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EPIDEMIOLOGY

Health-Related Quality of Life in Subjects With Low Back Pain and Knee Pain in a Population-Based Cohort Study of Japanese Men

The Research on Osteoarthritis Against Disability Study

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Study Design. Cross-sectional surveys of health-related quality of life (QOL) in subjects with low back pain and knee pain using a population-based cohort.

Objective. The purpose of the present study was to clarify the impact of low back pain and knee pain on QOL in men. In addition, we analyzed the impacts of vertebral fracture (VFx), lumbar spondylosis, and knee osteoarthritis (OA) on the magnitude of QOL loss in men with low back pain and knee pain.

Summary of Background Data. Low back pain and knee pain are major public health issues causing disability among the elderly men, but there were no population-based studies to compare the impact of low back pain on QOL with that of knee pain in Japanese men.

Methods. From 3040 participants in the Research on Osteoarthritis Against Disability study, data from 767 men older than 40 years who completed questionnaires (mean age = 69.7 years) were examined. To carry out the QOL assessment, the Medical Outcomes Study Short Form 8 (SF-8) and EuroQol (EQ-5D) were used. We examined the association of low back pain and knee pain with QOL. Furthermore, we also examined the presence of VFx and the severity of lumbar spondylosis and knee OA with the magnitude of QOL loss in men with low back pain and knee pain, respectively.

Results. The impact of low back pain on QOL was larger than that of knee pain. In men with low back pain, there were few associations between Kellgren-Lawrence grade and QOL, whereas VFx was associated with physical QOL. For men with knee pain, Kellgren-Lawrence grade equal to 4 knee OA was associated with QOL.

Conclusion. This study revealed that low back pain has a larger impact than knee pain on QOL. Furthermore, low back pain with VFx is strongly associated with physical QOL loss.

Key words: knee pain, low back pain, osteoarthritis, quality of life, vertebral fracture. **Spine 2011;36:1312–1319**

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Low back pain and knee pain are major public health issues causing disability among the elderly in most developed countries.[1–3] The prevalence of low back pain and knee pain is high in the elderly in Japan, ranging from 25% to 30%.[2,3] According to the recent National Livelihood Survey of the Ministry of Health, Labour, and Welfare in Japan, low back pain is rated first among symptoms that send men to the hospital.[4] Thus, it is important to clarify the impact of low back pain and knee pain on quality of life (QOL). Several studies have focused on the association of low back pain with

QOL in whites,[5–8] but for knee pain, there are few studies regarding its association with QOL.[9] Furthermore, to the best of our knowledge, there are no population-based studies that examine the impact of low back pain and knee pain on QOL in the same population using the same tool, although low back pain and knee pain may not be independent. Furthermore, the presence of pain at both sites may have more impact on QOL than pain at a single site. One of the main causes of low back pain in the elderly is vertebral fracture (VFx).[10] Low back pain is also believed to be one of the principal clinical symptoms of lumbar spondylosis, although the magnitude of the impact of lumbar spondylosis on low back pain is not as strong as one would expect.[2,11,12] A significant part of knee pain is caused by knee osteoarthritis (OA),[13,14] and the prevalence of knee pain increases as knee OA becomes more severe.[3] Thus, the impact of pain on QOL may differ on the basis of the cause and severity of the underlying disease. However, to the best of our knowledge, there are no population-based studies that examine the association of pain with QOL according to the cause or severity of the underlying disease.

Furthermore, sex differences have been observed in low back pain and knee pain. The prevalence of low back pain and knee pain differs between men and women,[2,3] and low back pain is rated as the first symptom that sends men to the hospital, although it is rated as the second symptom for women.[4] Thus, the impact of this pain on QOL may be stronger in men than in women. Although studies have examined the association of low back pain[5–8] or knee pain[9] with QOL, neither men nor women were analyzed separately[5,6,9] or the studies focused only on women.[7,8] There are no large-scale population-based studies examining the impact of low back pain or knee pain on QOL in men alone.

The objective of the present study was to clarify the independent association of low back pain and knee pain with QOL among 767 men using cohorts from Research on Osteoarthritis Against Disability (ROAD). We also examined whether the presence of both low back pain and knee pain had a larger impact on QOL than pain at only one site. Furthermore, we analyzed the impact of VFx, lumbar spondylosis, and knee OA on the magnitude of loss of QOL in men with low back pain and knee pain.

MATERIALS AND METHODS

Subjects

The ROAD study is a nationwide prospective study for bone and joint diseases (with OA and osteoporosis as the representative bone and joint diseases) consisting of population-based cohorts established in several communities in Japan. As detailed profile of the ROAD study has been described elsewhere,[15,16] and only a brief summary is provided here. To date, we have completed the creation of a baseline database including clinical and genetic information of 3040 inhabitants (1061 men and 1979 women) aged 23 to 95 years (mean = 70.6 years), who were recruited from listings of resident registrations in three communities: an urban region in Itabashi, Tokyo; a mountainous region in Hidakagawa, Wakayama; and a seacoast region in Taiji, Wakayama. All participants provided written informed consent, and the study was conducted with the approval of ethical 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 health-related QOL. We also examined the presence of cerebral stroke, diabetes mellitus, cardiac disease, and hypertension using an interviewer-administered questionnaire, as QOL may be affected by these comorbidities. Furthermore, because a lower level of physical activity may affect the association of pain with QOL, we obtained a history of leisure physical activity, including information on participation in sports and the frequency and duration of other leisure activities such as walking, jogging, swimming, playing tennis, playing baseball, playing golf, and muscle strength training. Anthropometric measurements included height and weight, and body mass index (BMI; weight [kg]/height^2 [m^2]) was calculated. All subjects were interviewed by experienced orthopedists regarding low back pain and knee pain and were asked, "Have you experienced low back pain on most days in the past month, in addition to now?" and "Have you experienced knee pain on most days in the past month, in addition to now?," respectively. Those who answered yes were defined as having pain. From the baseline data of the overall participants, the present study analyzed 767 men aged 40 years or older who completed a questionnaire of the Medical Outcomes Study Short Form 8 (SF-8) and the EuroQol (EQ-5D).

Radiographic Assessment

All participants underwent radiographic examination of the lumbar spine including intervertebral levels L1–L2 to L5–S with anteroposterior and lateral views, and both knees using anteroposterior and lateral views with weight-bearing and foot map positioning. Lumbar spine and knee radiographs were read without knowledge of participant clinical status by a single experienced orthopedist (S. M.). VFx was assessed by lateral radiographs of the lumbar spine (L1–L5) in terms of a wedge, biconcave, or crush appearance according to the Japanese Society of Bone and Mineral Research criteria[17] (Figure 1). Lumbar spondylosis and knee OA were assessed using the Kellgren-Lawrence (KL) radiographic atlas, and the

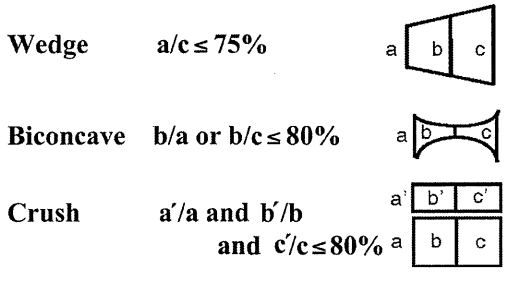

Figure 1. Diagnostic criteria for vertebral fractures according to the Japanese Society for Bone and Mineral Research.

severity was determined by KL grading.[18] We defined lumbar spondylosis and knee OA as KL 2 or more in at least one knee and one intervertebral level, respectively.

Instruments

The SF-8 scale was used for the QOL assessment. The SF-8 was constructed to provide a shorter alternative to the SF-36,[19] the most widely used patient-based health status survey, for use in large population-based surveys of general and specific populations. The SF-8 measures eight concepts: general health (GH), physical function (PF), role physical (RP), bodily pain (BP), vitality (VT), social function (SF), mental health (MH), and role emotional (RE). The SF-8 was scored by assigning the mean SF-36 scale score from the 2002 general Japanese population to each response category of the SF-8 measuring the same concept, and then weighting each SF-8 item to compute aggregate physical component scores (PCS) and mental component scores (MCS) summary scale measures. The SF-8 can be scored using a published algorithm for Japanese versions of the SF-8, which have been well-validated.[20] We also used the EuroQol (EQ-5D) questionnaire,[21] which was translated into Japanese.[22] The five-dimensional health care classification includes questions on the status of morbidity, self-care, usual activities, pain/discomfort, and anxiety/depression. Participants were asked to indicate current health status by choosing the most appropriate of the three statements about each of the five QOL dimensions. Each statement represents an increasing degree of severity. These results were coded and converted to a score of utility using a table of values.[22]

Statistical Analysis

We used the nonpaired student *t* test to examine differences between subjects with and without low back pain and knee pain. To determine the independent impact of low back pain and knee pain on QOL, multiple regression analysis was used with age, BMI, low back pain, and knee pain as independent variables. Furthermore, to examine the impact of the presence of both low back pain and knee pain on QOL, QOL scores in subjects with both low back pain and knee pain, with low back pain only, with knee pain only, and without these conditions were compared using the Tukey Honestly Significant Difference (HSD) test after adjustment for age and BMI. We further examined the association of KL grade at the lumbar spine and knee with the magnitude of QOL loss in subjects with low back pain and knee pain, respectively, using the Tukey HSD test after adjustment for age and BMI. If a subject had pain in both knees, the more severe KL grade was used for that subject. For the lumbar spine, the most severe KL grade among all intervertebral spaces was used. We also examined the association of the presence of VFx with the magnitude of QOL loss in subjects with low back pain using multiple regression analysis after adjustment for age, BMI, cerebral stroke, diabetes mellitus, cardiac disease, and hypertension. The association of physical activity with the magnitude of QOL loss in subjects with low back pain and in those with knee pain was determined using multiple regression analysis after adjustment for age, BMI, cerebral stroke, diabetes mellitus, cardiac disease, and hypertension. Data analyses were performed using SAS version 9.0 (SAS Institute Inc., Cary, NC).

RESULTS

Characteristics of the 767 participants aged 40 years and older in the ROAD study are shown in Table 1. The prevalence of low back pain and knee pain was approximately 15% and 21%, respectively. The prevalence of lumbar spondylosis and knee OA was 80% and 42%, respectively, which was high compared with that of VFx.

TABLE 1. Characteristics of Participants

N	767
Age, yr	69.7 ± 10.5
Height, cm	162.8 ± 6.7
Weight, kg	61.5 ± 10.8
BMI, kg/m^2	23.1 ± 3.4
Low back pain, %	15.4
Knee pain, %	20.6
Vertebral fracture, %	11.6
Lumbar spondylosis, %	80.0
Knee osteoarthritis, %	42.1
Comorbidities, %	
Cerebral stroke	5.8
Diabetes mellitus	13.8
Cardiac disease	13.4
Hypertension	41.1
Medical Outcomes Study Short Form 8	
GH	50.2 ± 5.5
PF	49.9 ± 6.2
RP	50.2 ± 6.7
BP	50.4 ± 9.2
VT	50.4 ± 6.3
SF	52.4 ± 5.5
MH	54.4 ± 5.3
RE	52.0 ± 5.2
PCS	47.4 ± 6.8
MCS	53.4 ± 5.3
EQ-5D	0.91 ± 0.14

Values are mean ± SD unless otherwise indicated.

BMI indicates body mass index; BP, bodily pain; EQ-5D, EuroQol; GH, general health; MCS, mental component summary; MH, mental health; PCS, physical component summary; PF, physical function; RE, role emotional; RP, role physical; SF, social function; VT, vitality;

TABLE 2. Mean (SD) Scores of All Domains, PCS, and MCS in the SF-8 and EQ-5D in Men with and Without Low Back Pain and Knee Pain

	Low Back Pain			Knee Pain		
	No	Yes	Adjusted Beta*	No	Yes	Adjusted Beta*
Medical Outcomes Study Short Form 8						
GH	50.5 (5.4)	48.3† (5.6)	−0.105‡	50.5 (5.4)	49.1† (5.5)	−0.100‡
PF	50.5 (5.8)	47.0† (7.5)	−0.135‡	50.4 (5.7)	48.2† (7.6)	−0.085‡
RP	50.7 (6.4)	47.4† (7.7)	−0.102‡	50.7 (6.2)	48.7† (7.9)	−0.073‡
BP	51.4 (9.2)	44.6† (7.2)	−0.235‡	51.1 (9.2)	47.6† (8.7)	−0.119‡
VT	50.8 (6.3)	48.4† (5.8)	−0.110‡	50.8 (6.1)	49.0† 6.5)	−0.109‡
SF	52.8 (5.0)	50.5† (7.5)	−0.100‡	52.5 (5.3)	52.4 (5.8)	0.028
MH	54.6 (5.1)	53.1† (6.0)	−0.078‡	54.4 (5.2)	54.6 (5.3)	0.034
RE	52.3 (4.9)	50.6† (5.5)	−0.087‡	52.1 (4.9)	51.9 6.2)	−0.0001
PCS	48.2 (6.5)	43.3† (7.2)	−0.191‡	48.1 (6.5)	44.8† (7.2)	−0.147‡
MCS	53.4 (5.1)	53.1 (6.3)	−0.010	53.2 (5.2)	54.2 (5.6)	0.076‡
EQ-5D	0.93 (0.13)	0.83† (0.17)	−0.180‡	0.92 (0.13)	0.87† (0.16)	−0.099‡

Values are mean (SD) unless otherwise indicated.

**The adjusted beta values are shown using multiple regression analysis after adjustment for age, body mass index, the other pain, cerebral stroke, diabetes mellitus, cardiac disease, and hypertension.*

†P < 0.05 versus subjects without the corresponding pain by nonpaired student t test.

‡P < 0.05 by multiple regression analysis.

BP indicates bodily pain; EQ-5D, EuroQol; GH, general health; MCS, mental component summary; MH, mental health; PCS, physical component summary; PF, physical function; RE, role emotional; RP, role physical; SF, social function; SF-8, 8-Item Short Form Health Survey; VT, vitality.

Table 2 shows the scores for all domains in the SF-8 and the EQ-5D utility score by the presence of low back pain and knee pain. We further examined the independent association of low back pain and knee pain with QOL using multiple regression analysis after adjustment for age, BMI, cerebral stroke, diabetes mellitus, cardiac disease, hypertension, and the other pain. Low back pain was significantly associated with lower QOL scores in all the domains of the SF-8 except for MCS, and in the EQ-5D utility scores, whereas knee pain was associated with lower scores of GH, PF, RP, BP, VT, and PCS in the SF-8 and the EQ-5D utility score, but not with SF, MH, and RE. For the MCS, knee pain was associated with higher scores. The adjusted beta values of low back pain were larger than those of knee pain in almost all QOL domains.

To examine the impact of the presence of both low back pain and knee pain on QOL, we next compared the QOL scores in the subjects with both low back pain and knee pain, only low back pain, only knee pain, and without any pain (Table 3). The Tukey HSD test after adjustment for age, BMI, cerebral stroke, diabetes mellitus, cardiac disease, and hypertension showed that the scores for almost all physical domains in the SF-8 were significantly lower in subjects with both low back pain and knee pain, only low back pain, and only knee pain than in those without pain. The EQ-5D utility score was also significantly lower in subjects with both low back pain and knee pain, those with only low back pain, and those with only knee pain than in those without pain. There were no significant differences in any domains between subjects with both low back pain and knee pain and those with only low back pain. Some domains tended to be lower in subjects with pain in both sites than in those with only knee pain, but differences were not significant.

Next, to clarify the impact of VFx and lumbar spondylosis on the magnitude of QOL loss in men with low back pain, we examined the association of KL grade of lumbar spine and the presence of VFx with QOL in the subjects with low back pain (Table 4). In men with low back pain, there were no associations of KL grade with any domain of the SF-8 and the EQ-5D utility scores, whereas the RP and PCS scores were significantly lower in subjects with VFx than in those without fracture.

Likewise, we examined the association of KL grade of knee with QOL in the subjects with knee pain (Table 5). After adjustment for age and BMI, the Tukey HSD test showed that the PCS in the SF-8 was significantly lower in men with KL 4 knee OA than in those with KL 0 or 1.

We next analyzed the association of physical activity with QOL in subjects with low back pain and in those with knee pain (see Table, Supplemental Digital Content 1, http://links.lww.com/BRS/A519). Multiple regression analysis

TABLE 3. Mean (SD) Scores of All Domains, PCS, and MCS in the SF-8 and EQ-5D in Men by the Combination of Low Back Pain and Knee Pain

	Low Back Pain and Knee Pain	Only Low Back Pain	Only Knee Pain	No Low Back Pain or Knee Pain
Prevalence, %	**5.2**	**9.8**	**15.5**	**69.6**
Medical Outcomes Study Short Form 8				
GH	48.2* (5.4)	48.7* (5.7)	49.3* (5.5)	50.8 (5.3)
PF	47.7* (6.2)	46.8* (8.2)	48.4* (8.1)	50.9 (5.0)
RP	48.0 (6.9)	47.6* (8.0)	49.0* (8.3)	51.1 (5.8)
BP	45.3* (7.7)	44.6* (6.9)	48.4* (8.9)	52.1 (9.1)
VT	47.9* (6.1)	48.8* (5.7)	49.3* (6.6)	51.1 (6.1)
SF	51.1 (6.5)	50.7 (7.9)	52.8 (5.5)	52.8 (4.8)
MH	54.4 (4.8)	52.7* (6.4)	54.7 (5.4)	54.6 (5.0)
RE	51.6 (5.0)	50.4* (7.2)	52.0 (6.5)	52.3 (4.4)
PCS	43.4* (6.5)	43.5* (7.5)	45.3* (7.4)	48.8 (6.1)
MCS	54.1 (5.6)	53.0 (6.7)	54.3 (5.5)	53.2 (5.0)
EQ-5D	0.82* (0.17)	0.84* (0.16)	0.88* (0.15)	0.94 (0.12)

Values are mean (SD) unless otherwise indicated.

**Significantly lower than that of subjects with no low back pain or knee pain by the Tukey Honestly Significant Difference test after adjustment for age, body mass index, cerebral stroke, diabetes mellitus, cardiac disease, and hypertension.*

BP indicates bodily pain; EQ-5D, EuroQol; GH, general health; MCS, mental component summary; MH, mental health; PCS, physical component summary; PF, physical function; RE, role emotional; RP, role physical; SF, social function; SF-8, 8-Item Short Form Health Survey; VT, vitality.

after adjustment for age, BMI, cerebral stroke, diabetes mellitus, cardiac disease, and hypertension showed that physical activity was not associated with any QOL parameter in subjects with low back pain or in those with knee pain.

DISCUSSION

This is the first large-scale, population-based cohort study in Japanese men that examined the impact of low back pain and knee pain on QOL measured by the SF-8 as well as the EQ-5D. In the present study, low back pain and knee pain were significantly associated with QOL in men, and multiple regression analysis showed that the adjusted beta values of low back pain were larger than that of knee pain in almost all QOL domains. Furthermore, in men with low back pain, VFx was significantly associated with QOL loss. For men with knee pain, KL 4 knee OA was strongly associated with magnitude of QOL loss compared with KL 0 or 1.

Previous studies showed that low back pain was associated with QOL,[5–8] but no studies focused on men, although sex differences were found in low back pain.[2,4] In addition, although low back pain and knee pain may not be independent, and the presence of pain at both sites may have more impact on QOL loss than pain at one site, no studies have examined the impact of low back pain and knee pain on QOL simultaneously in the same population. In the present study, low back pain and knee pain were significantly associated with lower QOL scores in men. The adjusted beta values of low back pain were higher than that of knee pain in almost all QOL domains, suggesting that low back pain had more impact on QOL loss than knee pain, although we did not evaluate the pain severity of low back pain and knee pain. Furthermore, the pain thresholds and pain onset in daily living in low back pain are not the same as in knee pain, so strict comparisons between low back pain and knee pain are limited, even though we examined the association of low back pain and knee pain with QOL in the same populations using the same method. The presence of both low back pain and knee pain was also significantly associated with QOL loss compared with no low back pain or knee pain, whereas there were no differences in QOL parameters between subjects with both low back pain and knee pain and those with only low back pain. These findings suggest that when both low back pain and knee pain exist, the combination may not result in any additional impact on QOL than pain in single site; it is possible that the impact of knee pain on QOL may be obscured by low back pain, because the impact of low back pain on QOL was larger than that of knee pain.

Previous clinical studies showed that strong impacts of clinical VFx on QOL were observed.[23,24] The present study also clarified that VFx had significant associations with the magnitude of QOL loss measured by RP and PCS of the SF-8 in subjects with low back pain, indicating that low back pain with VFx has a more severe impact on physical QOL than low back pain without VFx in men. This means that VFx may not

TABLE 4. Mean (SD) Scores on the SF-8 and EQ-5D by Vertebral Fracture and Kellgren-Lawrence Grade in Subjects with Low Back Pain

	Vertebral Fracture			Lumbar Spondylosis		
	No	Yes	KL 0,1	KL 2	KL 3	KL 4
Prevalence, %	**18.6**	**81.4**	**16.2**	**35.0**	**28.2**	**20.5**
Medical Outcomes Study Short Form 8						
GH	48.6 (5.6)	47.2 (5.9)	46.8 (6.8)	49.9 (5.3)	47.8 (5.4)	47.4 (5.3)
PF	47.5 (7.6)	44.8 (7.0)	48.6 (5.7)	49.4 (5.7)	43.6 (9.6)	46.3 (6.7)
RP	48.1 (7.3)	44.3* (8.7)	49.1 (6.9)	49.3 (6.9)	45.5 (8.5)	45.5 (8.2)
BP	44.9 (7.4)	43.2 (6.2)	42.3 (4.9)	46.2 (7.6)	45.2 (6.8)	43.2 (8.2)
VT	48.7 (6.0)	47.0 (5.0)	47.6 (7.7)	48.8 (5.3)	47.9 (5.5)	48.9 (5.6)
SF	50.4 (7.8)	51.2 (6.2)	49.4 (8.8)	52.6 (4.9)	49.6 (8.4)	49.0 (8.4)
MH	52.5 (6.1)	55.4 (4.5)	51.7 (7.6)	55.3 (4.0)	51.6 (6.1)	52.0 (6.4)
RE	50.2 (6.9)	52.2 (3.6)	49.0 (8.3)	52.6 (3.3)	49.1 (8.3)	50.5 (5.6)
PCS	44.2 (6.6)	39.4* (8.2)	44.0 (5.0)	44.9 (7.1)	41.9 (8.0)	42.0 (7.5)
MCS	52.4 (6.2)	56.4 (5.8)	51.0 (8.5)	54.9 (4.5)	52.2 (6.1)	52.8 (6.7)
EQ-5D	0.82 (0.17)	0.85 (0.16)	0.86 (0.15)	0.87 (0.14)	0.78 (0.17)	0.80 (0.19)

Values are mean (SD) unless otherwise indicated.

**P < 0.05 versus no vertebral fracture by the Tukey Honestly Significant Difference test after adjustment for age, body mass index, cerebral stroke, diabetes mellitus, cardiac disease, and hypertension.*

BP indicates bodily pain; EQ-5D, EuroQOL; GH, general health; MCS, mental component summary; MH, mental health; PCS, physical component summary; PF, physical function; RE, role emotional; RP, role physical; SF, social function; SF-8, 8-Item Short Form Health Survey; VT, vitality.

only be a cause of low back pain but also worsen the severity of low back pain. Meanwhile, the severity of lumbar spondylosis was not significantly associated with magnitude of QOL loss in subjects with low back pain. This finding may be partly explained by the weak association between lumbar spondylosis and low back pain reported by us and others.[2,11,12] Indeed, disc degeneration was reported to be detected by magnetic resonance imaging in at least one lumbar level in all but one asymptomatic volunteer in a group with volunteers aged 60 to 80 years.[25] Regarding the knee, the adjusted beta values of knee pain on QOL were weak compared with low back pain, whereas the KL 4 knee OA was significantly associated with magnitude of PCS loss in subjects with knee pain compared with KL 0 or 1. The PCS in subjects with KL 2 knee OA were similar to those with KL 0 or 1. Considering the definition of the KL grade, this may also mean that osteophytosis and joint space narrowing, which are representative features of knee OA, have a different impact on QOL; that is, osteophytosis may have a weak impact on QOL, whereas joint space narrowing may have a strong impact.

As measured by MCS of the SF-8, low back pain was not significantly associated with lower scores in the present study, whereas knee pain was significantly associated with higher scores on MCS, and significantly lower PCS scores. Several factors may contribute to the dissociation between MCS and PCS for low back pain and knee pain. First, MCS questions within the SF-8 include generic questions about energy levels, feelings of being "downhearted and blue," and interference in daily activities as a result of emotional problems. These questions are less sensitive to the presence of mental health issues than disease-specific scales such as the Kessler psychological distress scale.[26] In fact, Hill et al[27] showed that psychological distress has been shown to be significantly more frequent in those with arthritis than those without, although scores on MCS were not significantly different between these two groups. Second, the dissociation may be due to a disability paradox,[28] which suggests that people with chronic disabilities report serious limitations in Activities of Daily Living (ADL) and problems in performing social roles, yet state that they have excellent or good QOL. Low back pain and knee pain lead to functional impairment. This may be associated with lower PCS scores, but the individual may not feel that the impairment of social activity or ADL was due to mental factors. Particularly in elderly individuals, pain may be considered a natural consequence of being elderly and thus may not lead to lower MCS.

There are several limitations to the present study. First, this is a large-scale population-based study, but a cross-sectional study of baseline data, so a causal relationship could not be determined. The ROAD study is a longitudinal survey, so further progress will elucidate any causal relationships. Second, among the 1047 men 40 years or older in the ROAD

TABLE 5. Mean (SD) Scores of the SF-8 and EQ-5D by KL Grade in Subjects with Knee Pain

	KL 0,1	KL 2	KL 3	KL 4
Prevalence, %	**57.9**	**30.1**	**7.8**	**4.2**
Medical Outcomes Study Short Form 8				
GH	48.8 (5.2)	50.0 (4.8)	49.2 (6.5)	47.3 (6.9)
PF	49.4 (6.1)	48.9 (7.2)	47.0 (10.1)	43.6 (9.3)
RP	49.6 (7.5)	49.5 (6.9)	46.2 (12.0)	46.2 (6.7)
BP	47.5 (8.2)	50.1 (8.6)	43.8 (8.2)	44.8 (9.5)
VT	49.8 (5.7)	49.6 (7.1)	47.1 (7.4)	46.2 (6.3)
SF	53.5 (4.2)	51.2 (6.8)	51.9 (7.2)	52.3 (6.0)
MH	54.9 (5.1)	54.2 (5.0)	54.2 (6.6)	55.4 (5.5)
RE	52.7 (3.9)	51.3 (6.6)	50.9 (9.9)	51.6 (7.0)
PCS	45.4 (6.6)	46.7 (6.3)	42.2 (9.6)	40.3* (6.8)
MCS	54.8 (4.7)	52.9 (5.2)	54.4 (7.3)	55.8 (6.8)
EQ-5D	0.90 (0.15)	0.88 (0.16)	0.81 (0.20)	0.80 (0.17)

Values are mean (SD) unless otherwise indicated.

**P < 0.05 versus KL 0,1 by the Tukey Honestly Significant Difference test after adjustment for age, body mass index, cerebral stroke, diabetes mellitus, cardiac disease, and hypertension.*

BP indicates bodily pain; EQ-5D, EuroQol; GH, general health; KL, Kellgren-Lawrence; MCS, mental component summary; MH, mental health; PCS, physical component summary; PF, physical function; RE, role emotional; RP, role physical; SF, social function; SF-8, 8-Item Short Form Health Survey; VT, vitality.

study, 767 men had completed questionnaires for both the SF-8 and the EQ-5D, so the response rate was 73.7%. Subjects who completed questionnaires may have had better QOL than those who did not, so our results regarding QOL may have represented overestimations. Third, we did not include the onset of VFx in the analysis, although the severity of low back pain often appears to be associated with the interval from onset of VFx. In terms of clinical fractures, we examined the history of fracture, including VFx, in the ROAD study by self-report, and no clinical VFx occurred within the 1 month before baseline examination. However, we could not compare radiographs of the lumbar spine at baseline examination with those before the examination, as subjects had not undergone radiography of the lumbar spine before that examination. We were therefore unable to assess the incidence of subclinical fracture within the 1 month before baseline examination, although clinical and subclinical fractures are associated with lower QOL in women.[29] However, the association between severity of low back pain and the interval from onset of subclinical VFx may be weaker than that for clinical VFx, so the absence of data on the incidence of subclinical VFx may not strongly affect the present results.

In conclusion, the present study revealed that the impact of low back pain was larger than that of knee pain in almost all QOL domains. In men with low back pain, VFx had some association with physical QOL loss. In men with knee pain, KL 4 knee OA was strongly associated with QOL loss. Further progress will elucidate the backgrounds of low back pain and knee pain.

➢ Key Points

- ❑ Low back pain and knee pain are major public health issues causing disability among the elderly men, but there were no population-based studies to compare the impact of low back pain on QOL with that of knee pain in Japanese men.
- ❑ The objective of the present study was to clarify the independent association of low back pain and knee pain with QOL among 767 men using cohorts from ROAD.
- ❑ The impact of low back pain on QOL was larger than that of knee pain. In men with low back pain, there were few associations between KL grade and QOL, whereas VFx was associated with physical QOL, indicating that low back pain with VFx is strongly associated with physical QOL loss.

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Association of Knee Osteoarthritis with the Accumulation of Metabolic Risk Factors Such as Overweight, Hypertension, Dyslipidemia, and Impaired Glucose Tolerance in Japanese Men and Women: The ROAD Study

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ABSTRACT. ***Objective.*** To clarify the association of knee osteoarthritis (KOA) with overweight (OW), hypertension (HTN), dyslipidemia (DL), and impaired glucose tolerance (IGT), which are components of metabolic syndrome (MS), in a Japanese population.

Methods. We enrolled 1690 participants (596 men, 1094 women) from the large-scale cohort study Research on Osteoarthritis Against Disability (ROAD), begun in 2005 to clarify epidemiologic features of OA in Japan. KOA was evaluated by the Kellgren-Lawrence grade, minimum joint space width (MJSW), minimum joint space area (JSA), and osteophyte area (OPA). OW, HTN, DL, and IGT were assessed using standard criteria.

Results. The prevalence of KOA in the total population in the age groups ≤ 39, 40–49, 50–59, 60–69, 70–79, and ≥ 80 years was 2.2%, 10.7%, 28.2%, 50.8%, 69.0%, and 80.5%, respectively. Logistic regression analyses after adjustment for age, sex, regional difference, smoking habit, alcohol consumption, physical activities, regular exercise, and history of knee injuries revealed that the OR of KOA significantly increased according to the number of MS components present (1 component: OR 1.21, 95% CI 0.88–1.68, p = 0.237; 2 components: OR 1.89, 95% CI 1.33–2.70, p < 0.001; 3 or more components: OR 2.72, 95% CI 1.77–4.18; p < 0.001). The number of MS components was inversely related to medial MSJW (ß = –0.148, R^2 = 0.21, p < 0.001), medial JSA (women only; ß = –0.096, R^2 = 0.18, p = 0.001), and positively related to OPA (ß = 0.12, R^2 = 0.11, p < 0.001).

Conclusion. The accumulation of MS components is significantly related to presence of KOA. MS prevention may be useful to reduce cardiovascular disease and KOA risk. (First Release Feb 15 2011; J Rheumatol 2011;38:921–30; doi:10.3899/jrheum.100569)

Key Indexing Terms:
EPIDEMIOLOGY METABOLIC SYNDROME KNEE OSTEOARTHRITIS
RISK FACTORS ROAD STUDY

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 that affects activities of daily living (ADL) and quality of life, leading to increased morbidity and mortality[1,2,3]. 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 longterm care[4].

In the same report, cardiovascular disease (CVD) is

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ranked first in causing disabilities in the elderly[4]. Most individuals who develop CVD have multiple risk factors[5]. The presence of these risk factors in specific combinations, called metabolic syndrome (MS), is a complex risk factor that predisposes affected individuals to CVD morbidity and mortality. Although various terms have been used to define MS, it is generally thought to consist of a combination of overweight (OW), hypertension (HTN), dyslipidemia (DL), and impaired glucose tolerance (IGT)[6].

Knee OA (KOA) and MS share age and obesity as risk factors[1,7,8,9,10,11]. Many investigators have considered the association of OA with other components of MS. In an early population study, Lawrence first reported that diastolic blood pressure was associated with KOA in women[12]. Regarding DL, Kellgren reported a significant association between women with hand OA and above-average serum cholesterol levels in the 1960s[13]. Cimmino and Cutolo examined the role of glucose and OA, and observed significantly higher levels of plasma glucose in women with OA than in those without OA[14]. Although contradictory findings regarding the association of such metabolic factors with OA have been reported[15,16,17,18,19], Hart, *et al* found that metabolic factors such as blood glucose, hypercholesterolemia, and even treated HTN were associated with the development of KOA. Based on that evidence, they proposed that the etiology of OA had an important systemic and metabolic component[20]. This hypothesis has been supported by data from several population-based studies performed in the United States[21,22]. However, to our knowledge, few population-based studies have demonstrated a dose-response relationship between the severity of KOA and an increasing number of the components of MS. Our first purpose was to clarify the association between the presence of KOA, defined using the Kellgren-Lawrence (KL) scale, and the number of MS components in a Japanese population.

Moreover, in most of these studies that confirmed the association between the presence of KOA and the components of MS, KOA was defined according to KL grade[23]. KL grade is the most conventional system for measuring the radiographic severity of KOA, but does not separately assess joint space narrowing and osteophyte formation. Accumulating evidence has shown that osteophytosis and joint space narrowing have distinct etiologic mechanisms, and their progression is neither constant nor proportional[24,25,26]. Thus, to examine the factors associated with KOA, these 2 OA features should be assessed separately. However, no reports to date have clarified the association of indices of KOA, such as minimum joint space width (MJSW), joint space area (JSA), and osteophyte area (OPA), with the accumulation of the number of components of MS. Our second purpose was to determine whether the accumulation of MS components influenced the values of MJSW, JSA, and OPA.

Further, MS is an emerging epidemic in both men and women worldwide, and with the increase in the global population of Asians, an understanding of the epidemiology of diseases as they relate to Asian populations is required. We have reported that the prevalence of KOA was much higher in a Japanese population than in elderly whites in the United States and Europe, although not largely different from that of African American and Chinese populations[27]. In contrast, the prevalence of MS in East Asian countries including China, Korea, and Japan was reported to be lower than in white populations[28]. In light of the rapid increase in the population of Asian countries, prevention strategies for obesity-related chronic diseases such as MS and KOA should be implemented immediately. Our final aim was to clarify the association between MA components and KOA in people of Asian ethnicity.

MATERIALS AND METHODS

Study population. We used the cohorts established in 2005 for a program called Research on Osteoarthritis Against Disability (ROAD). The ROAD study is a nationwide, prospective study of OA composed of population-based cohorts in several communities in Japan. Details of the cohort profile have been reported[29,30], thus the study population is described here only in brief. We created a baseline database including clinical and genetic information from 3040 residents of Japan (1061 men and 1979 women) with a mean age (SD) of 70.3 (11.0) years [71.0 (10.7) years in men and 69.9 (11.2) years in women]. These subjects were recruited from resident registration listings in 3 communities with different characteristics: an urban region in Itabashi, Tokyo; a mountainous region in Hidakagawa, Wakayama; and a coastal region in Taiji, Wakayama.

We enrolled 1690 Japanese subjects (596 men; 1094 women) residing in the mountainous and coastal areas. Table 1 lists the background characteristics of all the participants. All participants provided written informed consent, and the study was conducted with the approval of the ethics committees of the University of Tokyo. Participants completed an interviewer administered questionnaire of 400 items that included lifestyle information such as occupation, smoking habit, alcohol consumption, family history, medical history, physical activity, reproductive variables, and health-related quality of life. Anthropometric measurements included height, weight, waist length (seaside region only), wrist circumference, bilateral grip strength, and body mass index [BMI; weight (kg)/height (m)^2]. Systolic and diastolic blood pressure (BP) were measured by an experienced public health nurse using a mercury sphygmomanometer. Medical information on systemic, local, and mental health status, including information concerning knee, hip, and lower back pain; swelling and range of motion of the joints; and patellar and Achilles tendon reflex was collected by experienced orthopedic surgeons.

Radiographic assessment. All participants underwent radiographic examination of both knees using an anterior-posterior view with weight-bearing and foot-map positioning. Fluoroscopic guidance with a horizontal anterior-posterior radiograph beam was used to visualize the joint space. Knee radiographs were read by a single experienced orthopedist without knowledge of participants' clinical status, and categorized using the KL grading scale[23]. Regarding the differences in knee OA grades between the 2 sides, among 1681 participants who underwent X-ray examinations of both knees, 1226 (72.9%) individuals had the same KL grades for both knees. For 396 (23.6%) participants, the difference in knee KL grades between the 2 knees was 1, and for the remaining 59 (3.5%) subjects, the KL grades differed by more than 2 grades. In such cases, the higher KL grade was assigned to the participant. The same observer scored 100 randomly selected knee radiographs more than 1 month after the first reading to determine intraobserver variability. The intraobserver variability (0.86) evaluated for KL grade (0–4) was confirmed by kappa analysis to be sufficient for the assessment.

Table 1. Background characteristics of the participants.

	Total	Men	Women
Age, yrs			
≤ 39	45	14	31
40–49	149	44	105
50–59	316	107	209
60–69	482	157	325
70–79	539	220	319
≥ 80	159	54	105
Total, n	1690	596	1094
Mean (SD) selected characteristics			
Age, yrs	65.2 (12.0)	66.3 (11.7)	64.7 (12.1)
Height, cm	155.2 (9.3)	163.4 (7.2)	150.7 (6.9)
Weight, kg	55.6 (10.8)	62.2 (10.9)	52.0 (8.8)
BMI, kg/m^2	23.0 (3.4)	23.2 (3.2)	22.9 (3.5)
Systolic BP, mm Hg	135.1 (20.7)	137.9 (19.6)	133.5 (21.1)
Diastolic BP, mm Hg	74.2 (11.5)	77.0 (11.6)	72.7 (11.2)
Serum levels of HDL cholesterol, mg/dl	60.8 (15.7)	56.1 (15.8)	63.4 (15.0)
Serum levels of HbA1c, %	5.20 (0.74)	5.23 (0.83)	5.19 (0.68)
Prevalence of selected characteristics, %			
Current smoking habit	13.1	29.9	3.8
Current alcohol consumption	39.8	66.7	25.1
Medication for hypertension	32.3	29.5	33.9
Medication for dyslipidemia	6.5	3.0	8.5
Medication for diabetes mellitus (including insulin injection)	5.9	7.7	4.9
Prevalence of each component of metabolic syndrome, %			
Obesity	25.3	26.7	24.6
Hypertension	69.7	74.8	66.9
Dyslipidemia	12.3	13.9	11.4
Impaired glucose tolerance	21.5	24.3	20.0

BMI: body mass index; BP: blood pressure; HDL: high-density lipoprotein; HbA1c: hemoglobin A1c.

Further, to evaluate the KOA severity using quantitative measurements, the medial and lateral MJSW, medial and lateral JSA, and OPA were measured separately, using a KOA computer-assisted diagnostic system (KOACAD). The KOACAD was programmed to measure MJSW and JSA in the medial and lateral compartments, OPA at the medial tibia, and femorotibial angle (FTA) using digitized knee radiographs. Initially, correction for radiographic magnification was performed on the basis of the image size of a rectangular metal plate.

Next, to determine the region of interest (ROI) including the tibiofemoral joint space, a vertical neighborhood difference filter was applied to identify points with high absolute values for difference of scales. The centers of all points were then calculated, and the ROI was selected. Within the ROI, the outline of the femoral condyle was designated as the upper rim of the joint space. The 2 ends were determined, and vertical lines from the ends were designated as the outside rims of the joint space. Outlines of the anterior and posterior margins of the tibial plateau were drawn similarly to that of the femoral condyle, and the middle line between the 2 outlines was designated as the lower rim of the joint space. A straight regression line for the lower rim outline was then drawn, and the intersection of the lower rim outline and the regression line were designated as the inside rims. Medial and lateral JSA were determined as areas surrounded by the upper, lower, inside, and outside rims. Medial and lateral MJSW were further determined as the minimum vertical distances in the respective JSA. To measure osteophyte area and FTA, medial and lateral outlines of the femur and tibia were drawn. Inflection points for these outlines were then calculated. The medial outline of the tibia from the inflection point was drawn upward to the joint level, and the area that was medially prominent over the smoothly extended outline was designated as the osteophyte area. For FTA, a middle line between the medial and lateral outlines of the femur from the top of the image to the inflection points was drawn, and the straight regression line was determined as the axis of the femur. Similarly, the straight regression line of the middle line of the tibia from the bottom to the inflection points was designated as the axis of the tibia. The lateral angle between the 2 axes lines was calculated as FTA. In general clinical practice, this system can quantify the major features of knee OA on standard radiographs and allows objective, accurate, simple, and easy assessment of the structural severity of knee OA without any manual operation.

Regarding the relationship between the measurements of KOA, we have confirmed the correlation values were more than 0.5 between medial JSA and medial MJSW, and between lateral JSA and lateral MJSW, indicating that these are confounding factors for each other. Osteophyte area was not significantly associated with either medial JSA or medial MJSW. Further, JSA and MJSW on the lateral side were positively correlated with those on the medial side. These measurements showed good correlation between KL grades ($p < 0.0001$)[31].

Blood examination. All blood and urine samples were extracted between 9:00 AM and 3:00 PM. Some samples were extracted under fasting conditions. After centrifugation of blood samples, sera were immediately placed in dry ice and transferred to a deep freezer within 24 hours. These samples were stored at –80°C until assayed.

For the samples of participants in the baseline study, the following items were measured: blood counts, hemoglobin, hemoglobin A1c (HbA1c), blood sugar, total protein, aspartate aminotransferase, alanine aminotransferase, γ-glutamyltranspeptidase, high-density lipoprotein (HDL) cholesterol, total cholesterol, triglycerides (TG), blood urea nitrogen, uric acid, and creatinine. These analyses were performed at the same laboratory within 24 hours after the extraction (Osaka Kessei Research Laboratories Inc., Osaka, Japan).

Definition of MS components. This definition was based mainly on the criteria of the Examination Committee of Criteria for Metabolic Syndrome in Japan[32]. According to these criteria, an abdominal circumference ≥ 85 cm in men and ≥ 90 cm in women is a necessary condition for MS. HTN was diagnosed as systolic BP ≥ 130 mm Hg and/or diastolic BP ≥ 85 mm Hg, DL as serum TG level ≥ 150 mg/dl and/or serum HDL cholesterol level < 40 mg/dl, and IGT as fasting serum glucose ≥ 110 mg/dl. Because there has been considerable debate regarding the measurement of abdominal circumference[33,34], we decided to use BMI ≥ 25 instead as an indicator of overweight, based on the criteria of the Japan Society for the Study of Obesity[33]. Also, because not all blood samples were obtained under fasting conditions, we did not use participants' data concerning serum levels of glucose and TG, because of their large variation depending on hours after eating. Instead, we used a serum HDL cholesterol level < 40 mg/dl to indicate DL, and serum HbA1c level ≥ 5.5% to indicate IGT. These are indices used in the National Health and Nutrition Survey in Japan, and they were adopted as criteria for MS in this national screening based on the difficulty of collecting the samples under fasting conditions[35]. Further, subjects being treated with medication for HTN, DL, or diabetes mellitus were regarded as having the respective disorder.

Statistical analysis. All statistical analyses were performed using Stata statistical software (Stata Corp., College Station, TX, USA). Differences in proportion were compared by the chi-squared test. Differences in continuous values were tested for significance using ANOVA for comparisons among multiple groups, and Scheffe's least significant difference test for pairs of groups. Significant items were selected, and multiple regression and logistic regression analyses were performed by adjusting selected variables. Various confounding factors were used for the adjustment for each multivariate analysis.

RESULTS

Study population. Table 1 shows selected characteristics of the participants including age, height, weight, BMI, systolic

and diastolic BP, and serum levels of HDL cholesterol and HbA1c, classified by sex. Two-thirds of the 1690 participants were women, and their mean age was 1.5 years younger than that of the men ($p = 0.0098$).

Height, weight, and BMI were significantly lower in women than in men (height, $p < 0.0001$; weight, $p < 0.0001$; BMI, $p = 0.049$). Both measurements of systolic BP and diastolic BP were significantly higher in men than in women (systolic BP and diastolic BP, $p < 0.0001$). However, there was no significant difference in serum levels of HbA1c between men and women ($p = 0.2472$). The serum level of HDL cholesterol was significantly lower in men than in women ($p < 0.0001$).

Table 1 also shows the proportion of subjects who smoked (regularly or more than once a month) and consumed alcohol (drinking regularly or more than once a month); medication use; and the prevalence of OW, HTN, DL, and IGT. Smoking and drinking were significantly more common in men than in women ($p < 0.001$). In the total population, the component of MS with the highest prevalence was HTN, followed by OW, IGT, and DL. The prevalence of HTN and IGT was significantly higher in men than in women (HTN, $p = 0.001$; IGT, $p = 0.039$).

Prevalence of KOA and its association with components for MS. The prevalence of KOA in the total population in the age groups ≤ 39, 40–49, 50–59, 60–69, 70–79, and ≥ 80 years was 2.2%, 10.7%, 28.2%, 50.8%, 69.0%, and 80.5%, respectively. KOA prevalence tended to be higher with increasing age in both the sexes. The prevalence of KOA was significantly higher in women than in men ($p < 0.001$). Table 2 shows the mean values of each component of MS compared between the absence and presence of KOA. In the overall population, mean values of age, BMI, systolic BP, and HbA1c were significantly higher, and HDL cholesterol significantly lower, in subjects with KOA than in those without KOA. This tendency was much more pronounced in women than in men.

Logistic regression analysis was performed using the presence of KOA as an objective variable and OW, HTN, DL, and IGT each as explanatory variables, after adjusting for age and sex. In the overall population, the analysis revealed that only OW was significantly positively associated with KOA (OR 2.33, 95% CI 1.79–3.04, $p < 0.001$). Logistic regression analysis using the same objective and explanatory factors and stratified according to sex indicated that only HTN was positively associated with KOA in men (OR 1.61, 95% CI 1.03–2.53, $p = 0.038$), and only OW in women (OR 3.48, 95% CI 2.42–5.01, $p < 0.001$).

Table 3 shows the prevalence of potential associated lifestyle factors for KOA classified by the absence or presence of KOA. In the overall population, significantly associated factors for KOA included residential area, smoking habit, alcohol consumption, bicycling regularly as a factor of physical activity, and regular exercises. These factors should be taken into consideration as confounders for the following multivariate analysis.

Then, logistic regression analysis was repeated using the presence of KOA as an objective variable and OW, HTN, DL, and IGT each as explanatory variables, after adjusting for age, sex, regional difference, smoking habit, alcohol consumption, physical activities including regular bicycling in the past 12 months, regular exercises such as football, tennis, baseball, and golf; and history of knee injuries. The analysis revealed that OW and HTN were significantly positively associated with KOA (OW: OR 2.74, 95% CI 1.07–3.62, $p < 0.001$; HTN: OR 1.43, 95% CI 1.09–1.86, $p < 0.001$). Logistic regression analysis using the same objective and explanatory factors and stratified according to sex indicated that OW and HTN were positively associated with KOA in men (OW: OR 1.76, 95% CI 1.13–2.74, $p < 0.05$; HTN: OR 1.77, 95% CI 1.11–2.84, $p < 0.05$), and only OW in women (OR 3.63, 95% CI 2.51–5.25, $p < 0.001$). These results suggest that all components of MS were not equally associated with the presence of KOA.

Then, to clarify the association between all the components of MS and KOA, logistic regression analysis was repeated using the presence of KOA as an objective variable and all components for MS, such as OW, HTN, DL, and IGT, as explanatory variables, after adjustment for age, sex, regional difference, smoking habit, alcohol consumption, physical activities, regular exercises, and history of knee injuries. In the overall population, the analysis revealed that

Table 2. Mean (SD) of each component of metabolic syndrome in the absence or presence of knee osteoarthritis (KOA).

	Total			Men			Women		
	KOA–	KOA+	p	KOA–	KOA+	p	KOA–	KOA+	p
Age, yrs	59.8 (12.1)	70.5 (9.1)	0.0001	62.5 (12.1)	71.5 (8.8)	0.0001	57.8 (11.8)	70.3 (9.1)	0.0001
BMI, kg/m^2	22.4 (3.2)	23.5 (3.4)	0.0001	23.0 (3.2)	23.5 (3.2)	0.0931	22.0 (3.1)	23.6 (3.6)	0.0001
Systolic BP, mm Hg	130.7 (19.9)	139.3 (20.7)	0.0001	134.5 (18.9)	142.5 (19.6)	0.0001	127.9 (20.0)	138.0 (21.0)	0.0001
Diastolic BP, mm Hg	74.2 (11.2)	74.2 (11.8)	0.9890	77.1 (11.6)	76.8 (11.5)	0.6970	72.1 (10.4)	73.1 (11.8)	0.1380
Serum levels of HDL cholesterol, mg/dl	62.8 (16.6)	58.9 (14.5)	0.0001	57.5 (16.2)	54.1 (15.0)	0.0095	6.6 (15.8)	60.8 (13.9)	0.0001
Serum levels of HbA1c, %	5.13 (0.68)	5.26 (0.78)	0.0003	5.22 (0.83)	5.23 (0.80)	0.9409	5.07 (0.53)	5.28 (0.77)	0.0001

BMI: body mass index; BP: blood pressure; HDL: high-density lipoprotein; HbA1c: hemoglobin A1c.

Table 3. Prevalence (%) of portential associated factors for knee osteoarthritis (KOA) classified by the absence or presence of KOA.

	Total			Men			Women		
	KOA–	KOA+	p	KOA–	KOA+	p	KOA–	KOA+	p
Residing in coastal area	65.6	32.1	0.000	60.8	26.7	0.000	69.0	34.3	0.000
Current smoking	16.7	9.5	0.000	34.7	23.5	0.012	3.92	3.53	0.060
Current alcohol drinking	46.2	33.4	0.000	68.1	65.3	0.475	30.8	20.2	0.000
Bicycling every day in the past 12 mo	52.6	59.3	0.006	55.1	55.1	0.998	50.8	61.0	0.001
Regular exercise such as football, tennis, baseball, and golf	18.3	10.6	0.000	34.9	30.0	0.209	6.53	2.51	0.001
Past injury of either knee	2.4	2.8	0.560	1.4	4.1	0.046	3.1	2.4	0.466

OW was significantly positively associated with KOA (OR 2.65, 95% CI 1.98–3.54, $p < 0.001$). Logistic regression analysis using the same objective and explanatory factors and stratified according to sex indicated that, in both sexes, OW was the only factor that was significantly associated with KOA (men: OR 1.64, 95% CI 1.04–2.59, $p < 0.05$; women: OR 3.64, 95% CI 2.48–5.34, $p < 0.001$), while in men, there was weak but not significant association between HTN and KOA (OR 1.61, 95% CI 0.99–2.60, $p = 0.053$). These results suggest that obesity, among the various components for MS, was most significantly correlated to KOA.

Prevalence of KOA and its association with the number of components for MS. Table 4 shows the prevalence of KOA classified by the number of components for MS: the prevalence of KOA tended to increase with the increase in the number of MS components (p for trend < 0.001) in the total population. However, the prevalence of KOA in men and women did not tend to increase monotonically. Thus, in men, the prevalence of KOA in the groups with 2 MS components was lower than that in the groups with 1 component. Similarly, in women, the prevalence of KOA in the group with 2 MS components was higher than that in the group with 3 or more components.

To clarify the effect of the accumulation of MS components on the presence of KOA, logistic regression analysis was performed using the presence of KOA as the objective variable and the MS components (OW, HTN, DL, and IGT) present as explanatory variables after adjustment for age and sex. Compared to the reference condition (no MS components), increasing the number of components of MS significantly increased the OR for the presence of KOA (vs no component; 1 component: OR 1.18, 95% CI 0.87–1.61, $p = 0.273$; 2 components: OR 1.74, 95% CI 1.25–2.44, $p = 0.001$; more than 3 components: OR 2.15, 95% CI 1.44–3.23; $p < 0.001$). Again, the same analysis was also performed stratified by sex. In men, although no dose-response effects of the accumulation of MS components on KOA were observed when the number of the components was 1 or 2, the accumulation of 3 or more components of MS tended to be significantly associated with a higher OR of KOA (vs no component; 1 component: OR 1.94, 95% CI 1.11–3.39, $p = 0.021$; 2 components: OR 1.61, 95% CI 0.89–2.91, $p = 0.117$; more than 3 components: OR 2.96, 95% CI 1.5–5.85, $p = 0.002$). In contrast, in women, no significant difference was observed between the presence of no components and 1 component; however, 2 or more components of MS increased the risk of KOA significantly (vs no component; 1 component: OR 0.89, 95% CI 0.61–1.29, $p = 0.527$; 2 components: OR 1.94, 95% CI 1.27–2.96, $p = 0.002$; more than 3 components: OR 1.71, 95% CI 1.01–2.87, $p = 0.044$).

Table 4. Prevalence (%) of knee osteoarthritis, classified by the number of components of metabolic syndrome (MS). MS components consisted of obesity, hypertension, dyslipidemia, and impaired glucose tolerance.

No. MS Components	Total	Men	Women
0	32.5	24.8	35.4
1	49.9	44.8	52.9
2	60.5	42.7	71.8
≥ 3	62.2	51.3	69.4

Logistic regression analysis was performed using the presence of KOA as the objective variable and the number of MS components present (OW, HTN, DL, and IGT) as explanatory variables, after adjustment for age, sex, regional difference, smoking habit, alcohol consumption, physical activities, regular exercises, and history of knee injuries. Figure 1 shows the OR of the association between accumulation of components of MS and presence of KOA. Compared to the reference condition (no components of MS), increasing the number of components of MS significantly increased the OR for the presence of KOA (vs no component; 1 component: OR 1.21, 95% CI 0.88–1.68, $p = 0.237$; 2 components: OR 1.89, 95% CI 1.33–2.70, $p < 0.001$; > 3 components: OR 2.72, 95% CI 1.77–4.18, $p < 0.001$). Again, the same analysis was also performed stratified by sex. In men, although no dose-response effects of the accumulation of MS components on KOA were observed when the number of the components was 1 or 2, the accumulation of 3 or more components of MS tended to be significantly associated with a higher OR of KOA (vs no com-

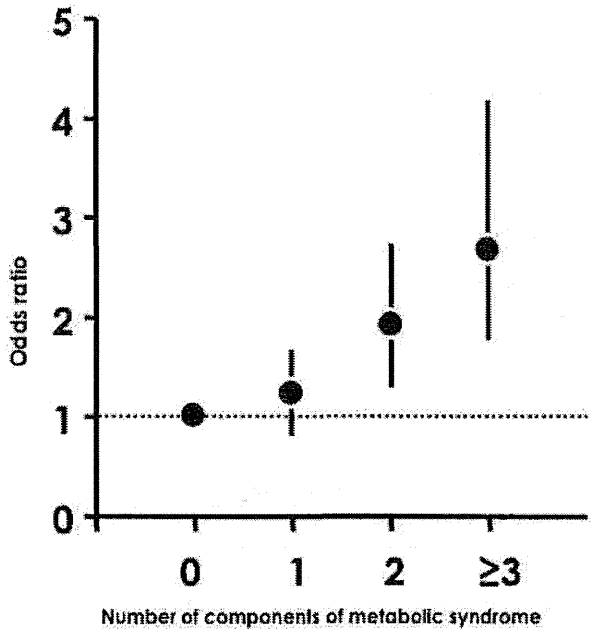

Figure 1. Odds ratios of the association between the number of components of metabolic syndrome and the presence of knee osteoarthritis, compared to no components present.

ponent; 1 component: OR 2.07, 95% CI 1.15–3.74, p = 0.016; 2 components: OR 1.68, 95% CI 0.89–3.17, p = 0.110; more than 3 components: OR 3.88, 95% CI 1.87–80.6, p < 0.001). In contrast, in women, no significant difference was observed between the presence of no component and 1 component; however, 2 or more components of MS increased the OR of KOA significantly (vs no component; 1 component: OR 0.88, 95% CI 0.59–1.32, p = 0.541; 2 components: OR 2.13, 95% CI 1.36–3.34, p = 0.001; > 3 components: OR 2.17, 95% CI 1.25–3.77, p = 0.006).

Joint space narrowing and areas of osteophytes in the knee, and their association with components of MS. Tables 5A and 5B show the mean measurements of indices for KOA, medial MJSW (mm), lateral MJSW (mm), medial JSA (mm^2), lateral JSA (mm^2), and OPA (mm^2), classified by the number of components of MS. The values of medial MJSW tended to be significantly lower, and those of OPA significantly higher, with the increasing number of components of MS. The values of medial JSA in women belonging to the group with no component of MS were significantly higher than in those belonging to the groups with 1, 2, 3, or more components of MS, but no such tendency was observed in men. There was no relationship between the values of lateral MJSW, lateral JSA, and the number of components of MS.

Multiple regression analysis was performed using values of medial MJSW as the objective variable and the number of components of MS present as explanatory variables, after adjustment for age, sex, regional difference, smoking habit, alcohol consumption, physical activities, regular exercises, and history of knee injuries. In the overall population, we found that the number of components of MS was inversely related to the values of medial MSJW (ß = –0.148, R^2 = 0.21, p < 0.001). An analysis performed using the same objective and explanatory factors and stratified by sex showed the same tendency in both men and women (men: ß = –0.152, R^2 = 0.14, p < 0.001; women: ß = –0.149, R^2 = 0.18, p < 0.001).

Multiple regression analysis was then performed using OPA values as the objective variable and the number of components of MS present as explanatory variables, after adjustment for age, sex, regional difference, smoking habit, alcohol consumption, physical activities, regular exercises, and history of knee injuries. The analysis revealed that the number of components of MS was positively related to OPA values (ß = 0.12, R^2 = 0.11, p < 0.001). An analysis performed using the same objective and explanatory factors and stratified by sex showed the same tendency in both men and women (men: ß = 0.15, R^2 = 0.08, p < 0.001; women: ß = 0.11, R^2 = 0.11, p < 0.001).

In women, multiple regression analysis was performed using values of medial JSA as the objective variable and the number of components of MS present as explanatory variables, after adjustment for age, regional difference, smoking habit, alcohol consumption, physical activities, regular exercises, and history of knee injuries. The analysis revealed that the number of components of MS was inversely related to the values of medial JSA in women (ß = –0.096, R^2 = 0.18, p = 0.001).

DISCUSSION

We found that an increase in the number of components of MS was significantly associated with the presence of KOA diagnosed by using the KL scale in Japanese men and women. We also clarified that the values of medial MJSW and OPA in men and women, and medial JSA in women as features of KOA, were significantly associated with the increase in the number of MS components.

KOA and MS share age and OW as risk factors[1,7,8,9,10,11]. We have already reported that higher BMI was associated with radiographic KOA based on an analysis using the same population evaluated in our study[36], and it was also clarified that OW was the strongest factor that influenced the prevalence of KOA.

Regarding the association between clustering of metabolic factors and KOA, Hart, *et al* found that metabolic factors including blood glucose, hypercholesterolemia, and HTN were associated with both unilateral and bilateral KOA and were independent of OW[20]. Sowers, *et al*[21] defined the presence of ≥ 2 of the following criteria as cardiometabolic clustering: low levels of HDL cholesterol, elevated levels of low-density lipoprotein cholesterol, TG, BP, C-reactive protein, waist/hip ratio, glucose levels, and dia-

Table 5A. Mean (SD) of medial and lateral minimum joint space width (MJSW) classified by the number of components of metabolic syndrome (MS). MS components consisted of obesity, hypertension, dyslipidemia, and impaired glucose tolerance.

No. MS Components	Medial MJSW, mm			Lateral MJSW, mm		
	Total	Men	Women	Total	Men	Women
0	2.98 (0.81)	3.33 (0.66)	2.85 (0.82)	4.00 (1.18)	4.37 (1.13)	3.86 (1.17)
1	2.69 (1.01)[a]	3.05 (0.97)	2.49 (0.98)[a]	3.96 (1.13)	4.43 (1.05)	3.70 (1.08)
2	2.43 (1.19)[ab]	2.87 (1.10)[a]	2.15 (1.17)[ab]	3.85 (1.19)	4.15 (1.10)	3.66 (1.22)
≥ 3	2.42 (1.22)[ab]	2.73 (1.24)[a]	2.22 (1.17)[a]	4.06 (1.27)	4.26 (1.29)	3.93 (1.24)

[a] Significantly different from values obtained in the absence of components ($p < 0.05$). [b] Significantly different from values obtained with 1 component ($p < 0.05$).

Table 5B. Mean (SD) of medial and lateral joint space area (JSA) and area of osteophytosis (OPA), classified by number of components of metabolic syndrome (MS). MS components consisted of obesity, hypertension, dyslipidemia, and impaired glucose tolerance.

No. MS Components	Medial JSA, mm^2			Lateral JSA, mm^2			OPA, mm^2		
	Total	Men	Women	Total	Men	Women	Total	Men	Women
0	96.3 (27.6)	111.4 (25.6)	98.8 (26.2)	111.0 (33.2)	132.2 (34.2)	103.3 (29.2)	1.81 (6.42)	0.93 (2.97)	2.13 (7.26)
1	90.2 (31.7)[a]	104.0 (30.7)	82.3 (29.6)[a]	111.0 (32.4)	131.2 (30.5)	99.5 (27.5)	3.06 (7.89)	1.33 (4.26)	4.05 (9.21)
2	85.2 (36.7)[a]	101.1 (34.3)	75.0 (34.6)[ab]	111.7 (32.2)	128.9 (29.6)	100.6 (28.8)	5.34 (11.25)[ab]	2.45 (5.36)	7.18 (13.44)[ab]
≥ 3	88.2 (39.3)	102.0 (40.1)	79.1 (36.0)[a]	118.2 (35.3)	132.5 (34.7)	108.8 (32.5)[b]	6.26 (9.59)[ab]	3.82 (8.70)[ab]	7.86 (9.85)[ab]

[a] Significantly different from values obtained in the absence of components ($p < 0.05$). [b] Significantly different from values obtained with 1 component ($p < 0.05$).

betes mellitus, and assessed the association between cardiometabolic clustering and KOA. They found that KOA was significantly more frequent in obese women with cardiometabolic clustering compared with those without it[21]. Using data from the National Health and Nutrition Examination Survey III (NHANES III), Singh, *et al* suggested that adults with OA in the United States have a high prevalence of CVD risk factors[19], and Puenpatom and Victor demonstrated that each of the 5 cardiovascular risk factors that comprise MS, HTN, abdominal OW, hyperglycemia, elevated TG, and low HDL cholesterol, was more prevalent in the population with OA than in the population without OA[22]. However, to our knowledge, few population-based studies have shown a dose-response relationship between the presence of KOA and the accumulation of the number of MS components.

In our study, the logistic regression analysis revealed that only OW was significantly associated with KOA, and other components were not significant, using the presence of KOA as an objective variable and all components for MS, such as OW, HTN, DL, and IGT as explanatory variables and after adjustment for potential confounders. However, we found that the higher the number of components of MS, the greater the OR of the presence of KOA. This result indicates that, even if the effect of each component of MS on KOA may be weak, accumulation of the number of components may significantly worsen KOA.

In addition, we found that medial MJSW values in men and women, and medial JSA values in women tended to be significantly lower with the increase in the number of components of MS. In contrast, OPA values became significantly higher with the increase in the number of components of MS. Regarding the association between JSW and KOA, Sowers, *et al* used statistical models that included variables representing obesity, cardiometabolic status, and lateral and medial JSW differences to show that a 1-mm increase in the difference between lateral and medial JSW was associated with 2.1 times greater odds of having KOA, and subjects who were obese with cardiometabolic clustering had 4.5 times greater odds of having KOA[21]. However, no other reports have addressed direct associations between indices of KOA, such as MJSW, JSA, and OPA values, with the accumulation of the number of components of MS. In our study, we confirmed that the accumulation of the number of MS components present influenced the values of both MJSW, JSA (women only), and OPA, which determine the features and severity of KOA.

Regarding the association of clustering of components for MS and KOA, a few hypotheses have been suggested. Hart, *et al* attributed the effect of excess endogenous estrogens to the aromatization of estrone in fat tissue[20]. Regarding the endogenous secreted products, Sowers, *et al* suggested that leptin and adiponectin levels influenced the development of OA[21]. They stated that leptin concentrations

in the synovial fluid of patients with OA correlated with their BMI, and levels of adiponectin are low in obese individuals and in those with CVD. Another hypothesis states that atherosclerotic change may play a role in the development of OA. Kornaat, *et al* reported the association between increased popliteal artery vessel wall thickness and generalized OA[37]. It has been hypothesized that atherosclerotic changes and obesity-associated metabolic changes in the subchondral bone are associated with OA[37,38]. In obese subjects, metabolic changes in the striated muscles induced by the interaction of insulin resistance and systemic inflammation might lead to fatigue and muscle weakness, which influences the balance between damage and repair mechanisms leading to OA[37,39]. In our study, we could not substantiate these hypotheses because of the lack of relevant measurements. However, in the followup study, we will obtain the ankle brachial pressure index and pulse wave velocity of the ROAD subjects, and thus we will further the evidence regarding the association between arteriosclerosis and KOA.

In our study, a sexual dimorphism pattern was shown in prevalence of KOA (women > men) and components of MS such as values of BMI (men > women), BP (men > women), and HDL cholesterol (women > men). Regarding KOA, being female is well known as a strong risk factor, according to our previous survey and other studies[27,40,41,42,43,44], possibly implicating an involvement of muscle strength to compensate for the mechanical stress, since women are known to have less muscle strength than men[45]. Sex differences in the prevalence of MS might be partly explained by endogenous sex steroids. As mentioned, Hart, *et al* attributed the effect of excess endogenous estrogens to the aromatization of estrone in fat tissue[20]. Recent systematic review and metaanalysis of observational studies concluded that there is a sex-dependent association between levels of testosterone and occurrence of MS[46]. In addition, the difference in prevalence of associated confounding factors may influence the effect of sex difference on the occurrence of MS. In our study, there are sex differences in lifestyle-related factors, which might influence the occurrence of MS. For example, the proportions of smokers and alcohol consumers are both significantly higher in men than in women (both $p < 0.001$). Regarding the physical activities, the proportion of men who exercised regularly was significantly higher than that of women ($p < 0.001$). Therefore, for the statistical analyses, we adjusted not only for age and sex, but also for such potentially confounding factors to show the association between components of MS and KOA.

With regard to ethnic differences in MS, Hoang, *et al* reviewed epidemiological studies and reported that the prevalence of MS in East Asians was lower than that in whites[28]. However, the prevalence of MS may increase rapidly. Nestel reported a dramatic increase in the prevalence of MS in a cohort from Beijing, from 9% to 21%, between 1992 and 2002[47]. In addition, as reported, the prevalence of KOA in Japanese as well as Chinese cohorts is significantly higher than in whites[27,36]. In light of the rapidly increasing population in Asian countries, prevention strategies for obesity-related chronic diseases, such as MS and KOA, should be implemented immediately. In our study, we clarified that components of MS and their accumulation were associated with KOA in Asian subjects. Based on these findings, the prevention of MS may be useful in the prevention of not only CVD, but also KOA, in both Asian and Western countries, and may lead to a reduction in the number of patients who have a disability arising from joint disorders.

There are several limitations in our study. First, although the ROAD study includes a large number of participants, these participants may not be truly representative of the general population. To confirm whether the participants of the ROAD study are representative of the Japanese population, we compared anthropometric measurements and the frequencies of smoking and alcohol consumption between study participants and the general Japanese population, and no significant differences were found, except that male ROAD study participants aged 70–74 years were significantly smaller in terms of body structure than the overall Japanese population ($p < 0.05$)[29]. This difference should be considered when evaluating the potential risk factors for men aged 70–74 years; factors such as body build, particularly heavy weight, are known to be associated with the presence of MS and KOA. Thus, our results might represent an underestimation. Second, this was a cross-sectional study, and the causal relationship between metabolic factors and KOA remains unclear. Metabolic factors may have changed recently or been longstanding; this can only be ascertained by a longitudinal study that clarifies the incidence and/or progression rates of KOA in the same cohort. The first such followup of the ROAD cohort is in progress; it intends to clarify the causal relationships between musculoskeletal diseases and MS for early prevention of the disabilities. Third, we categorized MS by using the criteria defined by the Examination Committee of Criteria for Metabolic Syndrome in Japan[29], except for the definition of overweight. We used BMI ≥ 25 as the criterion for OW status, as defined by the Japan Society for the Study of Obesity[30]. In addition, since the blood samples obtained were not always from participants under fasting conditions, we used serum HDL cholesterol level < 40 mg/dl to indicate DL, and serum HbA1c level ≥ 5.5% to indicate IGT, which are indices used by the National Health and Nutrition Survey in Japan[32]. These differences in the definition of MS may skew the true association between MS and KOA. However, our aim was to determine how the accumulation of MS components was related to KOA, and we believe the indices we used for OW, HTN, DL, and IGT accurately reflected the participants' physical condition.

Our study evaluated a large-scale population from the

ROAD study and revealed that the presence of KOA was significantly associated with increases in the number of components of MS. Additionally, the number of components of MS was inversely related to medial MSJW values and positively related to OPA values. The prevention of MS may be useful for both CVD and KOA in Asian populations. Further investigations, along with continued longitudinal surveys in the ROAD study, will elucidate the components of MS and occurrence or progress of KOA.

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ORIGINAL ARTICLE

Changes in serum levels of biochemical markers of bone turnover during 10 years among Japanese men and women: associated factors and birth-cohort effect. The Taiji Study

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Abstract We aimed to clarify changes in biochemical markers of bone turnover (BTMs) over 10 years, associations with changes in bone mineral density (BMD), and birth-cohort effects in a Japanese community. We randomly selected 400 individuals (age, 40–79 years; 50 of each gender and age stratum) from a list of registered residents in 1993. We measured BMD of the spine and hip, and serum concentrations of total osteocalcin (OC), beta-C-terminal cross-linking telopeptide of type I collagen (beta-CTX), and N-terminal cross-linking telopeptide of type I collagen (NTX), in 1993 and 2003. Of the 400 subjects, 322 (153 men, 169 women) completed the 10-year follow-up. Mean change rates (standard deviation) for serum total OC, beta-CTX, and NTX over 10 years were −1.00 (3.74)%/year, 5.10 (22.48)%/year, and 0.40 (3.41)%/year, respectively, in men, and 0.02 (5.32)%/year, 5.53 (14.54)%/year, and 0.62 (3.26)%/year, respectively, in women. Change rates of BTMs were higher for women in their forties than for women in their fifties to seventies ($P < 0.05$), and higher in the menstrual transition group than in pre- and postmenopausal groups ($P < 0.001$). Changes in levels of BTMs over 10 years in women were significantly associated with change rates of BMDs at L2–L4 and total hip after adjusting for potential confounders. A significant birth-cohort effect was observed among women in their fifties. We concluded that change rates of BTMs during the 10 years were influenced by menstrual transition, age, and sex and associated with bone loss at L2–L4 and total hip.

Keywords Biochemical markers of bone turnover · Bone loss · Menstrual transition · Birth-cohort effect

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Introduction

In Japan, about 10 million patients are estimated to have osteoporosis (OP) [1], and osteoporotic fractures are ranked fifth among the diseases responsible for causing disabilities requiring support [2]. Moreover, the number of cases of hip fracture has increased steeply in the past 20 years with the rapid aging of the population [3]. Early detection of OP to reduce the risk of osteoporotic fractures is therefore an urgent issue in terms of maintenance of quality of life in the elderly and containment of medical costs required for their care.

Biochemical markers of bone turnover (BTMs) are widely used in clinical situations to evaluate the efficacy of treatments for OP [4–6]. Several epidemiological studies have shown that BTMs can predict bone loss in women [7–10], but few reports appear to have examined trends in BTMs during more than one decade. In addition, few reports have clarified associations between changes in levels of BTMs and bone loss, particularly in men [11, 12].