Table 2. Incidence of radiographic knee OA, progressive knee OA, and knee pain according to sex*

	K/L grade ≥1		K/L grade ≥2		K/L grade ≥3		Progressive knee OA		Knee pain	
	No. at risk	Cumulative incidence, no. (%)	No. at risk	Cumulative incidence, no. (%)	No. at risk	Cumulative incidence, no. (%)	No. at risk	Cumulative incidence, no. (%)	No. at risk	Cumulative incidence, no. (%)
Overall	364	70 (19.2)	1,098	107 (9.7)	1,907	228 (12.0)	1,084	229 (21.1)	1,784	447 (25.1)
Men	177	35 (19.8)	467	32 (6.9)	688	58 (8.4)	276	49 (17.8)	652	138 (21.2)
Women	187	35 (18.7)	631	75 (11.9)†	1,219	169 (13.9)†	808	180 (22.3)	1,132	309 (27.3)†

* See Table 1 for definitions.
† $P < 0.05$ versus men, by chi-square test.

RESULTS

Of the 3,040 subjects in the baseline study in 2005–2007, 125 (4.1%) had died by the time of the review 3 years later, 123 (4.0%) did not participate in the followup study due to bad health, 69 (2.3%) had moved away, 83 (2.7%) declined the invitation to attend the followup study, and 155 (5.1%) did not participate in the followup study for other reasons. Among the 2,485 subjects who did participate in the followup study, 175 (5.8%) did not undergo plain radiography and 18 (0.6%) provided incomplete pain questionnaires; these were excluded. We also excluded 30 subjects (1.0%) who underwent total knee arthroplasty before the followup study, leaving a total of 2,262 subjects (74.4%) (763 men and 1,499 women) from whom paired radiographs and complete pain histories were obtained. Their mean ± SD age at followup was 72.2 ± 11.4 years. The mean ± SD duration of followup between initial and second radiographs was 3.3 ± 0.6 years. Those participating in the followup study were younger than those who did not survive or who did not participate for other reasons (mean age 68.6 years for responders versus 75.1 years for nonresponders; $P < 0.0001$). The followup study participants also were more likely to be women (66.3% of responders were women and 61.8% of nonresponders were women; $P = 0.03$) and were less likely to have knee OA at the baseline examination than either those who did not survive to followup or those who did not participate for other reasons (51.5% of responders versus 60.9% of nonresponders; $P < 0.0001$).

The characteristics of the 2,262 participants at baseline in the ROAD study are shown in Table 1. Men were significantly older than women, while BMI was higher in men than in women. The prevalence of knee OA and knee pain was significantly higher in women than in men at baseline. The proportion of previous knee injuries was also higher in women than in men. The number of subjects with each K/L grade at baseline and at followup is shown in Figure 1.

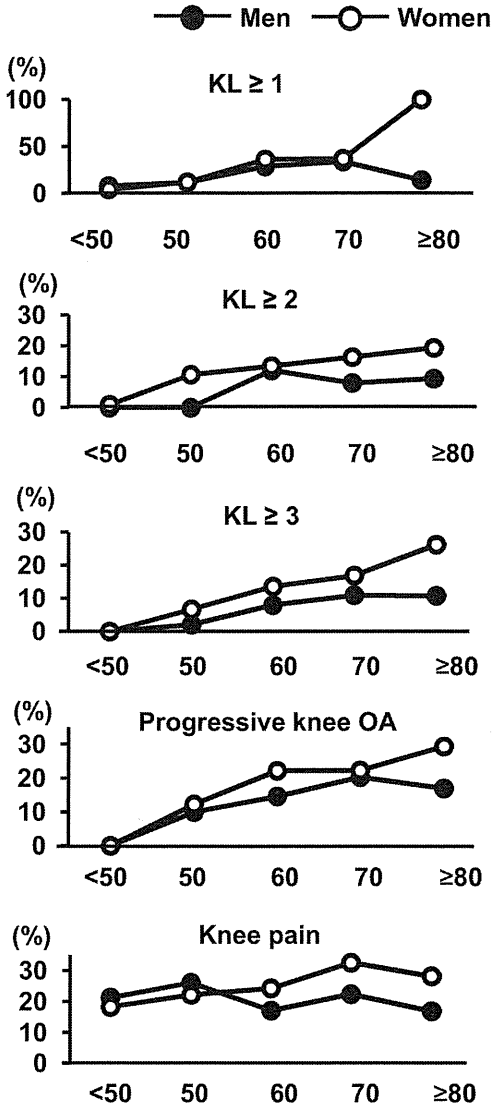

Figure 2. Percentage of subjects with incident radiographic knee osteoarthritis (OA) (Kellgren/Lawrence [K/L] grade ≥1, ≥2, or ≥3), progressive knee OA, and incident knee pain in each age stratum (<50 years, 50–59 years, 60–69 years, 70–79 years, and ≥80 years).

Table 3. Risk factors for incident radiographic knee osteoarthritis*

	K/L grade ≥2			K/L grade ≥3		
	No./total no. (%) of subjects	Crude OR (95% CI)	Adjusted OR (95% CI)	No./total no. (%) of subjects	Crude OR (95% CI)	Adjusted OR (95% CI)
Age (+5 years)	–	1.26 (1.15–1.39)	1.31 (1.15–1.49)	–	1.33 (1.23–1.44)	1.25 (1.13–1.39)
BMI (+5 kg/m^2)	–	2.00 (1.49–2.69)	2.43 (1.76–3.39)	–	1.67 (1.36–2.04)	1.68 (1.35–2.11)
Grip strength (+1 kg)	–	0.96 (0.94–0.98)	1.01 (0.97–1.04)	–	0.95 (0.94–0.97)	1.00 (0.97–1.02)
Sex						
Men	32/467 (6.9)	Referent	Referent	58/688 (8.4)	Referent	Referent
Women	75/631 (11.9)	1.83 (1.20–2.86)	2.76 (1.50–5.18)	169/1,219 (13.9)	1.75 (1.28–2.41)	1.42 (0.88–2.29)
K/L grade at baseline						
0	–	Referent	Referent	–	Referent	Referent
1	–	4.11 (2.33–7.83)	2.48 (1.35–4.87)	–	1.91 (0.69–5.43)	1.29 (0.45–3.80)
2	–	–	–	–	5.69 (2.38–14.30)	5.94 (1.07–35.83)
Knee pain at baseline						
No	–	Referent	–	–	Referent	Referent
Yes	–	0.91 (0.32–2.24)	–	–	3.77 (2.44–5.73)	2.53 (1.59–4.00)
Previous knee injury						
No	–	Referent	–	–	Referent	–
Yes	–	4.08 (0.66–18.8)	–	–	1.24 (0.45–3.11)	–
Smoking						
No	99/958 (10.3)	Referent	–	213/1,713 (12.4)	Referent	Referent
Yes	8/140 (5.7)	0.53 (0.23–1.04)	–	14/194 (7.2)	0.55 (0.30–0.93)	1.07 (0.55–1.94)
Alcohol use						
No	68/627 (10.9)	Referent	–	158/1,171 (13.5)	Referent	Referent
Yes	39/471 (8.3)	0.74 (0.49–1.12)	–	69/736 (9.4)	0.66 (0.49–0.89)	0.96 (0.67–1.36)

* Adjusted odds ratios (ORs) were calculated by multiple generalized estimating equation logistic regression analysis after adjustment for all other variables in addition to regions. We show all variables we analyzed in the present study. K/L = Kellgren/Lawrence; 95% CI = 95% confidence interval; BMI = body mass index.

Table 2 shows the rates of incident and progressive knee OA and incident knee pain in the overall population and subgroups classified by sex. The incidences of K/L grade ≥2 and K/L grade ≥3 knee OA and knee pain were significantly higher in women than in men, while there were no significant differences in the incidence of K/L grade ≥1 knee OA and the progression of knee OA between men and women. The incidence and progression rate of knee OA tended to increase with age in men and women (for 5-year increase: K/L grade ≥1, OR 1.22 [95% CI 1.06–1.43] and OR 1.52 [95% CI 1.29–1.84], respectively; K/L grade ≥2, OR 1.35 [95% CI 1.12–1.67] and OR 1.29 [95% CI 1.15–1.45], respectively; K/L grade ≥3, OR 1.34 [95% CI 1.15–1.58] and OR 1.35 [95% CI 1.24–1.49], respectively; progressive knee OA, OR 1.15 [95% CI 0.95–1.42] and OR 1.15 [95% CI 1.0–1.28], respectively) (Figure 2). Interestingly, the incidence rate of knee pain was age-dependent in women (OR 1.10 [95% CI 1.04–1.17]), while it was not age-dependent in men (OR 0.97 [95% CI 0.90–1.06]). Furthermore, in subjects age <60 years, the incidence of knee pain was similar between women and men (OR 1.12 [95% CI 0.88–1.42]), while in subjects age >60 years, the incidence of knee pain was significantly higher in women than in men (OR 0.78 [95% CI 0.68–0.88]) (Figure 2).

Table 3 shows the baseline risk factors for incident radiographic knee OA. Univariate logistic regression analysis showed that age, BMI, grip strength, sex, and K/L grade were associated with incident K/L grade ≥2 knee OA. Age, BMI, grip strength, sex, K/L grade, knee pain at baseline, previous knee injury, smoking, and alcohol consumption were associated with incident K/L grade ≥3 knee OA. We then determined independent risk factors using a multiple logistic regression analysis that included the above significant factors in the univariate model in addition to regions as independent variables. The results showed that age and BMI were risk factors for incident K/L grade ≥2 and incident K/L grade ≥3 knee OA. Female sex was a risk factor for incident K/L grade ≥2 knee OA, while being female was not significantly associated with incident K/L grade ≥3 knee OA. A more severe K/L grade at baseline was strongly associated with incident K/L grade ≥2 and incident K/L grade ≥3 knee OA. Knee pain at baseline was significantly associated with incident K/L grade ≥3 knee OA.

Univariate logistic regression analysis showed

Table 4. Risk factors for progressive knee OA and incident knee pain*

	Progressive knee OA			Knee pain		
	No./total no. (%) of subjects	Crude OR (95% CI)	Adjusted OR (95% CI)	No./total no. (%) of subjects	Crude OR (95% CI)	Adjusted OR (95% CI)
Age (+5 years)	–	1.14 (1.04–1.25)	1.17 (1.05–1.30)	–	1.05 (1.01–1.10)	1.01 (0.95–1.07)
BMI (+5 kg/m^2)	–	1.47 (1.20–1.80)	1.43 (1.16–1.77)	–	1.60 (1.37–1.88)	1.54 (1.30–1.82)
Grip strength (+1 kg)	–	0.98 (0.96–1.00)	0.99 (0.96–1.01)	–	0.98 (0.97–1.00)	1.00 (0.98–1.02)
Sex						
Men	49/276 (17.8)	Referent	–	138/652 (21.2)	Referent	Referent
Women	180/808 (22.3)	1.33 (0.94–1.90)	–	309/1,132 (27.3)	1.40 (1.11–1.76)	1.32 (0.94–1.84)
K/L grade at baseline						
0 and 1	–	–	–	–	Referent	Referent
2	–	–	–	–	1.89 (0.80–4.49)	1.58 (0.65–3.85)
3 and 4	–	–	–	–	3.17 (1.95–5.17)	2.54 (1.52–4.24)
Knee pain at baseline						
No	–	Referent	Referent	–	–	–
Yes	–	2.87 (1.99–4.14)	2.63 (1.81–3.81)	–	–	–
Previous knee injury						
No	–	Referent	–	–	Referent	Referent
Yes	–	0.79 (0.31–1.86)	–	–	3.09 (1.34–7.23)	2.91 (1.26–6.82)
Smoking						
No	219/1,016 (21.6)	Referent	–	411/1,603 (25.6)	Referent	–
Yes	10/68 (14.7)	0.63 (0.30–1.19)	–	36/181 (19.9)	0.72 (0.49–1.04)	–
Alcohol use						
No	168/746 (22.4)	Referent	–	281/1,093 (25.7)	Referent	–
Yes	61/338 (18.1)	0.76 (0.54–1.04)	–	166/691 (24.0)	0.91 (0.73–1.14)	–

* Adjusted ORs were calculated by multiple generalized estimating equation logistic regression analysis after adjustment for all other variables in addition to regions. We show all variables we analyzed in the present study. OA = osteoarthritis (see Table 3 for other definitions).

that age, BMI, grip strength, and knee pain at baseline were associated with progressive knee OA. We then included age, BMI, grip strength, and knee pain at baseline in addition to regions as independent variables in a multiple logistic regression analysis to determine independent risk factors (Table 4). Age and BMI at baseline were risk factors, but their adjusted ORs for progressive knee OA were lower than those for incident K/L grade ≥2 knee OA (Table 4). Knee pain was significantly associated with progressive knee OA.

We further investigated risk factors for incident knee pain (Table 4). Univariate logistic regression analysis showed that age, BMI, grip strength, sex, K/L grade, and previous knee injury were associated with incident knee pain. To determine independent risk factors for knee pain, multiple logistic regression analysis was used with age, BMI, grip strength, sex, K/L grade, and previous knee injury in addition to regions as independent variables. BMI was significantly associated with incident knee pain, but female sex was not associated with incident knee pain. Subjects with K/L grade ≥3 knee OA at baseline had an ~2.5-fold increased risk for incidence of knee pain compared with K/L grade 0 and K/L grade 1 knees. Previous knee injury was also significantly associated with incident knee pain.

DISCUSSION

This is the first population-based study to examine the incidence and progression of knee OA and risk factors for incident and progressive knee OA among Japanese men and women. We also examined the incident rate of knee pain and its risk factors. The present study showed high rates of incident knee OA, progressive knee OA, and incident knee pain.

Few population-based studies have examined incident radiographic knee OA (6–9). In the Framingham Osteoarthritis Study (6), given the ~8.1-year followup, the incident rate of K/L grade ≥2 knee OA was 11.1% and 18.1% (1.4% and 2.2% per year) in Caucasian men and women, respectively. A population-based study in the UK (18) showed that given the ~5.1-year followup, the incident rate of K/L grade ≥2 knee OA was 18.5% (2.3% per year), but men and women were not separated in the analysis. In the present study, the incidence of K/L grade ≥2 OA was 2.0% and 3.7% per year in men and women, respectively, which is a little higher than that in previous epidemiologic studies in the US and Europe (6,8), implying that the incidence is higher among Japanese than in Caucasians. This is compatible with our findings regarding prevalence of K/L grade ≥2 knee OA

in our previous study (2), which showed that the prevalence of K/L grade ≥2 knee OA was much higher in Japanese people than in Caucasians (10,11).

For incident K/L grade ≥3 knee OA, to the best of our knowledge no population-based studies have been previously reported. In the Chingford Study (7), knee OA was not defined according to K/L grade but according to osteophytosis and joint space narrowing. The Chingford Study showed that given the ~4-year followup, the incidence of joint space narrowing was 12.6% (3.2% per year) in women, which may be comparable to our results for incident K/L grade ≥3 knee OA, considering the K/L grade definition; however, a closer comparison provides quite limited accuracy.

In the present study, the incident rate of K/L grade ≥3 knee OA was 4.1% per year in Japanese women, which was also a little higher than that seen in Caucasian women. However, this higher incident rate of K/L grade ≥3 may be partly explained by the definition of K/L grade ≥3 knee OA, because by considering any knees that start at K/L grade <3 as eligible for this outcome, we combined incident (e.g., knees starting at K/L grade 0–1) and progressive (knees starting at K/L grade 2) disease. In the present study, we also examined progression of knee OA, and we found that the progression rate of knee OA was 5.2% and 6.3% per year in Japanese men and women, respectively, which was also higher than that in other studies in the US and the UK (2.2–3.9%) (6,8). The higher incidence of radiographic knee OA in Japan could also be due to lifestyle factors, because the traditional Japanese lifestyle includes sitting on the heels on a mat and using Japanese-style lavatories, requiring squatting and kneeling, which are associated with knee OA (31–33). These positions may cause mechanical stress to the knee joint and possibly lead to the acceleration of OA.

Although the rate of incident radiographic knee OA and progressive knee OA increased with age in both sexes, that of knee pain was age-dependent in women but not in men. This may be due to the fact that elderly men generally retire from their occupations at age ~60–70 years, and thus the load on the knees may be lighter in men age >60 years compared with those age <60 years, whereas women must often continue to do household chores even after age 70 years, and thus the load on the knees may not be lighter in women age >70 years compared with those age <70 years.

The present study also showed that age and BMI are risk factors for incident radiographic knee OA, consistent with findings of previous epidemiologic studies (5,7,8). Previous studies have shown that obesity is a strong risk factor for incident knee OA (34), possibly due to the accumulation of mechanical stress on the knee joint. More severe K/L grade was also a risk factor for incident radiographic knee OA in the present study, which is also consistent with findings of previous studies (7,8). Female sex was also a strong risk factor for incident K/L grade ≥2 knee OA, as in previous studies (6,8), possibly implicating the involvement of muscle strength to compensate for mechanical stress, as women are known to have less muscle strength than men in all decades of life (35). However, female sex was not a significant risk factor for incident K/L grade ≥3 knee OA or progressive knee OA. Furthermore, age and BMI at baseline were risk factors for progressive knee OA, but their ORs for progressive knee OA were lower than those for incident K/L grade ≥2 knee OA.

This discordance between the determinants of incidence of K/L grade ≥2 and K/L grade ≥3 knee OA or between those of incidence and progression of knee OA using K/L grade suggests that different mechanisms might influence the initiation of osteophytosis (the principal abnormality in K/L grade 2 disease) and joint space narrowing (the principal abnormality in K/L grade 3 disease). However, since K/L grade was defined by a categorical method, which is comparably insensitive to change, this discordance might simply be a function of the scoring system. Nevertheless, there is also accumulating evidence from previous studies that osteophytosis and joint space narrowing have distinct etiologic mechanisms. A recent cross-sectional study has shown that osteophytosis is unrelated not only to joint space narrowing on plain radiographs, but also to cartilage loss measured by quantitative magnetic resonance imaging (36). Furthermore, our study of an experimental mouse model of OA has identified a cartilage-specific molecule, carminerin, that regulates osteophytosis without affecting joint cartilage destruction during OA progression (37,38). Our most recent findings have implications for our understanding of the pathogenesis of knee OA, as well as for preventive strategies.

In the present study, knee pain was a risk factor for incident K/L grade ≥3 knee OA and progressive knee OA. Subjects with knee pain may tend not to go out or exercise because of the pain, which may lead to lower quadriceps strength. This may be one of the reasons why knee pain is a risk factor for incident and progressive knee OA, as quadriceps weakness has been previously associated with radiographic knee OA (39).

For incidence of knee pain, age was not a risk factor after adjustment for BMI, sex, and K/L grade at baseline. Knee pain occurrence may be mainly due to

environmental factors rather than individual factors. As described above, elderly men generally retire from their occupations at ages 60–70 years, and thus the load on the knees may be lighter in men age <60 years compared with those age >60 years, which may partly explain the lack of significant association between age and incidence of knee pain. BMI was a risk factor for incident knee pain even after adjustment for K/L grade at baseline, indicating that obesity is a strong risk factor not only for incident radiographic knee OA but also for incident knee pain. In addition, knee OA at baseline was a risk factor for knee pain, but the ORs for knee pain of K/L grade 2 knee OA and K/L grades 3 and 4 knee OA were just 1.6 and 2.5, respectively. In fact, the proportion of subjects with knee pain of those with K/L grade 2 knee OA and K/L grades 3 and 4 knee OA was just 28.0% and 47.1%, respectively, indicating that ~70% of subjects with K/L grade 2 knee OA who had no knee pain at baseline and ~50% of subjects with K/L grades 3 and 4 knee OA who had no knee pain at baseline also had no knee pain after 3 years.

Previous cross-sectional studies have also demonstrated that correlation of knee pain with radiographic severity of knee OA is not as strong as one would expect (2,40–42), most likely because knee pain may arise from a variety of structures other than joint cartilage, such as the menisci, synovium, ligaments, bursae, bone, and bone marrow (43–47). Hence, comprehensive mechanistic studies of 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.

We were unable to detect an association between knee injury and incident OA in the present study. Other cross-sectional studies of OA prevalence have observed strong association with previous knee injury (48), while the incidence data from the Zoetermeer Study, Framingham Study, and Chingford Study (5–7) also showed a slight increase in risk with interim knee injury but were based on small numbers; no significant association with past knee injury was seen in those groups. In the present study, K/L grade ≥2 knee OA in subjects with previous knee injury was not significantly associated with previous knee injury, which suggests that the association of incident radiographic knee OA with previous knee injury may be weak, although the number of subjects with incident K/L grade ≥2 knee OA who had previous knee injury was just 12. Thus, the small number may partly explain the lack of statistical significance. The present study showed that previous knee injury is a risk factor for incident knee pain. As mentioned above, the correlation of knee pain with radiographic severity of knee OA is not as strong as expected (2,40–42), as knee pain may arise from a variety of structures other than joint cartilage, such as menisci, synovium, ligaments, bursae, bone, and the bone marrow (43–47), and these tissues may have been damaged by a previous knee injury, which may lead to the incident knee pain.

We were unable to detect an association between smoking/drinking alcohol and incident knee OA or knee pain. The association between smoking and incident knee OA is controversial. The Zoetermeer Study showed that smoking has no association with incident knee OA (5), while incidence data from the Framingham Study showed that smoking protects against incident knee OA (49). We were also unable to show any effect of physical activity in this incidence study. However, the numbers and power were too low to examine this group and to confirm or exclude such effects on incidence.

The present study has several limitations. First, the radiographic investigators did not have readers calibrate their readings to those from other studies. Although we reported a higher incidence of radiographic knee OA than in previous studies, differences in 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 had a substantial impact on their incidence. The high incidence 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 concordance between radiographic knee OA and its pain. Third, we defined knee pain as present or absent, rather than as a continuous measure such as the Western Ontario and McMaster Universities Osteoarthritis Index (50) or visual analog scale score. Categorical methods are statistically less powerful than continuous methods. Thus, the association between knee pain and other variables might have been underestimated 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 knee OA in Japan compared with previous studies. Age, BMI, and female sex influence incidence more than radiographic progression of knee OA, indicating that different mechanisms might influence the initiation of osteophytosis and joint space narrowing. Knee pain was a risk factor for radiographic knee OA. Knee injury was not signifi-

cantly associated with radiographic knee OA, but was a risk factor for incident knee pain. Further progress, along with continued longitudinal surveys within the ROAD study, will elucidate the environmental and genetic backgrounds of knee OA.

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AUTHOR CONTRIBUTIONS

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

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

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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.

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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 $\geq$ 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 $\geq$2 disease at follow-up. Incident KL $\geq$ 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 $\geq$ 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 $\pm$ 11.5 years. The duration of follow-up between the initial and second radiographs was 3.3 $\pm$ 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 $\geq$ 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.

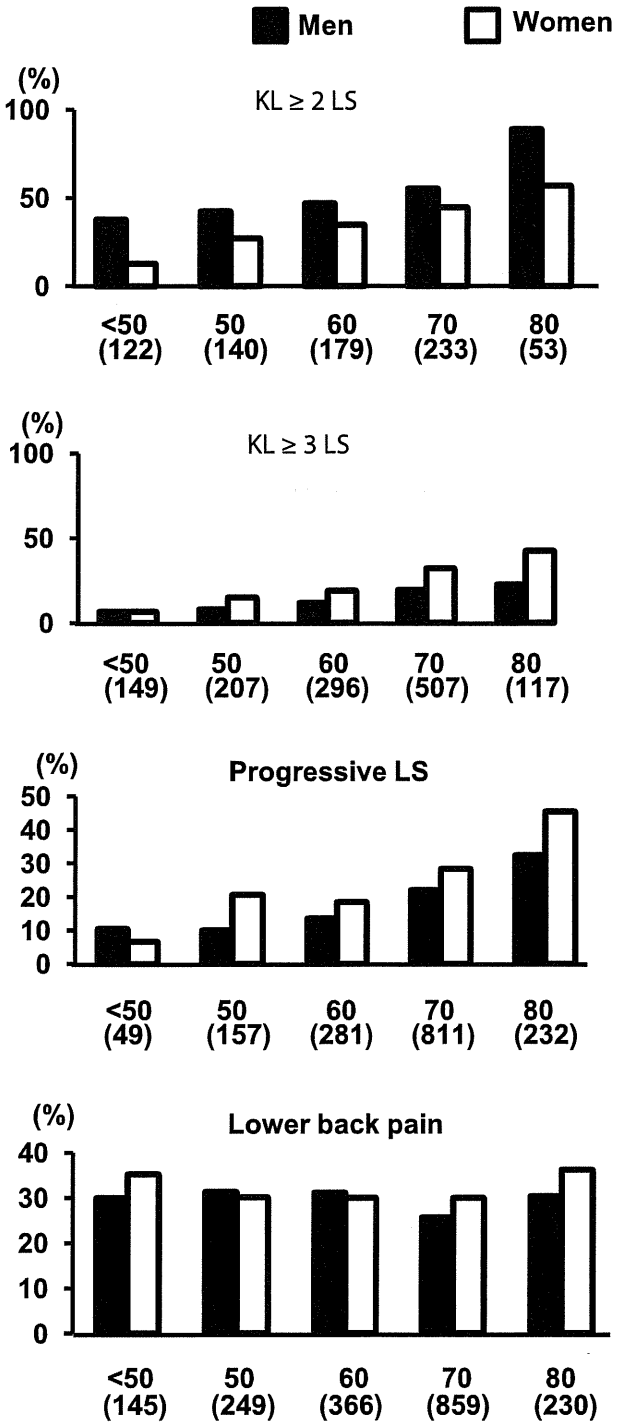

Fig. 1. Ratios (%) of individuals with incident radiographic LS (KL ≥ 2 and KL ≥ 3), progressive LS and incident lower back pain in each age stratum (<50, 50–59, 60–69, 70–79 and ≥80 years). Data in brackets are the number of individuals in each group.

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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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

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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

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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

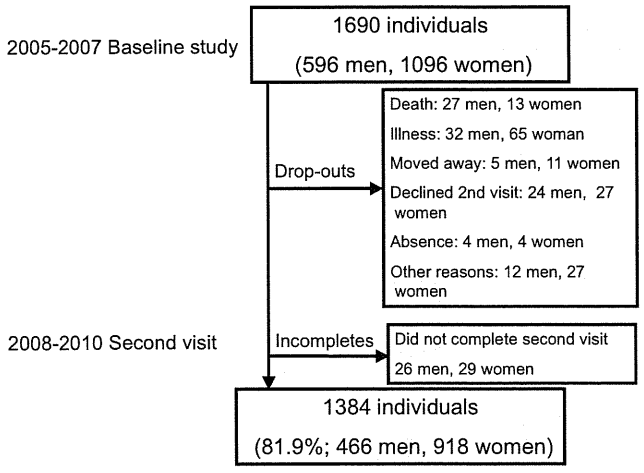


Fig. 1. Flow of participants in the baseline and second surveys.

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.

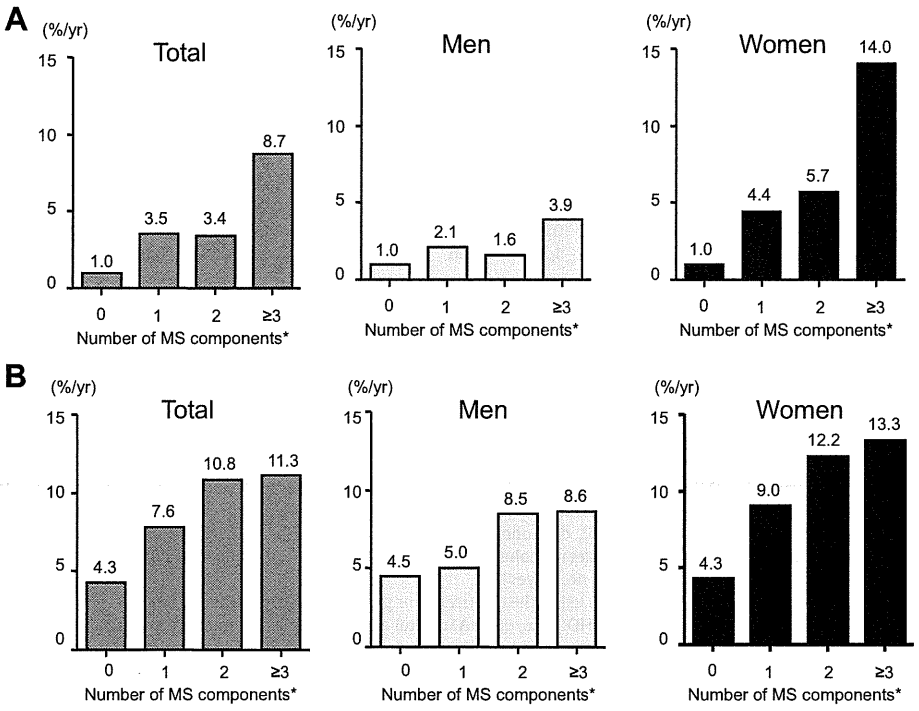
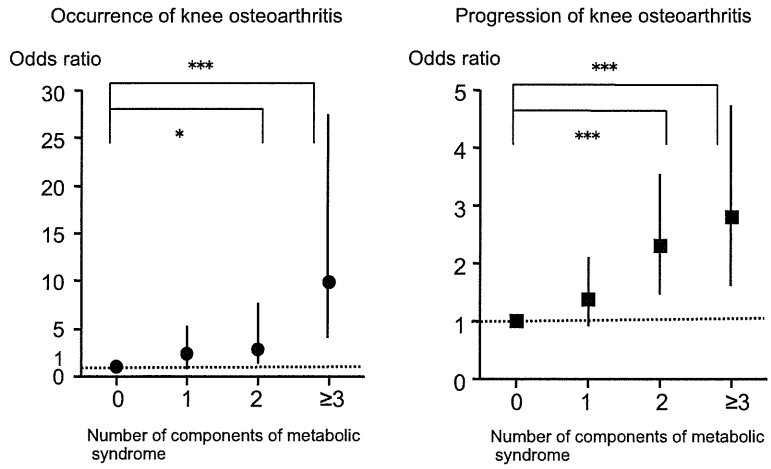


Fig. 2. Cumulative incidence (%/year) of KOA (A) and progression of the KL grade of either knee (%/year) (B) classified by the number of components of MS, including OW, HT, DL, and IGT.

for age and gender. The odds ratio (OR) and 95% CI for KOA occurrence were found to significantly increase with the number of MS components present (OR, 95% CI vs no component: one component, 2.16, 0.90–5.20, $P = 0.085$; two components, 2.49, 0.95–6.55, $P = 0.063$; ≥three components, 8.38, 3.12–22.5, $P < 0.001$). Similarly, KOA progression significantly increased with the number of MS components present (OR, 95% CI vs no component: one component, 1.41, 0.94–2.12, $P = 0.097$; two components, 2.25, 1.47–3.46, $P < 0.001$; ≥three components: 2.59, 1.57–4.27, $P < 0.001$).

Logistic regression model results obtained using KOA occurrence or progression as the objective variable and the number of MS components present as explanatory variables, after adjusting for age, gender, and the other potential risk factors listed in the Methods section, are shown in Fig. 3. The OR significantly increased with the number of MS components present after adjustment for



*:p < 0.05,***:p < 0.001

Multivariate logistic regression analysis using the occurrence or progression of KOA (over 3 years, 1: yes, 0: no) as the objective variable and the number of MS components as the explanatory variable, 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: curre nt drinker), bicycling every day (0: no, 1: yes), regular exercise (0: no, 1: yes), and past history of knee injuries (0: no, 1: yes).

Fig. 3. ORs for occurrence and progression of KOA during the 3-year follow-up period vs the number of risk factors for MS.