Results

Eligible participants and baseline characteristics

Background data including physical characteristics for all male participants at baseline are shown in Table 1. Mean weight and height in their fifties, sixties, and seventies, and mean body mass index (BMI) in their seventies were significantly lower than those in their forties ($P < 0.05$).

Among the 200 male participants at baseline, 1 man in his sixties declined to undergo blood and urinary examinations for endogenous hormones. Examinations at baseline were thus performed on 199 men. The second visit, aimed at evaluating changes in BMDs over 3 years, obtained measurements for 181 of the 200 initially recruited participants (90.5%). The following reasons were given for the loss of 19 participants at the 3-year follow-up: 8 men had died, 1 man had moved, 1 man was ill, 4 men declined to participate, and 2 men were away from the area at the time of follow-up. The third visit, aimed at evaluating changes in BMDs over 7 years, evaluated 170 of the 200 initially recruited participants (85%). Loss of 30 participants at the 7-year follow-up was explained as follows: 14 men had died, 3 men had moved, 6 men were ill, 5 men declined to participate, and 2 men were away from the area at the time of follow-up. Among the 200 male participants initially recruited, 153 men participated in the fourth visit held in 2003 (76.5%). Loss of 47 participants at the 10-year follow-up was explained as follows: 33 men had died, 6 men had moved, 4 men were ill, 2 men declined to participate, and 2 men were away from the area at the time of follow-up.

Mean levels of serum concentration of sex steroids at baseline

Age distributions of mean E_2 and FT levels at the initial survey are also shown in Table 1. Because data below the measurable range were excluded from analysis, E_2 and FT data could be obtained for 178 and 198 participants, respectively. Mean serum levels of E_2 and FT were 22.4 and 9.4 pg/ml, respectively. Although no significant age-related trends were seen for E_2, a significant trend toward low values of FT was noted according to age ($P < 0.001$). In addition, mean serum FT was significantly higher for men in their forties than for men in their sixties and seventies ($P < 0.05$).

Predictive capacity of endogenous sex steroids for bone change

Initial mean values and rates of change in L2–L4 BMD over the 3-, 7-, and 10-year periods, classified by age stratum, are shown in Table 2. BMD values at L2–L4 for men had increased slightly by the 10-year follow-up in their fifties and sixties but had decreased a little in the forties and seventies. BMD values at the femoral neck over 10 years had decreased for men in their forties and fifties and had increased considerably in their seventies.

According to multivariate regression analysis using each rate of change for BMD at the lumbar spine over 3, 7, and 10 years as an objective factor and serum levels of E_2 as an explanatory factor after adjusting for age and BMI, beta values for the rate of change for BMD for the first 3, 7, and 10 years were 0.02, 0.04, and –0.02, respectively. Similarly, on multivariate regression analysis using each rate of change for BMD at the femoral neck over 3, 7, and 10 years as an objective factor and serum levels of E_2 as an explanatory factor after adjusting for age and BMI, beta values for the rate of change for BMD for the first 3, 7, and 10 years were –0.07, 0.09, and –0.01, respectively. Total E_2 values could not predict bone change at the lumbar spine or femoral neck at 3, 7, or 10 years.

Again, using the results of multivariate regression analysis to clarify associations between serum FT and

Table 1 Summary characteristics for male participants at baseline classified by age

Birth cohort	Age-group (years)	*n*	Age (years)	Height (cm)	Weight (kg)	BMI (kg/m^2)	E2 (pg/mL)		FT (pg/mL)	
			Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)
1943–1952	40–49	50	44.2 (2.6)	168.8 (5.2)	69.0 (10.4)	24.2 (3.2)	46	22.1 (7.4)	50	10.9 (2.8)
1933–1942	50–59	50	54.8 (2.7)	165.6 (5.0)^{a}	63.5 (9.4)^{a}	23.1 (2.9)	43	22.2 (7.0)	50	9.8 (2.6)
1923–1932	60–69	50	64.6 (2.5)	163.0 (4.8)^{a}	62.9 (9.6)^{a}	23.6 (3.2)	46	23.1 (8.5)	49	8.8 (2.6)^{a}
1913–1922	70–79	50	74.0 (2.7)	160.7 (5.4)^{a,b}	57.5 (8.3)^{a,b,c}	22.2 (2.8)^{a}	43	22.3 (7.7)	49	8.2 (3.1)^{a}
1913–1952	40–79	200	59.4 (11.4)	164.5 (5.9)	63.2 (10.2)	23.3 (3.1)	178	22.4 (7.6)	198	9.4 (2.9)

BMI body mass index, *E2* total estradiol, *FT* free testosterone, *n* number of participants, *SD* standard deviation

[a] Significantly different ($P < 0.05$) from values of participants in their forties

[b] Significantly different ($P < 0.05$) from values of participants in their fifties

[c] Significantly different ($P < 0.05$) from values of participants in their sixties

BMD changes at the lumbar spine and femoral neck, beta values of FT for the rate of change for BMD at the lumbar spine at the first 3, 7, and 10 years were 0.08, 0.08, and 0.03, respectively, and those at the femoral neck were 0.21, 0.14, and 0.06, respectively. Mean FT levels were significantly related to the rate of change for BMD at the femoral neck during the first 3 years ($R^2 = 0.05$, $P < 0.01$), but could not predict bone change at any site at 7 or 10 years.

Table 2 Mean values (SD) of bone mineral density (g/cm^2) and change rate (%) at lumbar spine L2–L4 and femoral neck over 3, 7, and 10 years, classified by age and gender

Birth cohort	Age-group (years)	L2–L4								Femoral neck			
		Baseline		2nd visit (3-year follow-up)		3rd visit (7-year follow-up)		4th visit (10-year follow-up)		Baseline	2nd visit	3rd visit	4th visit
		n	BMD (g/cm^2)	*n*	Change rate (%/3 years)	*n*	Change rate (%/7 years)	*n*	Change rate (%/10 years)	BMD (g/cm^2)	Change rate (%/3 years)	Change rate (%/7 years)	Change rate (%/10 years)
1943–1952	40–49	50	1.05 (0.15)	48	0.6 (3.8)	46	−0.6 (5.1)	43	−0.2 (5.8)	0.86 (0.09)	0.3 (4.6)	−1.8 (4.8)	−1.5 (10.9)
1933–1942	50–59	50	0.98 (0.17)	47	1.0 (3.3)	46	−0.0 (6.3)	46	1.6 (8.0)	0.80 (0.13)^a	−0.2 (4.9)	0.7 (10.0)	−3.0 (6.8)
1923–1932	60–69	50	1.04 (0.21)	49	1.3 (3.6)	47	1.4 (7.1)	41	2.3 (9.4)	0.77 (0.11)^a	1.0 (7.0)	−0.1 (9.3)	0.3 (12.5)
1913–1922	70–79	50	0.97 (0.19)	37	0.1 (5.3)	31	−1.2 (7.9)	23	−1.5 (9.2)	0.71 (0.08)^{a,b,c}	0.9 (6.3)	4.6 (10.2)^a	6.6 (16.2)^b
1913–1952	40–79	200	1.01 (0.18)	181	0.8 (4.0)	170	0.0 (6.6)	153	0.8 (8.1)	0.79 (0.12)	0.5 (5.7)	0.5 (8.9)	−0.3 (11.7)

SD standard deviation, *BMD* bone mineral density, *n* number of participants

[a] Significantly different ($P < 0.05$) from values of subjects in their forties

[b] Significantly different ($P < 0.05$) from values of subjects in their fifties

[c] Significantly different ($P < 0.05$) from values of subjects in their sixties

Discussion

The present study examined endogenous hormone levels among men in Japan, measuring changes in BMD over spans of 3, 7, and 10 years. The present study clarified the age distribution of endogenous sex steroids, and a significant trend was seen toward low FT levels with age. FT tended to be significantly lower in the sixties and older when compared with levels in the forties in the present study. Our results support the findings of other reports. Orwoll et al. [26] showed that testosterone levels, particularly FT levels, for 2,623 men 65 years or older were associated with increasing age. Similar findings have been described in other cross-sectional and longitudinal studies [27–29]. Based on these results, we concluded that older men tended to show lower testosterone levels than younger men, similar to the situation with E_2 in women. Some men might display testosterone insufficiency, as seen in women with E_2 insufficiency. However, we do not yet have enough evidence regarding normal ranges in young men and thresholds for testosterone insufficiency. In addition, levels of testosterone may vary among individuals and be influenced by body composition such as adipose tissue, muscle, and bone.

In contrast to testosterone, no significant age-related trend in E_2 was found in the present study. Little information is available regarding E_2 levels in older men. Orwoll et al. [26] reported that E_2 concentrations decreased as age increased, and similar findings have been described in various reports [30–33]. However, other studies have noted stable [34–36] or rising [37] E_2 levels with increasing age. Although the reasons for these discrepancies are unclear, E_2 levels may vary among individuals and may be influenced by body composition such as adipose tissue, muscle, and bone, as well as testosterone.

Regarding the ethnic variations in serum sex steroid levels, as most previous reports have been based on studies of Caucasian men, ethnic variations in FT levels among men remain unclear. To the best of our knowledge, the Osteoporotic Fractures in Men Study (MrOS) is the only study in which a sufficient number of Asian men have participated [26]. For reasons of differences in measurement methods, direct comparison of the present results and those from the MrOS study is inappropriate, but FT levels among Japanese men tended to be lower than those in MrOS participants, although no significant difference in E_2 levels was apparent. Orwoll et al. [26] analyzed ethnic differences in the MrOS study and stated that FT levels were lower in Asian men than in other races such as Caucasian, African-American, and Hispanic subjects, but no such differences were seen for E_2. The present results support these findings.

The present study found that serum levels of FT could offer a useful predictor of bone loss at the femoral neck within 3 years, but this effect was diluted with longer observation. Regarding the effects of testosterone on bone loss at the hip, Cauley et al. [38] reported, in an epidemiological study of 1,327 men $\geq$65 years old, that men in the lowest FT category experienced greater hip bone loss over 1.8 years. In addition, Ensrud et al. [39] reported that among men with weight loss, the rate of decline in total hip BMD showed a stepwise increase in magnitude with greater decreases in bioavailable testosterone from baseline. In the present study, the effect of FT levels on bone loss within the relatively short term up to 3 years was observed at the femoral neck, independent of age and BMI, supporting previous reports. Although reasons for site-specific differences in the predictive capacity of FT remain uncertain, we have already reported that bone loss rate differs depending on the site involved in another cohort study [40]. We have also reported that characteristics differ between fast bone losers at the lumbar spine and femoral neck [41]. One reason for site-specific differences might be because degenerative changes that increase BMD, such as osteophytosis or sclerotic change, are observed more frequently at the lumbar spine than at the femoral neck. These results suggest that the predictive capacity of FT might differ according to the sites involved.

A recent study showed that older men with total testosterone or E_2 deficiency were more likely to be osteoporotic [19], but no report evaluated the capacity of serum sex steroids to predict occurrence of OP. Regarding the relationship between testosterone and fracture risk, Mellstrom et al. [42] reported that FT within the normal range was independently associated with the presence, but not occurrence, of osteoporotic fracture in elderly men. In contrast, an analysis from the Rotterdam Study failed to confirm any association between testosterone and fracture risk [43]. Data from the Framingham study indicated that men with low serum testosterone and E_2 levels were at increased risk for incident hip fractures [44]. A recent report from the Dubbo osteoporosis epidemiology study revealed that in men older than 60 years, serum testosterone is independently associated with the risk of osteoporotic fracture [45]. We also tried to evaluate the predictive capacity of serum levels of sex steroids and occurrence of OP based on WHO criteria [46] and osteoporotic fractures, but only identified 7 cases of OP and 10 cases of osteoporotic fractures including 1 vertebral fracture, 1 hip fracture, 2 wrist fractures, 3 costal fractures, 2 ankle fractures, and 1 finger fracture. After analysis using Cox proportional hazards models adjusted for age and BMI, serum levels of FT were significantly related to incidence of OP (hazard ratio, 0.42; 95% confidence interval, 0.19–0.90), but not to incidence of osteoporotic fractures. This analysis suggests the possibility of serum FT as a predictor for OP occurrence over 10 years. However, the number of occurrences of OP seems to be too small to reach any conclusion regarding the presence or absence of associations between sex steroids and OP or osteoporotic fractures.

There are several limitations in the present study. First, the small sample size seemed to be the most severe weakness. In fact, as already noted, only 7 cases of OP and 10 cases of osteoporotic fractures were accumulated during the 10 years of the study. Longer observation in the present cohort might be required to confirm the association between sex steroids and OP or osteoporotic fracture. Second, the dropout rate over 10 years for patients in their seventies was considerably high (54.0%). This high dropout rate might cause bias. In fact, the tendency toward an increase in BMD at the femoral neck for patients in their seventies was skewed by withdrawal bias. On the basis of this hypothesis, we reanalyzed the multivariate regression analysis to assess the change rate of BMD at the femoral neck and serum FT with exclusion of subjects in their seventies. However, the results were similar, with serum levels of FT predicting bone loss at the femoral neck within 3 years (beta $= 0.17$, $P = 0.05$), but diluted effects with longer observation (7 years: beta $= 0.8$, $P = 0.38$; 10 years: beta $= 0.03$, $P = 0.77$). Third, all serum samples were extracted between 0900 and 1500, not at a fixed time in the morning, although samples for measurement of FT are recommended to be collected in the morning. Serum levels of testosterone tend to increase toward night, peaking in the early morning, then decreasing rapidly and reaching a nadir between 1300 and 2300. We collected samples when FT levels would probably have been decreasing toward the nadir. The present study might thus have underestimated FT values compared to collection at a fixed time in the morning.

Conversely, the study design shows several notable strengths. In this population-based cohort study, subjects were selected randomly from the resident registration list. BMD was carefully measured by a single observer (N.Y.), and measurements were repeated 3, 7, and 10 years later with high participation rate by the same device and same observer. Another strength was that the effect of serum levels of sex steroids on changes in BMD could be estimated directly.

In conclusion, we clarified that serum levels of FT could predict bone loss within 3 years, but not longer. Further observations are required to confirm the relationship between FT, E_2, and spinal OP and osteoporotic fractures. Other environmental and genetic factors should also be evaluated to develop strategies for the early prevention of OP.

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Conflict of interest statement The authors have no conflicts/disclosures to declare regarding the present manuscript.

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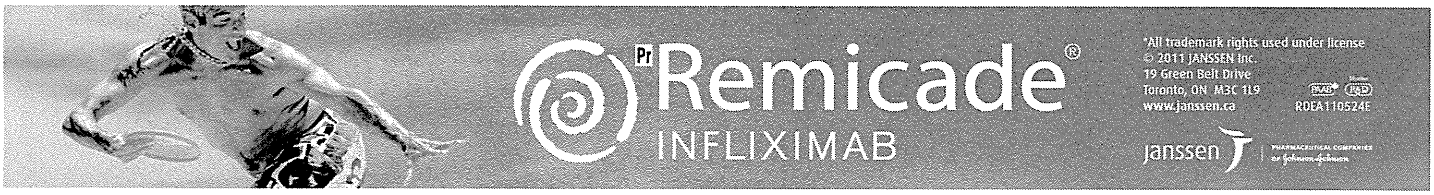

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Association of Knee Osteoarthritis with the Accumulation of Metabolic Risk Factors Such as Overweight, Hypertension, Dyslipidemia, and Impaired Glucose Tolerance in Japanese Men and Women: The ROAD Study

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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:
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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 $\geq 5.5\%$ 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-

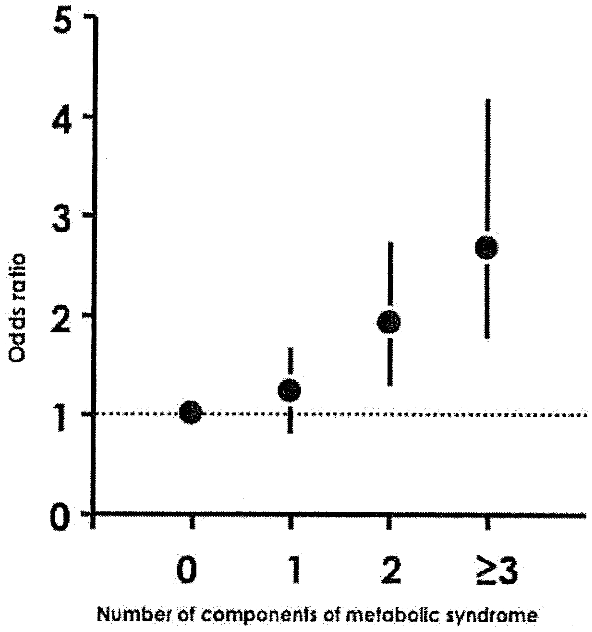

Figure 1. Odds ratios of the association between the number of components of metabolic syndrome and the presence of knee osteoarthritis, compared to no components present.

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 Total	Medial MJSW, mm Men	Medial MJSW, mm Women	Lateral MJSW, mm Total	Lateral MJSW, mm Men	Lateral MJSW, mm 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 Total	Medial JSA, mm^2 Men	Medial JSA, mm^2 Women	Lateral JSA, mm^2 Total	Lateral JSA, mm^2 Men	Lateral JSA, mm^2 Women	OPA, mm^2 Total	OPA, mm^2 Men	OPA, mm^2 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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Association of occupational activity with joint space narrowing and osteophytosis in the medial compartment of the knee: the ROAD study (*OAC5914R2*)

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SUMMARY

Objective: We investigated the association of occupational activity with joint space narrowing and osteophytosis at the knee separately in Japanese subjects using a large-scale population-based cohort of the Research on Osteoarthritis Against Disability (ROAD).

Methods: From the baseline survey of the ROAD study, 1,402 participants (512 men and 890 women) living in mountainous and seacoast communities were analyzed. Information collected included a lifetime occupational history and details of specific workplace physical activities. To estimate the severity of joint space narrowing and osteophytosis at the knee, minimum joint space width (mJSW) and osteophyte area (OPA) in the medial compartment of the knee were measured using a knee osteoarthritis (OA) computer-aided diagnosis system.

Results: For women, agricultural, forestry, and fishery workers had significantly lower mJSW values compared with clerical workers or technical experts, whereas OPA did not differ significantly among job titles in men or women. For occupational activities, kneeling and squatting were associated with lower mJSW as well as higher OPA. Walking and heavy lifting were associated with lower mJSW, but not with OPA.

Conclusion: This cross-sectional study using a population-based cohort suggests that an occupational activity that includes kneeling and squatting appears to have a greater effect on knee OA.

Introduction

Knee osteoarthritis (OA), which causes cartilage degeneration and osteophyte formation at joints in the limbs, is a major public health issue causing chronic disability in the elderly in developed countries[1–3]. The prevalence of knee OA is high in the elderly in Japan[4] and 25,300,000 subjects aged 40 years and older are estimated to experience radiographic knee OA[5]. Further, according to the recent National Livelihood Survey of the Ministry of Health, Labour and Welfare in Japan, OA is ranked fourth among diseases that cause disabilities that subsequently require support with regard to activities of daily living[6].

Established risk factors for knee OA in Caucasians include older age, female sex, evidence of OA in other joints, obesity, and previous injury or surgery of the knee[7–11]. Evidence is accumulating in Caucasians that the disease is more common in people who have performed heavy physical work[12–17], particularly in those whose jobs have involved kneeling or squatting[18–24]. We also showed that occupational activities that included sitting, standing, walking, climbing, and heavy lifting had a significant association with moderate knee OA, and kneeling and squatting were associated with severe knee OA[25]. However, in our and other studies regarding occupational risks for knee OA, the disease was defined according to the Kellgren–Lawrence (KL) grade[26] or whether subjects had undergone total knee arthroplasty. KL grade is the most conventional system to grade radiographic severity of knee OA, but in this categorical system, joint space narrowing and osteophyte formation are not assessed separately. In addition, because the KL system emphasizes osteophytosis, it is unclear how to handle knee OA with joint space narrowing but no osteophytosis. Further, we have already reported that occupational activities of

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kneeling and squatting were significantly associated with KL ≥3 knee OA, but not with KL ≥2 knee OA[25]. Considering the definition of the KL grade[26], this difference may suggest distinct risk factors between osteophytosis and joint space narrowing. However, we cannot clarify whether osteophytosis and joint space narrowing have distinct risk factors, because osteophytosis and joint space narrowing are not separately defined according to the KL grade. In addition, a recent cross-sectional study has shown that osteophytosis was unrelated not only to joint space narrowing on plain radiographs, but also to cartilage loss measured by quantitative magnetic resonance imaging[27]. Furthermore, our study on an experimental mouse model for OA has identified a cartilage-specific molecule, carminerin, that regulates osteophytosis without affecting joint cartilage destruction during OA progression[28,29]. This accumulating evidence has indicated that joint space narrowing and osteophytosis may have distinct etiologic mechanisms and their progression may be neither constant nor proportional. Thus, to examine factors associated with knee OA, these two OA features should be assessed separately. However, to the best of our knowledge, there are no large population-based studies that investigate occupational factors associated with joint space narrowing and osteophyte formation separately.

In the present study, we measured medial minimum joint space width (mJSW) and osteophyte area (OPA) in the large-scale population-based cohort study called the Research on Osteoarthritis Against Disability (ROAD). The purpose of the present study was to investigate the association of job title and occupational activity with joint space narrowing and osteophytosis at the knee separately, and to clarify which kinds of occupational activities were associated with joint space narrowing and osteophytosis. Furthermore, we aimed to clarify whether the association of each occupational activity with joint space width and OPA was different.

Subjects and methods

Subjects

The ROAD study is a nationwide prospective study to establish epidemiologic indexes for evaluation of clinical evidence for the development of a disease-modifying treatment for bone and joint diseases (with OA and osteoporosis as the representative bone and joint diseases) consisting of population-based cohorts in several communities in Japan. As a detailed profile of the ROAD study has been described in detail elsewhere[4,5,30,31], only a brief summary is provided here. To date, we have completed creation of a baseline database including clinical and genetic information on 3,040 inhabitants (1,061 men and 1,979 women) ranging in age from 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 ethics committees of the University of Tokyo and the Tokyo Metropolitan Institute of Gerontology. Information collected about job title and occupational activity included a lifetime occupational history with details of seven types of specific workplace physical activities: sitting on a chair, kneeling, squatting, standing, walking, climbing, and heavy lifting. Participants were asked whether they engaged in the following activities: sitting on a chair for ≥2 h/day, kneeling for ≥1 h/day, squatting for ≥1 h/day, standing for ≥2 h/day, walking for ≥3 km/day, climbing up slopes or steps for ≥1 h/day, and lifting loads weighing ≥10 kg ≥1 time/week. Information on these activities was obtained for the principal job, defined as the job at which the participant had worked longest. These definitions were chosen to be similar to definitions used in previous studies of occupations and OA[22,23,25]. Anthropometric measurements included height and weight, and body mass index (BMI; weight [kg]/height^2 [m^2]) was calculated. From baseline data of all participants, the present study analyzed 1,402 participants (512 men and 890 women) aged ≥50 years living in mountainous and seacoast cohorts, after excluding 69 subjects with lateral knee OA.

Radiographic assessment

All participants had radiographic examination of both knees using an anterior–posterior view with weight-bearing and foot map positioning. The beam was positioned parallel to the floor with no angle and aimed at the joint space. To visualize the joint space properly and to make the patella centralized over the lower end of the femur, we used fluoroscopic guidance with an anterior–posterior X-ray beam. The images were downloaded into Digital Imaging and Communication in Medicine (DICOM) format files. mJSW in the medial compartment and OPA at the medial tibia were measured by the KOACAD (knee osteoarthritis computer-aided diagnosis) system, and a knee with the lower mJSW was defined as the designated knee of a participant. The KOACAD system has been described in detail elsewhere[32], and is summarized here only briefly. The KOACAD 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 in general clinical practice. This system was programmed to measure mJSW in the medial and lateral compartments and OPA at the medial tibia using digitized knee radiographs. Initially, correction for radiographic magnification was performed based on the image size of a rectangular metal plate. Next, to determine the region of interest (ROI), the center of the tibiofemoral joint was determined as follows. A vertical neighborhood difference filter, that vertically scanned digital images to detect the margins of the tibial and femoral condyles, was applied to identify points with high absolute values for difference of scale, and then the center of all points was calculated, that was defined as the center of the tibiofemoral joint, and a 480 × 200 pixels of rectangle with the center was decided as the ROI (Supplementary Figure). Within the ROI, the outline of the femoral condyle was designated as the upper rim of the joint space by vertical filtering with the 3 × 3 square neighborhood difference filter. The both ends of the upper rim were determined using a Canny's filter to remove the noise associated with lines, and vertical lines from the ends were designated as the outside rims of the joint space. Outlines of anterior and posterior margins of the tibial plateau were drawn similarly to that of the femoral condyle, and the middle line between the two outlines was designated as the lower rim of the joint space [Fig. 1(A)]. A straight regression line for the lower rim outline was then drawn, and the intersection of the lower rim outline and the regression line was designated as the inside rim. Medial and lateral joint space areas were determined as areas surrounded by the upper, lower, inside, and outside rims as defined above. Medial and lateral mJSWs were further determined as the minimum vertical distances in the respective joint space area [Fig. 1(B)]. To measure the OPA, 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 OPA [Fig. 1(C)]. We have previously published reference values of joint space width and OPA by gender and age strata in Japan using the KOACAD system[33].

Statistical analysis

The differences of age, height, weight, BMI, mJSW, and OPA at the designated knee between men and women were examined by

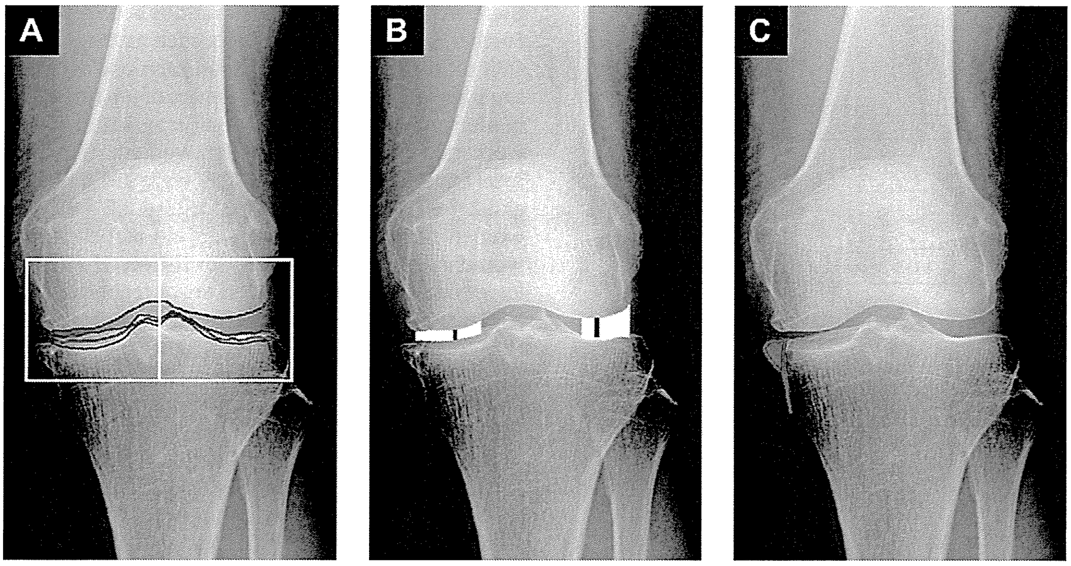

Fig. 1. Schema of image processing by KOACAD (cited from reference number[9]). (A). Outlines of anterior and posterior margins of the tibial plateau. The middle line between the two outlines is defined as the lower rim of the joint space. (B). Medial and lateral mJSWs were defined as the minimum vertical distances in the joint space area. (C). OPA (red area) that is medially prominent over the smoothly extended outline of the tibia.

the non-paired Student's *t*-test. The percentage of each occupational activity was compared between men and women by chi-square test. To determine the association of job title with mJSW and OPA, the Tukey Honestly Significant Differences (HSD) test was used after adjustment for age, gender, and BMI in the overall population and after adjustment for age and BMI in men and women. To determine the association of mJSW and OPA with each occupational activity separately after adjustment for age, gender, and BMI in the overall population, multiple regression analyses were used with age, gender, BMI, and each occupational activity as independent variables in the overall populations. Further, to determine the association of mJSW and OPA with each occupational activity separately after adjustment for age and BMI in men and women, multiple regression analyses were used with age, BMI, and each occupational activity as independent variables. Next, to determine the independent association of occupational activities with mJSW, multiple regression analysis was used with age, gender, BMI, and all significantly associated occupational activities in the overall subjects, and with age, BMI and all significantly associated occupational activities in men and women, as explanatory variables, statistical analyses were performed using SAS version 9.0 (SAS Institute Inc., Cary, NC).

Results

Characteristics of the 1,402 participants aged ≥50 in the mountainous and seacoast cohorts of the ROAD study are shown in Table I. mJSW was significantly lower in women than in men, whereas OPA was significantly higher in women compared with men. OPA was moderately associated with mJSW ($R^2 = 0.21$, $P < 0.05$) by linear regression analysis. When we analyzed the association of height with mJSW, the R^2 was 0.027 and 0.076 in men and women, respectively ($P < 0.05$). With regards to OPA, the R^2 was 0.01 and 0.006 in men and women, respectively ($P < 0.05$).

There was great diversity in job titles of study participants (Table II). Although a substantial proportion included clerical workers and technical experts, there were many agricultural, forestry, and fishery workers. Among various occupational activities, agricultural, forestry, and fishery workers had the highest rates of kneeling, squatting, standing, walking, climbing, and lifting weights, and the lowest rates for sitting on a chair, whereas clerical workers and technical experts had the lowest rates for the former activities and the highest rates for the latter activity (Fig. 2).

Table I
Characteristics of participants

	Overall	Men	Women
Number of subjects	1,402	512	890
Age, years	68.2 ± 9.2	68.9 ± 9.1	67.7 ± 9.2*
Height, cm	154.4 ± 9.3	162.4 ± 6.9	149.9 ± 7.2*
Weight, kg	55.3 ± 10.5	61.0 ± 10.3	52.0 ± 9.1*
BMI, kg/m^2	23.1 ± 3.4	23.1 ± 3.1	23.1 ± 3.5
mJSW, mm	2.5 ± 1.1	2.9 ± 1.0	2.3 ± 1.1*
OPA, mm^2	3.0 ± 7.9	1.4 ± 4.4	3.9 ± 9.3*

Values are mean ± SD except where indicated.
mJSW, minimum joint space width.
* $P < 0.05$ vs men by non-paired *t* test.

Table II
Number (percentage) of participants with job title and occupational activity reported as the principal job

	Overall	Men	Women
Job titles, *n* (%)			
Clerical workers/technical experts	350 (25.0)	164 (32.0)	186 (20.9)
Agricultural/forestry/fishery workers	299 (21.3)	158 (30.9)	141 (15.8)
Factory/construction workers	148 (10.6)	67 (13.1)	81 (9.1)
Shop assistants/managers	124 (8.8)	24 (4.7)	100 (11.2)
Housekeepers	118 (8.4)	0 (0.0)	118 (13.3)
Teachers	80 (5.7)	40 (7.8)	40 (4.5)
Dressmakers	46 (3.3)	1 (0.2)	45 (5.1)
Clinical workers	40 (2.9)	1 (0.2)	39 (4.4)
Hairdressers	17 (1.2)	6 (1.2)	11 (1.2)
Others (cook, taxi driver, etc.)	70 (5.0)	21 (4.1)	49 (5.5)
No answer	110 (7.8)	30 (5.9)	80 (9.0)
Occupational activities, n (%)			
Sitting on a chair ≥2 h/day	629 (44.9)	247 (48.2)	382 (42.9)
Kneeling ≥1 h/day	280 (20.0)	92 (18.0)	188 (21.1)
Squatting ≥1 h/day	368 (26.2)	127 (24.8)	241 (27.1)
Standing ≥2 h/day	1,179 (84.0)	439 (85.7)	740 (83.1)
Walking ≥3 km/day	638 (45.5)	255 (49.8)	383 (43.0)
Climbing ≥1 h/day	325 (23.2)	175 (34.2)	150 (16.9)*
Lifting weights ≥10 kg ≥1 time/week	750 (53.5)	336 (65.6)	414 (46.5)*

* $P < 0.05$ vs men by chi-square test.

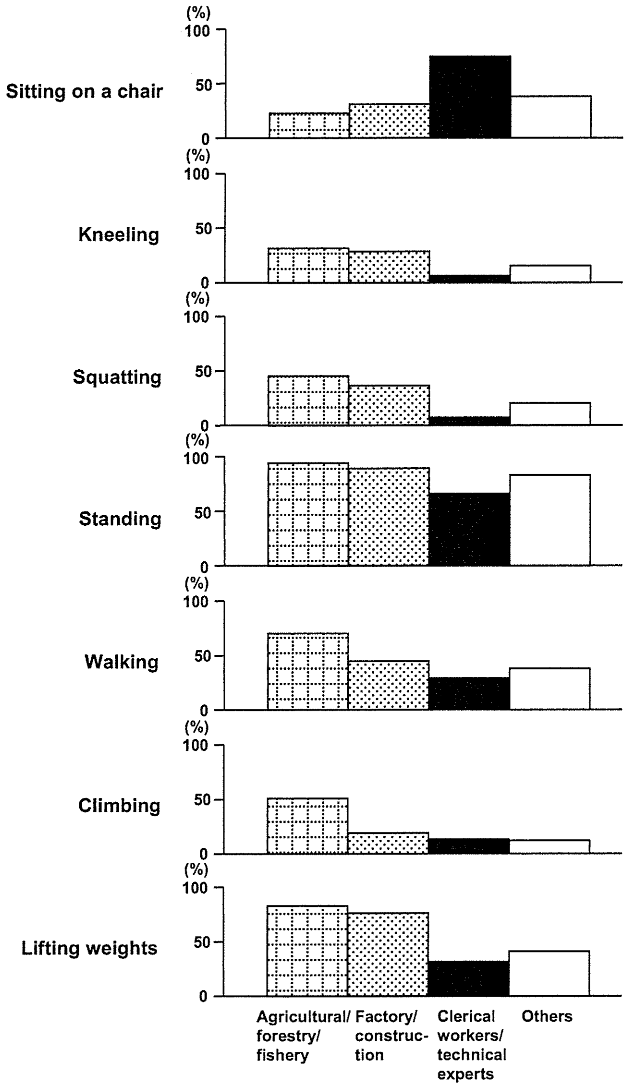

Fig. 2. Percentage of participants engaged in each occupational activity: sitting on a chair ≥2 h/day, kneeling ≥1 h/day, squatting ≥1 h/day, standing ≥2 h/day, walking ≥3 km/day, climbing ≥1 h/day, or lifting weights ≥10 kg ≥1 time/week among agricultural, forestry, and fishery workers; factory and construction workers; clerical workers and technical experts; and others.

Mean ± standard deviation (SD) values of mJSW (mm) in agricultural, forestry, or fishery workers; factory or construction workers; clerical workers or technical experts; and other workers were 2.4 ± 1.2, 2.5 ± 1.1, 2.8 ± 1.0, and 2.4 ± 1.1, respectively. Tukey HSD test after adjustment for age, gender, and BMI showed that there were no significant associations between job titles and mJSW. Further, because characteristics such as height, weight, mJSW and OPA differ significantly between men and women, we conducted separate analyses of the association of job title with mJSW and OPA in men and women. mJSW (mm) in agricultural, forestry, or fishery workers; factory or construction workers; clerical workers or technical experts; and other workers were 2.7 ± 1.1, 2.9 ± 0.9, 3.0 ± 0.9, and 2.9 ± 1.0 in men and 2.0 ± 1.1, 2.2 ± 1.1, 2.6 ± 0.9, and 2.3 ± 1.1 in women respectively. There were no associations in men, but for women, agricultural, forestry, or fishery workers had significantly lower mJSW than clerical workers or technical experts using Tukey HSD test without adjustment. To adjust for body size, we used Tukey HSD test after adjustment for height, and the results were similar ($P < 0.05$). Further, after adjustment for age and BMI, the results were also similar ($P < 0.05$). Mean ± SD values of OPA (mm^2) in agricultural, forestry, or fishery workers; factory or construction workers; clerical workers or technical experts; and other workers were 2.9 ± 6.5, 2.9 ± 6.8, 1.6 ± 4.0 and 3.9 ± 10.2, respectively. Tukey HSD test after adjustment for age and BMI showed no significant association between job titles and OPA in either men or women.

Tables III and IV show the mean values of mJSW and OPA according to occupational activity. SD for OPA was quite a large in the present study, because the range was 0–121.5 mm^2 and 1,055 (75.2%) had no osteophytes. Sitting was associated with higher mJSW and lower OPA by linear regression analysis without adjustment; after adjustment for age, gender, and BMI, the significance disappeared. Kneeling and squatting were significantly associated with lower mJSW as well as higher OPA. Walking and lifting weights were significantly associated with lower mJSW, but not with OPA. When we analyzed the association of occupational activities with mJSW and OPA in men and women separately, the results in women were similar to results in the overall population, but there were few factors associated with mJSW or OPA in men (Supplementary Tables I and II).

To determine independent associations of the significant occupational factors shown in Table III with mJSW, multiple regression analysis was performed with age, gender, BMI, and the significant occupational factors as independent variables. Because chi-square test showed that squatting was strongly associated with kneeling (odds ratio 139.5, $P < 0.0001$), we used kneeling when both squatting and kneeling were significantly associated KOACAD parameters. Squatting, kneeling, walking, and lifting weights were significantly associated with mJSW by the abovementioned analysis (Table III); thus, when we used age, gender, BMI, kneeling, walking, and lifting weights as independent variables, multiple regression analysis showed that kneeling was independently associated with mJSW (regression coefficient −0.17, 95% confidence interval [CI] −0.30 to −0.04, $P = 0.01$), and lifting weights tended to be independently associated with mJSW (regression coefficient −0.11, 95% CI −0.22 to 0.002, $P = 0.055$), but walking was not

Table III
mJSW according to occupational activity

	Occupational activity		Crude regression coefficient (95% CI)	P value	Adjusted regression coefficient* (95% CI)	P value
	No	Yes				
Sitting on a chair ≥2 h/day	2.4 ± 1.2	2.6 ± 1.0	0.22 (0.11–0.33)	0.0002	0.08 (−0.02 to 0.19)	0.117
Standing ≥2 h/day	2.6 ± 1.1	2.3 ± 1.2	−0.33 (−0.47 to −0.19)	<0.0001	−0.21 (−0.34 to −0.09)	0.0009
Kneeling ≥1 h/day	2.6 ± 1.0	2.3 ± 1.1	−0.36 (−0.49 to −0.23)	<0.0001	−0.24 (−0.35 to −0.12)	<0.0001
Squatting ≥1 h/day	2.7 ± 0.9	2.5 ± 1.1	−0.19 (−0.34 to −0.03)	0.016	−0.06 (−0.21 to 0.08)	0.364
Walking ≥3 km/day	2.6 ± 1.0	2.4 ± 1.2	−0.20 (−0.32 to −0.09)	0.0005	−0.11 (−0.21 to −0.002)	0.046
Climbing ≥1 h/day	2.5 ± 1.0	2.5 ± 1.2	−0.06 (−0.20 to 0.07)	0.038	−0.02 (−0.15 to 0.11)	0.733
Lifting weights ≥10 kg ≥ once/week	2.6 ± 1.0	2.5 ± 1.1	−0.10 (−0.21 to 0.01)	0.08	−0.16 (−0.26 to −0.06)	0.003

Values are mean ± SD.
* Adjusted regression coefficient was calculated using multiple regression analysis after adjustment for age, gender, and BMI.