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Joint space narrowing, body mass index, and knee pain: the ROAD study (OAC1839R1)

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SUMMARY

Objective: The objective of the present study was to clarify the association of joint space narrowing with knee pain in Japanese men and women using a large-scale population-based cohort of the Research on Osteoarthritis/osteoporosis Against Disability (ROAD) study.
Methods: This study examined the association between minimum joint space width (mJSW) in the medial compartment and pain at the knee. mJSW was measured in the medial and lateral compartments of the knee using a knee osteoarthritis (OA) computer-aided diagnosis system.
Results: From the 3040 participants in the ROAD study, the present study analyzed 2733 participants who completed the radiographic examinations and questionnaires regarding knee pain (975 men and 1758 women; mean age, 69.9 ± 11.2 years). Subjects with lateral knee OA were excluded. After adjustment for age and Body mass index (BMI), medial mJSW, as well as medial mJSW/lateral mJSW, was significantly associated with knee pain. Sex and BMI affected the association of medial mJSW with knee pain. The threshold of medial mJSW was approximately 3 mm in men and 2 mm in women, while that of medial mJSW/lateral mJSW was approximately 60% in both men and women. BMI was found to have a distinct effect on the association of mJSW with pain.
Conclusion: The present cross-sectional study using a large-scale population from the ROAD study showed that joint space narrowing had a significant association with knee pain. The thresholds of joint space narrowing for knee pain were also established.

Introduction

Knee osteoarthritis (OA) is a major public health issue that causes chronic pain and disability[1–3]. The prevalence of radiographic knee OA is high in Japan [4], with 25,300,000 persons aged 40 years and older estimated to have radiographic knee OA[5]. According to the recent National Livelihood Survey of the Ministry of Health, Labour and Welfare in Japan, OA is ranked fourth among diseases that cause disabilities that subsequently require support with activities of daily living[6].

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Knee pain is the principal clinical symptom of knee OA[7]. Although much effort has been devoted toward a definition of knee pain, the correlation with radiographic severity of the knee OA was not as strong as one would expect[4,8–10]. One of the reasons for this apparent discrepancy may be the definition of knee OA. Kellgren Lawrence (KL) grading is the conventional system most used to grade the radiographic severity of knee OA[11], but in this categorical system, joint space narrowing is not assessed separately. A recent cross-sectional study showed that the association between joint space narrowing and osteophytosis was not as high as expected on plain radiographs[12]. In addition, joint space narrowing and osteophytosis had distinct effects on QOL[12]. These accumulating lines of evidence have indicated that joint space narrowing and osteophytosis may have distinct etiologic mechanisms, and their progression may be neither constant nor proportional. Although osteophytosis also has some effect on ADL and QOL[12], joint space narrowing is the primary outcome in studies of OA[13]. Thus, to examine the association between knee OA and pain, joint space narrowing should be assessed separately. Chan *et al.* examined the association of joint space narrowing and duration of pain in patients with knee OA and found a significant association[14], but joint space narrowing was defined by categorical methods. Because categorical methods are statistically less powerful than continuous methods, the association between pain and knee OA might have been underestimated. To overcome this, a fully automatic system that can quantify the joint space width of knee OA on standard radiographs and allows for objective, accurate, and simple assessment of the structural severity of knee OA was developed[15]. Thus far, Kinds *et al.* measured joint space width and found significant associations with clinical outcomes[16], but the threshold of joint space width for clinical outcomes remains unclear.

Sex differences have been observed in knee OA. The prevalence of knee OA is higher in women than men, and the association of knee pain with knee OA also differs by sex[4]. Thus, the impact of joint space narrowing and osteophytosis on QOL may also differ between the sexes. Obesity is also one of the few established risk factors for knee OA and pain[17–23]. This suggests that a distinct association of joint space narrowing with pain may be found in subjects with and without obesity. However, to the best of our knowledge, there are no population-based studies that assess the effect of obesity on the association of joint space narrowing with pain.

Therefore, the objective of this study was to clarify the association of joint space narrowing with pain at the knee among Japanese men and women using a fully automatic system to measure joint space width in a large-scale, population-based cohort from the Research on Osteoarthritis/osteoporosis Against Disability (ROAD) study. Furthermore, the threshold of minimum joint space width (mJSW) or medial mJSW/lateral mJSW for pain was determined using receiver operating characteristic (ROC) curve analysis.

Subjects and methods

Subjects

The ROAD study is a nationwide prospective study designed to establish epidemiologic indices for the evaluation of clinical evidence for the development of a disease-modifying treatment for bone and joint diseases (with OA and osteoporosis as the representative bone and joint diseases). It consists of population-based cohorts in several communities in Japan. A detailed profile of the ROAD study has been reported elsewhere[4,5,24], and, thus, only a brief summary is provided here. To date, we have completed the creation of a baseline database including clinical and genetic information for 3040 inhabitants (1061 men and 1,979 women) ranging in age from 23 to 95 years (mean, 70.3 years), who were recruited from resident registration listings in three communities: an urban region in Itabashi, Tokyo, a mountainous region in Hidakagawa, Wakayama, and a coastal region in Taiji, Wakayama. All participants provided their written, informed consent, and the study was conducted with the approval of the ethics committees of the University of Tokyo and the Tokyo Metropolitan Institute of Gerontology. Anthropometric measurements, including height and weight, were taken, and body mass index (BMI; weight [kg]/height^2 [m^2]) was calculated. Furthermore, all participants were also interviewed by well-experienced orthopedists regarding pain in both knees, by asking: "Have you experienced right knee pain on most days in the past month, in addition to now?" and "Have you experienced left knee pain on most days in the past month, in addition to now?". Subjects who answered "yes" were defined as having knee pain. Among the 3040 subjects who participated in the baseline study, 30 (1.0%) who underwent unilateral or total knee arthroplasty were excluded. In addition, 35 (1.1%) whose radiographic examinations were insufficient for measuring joint space width, and 195 (6.4%) with lateral knee OA were excluded. One reason for excluding lateral knee OA is that most knee OA in Japan is medial type[4]. The other reason is that medial and lateral knee OA have distinct characteristics, and joint space narrowing occurs in the medial compartment in medial knee OA, but medial joint space width may not change or be larger in lateral knee OA. Furthermore, 47 patients (1.5%) who provided incomplete questionnaires regarding pain and so on were excluded, leaving a total of 2733 (89.9%) subjects (975 men and 1758 women).

Radiographic assessment

All participants underwent radiographic examinations of both knees using an anterior-posterior view with weight-bearing and foot map positioning by experienced radiological technologists. The beam was positioned parallel to the floor with no angle and aimed at the joint space. To visualize the joint space properly and to centralize the patella over the lower end of the femur, fluoroscopic guidance with an anterior-posterior X-ray beam was used, and the images were downloaded into Digital Imaging and Communication in Medicine (DICOM) format files. Knee radiographs were read without knowledge of participant clinical status by a single experienced orthopedist (S.M.) using the KL radiographic atlas for overall knee radiographic grades[11], and knee OA was defined as KL grade 2 or greater. The KOACAD system was used to measure mJSW in the medial compartment and OPA at the medial tibia[15], and the knee with the lower mJSW was defined as the designated knee for a participant. The KOACAD system is a fully automatic system that can quantify the major features of knee OA on standard radiographs and allows for objective, accurate, and simple assessment of the structural severity of knee OA in general clinical practice. This system was programmed to measure mJSW in the medial and lateral compartments using digitized knee radiographs. The KOACAD system has been described in detail elsewhere[15,25]. The KOACAD system was applied to the DICOM data by the experienced orthopedist who developed this system (H.O.); measurement reliability has been shown to be good[15], and the intraclass coefficient of correlation for medial mJSW measured on radiographs for an individual with weight-bearing and foot map positioning was 0.96. Reference values for OPA and mJSW by sex and age strata in Japan using the KOACAD system have been published previously[25]. Lateral knee OA was defined as KL grade 2 or greater with lower lateral mJSW than medial mJSW.

Statistical analysis

Differences in age, height, weight, BMI, mJSW, and medial/lateral mJSW between men and women and between subjects with and without pain were examined by the non-paired Student's *t*-test. The prevalence of knee OA was compared between men and women by the χ^2 test. Associations of age, BMI, mJSW, and medial/lateral mJSW with knee pain were determined using multiple logistic regression analysis after adjustment for age, sex, and BMI overall, and after adjustment for age and BMI in men and women. In addition, subjects were classified according to mJSW (<1 mm, ≥1–<2 mm, ≥2–<3 mm, ≥3–<4 mm, ≥4 mm), and the associations of mJSW<1 mm, ≥1–<2 mm, ≥2–<3 mm, and ≥3–<4 mm with pain were determined using multiple logistic regression analysis after adjustment for age and BMI, compared with mJSW≥4 mm. To clarify the effect of BMI on the association of mJSW with pain, subjects were further classified into 10 groups according to mJSW and BMI (BMI <23 kg/m^2: mJSW<1 mm, ≥1–<2 mm, ≥2–<3 mm, ≥3–<4 mm, ≥4 mm; BMI ≥ 23 kg/m^2: mJSW<1 mm, ≥1–<2 mm, ≥2–<3 mm, ≥3–<4 mm, ≥4 mm), and the association with pain was determined using multiple logistic regression analysis after adjustment for age, compared with BMI <23 kg/m^2 and mJSW ≥4 mm. Subjects were also classified according to medial/lateral mJSW (<30%, ≥30–<40%, ≥40–<50%, ≥50–<60%, ≥60–<70%, ≥70–<80%, ≥80%), and the associations of medial/lateral mJSW<30%, ≥30–<40%, ≥40–<50%, ≥50–<60%, ≥60–<70%, and ≥70–<80% with pain were determined using multiple logistic regression analysis after adjustment for age and BMI, compared with medial/lateral mJSW ≥80%. The thresholds of mJSW and medial/lateral mJSW for pain were determined using ROC curve analysis. Data analyses were performed using SAS version 9.0 (SAS Institute Inc., Cary, NC).

Results

The characteristics of the 2733 participants in the present study are shown in Table I. The prevalence of knee OA was significantly higher in women than in men. The mJSW and medial mJSW/lateral mJSW were significantly lower in women than in men. The participants in the present study were significantly younger than the non-participants ($P < 0.05$), while BMI was not significantly different between them (non-participants: age, 74.3 ± 7.9 years; BMI, 23.1 ± 3.2 kg/m^2).

Table II shows age, BMI, mJSW, and medial/lateral mJSW in subjects with and without pain. For the right knee, overall and in women, subjects with pain were older and had higher BMI, narrower mJSW, and smaller medial/lateral mJSW than those without pain. In men, subjects with pain had higher BMI, narrower mJSW, and smaller medial/lateral mJSW than subjects without pain, while age was not significantly different in men with and without pain. For the left knee, results were similar except for age in men. Associations of mJSW and medial/lateral mJSW with right and left knee pain were next examined using multiple logistic regression analysis after adjustment for age, sex, and BMI overall, and after adjustment for age and BMI in men and women (Table II). Odds ratios (ORs) of mJSW (1-mm decrease) for pain were higher than 2, and the ORs of medial/lateral mJSW (10% decrease) for pain were 1.2–1.3.

Subjects were then classified according to mJSW (<1 mm, ≥1–<2 mm, ≥2–<3 mm, ≥3–<4 mm, ≥4 mm), and the prevalence of knee pain was examined (Fig. 1, Supplementary Table I). The prevalence of knee pain was more than 60% in subjects with mJSW<1 mm, while it was less than 10% in those with mJSW ≥4 mm. The OR for pain was also calculated after adjustment for age and BMI. Men with mJSW <1 mm, ≥1–<2 mm, and ≥2–<3 mm had significantly higher rates of pain than those with mJSW ≥4 mm, but men with mJSW ≥3–<4 mm did not (Table III). The OR for pain in men with mJSW <1 mm was around 40. Women with mJSW <1 mm and ≥1–<2 mm had significantly higher rates of pain than those with mJSW ≥4 mm, but, women with mJSW ≥2–<3 mm and ≥3–<4 mm did not. The ORs for pain in women with mJSW <1 mm were 12–14. Subjects were further classified into 10 groups according to BMI and mJSW (BMI < 23 kg/m^2: mJSW < 1 mm, ≥1–<2 mm, ≥2–<3 mm, ≥3–<4 mm, ≥4 mm; BMI ≥ 23 kg/m^2: mJSW < 1 mm, ≥1–<2 mm, ≥2–<3 mm, ≥3–<4 mm, ≥4 mm), and the ORs for pain were calculated (Supplementary Table II). In men, mJSW<1 mm and ≥1–<2 mm with BMI <23 kg/m^2 and mJSW < 1 mm, ≥1–<2 mm, and ≥2–<3 mm with BMI ≥23 kg/m^2 were significantly associated with pain compared with mJSW ≥4 mm with BMI <23 kg/m^2. In women at the right knee, mJSW < 1 mm with BMI <23 kg/m^2 and mJSW ≥0–<1 mm and ≥1–<2 mm with BMI ≥23 kg/m^2 were significantly associated with pain compared with mJSW ≥4 mm with BMI <23 kg/m^2. In women at the left knee, mJSW < 1 mm and ≥1–<2 mm with BMI <23 kg/m^2 and mJSW < 1 mm, ≥1–<2 mm, and ≥2–<3 mm with BMI ≥23 kg/m^2 were significantly associated with pain compared with mJSW ≥4 mm with BMI <23 kg/m^2.

Subjects were also classified according to medial/lateral mJSW (<30%, ≥30–<40%, ≥40–<50%, ≥50–<60%, ≥60–<70%, ≥70–<80%, ≥80%), and the prevalence of knee pain was examined (Fig. 2, Supplementary Table III). The prevalence of knee pain was approximately 60% in subjects with medial mJSW/lateral mJSW < 30%, while it was approximately 10% in those with medial mJSW/lateral mJSW ≥80%. The ORs for pain were also calculated after adjustment for age and BMI (Table IV). Men and women with mJSW <30%, ≥30–<40%, ≥40–<50%, and ≥50–<60% had higher rates of pain compared with those with mJSW ≥80%, except for men with mJSW≥50–<60% at the right knee. The ORs for pain in men with mJSW <30% were 14–20. The OR for pain in women with mJSW <30% was around 10.

The threshold values of mJSW for knee pain were then determined using ROC curve analysis (Supplementary Fig. 1). In men, the threshold values of mJSW for pain at the right and left knees were 2.87 mm (sensitivity 0.67, specificity 0.65, AUC 0.70, 95% confidence interval (CI) 0.64–0.75) and 2.82 mm (sensitivity 0.62, specificity 0.67, AUC 0.72, 95% CI 0.66–0.77), respectively. In women, the threshold values of mJSW for pain at the right and left knees were 2.01 mm (sensitivity 0.43, specificity 0.689, AUC 0.69, 95% CI 0.66–0.73) and 2.44 mm (sensitivity 0.59, specificity 0.75, AUC 0.71, 95% CI 0.67–0.74), respectively. Threshold values of medial/lateral mJSW for knee pain were also determined using ROC curve analysis (Supplementary Fig. 2). In men, the threshold values of medial/lateral mJSW for pain at the right and left knees were 55.2% (sensitivity 0.45, specificity 0.68, AUC 0.66, 95% CI 0.60–0.72) and

Table I
Characteristics of the subjects in the present study

	Overall	Men	Women	*P* values
N	2733	975	1758	
Age, years	69.9 ± 11.2	70.8 ± 10.8	69.4 ± 11.4	0.0012
Height, cm	154.4 ± 8.9	162.5 ± 6.7	150.0 ± 6.4	<0.0001
Weight, kg	55.1 ± 10.3	61.4 ± 10.0	51.6 ± 8.7	<0.0001
BMI, kg/m^2	23.0 ± 3.3	23.2 ± 3.0	22.9 ± 3.5	0.0493
Right knee				
Knee OA, %	45.3	33.6	51.8	<0.0001
mJSW, mm	2.8 ± 1.0	3.2 ± 0.9	2.6 ± 0.9	<0.0001
medial mJSW/lateral mJSW, %	68.7 ± 30.1	71.1 ± 22.2	67.4 ± 33.6	0.0007
Left knee				
Knee OA, %	47.5	35.8	54	<0.0001
mJSW, mm	2.9 ± 1.0	3.3 ± 01.0	2.7 ± 0.9	<0.0001
medial mJSW/lateral mJSW, %	70.8 ± 26.3	73.9 ± 22.7	69.1 ± 28.0	<0.0001

Except where indicated otherwise, values are means ± SD.
Knee OA was defined as Kellgren Lawrence grade 2 or worse.
BMI, body mass index; OA, osteoarthritis; mJSW, minimum joint space width.

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Table II
Associations of age, BMI, mJSW, and medial mJSW/lateral mJSW with knee pain

	Right knee					Left knee				
	Pain +	Pain −	Adjusted OR	95% CI	P values	Pain +	Pain −	Adjusted OR	95% CI	P values
Overall										
N										
Age, years	72.4 ± 8.6	69.3 ± 11.6*	1.01	1.00–1.03	0.0499	72.8 ± 8.4	69.3 ± 11.6*	1.01	0.99–1.02	0.3226
BMI, kg/m^2	24.4 ± 3.6	22.7 ± 3.2*	1.12	1.08–1.16	<0.0001	24.2 ± 3.5	22.8 ± 3.2*	1.10	1.06–1.14	<0.0001
mJSW, mm (1-mm decrease)	2.1 ± 1.1	2.9 ± 0.9*	2.17	1.92–2.50	<0.0001	2.2 ± 1.1	2.9 ± 0.9*	2.22	1.96–2.56	<0.0001
medial mJSW/lateral mJSW, % (10% decrease)	54.3 ± 30.7	71.9 ± 29.0*	1.30	1.24–1.37	<0.0001	56.6 ± 30.4	71.0 ± 29.5*	1.22	1.16–1.29	<0.0001
Men										
N										
Age, years	71.7 ± 9.4	70.7 ± 11.0	0.99	0.96–1.02	0.5095	72.8 ± 8.7	70.5 ± 11.0*	0.98	0.95–1.01	0.2278
BMI, kg/m^2	24.2 ± 3.0	23.0 ± 3.0*	1.09	1.01–1.18	0.0207	24.1 ± 3.1	23.0 ± 3.0*	1.08	0.995–1.17	0.0635
mJSW, mm (1-mm decrease)	2.4 ± 1.2	3.3 ± 0.9*	2.33	1.82–3.03	<0.0001	2.6 ± 1.1	3.2 ± 0.9*	2.50	1.92–3.23	<0.0001
medial mJSW/lateral mJSW, % (10% decrease)	57.2 ± 27.6	72.8 ± 20.8*	1.33	1.19–1.49	<0.0001	61.3 ± 29.6	72.3 ± 20.8*	1.28	1.15–1.43	<0.0001
Women										
N										
Age, years	72.6 ± 8.4	68.5 ± 12.0*	1.02	1.005–1.04	0.0138	72.7 ± 8.3	68.6 ± 11.9*	1.02	0.997–1.04	0.0964
BMI, kg/m^2	24.4 ± 3.7	22.5 ± 3.3*	1.12	1.08–1.17	<0.0001	24.3 ± 3.6	22.6 ± 3.4*	1.11	1.06–1.16	<0.0001
mJSW, mm (1-mm decrease)	2.0 ± 1.1	2.8 ± 0.8*	2.13	1.82–2.50	<0.0001	2.1 ± 1.1	2.7 ± 0.8*	2.17	1.85–2.56	<0.0001
medial mJSW/lateral mJSW, % (10% decrease)	52.2 ± 31.5	71.4 ± 33.0*	1.30	1.22–1.38	<0.0001	55.1 ± 30.6	70.3 ± 33.7*	1.21	1.14–1.28	<0.0001

*$P < 0.05$ by non-paired Student's *t*-test.
Adjusted ORs were calculated by multiple logistic regression analysis after adjustment for age, sex, and BMI overall and after adjustment for age and BMI in men and women.
BMI, body mass index; mJSW, minimum joint space width; OR, odds ratio; CI, confidence interval.

57.9% (sensitivity 0.49, specificity 0.84, AUC 0.70, 95% CI 0.64–0.76), respectively. In women, the threshold values of medial/lateral mJSW for pain at the right and left knees were 57.9% (sensitivity 0.57, specificity 0.75, AUC 0.69, 95% CI 0.66–0.73) and 57.7% (sensitivity 0.58, specificity 0.76, AUC 0.71, 95% CI 0.68–0.74), respectively.

Discussion

Joint space narrowing is the primary outcome in studies of knee OA[20], because cartilage damage, which is one of the main causes of knee symptoms, is seen as a smaller mJSW[16]. Previous studies have shown significant associations of joint space narrowing with pain[14,16], though the threshold of joint space width for pain remained unclear. This is the first study to clarify the effect of joint space narrowing on knee pain using a large-scale, population-based, cohort study. In addition, joint space narrowing was evaluated not by categorical grade but by continuous values, using mJSW at the knee. In the present study, mJSW < 3 mm in men and mJSW < 2 mm in women were significantly associated with knee pain, compared with mJSW ≥4 mm, and the OR of mJSW < 1 mm for knee pain was quite high, particularly in men. It was also found that the effect of mJSW on pain was affected by BMI. Medial mJSW/lateral/mJSW < 60% was also significantly associated with knee pain in men and women, compared with medial mJSW/lateral mJSW ≥ 80%. Using ROC curve analysis, the thresholds of mJSW in men and women were found to be approximately 3 mm in men and

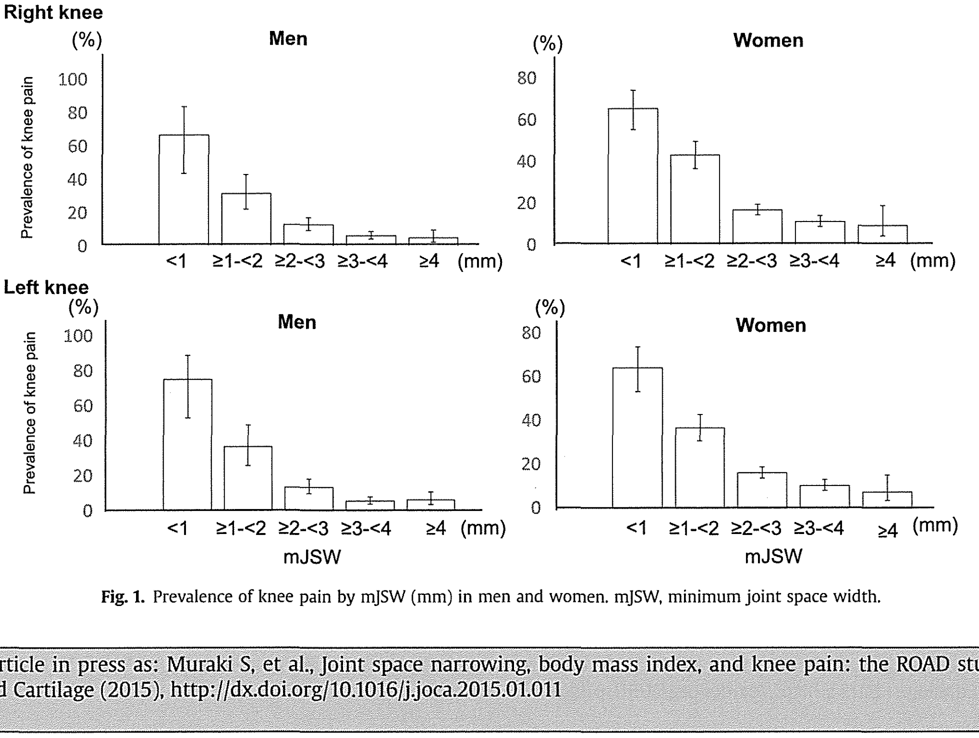

Fig. 1. Prevalence of knee pain by mJSW (mm) in men and women. mJSW, minimum joint space width.

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Table III
OR of knee pain by medial mJSW

	Men				Women			
	Crude OR	95% CI	Adjusted OR	95% CI	Crude OR	95% CI	Adjusted OR	95% CI
Right knee								
<1 mm	39.0	11.9–146.4	39.4	11.6–151.8	18.4	7.7–51.9	12.3	5.0–35.3
≥1–<2 mm	9.0	3.8–23.9	8.5	3.5–23.0	7.4	3.3–19.7	5.9	2.6–15.9
≥2–<3 mm	2.9	1.3–7.2	3	1.4–7.6	2	0.9–5.2	1.8	0.8–4.9
≥3–<4 mm	1.3	0.6–3.3	0.8	0.2–3.2	1.2	0.5–3.3	1.3	0.6–3.5
≥4 mm	1		1		1		1	
Left knee								
<1 mm	45.5	14.9–163.3	38.1	11.9–142.1	22.7	9.4–64.3	14.0	5.7–40.2
≥1–<2 mm	8.7	4.0–20.2	8.5	3.8–20.1	7.3	3.3–19.5	5.3	2.3–14.2
≥2–<3 mm	2.3	1.2–5.0	2.3	1.2–5.1	2.4	1.1–6.4	2.0	0.9–5.3
≥3–<4 mm	0.9	0.4–1.9	0.9	0.4–1.9	1.4	0.6–3.8	1.4	0.6–3.7
≥4 mm	1		1		1		1	

Adjusted ORs were calculated by multiple logistic regression analysis after adjustment for age and BMI.
mJSW, minimum joint space width; CI, confidence interval.

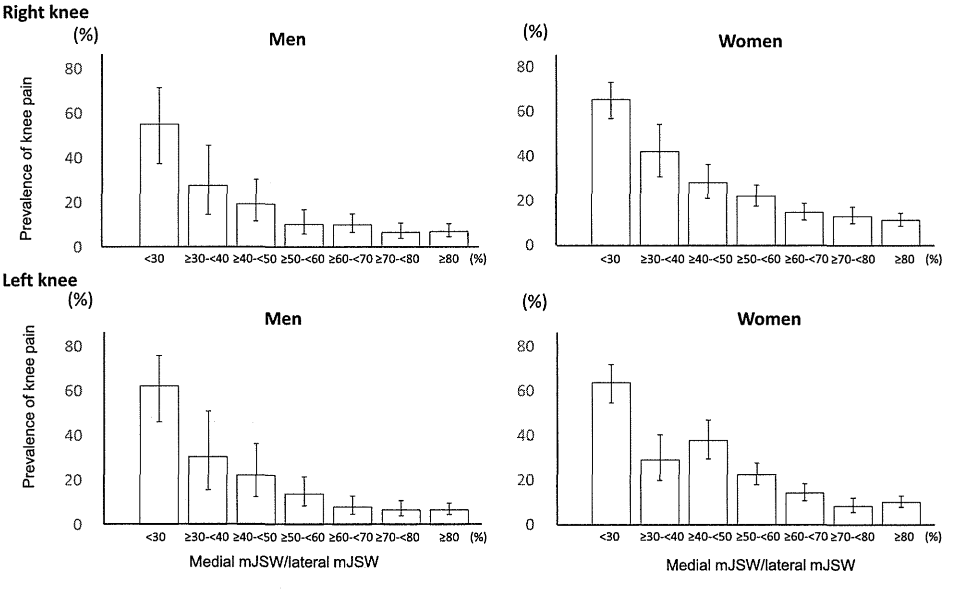

Fig. 2. Prevalence of knee pain by medial mJSW/lateral mJSW (%) in men and women. mJSW, minimum joint space width.

Table IV
OR of knee pain by the ratio of medial mJSW to lateral mJSW

	Men				Women			
	Crude OR	95% CI	Adjusted OR	95% CI	Crude OR	95% CI	Adjusted OR	95% CI
Right knee								
<30%	16.0	6.9–38.2	14.5	6.1–35.0	14.8	9.4–23.7	9.8	6.1–16.0
≥30–<40%	5.0	1.9–12.2	4.4	1.6–10.9	5.7	3.2–10.0	4.2	2.3–7.6
≥40–<50%	3.1	1.5–6.5	2.7	1.2–5.7	3.1	1.9–4.9	2.4	1.5–4.0
≥50–<60%	1.5	0.7–3.0	1.4	0.7–2.9	2.2	1.5–3.3	2.1	1.4–3.2
≥60–<70%	1.5	0.8–2.8	1.5	0.8–2.8	1.4	0.9–2.0	1.3	0.9–2.0
≥70–<80%	0.9	0.5–1.9	0.9	0.5–1.9	1.2	0.8–1.8	1.1	0.7–1.8
≥80%	1		1		1		1	
Left knee								
<30%	23.0	10.7–51.3	18.9	8.6–43.1	15.5	9.8–25.0	10.3	6.4–16.9
≥30–<40%	6.1	2.2–15.8	5.7	2.0–14.8	3.6	2.0–6.4	2.8	1.5–5.0
≥40–<50%	4.0	1.7–8.8	3.6	1.5–8.0	5.4	3.4–8.6	4.3	2.7–7.0
≥50–<60%	2.2	1.1–4.4	2.1	1.0–4.1	2.6	1.7–3.8	2.3	1.5–3.4
≥60–<70%	1.2	0.6–2.4	1.2	0.6–2.4	1.5	0.97–2.2	1.4	0.9–2.1
≥70–<80%	1.0	0.5–1.9	1.0	0.5–2.0	0.8	0.5–1.3	0.8	0.5–1.3
≥80%	1		1		1		1	

Adjusted ORs were calculated by multiple logistic regression analysis after adjustment for age and BMI.
mJSW, minimum joint space width; CI, confidence interval.

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2 mm in women, while those of medial mJSW/lateral mJSW were approximately 60% in both men and women.

Although much effort has been devoted toward a definition of knee pain, the correlation with radiographic severity of knee OA was not as strong as one would expect[4,8–10]. In fact, our previous study showed that the OR of severe knee OA defined as KL grade 3 or 4 for knee pain was 8.6 in men and 4.4 in women[4], which was significant, but the OR was not as high as expected. One of the reasons for this is that knee pain may arise from a variety of structures other than joint cartilage, such as menisci, synovium, ligaments, bursae, bone, and bone marrow[26–30]. Another reason may be due to the definition of knee OA. Knee OA is characterized by the pathological features of joint space narrowing and osteophytosis. However, most conventional systems for grading radiographic severity have been categorical grades, such as KL grading[11], which cannot assess joint space narrowing individually. Several studies have shown that knee OA has a strong effect on QOL[31–34], but in these studies, knee OA was defined by categorical grades such as KL grade or American College of Rheumatology (ACR) grade, total knee arthroplasty, and self-questionnaire. In addition, joint space narrowing was separately evaluated using a radiographic atlas of individual features published by the Osteoarthritis Research Society International (OARSI) in 1995[35] and revised in 2007[36]. Chan *et al.* examined the association of joint space narrowing and duration of pain in patients with knee OA using categorical methods[14]. However, the grading is still limited in reproducibility and sensitivity due to the subjective judgment of individual observers and the categorical classification. Furthermore, because categorical methods are statistically less powerful than continuous methods, the association between pain and knee OA might have been underestimated in previous studies. Kinds *et al.* measured joint space width and found significant associations with clinical outcomes[16], but the threshold of joint space width for clinical outcomes remained unclear. In the present study, to overcome this problem, joint space width was evaluated using a fully automatic system, and the OR of mJSW <1 mm for knee pain was quite high, particularly in men, and it was possible to establish the threshold values of mJSW for knee pain, which may indicate that mJSW is better for diagnosing knee OA than KL grade. In the present study, 6% of men with mJSW <3 mm and 14% of women with mJSW <2 mm, which were the threshold values in the present study, had knee pain. In addition, our previous study showed that 10% of men without knee OA and 20% of women without knee OA had knee pain[4]. These subjects have knee pain, despite having no radiographical changes. This indicates that at least 10% and 20% of knee pain in men and women, respectively, may be explained by factors other than radiographical changes.

In the present study, sex differences were found in the association of mJSW with pain. These discrepancies between the sexes are explained by several factors. First, women are more susceptible to pain than men[4]. In fact, our previous study showed that the OR for knee pain in women without radiographic knee OA (KL = 0/1) was greater than that in men without radiographic knee OA[4]. In the present study, the prevalence of knee pain was 5–6% in men with mJSW ≥4 mm, while it was 7–9% in women with mJSW ≥4 mm. This high prevalence of knee pain in women with mJSW ≥4 mm, which are reference data, may partly explain the lower OR for knee pain in women than men. Second, men with normal knees had wider joint space widths than women with normal knees. Our previous study showed that mean mJSW in men with KL = 0 was approximately 4 mm, while that in women with KL = 0 was approximately 3 mm[25]. This means that subjects with mJSW = 3 mm have a normal knee in women, while they have joint space narrowing at the knee in men. In addition, mJSW = 1 mm means 75% cartilage loss in men, while it represent 67% cartilage loss in women. In fact, the associations of medial mJSW/lateral mJSW with pain were similar in men and women, which may also explain the lower OR for knee pain in women than men.

Obesity is one of the few established risk factors for knee OA and pain[17–23]. A clinical review article reported that 69% of knee replacements in middle-aged females can be attributed to obesity[22], and it has been estimated that, if overweight and obese individuals reduced their weight to reach normal BMIs, about 50% of knee OA cases would be eliminated[21]. However, to the best of our knowledge, there are no population-based studies that assess the effect of obesity on the association of joint space narrowing with pain. In the present study, a distinct effect of BMI was found on the association of mJSW with pain. For example, at the right knee in women, mJSW ≥1–<2 mm in women with BMI ≥23 kg/m^2 was significantly associated with pain, while mJSW ≥1–<2 mm in women with BMI <23 kg/m^2 was not, compared to mJSW≥4 mm with BMI <23 kg/m^2. In addition, the OR was similar between mJSW ≥1–<2 mm with BMI ≥23 kg/m^2 and mJSW <1 mm with BMI <23 kg/m^2. These indicate that weight loss may be an effective way to reduce knee pain even when joint space narrowing is present at the knee.

There are limitations in the present study. First, this was a large-scale, population-based, cross-sectional study of baseline data. Thus, causal relationships could not be determined. The ROAD study is a longitudinal survey, so further progress may help elucidate any causal relationships. Second, the threshold in the present study was calculated by a particular statistical method, but certain situations may favor sensitivity over specificity, e.g., screening. In addition, the sensitivity and specificity were modest in the present study. These may be partly explained by the fact that knee pain can arise from a variety of structures other than joint cartilage, such as menisci, synovium, ligaments, bursae, bone, and bone marrow[26–30], which are unable to be assessed radiologically. However, using the KOACAD system, it was possible to demonstrate strong associations of mJSW with knee pain and to establish the threshold of mJSW for knee pain, which may indicate that mJSW is more useful than categorical methods for diagnosing knee OA. Third, cases with lateral knee OA were excluded, leading to a selective sample. One reason for excluding lateral knee OA is that most knee OA in Japan is medial type. There are racial differences in the ratio of lateral to medial knee OA, and previous studies showed that the ratio of lateral to medial knee OA was 0.20 in Caucasian and 0.64 in Chinese populations[37]. In the Amsterdam OA Cohort, lateral knee OA is rather common, and it occurs in association with OA features in other knee compartments[38]. However, our previous study showed that the ratio of lateral to medial knee OA was 0.10 in Japan, which indicates that knee OA was medial type. The other reason for excluding lateral knee OA is that medial and lateral knee OA have distinct characteristics, because, in medial knee OA, there is narrowing of the medial mJSW, while in lateral knee OA, there is narrowing of the lateral mJSW. Thus, the effect of medial mJSW on pain may be obscured by lateral knee OA, because medial joint space width may not change or be larger in lateral knee OA. Thus, the aim of the present study was to clarify the effect of medial knee OA on pain, although excluding lateral OA leads to a selective sample. Lastly, it was not possible to clarify whether the threshold in the present study can apply to other races or populations, because the prevalence of knee OA and the ratio of medial knee OA/lateral knee OA are quite different among races[4,37,38], and the association of knee OA with pain among them may be quite different. To clarify this, international collaborative studies using the KOACAD system are needed.

In conclusion, the present cross-sectional study using a large population from the ROAD study showed that joint space narrowing was strongly associated with knee pain. The threshold of mJSW with knee pain was approximately 3 mm in men and 2 mm

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in women, while the threshold of medial mJSW/lateral mJSW was approximately 60% in both men and women. BMI was found to have a distinct effect on the association of mJSW with pain. Further studies, along with continued longitudinal surveys in the ROAD study, will help improve our understanding of the mechanisms of joint space narrowing at the knee and their relationship with pain.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.joca.2015.01.011.

Author contributions

All authors have made substantial contributions to all three of the following sections:

(1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data;
(2) drafting the article or revising it critically for important intellectual content; and
(3) final approval of the version to be submitted.

Conflicts of interest

There are no conflicts of interest.

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ORIGINAL ARTICLE

Incidence of disability and its associated factors in Japanese men and women: the Longitudinal Cohorts of Motor System Organ (LOCOMO) study

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Abstract We investigated the incidence of disability and its risk factors in older Japanese adults to establish an evidence-based disability prevention strategy for this population. For this purpose, we used data from the Longitudinal Cohorts of Motor System Organ (LOCOMO) study, initiated in 2008 to integrate information from cohorts in nine communities across Japan: Tokyo (two regions), Wakayama (two regions), Hiroshima, Niigata, Mie, Akita, and Gunma prefectures. We examined the annual occurrence of disability from 8,454 individuals (2,705 men and 5,749 women) aged ≥65 years. The estimated incidence of disability was 3.58/100 person-years (p-y) (men: 3.17/100 p-y; women: 3.78/100 p-y). To determine factors associated with disability, Cox's proportional hazard model was used, with the occurrence of disability as an objective variable and age (+1 year), gender (vs. women), body build (0: normal/overweight range, BMI 18.5–27.5 kg/m^2; 1: emaciation, BMI <18.5 kg/m^2; 2: obesity, BMI >27.5 kg/m^2), and regional differences (0: rural areas including Wakayama, Niigata, Mie, Akita, and Gunma vs. 1: urban areas including Tokyo and Hiroshima) as explanatory variables. Age, body build, and regional difference significantly influenced the occurrence of disability (age, +1 year: hazard ratio 1.13, 95 % confidence interval 1.12–1.15, $p < 0.001$; body build, vs. emaciation: 1.24, 1.01–1.53, $p = 0.041$; body build, vs. obesity: 1.36, 1.08–1.71, $p = 0.009$; residence, vs. living in rural areas: 1.59, 1.37–1.85, $p < 0.001$). We concluded that higher age,

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both emaciation and obesity, and living in rural areas would be risk factors for the occurrence of disability.

Keywords Nation-wide population-based cohort study · Epidemiology · Incidence · Disability · Body build

Introduction

In Japan, the proportion of the population aged 65 years or older has increased rapidly over the years. In 1950, 1985, 2005, and 2010, this proportion was 4.9, 10.3, 19.9, and 23.0 %, respectively [1]. Further, this proportion is estimated to reach 30.1 % in 2024 and 39.0 % in 2051 [2]. The rapid aging of Japanese society, unprecedented in world history, has led to an increase in the number of disabled elderly individuals requiring support or long-term care. The Japanese government initiated the national long-term care insurance system in April 2000 in adherence with the Long-Term Care Insurance Act [3]. The aim of the national long-term care insurance system was to certify the level of care needed by elderly adults and to provide suitable care services to them according to the levels of their long-term care needs. According to the recent National Livelihood Survey by the Ministry of Health, Labour and Welfare in Japan, the number of elderly individuals certified as needing care services increases annually, having reached 5 million in 2011 [4].

However, few prospective, longitudinal, and cross-national studies have been carried out to inform the development of a prevention strategy against disability. To establish evidence-based prevention strategies, it is critically important to accumulate epidemiologic evidence, including the incidence of disability, and identify its risk factors. However, few studies have attempted to estimate the incidence of the disability and its risk factors by using population-based cohorts. In addition, to identify the incidence of disability, a study should have a large number of subjects. Further, to determine regional differences in epidemiological indices, a survey of cohorts across Japan is required.

The Longitudinal Cohorts of Motor System Organ (LOCOMO) study was initiated in 2008, through a grant from Japan's Ministry of Health, Labour and Welfare, for the prevention of knee pain, back pain, bone fractures, and subsequent disability. It aimed to integrate data gathered from cohorts from 2000 onwards and follow-up surveys from 2006 onwards, using a unified questionnaire, with an ultimate goal being the prevention of musculoskeletal diseases. The present study specifically aims at using LOCOMO data, which is based on the long-term care insurance system, to investigate the occurrence of disability in order to clarify its incidence and risk factors, especially in terms of body build and regional differences.

Materials and methods

Participants were residents of nine communities located in Tokyo (two regions: Tokyo-1, principal investigators (PIs): Shigeyuki Muraki, Toru Akune, Noriko Yoshimura, Kozo Nakamura; Tokyo-2, PIs: Yoko Shimizu, Hideyo Yoshida, Takao Suzuki), Wakayama [two regions: Wakayama-1 (mountainous region) and Wakayama-2 (coastal region), PIs: Noriko Yoshimura, Munehito Yoshida], Hiroshima (PI: Saeko Fujiwara), Niigata (PI: Go Omori), Mie (PI: Akihiro Sudo), Akita (PI: Hideyo Yoshida), and Gunma (PI: Yuji Nishiwaki) prefectures [5]. Figure 1 shows the location of each cohort in Japan.

Disability in the present study was defined as 'cases requiring long-term care', as determined by the long-term care insurance system. The procedure for identifying these cases is as follows: (1) each municipality establishes a long-term care approval board consisting of clinical experts, physicians, and specialists at the Division of Health and Welfare in each municipal office; (2) The long-term care approval board investigates the insured person by using an interviewer-administered questionnaire consisting of 82 items regarding mental and physical conditions, and makes a screening judgement based on the opinion of a regular doctor; (3) 'Cases requiring long-term care' are determined according to standards for long-term care certification that are uniformly and objectively applied nationwide [6].

In order to identify the incidence of disability, data were collected from participants aged 65 years and older within the above-mentioned cohorts. In Japan, most individuals certified as 'cases requiring long-term care' are 65 years and older. Table 1 shows the number of subjects per region, as well as the data obtained within the first year of the observation. The smallest cohort consisted of 239 subjects, residing in Mie, while the largest consisted of 1,758, who resided in Gunma.

The earliest baseline data were collected in 2000 in Hiroshima, while the latest were obtained in 2008 in Tokyo-2. The cohorts were subsequently followed until 2012. Data regarding participants' deaths, changes of residence, and occurrence or non-occurrence of certified disability were gathered annually from public health centres of the participating municipalities. As an index of body build, baseline data on participants' height and weight were collected, and used to calculate body mass index (BMI, kg/m^2). Participants were classified as follows: normal or overweight (BMI = 18.5–27.5), obese (BMI >27.5), or emaciated (BMI <18.5). These cut-off points were determined according to a WHO report [7]. From 2008 onwards, follow-up data was obtained using the unified questionnaire.

All participants provided written informed consent, and the study was conducted with the approval of the ethics committees of the University of Tokyo (nos. 1264 and 1326), the Tokyo Metropolitan Institute of Gerontology

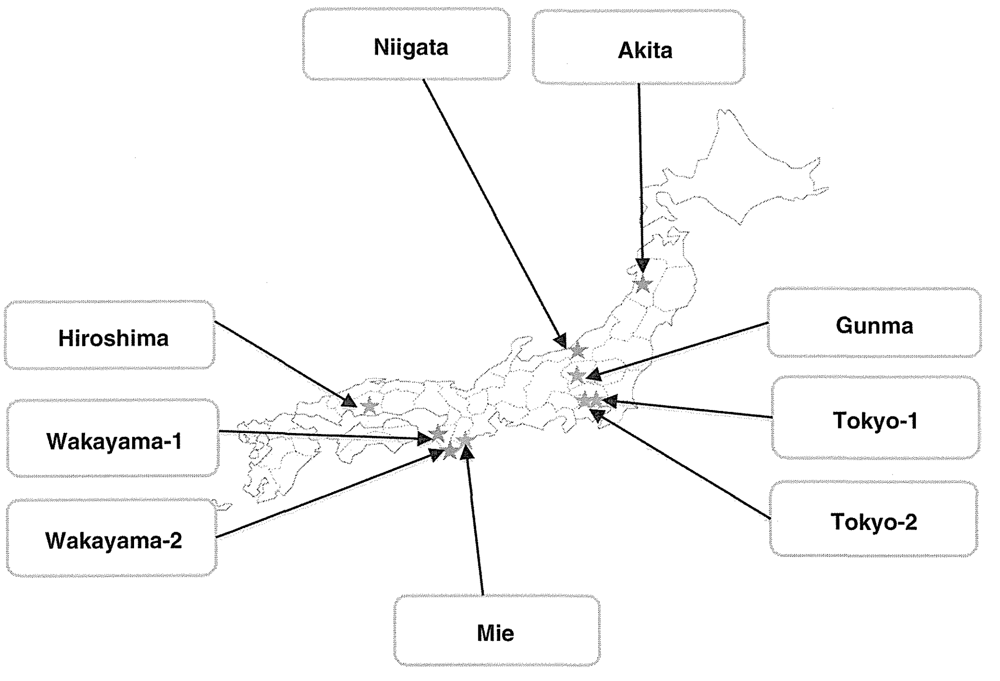

Fig. 1 Location of nine regions from which the study cohorts were selected

Table 1 Number of subjects classified by regions of each cohort

Region	Start year	Total	Men	Women
Tokyo-1	2005	1,332	461	871
Tokyo-2	2008	1,453	59	1,394
Wakayama-1 (Mountainous)	2005	610	239	371
Wakayama-2 (Coastal)	2006	357	129	228
Hiroshima	2000	1,341	351	990
Niigata	2007	805	343	462
Mie	2001	239	95	144
Akita	2006	559	223	336
Gunma	2005	1,758	805	953
Total		8,454	2,705	5,749

(no. 5), Wakayama (no. 373), the Radiation Effects Research Foundation (RP 03-89), Niigata University (no. 446), Mie University (nos. 837 and 139), Keio University (no. 16–20), and the National Center for Geriatrics and Gerontology (no. 249). Careful consideration was given to ensure the safety of the participants during all of the study procedures.

Statistical analysis

All statistical analyses were performed using STATA (STATA Corp., College Station, Texas, USA). Differences in proportions were compared using the chi-squared test. Differences in continuous variables were tested using an analysis of variance (ANOVA) with Scheffe's least significant difference test for post-hoc pairwise comparisons. To test the association between the occurrence of disability and other variables, Cox's proportional hazard regression analysis was used. Hazard ratios (HRs) were estimated using the occurrence of disability as an objective variable (0: non-occurrence, 1: occurrence) and the following explanatory variables: age (±1 year), gender (vs. female), body build (0: normal and overweight vs. 1: emaciation vs. 2: obesity), and regional differences (0: rural areas, including Wakayama-1, Wakayama-2, Niigata, Mie, Akita, and Gunma vs. 1: urban areas, including Tokyo-1, Tokyo-2, and Hiroshima). All p values and 95 % confidence intervals (CI) of two-sided analyses are presented.

Results

Table 2 shows the number of participants classified by age and gender. The majority of participants were 75–79 years old; two-thirds of the participants were women.

Selected characteristics of the study population, including age, height, weight, and BMI, are shown in Table 3. The mean values of age, height, and weight were significantly greater in women than in men ($p < 0.001$), but BMI did not significantly differ between men and women ($p = 0.479$).

The estimated incidence of disability is shown in Fig. 2. In total, the incidence of disability among individuals aged 65 years and older was 3.58/100 person-years (p-y) (p-y; men: 3.17/100 p-y; women: 3.78/100 p-y). The incidence of disability was 0.83/100 p-y, 1.70/100 p-y, 3.00/100 p-y,

Table 2 Number of subjects classified by age and gender

Age strata (years)	Total (%)	Men (%)	Women (%)
65–69	1,390 (16.4)	555 (20.5)	835 (14.5)
70–74	1,704 (20.2)	668 (24.7)	1,036 (18.0)
75–79	2,923 (34.6)	812 (30.0)	2,111 (36.7)
80–84	1,810 (21.4)	463 (17.1)	1,347 (23.4)
≥85	627 (7.4)	207 (7.7)	420 (7.3)
Total	8,454 (100.0)	2,705 (100.0)	5,749 (100.0)

Table 3 Baseline characteristics of subjects classified by age and gender

Variables	Men	Women	*p* (men vs. women)
Age (years)	75.3 (6.4)	76.5 (6.0)	<0.001
Height (cm)	160.5 (6.5)	147.7 (6.1)	<0.001
Weight (kg)	58.7 (9.1)	49.8 (8.4)	<0.001
BMI (kg/m^2)	22.7 (2.9)	22.8 (3.5)	0.479
Living in rural area (%)	84.8	58.5	<0.001

Values are represented as mean (standard deviation)

BMI body mass index

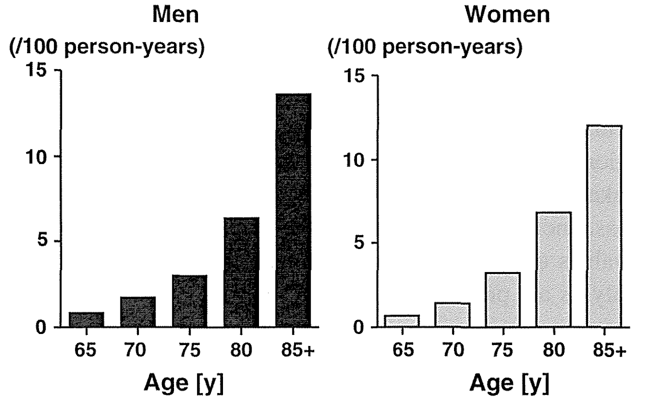

Fig. 2 Incidence of disability according to age and gender

6.36/100 p-y, and 13.54/100 p-y in 65–69-, 70–74-, 75–79-, 80–84-, and ≥85-year-old men, respectively. In women, the incidence of disability was 0.71/100 p-y, 1.40/100 p-y, 3.25/100 p-y, 6.85/100 p-y, and 12.01/100 p-y in the age ranges of 65–69, 70–74, 75–79, 80–84, and 85 or more years, respectively (Table 4).

Cox's proportional hazard regression analysis showed that occurrence of disability was significantly influenced by age, body build, and regional differences, but not gender (age, +1 years: hazard ratio 1.13, 95 % confidence interval 1.12–1.15, $p < 0.001$; sex, vs. female: 1.13, 0.97–1.31, $p = 0.125$; body build: emaciation: 1.24, 1.01–1.53, $p = 0.041$; body build; obesity: 1.36, 1.08–1.71, $p = 0.009$; residence, vs. living in rural areas: 1.59, 1.37–1.85, $p < 0.001$).

Discussion

Using the data of the LOCOMO study, we determined the incidence of disability and identified age, emaciation, obesity, and residence in rural areas as risk factors for the occurrence of disability. More specifically, we integrated data collected from subjects aged 65 and older in individual cohorts established in nine regions across Japan to determine the incidence of disability in the specified regions. We found an association between various risk factors and disability; these include age, emaciation, and obesity, as well as residence in rural areas.

The LOCOMO study was the first nation-wide prospective study to track a large number of the subjects from several population-based cohorts. The LOCOMO study aimed to integrate information from these cohorts, to prevent musculoskeletal diseases and subsequent disability. The data shed light on the prevalence and characteristics of targeted clinical symptoms such as knee pain or lumbar pain, or defined diseases such as knee osteoarthritis (KOA), lumbar spondylosis (LS), and osteoporosis (OP), as well as their prognosis in reference to either mortality or chances of developing a disability. In the present study, we also

Table 4 Hazard ratios (HRs) of potential risk factors for the occurrence and non-occurrence of disability

Disability (occurrence vs. non-occurrence)				
Explanatory variable	Reference	HR	95 % confidence interval	*p*
Age (years)	+1 year	1.13	1.12–1.15	<0.001***
Gender	0: men, 1: women	1.13	0.97–1.31	0.125
Body build	0: 18.5 ≤ BMI ≤ 27.5, 1: BMI < 18.5	1.24	1.01–1.53	0.041*
	0: 18.5 ≤ BMI ≤ 27.5, 2: BMI >27.5	1.36	1.08–1.71	0.009**
Type of residential area	0: urban area, 1: rural area	1.59	1.37–1.85	<0.001***

BMI body mass index

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

compared the above-mentioned symptoms, diseases, and prognoses between regions.

The overall incidence of disability among individuals aged 65 years and older was 3.58/100 person-years. When results from the present study are applied to the total age-sex distribution derived from the Japanese census in 2010 [1], it could be assumed that 1,110,000 people (410,000 men and 700,000 women) aged 65 years and older are newly affected by disability and require support. It has been reported that the total number of subjects who were certified as needing care increases annually [4]; however, few of these reports estimate the number of newly certified cases through a population-based cohort. Clarifying the incidence of disability and its risk factors was viewed as the first step toward preventing its occurrence.

Emaciation and obesity were both identified as risk factors for disability; thus, there appears to be a U-shaped association between BMI and disability as well as between BMI and mortality [8, 9]. According to the recent National Livelihood Survey, the leading cause of disabilities that require support and long-term care is cardiovascular disease (CVD), followed by dementia, senility, osteoarthrosis, and fractures [4]. Obesity is an established risk factor for chronic diseases, including hypertension, dyslipidemia, and diabetes mellitus, which increase the risk for CVD [10]; in turn, CVD causes ADL-related disabilities in older adults. In addition, numerous reports have shown an association between overweight or obesity and KOA [11–17]. In previous reports, we found a significant association between BMI and not only the presence of KOA, but also the occurrence and progression of KOA [18, 19]. In addition, emaciation is an established risk factor for OP and OP-related fractures [20]. OP might be related to low nutrition due to chronic wasting diseases.

The current study also found an association between living in a rural area and the occurrence of disability. There have been reports of regional differences in the certification rate of disability in Japan. For instance, Kobayashi reported a prefectural difference in the certification rate of disability, which was particularly prominent among individuals aged 75 years and older at lower nursing care levels in the long-term care insurance system [21]. In addition, Shimizutani et al. [22] pointed out that the financial condition of the insurer influenced the certification rate of disability. Further, Nakamura found that the certification of lower care levels was influenced by social and/or individual factors, such as the type of service provider, the application rate, and number of medical treatment recipients. However, certification of advanced nursing care levels was influenced by CVD and lifestyle-related diseases [23].

Other than differences in the social backgrounds of individuals in each prefecture, we posited that regional differences (rural or urban) in the occurrence of disability might be due to differences in the frequency of diseases and ailments that cause disability in each area. The prevalence of musculoskeletal diseases, such as KOA and LS, differs among mountainous, coastal, and urban areas [24]. Evidence also exists for regional differences in the incidence of hip fractures [25–27]. It was also found that mortality and incidence of ischemic stroke, which is related to CVD, was higher in the northeastern than in the southwestern part of Japan [28]. However, there is currently no information on regional differences in dementia prevalence and incidence in Japan. In general, differences in the frequency of diseases causing disability might influence regional differences in disability rates. In relation to this, in a future study on follow-up data from the LOCOMO study, it might be necessary to collect information on the prevalence and frequency of diseases that cause disability, such as musculoskeletal diseases, CVD, and dementia. This future study should also attempt to clarify mutual associations among risk factors for disability, so as to inform the development of measures for its primary prevention.

Despite its contribution to existing knowledge, the present study has several limitations. First, its sample does not truly represent the entire Japanese population, because our cohorts were not drawn from the northernmost and southernmost parts of Japan (e.g., Okinawa prefecture or Hokkaido prefecture). This limitation must be taken into consideration, especially when determining the generalisability of the results. However, the LOCOMO study is the first large-scale, population-based prospective study with approximately 9,000 participants aged 65 years and older. Second, data collected from the cohorts were not uniform, as certain information was obtained from some participants, but not others. For example, the X-ray examinations of subjects' knees were performed in Tokyo-1, Wakayama-1, Wakayama-2, Niigata, and Mie; lumbar spine X-ray examinations were performed in Tokyo-1, Wakayama-1, Wakayama-2, Hiroshima, and Mie. Therefore, we could not evaluate the presence or absence of KOA, LS, or OP as a possible cause of disability by using the data of the entire LOCOMO study. Further investigation following the integration of information on musculoskeletal disorders would enable us to evaluate all the factors that are associated with disability.

Nevertheless, our study has several strengths. As mentioned above, the large sample size is the study's biggest strength. The second strength is that we collected data from nine cohorts across Japan, which enabled us to compare regional differences in the incidence of disability. In addition, the variety of measures and assessments used in this study enabled us to collect a substantial amount of detailed information. However, given the fact that not all of the measures were administered in all cohorts, regional selection bias in the analysis should be considered when interpreting the results.

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Conflict of interest All authors declare no conflicts of interest.

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ORIGINAL ARTICLE

Does osteophytosis at the knee predict health-related quality of life decline? A 3-year follow-up of the ROAD study

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Abstract The objective of the present longitudinal study was to clarify whether osteophytosis and joint space narrowing predict quality of life (QOL) decline using a longitudinal population-based cohort of the Research on Osteoarthritis/osteoporosis Against Disability (ROAD) study. The present study analyzed 1,525 participants who completed the radiographic examination at baseline and questionnaires regarding QOL at a 3-year follow-up (546 men and 979 women; mean age, 67.0±11.0 years). This study examined the associations of osteophyte area (OPA) and minimum joint space width (mJSW) in the medial compartment of the knee at baseline with pain and physical functional disability measured by the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). OPA and mJSW in the medial compartment of the knee were measured using a knee osteoarthritis (OA) computer-aided diagnosis system. Overall, OPA independently predicted physical functional disability after 3 years of follow-up. When analyzed in men and women separately, OPA, rather than mJSW, was an independent predictor for pain and physical functional disability after 3 years of follow-up in men. OPA, rather than mJSW, also predicted worsening of pain in men during the 3-year follow-up, whereas in women, mJSW, rather than OPA, predicted worsening of pain. In conclusion, the present longitudinal study using a large-scale population from the ROAD study found gender differences in the association of osteophytosis and joint space narrowing with pain and physical functional disability.

Keywords Epidemiology · Longitudinal Studies · Osteoarthritis · Pain · WOMAC

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Introduction

Knee osteoarthritis (OA) is a major public health issue causing chronic pain and disability [1–3]. The prevalence of radiographically confirmed knee OA is high in Japan [4], with 25,300,000 persons aged 40 years and older estimated to experience radiographic knee OA [5]. According to the recent Japanese National Livelihood Survey of the Ministry of Health, Labour and Welfare, osteoarthritis is ranked fourth among diseases that cause disabilities that subsequently require support with activities of daily living [6].

The principal clinical symptoms of knee OA are pain and physical functional disability [7], but the correlation of these symptoms with radiographic severity of knee OA is controversial [4, 8–10]. In terms of disease-specific scales for estimating pain and physical functional disability due to knee OA, the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) has been used for Caucasians [11] and Asians [12, 13], although these reports were not population-based studies. Furthermore, there is little information on the impact of knee OA on incident pain and physical functional disability using WOMAC in Japan, although reports from a population survey suggest that the disease pattern differs among races [14–16].

Knee OA is characterized by the pathological features of osteophytosis and joint space narrowing, but there is controversy regarding the importance of osteophytes. Nevertheless, hand and hip joint researchers and clinicians have argued that separate radiographic features should be recorded and may be more meaningful than overall composite scores such as the Kellgren-Lawrence (KL) scale [17]. Furthermore, a previous study showed that osteophytes performed better as a primary diagnostic feature than joint space narrowing in cross-sectional knee OA epidemiologic studies [18]. However, most conventional systems for grading radiographic severity have been categorical grades, such as KL grading [19], which is unable to assess osteophytosis and joint space narrowing individually. Several studies have shown that knee OA had a strong effect on quality of life (QOL) [13, 20–22], but in these studies, knee OA was defined by categorical grades such as KL score or American College of Rheumatology grade, total knee arthroplasty, and self-administered questionnaires. In addition, osteophytosis and joint space narrowing were separately evaluated using a radiographic atlas of individual features published by the Osteoarthritis Research Society International in 1995 [23] and revised in 2007 [24]. However, the grading is still limited in reproducibility and sensitivity due to the subjective judgment of individual observers and the categorical classification into four grade scales (0–3). To overcome this problem, osteophyte area (OPA) or joint space width should be evaluated using a fully automatic system [25].

The objective of this study was to clarify whether osteophytosis and joint space narrowing at the knee independently predict decline of QOL measured by WOMAC pain and physical function score during a 3-year follow-up among Japanese men and women using a fully automatic system to measure OPA and joint space width in the longitudinal, population-based cohort from the Research on Osteoarthritis/osteoporosis Against Disability (ROAD) study.

Materials and methods

Study sample The ROAD study is a nationwide prospective study designed to establish epidemiologic indices for the evaluation of clinical evidence to allow for the development of disease-modifying treatments for bone and joint disorders (with OA and osteoporosis as the representative bone and joint diseases). The ROAD study consists of population-based cohorts in several Japanese communities. A detailed profile of the ROAD study has been published previously [4, 5, 26]; therefore, only a brief summary is provided here. To date, the ROAD study has completed the creation of a baseline database including clinical and genetic information for 3,040 inhabitants (1,061 men and 1,979 women) ranging in age from 23 to 95 years (mean, 70.6 years). Participants were recruited from resident registration listings in three communities: an urban region in Itabashi, Tokyo; a mountainous region in Hidakagawa, Wakayama; and a seacoast region in Taiji, Wakayama. All participants provided written informed consent, and the study was conducted with the approval of the ethics committees of the University of Tokyo and the Tokyo Metropolitan Institute of Gerontology. Anthropometric measurements, including height and weight and body mass index (BMI) (weight [kg]/height^2 [m^2]), were calculated. Grip strength was measured on bilateral sides using a TOEI LIGHT handgrip dynamometer (TOEI LIGHT CO., LTD, Saitama, Japan), and the better measurement was used to characterize maximum muscle strength.

Radiographic assessment All participants underwent radiographic examination of both knees using an anterior-posterior view with weight-bearing and foot map positioning by experienced radiological technologists. The beam was positioned parallel to the floor with no angle and aimed at the joint space. We used fluoroscopic guidance with an anterior-posterior X-ray beam to properly visualize the joint space and to centralize the patella over the lower end of the femur. The images were downloaded into Digital Imaging and Communication in Medicine (DICOM) format files. A single experienced orthopedist (S.M.) read the knee radiographs without knowledge of participant clinical status using the KL radiographic atlas for overall knee radiographic grades [19]. Knee OA was defined as KL ≥2. Medial compartment minimum joint space width (mJSW) and medial tibial OPA were measured with the knee osteoarthritis computer-aided diagnosis (KOACAD) system bilaterally. The knee with the least mJSW was defined as the designated knee for each participant. The KOACAD system has been previously described in detail [25, 27, 28]. The KOACAD system is a fully automatic system capable of quantifying the major features of knee OA on standard radiographs. This system allows for objective, accurate, and simple assessment of the structural severity of knee OA in general clinical practice. The KOACAD system was programmed to measure OPA at the medial tibia and mJSW in the medial and lateral compartments using digitized knee radiographs. The KOACAD system was applied to the DICOM data by the experienced orthopedist who developed this system (H.O.), and there is strong reliability for this measurement [25]. Reference values for OPA and mJSW by gender and age strata in Japan using the KOACAD system have been published previously [28]. Lateral OA was defined as being present when a knee had a KL grade ≥2 [19] and lateral joint space narrowing score ≥1 on a 0–3 scale according to the Osteoarthritis Research Society International atlas [24].

Instruments All 3,040 subjects were invited to attend a follow-up interview between 2008 and 2010. We used the WOMAC at the follow-up study to evaluate QOL. The WOMAC is a 24-item OA-specific index consisting of three domains: pain, stiffness, and physical function. Each of these 24 items is graded on either a 5-point Likert scale or a 100-mm visual analog scale [11, 29]. The Likert scale (version LK 3.0) was used in the present study. The domain score ranges from 0 to 20 for pain, 0 to 8 for stiffness, and 0 to 68 for physical function. Japanese versions of the WOMAC have also been validated [30].

Statistical analysis Differences in age, height, weight, BMI, grip strength, OPA, mJSW, and WOMAC scores between men and women were examined using a non-paired student *t* test. The associations of mJSW and OPA with pain and physical functional disability after 3 years were determined by using multiple regression analysis after adjustment for age, BMI, gender, grip strength, and pain score at baseline; after adjustment for age, BMI, gender, grip strength, and physical function score at baseline, respectively, in the overall population; and after adjustment for age, BMI, grip strength, and pain score at baseline and after adjustment for age, BMI, grip strength, and physical function score at baseline, respectively, in men and women. In addition, to determine the independent association of OPA and mJSW with pain and physical function scores, multiple regression analysis was used with age, BMI, gender, grip strength, pain score at baseline, OPA, and mJSW and with age, BMI, gender, grip strength, physical function score at baseline, OPA, and mJSW, respectively, as explanatory variables in the overall population, and with age, BMI, grip strength, pain score at baseline, OPA, and mJSW and with age, BMI, grip strength, physical function score at baseline, OPA, and mJSW, respectively, as explanatory variables in men and women. We classified men and women separately into three groups based on grip strength: <20, ≥20 to <30, and ≥30 and examined the associations of BMI, OPA, and mJSW with pain, using multiple regression analysis with age, BMI, OPA, mJSW, and pain score at baseline as explanatory variables. We also calculated changes of scores as follows: "scores at follow-up−scores at baseline" and determined the association of OPA and mJSW with changes of pain and physical function scores after adjustment for age, BMI, gender, grip strength, and pain score at baseline; after adjustment for age, BMI, gender, grip strength, and physical function score at baseline, respectively, in the overall population; and after adjustment for age, BMI, grip strength, and pain score at baseline and after adjustment for age, BMI, grip strength, and physical function score at baseline, respectively, in men and women. In addition, to determine independent associations of OPA and mJSW with changes of pain and physical function scores, multiple regression analysis was used with age, BMI, gender, grip strength, pain score at baseline, OPA, and mJSW and with age, BMI, gender, grip strength, physical function score at baseline, OPA, and mJSW, respectively, as explanatory variables in the overall population and with age, BMI, grip strength, pain score at baseline, OPA, and mJSW and with age, BMI, grip strength, physical function score at baseline, OPA, and mJSW, respectively, as explanatory variables in men and women. Data analyses were performed using SAS version 9.0 (SAS Institute Inc., Cary, NC).

Results

Of the 3,040 subjects in the baseline study in 2005–2007, 125 had died by the time of the review 3 years later, 123 did not participate in the follow-up study due to bad health, 69 had moved away, 83 declined the invitation to attend the follow-up study, and 155 did not participate in the follow-up study for other reasons. Among the 2,485 subjects who did participate in the follow-up study, we excluded 39 subjects younger than 40 years at baseline. Those participating in the follow-up study were younger than those who did not survive or who did not participate for other reasons (responders 68.6 years, non-responders 75.1 years; $P<0.0001$). The follow-up study participants also were significantly more likely to be women (responders 66.3 % women, non-responders 61.8 % women; $P=0.03$) and were significantly more likely to have knee OA at the baseline examination than either those who did not survive to follow-up or those who did not participate for other reasons (responders 51.5 %, non-responders 60.9 %; $P<0.0001$). Among them, 1,578 subjects provided complete questionnaires of WOMAC both at baseline and follow-up. We excluded 3 subjects who did not undergo plain radiography at the knee and 17 subjects who underwent total knee arthroplasty before the follow-up study. We also excluded 12 subjects whose X-rays were too obscure to measure mJSW and OPA and 21 subjects who had lateral knee OA, leaving a total of 1,525 subjects (546 men and 979 women). The mean duration between baseline and follow-up was 3.3±0.6 years.

Characteristics of the 1,525 participants in the present study are shown in Table 1. BMI was higher in men than women. The prevalence of knee OA was significantly higher in women than men. The OPA was significantly larger and mJSW was significantly narrower in women than men. The WOMAC pain score was similar in men and women, whereas the WOMAC physical function score was worse in women than men, both at baseline and follow-up.

Table 1 Characteristics of subjects

	Overall	Men	Women	p value
N	1,525	546	979	
Age (years)	67.0±11.0	68.2±10.7	66.3±11.1	0.001
Height (cm)	155.3±8.8	163.3±6.4	150.8±6.4	<0.0001
Weight (kg)	55.5±10.4	62.2±10.3	51.8±8.5	<0.0001
BMI (kg/m^2)	22.9±3.3	23.3±3.1	22.7±3.3	0.0027
Grip strength (kg)	27.2±9.4	35.4±8.7	22.7±6.4	<0.0001
Knee OA (%)	48.8	38.5	54.5	<0.0001
OPA (mm^2)	3.56±8.43	1.79±5.47	4.54±9.56	<0.0001
mJSW (mm)	2.67±0.94	2.99±0.88	2.50±0.92	<0.0001
WOMAC at baseline				
Pain	1.13±2.20	1.03±2.06	1.18±2.27	0.1753
Physical function	3.05±6.68	2.59±5.74	3.30±7.14	0.0328
WOMAC at follow-up				
Pain	1.82±2.81	1.74±2.69	1.87±2.88	0.3881
Physical function	5.56±9.61	4.79±8.34	5.99±10.22	0.0137

Knee OA was defined as Kellgren-Lawrence grade ≥2 at baseline; except where otherwise indicated, the values at baseline was shown

BMI body mass index, *OA* osteoarthritis, *OPA* osteophyte area, *mJSW* minimum joint space width, *WOMAC* Western Ontario and McMaster Universities Osteoarthritis Index

First, we analyzed the associations of age, BMI, and grip strength with WOMAC pain and physical function scores in men and women (Table 2). Age and grip strength were significantly associated with pain and physical function in men and women, while BMI was significantly associated with pain and physical function in women, but not in men.

Multiple regression analysis after adjustment for age, BMI, grip strength, and pain score at baseline showed that, overall, OPA and mJSW were significant predictors for pain (Table 3). To assess whether OPA and mJSW independently predicted pain, we used multiple regression analysis with age, BMI, grip strength, pain score at baseline, OPA, and mJSW as explanatory variables and found that the association of OPA with pain score after 3 years disappeared, whereas mJSW was an independent predictor for pain after 3 years. When analyzed in men and women, separately, OPA was an independent predictor for pain in men, but mJSW was not. In women, mJSW was an independent predictor for pain, but OPA was not.

In terms of physical function, multiple regression analysis after adjustment for age, BMI, grip strength, and physical function score at baseline showed that OPA and mJSW were significant predictors for physical functional disability (Table 4). To assess whether OPA and mJSW independently predicted physical functional disability, we used multiple regression analysis with age, BMI, grip strength, physical function score at baseline, OPA, and mJSW as explanatory variables and found that OPA and mJSW were independent predictors for physical functional disability. When analyzed in men and women separately, OPA was an independent predictor for physical functional disability in men, but mJSW was not. In women, mJSW was an independent predictor for physical functional disability, but OPA was not.

To clarify the association of OPA, mJSW, and BMI with pain according to muscle strength, men and women were separated into three groups based on grip strength: <20, ≥20 to <30, and ≥30 and the associations of BMI, OPA, and mJSW with pain were examined, using multiple regression analysis with age, BMI, OPA, mJSW, and pain score at baseline as explanatory variables (Supplementary Table 1). In women with grip strength <20, mJSW was significantly associated with pain and BMI tended to be associated with pain, but OPA was not. In men with grip strength <20, BMI, OPA, and mJSW were not significantly associated with pain, likely because only nine men had a grip strength <20. In women with grip strength ≥20 to <30, mJSW and BMI was significantly associated with pain, while OPA was not. In men with grip strength ≥20 to <30, BMI was significantly associated with pain, while OPA and mJSW were not. In men and women with grip strength >30, OPA was significantly associated with pain, while mJSW and BMI were not. We also

Table 2 Effect of age, BMI, and grip strength at baseline on WOMAC pain and physical function scores after 3 years

	Pain		Physical function	
	Regression coefficient (95 % CI)	P value	Regression coefficient (95 % CI)	P value
Men				
Age (years)	0.05 (0.03 to 0.07)	<0.0001	0.23 (0.17 to 0.29)	<0.0001
BMI (kg/m^2)	0.05 (−0.02 to 0.12)	0.1616	0.17 (−0.06 to 0.39)	0.1459
Grip strength (kg)	−0.05 (−0.07 to −0.02)	0.0003	−0.26 (−0.34 to −0.19)	<0.0001
Women				
Age (years)	0.06 (0.05 to 0.08)	<0.0001	0.33 (0.28 to 0.39)	<0.0001
BMI (kg/m^2)	0.20 (0.14 to 0.25)	<0.0001	0.66 (0.47 to 0.85)	<0.0001
Grip strength (kg)	−0.10 (−0.12 to −0.07)	<0.0001	−0.44 (−0.54 to −0.35)	<0.0001

WOMAC Western Ontario and McMaster Universities Osteoarthritis Index, *CI* confidence interval, *BMI* body mass index

Table 3 Effect of OPA and mJSW at baseline on WOMAC pain scores after 3 years

	Crude regression coefficient[b] (95 % CI)	P value	Adjusted regression coefficient[a] (95 % CI)	*P* value	Adjusted regression coefficient[b] (95 % CI)	*P* value	Standardized beta
Overall							
OPA (mm^2)	0.08 (0.06 to 0.09)	<0.0001	0.02 (0.006 to 0.04)	0.0051	0.01 (−0.003 to 0.03)	0.1036	0.04
mJSW (mm)	−0.76 (−0.90 to −0.61)	<0.0001	−0.30 (−0.44 to −0.16)	<0.0001	−0.26 (−0.41 to −0.12)	0.0005	−0.09
Men							
OPA (mm^2)	0.09 (0.04 to 0.13)	<0.0001	0.05 (0.01 to 0.08)	0.0078	0.05 (0.01 to 0.09)	0.0127	0.1
mJSW (mm)	−0.45 (−0.71 to −0.20)	0.0005	−0.11 (−0.33 to 0.12)	0.3466	0.02 (−0.22 to 0.27)	0.8574	0.007
Women							
OPA (mm^2)	0.08 (0.06 to 0.09)	<0.0001	0.02 (−0.0008 to 0.03)	0.0623	0.006 (−0.01 to 0.02)	0.4789	0.02
mJSW (mm)	−0.96 (−1.15 to −0.78)	<0.0001	−0.41 (−0.58 to −0.23)	<0.0001	−0.39 (−0.57 to −0.20)	<0.0001	−0.12

WOMAC Western Ontario and McMaster Universities Osteoarthritis Index, *CI* confidence interval, *OPA* osteophyte area, *mJSW* minimum joint space width

[a] Adjusted regression coefficients for pain scores were calculated by multiple regression analysis after adjustment for age, BMI, gender, grip strength, and pain score at baseline in the overall population and after adjustment for age, BMI, grip strength, and pain score at baseline in men and women

[b] Adjusted regression coefficients for pain scores were calculated by multiple regression analysis with age, BMI, gender, grip strength, pain score at baseline, OPA, and mJSW as explanatory variables in the overall population and with age, BMI, grip strength, pain score at baseline, OPA, and mJSW as explanatory variables in men and women

examined the association of OPA, mJSW, and BMI with physical function disability according to muscle strength (Supplementary Table 2). Results were similar to findings for pain.

To examine whether OPA and mJSW predicted worsening of pain during the 3-year follow-up, we calculated differences of the WOMAC pain scores between baseline and follow-up (Table 5). In the overall population, mJSW was a significant predictor for worsening of pain after adjustment for age, BMI, gender, and pain score at baseline, whereas OPA was not. When analyzed in men and women separately, OPA was a significant predictor for worsening of pain in men, whereas mJSW was a significant predictor for worsening of pain in women.

We also examined whether OPA and mJSW predicted worsening of physical functional disability during the 3-year follow-up (Table 6). In the overall population, OPA and mJSW were significant predictors for worsening of physical functional disability after adjustment for age, BMI, gender, grip strength, and physical function score at baseline. To

Table 4 Effect of OPA and mJSW at baseline on WOMAC physical function scores after 3 years

	Crude regression coefficient[b] (95 % CI)	*P* value	Adjusted regression coefficient[a] (95 % CI)	*P* value	Adjusted regression coefficient[b] (95 % CI)	*P* value	Standardized beta
Overall							
OPA (mm^2)	0.34 (0.29 to 0.40)	<0.0001	0.09 (0.04 to 0.14)	0.0002	0.05 (0.0004 to 0.10)	0.0480	0.04
mJSW (mm)	−3.24 (−3.73 to −2.75)	<0.0001	−1.36 (−1.80 to −0.92)	<0.0001	−1.22 (−1.68 to −0.76)	<0.0001	−0.12
Men							
OPA (mm^2)	0.35 (0.23 to 0.48)	<0.0001	0.19 (0.08 to 0.30)	0.0008	0.14 (0.02 to 0.26)	0.0204	0.09
mJSW (mm)	−2.21 (−2.99 to −1.44)	<0.0001	−1.07 (−1.77 to −0.37)	0.0027	−0.69 (−1.46 to 0.07)	0.0758	−0.07
Women							
OPA (mm^2)	0.34 (0.27 to 0.40)	<0.0001	0.06 (0.009 to 0.12)	0.0225	0.03 (−0.03 to 0.08)	0.3305	0.03
mJSW (mm)	−3.86 (−4.51 to −3.20)	<0.0001	−1.49 (−2.05 to −0.92)	<0.0001	−1.41 (−2.00 to −0.82)	<0.0001	−0.13

WOMAC Western Ontario and McMaster Universities Osteoarthritis Index, *CI* confidence interval, *OPA* osteophyte area, *mJSW* minimum joint space width

[a] Adjusted regression coefficients for physical function score were calculated by multiple regression analysis after adjustment for age, BMI, gender, grip strength, and physical function score at baseline in the overall population and after adjustment for age, BMI, grip strength, and physical function score at baseline in men and women

[b] Adjusted regression coefficients for physical function score were calculated by multiple regression analysis with age, BMI, gender, grip strength, physical function score at baseline, OPA, and mJSW as explanatory variables in the overall population and with age, BMI, grip strength, physical function score at baseline, OPA, and mJSW as explanatory variables in men and women

examine whether OPA and mJSW independently predicted worsening of physical functional disability, we used multiple regression analysis with age, BMI, gender, grip strength, physical function score at baseline, OPA, and mJSW as explanatory variables and found that mJSW was an independent predictor for worsening of physical functional disability, but the significant association of OPA disappeared. When analyzed in men and women separately, after adjustment for age, BMI, grip strength, and physical function scores at baseline, OPA and mJSW were significant predictors for worsening of physical functional disability in men; in women, mJSW was a significant predictor for worsening of physical functional disability, but OPA was not. To examine whether OPA and mJSW independently predicted worsening of physical functional disability in men, we used multiple regression analysis with age, BMI, grip strength, physical function score at baseline, OPA, and mJSW as explanatory variables and found that the significant association of OPA and mJSW with worsening in physical function disappeared.

Discussion

This is the first large-scale study to examine whether osteophytosis and joint space narrowing independently predict QOL decline measured by WOMAC pain and physical function score in a longitudinal model. In addition, osteophytosis and joint space narrowing were estimated not by categorical grade but by continuous values such as OPA and mJSW at the knee. In the present study, OPA, rather than mJSW, was an independent predictor for pain and physical functional disability after 3 years of follow-up in men. OPA, rather than mJSW, also predicted worsening of pain in men during the 3-year follow-up, whereas mJSW, rather than OPA, predicted worsening of pain in women.

Previous studies have shown that knee OA has a strong effect on QOL [13, 20–22]; however, the knee OA was defined by KL grade or other categorical methods. KL grade is the most conventional system to grade radiographic severity of knee OA, but in this categorical system, osteophyte formation and joint space narrowing are not assessed separately. Thus, we cannot clarify whether osteophytosis and joint space narrowing have distinct effects on QOL. In addition, our previous cross-sectional study showed that osteophytosis was not strongly related to joint space narrowing on plain radiographs [31]. Furthermore, our experimental mouse model for OA identified a cartilage-specific molecule, carminerin, that regulates osteophytosis without affecting joint cartilage destruction during OA progression [32, 33]. This accumulating evidence indicates that osteophytosis and joint space narrowing may have distinct etiologic mechanisms and their progression may be neither constant nor proportional. Thus, to examine factors associated with knee OA, these two OA features should be assessed separately. Furthermore, because categorical methods are statistically less powerful than continuous methods, the association between knee OA and QOL might have been underestimated in previous studies. In addition, most studies regarding the association of knee OA with QOL were cross-sectional designs; thus, a causal relationship could not be clarified. So far, the role of the osteophytes in OA is controversial, with several researchers believing that osteophytes are merely a reflection of age and not associated with any of the clinical symptoms of OA, though few reported data support or refute this argument. This study was the first longitudinal model to report that osteophytosis, rather than mJSW, predicted QOL decline in men.

Table 5 Effect of OPA and mJSW at baseline on worsening of WOMAC pain scores after 3 years

	Crude regression coefficient[a] (95 % CI)	*P* value	Adjusted regression coefficient (95 % CI)	*P* value
Overall				
OPA (mm^2)	0.01 (−0.004 to 0.03)	0.1443	–	–
mJSW (mm)	−0.16 (−0.29 to −0.03)	0.0132	−0.30 (−0.44 to −0.16)	<0.0001
Men				
OPA (mm^2)	0.04 (0.006 to 0.08)	0.0209	0.05 (0.01 to 0.08)	0.0078
mJSW (mm)	−0.06 (−0.28 to 0.15)	0.5684	–	–
Women				
OPA (mm^2)	0.006 (−0.01 to 0.02)	0.4880	–	–
mJSW (mm)	−0.24 (−0.41 to −0.07)	0.006	−0.41 (−0.58 to −0.23)	<0.0001

WOMAC Western Ontario and McMaster Universities Osteoarthritis Index, *CI* confidence interval, *OPA* osteophyte area, *mJSW* minimum joint space width

[a] Adjusted regression coefficients for change of scores were calculated by multiple regression analysis after adjustment for age, BMI, gender, grip strength, and pain score at baseline in the overall population and after adjustment for age, BMI, grip strength, and pain score at baseline in men and women