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, $P = 0.039$; ≥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, $P < 0.001$; ≥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 gradient[28]. 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/m^2) 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 Caucasians[38]. 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 2002[39]. 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 tissue[20]. Sowers *et al.* suggested that leptin and adiponectin levels influenced OA development[29]. 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 OA[46] 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 downregulation[47]. 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 factors[21], the ORs for ≥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 (AACE)[48]. As there has been considerable debate regarding abdominal circumference (≥85 cm in men, ≥90 cm in women) in the Japanese criteria[49], we decided to utilize BMI ≥ 25 kg/m^2 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 difficult[26], 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 system[50] 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; OR0.83, 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 (m^2) 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 (κ=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.

Table 1 Comparison of baseline characteristics of subjects without and with mild cognitive impairment (MCI)

	Total (n=1676)			Men (n=591)			Women (n=1085)		
	Without MCI (N=1601)	With MCI (N=75)	p Value (Without vs with MCI)	Without MCI (N=561)	With MCI (N=30)	p Value (Without vs with MCI)	Without MCI (N=1040)	With MCI (N=45)	p Value (Without vs with MCI)
Number of subjects (prevalence, %) classified by age-strata									
≤39 (year)	45	0 (0.0)		14	0 (0.0)		31	0 (0.0)	
40–49	148	1 (0.7)		43	1 (2.3)		105	0 (0.0)	
50–59	314	2 (0.6)	<0.001***	106	1 (0.9)	<0.001***	208	1 (0.5)	<0.001***
60–69	467	10 (2.1)		151	5 (3.2)		316	5 (1.6)	
70–79	496	35 (6.6)		202	14 (6.5)		294	21 (6.7)	
≥80	131	27 (17.1)		45	9 (16.7)		86	18 (17.3)	
Total	1601	75 (4.5)		561	30 (5.1)		1040	45 (4.2)	
Mean values (SDs) of MMSE summary score	28.5 (1.7)	21.2 (3.2)	<0.0001***	28.4 (1.8)	20.7 (4.4)	<0.0001***	28.6 (1.7)	21.5 (2.1)	<0.0001***
Mean values (SDs) of selected characteristics									
Age (year)	64.7 (11.9)	75.8 (8.1)	<0.0001***	65.8 (11.7)	74.0 (9.3)	0.0002***	64.1 (12.0)	77.0 (6.9)	<0.0001***
Height (cm)	155.5 (9.1)	148.7 (9.8)	<0.0001***	163.8 (7.1)	157.4 (5.8)	<0.0001***	151.1 (6.7)	142.9 (7.4)	<0.0001***
Weight (kg)	55.8 (10.7)	51.7 (11.7)	0.0011**	62.5 (10.8)	57.7 (12.1)	0.0181*	52.2 (8.8)	47.7 (9.6)	0.0007***
BMI (kg/m^2)	23.0 (3.4)	23.2 (3.7)	0.5845	23.2 (3.2)	23.2 (3.9)	0.9346	22.9 (3.5)	23.2	0.4877
Grip strength (better side) (kg)	27.8 (9.5)	20.8 (8.5)	<0.0001***	36.4 (8.8)	27.6 (8.2)	<0.0001***	23.3 (6.0)	16.5 (5.3)	<0.0001***
Grip strength (worse side) (kg)	24.6 (9.3)	16.8 (9.3)	<0.0001***	32.8 (9.1)	22.4 (10.6)	<0.0001***	20.1 (5.6)	13.1 (6.2)	<0.0001***
Percentage of selected characteristics (%)									
Residing in a coastal area	50.1	28.0	<0.001***	47.8	26.7	0.024*	51.4	28.9	0.003**
Current smoking habit (more than once a month)	13.3	10.0	0.428	30.4	21.4	0.312	3.9	2.4	0.624
Current alcohol consumption (more than once a month)	40.5	24.0	0.004**	67.6	46.7	0.018*	26.0	8.9	0.010*
Regular exercise after graduation from school	14.9	4.0	0.008**	34.4	6.7	0.002**	4.4	2.2	0.478
Prevalence of KOA at the baseline (%)	48.8	75.7	<0.001***	41.0	50.0	0.328	53.0	93.2	<0.001***

*p<0.05, **p<0.01, ***p<0.001
BMI, body mass index; KOA, knee osteoarthritis; MMSE, mini-mental state examination; n, number of subjects.

significantly higher than the percentage in the without-MCI group (48.8%, p<0.001). This significant tendency was observed in women, while in men the association was not significant.

Occurrence of radiographic KOA in participants with and without MCI

The baseline prevalence of KOA in the 1384 individuals who attended follow-up was 46.8% (men 37.3%; women 51.6%). After the exclusion of participants with a baseline KL grade ≥2 at one or both knees, the cumulative incidence of OA during the 3-year follow-up period was estimated using an at-risk population of 728 individuals (290 men, 438 women) without OA in either knee at baseline. Among these, 71 participants (18 men, 53 women) were newly diagnosed with KOA, and the annual cumulative incidence was estimated as 3.3% (men 2.1%; women 4.0%). The incidence of KOA increased with age (table 2).

The MMSE score was significantly lower in participants with, compared to those without, incident radiographic KOA (p<0.0001), and the prevalence of MCI at baseline was significantly higher (p=0.003). Those with KOA tended to reside in a mountainous area, were significantly taller, had greater BMI and weaker grip strength in both hands and were less likely to smoke, drink alcohol or exercise regularly compared with those without OA. History of knee injury was more common among those without KOA (table 2).

On univariate regression analysis, a one-digit increase in the MMSE score was associated with a 24% decreased risk of incident radiographic KOA (p<0.001; table 3). This trend remained after adjustment for age, gender, regional differences and BMI in model 1 (OR 0.85 for +1 MMSE score; p=0.015) and after adjustment for age, gender, regional differences, BMI, grip strength (kg) on the worse side, smoking, alcohol consumption, regular exercise and history of knee injury in model 2 (OR 0.83; p=0.010). The presence of MCI was associated with a fivefold increased risk of incident KOA (p=0.008), with ORs of 4.59 (p=0.027) in model 1 and 4.90 (p=0.027) in model 2.

Progression of radiographic KOA with and without MCI

We excluded 88 participants (21 men, 67 women) with a baseline KL grade of 4 at one or both knees, before estimating the cumulative rate for the progression of KOA during a 3-year follow-up. We estimated the rate of progression rate in KL grades over the 3 years using the population at risk comprising 1296 individuals (445 men, 851 women). Among these, 311 individuals (86 men, 225 women) had a higher KL grade assigned to one or both knees at follow-up than at baseline. The annual rate of progression in KL grades for either knee over the 3-year period was 8.0% (men 6.4%, women 8.8%) in the overall population at risk, and the rate increased with age (table 4). The MMSE summary score was significantly lower (p<0.0001) and the baseline prevalence of MCI was significantly higher (p=0.008) in participants with, than in those without, progression of radiographic KOA. Participants with progression of radiographic KOA tended to reside in a mountainous area, were significantly older and taller, had greater BMI and weaker grip strength in both hands and were less likely to smoke, drink alcohol or take regular exercise compared to those who did not have progression of KOA (table 4).

A one-digit increase in the MMSE was associated with a 16% increased risk of progression of radiographic KOA (OR 0.84; p<0.001). This tendency was no longer significant after adjustment for age, gender, regional differences and BMI in model 1 (OR 0.95; p=0.131), and for age, gender, regional differences, BMI, grip strength (worst side), smoking, alcohol consumption, regular exercise and history of knee injuries in model 2 (OR 0.96; p=0.232; table 5). On univariate analysis, the presence of MCI was associated with a 2.5-fold increased risk of progression of KOA (OR 2.54; p=0.010), but this was not significant after adjustment for confounding factors in model 1 (OR 1.56; p=0.242) or model 2 (OR 1.38; p=0.416).

Association of inflammation and metabolic risk factors with both KOA and MCI

In addition to the factors adjusted in model 2, we assessed the following two factors as potential confounders influencing both KOA and MCI: subclinical inflammation and metabolic risk factors.

As an index of inflammation, baseline serum C reactive protein (CRP) level was added as an explanatory factor in a logistic regression analysis similar to that performed in model 2. The adjusted ORs for the occurrence of OA in relation to the MMSE summary score (OR 0.83; 95% CI, 0.72 to 0.96 for +1 MMSE score; p=0.010) or to the presence of MCI (OR 5.18; 95% CI, 1.24 to 21.6 for presence of MCI; p=0.024) remained unchanged, and the serum CRP level was not significantly associated with occurrence (OR 0.47; 95% CI, 0.09 to 2.40 for +1 CRP level; p=0.365) or progression of OA (OR 0.96; 95% CI, 0.67 to 1.37; p=0.818).

Then, we performed logistic regression analysis, similar to that performed in model 2, by using the metabolic risk factors overweight (1: BMI≥25 kg/m^2, 0: BMI<25 kg/m^2), hypertension (1: systolic blood pressure (BP) ≥130 mm Hg and/or diastolic BP ≥85 mm Hg, 0: systolic BP <130 mm Hg and diastolic BP <84 mm Hg), dyslipidaemia (1: serum high-density lipoprotein cholesterol (HDL-cho) level <40 mg/dl, 0: HDL-cho level ≥40 mg/dl) and impaired glucose tolerance (1: serum haemoglobin A1c (HbA1c) level ≥5.5%, 0: HbA1c level <5.5%). Furthermore, subjects receiving medication for hypertension, dyslipidaemia or diabetes mellitus were regarded as having hypertension, dyslipidaemia or impaired glucose tolerance, respectively. The adjusted ORs for the occurrence of KOA in relation to the MMSE summary score (OR 0.84; 95% CI, 0.73 to

Table 2 Mean values (SDs) of anthropometric factors, mini-mental state examination (MMSE) and prevalence of mild cognitive impairment (MCI) and selected characteristics vs the occurrence of knee osteoarthritis

Occurrence of KOA		Total			Men			Women	
	KOA (–) (n=657)	KOA (+) (n=71)	p Value	KOA (–) (n=272)	KOA (+) (n=18)	p Value	KOA (–) (n=385)	KOA (+) (n=53)	p Value
Number of subjects classified by age-strata (cumulative incidence, %/year)									
≤39 (year)	38	0 (0.0)		10	0 (0.0)		28	0 (0.0)	
40–49	118	1 (0.3)		36	0 (0.0)		82	1 (0.4)	
50–59	201	15 (2.3)	<0.001***	77	0 (0.0)	0.009**	124	(3.6)	<0.001***
60–69	177	27 (4.4)		76	11 (4.2)		101	(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 (SDs) for MMSE summary score and prevalence of MCI									
MMSE summary score	29.1 (1.6)	28.0 (2.3)	<0.0001***	28.8 (1.9)	27.3 (2.7)	0.0017**	29.3 (1.3)	28.2 (2.1)	<0.0001***
Prevalence of MCI (%)	7/654 (1.1)	4/71 (5.6)	0.003**	6/270 (2.2)	2/18 (11.1)	0.026*	1/384 (0.3)	2/53 (3.8)	0.004*
Mean values (SDs) for age, anthropometric factors and neuromuscular function									
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***
Height (cm)	158.8 (8.6)	153.9 (7.6)	<0.0001***	165.6 (7.0)	162.0 (5.0)	0.0360*	154.0 (6.0)	151.2 (6.2)	0.0018**
Weight (kg)	56.8 (11.0)	56.0 (8.8)	0.5560	63.7 (11.0)	63.7 (9.2)	0.9859	51.9 (8.1)	53.4 (7.1)	0.2051
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**
Grip strength (better side) (kg)	31.3 (9.9)	26.7 (8.1)	0.0002***	39.4 (8.8)	35.9 (7.1)	0.0996	25.6 (6.0)	23.5 (5.6)	0.0171*
Grip strength (worse side) (kg)	28.0 (9.6)	23.0 (8.5)	<0.0001***	35.9 (9.0)	30.7 (11.0)	0.0188*	22.5 (5.1)	20.4 (5.5)	0.0065**
Percentage of selected characteristics, %									
Residing in a coastal area	70.8	56.3	0.012*	66.9	55.6	0.324	73.5	56.6	0.011*
Current smoking habit (more than once a month)	16.9	7.1	0.034*	34.2	27.8	0.577	4.7	0.0	0.110
Current alcohol consumption (more than once a month)	47.9	35.2	0.041*	70.0	61.1	0.428	32.5	26.4	0.375
Regular exercise after graduation from school	19.9	7.0	0.008**	37.5	27.8	0.408	7.5	0.0	0.039*
Past injury of either knee	1.8	5.6	0.038*	0.4	5.6	0.010*	2.9	5.7	0.277

*p<0.05, **p<0.01, ***p<0.001
BMI, body mass index; KOA, knee osteoarthritis; KOA(–), non-occurrence of KOA; KOA(+), occurrence of KOA; n, number of subjects.

Table 3 ORs for occurrence of knee osteoarthritis during the 3-year follow-up period versus mild cognitive impairment (MCI)

MMSE summary score		Univariate analysis			Logistic regression model 1			Logistic regression model 2		
Explanatory variables	**Reference**	**OR**	**95% CI**	**p Value**	**OR**	**95% CI**	**p Value**	**OR**	**95% CI**	**p Value**
MMSE summary score	+1 score	0.76	0.68 to 0.85	<0.001***	0.85	0.73 to 0.97	0.015*	0.83	0.72 to 0.96	0.010*
Other potential risk actors										
Age (year)	1 year				1.09	1.06 to 1.13	<0.001**	1.10	1.06 to 1.14	<0.001***
Gender	0: men, 1: women				4.36	2.33 to 8.16	<0.001**	4.02	1.50 to 10.74	0.006**
Region	0: mountainous area, 1: coastal area				0.78	0.45 to 1.35	0.380	0.76	0.43 to 1.35	0.354
BMI (kg/m^2)	+1 kg/m^2				1.23	1.12 to 1.34	<0.001**	1.22	1.11 to 1.34	<0.001***
Grip strength (worse side) (kg)	+1 kg							1.01	0.96 to 1.06	0.730
Smoking	0: exsmoker or never smoker, 1: current smoker							1.01	0.35 to 2.91	0.986
Alcohol consumption	0: exdrinker or never drinker, 1: current drinker							1.11	0.60 to 2.04	0.746
Regular exercise after graduation from school	0: no, 1: yes							0.57	0.20 to 1.65	0.302
History of knee injuries	0: no, 1: yes							4.76	1.26 to 17.97	0.021*
MCI		Univariate analysis			Logistic regression model 1			Logistic regression model 2		
Explanatory variables										
MCI	0: absence, 1 :presence	5.52	1.57 to 19.34	0.008**	4.59	1.18 to 17.7	0.027*	4.90	1.20 to 20.05	0.027*
Other potential risk actors										
Age (year)	1 year				1.10	1.07 to 1.14	<0.001**	1.10	1.07 to 1.15	<0.001***
Gender	0: men, 1: women				4.36	2.32 to 8.17	<0.001**	3.80	1.42 to 10.19	0.008**
Region	0: mountainous area, 1: coastal area				0.75	0.44 to 1.30	0.310	0.73	0.41 to 1.29	0.280
BMI (kg/m^2)	+1 kg/m^2				1.23	1.13 to 1.35	<0.001**	1.23	1.12 to 1.34	<0.001***
Grip strength (worse side) (kg)	+ 1 kg							1.00	0.96 to 1.05	0.870
Smoking	0: exsmoker or never smoker, 1: current smoker							1.08	0.38 to 3.12	0.885
Alcohol consumption	0: exdrinker or never drinker, 1: current drinker							1.10	0.59 to 2.02	0.770
Regular exercise after graduation from school	0: no, 1: yes							0.57	0.20 to 1.65	0.304
Past history of knee injuries	0: no, 1: yes							4.28	1.13 to 16.19	0.032*

*p<0.05, **p<0.01, ***p<0.001.
BMI, body mass index; n, number of subjects; MMSE, mini-mental state examination.

Table 4 Mean values (SDs) of anthropometric factors, mini-mental state examination (MMSE) and prevalence of mild cognitive impairment (MCI) and selected characteristics versus progression of knee osteoarthritis

Progression of KOA Women	Total			Men			Women		
	Progression			Progression			Progression		
	(–) (n=985)	(+) (n=311)	p Value	(–) (n=359)	(+) (n=86)	p Value	(–) (n=626)	(+) (n=225)	p Value
Number of subjects classified by age-strata (Proportion of progression, %/year)									
≤39 (year)	37	2 (1.7)		9	1 (3.3)		28	1 (1.1)	
40–49	128	7 (1.7)		38	2 (1.7)		90	5 (1.8)	
50–59	248	44 (5.0)	<0.001***	89	8 (2.8)	<0.001***	159	36 (6.2)	<0.001***
60–69	292	105 (8.2)		101			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 (SDs) for MMSE summary score and prevalence of MCI									
MMSE summary score	28.7 (1.8)	28.0 (2.2)	<0.0001***	28.5 (1.9)	27.9 (2.3)	0.0056**	28.8 (1.8)	28.1 (2.1)	<0.0001***
Prevalence of MCI (%)	18/980 (1.8)	14/295 (4.5)	0.008**	9/357 (2.5)	5/85 (5.9)	0.112	9/623 (1.4)	9/224 (4.0)	0.022*
Mean values (SDs) for age, anthropometric factors and neuromuscular function									
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***
Height (cm)	156.7 (8.9)	153.1 (8.6)	<0.0001***	164.6 (7.1)	161.8 (6.2)	0.0010**	152.2 (6.4)	149.7 (6.9)	<0.0001***
Weight (kg)	56.0 (10.9)	55.6 (9.9)	0.5496	63.1 (10.9)	62.8 (10.2)	0.8520	52.0 (8.6)	52.9 (8.4)	0.1883
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***
Grip strength (better side) (kg)	29.3 (9.7)	25.7 (8.0)	<0.0001***	38.1 (8.7)	34.4 (7.2)	0.0003***	24.3 (6.0)	22.4 (5.3)	<0.0001***
Grip strength (worse side) (kg)	26.0 (9.4)	22.5 (7.9)	<0.0001***	34.6 (8.8)	30.1 (8.7)	<0.0001***	21.1 (5.3)	19.6 (5.2)	0.0003***
Percentage of selected characteristics (%)									
Residing in a coastal area	57.9	42.1	<0.001***	53.8	44.2	0.110	60.4	41.3	<0.001***
Current smoking habit (more than once a month)	14.1	8.6	0.013*	31.2	24.4	0.220	4.1	2.3	0.222
Current alcohol consumption (more than once a month)	44.4	32.5	<0.001***	72.1	57.0	0.006**	28.6	23.1	0.114
Regular exercise after graduation from school	18.1	8.0	<0.001***	39.6	23.3	0.005**	5.8	2.2	0.034*
Past injury of either knee	2.0	3.2	0.226	1.1	3.5	0.112	2.6	3.1	0.660

*p<0.05, **p<0.01, ***p<0.001.
KOA, knee osteoarthritis; progression(–), no progression of the Kellgren-Lawrence grade; progression(+), progression of the Kellgren-Lawrence grade.
BMI, body mass index; n, number of subjects.

Table 5 OR for the progression of the Kellgren-Lawrence grade for either knee during the 3-year follow-up period versus mild cognitive impairment (MCI)

MMSE summary score			Univariate analysis		Logistic regression model 1			Logistic regression model 2		
Explanatory variables	**Reference**	**OR**	**95% CI**	**p Value**	**OR**	**95% CI**	**p Value**	**OR**	**95% CI**	**p Value**
MMSE summary score	+1 score	0.84	0.79 to 0.90	<0.001***	0.95	0.88 to 1.02	0.131	0.96	0.89 to 1.03	0.232
Other potential risk actors										
Age (year)	+1 year				1.06	1.05 to 1.08	<0.001***	1.06	1.04 to 1.07	<0.001***
Gender	0: men, 1: women				1.89	1.40 to 2.55	<0.001***	1.29	0.798 to 2.11	0.308
Region	0: mountainous area, coastal 1: area				0.75	0.57 to 1.00	0.048*	0.69	0.52 to 0.92	0.011*
BMI (kg/m^2)	+ 1 kg/m^2				1.12	1.07 to 1.17	<0.001***	1.13	1.08 to 1.18	<0.001***
Grip strength (worse side) (kg)	+1 kg							0.99	0.97 to 1.02	0.572
Smoking	0: exsmoker or never smoker, 1: current smoker							0.99	0.59 to 1.64	0.964
Alcohol consumption	0: exdrinker or never drinker, 1 current drinker							0.84	0.61 to 1.15	0.274
Regular exercise after graduation from school	0: no, 1: yes							0.55	0.33 to 0.91	0.021*
History of knee injuries	0: no, 1: yes							2.27	0.99 to 5.22	0.053
MCI			Univariate analysis		Logistic regression model 1			Logistic regression model 2		
Explanatory variables										
MCI	0: absence, 1: presence	2.54	1.25 to 5.16	0.010*	1.56	0.74 to 3.30	0.242	1.38	0.63 to 3.03	0.416
Other potential risk actors										
Age (year)	+1 year				1.07	1.05 to 1.08	<0.001***	1.06	1.04 to 1.08	<0.001***
Gender	0: men, 1: women				1.89	1.40 to 2.54	<0.001***	1.26	0.77 to 2.05	0.353
Region	0: mountainous area, coastal 1: area				0.75	0.56 to 0.99	0.041*	0.68	0.51 to 0.91	0.010*
BMI (kg/m^2)	+ 1 kg/m^2				1.13	1.08 to 1.17	<0.001***	1.13	1.08 to 1.18	<0.001***
Grip strength (worse side) (kg)	+1 kg							0.99	0.97 to 1.02	0.484
Smoking	0: exsmoker or never smoker, 1: current smoker							0.99	0.60 to 1.65	0.974
Alcohol consumption	0: exdrinker or never drinker, 1: current drinker							0.83	0.61 to 1.15	0.264
Regular exercise after graduation from school	0: no, 1: yes							0.55	0.33 to 0.91	0.021*
History of knee injuries	0: no, 1: yes							2.27	0.99 to 5.21	0.053

*p<0.05, **p<0.01, ***p<0.001
BMI, body mass index; ; MMSE, mini mental state examination; n, number of subjects.

0.97 for +1 MMSE score; p=0.019) or to the presence of MCI (OR 4.78; 95% CI, 1.15 to 19.9 for the presence of MCI; p=0.032) remained significant, and hypertension was also significantly associated with the occurrence of KOA in relation to MMSE summary score (OR 2.23; 95% CI, 1.04 to 4.79 for the presence of hypertension; p=0.039) or to the presence of MCI (OR 2.26; 95% CI, 1.06 to 4.85; p=0.036). However, there was no significant association between the occurrence of KOA and overweight, dyslipidaemia and impaired glucose tolerance after adjustment for the factors used in model 2.

DISCUSSION

We studied a population-based cohort with a high participation rate (81.9%) over a period of 3 years, and observed a significant association between the baseline presence of MCI and incident radiographic KOA identified at 3-year follow-up. This association persisted after adjustment for potential confounding factors.

In contrast, we did not observe an association between MCI and further progression of radiographic KOA identified at baseline. We identified progression of KOA when the KL grade was higher at follow-up than at baseline; MCI might have had less influence in patients with an increase of at least one KL grade compared to baseline. We reanalysed the influence of the MMSE score or the presence of MCI on rapid progression of OA, which was defined as an increase of at least two KL grades at either knee at follow-up. The results were similar after adjustment for confounders as in model 2; that is, we identified a significant association between MMSE score and rapid progression of OA (OR 0.84; 95% CI, 0.73 to 0.98, for +1 MMSE score; p=0.026). The OR for rapid progression of OA was increased in the presence of MCI, but not significantly so (OR 2.73; 95% CI, 0.71 to 10.5; p=0.144). Then we concluded that the influence of cognitive decline in the future KOA was more pronounced in occurrence of radiographic KOA than in progression.

Links between musculoskeletal disease and dementia have been reported previously; osteoporosis at the femoral neck, for example, is more common in patients with Alzheimer's disease than in healthy volunteers,[19] but the relationship between KOA and dementia has not been examined. In the current analysis, we showed that the occurrence of KOA was influenced not only by the MMSE scores but also by the presence of MCI. We think that this may be the effect of subclinical inflammation in both MCI and KOA, as inflammatory mechanisms could be involved in the pathogenesis of MCI[19 20] as well as OA.[21] Therefore, we performed logistic regression analysis similar to that performed in model 2, with the addition of the CRP values. The adjusted ORs for the occurrence of OA in relation to the MMSE summary score or to the presence of MCI remained unchanged, and serum CRP level was not significantly associated with occurrence or progression of OA. However, we used a standard method to measure CRP levels, and further studies using a more sensitive measurement method are required to assess the effect of systemic inflammation on cognitive impairment and KOA.

Another hypothesis is that there are hidden confounding factors that might affect both MCI and the onset of KOA. We considered risk factors for metabolic syndrome as potential confounders. Metabolic risk factors such as hypertension and diabetes have been suggested to play a role in the pathogenesis of Alzheimer's disease as well as in the development of vascular dementia.[22–24] We have also already reported the presence of hypertension and impaired glucose tolerance, and shown that accumulation of metabolic risk factors may cause the occurrence of KOA.[25] These findings may indicate that the MCI is a candidate surrogate index for metabolic risk factors as a predictor of KOA occurrence. Therefore, we performed logistic regression analysis similar to that performed for model 2, with the addition of metabolic risk factors. The adjusted ORs for the occurrence of KOA in relation to the MMSE summary score or to the presence of MCI remained significant. In addition, hypertension was also significantly associated with the occurrence of KOA in relation to the MMSE summary score and the occurrence of KOA in relation to MCI, but there was no significant association between the occurrence of KOA and overweight, dyslipidaemia and impaired glucose tolerance. This result shows that components of metabolic syndrome, such as hypertension and MCI, coexist as risk factors for onset of KOA, and MCI might not be a surrogate index for metabolic risk factors for indicating the occurrence of KOA. There might be a direct or an indirect pathway between cognitive impairment and onset of KOA, but based on the information currently available, a causal relationship between MCI and onset of KOA seems to be biologically improbable.

Besides inflammation and metabolic risk factors, there might be other hidden confounders, which could influence both MCI and OA, for example, nutritional factors. Further investigation would be needed to clarify whether the causal relationship still remains after careful consideration with analysis of other possible confounders.

There were several limitations to our study. First, although we used a standard measure of global cognitive function, 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. Consequently, we may have underdiagnosed MCI. Second, we used KL grade ≥2 for diagnosis of KOA. However, the KL scale is a categorical index, and it is impossible to separately evaluate osteophytosis and the minimum joint space. A computer-assisted diagnostic system for the measurement of minimum joint space width and area of osteophytosis is currently under development;[26] this will help measure the severity of KOA using quantitative parameters, and allow us to establish a more accurate assessment of the association between MCI and the development of OA, and facilitate early

prevention of disability. Further, the small proportion of the population with MCI at risk for KOA onset detection might raise the bias in the results of the study.

On the contrary, the strengths of the present study include 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.

CONCLUSION

Our results indicated that MCI significantly influences the occurrence of radiographic KOA, and that KOA occurs more frequently with an decrease in the summary score of the MMSE and the presence of MCI. Prevention of MCI may be useful in preventing the occurrence of KOA and subsequent disability, while further investigation is needed to clarify whether such causalities were caused by direct or indirect associations.

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Contributors NY conceptualised 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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Competing interests None.

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CERVICAL SPINE

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

The Wakayama Spine Study

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

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

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

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

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

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

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

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

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

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

	Men	Women
N	324	653
Age (yr)	67.2 ± 13.9	66.0 ± 13.4
Height (cm)	164.6 ± 7.2*	151.5 ± 7.2
Weight (kg)	64.5 ± 11.6*	53.0 ± 9.4
Body mass index (kg/m^2)	23.7 ± 3.4†	23.1 ± 3.6
Physical performance measures		
Grip strength (kg)	38.0 ± 9.1*	23.9 ± 5.8
Grip and release test, number of times	24.9 ± 5.8*	22.5 ± 5.3
6-m walking time at a usual pace (s)	5.4 ± 1.5	5.8 ± 2.4
Step length at a usual pace (cm)	58.6 ± 9.2*	54.6 ± 10.1
6-m walking time at a maximal pace (s)	3.6 ± 1.1*	4.0 ± 1.6
Step length at a maximal pace (cm)	70.7 ± 10.7*	61.1 ± 11.2
Chair-stand time (s)	8.8 ± 3.4	9.0 ± 4.2
One-leg standing time (s)	35.9 ± 24.1	35.9 ± 23.6

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

Values are mean ± SD.

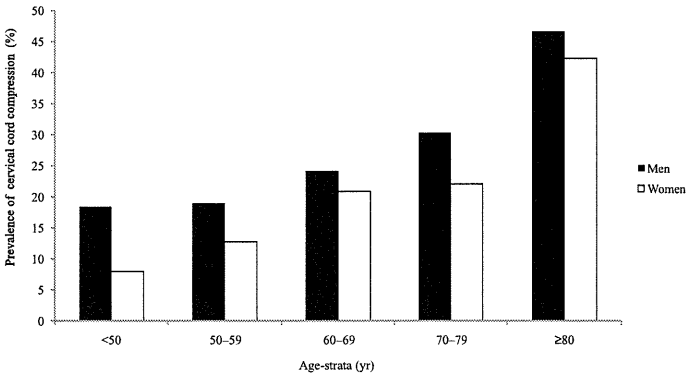

Figure 1. Prevalence of Cervical Cord Compression (≥grade 2) in sexes by age strata.

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

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

MATERIALS AND METHODS

Participants

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

The second visit of the ROAD study to Hidakagawa and Taiji was performed between 2008 and 2010. From inhabitants participating in the second visit of the ROAD study, 1063 inhabitants were recruited for MRI examinations. Among those 1063 inhabitants, 52 declined the examination; therefore, 1011 inhabitants were registered in this study. Among those 1011 participants, those who had MRI-sensitive implanted devices (such as a pacemaker) and other disqualifiers were excluded. The cervical spine was scanned with MRI in 985 participants. Furthermore, 4 participants who had undergone a previous cervical operation were excluded from the analysis, and another 4 participants whose MRI interpretation was difficult because of poor image quality were also excluded. In total, MRI results were available for 977 participants (324 men and 653 women), with an age range of 21 to 97 years (mean, 67.2 yr for men and 66.0 yr for women). Anthropometric measurements included height (m), weight (kg), and body mass index (BMI) (weight [kg]/height^2 [m^2]).

EVALUATION OF MYELOPATHIC SIGNS AND PHYSICAL PERFORMANCE

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

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

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

Values are percentages for each intervertebral disc level.

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

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

Magnetic Resonance Imaging

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

MRI Assessment

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

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

Statistical Analysis

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

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

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

Values are mean ± SD except where otherwise indicated.

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

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

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

RESULTS

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

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

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

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