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ORIGINAL ARTICLE

Reference values for hand grip strength, muscle mass, walking time, and one-leg standing time as indices for locomotive syndrome and associated disability: the second survey of the ROAD study

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Abstract

Background We established reference values for hand grip strength, muscle mass, walking time, and one-leg standing time as indices reflecting components of locomotive syndrome and associated disability using a large-scale population-based sample from the second survey of the Research on Osteoarthritis/Osteoporosis Against Disability (ROAD) cohort.

Methods We measured the above-mentioned indices in 2,468 individuals ≥40 years old (826 men, 1,642 women; mean age 71.8 years) during the second visit of the ROAD study. Disability was defined as certified disability according to the long-term care insurance system through public health centres of each municipality.

Results Mean values for hand grip strength (weaker side), muscle mass of the thighs, walking time for 6 m at the usual pace, and the fastest pace for men were 32.7 kg, 7.0 kg, 5.6 s, and 3.7 s, respectively, and those for women were 20.8 kg, 5.2 kg, 5.9 s, and 4.1 s, respectively. The median values for one-leg standing time (weaker side) were 14 s for men and 12 s for women. The prevalence of disability in men aged 65–69, 70–74, 75–79, and ≥80 was 0.0, 1.0, 6.3, and 8.8%, respectively, and in women was 3.4, 3.5, 9.2, and 14.7%, respectively. There were significant associations between the presence of disability and walking time for 6 m at the usual pace and at the fastest pace, and between the presence of disability and walking speed.

Conclusions We established reference values for indices reflecting components of locomotive syndrome, and identified significant associations between walking ability and disability.

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Introduction

Musculoskeletal diseases, including osteoarthritis (OA) and osteoporosis (OP), are major public health problems among the elderly that affect activities of daily living (ADL) and quality of life (QOL), leading to increased morbidity and mortality. According to the recent National Livelihood Survey by the Ministry of Health, Labour, and Welfare in Japan, OA is ranked fourth, while falls and osteoporotic fractures are ranked fifth among diseases that cause disabilities and subsequently require support for ADL [1]. Previous studies have reported increased mortality following osteoporotic fractures at the hip and other sites [2], and have estimated that a total of 47,000,000 people (21,000,000 men and 26,000,000 women) aged ≥40 years will eventually be affected by either OA or OP. Considering that the population of Japan is aging very rapidly—more than 22% of the population is aged ≥65 years [3]—a comprehensive and evidence-based prevention strategy for musculoskeletal diseases is urgently needed.

The Japanese Orthopaedic Association has proposed the term 'locomotive syndrome' to designate a condition in high-risk groups with musculoskeletal diseases who are highly likely to require nursing care [4]. Locomotive syndrome is caused by weakening of musculoskeletal organs such as bone, joint, and muscle, which in turn interferes with physical performance, especially self-transportation. Loss of locomotor abilities such as walking causes disabilities requiring support. Therefore, to prevent decline into disability, it is important to maintain a healthy range of bone, joint, muscle, and physical performance.

These four components, bone, joint, muscle, and physical performance, each have objective measurements that can be used as indices to evaluate their present condition. For example, bone mineral density (BMD) is a representative index of the condition of the bone. Joint space width (JSW), joint space area (JSA), and osteophyte area (OPA) are indices reflecting the condition of the joint. Regarding muscle, although the best index remains controversial, hand grip strength can be used to reflect muscle strength [5], and muscle mass is one index of muscle volume [6]. In addition, as objective indices of physical performance, walking speed and/or one-leg standing times are candidates [7, 8]. However, at present, it is difficult to use such indices for evaluating, diagnosing, or predicting the future occurrence and progression of locomotive syndrome in Japan, because there is little information on reference values for such indices to distinguish patients at risk from normal individuals in a large population-based cohort.

In 2005–2007, we began a large-scale population-based cohort study entitled Research on Osteoarthritis/Osteoporosis Against Disability (ROAD), consisting of 3,040 participants in three communities located in urban, mountainous, and coastal areas (baseline study). Following the baseline study, a second survey was performed in the same communities in 2008–2010, in which 2,674 inhabitants participated (second visit).

Through analysis of the baseline data of the ROAD, the age-gender distribution of BMD has been reported as an index for bone mass [3], and the medial and lateral JSW, medial and lateral JSA, OPA, and femorotibial angle of the knee have been reported as indices of the health of joints [9] in these populations. However, there is still scant information regarding the condition of the muscles and physical performance. Therefore, in the present study, we aimed to establish reference values for hand grip strength as an index of muscle power, muscle mass as an index of muscle volume, and walking time and one-leg standing time as indices of physical performance, classified by age and gender, using the data from the second visit of the ROAD study. This information is expected to be valuable for early diagnosis and prevention of locomotive syndrome. In addition, we evaluated the prevalence of disabilities in participants in the ROAD study second visit, and identified associations between hand grip strength, muscle mass, walking time, and one-leg standing time and the presence of disability.

Participants and methods

Participants

Reference values were obtained from the results of cross-sectional measurements of participants enrolled in the second visit of the ROAD study. The ROAD study, which began in 2005, is a nationwide prospective study comprising population-based cohorts established in three communities, such as urban, mountainous, and coastal regions in Japan. Recruitment methods for this study have been described in detail elsewhere [3]. To date, participants in the urban region, aged ≥60 years, were recruited from among those enrolled in a randomly selected cohort study from the previously established Itabashi Ward resident's registration database. The response rate was 75.6%. Participants in the mountainous and coastal regions, aged ≥40 years, were recruited from listings of resident registration. Residents aged ≤60 years in the urban area and ≤40 years in the mountainous and coastal areas who were interested in participating in the study were invited. We have completed development of a baseline database including clinical and genetic information for 3,040 inhabitants aged 23–95 years (1,061 men, 1,979 women).

The second visit of the ROAD study began in 2008 and was completed in 2010. All the participants in the baseline study were invited to participate in the second visit. In addition to the former participants, inhabitants aged ≥60 years in the urban area and those aged ≥40 years in the mountainous and coastal areas who were willing to participate in the ROAD survey performed in 2008–2010 were also included in the second visit. In addition, residents aged ≤60 years in the urban area and ≤40 years in the mountainous and coastal areas who were interested in participating in the study were invited to be examined as well as the baseline.

The inclusion criteria of participants were as follows: (1) ability to walk to the clinic where the survey was performed, (2) ability to provide self-reported data, and (3) ability to understand and sign an informed consent form. No other exclusion criteria were used.

Thus, a total of 2,674 residents (892 men, 1,782 women) aged 21–97 years participated in the second visit. In the present study, we analysed the data for 2,468 individuals (826 men, 1,642 women; mean age 71.8 years); this population comprised 956 individuals (318 men, 638 women) in the urban region, 726 individuals (258 men, 468 women) in the mountainous region, and 786 individuals (250 men, 536 women) in the coastal region who participated in the second visit and were ≥40 years old.

All the participants provided written informed consent, and the study was conducted with the approval of the ethics committees of the participating institutions.

Hand grip strength, muscle mass, walking time, and one-leg standing time

Hand grip strength was measured bilaterally using a Toei Light handgrip dynamometer (Toei Light Co., Ltd., Saitama, Japan). Both hands were tested, and the better value was used to characterise the maximum muscle strength of the subject.

Among the 2,468 participants who participated in the second visit of the ROAD study, 778 residents (248 men, 530 women) in the coastal town of Taiji were examined to determine their segmental muscle mass using the bioelectrical impedance method (BIP; Physion MD; Physion Inc., Kyoto, Japan). We obtained values for the muscle masses of the right and left forearms, upper arms, upper limbs, quadriceps, thighs, lower legs, and lower limbs. This method had previously been validated as having a close correlation to muscle volume as measured by magnetic resonance imaging [10].

Among the 2,468 participants who participated in the second visit of the ROAD study, 1,637 residents (559 men, 1,078 women) of the mountainous town of Hidakagawa and the coastal town of Taiji were examined to determine their walking time. Walking time was measured as the time required to complete a 6-m course. All participants walked the 6-m course twice; they first walked at their usual walking speed and then repeated the course at their fastest pace.

Among the 2,468 participants who participated in the second visit of the ROAD study, one-leg standing time with eyes open was measured on both sides for 2,433 individuals (816 men, 1,617 women). The time until the raised leg was set down on the floor was measured, with a maximum time of 60 s recorded for those who could stand on one leg for at least that length of time. The shorter value of the two measurements was used as the worse side and the longer measurement as the better side for the one-leg standing time of the subject.

Mean values and standard deviations (SDs) of hand grip strength, muscle mass, and walking time were classified by gender and age group (40, 50, 60, 70, and ≥80 s) to establish age-gender reference values for the general population. However, reference values classified by gender and age group for one-leg standing time were established using median (50th percentile) values and 25th–75th percentile ranges. These values were recorded using a maximum time of 60 s for anyone who could exceed that time; thus, the data do not fit a normal distribution, and use of means and SDs is unsuitable for one-leg standing time reference values.

Presence of disability

Disability in the present study was defined as 'cases requiring long-term care' as determined by the long-term care insurance system based on the Long-Term Care Insurance Act of 1997 in Japan. The procedure for identifying cases requiring long-term care is as follows: (1) each municipality establishes a long-term care approval board consisting of clinical experts, physicians, and specialists at the Division of Health and Welfare in each municipal office; (2) the long-term care approval board investigates the insured person using an interviewer-administered questionnaire consisting of 82 items regarding mental and physical condition and makes a screening judgement based on the opinion of a regular doctor; and (3) 'cases requiring long-term care' are determined according to standards for long-term care certification uniformly and objectively applied nationwide [11].

During the 3 years between the baseline and the second visit of the ROAD study, we annually obtained information on the participating residents regarding deaths, changes of residence, and presence or absence of certified disability according to the long-term care insurance system from the public health centres of the participating municipalities.

Statistical analysis

All statistical analyses were performed using Stata statistical software (Stata, College Station, TX, USA). Differences in the values of the indices were tested for significance using analysis of variance for comparisons among multiple groups. Scheffé's least significant difference test was then used for pairs of age groups.

To ascertain associations between the presence of disability and hand grip strength, muscle mass, walking time, and one-leg standing time, logistic regression analyses were performed using the presence of disability (yes, 1; no, 0) as an objective factor, and values for hand grip strength, muscle mass, walking time, and one-leg standing time as the explanatory factor after adjusting for age, gender, and body mass index (BMI, kg/m^2).

Results

Characteristics of participants

Summary characteristics including age, height, weight, and BMI of the participants in the present study are shown in Table 1. Two-thirds of the 2,468 subjects were women, and the mean age of the female participants was 1 year younger than that of the male participants. Height and weight were significantly lower for women than for men, but no significant difference in BMI was noted between the genders. All anthropometric measurements other than BMI of females tended to decrease with age. BMI of women in their 80s and older was significantly lower than that in younger age groups, while there were no significant differences among age groups 40–70 years old.

Reference values for hand grip strength, muscle mass, walking time, and one-leg standing time

Table 1 also shows the age-gender distribution of hand grip strength for both the better and worse sides. Mean hand grip strength in men was significantly higher than that in women ($p < 0.001$) and decreased with age in both men and women ($p < 0.001$).

Mean muscle mass for both forearms, both upper arms, both upper limbs, both quadriceps, both thighs, both lower legs, and both lower limbs are shown in Table 2. Muscle masses for all parts of the body were significantly higher in men than in women ($p < 0.001$). Mean muscle mass in men decreased with age for all areas except the lower leg. Particularly in the quadriceps and thighs, muscle masses in men aged ≥70 were significantly lower than those in their 40s–50s ($p < 0.05$). By contrast, although muscle mass for women aged ≥80 and older tended to be lower than those of younger age groups (other than the lower legs), there

Table 1 Mean values (standard deviation) of anthropometric measurements and hand grip strength of the participants classified by sex and gender

Age strata (years)	Number of subjects	Weight (kg)	Height (cm)	Body mass index (g/cm^2)	Grip strength (better side) (kg)	Grip strength (worse side) (kg)
Men						
40–49	32	73.5 (10.2)	170.3 (7.3)	25.4 (3.6)	49.5 (8.2)	49.3 (8.4)
50–59	100	68.8 (10.6)	168.0 (5.2)	24.3 (3.3)	47.3 (7.0)	42.6 (6.9)
60–69	137	65.4 (11.1)^{a}	165.2 (6.2)^{a,b}	23.9 (3.5)	41.4 (6.6)^{a,b}	36.9 (7.9)^{a,b}
70–79	308	60.0 (8.1)^{a,b,c}	161.1 (5.7)^{a,b,c}	23.1 (2.7)^{a,b}	35.4 (6.8)^{a,b,c}	31.5 (7.1)^{a,b,c}
80 and older	249	57.2 (8.9)^{a,b,c,d}	159.7 (6.0)^{a,b,c}	22.4 (2.9)^{a,b,c}	29.7 (6.2)^{a,b,c,d}	26.3 (6.3)^{a,b,c,d}
Total	826	61.6 (10.3)	162.5 (6.7)	23.3 (3.1)	36.6 (9.1)	32.7 (9.1)
Women						
40–49	93	55.9 (9.5)	157.0 (4.4)	22.6 (3.5)	31.2 (4.3)	28.2 (4.4)
50–59	191	55.3 (8.9)	154.4 (5.8)^{a}	23.2 (3.7)	28.7 (4.9)^{a}	25.4 (4.9)^{a}
60–69	316	54.2 (8.0)	152.0 (5.5)^{a,b}	23.4 (3.2)	26.6 (4.3)^{a,b}	23.77 (4.5)^{a,b}
70–79	599	51.3 (8.5)^{a,b,c}	148.4 (5.9)^{a,b,c}	23.3 (3.5)	22.6 (4.6)^{a,b,c}	19.7 (4.7)^{a,b,c}
80 and older	443	47.4 (8.3)^{a,b,c,d}	145.5 (5.9)^{a,b,c,d}	22.4 (3.6)^{c,d}	19.4 (4.4)^{a,b,c,d}	16.6 (4.6)^{a,b,c,d}
Total	1,642	51.6 (8.9)	149.5 (6.7)	23.0 (3.5)	23.7 (5.8)	20.8 (5.8)

[a] Significantly different ($p < 0.05$) from values of the age group in their 40s

[b] Significantly different ($p < 0.05$) from values of the age group in their 50s

[c] Significantly different ($p < 0.05$) from values of the age group in their 60s

[d] Significantly different ($p < 0.05$) from values of the age group in their 70s

Table 2 Mean values (standard deviation) of segmental muscle mass (kg) in total right and left sides classified by age and gender

Age strata (years)	Number of subjects	Forearm	Upper arm	Upper limb	Quadriceps	Thigh	Lower leg	Lower limb
Men								
40–49	25	1.20 (0.19)	1.59 (0.36)	2.79 (0.54)	3.91 (0.64)	7.76 (1.19)	3.41 (0.66)	11.16 (1.69)
50–59	60	1.18 (0.16)	1.53 (0.28)	2.71 (0.41)	3.73 (0.64)	7.45 (1.22)	3.41 (0.66)	10.86 (1.60)
60–69	67	1.15 (0.17)	1.50 (0.28)	2.65 (0.42)	3.50 (0.68)	7.02 (1.28)	3.52 (0.86)	10.54 (1.89)
70–79	66	1.17 (0.20)	1.43 (0.28)	2.60 (0.46)	3.37 (0.66)[a]	6.78 (1.26)[a]	3.51 (0.68)	10.29 (1.70)
80 and older	30	1.11 (0.17)	1.37 (0.26)	2.48 (0.38)	3.10 (0.62)[a,b]	6.27 (1.18)[a,b]	3.92 (1.11)	10.18 (2.05)
Total	248	1.16 (0.18)	1.48 (0.29)	2.65 (0.44)	3.52 (0.69)	7.04 (1.30)	3.53 (0.80)	10.57 (1.79)
Women								
40–49	67	0.77 (0.12)	0.86 (0.19)	1.63 (0.30)	2.65 (0.60)	5.37 (1.12)	2.65 (0.47)	8.02 (1.45)
50–59	124	0.76 (0.10)	0.82 (0.16)	1.58 (0.24)	2.56 (0.44)	5.20 (0.82)	2.58 (0.51)	7.78 (1.20)
60–69	161	0.78 (0.11)	0.84 (0.16)	1.62 (0.25)	2.55 (0.45)	5.18 (0.84)	2.57 (0.42)	7.74 (1.10)
70–79	130	0.80 (0.12)[b]	0.85 (0.16)	1.66 (0.27)	2.54 (0.46)	5.17 (0.85)	2.66 (0.53)	7.83 (1.24)
80 and older	48	0.79 (0.43)	0.82 (0.16)	1.61 (0.28)	2.39 (0.45)	4.90 (0.84)	2.91 (0.69)[b,c]	7.81 (1.38)
Total	530	0.78 (0.11)	0.84 (0.16)	1.62 (0.26)	2.55 (0.47)	5.18 (0.88)	2.63 (0.51)	7.81 (1.23)

[a] Significantly different ($p < 0.05$) from values of the age group in their 40s

[b] Significantly different ($p < 0.05$) from values of the age group in their 50s

[c] Significantly different ($p < 0.05$) from values of the age group in their 60s

were no specific trends in muscle mass among age groups ≤79 years old. However, as for men, the muscle mass of the quadriceps in women tended to decline with age, although the difference was not statistically significant.

Mean 6-m walking time and the calculated walking speed (m/s) using the walking time, classified by age and gender, are shown in Table 3. Six-meter walking time was significantly lower in men than in women ($p < 0.05$), indicating that men tended to walk faster than women in this study population. Mean 6-m walking time for both men and women increased with age. In particular, 6-m walking times for men and women ≥70 years old were significantly higher than those in younger age groups ($p < 0.05$).

Table 4 shows median one-leg standing time classified by age and gender with 25th–75th percentile ranges. For both men and women in their 40s–50s, all median, 25th percentile, and 75th percentile values were 60 s, with no gender difference. One-leg standing times for men ≥60 years old tended to be higher than those for women, and median values declined with age in both men and women.

Prevalence of disability among subjects ≥65 years old

Among the 2,468 participants in the second visit of the ROAD study, we surveyed 1,845 subjects (625 men, 1,220 women) ≥65 years old and obtained information on the presence or absence of disability certified for long-term care insurance. We found a total of 149 individuals (8.1%; 36 men, 5.8%; 113 women, 9.3%) that were certified as requiring support. Figure 1 shows the prevalence of disability classified by gender and age. The prevalence of disability in men 65–69, 70–74, 75–79, and ≥80 years old was 0.0, 1.0, 6.3, and 8.8%, respectively, and that in women in the same age groups was 3.4, 3.5, 9.2, and 14.7%, respectively (Fig. 1). The prevalence of disability in women was significantly higher than that in men ($p < 0.05$) and increased with age in both genders ($p < 0.01$).

Associations between disability and hand grip strength, muscle mass, walking speed, and one-leg standing time

Logistic regression analysis was performed using the presence of disability (1, yes; 0, no) as an objective factor, and hand grip strength on the better side and the worse side; muscle mass of the forearms, upper arms, upper limbs, quadriceps, thighs, lower legs, and lower limbs; walking time for 6 m at the usual pace and at the fastest pace; and quartile of one-leg standing time [0: 0–25% (highest quartile), 1: 25–50% (higher quartile), 2: 50–75% (lower quartile), 3: 75–100% (the lowest quartile] on the better and worse sides as explanatory factors, after adjusting for age, gender, and BMI. No significant associations were found between the presence of disability and hand grip strength, muscle mass, or one-leg standing time. However, there were significant associations between the presence of disability and 6-m walking time at the usual

Table 3 Mean values (standard deviation) of 6-m walking time (s) and walking speed (m/s) with usual pace and the fastest pace classified by age and gender

Age strata (years)	Number of subjects	Usual pace		Fastest pace	
		Time for 6 m (s)	Walking speed (m/s)	Time for 6 m (s)	Walking speed (m/s)
Men					
40–49	32	4.4 (0.6)	1.38 (0.19)	3.0 (0.5)	2.09 (0.43)
50–59	100	4.8 (0.9)	1.29 (0.20)	3.2 (0.6)	1.97 (0.36)
60–69	134	5.1 (0.9)	1.21 (0.20)[a]	3.4 (0.7)	1.82 (0.33)[a]
70–79	196	5.9 (1.8)[a,b,c]	1.09 (0.25)[a,b,c]	4.0 (1.4)[a,b,c]	1.62 (0.39)[a,b,c]
80 and older	97	6.8 (3.0)[a,b,c,d]	0.99 (0.33)[a,b,c,d]	4.5 (1.8)[a,b,c,d]	1.48 (0.44)[a,b,c]
Total	559	5.6 (1.9)	1.15 (0.27)	3.7 (1.3)	1.73 (0.42)
Women					
40–49	92	4.7 (1.0)	1.32 (0.24)	3.2 (0.6)	1.95 (0.31)
50–59	190	4.9 (0.9)	1.27 (0.23)	3.3 (0.7)	1.87 (0.33)
60–69	299	5.1 (1.1)	1.22 (0.23)	3.7 (0.8)	1.71 (0.32)[a,b]
70–79	345	6.3 (2.4)[a,b,c]	1.03 (0.25)[a,b,c]	4.4 (1.5)[a,b,c]	1.46 (0.36)[a,b,c]
80 and older	152	8.4 (3.9)[a,b,c,d]	0.82 (0.27)[a,b,c,d]	5.8 (2.7)[a,b,c,d]	1.17 (0.36)[a,b,c,d]
Total	1,078	5.9 (2.4)	1.12 (0.29)	4.1 (1.6)	1.60 (0.42)

[a] Significantly different ($p < 0.05$) from values of the age group in their 40s
[b] Significantly different ($p < 0.05$) from values of the age group in their 50s
[c] Significantly different ($p < 0.05$) from values of the age group in their 60s
[d] Significantly different ($p < 0.05$) from values of the age group in their 70s

Table 4 Values of median (25–75 percentile) of one-leg standing time (s, maximum = 60 s) in a better side and a worse side classified by age and gender

Age strata (years)	Number of subjects	One-leg standing time (better side) (s)	One-leg standing time (worse side) (s)
Men			
40–49	32	60 (60–60)	60 (60–60)
50–59	99	60 (60–60)	60 (60–60)
60–69	136	60 (34.5–60)	45 (14.25–60)
70–79	303	27 (9–60)	9 (4–35)
80 and older	246	8 (4–32)	4 (2–12)
Total	816	39.5 (8–30)	14 (4–60)
Women			
40–49	92	60 (60–60)	60 (60–60)
50–59	191	60 (60–60)	60 (43–60)
60–69	317	60 (41.5–60)	43 (13–60)
70–79	593	21 (8–57.5)	8 (3–25)
80 and older	424	7 (3–18.8)	3 (2–7)
Total	1,617	31 (8–60)	12 (4–60)

pace [+1 s, odds ratio (OR) 1.15, 95% confidential interval (CI) 1.07–1.24, $p < 0.001$] and at the fastest pace (+1 s, OR 1.22, 95% CI 1.08–1.38, $p < 0.01$). In addition, there were significant associations between the presence of disability and walking speed at the usual pace (+1 m/s, OR 0.07, 95% CI 0.02–0.27, $p < 0.001$) and at the fastest pace (+1 m/s, OR 0.16, 95% CI 0.06–0.41, $p < 0.001$).

Discussion

In this study, we established age-gender-classified mean values for hand grip strength as an index of muscle strength, muscle mass as an index of muscle volume, and walking time and median one-leg standing time as indices of physical performance, using data for a large-scale

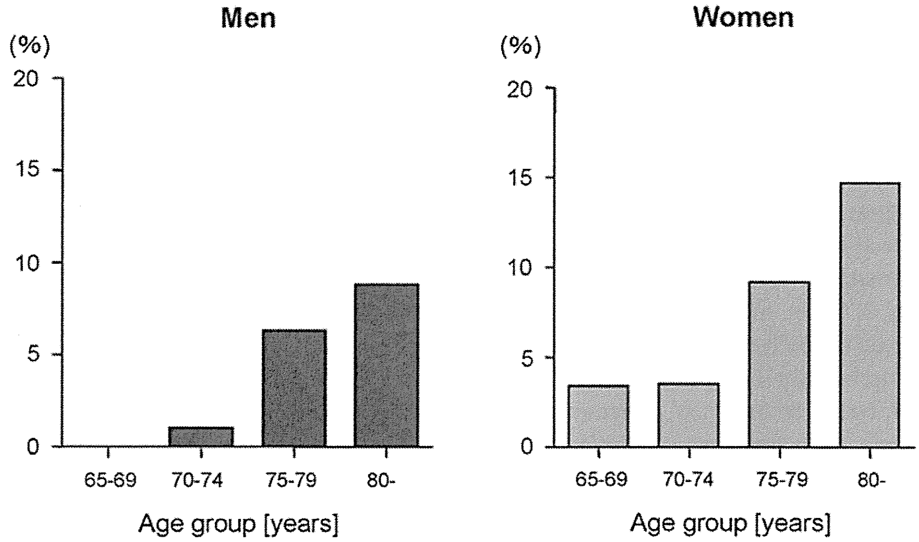

Fig. 1 Prevalence of disability among subjects ≥65 years old classified by gender and age

population-based cohort. We found that mean hand grip strength, muscle mass, walking time, and median one-leg standing time were higher in men than in women, and decreased with age (with the exception of the muscle mass of the lower legs).

The Japanese Ministry of Education, Culture, Sports, Science, and Technology has reported ranges for physical strength and sporting ability in 69,745 Japanese men and women 6–79 years old. Mean hand grip strength in both men and women reaches peak values between the ages of 20–40, and decreases with age after 40 [12]. In the present study of a population aged ≥40 years, hand grip strength declined significantly with age, consistent with the previous report of the Japanese government.

Although computed tomography or MRI scans are the most reliable methods of measuring segmental muscle mass, these methods are not suitable for a large-scale population-based study. The BIA method is rapid, inexpensive, portable, and importantly, a noninvasive measuring method. Previous studies have shown that there is a strong correlation between BIA resistance and measurements of skeletal muscle mass in the arms [13], legs [13], and whole body [14]. For the BIA method used in the present study, Miyatani et al. [10] had previously compared values for muscle mass using a series of cross-sectional images of the forearm, upper arm, lower leg, and thigh on the right side of 22 male subjects as determined by the BIA and MRI methods. The BIA impedance index (L^2/Z) for every segment, calculated as the ratio of the segment length squared to the impedance, was significantly correlated with the muscle volume measured by MRI, with $r = 0.902$–0.976 ($p < 0.05$). These previous results demonstrate that the BIA method used in the present study is sufficiently reliable as an index of muscle volume.

In the present study, age-related differences were observed in the thighs and quadriceps. In addition, the age-related decreases in muscle mass were greater in the lower limbs than in the upper limbs, and in proximal sites than in distal sites. Yamada et al. [15] estimated the bioelectrical impedance (BI) index, calculated as the ratio of the square of segmental length to impedance in a Japanese population consisting of 1,006 individuals (374 men, 632 women) and reported that the BI index decreased most with age in the thighs, whereas there were no significant age-related changes in the forearms or lower limbs. Miyatani et al. [16] studied muscle thickness at nine sites, the forearm, anterior and posterior upper arm, abdomen, subscapular, anterior and posterior thigh, and anterior and posterior lower leg, using brightness-mode ultrasonography in 348 Japanese men aged 20–79 years. They found a greater decrease in muscle thickness in the trunk and anterior thigh than at other sites, consistent with our results. They speculated that site-related differences in muscle loss with aging may be attributed to age-related changes in the patterns of loading to and/or activation of individual muscles in daily life. However, because these results were obtained from a cross-sectional study, longitudinal data would be required to determine the mechanism of these differences. We have begun the third visit of the ROAD study, 6 years after the baseline and 3 years after the second visit, to measure losses of skeletal muscle mass at various sites. Losses of muscle mass in the quadriceps and/or thighs may result in a decrease in walking ability, including walking speed. Therefore, establishment of reference values for muscle mass is useful for prediction of future disability.

Walking ability is regarded as the most important activity for the elderly to maintain an independent life in the community, and walking speed is an important index of walking ability. Reference values have been published for populations in western countries [17, 18]; however, there has been little information available for the Japanese population. Takahashi et al. [19] surveyed walking speed at 130 crosswalks and reported that at least 1.0 m/s was required to safely cross the street. In the present study, we determined that the mean 6-m walking time at the usual pace at an age of ≥40 years was 5.6 s for men and 5.9 s for women, and the mean 6-m walking time at the fastest pace was 3.7 s in men and 4.1 s in women. These walking speeds for both the usual pace and the fastest pace provide a baseline for clinical judgments of patient performance and could be used to determine which subjects would benefit from therapeutic intervention to improve locomotive function.

The Japanese Ministry of Education, Culture, Sports, Science and Technology published mean values for one-leg standing time with a maximum time of 120 s using 5,500 individuals (2,741 men, 2,759 women) with an age range of 65–79 years in each prefecture who participated in an examination of sporting ability, including walking ability [12]. They reported that mean one-leg standing times for men 65–69, 70–74, and 75–79 years old were 79.9, 66.5, and 50.5 s, respectively, and those for women were 80.8, 62.1, and 45.0 s, respectively. These values were measured up to 120 s, and ours were measured up to 60 s. Because the measuring method was different and their outcomes are means while our results are medians, the results cannot be compared directly. However, one-leg standing time was significantly lower with age in both studies. Again, establishment of reference values for physical performance, including walking and standing ability, would be useful for prediction of future disability.

We then evaluated associations between hand grip strength, muscle mass, walking time, and one-leg standing time, as indices reflecting components of locomotive syndrome and the presence of disability. We found that the 6-m walking time may be a useful index for detection of disability. To evaluate the independence of elderly persons in daily life, physical performance has been measured using various outcomes. Walking speed has been reported to be one important index that can predict future disability, hospitalisation, and mortality in the general geriatric population [20, 21]. In a Japanese population, Shinkai et al. [22] demonstrated that lower scores on baseline performance measures, particularly maximum walking speed, predicted an increased risk of onset of functional dependence, based on their 6-year follow-up of a cohort in a rural community consisting of 736 participants. In the present study, a 1-s slower normal walking time for 6 m was associated with a 15% increase in the presence of disability, and a 1-s slower fastest walking time for 6-m was associated with a 22% increase in the presence of disability. Our study evaluated only walking ability and the presence of disability, not the occurrence of disability; however, we expect to follow these populations and clarify the predictive ability of walking speed for the occurrence of disability over the next few years.

On the other hand, no associations were found between indices such as hand grip strength, muscle mass, and one-leg standing time and the presence of disability. There is growing evidence that reduced hand grip strength is associated with adverse outcomes in older years, including morbidity, lower quality of life, higher fracture rates, increased length of hospital stay, and mortality [23–25]. Progressive decline in muscle mass has been defined as sarcopenia, which represents an impaired state of health associated with morbidity disorders, increased risk of falls and fractures, impaired ADL, loss of independence, and increased risk of death [6, 26–29]. Lang et al. [29] stated that loss of muscle mass and power increases the difficulties associated with procuring adequate nutrition and the effort required to undertake exercise; the combination of nutritional loss and reduced physical activity levels results in further loss of muscle mass and power. The resulting decrements in power, endurance, and physical performance lead to a loss of independence. In addition to muscle strength and mass, balance appears to be an important index of disability. Shinkai et al. [22] measured the one-leg standing time of 736 participants in a cohort established in a rural community, and the individuals in the lowest performance quartile had a significantly higher occurrence of disability.

Self-selection bias is suggested as a possible reason for the lack of associations between hand grip strength, muscle mass, and one-leg standing time and disability observed here, compared with previous reports. Self-selection bias is one type of sampling bias exhibited by subjects who voluntarily enrol in an epidemiological study. In this second visit of the ROAD study, volunteers who could walk to the clinic where the survey was performed, and could understand and sign an informed consent form, and who wanted to learn about their bone and joint conditions were welcomed. Therefore, the participants in the second survey may have been healthier than the general Japanese population. In fact, the estimated number of persons with disability in Japan using the age-gender prevalence of the second visit and the age-gender distribution of the Japanese population based on the national census in 2007 would be estimated at 1,510,000 (350,000 men, 1,160,000 women), considerably lower than the 4,940,000 reported by the government in 2010. Thus, self-selection bias likely affected the reference values; the reference values for hand grip strength, muscle mass, and one-leg standing time obtained from the present study may be higher, and walking speed faster, than the actual values. However, self-selection bias is somewhat unavoidable in such an examination, because it is impossible to obtain measurements for individuals who cannot grasp a handgrip dynamometer or walk 6 m. This bias should be taken into consideration when reference values are used, including not only those obtained from the present study, but also from the national survey of physical strength and sporting ability published by the government.

In addition to self-selection bias, this study has several limitations. First, our results were obtained from a cross-sectional study of the second visit of the ROAD study; thus, we can not conclude causal relationships between such indices and disability, since some of the indices, such as muscle mass and one-leg standing time, were first introduced and performed during the second visit. We have begun the third visit of the ROAD study to clarify the relationships between physical performance and the occurrence of disability. Once the significance of indices reflecting components of locomotive syndrome can be determined as predictors for the occurrence of disability, appropriate thresholds can be developed as predictors of future disability. In addition, because of the lack of sufficient information, we could not determine the disorders that caused the disability. Thus, the disabled status of the participants in the present study might have been affected by various diseases such as cardiovascular diseases, dementia, or other diseases. However, regardless of the cause of disability, we found that walking ability was significantly associated with the presence of disability.

Conclusions

We have established reference values for hand grip strength, muscle mass, walking time, and one-leg standing time using data for a large-scale population-based cohort, and identified gender and age differences in the reference values. In addition, we determined that walking ability, including walking time and walking speed at the usual and maximum pace, was significantly associated with the presence of disability.

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Conflict of interest No conflict of interest has been declared by the authors.

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Incidence and Risk Factors for Radiographic Knee Osteoarthritis and Knee Pain in Japanese Men and Women

A Longitudinal Population-Based Cohort Study

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Objective. **To examine the incidence and progression of radiographic knee osteoarthritis (OA) and the incidence of knee pain, and their risk factors in Japan, using the large-scale population of the nationwide cohort study ROAD (Research on Osteoarthritis/osteoporosis Against Disability).**

Methods. **Subjects from the ROAD study who had been recruited in 2005–2007 were followed up with knee radiography 3 years later. A total of 2,262 paired radiographs (74.4% of the original sample) were scored using the Kellgren/Lawrence (K/L) grading system, and the incidence and progression rate of knee OA was examined. The incidence rate of knee pain was also examined. In addition, risk factors were tested for their association with incident and progressive radiographic knee OA and incident knee pain.**

Results. **Given the ~3.3-year followup, the rate of incident K/L grade ≥2 radiographic knee OA was 6.9% and 11.9% in men and women, respectively, while that of K/L grade ≥3 knee OA was 8.4% and 13.9% in men and women, respectively. The rate of progressive knee OA was 17.8% and 22.3% in men and women, respectively. The incident rate of knee pain was 21.2% and 27.3% in men and women, respectively. Female sex was a risk factor for incident K/L grade ≥2 knee OA, but was not associated with incident K/L grade ≥3 knee OA or progressive knee OA. Knee pain was a risk factor for incident and progressive knee OA. Previous knee injury was a risk factor for knee pain but not for radiographic knee OA.**

Conclusion. **The present longitudinal study revealed a high incidence of radiographic knee OA in Japan.**

Knee osteoarthritis (OA), characterized by pathologic features including joint space narrowing and osteophytosis, is a major public health issue causing chronic pain and disability in the elderly in most developed countries (1). The prevalence of radiographic knee OA is high in Japan (2), with 25,300,000 subjects ages ≥40 years estimated to experience radiographic knee OA (3). According to the recent National Livelihood Survey of the Ministry of Health, Labor, and Welfare in Japan, OA is ranked fourth among diseases that cause

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disabilities that subsequently require support with activities of daily living (4). Despite the urgent need of strategies for the prevention and treatment of this condition, there have only been a few studies of rates of incidence and progression of knee OA (5–9). Furthermore, to the best of our knowledge, there has been no study of the incidence or progression of knee OA in Asians, although large differences in prevalence of knee OA exist among the different races (2,10,11).

Previous studies that investigated risk factors for knee OA (12–23) showed that obesity, previous knee injury, female sex, muscle strength, occupational activities, and older age were risk factors for knee OA mainly in Caucasians. However, in addition to the differences in prevalence among different ethnic groups, anthropometric measurements and environmental situations varied substantially in different countries. Thus, findings in Caucasians cannot be applied to different ethnic groups. Few population-based cohort studies have examined risk factors for knee OA in Asians.

The principal clinical symptom of knee OA is knee pain (24). Ours and other previous studies have demonstrated that the impact of knee pain on quality of life is disproportionate to the radiographic changes themselves in the knee (25,26). Several cross-sectional studies have investigated the factors associated with knee pain (25,27), but in most of those studies, radiographic findings were not included in the analysis, although radiographic severity of knee OA is an important factor for knee pain (2). Furthermore, there have been few longitudinal studies of the incidence of knee pain that include radiographic findings in the analysis.

The objective of the present study was to clarify the incidence and progression rate of radiographic knee OA as well as the incidence of knee pain in Japanese men and women using the large-scale, population-based cohort study known as the Research on Osteoarthritis/osteoporosis Against Disability (ROAD). In addition, we examined the risk factors for the incidence and progression of knee OA as well as for the incidence of knee pain.

SUBJECTS AND METHODS

Subjects. The ROAD study was a nationwide prospective study of bone and joint diseases (with osteoarthritis and osteoporosis as the representative bone and joint diseases) constituting population-based cohorts established in several communities in Japan. As a detailed profile of the ROAD study has already been described elsewhere (2,3,28), a brief summary is provided here. In 2005–2007, we created a baseline database that included the 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), recruited from listings of resident registrations in 3 communities: an urban region in Itabashi, Tokyo; a mountainous region in Hidakagawa, Wakayama; and a coastal region in Taiji, Wakayama. Participants in the urban region were recruited from a randomly selected cohort from the Itabashi-ward residents' registration database (29). 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 2 areas were 56.7% and 31.7%, respectively. The inclusion criteria, apart from residence in the communities mentioned above, were the ability to walk to the survey site, report data, and understand and sign an informed consent form. 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 Geriatric Medical Center.

Participants completed an interviewer-administered questionnaire of 400 items that included lifestyle information such as smoking habit, alcohol consumption, family history, medical history, and previous knee injury history. Anthropometric measurements included height and weight, from which the body mass index (BMI) (weight [kg]/height [m^2]) was calculated. Grip strength was measured on bilateral sides using a TOEI LIGHT handgrip dynamometer, and the better measurement was used to represent maximum muscle strength. Furthermore, all participants were interviewed by well-experienced orthopedists regarding pain in both knees, who asked "Have you experienced right knee pain on most days in the past month, in addition to now?" and "Have you experienced left knee pain on most days in the past month, in addition to now?" Subjects who answered "yes" were defined as having knee pain.

In 2008–2010, we attempted to trace and review all 3,040 subjects; they were invited to attend a followup interview and undergo repeat radiography. The interviews, which included questions about current knee pain, were conducted by the same trained orthopedists who undertook the baseline study in 2005–2007. Anthropometric measurements also included height, weight, and grip strength at followup.

Radiographic assessment. All participants underwent radiographic examination of both knees using an anteroposterior view with weight-bearing and foot map positioning. Fluoroscopic guidance with a horizontal anteroposterior x-ray beam was used to properly visualize the joint space. Knee radiographs at baseline and followup were read in pairs without knowledge of the participant's clinical status by a single well-experienced orthopedist (SM), and the Kellgren/Lawrence (K/L) grade was defined using the K/L radiographic atlas for overall knee radiographic grades (30). In the K/L grading system, radiographs are scored from grade 0 to grade 4, with the higher grades being associated with more severe OA. To evaluate the intraobserver variability of the K/L grading, 100 randomly selected radiographs of the knee were scored by the same observer >1 month after the first reading. One hundred other radiographs were also scored by 2 experienced orthopedic surgeons (SM and HO) using the same atlas for interobserver variability. The intra- and intervariabilities evaluated for K/L grade (0–4) were confirmed by kappa

Table 1. Baseline characteristics of the participants*

	Overall (n = 2,262)	Men (n = 763)	Women (n = 1,499)
Age, years	68.7 ± 11.3	69.6 ± 11.1	68.2 ± 11.4†
Height, cm	154.6 ± 8.8	163.1 ± 6.6	150.3 ± 6.4†
Weight, kg	55.4 ± 10.2	62.2 ± 9.9	51.9 ± 8.4†
BMI, kg/m^2	23.1 ± 3.3	23.3 ± 3.0	23.0 ± 3.4†
Grip strength, kg	26.2 ± 9.2	34.3 ± 8.8	22.1 ± 6.2†
OA prevalence, no. (%)			
K/L grade ≥1	1,898 (83.9)	586 (76.8)	1,312 (87.5)‡
K/L grade ≥2	1,164 (51.5)	296 (38.8)	868 (57.9)‡
K/L grade ≥3	355 (15.7)	75 (9.8)	280 (18.7)‡
Knee pain, no. (%)	478 (21.1)	111 (14.6)	367 (24.5)‡
Previous knee injury, no. (%)	217 (9.6)	52 (6.8)	165 (11.0)‡
Smoking, no. (%)	212 (9.4)	165 (21.6)	47 (3.1)‡
Alcohol, no. (%)	831 (36.7)	483 (63.3)	348 (23.2)‡

* Except where indicated otherwise, values are the mean ± SD. BMI = body mass index; OA = osteoarthritis; K/L = Kellgren/Lawrence.
† $P < 0.05$ versus men, by Student's unpaired t-test.
‡ $P < 0.05$ versus men, by chi-square test.

analysis to be sufficient for assessment ($\kappa = 0.86$ and $\kappa = 0.80$, respectively).

For the purposes of this study, we defined 4 knee OA outcomes. First, a subject was defined as having incident K/L grade ≥1 radiographic knee OA if both knees had less than grade 1 disease at baseline and if at least one knee had grade 1 or higher disease at followup. Second, a subject was defined as having incident K/L grade ≥2 radiographic knee OA if both knees had less than grade 2 disease at baseline and if at least one knee had grade 2 or higher disease at followup. Third, incident K/L grade ≥3 radiographic knee OA was defined as less than grade 3 disease in both knees at baseline and grade 3 or higher disease in at least one knee at followup. Fourth, progressive knee OA was defined as K/L grade 2 and K/L grade 3 knee OA at baseline (because K/L grade 4 knee OA cannot progress) and an increase by at least 1 grade in the affected knee at followup.

Statistical analysis. Odds ratios (ORs) and 95% confidence intervals (95% CIs) are provided. The differences in age, height, weight, BMI, and grip strength between men and women were examined using Student's unpaired t-test. To compare the prevalence of radiographic knee OA and knee pain between men and women, we performed the chi-square test. A logistic regression analysis was used to determine the association of incident radiographic knee OA, progressive knee OA, and incident knee pain with age in men and women. To determine risk factors for incident knee OA and progressive knee OA, a univariate generalized estimating equation (GEE) logistic regression analysis was used. Furthermore, to determine independent risk factors, multiple GEE logistic regression analysis was used with significant risk factors in a univariate GEE logistic regression analysis model as independent variables. Incident knee pain was defined as no knee pain in both knees at baseline and knee pain in at least one knee at followup. To determine risk factors for incident knee pain, a univariate GEE logistic regression analysis was used. Furthermore, to determine independent risk factors, multiple GEE logistic regression analysis was used with significant risk factors in a univariate logistic regression analysis model in addition to regions as independent variables. When we analyzed risk factors for incident knee OA, progressive knee OA, and incident knee pain, K/L grade at baseline, knee pain at baseline, and previous knee injury were defined for the knee which had the incident OA, progressive OA, and incident pain, respectively. Data analyses were performed using SAS software, version 9.0 (SAS Institute).

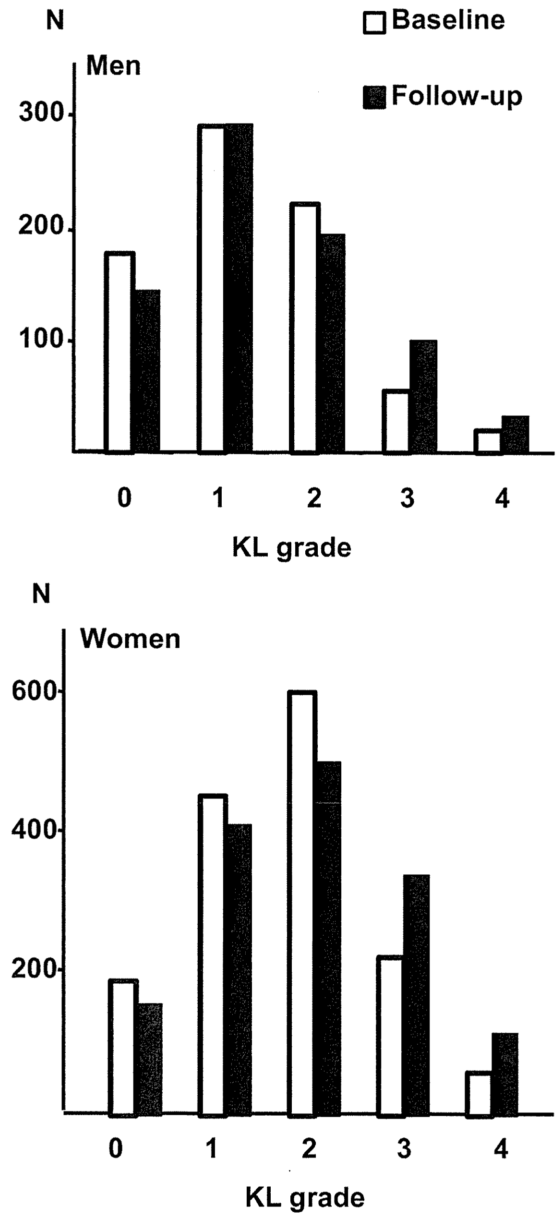

Figure 1. Number (N) of male and female subjects by Kellgren/Lawrence (K/L) grade at baseline and followup.

Table 2. Incidence of radiographic knee OA, progressive knee OA, and knee pain according to sex*

	K/L grade ≥1		K/L grade ≥2		K/L grade ≥3		Progressive knee OA		Knee pain	
	No. at risk	Cumulative incidence, no. (%)	No. at risk	Cumulative incidence, no. (%)	No. at risk	Cumulative incidence, no. (%)	No. at risk	Cumulative incidence, no. (%)	No. at risk	Cumulative incidence, no. (%)
Overall	364	70 (19.2)	1,098	107 (9.7)	1,907	228 (12.0)	1,084	229 (21.1)	1,784	447 (25.1)
Men	177	35 (19.8)	467	32 (6.9)	688	58 (8.4)	276	49 (17.8)	652	138 (21.2)
Women	187	35 (18.7)	631	75 (11.9)†	1,219	169 (13.9)†	808	180 (22.3)	1,132	309 (27.3)†

* See Table 1 for definitions.
† $P < 0.05$ versus men, by chi-square test.

RESULTS

Of the 3,040 subjects in the baseline study in 2005–2007, 125 (4.1%) had died by the time of the review 3 years later, 123 (4.0%) did not participate in the followup study due to bad health, 69 (2.3%) had moved away, 83 (2.7%) declined the invitation to attend the followup study, and 155 (5.1%) did not participate in the followup study for other reasons. Among the 2,485 subjects who did participate in the followup study, 175 (5.8%) did not undergo plain radiography and 18 (0.6%) provided incomplete pain questionnaires; these were excluded. We also excluded 30 subjects (1.0%) who underwent total knee arthroplasty before the followup study, leaving a total of 2,262 subjects (74.4%) (763 men and 1,499 women) from whom paired radiographs and complete pain histories were obtained. Their mean ± SD age at followup was 72.2 ± 11.4 years. The mean ± SD duration of followup between initial and second radiographs was 3.3 ± 0.6 years. Those participating in the followup study were younger than those who did not survive or who did not participate for other reasons (mean age 68.6 years for responders versus 75.1 years for nonresponders; $P < 0.0001$). The followup study participants also were more likely to be women (66.3% of responders were women and 61.8% of nonresponders were women; $P = 0.03$) and were less likely to have knee OA at the baseline examination than either those who did not survive to followup or those who did not participate for other reasons (51.5% of responders versus 60.9% of nonresponders; $P < 0.0001$).

The characteristics of the 2,262 participants at baseline in the ROAD study are shown in Table 1. Men were significantly older than women, while BMI was higher in men than in women. The prevalence of knee OA and knee pain was significantly higher in women than in men at baseline. The proportion of previous knee injuries was also higher in women than in men. The number of subjects with each K/L grade at baseline and at followup is shown in Figure 1.

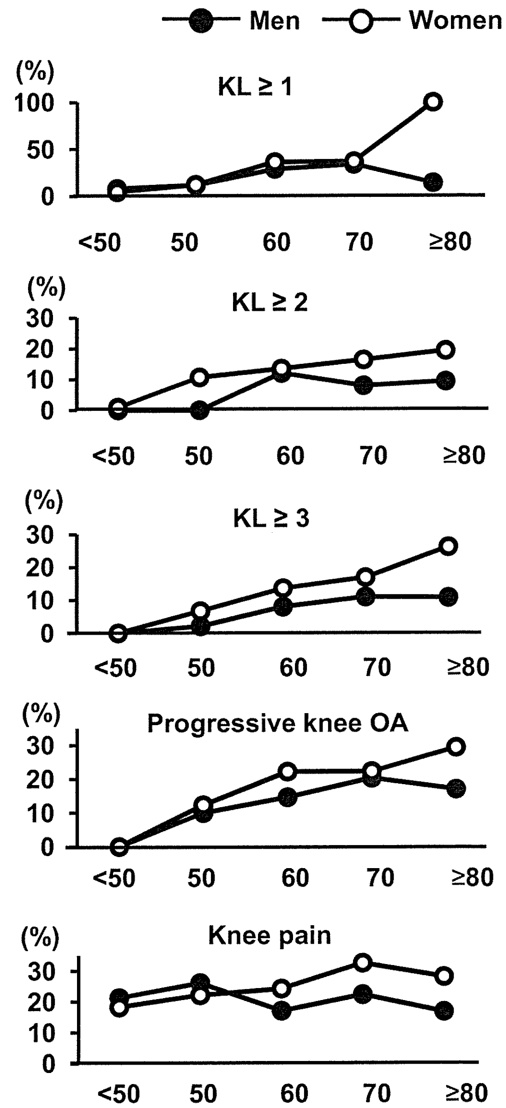

Figure 2. Percentage of subjects with incident radiographic knee osteoarthritis (OA) (Kellgren/Lawrence [K/L] grade ≥1, ≥2, or ≥3), progressive knee OA, and incident knee pain in each age stratum (<50 years, 50–59 years, 60–69 years, 70–79 years, and ≥80 years).

Table 3. Risk factors for incident radiographic knee osteoarthritis*

	K/L grade ≥2			K/L grade ≥3		
	No./total no. (%) of subjects	Crude OR (95% CI)	Adjusted OR (95% CI)	No./total no. (%) of subjects	Crude OR (95% CI)	Adjusted OR (95% CI)
Age (+5 years)	–	1.26 (1.15–1.39)	1.31 (1.15–1.49)	–	1.33 (1.23–1.44)	1.25 (1.13–1.39)
BMI (+5 kg/m²)	–	2.00 (1.49–2.69)	2.43 (1.76–3.39)	–	1.67 (1.36–2.04)	1.68 (1.35–2.11)
Grip strength (+1 kg)	–	0.96 (0.94–0.98)	1.01 (0.97–1.04)	–	0.95 (0.94–0.97)	1.00 (0.97–1.02)
Sex						
Men	32/467 (6.9)	Referent	Referent	58/688 (8.4)	Referent	Referent
Women	75/631 (11.9)	1.83 (1.20–2.86)	2.76 (1.50–5.18)	169/1,219 (13.9)	1.75 (1.28–2.41)	1.42 (0.88–2.29)
K/L grade at baseline						
0	–	Referent	Referent	–	Referent	Referent
1	–	4.11 (2.33–7.83)	2.48 (1.35–4.87)	–	1.91 (0.69–5.43)	1.29 (0.45–3.80)
2	–	–	–	–	5.69 (2.38–14.30)	5.94 (1.07–35.83)
Knee pain at baseline						
No	–	Referent	–	–	Referent	Referent
Yes	–	0.91 (0.32–2.24)	–	–	3.77 (2.44–5.73)	2.53 (1.59–4.00)
Previous knee injury						
No	–	Referent	–	–	Referent	–
Yes	–	4.08 (0.66–18.8)	–	–	1.24 (0.45–3.11)	–
Smoking						
No	99/958 (10.3)	Referent	–	213/1,713 (12.4)	Referent	Referent
Yes	8/140 (5.7)	0.53 (0.23–1.04)	–	14/194 (7.2)	0.55 (0.30–0.93)	1.07 (0.55–1.94)
Alcohol use						
No	68/627 (10.9)	Referent	–	158/1,171 (13.5)	Referent	Referent
Yes	39/471 (8.3)	0.74 (0.49–1.12)	–	69/736 (9.4)	0.66 (0.49–0.89)	0.96 (0.67–1.36)

* Adjusted odds ratios (ORs) were calculated by multiple generalized estimating equation logistic regression analysis after adjustment for all other variables in addition to regions. We show all variables we analyzed in the present study. K/L = Kellgren/Lawrence; 95% CI = 95% confidence interval; BMI = body mass index.

Table 2 shows the rates of incident and progressive knee OA and incident knee pain in the overall population and subgroups classified by sex. The incidences of K/L grade ≥2 and K/L grade ≥3 knee OA and knee pain were significantly higher in women than in men, while there were no significant differences in the incidence of K/L grade ≥1 knee OA and the progression of knee OA between men and women. The incidence and progression rate of knee OA tended to increase with age in men and women (for 5-year increase: K/L grade ≥1, OR 1.22 [95% CI 1.06–1.43] and OR 1.52 [95% CI 1.29–1.84], respectively; K/L grade ≥2, OR 1.35 [95% CI 1.12–1.67] and OR 1.29 [95% CI 1.15–1.45], respectively; K/L grade ≥3, OR 1.34 [95% CI 1.15–1.58] and OR 1.35 [95% CI 1.24–1.49], respectively; progressive knee OA, OR 1.15 [95% CI 0.95–1.42] and OR 1.15 [95% CI 1.0–1.28], respectively) (Figure 2). Interestingly, the incidence rate of knee pain was age-dependent in women (OR 1.10 [95% CI 1.04–1.17]), while it was not age-dependent in men (OR 0.97 [95% CI 0.90–1.06]). Furthermore, in subjects age <60 years, the incidence of knee pain was similar between women and men (OR 1.12 [95% CI 0.88–1.42]), while in subjects age >60 years, the incidence of knee pain was significantly higher in women than in men (OR 0.78 [95% CI 0.68–0.88]) (Figure 2).

Table 3 shows the baseline risk factors for incident radiographic knee OA. Univariate logistic regression analysis showed that age, BMI, grip strength, sex, and K/L grade were associated with incident K/L grade ≥2 knee OA. Age, BMI, grip strength, sex, K/L grade, knee pain at baseline, previous knee injury, smoking, and alcohol consumption were associated with incident K/L grade ≥3 knee OA. We then determined independent risk factors using a multiple logistic regression analysis that included the above significant factors in the univariate model in addition to regions as independent variables. The results showed that age and BMI were risk factors for incident K/L grade ≥2 and incident K/L grade ≥3 knee OA. Female sex was a risk factor for incident K/L grade ≥2 knee OA, while being female was not significantly associated with incident K/L grade ≥3 knee OA. A more severe K/L grade at baseline was strongly associated with incident K/L grade ≥2 and incident K/L grade ≥3 knee OA. Knee pain at baseline was significantly associated with incident K/L grade ≥3 knee OA.

Univariate logistic regression analysis showed

Table 4. Risk factors for progressive knee OA and incident knee pain*

	Progressive knee OA			Knee pain		
	No./total no. (%) of subjects	Crude OR (95% CI)	Adjusted OR (95% CI)	No./total no. (%) of subjects	Crude OR (95% CI)	Adjusted OR (95% CI)
Age (+5 years)	–	1.14 (1.04–1.25)	1.17 (1.05–1.30)	–	1.05 (1.01–1.10)	1.01 (0.95–1.07)
BMI (+5 kg/m^2)	–	1.47 (1.20–1.80)	1.43 (1.16–1.77)	–	1.60 (1.37–1.88)	1.54 (1.30–1.82)
Grip strength (+1 kg)	–	0.98 (0.96–1.00)	0.99 (0.96–1.01)	–	0.98 (0.97–1.00)	1.00 (0.98–1.02)
Sex						
Men	49/276 (17.8)	Referent	–	138/652 (21.2)	Referent	Referent
Women	180/808 (22.3)	1.33 (0.94–1.90)	–	309/1,132 (27.3)	1.40 (1.11–1.76)	1.32 (0.94–1.84)
K/L grade at baseline						
0 and 1	–	–	–	–	Referent	Referent
2	–	–	–	–	1.89 (0.80–4.49)	1.58 (0.65–3.85)
3 and 4	–	–	–	–	3.17 (1.95–5.17)	2.54 (1.52–4.24)
Knee pain at baseline						
No	–	Referent	Referent	–	–	–
Yes	–	2.87 (1.99–4.14)	2.63 (1.81–3.81)	–	–	–
Previous knee injury						
No	–	Referent	–	–	Referent	Referent
Yes	–	0.79 (0.31–1.86)	–	–	3.09 (1.34–7.23)	2.91 (1.26–6.82)
Smoking						
No	219/1,016 (21.6)	Referent	–	411/1,603 (25.6)	Referent	–
Yes	10/68 (14.7)	0.63 (0.30–1.19)	–	36/181 (19.9)	0.72 (0.49–1.04)	–
Alcohol use						
No	168/746 (22.4)	Referent	–	281/1,093 (25.7)	Referent	–
Yes	61/338 (18.1)	0.76 (0.54–1.04)	–	166/691 (24.0)	0.91 (0.73–1.14)	–

* Adjusted ORs were calculated by multiple generalized estimating equation logistic regression analysis after adjustment for all other variables in addition to regions. We show all variables we analyzed in the present study. OA = osteoarthritis (see Table 3 for other definitions).

that age, BMI, grip strength, and knee pain at baseline were associated with progressive knee OA. We then included age, BMI, grip strength, and knee pain at baseline in addition to regions as independent variables in a multiple logistic regression analysis to determine independent risk factors (Table 4). Age and BMI at baseline were risk factors, but their adjusted ORs for progressive knee OA were lower than those for incident K/L grade ≥2 knee OA (Table 4). Knee pain was significantly associated with progressive knee OA.

We further investigated risk factors for incident knee pain (Table 4). Univariate logistic regression analysis showed that age, BMI, grip strength, sex, K/L grade, and previous knee injury were associated with incident knee pain. To determine independent risk factors for knee pain, multiple logistic regression analysis was used with age, BMI, grip strength, sex, K/L grade, and previous knee injury in addition to regions as independent variables. BMI was significantly associated with incident knee pain, but female sex was not associated with incident knee pain. Subjects with K/L grade ≥3 knee OA at baseline had an ~2.5-fold increased risk for incidence of knee pain compared with K/L grade 0 and K/L grade 1 knees. Previous knee injury was also significantly associated with incident knee pain.

DISCUSSION

This is the first population-based study to examine the incidence and progression of knee OA and risk factors for incident and progressive knee OA among Japanese men and women. We also examined the incident rate of knee pain and its risk factors. The present study showed high rates of incident knee OA, progressive knee OA, and incident knee pain.

Few population-based studies have examined incident radiographic knee OA (6–9). In the Framingham Osteoarthritis Study (6), given the ~8.1-year followup, the incident rate of K/L grade ≥2 knee OA was 11.1% and 18.1% (1.4% and 2.2% per year) in Caucasian men and women, respectively. A population-based study in the UK (18) showed that given the ~5.1-year followup, the incident rate of K/L grade ≥2 knee OA was 18.5% (2.3% per year), but men and women were not separated in the analysis. In the present study, the incidence of K/L grade ≥2 OA was 2.0% and 3.7% per year in men and women, respectively, which is a little higher than that in previous epidemiologic studies in the US and Europe (6,8), implying that the incidence is higher among Japanese than in Caucasians. This is compatible with our findings regarding prevalence of K/L grade ≥2 knee OA in our previous study (2), which showed that the prevalence of K/L grade ≥2 knee OA was much higher in Japanese people than in Caucasians (10,11).

For incident K/L grade ≥3 knee OA, to the best of our knowledge no population-based studies have been previously reported. In the Chingford Study (7), knee OA was not defined according to K/L grade but according to osteophytosis and joint space narrowing. The Chingford Study showed that given the ~4-year followup, the incidence of joint space narrowing was 12.6% (3.2% per year) in women, which may be comparable to our results for incident K/L grade ≥3 knee OA, considering the K/L grade definition; however, a closer comparison provides quite limited accuracy.

In the present study, the incident rate of K/L grade ≥3 knee OA was 4.1% per year in Japanese women, which was also a little higher than that seen in Caucasian women. However, this higher incident rate of K/L grade ≥3 may be partly explained by the definition of K/L grade ≥3 knee OA, because by considering any knees that start at K/L grade <3 as eligible for this outcome, we combined incident (e.g., knees starting at K/L grade 0–1) and progressive (knees starting at K/L grade 2) disease. In the present study, we also examined progression of knee OA, and we found that the progression rate of knee OA was 5.2% and 6.3% per year in Japanese men and women, respectively, which was also higher than that in other studies in the US and the UK (2.2–3.9%) (6,8). The higher incidence of radiographic knee OA in Japan could also be due to lifestyle factors, because the traditional Japanese lifestyle includes sitting on the heels on a mat and using Japanese-style lavatories, requiring squatting and kneeling, which are associated with knee OA (31–33). These positions may cause mechanical stress to the knee joint and possibly lead to the acceleration of OA.

Although the rate of incident radiographic knee OA and progressive knee OA increased with age in both sexes, that of knee pain was age-dependent in women but not in men. This may be due to the fact that elderly men generally retire from their occupations at age ~60–70 years, and thus the load on the knees may be lighter in men age >60 years compared with those age <60 years, whereas women must often continue to do household chores even after age 70 years, and thus the load on the knees may not be lighter in women age >70 years compared with those age <70 years.

The present study also showed that age and BMI are risk factors for incident radiographic knee OA, consistent with findings of previous epidemiologic studies (5,7,8). Previous studies have shown that obesity is a strong risk factor for incident knee OA (34), possibly due to the accumulation of mechanical stress on the knee joint. More severe K/L grade was also a risk factor for incident radiographic knee OA in the present study, which is also consistent with findings of previous studies (7,8). Female sex was also a strong risk factor for incident K/L grade ≥2 knee OA, as in previous studies (6,8), possibly implicating the involvement of muscle strength to compensate for mechanical stress, as women are known to have less muscle strength than men in all decades of life (35). However, female sex was not a significant risk factor for incident K/L grade ≥3 knee OA or progressive knee OA. Furthermore, age and BMI at baseline were risk factors for progressive knee OA, but their ORs for progressive knee OA were lower than those for incident K/L grade ≥2 knee OA.

This discordance between the determinants of incidence of K/L grade ≥2 and K/L grade ≥3 knee OA or between those of incidence and progression of knee OA using K/L grade suggests that different mechanisms might influence the initiation of osteophytosis (the principal abnormality in K/L grade 2 disease) and joint space narrowing (the principal abnormality in K/L grade 3 disease). However, since K/L grade was defined by a categorical method, which is comparably insensitive to change, this discordance might simply be a function of the scoring system. Nevertheless, there is also accumulating evidence from previous studies that osteophytosis and joint space narrowing have distinct etiologic mechanisms. A recent cross-sectional study has shown that osteophytosis is unrelated not only to joint space narrowing on plain radiographs, but also to cartilage loss measured by quantitative magnetic resonance imaging (36). Furthermore, our study of an experimental mouse model of OA has identified a cartilage-specific molecule, carminerin, that regulates osteophytosis without affecting joint cartilage destruction during OA progression (37,38). Our most recent findings have implications for our understanding of the pathogenesis of knee OA, as well as for preventive strategies.

In the present study, knee pain was a risk factor for incident K/L grade ≥3 knee OA and progressive knee OA. Subjects with knee pain may tend not to go out or exercise because of the pain, which may lead to lower quadriceps strength. This may be one of the reasons why knee pain is a risk factor for incident and progressive knee OA, as quadriceps weakness has been previously associated with radiographic knee OA (39).

For incidence of knee pain, age was not a risk factor after adjustment for BMI, sex, and K/L grade at baseline. Knee pain occurrence may be mainly due to environmental factors rather than individual factors. As described above, elderly men generally retire from their occupations at ages 60–70 years, and thus the load on the knees may be lighter in men age <60 years compared with those age >60 years, which may partly explain the lack of significant association between age and incidence of knee pain. BMI was a risk factor for incident knee pain even after adjustment for K/L grade at baseline, indicating that obesity is a strong risk factor not only for incident radiographic knee OA but also for incident knee pain. In addition, knee OA at baseline was a risk factor for knee pain, but the ORs for knee pain of K/L grade 2 knee OA and K/L grades 3 and 4 knee OA were just 1.6 and 2.5, respectively. In fact, the proportion of subjects with knee pain of those with K/L grade 2 knee OA and K/L grades 3 and 4 knee OA was just 28.0% and 47.1%, respectively, indicating that ~70% of subjects with K/L grade 2 knee OA who had no knee pain at baseline and ~50% of subjects with K/L grades 3 and 4 knee OA who had no knee pain at baseline also had no knee pain after 3 years.

Previous cross-sectional studies have also demonstrated that correlation of knee pain with radiographic severity of knee OA is not as strong as one would expect (2,40–42), most likely because knee pain may arise from a variety of structures other than joint cartilage, such as the menisci, synovium, ligaments, bursae, bone, and bone marrow (43–47). Hence, comprehensive mechanistic studies of knee pain taking various tissues in and around the knee joint into consideration will be needed to elucidate the relationship between radiographic OA and symptomatic OA.

We were unable to detect an association between knee injury and incident OA in the present study. Other cross-sectional studies of OA prevalence have observed strong association with previous knee injury (48), while the incidence data from the Zoetermeer Study, Framingham Study, and Chingford Study (5–7) also showed a slight increase in risk with interim knee injury but were based on small numbers; no significant association with past knee injury was seen in those groups. In the present study, K/L grade ≥2 knee OA in subjects with previous knee injury was not significantly associated with previous knee injury, which suggests that the association of incident radiographic knee OA with previous knee injury may be weak, although the number of subjects with incident K/L grade ≥2 knee OA who had previous knee injury was just 12. Thus, the small number may partly explain the lack of statistical significance. The present study showed that previous knee injury is a risk factor for incident knee pain. As mentioned above, the correlation of knee pain with radiographic severity of knee OA is not as strong as expected (2,40–42), as knee pain may arise from a variety of structures other than joint cartilage, such as menisci, synovium, ligaments, bursae, bone, and the bone marrow (43–47), and these tissues may have been damaged by a previous knee injury, which may lead to the incident knee pain.

We were unable to detect an association between smoking/drinking alcohol and incident knee OA or knee pain. The association between smoking and incident knee OA is controversial. The Zoetermeer Study showed that smoking has no association with incident knee OA (5), while incidence data from the Framingham Study showed that smoking protects against incident knee OA (49). We were also unable to show any effect of physical activity in this incidence study. However, the numbers and power were too low to examine this group and to confirm or exclude such effects on incidence.

The present study has several limitations. First, the radiographic investigators did not have readers calibrate their readings to those from other studies. Although we reported a higher incidence of radiographic knee OA than in previous studies, differences in radiographic acquisition, scoring techniques, and methodology across studies limit strict comparisons between our results and previous reports. Differences across studies in the thresholds used by readers to define osteophytes may have had a substantial impact on their incidence. The high incidence of knee OA in our study compared to that in other populations may be due to such differences. Second, our analysis did not include patellofemoral joint radiographs, which would likely increase the concordance between radiographic knee OA and its pain. Third, we defined knee pain as present or absent, rather than as a continuous measure such as the Western Ontario and McMaster Universities Osteoarthritis Index (50) or visual analog scale score. Categorical methods are statistically less powerful than continuous methods. Thus, the association between knee pain and other variables might have been underestimated in the present study.

In conclusion, the present longitudinal study, using a large-scale population from the ROAD study, revealed a high incidence of radiographic knee OA in Japan compared with previous studies. Age, BMI, and female sex influence incidence more than radiographic progression of knee OA, indicating that different mechanisms might influence the initiation of osteophytosis and joint space narrowing. Knee pain was a risk factor for radiographic knee OA. Knee injury was not significantly associated with radiographic knee OA, but was a risk factor for incident knee pain. Further progress, along with continued longitudinal surveys within the ROAD study, will elucidate the environmental and genetic backgrounds of knee OA.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Muraki had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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