specific combination, entitled metabolic syndrome (MS), is a multiplex risk factor that predisposes affected individuals to CVD morbidity and mortality. MS is generally considered a combination of being overweight (OW) and having hypertension (HT), dyslipidaemia (DL), and impaired glucose tolerance (IGT)[6].

Knee OA (KOA) and MS share age and obesity as risk factors[1,7–12]. Numerous investigators have associated OA with

* Address correspondence and reprint requests to: N. Yoshimura, Department of Joint Disease Research, 22nd Century Medical and Research Center, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan. Tel: 81-3-5800-9178; Fax: 81-3-5800-9179.
E-mail address: YOSHIMURAN-ORT@h.u-tokyo.ac.jp (N. Yoshimura).

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various MS components. Lawrence first reported that diastolic blood pressure (BP) was associated with KOA in women[13]. Kellgren reported that hand OA was significantly associated with above-average serum cholesterol levels in women[14]. Cimmino *et al.* observed significantly higher plasma glucose levels in women with OA than in those without[15]. Contradictory findings regarding the association of such metabolic factors with OA have been reported[16–19]. Hart *et al.* found that metabolic factors such as blood glucose, hypercholesterolaemia, and even treated HT were associated with KOA development[20]. A few population-based studies have demonstrated a dose–response relationship between risk factor accumulation for MS and KOA; we have previously reported that KOA presence was significantly associated with increase in the number of MS components[21]. However, to our knowledge, no study has clarified the associations between KOA occurrence or progression and MS component accumulation, using a prospective cohort of general inhabitants.

This study evaluated the incidence and progression of radiographic KOA and its associations with individual and cumulative MS components (OW, HT, DL, and IGT) among men and women using the large-scale, population-based cohort from the Research on Osteoarthritis/Osteoporosis Against Disability (ROAD) study.

Method

Participants

This study involved the cohorts established in 2005 for the ROAD study. Details of the cohort profile have been reported elsewhere[22,23] and are only briefly described here. In 2005–2007, we created a baseline database including clinical information for 3,040 residents of Japan (men, 1,061; women, 1,979). The subjects were recruited from resident registration listings in three communities with different characteristics: 1,350 individuals (men, 465; women, 885) from an urban region in Itabashi, Tokyo; 864 individuals (men, 319; women, 545) from a mountainous region in Hidakagawa, Wakayama; and 826 individuals (men, 277; women, 549) from a coastal region in Taiji, Wakayama. In 2008–2010, we attempted to locate and follow-up all 3,040 subjects. They were invited for the second survey of the ROAD study, a 3-year follow-up examination identical to the baseline examinations.

For the current study, we enrolled all 1,690 subjects (men, 596; women, 1,094) resided in the mountainous and coastal areas, where blood examination had been performed on all participants at baseline. All participants provided written informed consent, and the study was conducted with approval from the ethics committees of the University of Tokyo.

Baseline examination procedures

At the baseline examination, participants completed an interviewer-administered questionnaire of 400 items, including lifestyle information such as primary occupation; smoking habits (0: ex- or non-smoker, 1: current smoker); alcohol consumption (0: ex- or non-drinker, 1: current drinker); physical activity, including bicycling every day over the past 12 months (0: no, 1: yes); regular exercise (0: no, 1: yes); and medical history, including history of knee injuries (0: no, 1: yes). The participants were asked whether they took prescription medication daily or nearly every day (0: no, 1: yes). If they did not know what their medications were prescribed for, they were asked to bring their medications to the medical doctor (NY).

Anthropometric measurements included height, weight, and body mass index [BMI: weight (kg)/height^2 (m^2)]. Systolic and diastolic BP was measured by an experienced public health nurse using a mercury sphygmomanometer. Medical information, including information on knee joints, was collected by experienced orthopaedic surgeons (SM and HO). All participants underwent radiographic examination of both knees using an anterior–posterior view with weight-bearing and foot-map positioning.

All blood samples were obtained between 09:00 and 15:00. Haemoglobin A1c (HbA1c), blood sugar, high-density lipoprotein cholesterol (HDL-cho), total cholesterol, and triglyceride (TG) levels were measured. All analyses were performed at the same laboratory within 24 h of extraction (Osaka Kessei Research Laboratories, Inc., Osaka, Japan).

In this study, definitions of MS components were based on criteria defined by the Examination Committee of Criteria for Metabolic Syndrome in Japan[24] and the Japan Society for the Study of Obesity[25]. However, because not all blood samples were obtained under fasting conditions, we used indices from the National Health and Nutrition Survey in Japan adopted as MS criteria in this national screening study due to the difficulty of collecting samples under fasting conditions[26]. The following definitions were used for MS components: OW, BMI $\geq$ 25 kg/m^2; HT, systolic BP $\geq$ 130 mm Hg and/or diastolic BP $\geq$ 85 mm Hg; DL, serum HDL-cho level $<$ 40 mg/dL; and IGT, serum HbA1c level $\geq$ 5.5%. Furthermore, subjects being treated with medication for HT, DL, or diabetes mellitus were regarded as having HT, DL, or IGT, respectively.

Three-year follow-up and definition of KOA occurrence and progression

In 2008–2010, the 1,690 subjects were invited to attend the second survey of the ROAD study, a 3-year follow-up consisting of examinations identical to those at baseline. Knee radiographs were read by a single experienced orthopaedist (SM) without knowledge of participants' clinical status and were categorized using the Kellgren–Lawrence (KL) grading scale[27]. When there were differences in the KL grades between the two knees, the higher KL grade was assigned to the participant. A subject with KL $\geq$ 2 was defined as having radiographic KOA. A new KOA case was identified if both knees had a KL grade $<$ 2 at baseline and if at least one knee developed a KL of $\geq$2 during follow-up. KOA progression was defined as the KL grade for either knee being higher during follow-up than at baseline.

Statistical analysis

All statistical analyses were performed using STATA statistical software (STATA Corp., College Station, TX, USA). Differences in proportions were compared using the chi-square test. Differences in continuous variables were tested for significance using analysis of variance for multiple groups or Scheffe's least significant difference test for pairs of groups. All P values and 95% confidence intervals (CI) are two-sided.

To clarify associations between KOA occurrence or progression and MS risk factors, we performed three types of multivariate logistic regression analysis. Model 1 was performed using KOA occurrence or progression (over 3 years, 1: yes, 0: no) as the objective variable. Each risk factor for MS, that is, continuous variables such as BMI, systolic BP, diastolic BP, and serum HDL-cho and HbA1c levels, and categorical variables such as OW (1: presence, 0: absence), HT (1: presence, 0: absence), DL (1: presence, 0: absence), and IGT (1: presence, 0: absence) were considered as an individual explanatory variable after adjusting for age and gender. Model 2 was performed using the same objective variable and individual explanatory factor for MS as in Model 1, after adjustment for age, gender, regional differences, smoking, alcohol

consumption, bicycling, regular exercise, and history of knee injuries, all of which had been found to be significantly associated with KOA presence in a previous study using the same population[17]. Model 3 was obtained by multivariate logistic regression analysis using the same objective variable and the same adjustment factors as in Model 2; furthermore, other MS components were included in the mutual adjustment model. For example, when BMI was selected as an objective factor, Model 3 was obtained by multivariate logistic regression after adjustment for age, gender, regional differences, smoking, alcohol consumption, bicycling, regular exercise, history of knee injuries, systolic BP, and serum HDL-cho and HBA1c levels. Similarly, when OW was selected as an objective factor, Model 3 was obtained by multivariate logistic regression after adjustment for age, gender, regional differences, smoking, alcohol consumption, bicycling, regular exercise, history of knee injuries, HT, DL, and IGT. Because systolic and diastolic BP was moderately correlated ($r = 0.5643$, $P < 0.001$), only values of systolic BP were used as representative of BP in Model 3.

To further evaluate associations between the number of MS components and KOA occurrence and progression, we used two multivariate logistic regression models. In Model 4, we used KOA occurrence or KL grade progression as the objective variable and the number of MS components present (OW, HT, DL, and IGT) as the explanatory variable, after adjusting for age and gender. In Model 5, we used KOA occurrence or progression as the objective variable and the number of MS components present as the explanatory variable, after adjusting for age, gender, regional differences, smoking, alcohol consumption, bicycling, regular exercise, and history of knee injuries.

Results

Eligible participants

Of the 1,690 baseline survey participants, 251 (14.9%; men, 104; women, 147) dropped out of the follow-up study. The reasons for the drop-outs are shown in Fig. 1. In this study, we used the data for the remaining 1,384 subjects (81.9%; men, 466; women, 918) who completed all examinations in both baseline and follow-up surveys.

Table I shows baseline characteristics of the 1,384 participants and mean values for BMI, systolic and diastolic BP, and serum HDL-cho and HbA1c levels, classified by gender. Men had significantly higher BMI, higher systolic and diastolic BP, and lower serum HDL-cho levels than women. However, serum HbA1c levels did not show

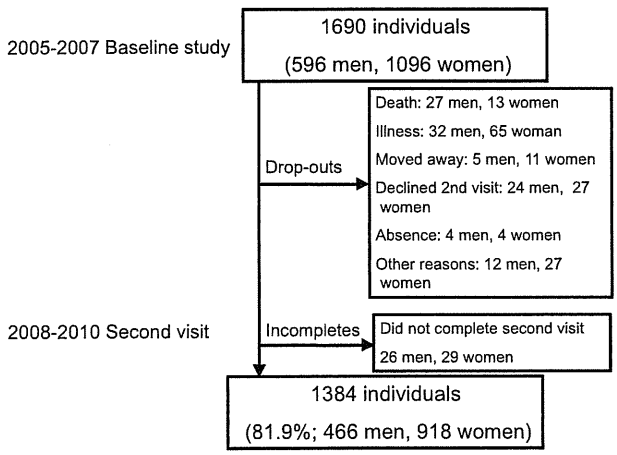

Fig. 1. Flow of participants in the baseline and second surveys.

Table I
Baseline characteristics of subjects who participated in both the first and second surveys

	Total	Men	Women	*P* (men vs women)
Number of subjects classified by age-strata (%)				
≤39 (year)	39 (2.8)	10 (2.1)	29 (3.2)	0.23
40–49	135 (9.8)	40 (8.6)	95 (10.3)	
50–59	298 (21.5)	99 (21.2)	199 (21.7)	
60–69	413 (29.8)	131 (28.1)	282 (30.7)	
70–79	404 (29.2)	155 (33.3)	249 (27.1)	
≥80	95 (6.9)	31 (6.7)	64 (7.0)	
Total	1384 (100.0)	466 (100.0)	918 (100.0)	
Means (standard deviations) of selected characteristics				
Age (year)	63.9 (11.8)	64.9 (11.6)	63.4 (11.9)	0.0246*
Height (cm)	155.6 (9.0)	164.0 (7.0)	151.3 (6.7)	<0.001***
Weight (kg)	56.0 (10.7)	62.1 (10.7)	52.5 (8.7)	<0.001***
Prevalence of selected characteristics, %				
Residing in a coastal area	54.1	51.9	55.2	0.245
Current smoking habit (more than once a month)	12.3	29.4	3.5	<0.001***
Current alcohol consumption (more than once a month)	40.6	68.2	26.6	<0.001***
Bicycling every day in the past 12 months	55.5	55.2	55.7	0.859
Regular exercise, i.e., football, tennis, baseball, or golf, after graduation from school (%)	15.3	36.1	4.7	<0.001***
Past injury of either knee (%)	2.5	1.9	2.8	0.313
Medication for components of MS, %				
Medication for HT	29.8	27.5	31.1	0.169
Medication for DL	7.2	3.4	9.2	<0.001***
Medication for diabetes mellitus, including insulin injection	5.6	7.3	4.8	0.056
Mean values (standard deviations) for components of MS				
BMI (kg/m^2)	23.1 (3.4)	23.4 (3.2)	22.9 (3.4)	0.0089
Systolic BP (mm Hg)	134.1 (20.4)	136.6 (18.3)	132.9 (21.4)	0.0015**
Diastolic BP (mm Hg)	74.2 (11.4)	77.0 (11.5)	72.8 (11.0)	<0.0001***
Serum levels of HDL-cho (mg/dL)	61.2 (15.9)	55.8 (16.1)	64.0 (15.0)	<0.0001***
Serum levels of HbA1c (%)	5.19 (0.73)	5.23 (0.85)	5.17 (0.67)	0.1900
Prevalence of components of MS, %				
OW	25.7	28.1	24.4	0.135
HT	67.2	72.7	64.4	0.002**
DL	13.0	15.2	11.9	0.079
IGT	21.1	24.7	19.3	0.020*

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

significant gender-based differences. In the total population, the MS component with the highest prevalence was HT, followed by OW, IGT, and DL. The prevalences of HT and IGT were significantly higher in men than in women.

KOA occurrence and progression and MS components

Baseline KOA prevalence in the 1,384 individuals was 46.8% (men, 37.3%; women, 51.6%). After exclusion of subjects having KOA (KL grade ≥ 2 in at least one knee) at baseline, the cumulative KOA incidence during the 3-year follow-up was estimated using a population-at-risk of 728 individuals (men, 290; women, 438) without

KOA in either knee at baseline. Among these subjects, 71 new KOA cases (men, 18; women, 53) were detected, with a cumulative incidence of 3.3%/year (men, 2.1%/year; women, 4.0%/year). After excluding subjects with KL grade = 4 for at least one knee at baseline, the progression rate over the 3-year follow-up was estimated using the population-at-risk of 1,296 individuals (men, 445; women, 851). Among these, 311 individuals (men, 86; women, 225) had a higher KL grade for one or both knees at follow-up than at baseline. The progression proportion of the KL grade for either knee over the 3-year period was 24.0% (8.0%/year; men, 6.4%/year; women, 8.8%/year) in the overall population-at-risk.

Table II shows cumulative KOA incidence and progression, classified by age groups of ≤39, 40–49, 50–59, 60–69, 70–79, and ≥80 years, which significantly increased with age. BMI, systolic BP, and HbA1c levels at baseline were significantly higher and HDL-cho levels significantly lower in subjects with KOA than in those without KOA. Similar to KOA, BMI, systolic BP, and HbA1c levels were significantly higher and HDL-cho levels significantly lower in subjects with KL grade progression than in those without. This tendency was much more pronounced in women than in men.

Table III shows multivariate logistic regression analysis results for KOA occurrence vs values for each MS component, including BMI, systolic BP, diastolic BP, and serum HDL-cho and HbA1c levels measured at baseline (Table III). Model 2 showed that BMI, systolic BP, and serum HDL-cho levels were significantly associated with KOA occurrence after adjustment for various risk factors. However, Model 3, incorporating mutual adjustment for each MS component, indicated that only BMI was significantly associated with KOA occurrence. The three types of multivariate logistic regression analyses using KOA progression as the objective factor showed similar results as for KOA occurrence described above.

Table IV shows associations between KOA occurrence and MS risk factors. Both Models 1 and 2 revealed that OW, HT, and IGT were significantly associated with KOA. Analysis using OW, HT, DL, and IGT as explanatory variables with mutual adjustment (Model 3) indicated that HT and IGT were significantly associated with KOA. Table IV also shows associations between KOA progression and MS risk factors, indicating that OW and HT were significantly associated with KOA progression. Although IGT was significantly associated with KOA progression after adjustment for age and gender, the effect diminished after adjustment for various other risk factors.

KOA occurrence and progression and the number of MS components

Figure 2 shows the cumulative KOA incidence (%/year) classified by the number of MS components present. In the total population, the cumulative incidence classified by the number of MS

Table II
Mean values (standard deviations) for components of MS vs occurrence and progression of KOA

	Total			Men			Women		
	KOA (−)	KOA (+)	*P*	KOA (−)	KOA (+)	*P*	KOA (−)	KOA (+)	*P*
	(*n* = 657)	(*n* = 71)		(*n* = 272)	(*n* = 18)		(*n* = 385)	(*n* = 53)	
Occurrence of KOA									
Number of subjects classified by age-strata (cumulative incidence, %/year)									
≤39 (year)	38	0 (0.0)	<0.001	10	0 (0.0)	0.009	28	0 (0.0)	<0.001
40–49	118	1 (0.3)		36	0 (0.0)		82	1 (0.4)	
50–59	201	15 (2.3)		77	0 (0.0)		124	15 (3.6)	
60–69	177	27 (4.4)		76	11 (4.2)		101	16 (4.6)	
70–79	108	23 (5.9)		62	6 (2.9)		46	17 (9.0)	
≥80	15	5 (8.3)		11	1 (2.8)		4	4 (16.7)	
Mean values (standard deviations) for age and components of MS									
Age (year)	58.2 (11.8)	67.3 (8.2)	<0.0001	61.0 (11.8)	70.0 (6.1)	0.0021	56.4 (11.4)	66.4 (8.7)	<0.0001
BMI (kg/m^2)	22.4 (3.2)	23.6 (2.9)	0.0035	23.2 (3.2)	24.2 (3.1)	0.1709	21.9 (3.1)	23.4 (2.8)	0.0012
Systolic BP (mm Hg)	129.6 (19.4)	138.2 (19.1)	0.0005	133.4 (17.9)	143.4 (17.7)	0.0255	127.0 (20.0)	136.5 (19.4)	0.0014
Diastolic BP (mm Hg)	74.3 (11.2)	74 (11.0)	0.8599	77.5 (11.8)	76.7 (10.7)	0.7907	72.0 (10.2)	73.2 (11.0)	0.4544
Serum levels of HDL-cho (mg/dL)	63.4 (16.8)	59.2 (13.3)	0.0414	57.3 (16.3)	54.6 (15.7)	0.5017	67.7 (15.8)	60.8 (12.1)	0.0021
Serum levels of HbA1c (%)	5.11 (0.67)	5.32 (0.79)	0.0142	5.24 (0.87)	5.09 (0.75)	0.4644	5.01 (0.46)	5.39 (0.80)	<0.0001
	Total			Men			Women		
	Progression (−) (*n* = 985)	Progression (+) (*n* = 311)	*P*	Progression (−) (*n* = 359)	Progression (+) (*n* = 86)	*P*	Progression (−) (*n* = 626)	Progression (+) (*n* = 255)	*P*
Progression of KOA									
Number of subjects classified by age-strata (proportion of progression, %/year)									
≤39 (year)	37	2 (1.7)	<0.001***	9	1 (3.3)	<0.001***	28	1 (1.1)	<0.001***
40–49	128	7 (1.7)		38	2 (1.7)		90	5 (1.8)	
50–59	248	44 (5.0)		89	8 (2.8)		159	36 (6.2)	
60–69	292	105 (8.2)		101	26 (6.8)		191	79 (9.8)	
70–79	241	115 (10.8)		105	38 (8.9)		136	77 (12.1)	
≥80	39	38 (16.5)		17	11 (13.1)		22	27 (18.4)	
Mean values (standard deviations) for age and components of MS									
Age (year)	61.6 (11.9)	68.7 (9.3)	<0.0001***	63.3 (11.8)	70.0 (9.4)	<0.0001***	60.7 (11.9)	68.2 (9.3)	<0.0001***
BMI (kg/m^2)	22.7 (3.3)	23.6 (3.1)	<0.0001***	23.2 (3.2)	23.9 (3.1)	0.0643	22.4 (3.3)	23.5 (3.1)	<0.0001***
Systolic BP (mm Hg)	132.2 (20.0)	137.9 (19.3)	<0.0001***	135.4 (17.9)	138.6 (17.0)	0.1390	130.4 (20.9)	137.6 (20.1)	<0.0001***
Diastolic BP (mm Hg)	74.0 (11.2)	74.5 (11.8)	0.5517	77.1 (11.6)	76.3 (10.6)	0.5698	72.3 (10.5)	73.8 (12.2)	0.0792
Serum levels of HDL-cho (mg/dL)	62.3 (16.6)	59.0 (13.8)	0.0018**	56.7 (16.4)	53.5 (15.2)	0.0921	65.4 (15.8)	61.1 (12.6)	0.0003***
Serum levels of HbA1c (%)	5.15 (0.72)	5.27 (0.74)	0.0133*	5.20 (0.84)	5.30 (0.88)	0.3687	5.11 (0.64)	5.25 (0.68)	0.0069**

KOA(−), non-occurrence of KOA; KOA(+), occurrence of KOA; progression(−), no progression of the KL grade; progression(+), progression of the KL grade.
n, number of subjects.
*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

Table III
ORs for occurrence and progression of KOA during the 3-year follow-up period vs BMI, systolic and diastolic BP, serum levels of HDL-cho, and HbA1c level

Explanatory variables	Reference	Model 1*			Model 2†			Model 3‡		
		Adjusted OR1	95% CI	P	Adjusted OR2	95% CI	P	Adjusted OR3	95% CI	P
Occurrence of KOA										
BMI (kg/m^2)	+1 kg/m^2	1.22	1.12–1.33	<0.001***	1.22	1.12–1.34	<0.001***	1.18	1.07–1.30	0.001**
Systolic BP (mm Hg)	+1 mm Hg	1.54	0.87–2.72	0.136	1.01	1.00–1.03	0.038*	1.01	1.00–1.03	0.188
Diastolic BP (mm Hg)	+1 mm Hg	1.51	0.71–3.19	0.282	1.01	0.99–1.04	0.373	–	–	–
Serum levels of HDL-cho (mg/dL)	+1 mg/dL	0.980	0.962–0.999	0.039*	0.980	0.960–0.999	0.039*	0.989	0.968–1.009	0.256
Serum levels of HbA1c (%)	+1%	1.29	0.92–1.81	0.136	1.34	0.96–1.88	0.089	1.07	0.73–1.56	0.743
Progression of KOA										
BMI (kg/m^2)	+1 kg/m^2	1.12	1.08–1.17	<0.001***	1.13	1.08–1.18	<0.001***	1.11	1.06–1.17	<0.001***
Systolic BP (mm Hg)	+1 mm Hg	1.47	1.10–1.97	0.010*	1.01	1.00–1.01	0.039*	1.00	1.00–1.01	0.352
Diastolic BP (mm Hg)	+1 mm Hg	1.33	0.92–1.91	0.124	1.01	1.00–1.025	0.057	–	–	–
Serum levels of HDL-cho (mg/dL)	+1 mg/dL	0.988	0.979–0.997	0.011*	0.987	0.978–0.997	0.008**	0.992	0.983–1.002	0.137
Serum levels of HbA1c (%)	+1 %	1.11	0.94–1.33	0.227	1.11	0.93–1.32	0.277	0.99	0.81–1.19	0.881

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

* Model 1 was obtained by a series of multivariate logistic regression analyses using the occurrence or progression of KOA (over 3 years, 1: yes, 0: no) as the objective variable and each individual explanatory variable (BMI, systolic BP, diastolic BP, serum HDL-cho, or HbA1c) after adjusting for age and gender.

† Model 2 was obtained by a series of multivariate logistic regression analyses using the occurrence or progression of KOA (over 3 years, 1: yes, 0: no) as the objective variable and each individual explanatory variable (BMI, systolic BP, diastolic BP, serum HDL-cho, or HbA1c) after adjusting for age, gender, region (0: coastal area, 1: mountainous area), smoking (0: ex- or non-smoker, 1: current smoker), alcohol consumption (0: ex- or non-drinker, 1: current drinker), bicycling every day (0: no, 1: yes), regular exercise (0: no, 1: yes), and past history of knee injuries (0: no, 1: yes).

‡ Model 3 was obtained by multivariate logistic regression analysis using the occurrence or progression of KOA (over 3 years, 1: yes, 0: no) as the objective variable and each individual explanatory variable (BMI, systolic BP, diastolic BP, serum HDL-cho, or HbA1c) after adjusting for age, gender, region (0: coastal area, 1: mountainous area), smoking (0: ex- or non-smoker, 1: current smoker), alcohol consumption (0: ex- or non-drinker, 1: current drinker), bicycling every day (0: no, 1: yes), regular exercise (0: no, 1: yes), and past history of knee injuries (0: no, 1: yes), and other potential risk factors such as BMI, systolic BP, serum levels of HDL-cho, and HbA1c levels, mutually.

components (0, 1, 2, or ≥3) was 1.0, 3.5, 3.4, and 8.7, respectively, which increased with the number of MS components (*P* for trend < 0.001). Figure 2(A) also shows the cumulative KOA incidence according to the number of MS components by gender. The cumulative incidence among individuals with one or more MS components was higher in women than in men.

Figure 2 also shows KL grade progression (%/year) for either knee classified by the number of MS components present. In the total population, KL grade progression classified by 0, 1, 2, or ≥3 MS components was 4.3, 7.6, 10.8, and 11.3, respectively, which significantly increased with the number of MS components (*P* for trend < 0.001). The progression among individuals with one or more MS components was higher in women than in men [Fig. 2(B)].

To further illustrate the effects of the number of MS components on KOA occurrence and progression, Fig. 3 presents the results of the multivariate logistic regression analysis models for KOA occurrence. Model 4 used KOA occurrence or KL grade progression as the objective variable and the number of MS components present (OW, HT, DL, and IGT) as the explanatory variable, adjusted

Table IV
ORs for occurrence and progression of KOA during the 3-year follow-up period vs risk factors for MS

Explanatory variables	Reference	Model 1*			Model 2†			Model 3‡		
		Adjusted OR1	95% CI	P	Adjusted OR2	95% CI	P	Adjusted OR3	95% CI	P
Occurrence of KOA										
Component of MS										
OW	Yes vs no	2.36	1.28–4.34	0.006**	2.46	1.32–4.59	0.005**	1.71	0.88–3.33	0.114
HT	Yes vs no	3.02	1.47–6.23	0.003**	3.27	1.57–6.80	0.002**	2.74	1.30–5.78	0.008**
DL	Yes vs no	1.34	0.65–2.73	0.425	1.55	0.75–3.23	0.240	1.20	0.55–2.59	0.646
IGT	Yes vs no	2.42	1.37–4.27	0.002**	2.47	1.38–4.41	0.002**	1.94	1.05–3.59	0.033*
Progression of KOA										
Component of MS										
OW	Yes vs no	1.76	1.30–2.38	<0.001***	1.87	1.37–2.55	<0.001***	1.66	1.21–2.29	0.002**
HT	Yes vs no	1.75	1.26–2.42	0.001**	1.75	1.26–2.43	0.001**	1.54	1.10–2.17	0.012*
DL	Yes vs no	1.18	0.81–1.71	0.400	1.36	0.93–2.01	0.117	1.26	0.85–1.87	0.248
IGT	Yes vs no	1.42	1.04–1.94	0.029*	1.35	0.98–1.87	0.068	1.18	0.84–1.64	0.336

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

Being OW was defined as BMI ≥ 25 kg/m^2, HT as systolic BP ≥ 130 mm Hg and/or diastolic BP ≥ 85 mm Hg, DL as serum HDL-cho level < 40 mg/dL, and IGT as serum HbA1c level ≥ 5.5%. Further, subjects being treated with medication for HT, DL, or IGT were regarded as having the respective disorder.

* Model 1 was obtained by a series of multivariate logistic regression analyses using the occurrence or progression of KOA (over 3 years, 1: yes, 0: no) as the objective variable and each individual explanatory variable (being OW, HT, DL, or IGT) after adjusting for age and gender.

† Model 2 was obtained by a series of multivariate logistic regression analyses using the occurrence or progression of KOA (over 3 years, 1: yes, 0: no) as the objective variable and each individual explanatory variable (being OW, HT, DL, and IGT) after adjusting for age, gender, region (0: coastal area, 1: mountainous area), smoking (0: ex- or non-smoker, 1: current smoker), alcohol consumption (0: ex- or non-drinker, 1: current drinker), bicycling every day (0: no, 1: yes), regular exercise (0: no, 1: yes), and past history of knee injuries (0: no, 1: yes).

‡ Model 3 was obtained by multivariate logistic regression analysis using the occurrence or progression of KOA (over 3 years, 1: yes, 0: no) as the objective variable and being OW, HT, DL, and IGT as explanatory variables, after adjusting for age, gender, region (0: coastal area, 1: mountainous area), smoking (0: ex- or non-smoker, 1: current smoker), alcohol consumption (0: ex- or non-drinker, 1: current drinker), bicycling every day (0: no, 1: yes), regular exercise (0: no, 1: yes), past history of knee injuries (0: no, 1: yes), and other components of MS, mutually.