

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.

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

	KOA-	Total KOA+	p	KOA-	Men KOA+	p	KOA-	Women 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 signifi-

cantly 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, $p = 0.044$).

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-

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

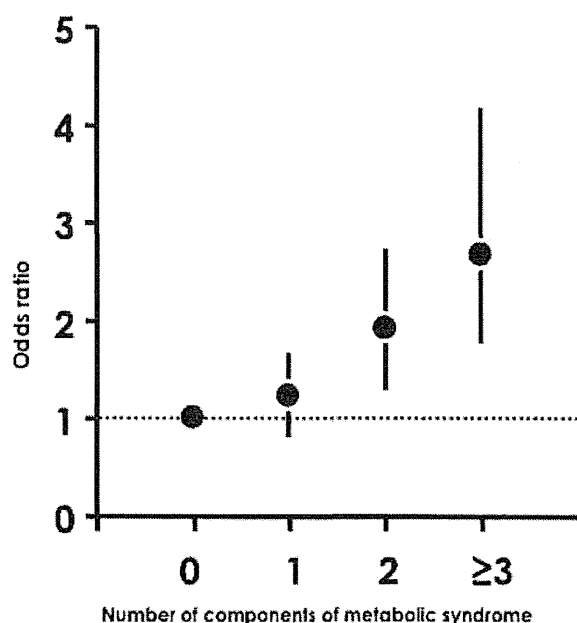


Figure 1. Odds ratios of the association between the number of components of metabolic syndrome and the presence of knee osteoarthritis, compared to no components present.

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 MJSW ($\beta = -0.148$, $R^2 = 0.21$, $p < 0.001$). An analysis performed using the same objective and explanatory factors and stratified by sex showed the same tendency in both men and women (men: $\beta = -0.152$, $R^2 = 0.14$, $p < 0.001$; women: $\beta = -0.149$, $R^2 = 0.18$, $p < 0.001$).

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 ($\beta = 0.12$, $R^2 = 0.11$, $p < 0.001$). An analysis performed using the same objective and explanatory factors and stratified by sex showed the same tendency in both men and women (men: $\beta = 0.15$, $R^2 = 0.08$, $p < 0.001$; women: $\beta = 0.11$, $R^2 = 0.11$, $p < 0.001$).

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 ($\beta = -0.096$, $R^2 = 0.18$, $p = 0.001$).

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 study³⁶, 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 OW²⁰. 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 it²¹. 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 factors¹⁹, 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 OA²². 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 KOA²¹. 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 tissue²⁰. Regarding the endogenous secreted products, Sowers, *et al* suggested that leptin and adiponectin levels influenced the development of OA²¹. 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 OA³⁷. 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 men⁴⁵. 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 tissue²⁰. Recent systematic review and metaanalysis of observational studies concluded that there is a sex-dependent association between levels of testosterone and occurrence of MS⁴⁶. 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 whites²⁸. 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 2002⁴⁷. 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 Japan²⁹, 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 Obesity³⁰. 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 $\geq 5.5\%$ to indicate IGT, which are indices used by the National Health and Nutrition Survey in Japan³². 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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Osteoarthritis and Cartilage



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

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SUMMARY

Objective: To clarify the association between the occurrence and progression of knee osteoarthritis (KOA) with components of metabolic syndrome (MS), including overweight (OW), hypertension (HT), dyslipidaemia (DL), and impaired glucose tolerance (IGT), in a general population.

Design: From the large-scale population-based cohort study entitled Research on Osteoarthritis/Osteoporosis Against Disability (ROAD) initiated in 2005, 1,690 participants (596 men, 1,094 women) residing in mountainous and coastal areas were enrolled. Of these, 1,384 individuals (81.9%; 466 men, 918 women) completed the second survey, including knee radiography, 3 years later. KOA was defined as Kellgren–Lawrence (KL) grade ≥ 2 using paired X-ray films. Based on changes in KL grades between the baseline and second surveys, cumulative incidence and progression of KOA were determined. OW, HT, DL, and IGT at baseline were assessed using standard criteria.

Results: The cumulative incidence of KOA among 1,384 completers over 3 years was 3.3%/year, and progression in KL grades for either knee, 8.0%/year. Logistic regression analyses after adjusting for potential risk factors revealed that the odds ratio (OR) for the occurrence of KOA significantly increased according to the number of MS components present (OR vs no component: one component, 2.33; two components, 2.82; \geq three components, 9.83). Similarly, progression of KOA significantly increased according to the number of MS components present (OR vs no component: one component, 1.38; two components, 2.29; \geq three components: 2.80).

Conclusion: Accumulation of MS components is significantly related to both occurrence and progression of KOA. MS prevention may be useful in reducing future KOA risk.

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Introduction

Osteoarthritis (OA), which causes cartilage and disc degeneration and osteophyte formation at joints in the limbs and spine, is a major public health problem in the elderly and affects activities of daily living and quality of life, leading to increased morbidity and mortality^{1–3}. According to the recent National Livelihood Survey by

the Ministry of Health, Labour and Welfare in Japan, OA is ranked fourth among diseases that cause disabilities requiring support and long-term care⁴. The National Livelihood Survey also shows that cardiovascular disease (CVD) is ranked first in causing disabilities in the elderly⁴. Most CVD patients have multiple risk factors⁵. The presence of these risk factors in a specific combination, entitled metabolic syndrome (MS), is a multiplex risk factor that predisposes affected individuals to CVD morbidity and mortality. MS is generally considered a combination of being overweight (OW) and having hypertension (HT), dyslipidaemia (DL), and impaired glucose tolerance (IGT)⁶.

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

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various MS components. Lawrence first reported that diastolic blood pressure (BP) was associated with KOA in women¹³. Kellgren reported that hand OA was significantly associated with above-average serum cholesterol levels in women¹⁴. Cimmino *et al.* observed significantly higher plasma glucose levels in women with OA than in those without¹⁵. Contradictory findings regarding the association of such metabolic factors with OA have been reported^{16–19}. Hart *et al.* found that metabolic factors such as blood glucose, hypercholesterolaemia, and even treated HT were associated with KOA development²⁰. A few population-based studies have demonstrated a dose–response relationship between risk factor accumulation for MS and KOA; we have previously reported that KOA presence was significantly associated with increase in the number of MS components²¹. However, to our knowledge, no study has clarified the associations between KOA occurrence or progression and MS component accumulation, using a prospective cohort of general inhabitants.

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

Method

Participants

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

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

Baseline examination procedures

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

Anthropometric measurements included height, weight, and body mass index [BMI: weight (kg)/height² (m²)]. Systolic and diastolic BP was measured by an experienced public health nurse using

a mercury sphygmomanometer. Medical information, including information on knee joints, was collected by experienced orthopaedic surgeons (SM and HO). All participants underwent radiographic examination of both knees using an anterior–posterior view with weight-bearing and foot-map positioning.

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

In this study, definitions of MS components were based on criteria defined by the Examination Committee of Criteria for Metabolic Syndrome in Japan²⁴ and the Japan Society for the Study of Obesity²⁵. However, because not all blood samples were obtained under fasting conditions, we used indices from the National Health and Nutrition Survey in Japan adopted as MS criteria in this national screening study due to the difficulty of collecting samples under fasting conditions²⁶. The following definitions were used for MS components: OW, BMI ≥ 25 kg/m²; HT, systolic BP ≥ 130 mm Hg and/or diastolic BP ≥ 85 mm Hg; DL, serum HDL-cho level < 40 mg/dL; and IGT, serum HbA1c level $\geq 5.5\%$. Furthermore, subjects being treated with medication for HT, DL, or diabetes mellitus were regarded as having HT, DL, or IGT, respectively.

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

In 2008–2010, the 1,690 subjects were invited to attend the second survey of the ROAD study, a 3-year follow-up consisting of examinations identical to those at baseline. Knee radiographs were read by a single experienced orthopaedist (SM) without knowledge of participants' clinical status and were categorized using the Kellgren–Lawrence (KL) grading scale²⁷. When there were differences in the KL grades between the two knees, the higher KL grade was assigned to the participant. A subject with KL ≥ 2 was defined as having radiographic KOA. A new KOA case was identified if both knees had a KL grade < 2 at baseline and if at least one knee developed a KL of ≥ 2 during follow-up. KOA progression was defined as the KL grade for either knee being higher during follow-up than at baseline.

Statistical analysis

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

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

consumption, bicycling, regular exercise, and history of knee injuries, all of which had been found to be significantly associated with KOA presence in a previous study using the same population¹⁷. Model 3 was obtained by multivariate logistic regression analysis using the same objective variable and the same adjustment factors as in Model 2; furthermore, other MS components were included in the mutual adjustment model. For example, when BMI was selected as an objective factor, Model 3 was obtained by multivariate logistic regression after adjustment for age, gender, regional differences, smoking, alcohol consumption, bicycling, regular exercise, history of knee injuries, systolic BP, and serum HDL-cho and HbA1c levels. Similarly, when OW was selected as an objective factor, Model 3 was obtained by multivariate logistic regression after adjustment for age, gender, regional differences, smoking, alcohol consumption, bicycling, regular exercise, history of knee injuries, HT, DL, and IGT. Because systolic and diastolic BP was moderately correlated ($r = 0.5643$, $P < 0.001$), only values of systolic BP were used as representative of BP in Model 3.

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

Results

Eligible participants

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

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

Table I

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

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

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

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

KOA occurrence and progression and MS components

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

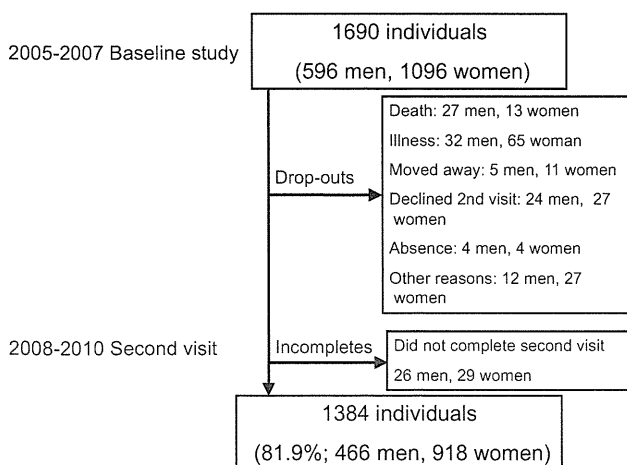


Fig. 1. Flow of participants in the baseline and second surveys.

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

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

Table III shows multivariate logistic regression analysis results for KOA occurrence vs values for each MS component, including BMI, systolic BP, diastolic BP, and serum HDL-cho and HbA1c levels measured at baseline (Table III). Model 2 showed that BMI, systolic

BP, and serum HDL-cho levels were significantly associated with KOA occurrence after adjustment for various risk factors. However, Model 3, incorporating mutual adjustment for each MS component, indicated that only BMI was significantly associated with KOA occurrence. The three types of multivariate logistic regression analyses using KOA progression as the objective factor showed similar results as for KOA occurrence described above.

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

KOA occurrence and progression and the number of MS components

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

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

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

KOA(–), non-occurrence of KOA; KOA(+), occurrence of KOA; progression(–), no progression of the KL grade; progression(+), progression of the KL grade. n, number of subjects.

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

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

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

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

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

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

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

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

Figure 2 also shows KL grade progression (%/year) for either knee classified by the number of MS components present. In the total population, KL grade progression classified by 0, 1, 2, or ≥ 3 MS components was 4.3, 7.6, 10.8, and 11.3, respectively, which

significantly increased with the number of MS components (*P* for trend < 0.001). The progression among individuals with one or more MS components was higher in women than in men [Fig. 2(B)].

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

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

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

P* < 0.05, *P* < 0.01, ****P* < 0.001.Being OW was defined as BMI ≥ 25 kg/m², HT as systolic BP ≥ 130 mm Hg and/or diastolic BP ≥ 85 mm Hg, DL as serum HDL-cho level < 40 mg/dL, and IGT as serum HbA1c level $\geq 5.5\%$. Further, subjects being treated with medication for HT, DL, or IGT were regarded as having the respective disorder.

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

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

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

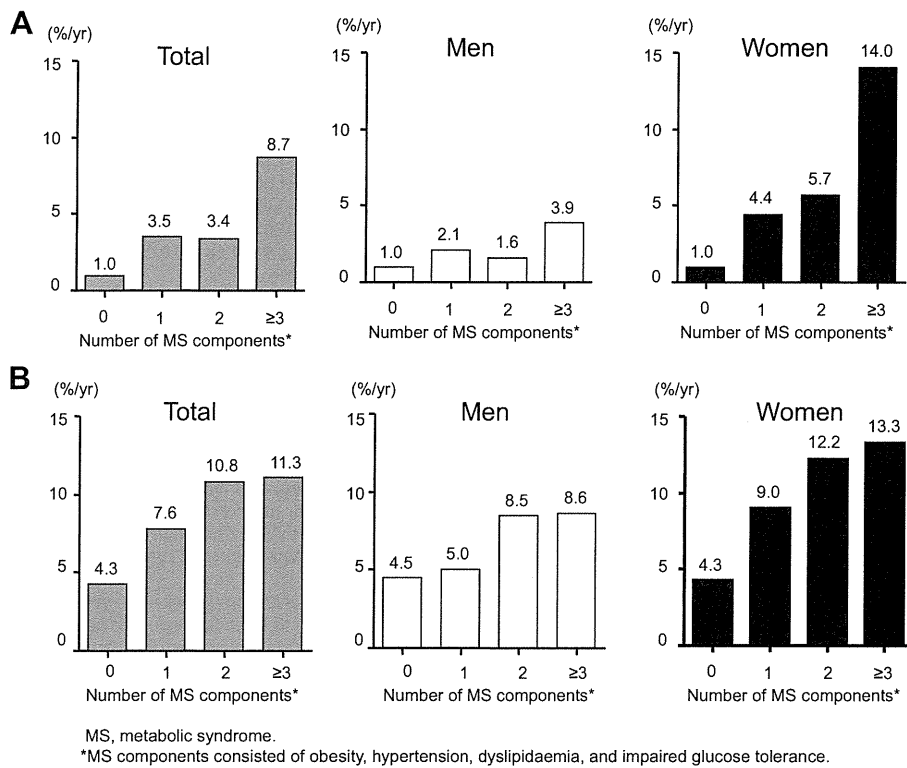
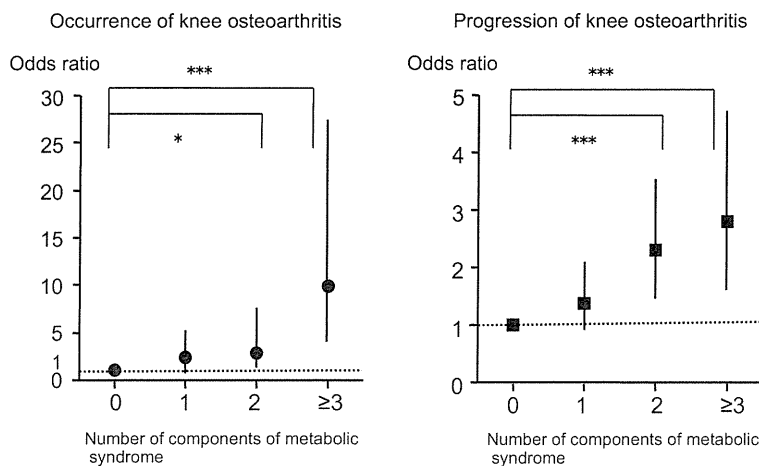


Fig. 2. Cumulative incidence (%/year) of KOA (A) and progression of the KL grade of either knee (%/year) (B) classified by the number of components of MS, including OW, HT, DL, and IGT.

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

1.47–3.46, $P < 0.001$; ≥three components: 2.59, 1.57–4.27, $P < 0.001$).

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



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

Multivariate logistic regression analysis using the occurrence or progression of KOA (over 3 years, 1: yes, 0: no) as the objective variable and the number of MS components as the explanatory variable, after adjusting for age, gender, region (0: coastal area, 1: mountainous area), smoking (0: ex- or non-smoker, 1: current smoker), alcohol consumption (0: ex- or non-drinker, 1: current drinker), bicycling every day (0: no, 1: yes), regular exercise (0: no, 1: yes), and past history of knee injuries (0: no, 1: yes).

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

other risk factors (OR, 95% CI vs no component: one component, 2.33, 0.96–5.65, $P = 0.065$; two components, 2.82, 1.05–7.54, $P = 0.039$; \geq three components, 9.83, 3.57–27.1, $P < 0.001$). Similarly, KOA progression significantly increased with the number of MS components present after adjustment for other risk factors (OR, 95% CI vs no component: one component, 1.38, 0.91–2.08, $P = 0.126$; two components, 2.29, 1.49–3.54, $P < 0.001$; \geq three components: 2.80, 1.68–4.68, $P < 0.001$). In both models, the OR for KOA occurrence significantly increased with the number of MS components present. Similar trends were observed for KOA progression with both models.

Discussion

In this study, we determined the cumulative incidence and progression rate of KOA diagnosed using the KL scale. We demonstrated that KOA occurrence and progression are associated with higher systolic BP, lower serum HDL-cho levels, and higher serum HbA1c levels, as well as higher BMI. Incorporating mutual adjustment for each MS component indicated that only BMI was significantly associated with KOA occurrence and progression. Regarding the risk factors for MS and KOA, even after adjusting for potential risk factors, multivariate analysis determined that HT and IGT were significantly associated with KOA occurrence, and OW and HT were significantly associated with KOA progression. The presence of a greater number of MS components was associated with a higher rate of KOA occurrence and progression. This tendency was much more pronounced in occurrence of KOA than in progression.

Numerous reports have presented an association between being OW or obese and KOA^{1,7–12}. Lohmander *et al.* reported that being OW was associated with higher KOA incidence, and among measures of excess weight, BMI was observed to have the strongest relative risk gradient²⁸. In the present study, we confirmed that BMI was the only continuous value significantly associated with KOA occurrence and progression among the MS risk factors (e.g., BMI, systolic BP, and serum levels of HDL-cho and HbA1c), consistent with previous studies. In contrast, several reports have shown that HT is associated with KOA presence, independent of OW^{20,29–31}. In the present study, we confirmed a significant association between HT and IGT and KOA occurrence, and between OW and HT and KOA progression. Although several studies have found that obesity or increased BMI were risk factors for KOA onset^{32–35}, this appears to be the first report of associations between MS risk factors other than OW and KOA occurrence and progression.

There were differences between the results for continuous variables such as BMI, BP, and serum HDL-cho and HbA1c levels and those for categorical clinical criteria such as OW, HT, DL, and IGT. In analysis involving continuous variables, BMI was the only predictor of future KOA occurrence or progression. In contrast, clinical criteria-based analysis clearly showed associations between metabolic risk factors other than OW and KOA. This discrepancy suggests that the clinical criterion for OW (BMI ≥ 25 kg/m²) may be less sensitive than continuous BMI values in reflecting the association of excess weight with KOA. We then performed additional analyses using KOA occurrence or progression as the objective variable and categorical risk factors for MS, such as HT, DL, and IGT, as explanatory variables. We also added continuous values for BMI at baseline rather than OW, after adjusting for multiple risk factors as listed for Model 2. The resulting overall ORs for HT, DL, and IGT adjusted for BMI on KOA occurrence or progression became smaller than those adjusted for OW. However, the association between HT and KOA occurrence remained significant (OR, 2.43; 95% CI, 1.14–5.18; $P = 0.021$), while IGT was no longer significant (OR, 1.70; 95% CI, 0.91–3.19; $P = 0.096$). Similarly, the association between HT and KOA progression remained significant (OR, 1.41; 95% CI,

1.00–2.00; $P = 0.049$). These results indicate that, even if associations between KOA and categorical MS components other than BMI are weak, if adjustments are made for OW using clinical criteria, then HT and IGT may be risk factors for KOA occurrence and HT may be a risk factor for KOA progression.

Regarding ethnic differences in KOA, we previously reported that KOA prevalence and incidence in the original ROAD study of 3,040 baseline participants was higher than those of Caucasians^{36,37}. In contrast, with regard to ethnic differences in MS, Hoang *et al.* reviewed epidemiological studies and reported that MS prevalence in East Asians was lower than that in Caucasians³⁸. MS prevalence in Asia may be increasing rapidly, as Nestel *et al.* reported a substantial increase in a cohort from Beijing from 9% in 1992 to 21% in 2002³⁹. These ethnic differences have been suggested as resulting from genetic factors that modulate the association between KOA and obesity^{40,41}.

Regarding associations between risk factors of MS and KOA, Hart *et al.* attributed the effect of excess endogenous oestrogens to aromatization of oestrone in fat tissue²⁰. Sowers *et al.* suggested that leptin and adiponectin levels influenced OA development²⁹. Another hypothesis suggests that in obese subjects, metabolic changes in the striated muscles induced by interactions between insulin resistance and systemic inflammation may lead to fatigue and muscle weakness, influencing the balance between damage and repair mechanisms and ultimately leading to OA^{42,43}. Inflammatory factors are suggested to be associated with both obesity and KOA^{44,45}. Findlay evaluated the concept that vascular pathology might play a role in the initiation and/or progression of OA⁴⁶ and proposed that peripheral reduced blood flow associated with HT caused subchondral ischaemia. This ischaemia may in turn compromise nutrient and gas exchange into the articular cartilage and contribute to apoptosis of regional osteocytes of the subchondral bone. Furthermore, chondrocytes of OA exposed to high glucose concentrations exhibit impaired glucose transporter-1 downregulation⁴⁷. Thus, impaired glucose transporter-1 downregulation may constitute an important pathogenic mechanism by which conditions characterized by hyperglycaemia may promote degenerative changes in chondrocytes, facilitating OA progression. However, in the present study, after adjustment for BMI, the effect of IGT was weak. Further studies are required to confirm whether IGT is a risk factor for KOA occurrence. Furthermore, because the present study aimed to identify associations between metabolic risk factors and future KOA occurrence or progression, we did not evaluate the effects of genetic factors and other risk factors potentially influencing MS and KOA. However, additional risk factors for both conditions should be addressed in further analysis of the ROAD study.

No previous studies have been performed on metabolic risk factor clustering and KOA occurrence or progression, although some cross-sectional epidemiological studies have evaluated the association between metabolic risk factor clustering and KOA presence^{29,31}. In the present study, we demonstrated that KOA occurrence and progression are influenced not only by individual MS components but also by their clustering. An increase in the number of MS components significantly increases the risk of both KOA occurrence and progression. This effect of clustering was stronger for KOA occurrence than for KOA progression. Combining the present results with those of our previous report using the same analytical methods and adjustment factors²¹, the ORs for \geq three components vs no components were 9.95, 2.79, and 2.72 for KOA occurrence, progression, and presence, respectively. Thus, preventing MS would aid in reducing every stage of KOA, including onset, worsening, and presence.

This study has several limitations. First, although it includes a relatively large number of participants, these participants do not

represent the entire general population because they were recruited from only two areas. Regarding potential selection bias of the ROAD study, we previously reported that no significant differences were identified between our participants and the general Japanese population, except that male participants aged 70–74 years in the ROAD study were significantly smaller in terms of body structure than the overall Japanese population ($P < 0.05$)²³. Although we could locate and include baseline participants after 3 years with a high participation rate, this selection bias at baseline should be considered when generalising the results. Second, the definitions used for MS components were not completely identical to international criteria such as the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III, World Health Organization (WHO), or The American Association of Clinical Endocrinologists (AAACE)⁴⁸. As there has been considerable debate regarding abdominal circumference (≥ 85 cm in men, ≥ 90 cm in women) in the Japanese criteria⁴⁹, we decided to utilize BMI ≥ 25 kg/m² to indicate OW rather than abdominal circumference. Furthermore, because not all blood samples were obtained under fasting conditions, we did not use blood glucose and serum TG levels as indicators. Therefore, our results may underestimate the presence of MS components, especially DL and IGT. However, we used the alternative index for each condition, recommended by the National Health and Nutrition Survey for cases where collecting samples under fasting conditions is difficult²⁶, and thus our criteria likely reflect dysfunction in lipid and glucose metabolism. Finally, we used KL grade ≥ 2 for diagnosing KOA. However, the KL scale is a categorical index, and it is impossible to evaluate the minimum joint space and osteophytosis separately. To evaluate KOA severity using quantitative parameters, a KOA computer-assisted diagnostic system⁵⁰ measuring minimum joint space width and osteophytosis area is under development; this system will provide increased accuracy in determining the association between MS components and KOA development for early prevention of disability.

In conclusion, this study revealed that HT and IGT influence KOA occurrence and that OW and HT are associated with KOA progression. KOA occurred or worsened more frequently with increase in the number of MS components. Preventing MS may be useful in preventing both KOA occurrence and progression.

Author contributions

NY conceptualized the study, was primarily responsible for developing the protocol, and acts as the guarantor for this study. SM, HO, and TA conducted data collection and X-ray assessment. All authors reviewed the protocol and contributed to interpretation of the results. All authors were involved in drafting the article and approved the final version submitted for publication. All authors had full access to all of the data in the study and take responsibility for the integrity and accuracy of the data analyses.

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Conflict of interest

All authors declare that (1) no authors have received corporate support for the submitted work; (2) the authors have no relationships with companies that might have an interest in the submitted work in the previous 3 years; (3) the authors' spouses, partners, or children do not have financial relationships that may be relevant to the submitted work; and (4) the authors have no non-financial interests that may be relevant to the submitted work.

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Does mild cognitive impairment affect the occurrence of radiographic knee osteoarthritis? A 3-year follow-up in the ROAD study

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ABSTRACT

Objective: To determine whether mild cognitive impairment (MCI) increases the risk of occurrence or progression of radiographic knee osteoarthritis (KOA) in a general population.

Design: Population-based cohort study.

Setting: Residents in mountain and seaside areas of Wakayama Prefecture, Japan.

Participants: 1690 participants (596 men, 1094 women; mean age 65.2 years old) were enrolled from the large-scale cohort for the Research on Osteoarthritis (OA)/osteoporosis Against Disability (ROAD) study initiated in 2005 to investigate epidemiological features of OA in Japan. Of these, 1384 individuals (81.9%; 466 men, 918 women) completed the second survey including knee radiography 3 years later.

Primary outcome measures: Radiographic KOA was defined as Kellgren-Lawrence (KL) grade ≥ 2 using paired x-ray films. Incidence of KOA during follow-up defined on radiographs as KL grade ≥ 2 , progression of KOA defined as a higher KL grade (either knee) at follow-up compared with baseline. MCI defined as a summary mini-mental state examination (MMSE) score ≤ 23 . Associations between MCI and incidence or progression of KOA were analysed.

Results: The annual cumulative incidence of KOA was 3.3%; for progression of OA it was 8.0%. On logistic regression analysis adjusted for age, gender, regional differences, body mass index, grip strength (worse side), smoking, alcohol consumption, regular exercise and history of knee injury, baseline MMSE summary score was significantly associated with the incidence of KOA (+1 MMSE score; OR 0.83, $p=0.010$). Baseline MCI was also significantly associated with the incidence of KOA (vs non-occurrence of KOA; OR 4.90, $p=0.027$). There was no significant association between MMSE scores, the presence of MCI and progression of KOA (+1 MMSE score; OR 0.96, $p=0.232$; vs non-progression of KOA; OR 1.38, $p=0.416$).

Conclusions: MCI significantly increases the risk of incident radiographic KOA, but not the progression of KOA.

ARTICLE SUMMARY

Article focus

- Both cognitive impairment and osteoarthritis (OA) are top-ranked causes of disability requiring support, but there have been no previous reports on the association between cognitive impairment and OA.
- We aimed to investigate the association between mild cognitive impairment (MCI) and the occurrence and progression of radiographic knee osteoarthritis (KOA) among men and women who participated in the Research on Osteoarthritis/osteoporosis against Disability (ROAD) study.

Key messages

- Of 1690 participants at the baseline, 1384 individuals (81.9%; 466 men, 918 women) completed the second survey including knee radiography 3 years later.
- The annual cumulative incidence of radiographic KOA in these 1384 participants was 3.3%; for progression of KOA, it was 8.0%.
- The prevalence of MCI in the 1384 participants defined as summary mini-mental state examination score ≤ 23 was 4.5%.
- Baseline mini-mental state examination (MMSE) summary score was significantly associated with the incidence of radiographic KOA after adjustment for confounders (+1 score; OR 0.83, $p=0.010$). Baseline MCI was also significantly associated with the incidence of radiographic KOA (vs non-occurrence of KOA; OR 4.90, $p=0.027$). There was no significant association between MMSE scores, the presence of MCI and the progression of radiographic KOA (+1 score; OR 0.96, $p=0.232$; vs non-progression of KOA; OR 1.38, $p=0.416$).

INTRODUCTION

Plural chronic diseases have a high prevalence in the elderly population. In the USA, about 77% of older adults have two or more chronic illnesses, and these can lead to

ARTICLE SUMMARY

Strengths and limitations of this study

- The present study includes a population-based design of a cohort, large number of participants with KOA, and a 3-year follow-up with a high participation rate of 81.9%.
- Substantial amount of detailed information, including an interviewer-administered questionnaire, dietary assessment, anthropometric measurements, neuromuscular function assessment, biochemical measurements, medical history, radiographic assessment and bone mineral density measurement, was collected at both the baseline and the second visit.
- We used KL grade ≥ 2 for the diagnosis of radiographic KOA, but the KL scale is a categorical index, and it might be impossible to evaluate the minimum joint space and osteophytosis separately.
- We used only the MMSE to diagnose MCI, and were unable to perform additional examinations such as MRI to improve the accuracy of the diagnosis.
- The small proportion of the population with MCI at risk of KOA onset detection might raise a bias in the results of the study.

severe and immediate disabilities.¹ According to the recent national livelihood survey by the Japanese Ministry of Health, Labour and Welfare, the leading causes of disability requiring support and long-term care were cardiovascular disease (CVD) followed by dementia, cognitive impairment, senility and osteoarthritis (OA).²

It is important to establish associations among these diseases causing disability, in order to reduce the risk of disability. In terms of CVD and dementia, the existence of vascular dementia, for example, indicates that there are links between CVD and dementia, and cardiovascular and metabolic risk factors such as hypertension and diabetes may play a role in the pathogenesis of Alzheimer's disease as well as in the development of vascular dementia.³⁻⁶ Association between metabolic syndrome and risk of developing cognitive impairment has been demonstrated in older women, with a 23% age-adjusted increase in the risk of developing cognitive impairment in the number of components of metabolic syndrome.⁷ Higher total cholesterol and low-density lipoprotein, and history of diabetes have been associated with faster cognitive decline in patients with incident Alzheimer's disease.⁸

However, as per our knowledge, there have been no previous reports on the association between OA and dementia. Mild cognitive impairment (MCI), a transitional state associated with memory impairment, has been associated with an increased risk of progression of Alzheimer's disease.^{9, 10} We aimed to investigate the association between MCI and the occurrence and progression of radiographic knee osteoarthritis (KOA) among men and women who participated in the Research on Osteoarthritis/Osteoporosis Against Disability (ROAD) study.

PARTICIPANTS AND METHODS

Participants

Our analysis was based on data collected from cohorts established in 2005 for the ROAD study. Details of the cohort have been reported elsewhere.^{11, 12} In brief, we created a baseline database in 2005–2007, which included clinical and genetic information for 3040 residents of Japan (1061 men, 1979 women). Participants were recruited from resident registration listings in three communities, each with different characteristics, namely an urban region in Itabashi, Tokyo; a mountainous region in Hidakagawa, Wakayama; and a coastal region in Taiji, Wakayama.

For the present study, we enrolled 1690 participants (596 men, 1094 women) residing in the mountainous and coastal areas, where the mental test was performed at baseline. Participants provided written informed consent, and the study was conducted with the approval of the ethics committees of the University of Tokyo (approval number 1264).

Baseline procedures

Participants completed an interviewer-administered questionnaire comprising 400 items. These included lifestyle-related questions to obtain information about main occupation; smoking habits (0: exsmoker or never smoked, 1: current smoker); alcohol consumption (0: exdrinker or never drank, 1: current drinker); alcohol consumption; physical activity including cycling every day in the past 12 months (0: no, 1: yes); regular exercise, that is, football, tennis, baseball, golf or other sports after graduation from school (0: no, 1: yes); and medical history including history of knee injury (0: no, 1: yes).

Anthropometric measurements included height, weight, body mass index (BMI) calculated as weight (kg)/height (m²) and grip strength of both hands. Experienced orthopaedic surgeons (SM and HO) collected medical information about pain, swelling and the range of motion in the knee.

All participants underwent a radiographic examination of both knees using an anteroposterior view with weight-bearing and foot map positioning. Fluoroscopic guidance with a horizontal anteroposterior x-ray beam was used to properly visualise the joint space.

Cognitive functioning was measured using the mini-mental state examination (MMSE).¹³ This is a 30-item cognitive screening test that measures orientation, registration, short-term memory, attention and concentration, language and constructional capacity. The test-retest reliability of the original version of the MMSE is 0.83,¹³ and the criterion validity is 0.66–0.79 with the Wechsler Adult Intelligence Scale, 0.83 with the Short Portable Mental Status Questionnaire and 0.88 with the Cognitive Capacity Screening Examination.^{14, 15} We used the validated Japanese version of the MMSE.¹⁶ Summary scores from the MMSE were used to measure cognitive

functioning and the criterion for MCI was a summary score ≤ 23 .

Three-year follow-up and definition of the occurrence and progression of radiographic Knee osteoarthritis

In 2008–2010, the 1690 participants were invited to attend the 3-year follow-up of the second ROAD survey, which involved a repeat of the baseline examinations. Knee radiographs obtained at baseline and follow-up were read in pairs without knowledge of the participant's clinical status by a single well-experienced orthopaedist (SM), and the Kellgren/Lawrence (K/L) grade was defined using the K/L radiographic atlas for overall knee radiographic grades.¹⁷ To evaluate the intraobserver variability of the K/L grading, 100 randomly selected radiographs of the knee were scored by the same observer 1 month after the first reading. One hundred other radiographs were also scored by two experienced orthopaedic surgeons (SM and HO) using the same atlas for interobserver variability. The intravariabilities and intervariabilities evaluated for K/L grade (0–4) were confirmed by kappa analysis to be sufficient for assessment ($\kappa=0.86$ and 0.80 , respectively). When a different grade was assigned to each knee, the participant was classified by the higher grade. A participant with a KL grade ≥ 2 was defined as having radiographic KOA. A new case of radiographic KOA was identified if the KL grade at baseline had been < 2 for both knees, and if one or both knees were assigned grade ≥ 2 at follow-up. A higher KL grade for either knee at follow-up compared with the baseline was defined as progression of OA.

Statistical analysis

Statistical analyses were performed using STATA statistical software (STATA Corp, College Station, Texas, USA). Differences in proportions were compared using the χ^2 test. Differences in continuous variables were tested for significance using analysis of variance (ANOVA) for multiple groups or Scheffé's least significant difference test for pairs of groups. To test the association between occurrence or progression of radiographic KOA and the presence of MCI after adjustment for confounding factors, we performed two types of multivariate logistic regression analysis. For both, we entered the occurrence or progression of OA over 3 years (1: yes, 0: no) as the dependent variable, and the MMSE summary score or presence of MCI (1: presence, 0: absence) as the independent variable. In model 1, the analysis was performed after adjusting for age, gender, regional differences and BMI. In model 2, we adjusted for potential risk factors that had previously been identified in this cohort as significantly associated with the presence of KOA,^{9–18} namely age, gender, regional differences, BMI, grip strength (kg) on the worse side, smoking, alcohol consumption, regular exercise and history of knee injuries. All p values and 95% CI of two-sided analysis are presented.

RESULTS

Eligible participants

Of the all 1690 participants in the baseline survey performed in the mountainous and coastal regions, 251 individuals (14.9%; 104 men, 147 women) did not attend the 3-year follow-up. Among them, 40 (27 men, 13 women) had died, 97 (32 men, 65 women) did not attend follow-up due to bad health, 16 (5 men, 11 women) had moved away, 51 (24 men, 27 women) declined the invitation to attend the second survey, 8 (4 men, 4 women) were absent and 39 (12 men, 27 women) did not participate for other reasons. In addition, 55 participants in the second survey (3.3%; 26 men, 29 women) did not complete all the follow-up examinations, including the interviewer-administered questionnaire, anthropometric measurements, radiographic examination and blood tests. Thus, our analysis was based on the remaining 1384 subjects (81.9%; 466 men, 918 women) who completed all examinations at both the baseline and follow-up (figure 1).

Prevalence of MCI and its baseline characteristics

The prevalence of MCI and baseline characteristics of the 1384 participants are shown in table 1. Based on the MMSE summary score, 75 participants (30 men, 45 women) were diagnosed with MCI (prevalence, 4.5%; men, 5.1%, women, 4.2%). The prevalence of MCI was significantly higher in the older age groups (trend, $p<0.001$). The mean MMSE summary score was significantly lower in participants with MCI than in those without (21.2 vs 28.5). Participants with MCI tended to reside in mountainous areas, and they had significantly lower weight, height and grip strength; drank less alcohol and exercised less compared with those without MCI (table 1). In addition, the prevalence of radiographic KOA classified by presence of MCI was compared in table 1. In total, 75.7% of patients in the MCI group were observed to have KOA, which was

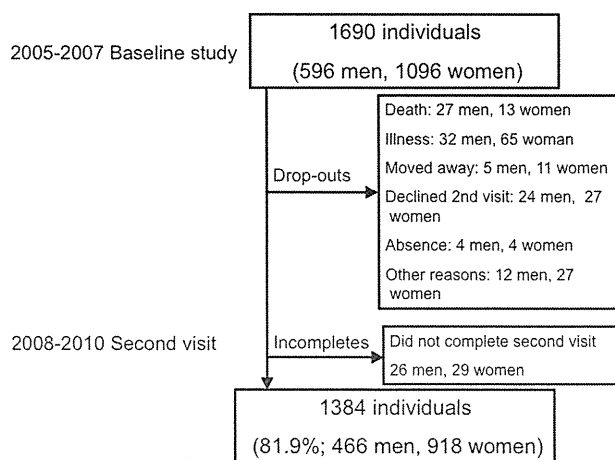


Figure 1 Flow diagram for participation in the baseline and follow-up Research on Osteoarthritis/osteoporosis Against Disability surveys.