Osteoarthritis and Cartilage 20 (2012) 1217–1226

Osteoarthritis and Cartilage

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

N. Yoshimura †*, S. Muraki ‡, H. Oka †, S. Tanaka §, H. Kawaguchi §, K. Nakamura ||, T. Akune ‡

† *Department of Joint Disease Research, 22nd Century Medical and Research Center, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan*
‡ *Department of Clinical Motor System Medicine, 22nd Century Medical and Research Center, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan*
§ *Department of Orthopaedic Surgery, Faculty of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan*
|| *Rehabilitation Services Bureau, National Rehabilitation Center for Persons with Disabilities, 1, Namiki 4-chome, Tokorozawa City, Saitama Prefecture 359-8555, Japan*

ARTICLE INFO

Article history:
Received 15 March 2012
Accepted 21 June 2012

Keywords:
Knee osteoarthritis
Incidence
Progression
Metabolic syndrome
Population-based cohort study

SUMMARY

Objective: To clarify the association between the occurrence and progression of knee osteoarthritis (KOA) with components of metabolic syndrome (MS), including overweight (OW), hypertension (HT), dyslipidaemia (DL), and impaired glucose tolerance (IGT), in a general population.
Design: From the large-scale population-based cohort study entitled Research on Osteoarthritis/Osteoporosis Against Disability (ROAD) initiated in 2005, 1,690 participants (596 men, 1,094 women) residing in mountainous and coastal areas were enrolled. Of these, 1,384 individuals (81.9%; 466 men, 918 women) completed the second survey, including knee radiography, 3 years later. KOA was defined as Kellgren–Lawrence (KL) grade ≥ 2 using paired X-ray films. Based on changes in KL grades between the baseline and second surveys, cumulative incidence and progression of KOA were determined. OW, HT, DL, and IGT at baseline were assessed using standard criteria.
Results: The cumulative incidence of KOA among 1,384 completers over 3 years was 3.3%/year, and progression in KL grades for either knee, 8.0%/year. Logistic regression analyses after adjusting for potential risk factors revealed that the odds ratio (OR) for the occurrence of KOA significantly increased according to the number of MS components present (OR vs no component: one component, 2.33; two components, 2.82; ≥three components, 9.83). Similarly, progression of KOA significantly increased according to the number of MS components present (OR vs no component: one component, 1.38; two components, 2.29; ≥three components: 2.80).
Conclusion: Accumulation of MS components is significantly related to both occurrence and progression of KOA. MS prevention may be useful in reducing future KOA risk.

Introduction

Osteoarthritis (OA), which causes cartilage and disc degeneration and osteophyte formation at joints in the limbs and spine, is a major public health problem in the elderly and affects activities of daily living and quality of life, leading to increased morbidity and mortality[1–3]. According to the recent National Livelihood Survey by the Ministry of Health, Labour and Welfare in Japan, OA is ranked fourth among diseases that cause disabilities requiring support and long-term care[4]. The National Livelihood Survey also shows that cardiovascular disease (CVD) is ranked first in causing disabilities in the elderly[4]. Most CVD patients have multiple risk factors[5]. The presence of these risk factors in a specific combination, entitled metabolic syndrome (MS), is a multiplex risk factor that predisposes affected individuals to CVD morbidity and mortality. MS is generally considered a combination of being overweight (OW) and having hypertension (HT), dyslipidaemia (DL), and impaired glucose tolerance (IGT)[6].

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

* Address correspondence and reprint requests to: N. Yoshimura, Department of Joint Disease Research, 22nd Century Medical and Research Center, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan. Tel: 81-3-5800-9178; Fax: 81-3-5800-9179.
E-mail address: YOSHIMURAN-ORT@h.u-tokyo.ac.jp (N. Yoshimura).

1063-4584/$ – see front matter © 2012 Osteoarthritis Research Society International. Published by Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.joca.2012.06.006

various MS components. Lawrence first reported that diastolic blood pressure (BP) was associated with KOA in women[13]. Kellgren reported that hand OA was significantly associated with above-average serum cholesterol levels in women[14]. Cimmino *et al.* observed significantly higher plasma glucose levels in women with OA than in those without[15]. Contradictory findings regarding the association of such metabolic factors with OA have been reported[16–19]. Hart *et al.* found that metabolic factors such as blood glucose, hypercholesterolaemia, and even treated HT were associated with KOA development[20]. A few population-based studies have demonstrated a dose–response relationship between risk factor accumulation for MS and KOA; we have previously reported that KOA presence was significantly associated with increase in the number of MS components[21]. However, to our knowledge, no study has clarified the associations between KOA occurrence or progression and MS component accumulation, using a prospective cohort of general inhabitants.

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

Method

Participants

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

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

Baseline examination procedures

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

Anthropometric measurements included height, weight, and body mass index [BMI: weight (kg)/height^2 (m^2)]. Systolic and diastolic BP was measured by an experienced public health nurse using a mercury sphygmomanometer. Medical information, including information on knee joints, was collected by experienced orthopaedic surgeons (SM and HO). All participants underwent radiographic examination of both knees using an anterior–posterior view with weight-bearing and foot-map positioning.

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

In this study, definitions of MS components were based on criteria defined by the Examination Committee of Criteria for Metabolic Syndrome in Japan[24] and the Japan Society for the Study of Obesity[25]. However, because not all blood samples were obtained under fasting conditions, we used indices from the National Health and Nutrition Survey in Japan adopted as MS criteria in this national screening study due to the difficulty of collecting samples under fasting conditions[26]. The following definitions were used for MS components: OW, BMI $\geq$ 25 kg/m^2; HT, systolic BP $\geq$ 130 mm Hg and/or diastolic BP $\geq$ 85 mm Hg; DL, serum HDL-cho level $<$ 40 mg/dL; and IGT, serum HbA1c level $\geq$ 5.5%. Furthermore, subjects being treated with medication for HT, DL, or diabetes mellitus were regarded as having HT, DL, or IGT, respectively.

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

In 2008–2010, the 1,690 subjects were invited to attend the second survey of the ROAD study, a 3-year follow-up consisting of examinations identical to those at baseline. Knee radiographs were read by a single experienced orthopaedist (SM) without knowledge of participants' clinical status and were categorized using the Kellgren–Lawrence (KL) grading scale[27]. When there were differences in the KL grades between the two knees, the higher KL grade was assigned to the participant. A subject with KL $\geq$ 2 was defined as having radiographic KOA. A new KOA case was identified if both knees had a KL grade $<$ 2 at baseline and if at least one knee developed a KL of $\geq$2 during follow-up. KOA progression was defined as the KL grade for either knee being higher during follow-up than at baseline.

Statistical analysis

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

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

consumption, bicycling, regular exercise, and history of knee injuries, all of which had been found to be significantly associated with KOA presence in a previous study using the same population[17]. Model 3 was obtained by multivariate logistic regression analysis using the same objective variable and the same adjustment factors as in Model 2; furthermore, other MS components were included in the mutual adjustment model. For example, when BMI was selected as an objective factor, Model 3 was obtained by multivariate logistic regression after adjustment for age, gender, regional differences, smoking, alcohol consumption, bicycling, regular exercise, history of knee injuries, systolic BP, and serum HDL-cho and HBA1c levels. Similarly, when OW was selected as an objective factor, Model 3 was obtained by multivariate logistic regression after adjustment for age, gender, regional differences, smoking, alcohol consumption, bicycling, regular exercise, history of knee injuries, HT, DL, and IGT. Because systolic and diastolic BP was moderately correlated ($r = 0.5643$, $P < 0.001$), only values of systolic BP were used as representative of BP in Model 3.

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

Results

Eligible participants

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

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

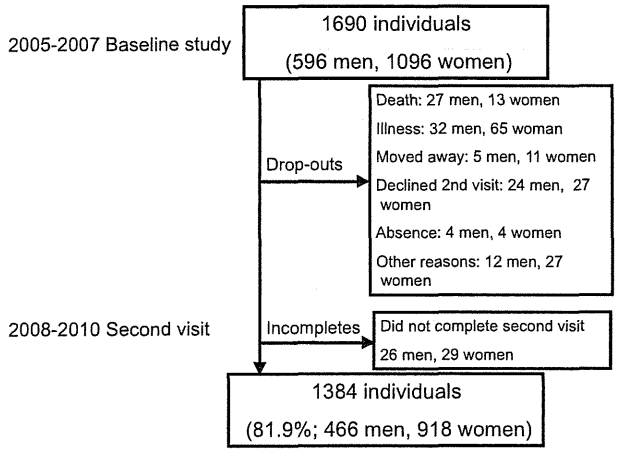


Fig. 1. Flow of participants in the baseline and second surveys.

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

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

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

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

KOA occurrence and progression and MS components

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

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

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

Table III shows multivariate logistic regression analysis results for KOA occurrence vs values for each MS component, including BMI, systolic BP, diastolic BP, and serum HDL-cho and HbA1c levels measured at baseline (Table III). Model 2 showed that BMI, systolic BP, and serum HDL-cho levels were significantly associated with KOA occurrence after adjustment for various risk factors. However, Model 3, incorporating mutual adjustment for each MS component, indicated that only BMI was significantly associated with KOA occurrence. The three types of multivariate logistic regression analyses using KOA progression as the objective factor showed similar results as for KOA occurrence described above.

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

KOA occurrence and progression and the number of MS components

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

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

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

KOA(−), non-occurrence of KOA; KOA(+), occurrence of KOA; progression(−), no progression of the KL grade; progression(+), progression of the KL grade.
n, number of subjects.
*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

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

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

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

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

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

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

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

Figure 2 also shows KL grade progression (%/year) for either knee classified by the number of MS components present. In the total population, KL grade progression classified by 0, 1, 2, or ≥3 MS components was 4.3, 7.6, 10.8, and 11.3, respectively, which significantly increased with the number of MS components (P for trend < 0.001). The progression among individuals with one or more MS components was higher in women than in men [Fig. 2(B)].

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

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

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

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

Being OW was defined as BMI ≥ 25 kg/m^2, HT as systolic BP ≥ 130 mm Hg and/or diastolic BP ≥ 85 mm Hg, DL as serum HDL-cho level < 40 mg/dL, and IGT as serum HbA1c level ≥ 5.5%. Further, subjects being treated with medication for HT, DL, or IGT were regarded as having the respective disorder.

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

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

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

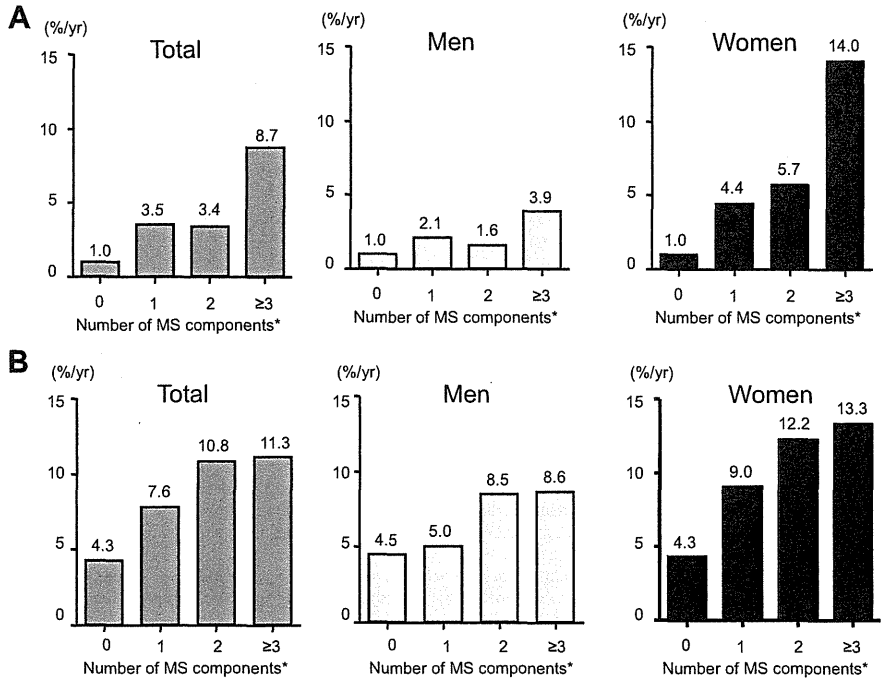
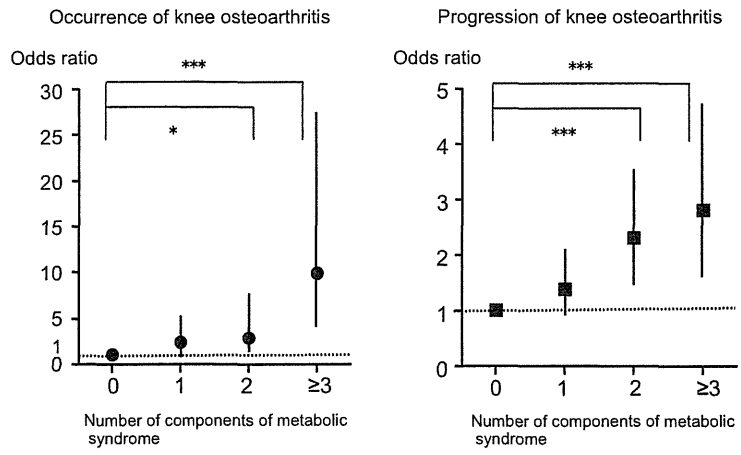


Fig. 2. Cumulative incidence (%/year) of KOA (A) and progression of the KL grade of either knee (%/year) (B) classified by the number of components of MS, including OW, HT, DL, and IGT.

for age and gender. The odds ratio (OR) and 95% CI for KOA occurrence were found to significantly increase with the number of MS components present (OR, 95% CI vs no component: one component, 2.16, 0.90–5.20, $P = 0.085$; two components, 2.49, 0.95–6.55, $P = 0.063$; ≥three components, 8.38, 3.12–22.5, $P < 0.001$). Similarly, KOA progression significantly increased with the number of MS components present (OR, 95% CI vs no component: one component, 1.41, 0.94–2.12, $P = 0.097$; two components, 2.25, 1.47–3.46, $P < 0.001$; ≥three components: 2.59, 1.57–4.27, $P < 0.001$).

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



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

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

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

other risk factors (OR, 95% CI vs no component: one component, 2.33, 0.96–5.65, $P = 0.065$; two components, 2.82, 1.05–7.54, $P = 0.039$; ≥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.

Role of the funding source

This work was supported by Grants-in-Aid for Scientific Research B23390172 and B20390182 to NY, B23390357 and C20591737 to TA, B23390356 and C20591774 to SM, for Young Scientists A18689031 to HO, and Collaborating Research with NSF 08033011-00262 (Director, NY) from the Ministry of Education, Culture, Sports, Science, and Technology; and H17-Men-eki-009 (Director, KN), H18-Choujyu-037 (Director, TN), H20-Choujyu-009 (Director, NY), and H23-Chojyu-002 (Director, TA) from the Ministry of Health, Labour and Welfare in Japan. This study was also supported by grants from the Japan Osteoporosis Society (NY, SM, HO, and TA) and research aid from the Japanese Orthopaedic Association (JOA-Subsidized Science Project Research 2006-1 & 2010-2, Director, HK).

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.

Acknowledgements

The authors wish to thank Dr Takako Nojiri and Mr Kazuhiro Hatanaka of the Gobo Public Health Centre; Dr Naoki Hirabayashi of the Kawakami Clinic, Hidakagawa Town; Mrs Tomoko Takijiri, Mrs Kumiko Shinou, Mrs Rie Takiguchi, Mrs Kyoko Maeda, Ms Ikuyo Ueyama, Mrs Michiko Mori, Mrs Hisayo Sugimoto, and other members of the public office in Hidakagawa Town; Dr Shinji Matsuda of the Shingu Public Health Centre; and Mrs Tamako Tsutsumi, Mrs Kanami Maeda, Mr Shoichi Shimoichi, Mrs Megumi Takino, Mrs Shuko Okada, Mrs Kazuyo Setoh, Mrs Chise Ryouno, Mrs Miki Shimosaki, Mrs Chika Yamaguchi, Mrs Yuki Shimoji, and other members of the public office in Taiji Town for their assistance in locating and scheduling participants for examinations. We also thank Ms Kyoko Yoshimura, Mrs Toki Sakurai, and Mrs Saeko Sahara for their assistance with data reduction and administration.

References

1. Sharma L, Kapoor D. Epidemiology of Osteoarthritis. Osteoarthritis: Diagnosis and Medical/Surgical Management. 4th edn. Philadelphia: Lippincott Williams & Wilkins; 2007.
2. Guccione AA, Felson DT, Anderson JJ, Anthony JM, Zhang Y, Wilson PW, *et al.* The effects of specific medical conditions on the functional limitations of elders in the Framingham study. Am J Public Health 1994;84:351–8.
3. Felson DT, Zhang Y. An update on the epidemiology of knee and hip osteoarthritis with a view to prevention. Arthritis Rheum 1998;41:1343–55.
4. Ministry of Health, Labour and Welfare. The Outline of the Results of National Livelihood Survey, http://www.mhlw.go.jp/toukei/list/20-19-1.html.
5. Dahlöf B. Cardiovascular disease risk factors: epidemiology and risk assessment. Am J Cardiol 2010;105:3A–9A.
6. Day C. Metabolic syndrome, or what you will: definitions and epidemiology. Diab Vasc Dis Res 2007;4:32–8.
7. Felson DT, Anderson JJ, Naimark A, Walker WM, Meenan RF. Obesity and knee osteoarthritis: the Framingham study. Ann Intern Med 1988;109:18–24.
8. Hart DJ, Spector TD. The relationship of obesity, fat distribution and osteoarthritis in the general population: the Chingford study. J Rheumatol 1993;20:331–5.
9. Van Saase JL, Vandenbroucke JP, Van Romunde LK, Valkenburg HA. Osteoarthritis and obesity in the general population. A relationship calling for an explanation. J Rheumatol 1998;15:1152–8.
10. Magliano M. Obesity and arthritis. Menopause Int 2008;14:149–54.
11. Zhang W, Moskowitz RW, Nuki G, Abramson S, Altman RD, Arden N, *et al.* OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines. Osteoarthritis Cartilage 2008;16:137–62.

12. Muraki S, Akune T, Oka H, Mabuchi A, En-yo Y, Yoshida M, *et al.* Association of occupational activity with radiographic knee osteoarthritis and lumbar spondylosis in elderly patients of population-based cohorts: a large-scale population-based study. Arthritis Rheum 2009;61:779–86.
13. Lawrence JS. Hypertension in relation to musculoskeletal disorders. Ann Rheum Dis 1975;34:451–6.
14. Kellgren JH. Osteoarthritis in patients and populations. BMJ 1961;1:1–6.
15. Cimmino MA, Cutolo M. Plasma glucose concentration in symptomatic osteoarthritis: a clinical and epidemiological survey. Clin Exp Rheumatol 1990;8:251–7.
16. Davis MA, Ettinger WH, Neuhaus JM. The role of metabolic factors and blood pressure in the association of obesity with osteoarthritis of the knee. J Rheumatol 1988;15:1827–32.
17. Cooper C, McAlindon T, Snow S, Vines K, Young P, Kirwan J, *et al.* Mechanical and constitutional risk factors for symptomatic knee osteoarthritis: differences between medial tibiofemoral and patellofemoral disease. J Rheumatol 1994;21:307–13.
18. Martin K, Lethbridge-Cejku M, Muller DC, Elahi D, Andres R, Tobin JD, *et al.* Metabolic correlates of obesity and radiographic features of knee osteoarthritis: data from the Baltimore Longitudinal Study of Aging. J Rheumatol 1997;24:702–7.
19. Stürmer T, Brenner H, Brenner RE, Günther KP. Non-insulin dependent diabetes mellitus (NIDDM) and patterns of osteoarthritis. The Ulm osteoarthritis study. Scand J Rheumatol 2001;30:169–71.
20. Hart DJ, Doyle DV, Spector TD. Association between metabolic factors and knee osteoarthritis in women: the Chingford study. J Rheumatol 1995;22:1118–23.
21. Yoshimura N, Muraki S, Oka H, Kawaguchi H, Nakamura K, Akune T. Association of knee osteoarthritis with the accumulation of metabolic risk factors such as overweight, hypertension, dyslipidaemia, and impaired glucose tolerance in Japanese men and women: the ROAD study. J Rheumatol 2011;38:921–30.
22. Yoshimura N, Muraki S, Oka H, Kawaguchi H, Nakamura K, Akune T. Cohort profile: Research on Osteoarthritis/Osteoporosis Against Disability (ROAD) study. Int J Epidemiol 2010;39:988–95.
23. Yoshimura N, Muraki S, Oka H, Mabuchi A, En-yo Y, Yoshida M, *et al.* Prevalence of knee osteoarthritis, lumbar spondylosis, and osteoporosis in Japanese men and women: the research on osteoarthritis/osteoporosis against disability study. J Bone Miner Metab 2009;27:620–8.
24. The Examination Committee of Criteria for Metabolic Syndrome. The definition and criteria of metabolic syndrome. Nihon Naika Gakkai zasshi 2005;94:794–809 (In Japanese).
25. Examination Committee of Criteria for Obesity Disease in Japan, Japan Society for the Study of Obesity. New criteria for 'obesity disease' in Japan. Circ J 2002;66:987–92.
26. Ministry of Health, Labour and Welfare. The Outline of the Results of National Health and Nutrition Survey, http://www.mhlw.go.jp/houdou/2009/11/dl/h1109-1b.pdf.
27. Kellgren JH, Lawrence JS. The Epidemiology of Chronic Rheumatism: Atlas of Standard Radiographs of Arthritis. Oxford: Blackwell Scientific; 1963.
28. Lohmander LS, Gerhardsson de Verdier M, Rollof J, Nilsson PM, Engstrom G. Incidence of severe knee and hip osteoarthritis in relation to different measures of body mass: a population-based prospective cohort study. Ann Rheum Dis 2009;68:490–6.
29. Sowers M, Karvonen-Gutierrez CA, Palmieri-Smith R, Jacobson JA, Jiang Y, Ashton-Miller JA. Knee osteoarthritis in obese women with cardiometabolic clustering. Arthritis Rheum 2009;61:1328–36.
30. Singh G, Miller JD, Lee FH, Pettitt D, Russell MW. Prevalence of cardiovascular disease risk factors among US adults with self-reported osteoarthritis: data from the Third National Health and Nutrition Examination Survey. Am J Manag Care 2002;8:S383–91.
31. Puenpatom RA, Victor TW. Increased prevalence of metabolic syndrome in individuals with osteoarthritis: an analysis of NHANES III data. Postgrad Med 2009;121:9–20.
32. Hart DJ, Doyle DV, Spector TD. Incidence and risk factors for radiographic knee osteoarthritis in middle-aged women: the Chingford study. Arthritis Rheum 1999;42:17–24.
33. Reijman M, Pols HA, Bergink AP, Hazes JM, Belo JN, Lievense AM, *et al.* Body mass index associated with onset and progression of osteoarthritis of the knee but not of the hip: the Rotterdam study. Ann Rheum Dis 2007;66:158–62.
34. Cooper C, Snow S, McAlindon TE, Kellingray S, Stuart B, Coggon D, *et al.* Risk factors for the incidence and progression of radiographic knee osteoarthritis. Arthritis Rheum 2000;43:995–1000.
35. Engström G, Gerhardsson de Verdier M, Rollof J, Nilsson PM, Lohmander LS. C-reactive protein, metabolic syndrome and incidence of severe hip and knee osteoarthritis. A population-based cohort study. Osteoarthritis Cartilage 2009;17:168–73.
36. Muraki S, Oka H, Akune T, Mabuchi A, En-yo Y, Yoshida M, *et al.* Prevalence of radiographic knee osteoarthritis and its association with knee pain in the elderly of Japanese population-based cohorts: the ROAD study. Osteoarthritis Cartilage 2009;17:1137–43.
37. Muraki S, Akune T, Oka H, Ishimoto Y, Nagata K, Yoshida M, *et al.* Incidence and risk factors for radiographic knee osteoarthritis and knee pain in Japanese men and women: a longitudinal population-based cohort study. Arthritis Rheum 2012;64:1447–56.
38. Hoang KC, Le TV, Wong ND. The metabolic syndrome in East Asians. J Cardiometab Syndr 2007;2:276–82.
39. Nestel P. Nutritional aspects in the causation and management of the metabolic syndrome. Endocrinol Metab Clin North Am 2004;33:483–92.
40. Manek NJ, Hart D, Spector TD, MacGregor AJ. The association of body mass index and osteoarthritis of the knee joint: an examination of genetic and environmental influences. Arthritis Rheum 2003;48:1024–9.
41. Qin J, Shi D, Dai J, Zhu L, Tsezou A, Jiang Q. Association of the leptin gene with knee osteoarthritis susceptibility in a Han Chinese population: a case-control study. J Hum Genet 2010;55:7046.
42. Kornaat PR, Sharma R, van der Geest RJ, Lamb HJ, Kloppenburg M, Hellio le Graverand MP, *et al.* Positive association between increased popliteal artery vessel wall thickness and generalized osteoarthritis: is OA also part of the metabolic syndrome? Skeletal Radiol 2009;38:1147–51.
43. Rojas-Rodríguez J, Escobar-Linares LE, Garcia-Carrasco M, Escárcega RO, Fuentes-Alexandro S, Zamora-Ustaran A. The relationship between the metabolic syndrome and energy-utilization deficit in the pathogenesis of obesity-induced osteoarthritis. Med Hypotheses 2007;69:860–8.
44. Pottie P, Presle N, Terlain B, Netter P, Mainard D, Berenbaum F. Obesity and osteoarthritis: more complex than predicted!. Ann Rheum Dis 2006;65:1403–5.
45. Goldring MB, Otero M. Inflammation in osteoarthritis. Curr Opin Rheumatol 2011;23:471–8.
46. Findlay DM. Vascular pathology and osteoarthritis. Rheumatology (Oxford) 2007;46:1763–8.
47. Rosa SC, Gonçalves J, Judas F, Mobasheri A, Lopes C, Mendes AF. Impaired glucose transporter-1 degradation and increased glucose transport and oxidative stress in response to

high glucose in chondrocytes from osteoarthritic versus normal human cartilage. Arthritis Res Ther 2009;11:R80.
48. Grundy SM, Brewer Jr HB, Cleeman JI, Smith Jr SC, Lenfant C, American Heart Association; National Heart, Lung, and Blood Institute. Definition of metabolic syndrome: report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. Circulation 2004;109:433–8.
49. Shibata K, Suzuki S, Sato J, Ohsawa I, Goto S, Hashiguchi M, *et al.* Abdominal circumference should not be a required criterion for the diagnosis of metabolic syndrome. Environ Health Prev Med 2010;15:229–35.
50. Oka H, Muraki S, Akune T, Mabuchi A, Suzuki T, Yoshida H, *et al.* Fully automatic quantification of knee osteoarthritis severity on standard radiographs. Osteoarthritis Cartilage 2008;16:1300–6.

Osteoarthritis and Cartilage 20 (2012) 1103–1108

Osteoarthritis and Cartilage

Prevalence of symptomatic lumbar spinal stenosis and its association with physical performance in a population-based cohort in Japan: the Wakayama Spine Study

Y. Ishimoto †, N. Yoshimura ‡, S. Muraki ‡, H. Yamada †, K. Nagata †, H. Hashizume †, N. Takiguchi †, A. Minamide †, H. Oka ‡, H. Kawaguchi ‡, K. Nakamura §, T. Akune ‡, M. Yoshida †*

† *Wakayama Medical University, Japan*
‡ *The University of Tokyo, Japan*
§ *Rehabilitation Services Bureau, National Rehabilitation Center for Persons with Disabilities, Japan*

ARTICLE INFO

Article history:
Received 30 December 2011
Accepted 27 June 2012

Keywords:
Magnetic resonance imaging
Prevalence
Lumbar spinal stenosis
Cross-sectional

SUMMARY

Objective: The purpose of this study was to investigate the prevalence of symptomatic lumbar spinal stenosis (LSS) and to clarify the association between symptomatic LSS and physical performance using magnetic resonance imaging (MRI) in a population-based cohort.

Design: This cross-sectional study was performed as a part of the Research on Osteoarthritis/osteoporosis Against Disability (ROAD) in Japan and 1,009 subjects (335 men, 674 women, mean age 66.3 years, age range 21–97 years) were analyzed. An experienced orthopedic surgeon obtained the medical history and performed the physical testing for all participants. Symptomatic LSS diagnostic criteria required the presence of both symptoms and radiographic LSS findings. A 6-m walking time, chair standing time, and one-leg standing time were obtained from all participants.

Results: The prevalence of symptomatic LSS was 9.3% (95% confidence interval [CI]: 7.7–11.3) overall, 10.1% (CI: 7.4–13.8) in men and 8.9% (CI: 7.0–11.3) in women. There was a difference in the prevalence with increasing age by gender. The LSS prevalence showed little difference with age greater than 70 years for men, but the LSS prevalence for women was higher with increasing age. Among physical performance measures, 6-m walking time at a maximal pace was significantly associated with symptomatic LSS ($P = 0.03$).

Conclusion: The prevalence of symptomatic LSS was approximately 10% in a cohort resembling the general Japanese population. A 6-m walking time at a maximal pace was a more sensitive index than walking at a usual pace in assessing decreased physical performance associated with symptomatic LSS.

Introduction

Symptomatic lumbar spinal stenosis (LSS) is usually associated with impaired walking and other disabilities in the elderly. Symptomatic LSS has been shown to be the most frequent indication for spinal surgery in patients more than 65 years old[1,2]. However, little is known about the prevalence of symptomatic LSS in the general population. This is because the subjects in previous symptomatic LSS studies were limited to patients who visited the hospital[3,4]. Hence, people with minor symptomatic LSS who did not visit the hospital were not included in those studies. Furthermore, an examination that can capture minute changes of the intervertebral discs and ligaments using a tool like magnetic resonance imaging (MRI) is essential for the diagnosis of symptomatic LSS. This is because the definition of stenosis includes a morphological element. Many previous studies have reported the utility of MRI[5,6], but, to our knowledge, there have been no population-based cohort studies of symptomatic LSS using MRI.

It is well-known that the principal symptoms for LSS are sciatica and intermittent claudication (IC)[1,2]. Although most patients with MRI evidence of radiographic LSS are asymptomatic[7,8], when symptoms are present, severe symptoms are probably associated with poor physical performance. There have been few reports concerning physical performance of patients with symptomatic LSS[9,10]. According to a previous report concerning walking ability of

* Address correspondence and reprint requests to: M. Yoshida, Wakayama Medical University, Orthopedic surgery, 811-1 Kimidera, Wakayama city 641-8509 Japan. Tel: 81-73-447-2300; Fax: 81-73-448-3008.
E-mail address: sekitui@wakayama-med.ac.jp (M. Yoshida).

1063-4584/$ – see front matter © 2012 Osteoarthritis Research Society International. Published by Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.joca.2012.06.018

subjects with three different degenerative musculoskeletal disorders (knee osteoarthritis, hip osteoarthritis, and symptomatic LSS) who were scheduled for either joint replacement or spinal decompression surgery, walking ability was limited in all three groups compared to healthy controls[9]. However, patients with symptomatic LSS showed the greatest restrictions in walking ability. In another report regarding subjects with symptomatic LSS in an orthopedic clinical practice, subjects in the healthy group showed greater functional mobility than those in the symptomatic LSS group[10]. The subjects included in the previous studies had enough symptoms to have visited the hospital, however, the association of physical performance measures with symptomatic LSS in subjects with minor symptoms who do not visit the hospital has not been well characterized. Although there may be a latent diminished physical functioning in symptomatic LSS with even minor radiographic changes and symptoms, there have been no population-based studies on symptomatic LSS that have included people with minor signs and symptoms of LSS.

Symptomatic LSS in this study was diagnosed by the presence of both clinical symptoms and radiographic LSS findings consistent with the clinical presentation. The aim of the present study was to clarify the prevalence of symptomatic LSS by gender and age strata using a population-based cohort. In addition, the association of symptomatic LSS with physical performance measures (walking speed, chair standing time, and one-leg standing time) was evaluated.

Methods

Participants

The present study, entitled "the Wakayama Spine Study: population-based cohort", was a population-based study for degenerative spinal disease and performed in a subcohort of the large-scale population-based cohort study called Research on Osteoarthritis/osteoporosis Against Disability (ROAD). ROAD is a nationwide, prospective study of bone and joint diseases consisting of population-based cohorts established in several communities in Japan. As a detailed profile of the ROAD study has already been described elsewhere, only a brief summary is provided here[11–14]. To date, creation of a baseline database including clinical and genetic information for 3,040 inhabitants (1,061 men, 1,979 women) in the age range of 23–95 years (mean, 70.6 years) has been completed. Participants were recruited from listings of resident registrations 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 written informed consent, and the study was conducted with the approval of ethical committees of the University of Tokyo and the Tokyo Metropolitan Institute of Gerontology. Participants completed an interviewer-administered questionnaire of 400 items that included lifestyle information, underwent anthropometric measurements, and physical performance measures were recorded. A second visit of the ROAD study to the mountainous region of Hidakagawa and the seacoast region of Taiji was performed between 2008 and 2010. From inhabitants participating in the second visit of the ROAD study, 1,063 volunteers were recruited to undergo MRI examinations. Fifty-two of the 1,063 volunteers declined the MRI examination, therefore, 1,011 were registered in the present study. All participants provided another written informed consent for the MRI examination. Among those 1,011 participants, two participants with LSS symptoms for whom MRI was contraindicated (due to presence of a pacemaker) were excluded, because a final diagnosis of symptomatic LSS could not be made (Fig. 1). Thus, 1,009 participants (335 men and 674 women, mean age 66.3 years, age range of 21–97 years) were analyzed in the present study. Similar to the baseline study, participants in the second visit of the ROAD study completed an interviewer-administered questionnaire of 400 items that included lifestyle information such as smoking habits, alcohol consumption, family history, past history, physical activity, reproductive variables, and health-related quality of life (QOL). Anthropometric measurements included height, weight, bilateral grip strength, and body mass index (BMI) (weight [kg]/height^2 [m^2]). The ankle-brachial index (ABI) was measured using PWV/ABI (OMRON Co., Kyoto, Japan) for all participants. A timed 6-m walk at the participant's usual pace in a hallway was recorded to measure physical performance. Similarly, 6-m walking time at a maximal pace was measured[15–18]. The time taken for five consecutive chair rises without the use of hands was also recorded[18–20]. One-leg standing time with each leg was measured using a stopwatch (upper limit, 60 s) and the time adopted was the mean value of both legs[21,22].

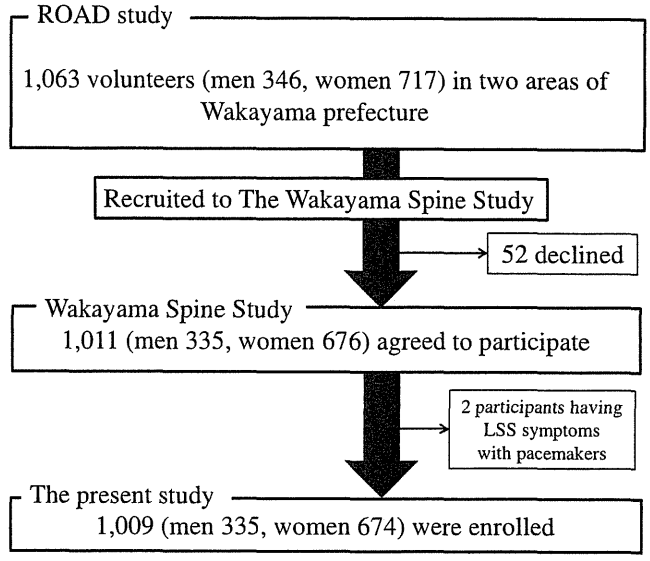


Fig. 1. Flow diagram depicting participants recruited to the Wakayama Spine Study from the ROAD study.

MRI

A mobile MRI (Excelart 1.5 T, Toshiba, Tokyo, Japan) unit was used in the present study, and total spinal MRI was performed for all participants on the same day as the examination. MRI exclusion criteria included presence of a cardiac pacemaker, claustrophobia, or other contraindications. The participants were positioned in supine during the MRI, and those with rounded backs used triangular pillows under their head and knees. The imaging protocol included sagittal T2-weighted fast spin echo (FSE) (repetition time (TR): 4,000 ms/echo, echo time (TE): 120 ms, field of view (FOV): 300 × 320 mm), and axial T2-weighted FSE (TR: 4,000 ms/echo, TE: 120 ms, FOV: 180 × 180 mm). Sagittal images were taken for the entire spine, but axial images were done at each lumbar intervertebral level (L1/2–L5/S1) parallel to the vertebral endplates.

Symptomatic LSS diagnosis

An experienced orthopedic surgeon (YI) consistently took the medical history and performed the physical testing for all the participants in this study. The history included information on the

presence of low back, buttock and leg pain, the area of pain or other discomfort, the presence of IC and its distance, and a modified Zurich Claudication Questionnaire[23] (excepting six items about satisfaction and a history of lumbar surgery for symptomatic LSS). Physical examinations included symptoms induced by lumbar extension, symptoms improved or induced with lumbar flexion, floor finger distance (cm), peripheral circulation (good or poor), a straight leg raising test, manual muscle testing of both upper and lower extremities, tendon reflex testing for both upper and lower extremities, and Babinski reflex testing. In addition, the MRI study of the entire spine was performed on all participants on the same day as the physical examination.

The diagnostic criteria for symptomatic LSS used in the present study were based on the LSS definition from the North American Spine Society (NASS) guideline, which requires presentation of both LSS symptoms and radiographic signs of LSS[24]. The orthopedic surgeon (YI) made the diagnosis of symptomatic LSS using this definition. The diagnosis for LSS symptoms required one or more of the following symptoms: pain, numbness and neurological deficits in the lower extremities and buttocks, and bladder/bowel dysfunction. The symptom characteristics should be induced or exacerbated with walking or prolonged standing and relieved with lumbar flexion, sitting and recumbency. The severity of radiographic LSS was assessed by qualitative measurements, which were performed by a well-experienced orthopedic surgeon (YI) and images were provided on films. The features assessed for LSS included severity of central, lateral recess, and foraminal stenosis, rated as four grades: none, mild, moderate and severe. The lateral recess was defined, as per Fardon and Millette[25], as extending from the medial edge of the facet to the edge of the neural foramen. We applied the general guideline classification of a[26] mild stenosis as narrowing of the normal area by one-third or less, moderate stenosis as narrowing between one-third and two-thirds, and severe stenosis as narrowing of more than two-thirds. Central and lateral recess stenosis was rated on the axial images and foraminal stenosis on the sagittal images. We used the most severe side for the rating of lateral and foraminal stenosis at each level. The same observer scored 50 randomly selected lumbar MRI films more than 1 month after the first reading to evaluate the intraobserver variability of the severity rating. Two experienced orthopedic surgeons also scored 50 different lumbar MRI films (YI & KN) for interobserver variability. The intraobserver variability was confirmed by a kappa analysis which dichotomized radiographic LSS severity as no/mild stenosis vs moderate/severe stenosis, and showed sufficient reliability for assessment of central, lateral and foraminal stenosis (0.77, 0.70 and 0.65, respectively). Interobserver variability was also sufficient for assessment using the kappa analysis (0.71, 0.65 and 0.65, respectively).

Radiographic LSS also required the severity to be more than moderate and the radiographic finding needs to be consistent with the symptoms as outlined above. An experienced orthopedic surgeon (YI) made the final diagnosis of symptomatic LSS using this definition, which requires presentation of both LSS symptoms and radiographic LSS findings. There were no participants with LSS symptoms due to tumor, inflammatory, or traumatic pathologies.

Statistical analysis

All statistical analyses were performed using JMP version 8 (SAS Institute Japan, Tokyo, Japan). Differences in age, height, weight, BMI, 6-m walking time at a usual pace, 6-m walking time at a maximal pace, chair standing time, and one-leg standing time between men and women were examined by the non-paired Student's *t*-test. The non-paired Student's *t*-test was also used to compare age between participants with and without symptomatic LSS. The prevalence of symptomatic LSS was also compared between men and women by the chi-square test. Differences in physical performance measures (6-m walking time at a usual pace, 6-m walking time at a maximal pace, chair standing time, and one-leg standing time) between participants with and without symptomatic LSS were examined by the non-paired Student's *t*-test. Furthermore, logistic regression analysis was used to estimate the odds ratios (ORs) of physical performance measures (6-m walking time at a usual pace, 6-m walking time at a maximal pace, chair standing time, and one-leg standing time) for symptomatic LSS after adjustment for age, gender and BMI.

Results

Table I shows the characteristics of 1,009 participants (335 men and 674 women, mean age 66.3 years, age range of 21–97 years) including age, anthropometric measurements, and physical performance in the present study. Two-thirds of the 1,009 participants were women. Mean age was not significantly different between men and women. BMI was significantly lower in women than in men ($P = 0.005$). Physical performance measures of the 6-m walking time at a usual pace and at a maximal pace were significantly shorter in men than in women ($P < 0.05$ for both), while chair standing time and one-leg standing time were not significantly different between men and women.

The prevalence of radiographic LSS findings was much greater than the prevalence of symptomatic LSS for the participants in this study. The percentage of participants with moderate or severe radiographic central stenosis was 76.5% (95% confidence interval [CI]: 73.7–79.0) in total, while the prevalence of symptomatic LSS was 9.3% (95% CI: 7.7–11.3) in total, 10.1% (CI: 7.4–13.8) in men, and 8.9% (CI: 7.0–11.3) in women. There was no significant difference between men and women ($P = 0.52$). The prevalence in men less than 39 years, 40–49, 50–59, 60–69, 70–79, and 80 years and older was 0%, 3.8% (CI: 0.7–18.9), 9.8% (CI: 4.6–19.8), 11.8% (CI: 6.1–21.5), 11.7% (CI: 6.7–19.8), and 10.7% (CI: 5.6–19.7), respectively, while that in women was 0%, 1.4% (CI: 0.2–7.3), 5.7% (CI: 2.8–11.3), 9.3% (5.7–14.8), 11.9% (CI: 7.9–17.5), and 13.3% (CI: 8.4–20.6), respectively (Fig. 2). The prevalence of both genders

Table I
Characteristics of participants

	Total	Men	Women	*P* value for gender
No. of participants	1009	335	674	
Age group (years)				
≦39	30	11	19	–
40–49	100	26	74	–
50–59	184	61	123	–
60–69	229	68	161	–
70–79	271	94	177	–
≧80	195	75	120	–
Demographic characteristics				
Age, years	66.3 ± 13.6	67.3 ± 13.8	65.9 ± 13.4	0.11
Height, cm	155.9 ± 9.4	164.5 ± 7.1	151.6 ± 7.2	<0.0001
Weight, kg	56.8 ± 11.5	64.4 ± 11.7	53.1 ± 9.4	<0.0001
BMI, kg/m^2	23.3 ± 3.6	23.7 ± 3.5	23.1 ± 3.6	0.005
Physical performance				
Six-meter walking time at a usual pace, s	5.7 ± 2.2	5.5 ± 1.5	5.8 ± 2.4	0.04
Six-meter walking time at a maximal pace, s	3.9 ± 1.4	3.6 ± 1.1	4.0 ± 1.6	<0.0001
Chair standing time, s	8.9 ± 4.0	8.8 ± 3.4	8.9 ± 4.2	0.61
One-leg standing time, s	36.0 ± 23.7	35.7 ± 24.0	36.1 ± 23.6	0.82

Non-paired *t*-test was used to determine differences in demographic characteristics and measurements of physical performance between men and women. Values are the means ± standard deviation.

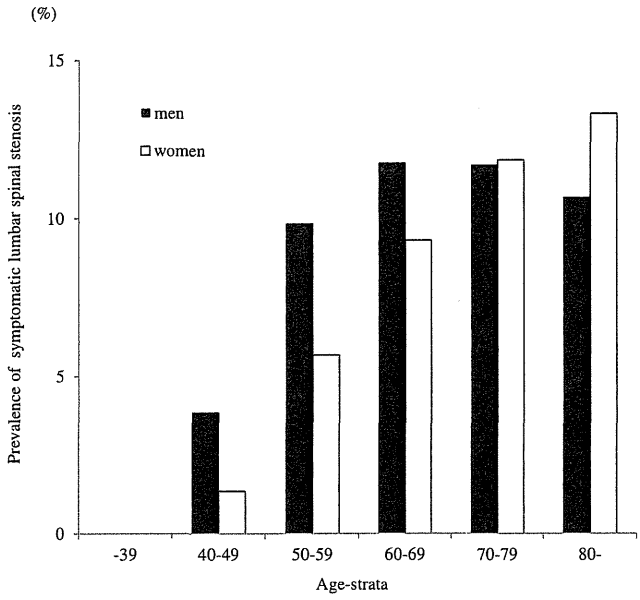


Fig. 2. Prevalence of symptomatic LSS classified by age and gender among 1,009 participants from a community cohort in Japan.

increased until reaching the 60–69 year old age group in which the prevalence in men was higher than that of women. However, the prevalence for women was higher than that of men after age 70. The prevalence of symptomatic LSS in men demonstrated little difference between age groups 60–69 years to over 80 years, but the prevalence for women became significantly higher with increasing aging ($P = 0.036$).

Fifty-five (58.5%) of 94 participants defined as having symptomatic LSS had IC. Five of these 55 participants presented with an ABI < 0.9. However, these five participants also had symptomatic LSS and their leg symptoms were positionally dependent. In this study, there were fifty neurogenic IC cases. There were five cases of unspecified IC, which was caused by both neurogenic and vascular claudication.

Table II shows the physical performance measures in participants with and without symptomatic LSS. In the overall population, 6-m walking time at a usual pace, 6-m walking time at a maximal pace, chair standing time, and one-leg standing time were significantly worse in participants with symptomatic LSS than those without symptomatic LSS ($P < 0.01$ for all). When analyzed in men and women separately, the results were similar to those overall, although the significant differences disappeared in some physical performance measures in men. The significant differences of 6-m walking time at a usual pace in both genders and one-leg standing time in men disappeared after a Bonferroni adjustment. Logistic regression analysis after adjustment for age, gender and BMI showed that 6-m walking time at a maximal pace was significantly associated with symptomatic LSS (OR: 1.17, 95% CI: 1.01–1.34). The physical performance measures of 6-m walking time at a usual pace, chair standing time, and one-leg standing time were not significantly associated with symptomatic LSS (OR: 1.04, 95% CI: 0.94–1.13, OR: 1.03, 95% CI: 0.97–1.09 and OR: 1.00, 95% CI: 0.98–1.01, respectively).

Discussion

The present study is the first to clarify the prevalence of symptomatic LSS by gender and age strata and the association of symptomatic LSS with physical performance measures using a population-based cohort. The prevalence of symptomatic LSS was found to be 9.3% in the general Japanese population, 10.1% in men, 8.9% in women, and there were no significant differences between genders. Interestingly, although the prevalence in women was higher with increasing age, the prevalence in men was the highest at 60–69 years, and little difference in prevalence was seen in men aged 60–69 years to 80 years or older. The prevalence of radiographic LSS was much greater than the prevalence of symptomatic LSS, with only a small proportion of participants with radiographic LSS actually showing symptoms suggestive of the clinical syndrome. The 6-m walking time at a maximal pace was significantly associated with symptomatic LSS, while the 6-m walking time at a usual pace was not.

We have identified no previous studies of symptomatic LSS prevalence. Johnsson[4] reported that the incidence of symptomatic LSS was 50/million person-years in southern Sweden in a study of patients who consulted the orthopedic department in two cities. However, as the author of that report described, the incidence of symptomatic LSS could be underestimated, because the studies did not include patients with minor symptoms who did not visit the hospital. This study is the first to clarify the prevalence of symptomatic LSS using a population-based cohort study.

Reported differences in prevalence of symptomatic LSS between men and women are mixed[27–29]. Verbiest reported a preponderance of symptomatic LSS in men as compared to women among his patients diagnosed by clinical symptoms and myelography[28]. However, Getty reported an equal gender distribution of symptomatic LSS prevalence in a series in which subjects were treated surgically for symptomatic LSS[29]. It is important to note that the subjects in those studies were patients who visited hospitals. In the present study, differences in the prevalence of symptomatic LSS between men and women in the general population were clarified. The prevalence of symptomatic LSS in men was slightly higher than in women, but there was no significant difference between genders. There was a difference in distribution of symptomatic LSS between men and women. The prevalence in women was higher with increasing age, but that in men was the highest at 60–69 years and

Table II
Measurements of each physical performance in participants with and without symptomatic LSS

	Total			Men			Women		
	LSS	*Non-LSS*	*P* value	*LSS*	*Non-LSS*	*P* value	*LSS*	*Non-LSS*	*P* value
Number of participants	94	915		34	301		60	614	
Physical performance									
Six-meter walking time at a usual pace, s	6.3 ± 2.7	5.6 ± 2.1	0.003	6.0 ± 1.6	5.4 ± 1.5	0.03	6.5 ± 3.1	5.7 ± 2.3	0.02
Six-meter walking time at a maximal pace, s	4.5 ± 2.1	3.8 ± 1.3	<0.0001	3.9 ± 1.1	3.6 ± 1.1	0.09	4.8 ± 2.4	3.9 ± 1.5	<0.0001
Chair standing time, s	10.1 ± 4.0	8.8 ± 3.9	0.002	9.7 ± 2.8	8.7 ± 3.4	0.10	10.3 ± 4.6	8.8 ± 4.1	0.008
One-leg standing time, s	27.9 ± 23.5	36.8 ± 23.6	0.0005	27.7 ± 25.4	36.7 ± 23.7	0.04	28.0 ± 22.6	36.9 ± 23.5	0.006

Values are the means ± standard deviation.
Non-paired *t*-test was used to determine differences in measurements of physical performance between LSS and non-LSS.

little different in men aged 60–69 years to 80 years and older. The prevalence of lumbar spondylosis (LS) diagnosed as Kellgren/Lawrence (KL) grade two or greater (defined as osteophyte formation with and without disc space narrowing) was found to be significantly higher in men than in women[30]. The prevalence of LS in women was found to be higher with increasing age, while that in men found little difference over 60 years[13]. Interestingly, these distribution patterns are similar to the prevalence of symptomatic LSS in the present study. Anatomical LSS arises from degenerative LS, and facet osteoarthritis and/or hypertrophy, which is associated with narrowing of the space available for the neural elements[1]. This may be one reason for the similarity between LS and symptomatic LSS prevalence.

The present study was the first to show that, among the general population, 6-m walking time at a maximal pace was significantly associated with symptomatic LSS, while 6-m walking time at a usual pace was not. This may mean that participants with symptomatic LSS appeared to have no disadvantage concerning activities of daily living compared to those without symptomatic LSS. However, when requiring greater functional reserve, such as 6-m walking time at a maximal pace, differences between participants with and without symptomatic LSS appeared. This is also the first study to indicate that tasks requiring greater functional reserve, such as walking at a maximal speed, could be a more sensitive index in assessment of decreased physical performance due to symptomatic LSS.

There are several limitations in the present study. First, although the present study included more than 1,000 participants, these participants may not represent the general population as they were recruited from only two areas. However, anthropometric measurements were compared between participants and the general Japanese population, and no significant differences were found in BMI (men: 23.71 (3.41) and 23.95 (2.64), $P = 0.33$, women: 23.06 (3.42) and 23.50 (3.69), $P = 0.07$)[31]. In addition, the proportion of current smokers and current drinkers (those who regularly smoked or drank more than one drink/month) in the general Japanese population was compared with that in the study population. Proportions of current smokers and drinkers in men and that of current drinkers in women were significantly higher in the general Japanese population than in the study population, but there were no significant differences in that of current smokers in women (smokers: men, 32.6% in the Japanese population, 25.2% in study participants, $P = 0.015$; women, 4.9% in the Japanese population, 4.1% in study participants, $P = 0.50$; drinkers: men, 73.9% in the Japanese population, 56.8% in study participants, $P < 0.0001$; women, 28.1% in the Japanese population, 18.8% in study participants, $P < 0.0001$), suggesting that it is likely that the participants (both men and women) had healthier lifestyles than the general Japanese population. Second, this is a cross-sectional study, so any causal relationship between symptomatic LSS and physical performance cannot be clarified. The Wakayama Spine Study is a longitudinal survey, so further progress will help to elucidate any causal relationships. Thirds, total walking distance/duration was not measured, and this metric for walking would likely have been of greater relevance to symptomatic LSS than speed of walking. In addition, this study only represents the Japanese population, hence, prevalence in other countries may be quite different.

In conclusion, the present study clarified that the prevalence of symptomatic LSS was about 10% in a cohort resembling the Japanese general population. There was a difference in the prevalence of symptomatic LSS distribution by age strata between men and women. The 6-m walking time at a maximal pace was a more sensitive index for assessing decreased physical performance due to LSS than the 6-m walking time at a usual pace. Further longitudinal surveys of the Wakayama Spine Study will help to further clarify the incidence and risk factors for symptomatic LSS.

Author contributions

All authors worked collectively to develop the protocols and methods described in this paper. YI, SM, KN, NO, HO, TA, and NY were principal investigators responsible for the fieldwork in the Wakayama Spine Study. YI and SM performed the statistical analysis. YI, HY, SM, KN, HH, HO, TA, MY, and NY contributed to the analysis and interpretation of results. YI wrote the report. All authors read and approved the final report.

Role of the funding source

The study sponsors played no role in the study design, the collection, analysis, and interpretation of data, writing of the report, or the decision to submit the paper for publication. The corresponding author had full access to all the data and had the final decision to submit for publication.

Conflict of interest

The authors declare that we have no conflicts of interest.

Acknowledgments

This study was supported by a Grant-in-Aid for Scientific Research (B20390182, B23390357, C20591737, C20591774), for Young Scientists (A18689031), and for Exploratory Research (19659305) from the Japanese Ministry of Education, Culture, Sports, Science and Technology, H17-Men-eki-009, H18-Choujyu-037, and H20-Choujyu-009 from the Ministry of Health, Labour and Welfare, Research Aid from the Japanese Orthopaedic Association, a Grant from the Japanese Orthopaedics and Traumatology Foundation, Inc. (No. 166), and a Grant-in-Aid for Scientific Research, Scientific Research (C22591639) from the Japanese Society for the Promotion of Science. The sponsors had no role in study design, data collection, data analysis, data interpretation, or in writing of the report.

The authors wish to thank Mrs Tomoko Takijiri and other members of the Public Office in Hidakagawa Town, and Mrs Tamako Tsutsumi, Mrs Kanami Maeda, and other members of the Public Office in Taiji Town for their assistance in the location and scheduling of participants for examinations.

References

1. Katz JN, Harris MB. Lumbar spinal stenosis. N Engl J Med 2008;358:818–25.
2. Deyo RA, Mirza SK, Martin BI, Kreuter W, Goodman DC, Jarvik JG. Trends, major medical complications, and charges associated with surgery for lumbar spinal stenosis in older adults. JAMA 2010;303:1259–65.
3. Roberson GH, Llewellyn HJ, Taveras JM. The narrow lumbar spinal canal syndrome. Radiology 1973;107:89–97.
4. Johnsson KE. Lumbar spinal stenosis. A retrospective study of 163 cases in southern Sweden. Acta Orthop Scand 1995;66:403–5.
5. Bischoff RJ, Rodriguez RP, Gupta K, Righi A, Dalton JE, Whitecloud TS. A comparison of computed tomography–myelography, magnetic resonance imaging, and myelography in the diagnosis of herniated nucleus pulposus and spinal stenosis. J Spinal Disord 1993;6:289–95.

6. Jia LS, Shi ZR. MRI and myelography in the diagnosis of lumbar canal stenosis and disc herniation. A comparative study. Chin Med J (Engl) 1991;104:303–6.
7. Jensen MC, Brant-Zawadzki MN, Obuchowski N, Modic MT, Malkasian D, Ross JS. Magnetic resonance imaging of the lumbar spine in people without back pain. N Engl J Med 1994;331:69–73.
8. Boden SD, Davis DO, Dina TS, Patronas NJ, Wiesel SW. Abnormal magnetic-resonance scans of the lumbar spine in asymptomatic subjects. A prospective investigation. J Bone Joint Surg Am 1990;72:403–8.
9. Winter CC, Brandes M, Müller C, Schubert T, Ringling M, Hillmann A, *et al.* Walking ability during daily life in patients with osteoarthritis of the knee or the hip and lumbar spinal stenosis: a cross sectional study. BMC Musculoskelet Disord 2010;11:233.
10. Whitehurst M, Brown LE, Eidelson SG, D'angelo A. Functional mobility performance in an elderly population with lumbar spinal stenosis. Arch Phys Med Rehabil 2001;82:464–7.
11. Muraki S, Oka H, Akune T, Mabuchi A, En-yo Y, Yoshida M. Prevalence of radiographic lumbar spondylosis and its association with low back pain in the elderly of population-based cohorts: the ROAD study. Ann Rheum Dis 2008;68:1401–6.
12. Muraki S, Oka H, Akune T, Mabuchi A, En-yo Y, Yoshida M. Prevalence of radiographic knee osteoarthritis and its association with knee pain in the elderly of Japanese population-based cohorts: the ROAD study. Osteoarthritis Cartilage 2009;17:1137–43.
13. Yoshimura N, Muraki S, Oka H, Mabuchi A, En-yo Y, Yoshida M. Prevalence of knee osteoarthritis, lumbar spondylosis and osteoporosis in Japanese men and women: the Research on Osteoarthritis/osteoporosis Against Disability (ROAD). J Bone Miner Metab 2009;27:620–8.
14. Yoshimura N, Muraki S, Oka H, Kawaguchi H, Nakamura K, Akune T. Cohort profile: Research on Osteoarthritis/osteoporosis Against Disability (ROAD) study. Int J Epidemiol 2010;39:988–95.
15. Judge JO, Davis 3rd RB, Ounpuu S. Step length reductions in advanced age: the role of ankle and hip kinetics. J Gerontol A Biol Sci Med Sci 1996;51:M303–12.
16. Steffan TM, Hacker TA, Mollinger L. Age- and gender-related test performance in community-dwelling older people: six-minute walk test, Berg balance scale, timed up and go test, and gait speeds. Phys Ther 2002;82:128–37.
17. Bohannon RW. Comfortable and maximum walking speed of adults aged 20–79 years: reference values and determinants. Age Ageing 1997;26:15–9.
18. Judge JO, Lindsey C, Underwood M, Winsemius D. Balance improvements in older women: effects of exercise training. Phys Ther 1993;73:254–64.
19. Guralnik JM, Simonsick EM, Ferrucci L, Glynn RJ, Berkman LF, Blazer DG. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. J Gerontol 1994;49:85–94.
20. Bohannon RW. Sit-to-stand test for measuring performance of lower extremity muscles. Percept Mot Skills 1995;80:163–6.
21. Bohannon RW, Larkin PA, Cook AC, Gear J, Singer J. Decrease in timed balance test scores with aging. Phys Ther 1984;64:1067–70.
22. Springer BA, Marin R, Cyhan T, Roberts H, Gill NW. Normative values for the unipedal stance test with eyes open and closed. J Geriatr Phys Ther 2007;30(2001):8–15.
23. Stucki G, Daltroy L, Liang MH, Lipson SJ, Fossel AH, Katz JN. Measurement properties of a self-administered outcome measure in lumbar spinal stenosis. Spine 1996;21:796–803.
24. North American Spine Society Clinical Guidelines. III. Definition and Natural History of Degenerative Lumbar Spinal Stenosis 2008. 11.
25. Fardon DF, Milette PC. Nomenclature and classification of lumbar disc pathology. Recommendations of the combined task forces of the North American spine society, American society of spine radiology, and American society of neuroradiology. Spine 2001;26:93–113.
26. Suri P, Rainville J, Kalichman L, Katz JN. Does this older adult with lower extremity pain have the clinical syndrome of lumbar spinal stenosis? JAMA 2010;304:2628–36.
27. Martinelli TA, Wiesel SW. Epidemiology of spinal stenosis. Instr Course Lect 1992;41:179–81.
28. Verbiest H. Pathomorphologic aspects of developmental lumbar stenosis. Orthop Clin North Am 1975;6:177–96.
29. Getty CJ. Lumbar spinal stenosis: the clinical spectrum and the results of operation. J Bone Joint Surg Br 1980;62:481–5.
30. Kellgren JH, Lawrence JS, Eds. The Epidemiology of Chronic Rheumatism: Atlas of Standard Radiographs of Arthritis. Oxford: Blackwell Scientific; 1963.
31. Ministry of Health, Labour and Welfare. The Report of National Health and Nutrition Survey, http://www.mhlw.go.jp/bunya/kenkou/eiyou07/01.html;.

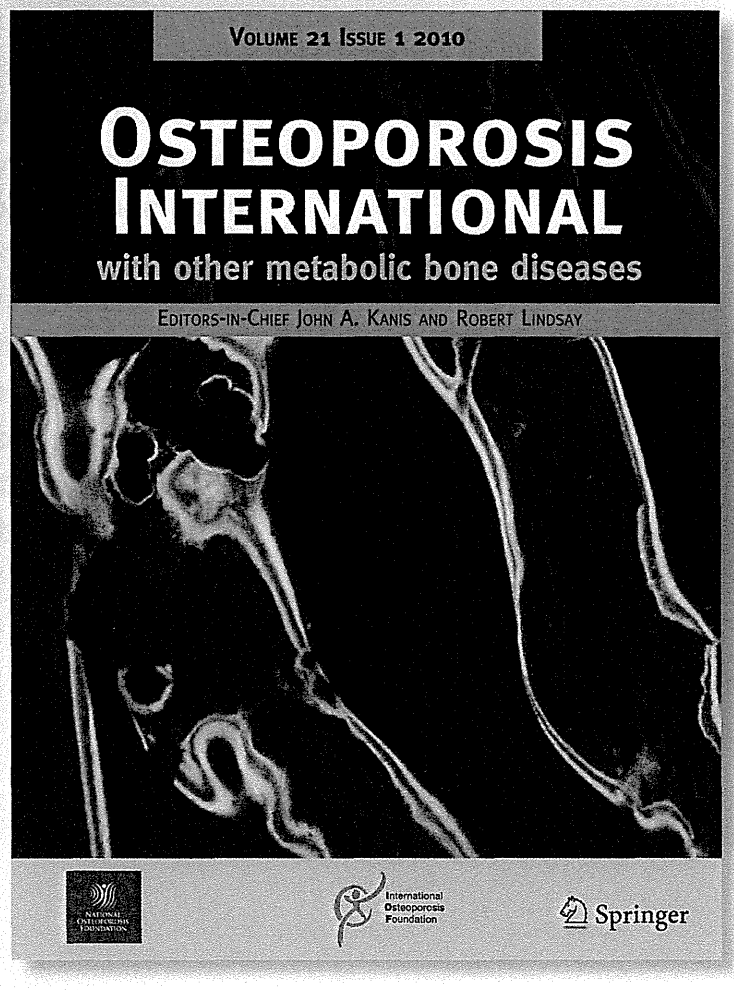
Physical performance, bone and joint diseases, and incidence of falls in Japanese men and women: a longitudinal cohort study

S. Muraki, T. Akune, H. Oka, Y. Ishimoto, K. Nagata, M. Yoshida, F. Tokimura, K. Nakamura, H. Kawaguchi & N. Yoshimura

Osteoporosis International
With other metabolic bone diseases

ISSN 0937-941X

Osteoporos Int
DOI 10.1007/s00198-012-1967-0



Springer

Osteoporos Int
DOI 10.1007/s00198-012-1967-0

ORIGINAL ARTICLE

Physical performance, bone and joint diseases, and incidence of falls in Japanese men and women: a longitudinal cohort study

S. Muraki · T. Akune · H. Oka · Y. Ishimoto · K. Nagata · M. Yoshida · F. Tokimura · K. Nakamura · H. Kawaguchi · N. Yoshimura

Received: 20 October 2011 / Accepted: 27 February 2012

Abstract
Summary This study examined whether physical performance and bone and joint diseases were risk factors for falls in 745 men and 1,470 women from the Research on Osteoarthritis/osteoporosis Against Disability (ROAD) study (mean, 69.7 years). Slower walking speed was a risk factor for falls in men and women. Knee pain was a risk factor for falls in women.

Introduction The objective of the present study was to clarify the incidence of falls by sex and age and to determine whether physical performance and bone and joint diseases are risk factors for falls in men and women using a large-scale population-based cohort of the ROAD.
Methods A total of 745 men and 1,470 women were analyzed in the present study (mean age, 68.5 years). A questionnaire assessed the number of falls during 3 years of follow-up. Grip strength and walking speed were measured at baseline. Knee and lumbar spine radiographs were read by Kellgren–Lawrence (KL) grade; radiographic knee osteoarthritis and lumbar spondylosis were defined as KL=3 or 4. Knee and lower back pain were estimated by an interview.
Results During a mean follow-up of 3 years, 141 (18.9 %) men and 362 (24.6 %) women reported at least one fall. Slower walking speed was a risk factor for falls in men (0.1 m/s decrease; odds ratio [OR], 1.15; 95 % confidence interval [CI], 1.09–1.23) and women (0.1 m/s decrease; OR, 1.05; 95 % CI, 1.01–1.10). Knee pain was also a risk factor for falls (OR, 1.38; 95 % CI, 1.03–1.84) in women, but lower back pain was not.
Conclusion We examined the incidence and risk factors for falls in men and women. Slower walking speed was a risk factor for falls in men and women. Knee pain was a risk factor for falls in women.

Keywords Falls · Longitudinal study · Osteoarthritis · Pain · Walking speed

S. Muraki (✉) · T. Akune
Department of Clinical Motor System Medicine, 22nd Century Medical and Research Center, Faculty of Medicine, The University of Tokyo,
Hongo 7-3-1,
Bunkyo-ku, Tokyo 113-8655, Japan
e-mail: murakis-ort@h.u-tokyo.ac.jp

H. Oka · N. Yoshimura
Department of Joint Disease Research, 22nd Century Medical and Research Center, Faculty of Medicine, The University of Tokyo, Tokyo, Japan

Y. Ishimoto · K. Nagata · M. Yoshida
Department of Orthopaedic Surgery, Wakayama Medical University, Wakayama, Japan

F. Tokimura
Department of Orthopaedic Surgery, Tokyo Metropolitan Geriatric Hospital, Tokyo, Japan

K. Nakamura
Rehabilitation Services Bureau, National Rehabilitation Center for Persons with Disabilities, Saitama, Japan

H. Kawaguchi
Department of Sensory and Motor System Medicine, Faculty of Medicine, The University of Tokyo, Tokyo, Japan

Introduction

Falls are one of the main causes of injury, disability, and death among the elderly [1, 2]. In Japan, according to the

Published online: 21 March 2012

recent National Livelihood Survey of the Ministry of Health, Labour and Welfare, falls and fractures are ranked fifth among diseases that cause disabilities and subsequently require support with activities of daily living [3]. However, there have been few population-based studies on the incidence of falls based on sex and age. Further, in terms of factors associated with falls, muscle strength, balance, vision, functional capacities, and cognitive impairment are traits that diminish with aging, and these factors have been suggested as predictive risk factors for falls and fractures [4, 5]. However, there have been few studies regarding the association of bone and joint diseases, especially osteoarthritis (OA), with falls [6–10].

The representative sites of OA are the knee and lumbar spine. Knee OA and lumbar spondylosis (LS) are major public health issues because they cause chronic pain and disability [11–16]. The prevalence of radiographic knee OA and LS is high in Japan [17, 18], with 25,300,000 and 37,900,000 subjects aged 40 years and older estimated to experience radiographic knee OA and LS, respectively [19]. The National Livelihood Survey ranked OA fourth among diseases that cause disabilities and subsequently require support with activities of daily living [3], but there have been few studies of the association between falls and OA [6–10]. In previous studies, knee OA was assessed only by interview and not by radiography [6, 7]. The principal clinical symptom of knee OA is pain [20], but its correlation with the radiographic severity of knee OA is not as strong as expected [17, 21–23]. Thus, knee OA diagnosed by interview could be limited by variable accuracy. In addition, men and women were not examined separately in these previous studies, although sex differences have been found in the prevalence of knee OA [17]. Further, prevalence of OA has been shown to be different between races [17]; thus, the association of OA with falls may be different among races. To the best of our knowledge, there are no population-based studies of Japanese men and women to determine the association of OA with falls in a longitudinal model. Our previous study showed that knee pain was significantly associated with falls in Japanese women [24], but that study used a cross-sectional design; thus, a causal relationship remains unclear. With regard to LS, to the best of our knowledge, there have been no population-based studies regarding its association with falls except for our previous cross-sectional study [24], which showed that LS was not significantly associated with falls.

Measuring walking speed is a simple way to assess health and function in older adults [25–27]. Walking speed has been found to be associated with falls in a few studies [4, 28–32], although most studies were limited by small sample size or cross-sectional design [29, 30] or evaluation of a single sex [4, 32]. In addition, although walking abnormalities such as slower walking speed are significantly associated with bone and joint diseases such as knee OA, LS, and their pain [24], there have been no longitudinal studies to determine the associations of falls with bone and joint diseases and walking abnormalities at the same time. Thus, whether the association of slower walking speeds with falls is independent of bone and joint diseases remains unclear.

The objectives of this study were to clarify the incidence of falls by sex and age in Japan using a population-based longitudinal cohort study known as Research on Osteoarthritis/osteoporosis Against Disability (ROAD). Further, we examined the associations of physical performance and bone and joint diseases with the incidence of falls in Japanese men and women.

Methods

Subjects

The ROAD study is a nationwide, prospective study designed to establish epidemiologic indexes for the evaluation of clinical evidence for the development of a disease-modifying treatment for bone and joint diseases (OA and osteoporosis are the representative bone and joint diseases, respectively). It consists of population-based cohorts in three communities in Japan. A detailed profile of the ROAD study has been described elsewhere [17–19, 33]; a brief summary is provided here. To date, we have completed the creation of a baseline database that includes clinical and genetic information for 3,040 subjects (1,061 men and 1,979 women) of age ranging from 23 to 95 years (mean, 70.6 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.

Residents of these regions were recruited from the resident registration lists of the relevant region. Participants in the urban region were recruited from a randomly selected cohort from the Itabashi Ward residents' registration database [34]. The participation rate was 75.6 %. Participants in mountainous and coastal regions were also recruited from the resident registration lists, and the participation rates in these two areas were 56.7 and 31.7 %, respectively. The inclusion criteria, apart from residence in the communities mentioned above, were the ability to (1) walk to the survey site, (2) report data, and (3) understand and sign an informed consent form. The baseline survey of the ROAD study was completed in 2006. 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.