

IV. 研究成果の刊行物・別刷

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

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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.

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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

Introduction

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

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.

Falls assessment

In 2008–2010, we attempted to trace and review all 3,040 subjects; they were invited to attend a follow-up interview. All subjects were interviewed with regard to falls by experienced interviewers and were asked the following questions: “Have you experienced falls during 3 years of follow-up, and if yes, how many falls did you experience?” According to a previous study on falls [35], a fall is defined as a sudden, unintentional change in position causing an individual to land at a lower level on an object, the floor, or the ground, other than as a consequence of a sudden onset of paralysis, epileptic seizure, or overwhelming external force.

Pain assessment

All subjects were interviewed by experienced orthopedists with regard to knee pain and lower back pain at baseline and were asked the following questions based on previous studies [17, 18]: “Have you experienced knee pain on most days in the past year, in addition to now?” and “Have you experienced lower back pain on most days in the past year, in addition to now?” Those who answered yes were defined as having pain.

Radiographic assessment

At baseline, all participants underwent radiographic examination of both knees using anteroposterior and lateral views with weight-bearing and foot map positioning; radiographic examination of the anteroposterior and lateral views of the lumbar spine, including intervertebral levels L1/2 to L5/S, was also performed. Knee and lumbar spine radiographs were read without the knowledge of participant clinical status by a single, experienced orthopedist (S.M.) using the Kellgren–Lawrence (KL) radiographic atlas [36] to determine the severity of KL grading. Radiographs were scored as grade 0 through 4, with higher grades being associated with more severe OA. We defined knee OA and LS as $KL \geq 3$ in at least one knee and one intervertebral level, respectively. To evaluate the intraobserver variability of KL grading, 100 randomly selected radiographs of the knee and the lumbar spine were scored by the same observer more than 1 month after the first reading. One hundred other radiographs were also scored by two experienced orthopedic surgeons (S.M. and H.O.) using the same atlas for interobserver variability. The intraobserver and interobserver variabilities evaluated were confirmed by kappa analysis to be sufficient for assessment (0.86 and 0.80 for knee OA and 0.84 and 0.76 for LS, respectively).

Physical performance

Anthropometric measurements included height, weight, and body mass index (BMI) (weight [in kilograms]/height² [in

square meters]) at baseline. Grip strength was also measured on bilateral sides using a TOEI LIGHT handgrip dynamometer (TOEI LIGHT CO., LTD., Saitama, Japan) at baseline, and the best measurement was used to characterize maximum muscle strength. To measure physical performance, the time taken to walk 6 m at normal walking speed in a hallway was recorded. Subjects were told to walk from a marked starting line to a 6-m mark as if they were walking down their hallway at home. Time was measured in seconds with a stopwatch and rounded to the nearest hundredth of a second. These walking speed trial measurements are considered highly reliable in community-dwelling elderly subjects [34, 37–39].

Statistical analyses

The differences in age, anthropometric measurements, and physical performance measurements between men and women and between nonfallers and fallers were examined by a nonpaired Student's *t* test. The incidence of falls was also compared between men and women, among subjects with no severe knee OA (KL=0, 1, or 2) and KL=3 or 4 knee OA, among subjects with no severe LS (KL=0, 1, or 2) and KL=3 or 4 LS, among subjects with and without knee pain, and among subjects with and without lower back pain using the chi-square test. Multiple logistic regression analysis after adjustment for age and BMI was used to determine the association of anthropometric measurements, physical performance, radiographic knee OA and LS defined as KL=3 or 4, and knee and lower back pain and with falls compared with nonfalls in men and women. Further, to determine an independent association of physical performance, radiographic knee OA, and knee pain with falls compared with nonfalls, we used multiple logistic regression analysis with age, BMI, walking speed, radiographic knee OA, and knee pain as independent variables. Data analyses were performed using SAS version 9.0 (SAS Institute Inc., Cary, NC, USA).

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 follow-up study due to bad health, 69 (2.3 %) had moved away, 83 (2.7 %) declined the invitation to attend the follow-up study, and 155 (5.1 %) did not participate in the follow-up study for other reasons. Among the 2,485 subjects who did participate in the follow-up study, 182 (6.0 %) provided incomplete fall questionnaires. In addition, 15 (0.5 %) provided incomplete pain questionnaires; these were excluded. We also excluded 14 (0.5 %) subjects who had undergone total knee arthroplasty at baseline. Further, 59 (1.9 %) subjects did not measure

walking speed, leaving a total of 2,215 (72.9 %) subjects (745 men and 1,470 women) from whom radiographs at baseline and complete fall and pain histories were obtained. The mean \pm SD duration of follow-up between initial and second surveys was 3.3 ± 0.6 years.

Table 1 shows the age, anthropometric measurements, physical performance, and prevalence of radiographic knee OA and LS as well as knee and lower back pain of participants at baseline. Regarding physical performance, grip strength and walking speed were significantly better in men than in women. The prevalence of radiographic knee OA and knee pain was significantly higher in women than in men, whereas that of LS and lower back pain was not different between men and women.

During the approximately 3-year follow-up, 141 (18.9 % [95 % confidence interval [CI], 16.3–21.9]) men and 362 (24.6 % [95 % CI, 22.5–26.9]) women reported at least one fall. Chi-square test showed that the incidence of falls were significantly different between men and women ($p=0.0025$). With increasing age, the incidence of falls tended to increase in men and women (Fig. 1).

Table 2 shows the age, anthropometric measurements, and physical performance at baseline between nonfallers and fallers. Age was significantly higher in fallers than nonfallers in men and women. Height was higher in fallers than in nonfallers in women, whereas weight and BMI was not significantly different between nonfallers and fallers in men and women. Grip strength and walking speed were worse in fallers than nonfallers in men and women.

Figure 2 shows the incidence rate of falls according to knee OA, knee pain, LS, and lower back pain. The incidence rate of falls was higher in subjects with knee OA than those without knee OA in men (27.9 and 18.0 %, $p<0.05$,

respectively) and women (33.1 and 22.6 %, $p<0.05$, respectively). The incidence rate of falls was also higher in subjects with knee pain than those without knee pain in men (30.4 and 17.1 %, $p<0.05$, respectively) and women (32.6 and 22.1 %, $p<0.05$, respectively). There were no significant differences in incidence rate of falls between subjects with and without LS in men (20.5 and 17.8 %, $p=0.35$, respectively) and women (25.5 and 23.5 %, $p=0.39$, respectively). Men with lower back pain had significantly higher incidence rate of falls than men without lower back pain (25.6 and 17.6 %, $p<0.05$, respectively), whereas women with lower back pain did not (23.8 and 24.8 %, $p=0.76$, respectively).

In men, multiple logistic regression analysis after adjustment for age and BMI showed that slower walking speed ($p<0.001$) and knee pain ($p=0.0046$) were risk factors for falls, but grip strength ($p=0.4903$), radiographic knee OA ($p=0.1569$), LS ($p=0.8312$), and lower back pain ($p=0.0553$) were not (Table 3). In women, multiple logistic regression analysis after adjustment for age and BMI showed that walking speed ($p=0.013$), knee OA ($p=0.0218$), and knee pain ($p=0.0021$) were risk factors for falls, whereas grip strength ($p=0.1209$) and lower back pain ($p=0.5293$) were not. LS was not significantly associated with falls in the crude model ($p=0.3890$). To determine independent associations of walking speed, radiographic knee OA, and knee pain, we used multiple logistic regression analysis with age, BMI, walking speed, radiographic knee OA, and knee pain as independent variables and found that slower walking speed was an independent risk factor for falls in men and women ($p<0.0001$ and $p=0.0104$, respectively). Knee pain was an independent risk factor for falls in women ($p=0.0305$), but not in men ($p=0.0632$).

Table 1 Characteristics of participants

	Overall	Men	Women
Number of subjects	2,215	745	1,470
Age (years)	68.5 \pm 11.3	69.4 \pm 11.1	68.1 \pm 11.4*
Height (cm)	154.7 \pm 8.8	163.2 \pm 6.6	150.4 \pm 6.3*
Weight (kg)	55.5 \pm 10.2	62.2 \pm 9.9	52.0 \pm 8.5*
BMI (kg/m ²)	23.1 \pm 3.3	23.3 \pm 3.0	23.0 \pm 3.4*
Grip strength (kg)	26.3 \pm 9.3	34.5 \pm 8.8	22.1 \pm 6.2*
Walking speed (m/s)	1.24 \pm 0.34	1.26 \pm 0.35	1.23 \pm 0.33*
Radiographic knee OA (%)	15.8	9.1	19.1**
Radiographic LS (%)	43.7	42.6	44.2
Knee pain (%)	20.8	13.7	24.4**
Lower back pain (%)	18.7	16.8	19.7

Values are presented as the mean \pm SD, except where indicated

BMI body mass index, OA osteoarthritis

* $p<0.05$ vs. men by nonpaired Student's *t* test; ** $p<0.05$ vs. men by chi-square test

Discussion

The present study is a large-scale, population-based cohort study regarding the incidence of falls and their association with physical performance and radiographic knee OA and LS as well as pain in Japanese men and women. We found that slower walking speed was a risk factor for falls in men and women and knee pain was a risk factor for falls in women only.

The present population-based longitudinal study determined whether radiographic knee OA is a risk factor for falls in Japanese men and women. Jones et al. showed that individuals with self-reported arthritis had an increased tendency to fall [8]. In the present study, after adjustment for age and BMI, radiographic knee OA was a risk factor for falls in women, but not in men. The sex differences identified in the association between radiographic knee OA and falls may be partly explained by the weaker quadriceps

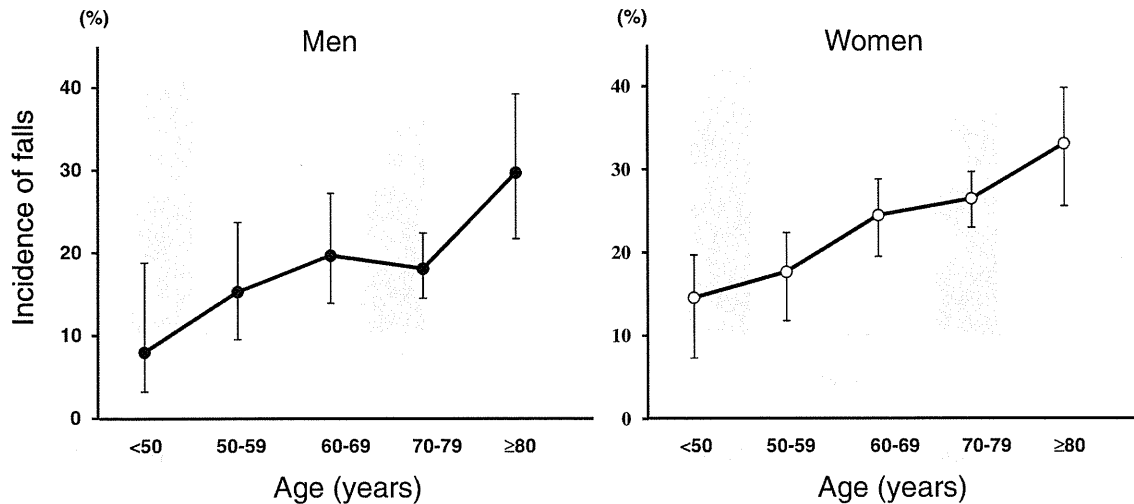


Fig. 1 Incidence rate of falls (95 % CI) by gender and age

muscles and increased postural sway associated with knee OA [8, 40], both of which are known to be independent risk factors for falls [7, 41]. In men, muscle strength is higher than that in women in all decades [42], which may obscure the association between radiographic knee OA and falls. LS was not a risk factor for falls in this study. Thus, falls may be more strongly associated with problems of the lower limbs rather than the trunk.

After adjustment for age, BMI, walking speed, and radiographic knee OA, knee pain was independently associated with the incidence of falls in women. Given that the significant association of radiographic knee OA with falls disappeared after adjustment, falls may occur due to symptoms such as pain caused by radiographic knee OA rather than radiographic changes in the knee itself. Our study and other previous cross-sectional studies also suggested that knee pain was significantly associated with falls [6, 24]. In addition, a prospective study also showed that knee pain increases in falls risk in Tasmanian men and women [10]. Jones et al. showed that, for the hand, the presence of pain is what weakens grip strength [43]. In a similar way, knee pain may weaken leg strength, leading to falls. In other words,

falls may be preventable when pain is relieved by medical care, even if subjects have radiographic knee OA.

In the present study, after adjustment for knee OA and knee pain, slower walking speed was an independent risk factor for falls in men and women. Verghese et al. also showed that risk for falls increased to approximately 7 % as walking speed decreased per 0.1 m/s [44], although bone and joint diseases were not included and men and women were not separately analyzed in the study. In the present study, multiple logistic regression analysis after adjustment for knee OA and knee pain showed that, as walking speed decreased per 0.1 m/s, the risk for falls were 15 and 5 % higher in men and women, respectively, indicating that slower walking speed may more strongly affect the risk of falls in men than women. Although dependent on the availability of equipment, quantitative gait measures can be easily and quickly collected in clinical and research settings without requiring attachment of monitoring devices or extensive training. The present study may indicate that walking speed is a simple and quick option for measuring fall risk, particularly in men.

The present study has several limitations. First, our subjects lived in the community, and thus, our findings may not

Table 2 Comparison of characteristics among nonfallers and fallers in men and women

	Men			Women		
	Nonfallers	Fallers	<i>p</i> value	Nonfallers	Fallers	<i>p</i> value
Number of subjects	604	141		1,108	362	
Age (years)	68.9±11.2	71.8±10.2	0.003	67.3±11.4	70.3±10.8	<0.001
Height (cm)	163.3±6.9	162.6±5.4	0.18	150.8±6.2	149.0±6.5	<0.001
Weight (kg)	62.2±10.0	62.1±9.8	0.92	52.1±8.6	51.7±8.2	0.34
BMI (kg/m ²)	23.3±3.0	23.5±3.3	0.51	22.9±3.4	23.3±3.4	0.06
Grip strength (kg)	34.8±8.9	33.0±8.2	0.02	22.4±6.2	21.1±6.1	<0.001
Walking speed (m/s)	1.30±0.36	1.11±0.28	<0.001	1.25±0.33	1.15±0.33	<0.001

Values are presented as the mean ± SD, except where indicated. Nonpaired Student's *t* test was used to determine the differences in age, height, weight, BMI, grip strength, and walking speed between nonfallers and fallers
BMI body mass index

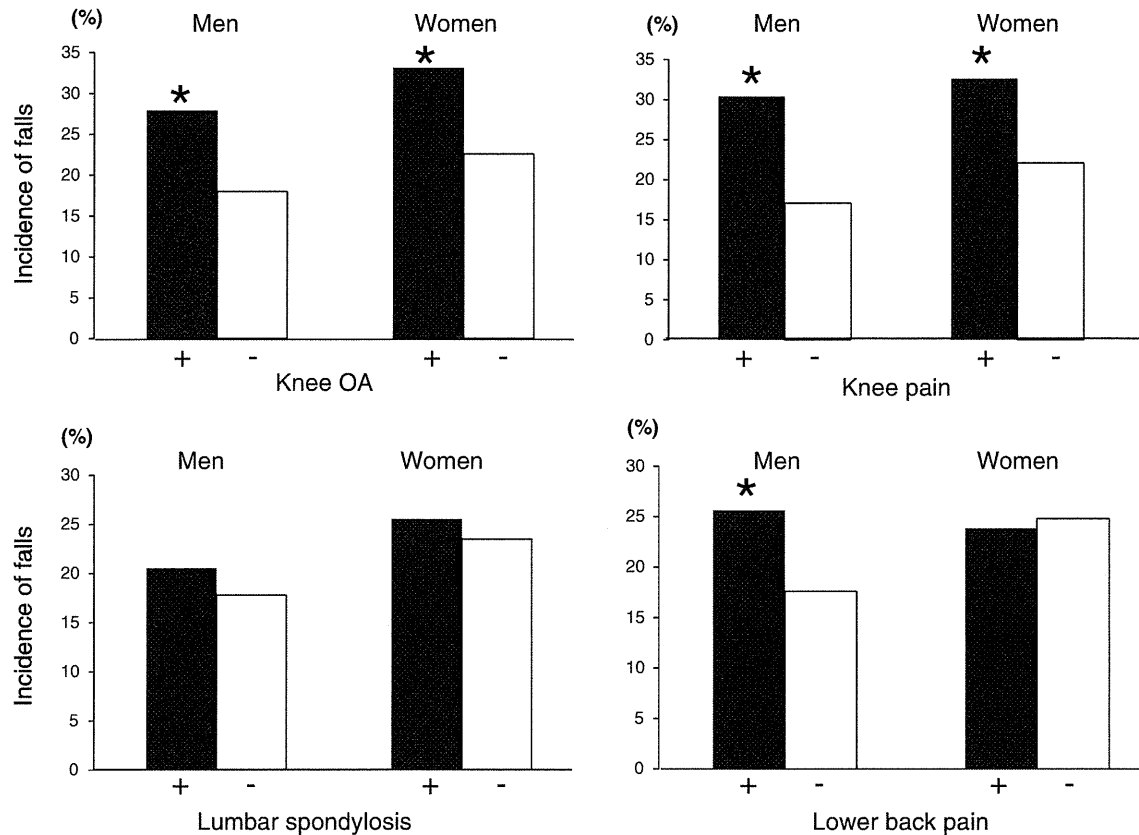


Fig. 2 Incidence of falls by knee OA, knee pain, LS, and lower back pain. * $p < 0.05$ vs. subjects without knee OA, LS, knee pain, and lower back pain, respectively, by chi-square test

apply to elderly persons residing in institutions. Second, we did not include other weight-bearing OAs such as hip OA in the analysis, although this disorder also affect falls [45]. However, the prevalence of KL=3 or 4 hip OA is 1.4 and 3.5 % in Japanese men and women [46], respectively, which is smaller than that of KL=3 or 4 knee OA in the present

study. Thus, it is possible that hip OA would not strongly affect the results of the present study.

In conclusion, the present longitudinal analysis using a large-scale population from the ROAD study revealed the incidence and risk factors for falls in men and women. Slower walking speed was a risk factor for falls in men

Table 3 Association of physical performance and bone and joint diseases with the incidence of falls in men and women

	Men			Women		
	Crude OR (95 % CI)	Adjusted OR ₁ (95 % CI)	Adjusted OR ₂ (95 % CI)	Crude OR (95 % CI)	Adjusted OR ₁ (95 % CI)	Adjusted OR ₂ (95 % CI)
Grip strength (5-kg decrease)	1.14 (1.02–1.27)	1.05 (0.92–1.20)	–	1.20 (1.09–1.33)	1.10 (0.98–1.25)	–
Walking speed (0.1-m/s decrease)	1.19 (1.11–1.25)	1.16 (1.10–1.25)	1.15 (1.09–1.23)	1.10 (1.05–1.14)	1.06 (1.02–1.11)	1.05 (1.01–1.10)
Radiographic knee OA	1.76 (0.98–3.06)	1.52 (0.83–2.67)	1.12 (0.59–2.08)	1.69 (1.27–2.24)	1.43 (1.05–1.93)	1.21 (0.87–1.66)
Knee pain	2.12 (1.31–3.36)	1.99 (1.22–3.18)	1.63 (0.96–2.70)	1.71 (1.31–2.22)	1.54 (1.17–2.02)	1.38 (1.03–1.84)
LS	1.19 (0.83–1.73)	1.04 (0.71–1.52)	–	0.90 (0.71–1.14)	0.74 (0.57–0.94)	–
Low back pain	1.61 (1.02–2.51)	1.59 (0.99–2.49)	–	0.95 (0.79–1.27)	0.91 (0.67–1.23)	–

Multiple logistic regression analysis was used to calculate the odds ratio (OR) and 95 % confidence interval (CI) compared with nonfallers. Adjusted OR₁ was calculated using multiple logistic regression analysis after adjustment for age and BMI. Adjusted OR₂ was calculated using multiple logistic regression analysis with age, BMI, walking speed, radiographic knee OA, and knee pain as independent variables. Radiographic knee OA and LS were defined as KL grade 3 or 4

OA osteoarthritis

and women. Knee pain was a risk factor for falls in women. Further studies, along with continued longitudinal surveys in the ROAD study, will help elucidate the background of knee OA and LS and their relationship with falls.

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Conflicts of interest None.

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Original Full Length Article

Risk factors for falls in a longitudinal population-based cohort study of Japanese men and women: The ROAD Study

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ABSTRACT

The objective of this study was to clarify the associations of physical performance and bone and joint diseases with single and multiple falls in Japanese men and women using a population-based longitudinal cohort study known as Research on Osteoarthritis/osteoporosis Against Disability (ROAD). A total of 452 men and 896 women were analyzed in the present study (mean age, 63.9 years). A questionnaire was used to assess the number of falls during the 3-year follow-up. Grip strength, 6-m walking time, and chair stand time were measured at baseline. Knee osteoarthritis (OA) and lumbar spondylosis were defined as Kellgren Lawrence = 2, 3 or 4. Vertebral fracture (VFX) was assessed with the Japanese Society of Bone and Mineral Research criteria. Osteoporosis was defined by bone mineral density using dual energy X-ray absorptiometry based on World Health Organization criteria. Knee and lower back pain were estimated by an interview. During a 3-year follow-up, 79 (17.4%) men and 216 (24.1%) women reported at least one fall, and 54 (11.9%) men and 111 (12.4%) women reported multiple falls. Knee pain was a risk factor for multiple falls in women, but not in men. VFX tended to be associated with multiple falls in women, but not in men. A longer 6-m walking time was a risk factor for multiple falls in women, whereas a longer chair stand time was a risk factor for multiple falls in men. We found gender differences in risk factors for falls.

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Introduction

Falls are one of the main causes of injury, disability, and death among the elderly [1,2]. In Japan, according to the 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, few population-based studies have been performed on the incidence of falls based on sex and age. Furthermore, 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, the association of bone and joint diseases, especially osteoarthritis (OA), with falls remains unclear.

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 [6,7]. The prevalence rates of radiographic knee OA and LS are 54.6% and 70.2%, respectively, in persons aged 40 years and older in Japan, which indicates that 25,300,000 and 37,900,000 persons aged 40 years and older are estimated to experience radiographic knee OA and LS, respectively [10]. 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 [11,12]. In previous studies, knee OA was assessed only by interview and not by radiography. The principal clinical symptom of knee OA is pain [13], but its correlation with the radiographic severity of knee OA is not as strong as expected [8]. In fact, in a study in Japan, approximately 20% of persons without knee OA had knee pain, and 30% of persons with severe knee OA had no knee pain [8]. 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 [8]. Our previous study showed that knee pain is significantly associated with falls in women [14], but that study used a cross-sectional design; thus, a causal relationship remains unclear. Regarding LS, to the best of our knowledge, no population-based studies have been performed

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regarding its association with falls except for our previous cross-sectional study [14], which showed that LS is not significantly associated with falls. In addition, among fractures due to osteoporosis (OP), vertebral fracture (Vfx) is the most likely to lead to marked public health problems. Vfx is reportedly associated with functional impairment [15], back pain, kyphosis [16,17], esophageal reflux [18], depressive mood [19], respiratory dysfunctions [20], and mortality [21]. However, whether Vfx is an independent risk factor for the incidence of falls remains unclear.

Measuring walking speed is a simple way to assess health and function in older adults [22,23]. Walking speed has been found to be associated with falls in a few studies [4,24–26], although most studies were limited by a small sample size, a cross-sectional design [24,25], or evaluation of a single sex [4,26]. In addition, although walking abnormalities indicative by a slower walking speed are significantly associated with bone and joint diseases such as knee OA, LS, and their associated pain [14], no longitudinal studies have been performed to determine the associations of falls with bone and joint diseases and walking abnormalities at the same time. Furthermore, measuring the chair stand time is also reported to be a simple and established method to assess health and function in the elderly [27,28], but to the best of our knowledge, no longitudinal studies have been performed to determine the associations of falls with chair stand time.

Previous studies have shown that associations between individual risk factors and a single fall are few in number and weak compared to risk factors for multiple falls [12], indicating that single and multiple falls may have different backgrounds. Thus, to determine factors associated with falls, single and multiple falls should be analyzed separately.

The objective of this study was to clarify the associations of physical performance and bone and joint diseases with the incidence of single and multiple falls in Japanese men and women using a population-based longitudinal cohort study known as Research on Osteoarthritis/osteoporosis Against Disability (ROAD).

Methods

Participants

The ROAD study is a nationwide, prospective study designed to establish epidemiologic indices for evaluation of clinical evidence for the development of a disease-modifying treatment for bone and joint diseases (OP and OA are the representative bone and joint diseases, respectively). ROAD consists of population-based cohorts in three communities in Japan. A detailed profile of the ROAD study has been described elsewhere [8–10,29]; 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 participants (1,061 men and 1,979 women) ranging in age 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 list of the relevant region. Participants in the urban region were recruited from a randomly selected cohort from the Itabashi-ward residents' registration database [30]. 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.

Assessment of falls

Three years after the baseline data were obtained, we attempted to trace and review all 3,040 participants between 2008 and 2010; they were invited to attend a follow-up interview. All participants were interviewed with regard to falls by experienced interviewers and were asked the following questions: "Have you experienced falls during the 3-year follow-up, and if yes, how many falls did you experience"? At baseline, all participants were also interviewed regarding falls by experienced interviewers and were asked the following questions: "Have you experienced falls during the 12 months preceding baseline, and if yes, how many falls did you experience"? According to a previous study on falls [31], a fall is defined as a sudden, unintentional change in position causing an individual to land at a lower level on an object, the floor, or the ground, other than as a consequence of a sudden onset of paralysis, epileptic seizure, or overwhelming external force.

Pain assessment

All participants were interviewed by experienced orthopedists regarding knee pain and lower back pain at baseline and were asked the following questions based on previous studies [8,9]: "Have you experienced knee pain on most days in the past month, in addition to now?" and "Have you experienced lower back pain on most days in the past month, in addition to now"? Those who answered "yes" were defined as having pain. Buttock pain and sciatica were not included as lower back pain in the present study.

Radiographic assessment

At baseline, all participants underwent radiographic examination of both knees using anteroposterior and lateral views with weight-bearing and foot-map positioning; radiographic examination of the anteroposterior and lateral views of the lumbar spine, including intervertebral levels L1/2 to L5/S, was also performed. Vfx was assessed by lateral radiographs of the lumbar spine (L1–L5) in terms of a wedge, biconcave, or crush appearance according to the Japanese Society of Bone and Mineral Research criteria [32]. The films were marked up, and morphometric measurements of anterior, middle, and posterior heights on lateral radiography of the thoracic and lumbar spine were made. Wedge appearance was defined as a site at which the anterior height of the vertebra was $\leq 75\%$ of the posterior height. Biconcave appearance occurred if the height of the central part of the vertebra was $\leq 80\%$ of that of the anterior or posterior parts of the vertebra. Crush appearance occurred if the height of the anterior, central, and posterior parts of an axial vertebra were all reduced to $\leq 80\%$ of the normal value (Supplementary Fig. 1). Knee and lumbar spine radiographs were also read without knowledge of the participant's clinical status by a single, experienced orthopedist (S.M.) using the Kellgren Lawrence (KL) radiographic atlas [33] to determine the severity of KL grading. Radiographs were scored as grade 0–4, with higher grades associated with more severe OA. We defined knee OA and LS as $KL \geq 2$ in at least one knee and one intervertebral level, respectively. To evaluate the intraobserver variability of KL grading, 100 randomly selected radiographs of the knee and lumbar spine were scored by the same observer more than 1 month after the first reading. One hundred other radiographs were also scored by two experienced orthopedic surgeons (S.M. and H.O.) using the same atlas for interobserver variability. The intra- and interobserver variabilities evaluated were confirmed by kappa analysis to be sufficient for assessment (0.86 and 0.80 for knee OA, and 0.84 and 0.76 for LS, respectively).

Bone mineral density (BMD) measurement

BMD was measured at the lumbar spine (L2–4) and the proximal femur using dual energy X-ray absorptiometry (DXA) (Hologic

Discovery; Hologic, Waltham, MA, USA) at baseline. For quality control, the same DXA equipment was used, and the same spine phantom was scanned daily to monitor the machine's performance in study populations at different regions. The BMD of the phantom was adjusted to $1.032 \pm 0.016 \text{ g/cm}^2$ ($\pm 1.5\%$) during all examinations. In addition, the same physician (N.Y.) examined all participants to prevent observer variability. Coefficient of variance (CV) for L2–L4 in the phantom was 0.35%, and CVs for L2–L4, the proximal femur, Ward's triangle, and the trochanter examined in five volunteers were 0.61–0.90, 1.02–2.57, 1.97–5.45, and 1.77–4.17%, respectively [34].

OP was defined based on World Health Organization (WHO) criteria in which OP was diagnosed as T-scores of BMD ≤ 2.5 standard deviations (SDs) lower than peak bone mass [35]. Mean L2–4 BMD (SD) for young adult men and women measured using the Hologic QDR devices in Japan is reportedly 1.011 g/cm^2 (0.119 g/cm^2) [36]. Mean femoral neck BMD (SD) in Japan is reported to be 0.863 g/cm^2 (0.127 g/cm^2) for young men and 0.787 (0.109) for young women [36]. The present study therefore defined OP using these indices as lumbar spine BMD $< 0.714 \text{ g/cm}^2$ for both men and women, and as femoral neck BMD $< 0.546 \text{ g/cm}^2$ for men and $< 0.515 \text{ g/cm}^2$ for women.

Physical performance

At baseline, anthropometric measurements were taken, including height and weight, and body mass index (BMI) ($\text{kg}/\text{height}^2$ [m^2]) was estimated based on the measured height and weight. Grip strength was measured on bilateral sides using a TOEI LIGHT handgrip dynamometer (TOEI LIGHT CO., LTD, Saitama, Japan), and the best measurement was used to characterize maximum muscle strength. To measure physical performance, the time taken to walk 6 m at normal walking speed in a hallway was recorded. Participants were told to walk from a marked starting line to a 6-m mark as if they were walking down their hallway at home. Time was measured in seconds with a stopwatch and rounded to the nearest hundredth of a second. The average of two trials was recorded. These gait-speed trial measurements are considered highly reliable in community-dwelling elderly persons [37]. The time taken for five consecutive chair rises without the use of hands was also recorded. Hands were folded in front of the chest with feet flat on the floor, following the protocol described by Guralnik et al. [27] and used by other researchers [28]. Time was measured in seconds with a stopwatch and rounded to the nearest hundredth of a second. Timing began with the command "Go" and ended when the buttocks contacted the chair on the fifth landing. The reliability of this protocol is adequate [27].

Cognition assessment

At baseline, cognition was also evaluated for all participants using a Mini-Mental State Examination, and a cut-off score of < 24 was used to select participants with cognitive impairment [38].

Statistical analyses

The differences in age and anthropometric measurements between the responders (those who completed the study) and non-responders (those lost to follow-up or who did not complete the study as described below) and between men and women were examined with a non-paired Student's *t*-test. Differences in physical performance measurements between the responders and non-responders and between men and women were examined with Wilcoxon signed-rank test. Differences in age and anthropometric measurements, among non-fallers, single fallers, and multiple fallers, were examined with one-way analysis of variance. Differences in physical performance measurements among non-fallers, single fallers, and multiple fallers were examined with the Kruskal–Wallis test. The prevalence of bone and joint diseases and cognitive impairment was compared between men

and women and among non-fallers, single fallers, and multiple fallers with the chi square test. Multinomial logistic regression analysis after adjusting for age and BMI was used to determine the association of anthropometric measurements, physical performance, bone and joint diseases, and cognitive impairment with single and multiple falls compared with the absence of falls in men and women. Further, to determine an independent association of physical performance with single and multiple falls compared with the absence of falls, we used multinomial logistic regression analysis with age, BMI, 6-m walking time, and chair stand time as explanatory variables. To determine independent risk factors for single and multiple falls, we used multinomial logistic regression analysis with age, BMI, physical performance, bone and joint diseases, and cognitive impairment as explanatory variables. Data analyses were performed using SAS version 9.0 (SAS Institute Inc., Cary, NC, USA).

Results

Of the 1,690 participants in the mountainous and seaside cohorts at baseline in 2006 and 2007, 40 (2.4%) had died by the time of the review 3 years later, 97 (5.7%) did not participate in the follow-up study due to poor health, 16 (0.9%) had moved away, 51 (3.0%) declined the invitation to attend the follow-up study, and 47 (2.8%) did not participate in the follow-up study for other reasons. Among the 1,439 volunteers who did participate in the follow-up study, 68 (4.0%) provided incomplete fall questionnaires. In addition, six (0.4%) provided incomplete pain questionnaires; these were excluded. We also excluded eight (0.5%) participants who had undergone total knee arthroplasty before baseline. An additional nine (1.9%) participants did not perform the 6-m walking time or chair stand time, leaving a total of 1,348 (79.8%) participants (452 men and 896 women) from whom radiographs at baseline and complete fall and pain histories were obtained. The mean followup time was 2.93 ± 0.12 years, ranging from 2.65 to 3.22 years. Table 1 shows characteristics of responders and non-responders. The responders were significantly younger than the non-responders (63.9 and 70.7 years, respectively). Physical performance measurements were better in responders than non-responders. Prevalence of knee OA, LS and knee pain was lower in responders (47.0, 61.6 and 9.7%,

Table 1
Baseline characteristics of responders and non-responders.

	Overall	Responders	Non-responders
Number of participants	1,690	1,348	342
Female (%)	64.7	66.5	57.9***
Age (years)	65.2 ± 12.0	63.9 ± 11.8	$70.7 \pm 11.4^*$
Height (cm)	155.2 ± 9.3	155.6 ± 9.0	$153.6 \pm 10.1^*$
Weight (kg)	55.6 ± 10.8	56.1 ± 10.7	$53.7 \pm 10.8^*$
BMI (kg/m^2)	23.0 ± 3.4	23.1 ± 3.4	22.7 ± 3.4
Grip strength (kg) (median [IQR])	26.0 [21.0–33.0]	26.0 [21.0–34.0]	24.0 [18.0–30.0]**
6-m walking time (s) (median [IQR])	5.0 [4.0–7.0]	5.0 [4.0–6.0]	7.0 [5.0–9.0]**
Chair stand time (s) (median [IQR])	9.0 [7.0–12.0]	9.0 [7.0–11.0]	12.0 [8.25–15.0]**
Cognitive impairment (%)	4.5	2.8	11.4***
Radiographic knee OA (%)	50.4	47.0	63.8***
Radiographic LS (%)	63.2	61.6	69.1***
Radiographic VFX	10.1	9.7	12.0
Knee pain (%)	24.3	22.2	32.6***
Lower back pain (%)	21.1	20.6	22.9
Previous falls (%)	17.3	16.3	21.0***

Values are mean \pm SD, except where indicated.

BMI: body mass index, OA: osteoarthritis, LS: lumbar spondylosis, VFX: vertebral fracture, IQR: interquartile range.

* $p < 0.05$ vs. responders by non-paired Student's *t*-test.

** $p < 0.05$ vs. men by Wilcoxon signed-rank test.

*** $p < 0.05$ vs. men by chi square test.

Table 2
Baseline characteristics of participants.

	Men	Women
Number of participants	452	896
Age (years)	64.9±11.7	63.3±11.8*
Height (cm)	164.0±7.0	151.3±6.6*
Weight (kg)	63.3±10.7	52.5±8.7*
BMI (kg/m ²)	23.5±3.2	22.9±3.4*
Grip strength (kg) (median [IQR])	37.0 [32.0–42.5]	23.5 [20.0–23.5]**
6-m walking time (s) (median [IQR])	5.0 [4.0–6.0]	5.0 [4.0–6.0]
Chair stand time (s) (median [IQR])	8.5 [7.0–11.0]	9.0 [7.0–11.0]
Cognitive impairment (%)	3.6	2.4
Radiographic knee OA (%)	37.4	51.9***
Radiographic LS (%)	76.1	54.2
Radiographic VFX	8.9	10.1
Knee pain (%)	15.3	25.7***
Lower back pain (%)	18.8	21.5
Previous falls (%)	13.1	18.0***

Values are mean ± SD, except where indicated.

BMI: body mass index, OA: osteoarthritis, LS: lumbar spondylosis, VFX: vertebral fracture, IQR: interquartile range.

* $p < 0.05$ vs. men by non-paired Student's t -test.

** $p < 0.05$ vs. men by Wilcoxon signed-rank test.

*** $p < 0.05$ vs. men by chi square test.

respectively) than non-responders (63.8, 69.1 and 12.0, respectively). Prevalence of previous falls was significantly lower in responders than non-responders (16.3 and 21.0%, respectively).

Table 2 shows the age, anthropometric measurements, physical performance, and prevalence of cognitive impairment, bone and joint diseases, and previous falls of participants at baseline in men and women. Regarding physical performance, grip strength and chair stand time were significantly better in men (37.0 kg and 8.5 s, respectively) than in women (23.5 kg and 9.0 s, respectively), but the 6-m walking time was not (5.0 s and 5.0 s, respectively). The prevalence of radiographic knee OA and knee pain was significantly higher in women (51.9% and 25.7%, respectively) than in men (37.4% and 15.3%, respectively), whereas that of LS and lower back pain was not different between men and women. The prevalence of previous falls was significantly higher in women than in men (18.0% and 13.1%, respectively).

During the 3-year follow-up, 79 (17.4% [95% confidence interval [CI] 14.3–21.2]) men and 216 (24.1% [95% CI 21.4–27.0]) women reported at least one fall, and 54 (11.9% [95% CI 9.3–15.3]) men and 111 (12.4% [95% CI 10.4–14.7]) women reported multiple falls. The chi square test showed that the incidence of falls was significantly different between men and women ($p = 0.0011$). The incidence of single and multiple falls was significantly higher in the mountainous regions (11.5% and

17.4%, respectively) than coastal regions (8.1% and 7.8%, respectively). With increasing age, the incidence of falls increased in women, but the incidence of falls was similar in men in their 60s and 70s (Fig. 1).

Table 3 shows the age, anthropometric measurements, physical performance, and BMD at baseline between non-fallers, single fallers, and multiple fallers. Age and BMI were significantly higher in female fallers than non-fallers, but this was not the case in men. Grip strength was worse in female fallers than non-fallers, but this was not the case in men. The 6-m walking time and chair stand time were longer in both male and female fallers than in non-fallers. LS and neck BMD were significantly lower in female fallers than non-fallers, but this was not the case in men.

We next examined the incidence rate of falls during the 3-year follow-up according to previous falls at baseline in men and women (Supplementary Fig. 2). The incidence rates of multiple falls were 7.9%, 22.7%, and 48.7% in men and 8.8%, 20.4%, and 43.1% in women among non-fallers, single fallers, and multiple fallers, respectively. The incidence rates of single falls were 5.9%, 9.1%, and 0.0% in men and 12.5%, 7.8%, and 8.6% in women among non-fallers, single fallers, and multiple fallers, respectively. The chi square test showed that the incidence of falls during the 3-year follow-up was significantly associated with previous falls at baseline in men and women ($p < 0.0001$).

Fig. 2 shows the incidence rate of falls during the 3-year follow-up according to the presence of bone and joint diseases and cognitive impairment. The incidence rates of multiple falls were 16.6% and 9.2% in men and 14.8% and 9.7% in women in those with and without knee OA, respectively. The incidence rates of a single fall were 8.3% and 3.9% in men and 14.2% and 9.1% in women in those with and without knee OA, respectively. The chi square test showed that knee OA at baseline was significantly associated with the incidence rate of falls during the 3-year follow-up in men and women ($p < 0.0001$). Regarding knee pain, the incidence rates of multiple falls were 18.8% and 10.7% in men and 18.7% and 10.2% in women in those with and without knee pain, respectively. The incidence rates of a single fall were 8.7% and 5.0% in men and 10.4% and 10.4% in women in those with and without knee OA, respectively. The chi square test showed that knee pain at baseline was significantly associated with the incidence of falls during the 3-year follow-up in men and women ($p < 0.0001$). LS and lower back pain were not significantly associated with the incidence of falls in men ($p = 0.52$ and 0.77 , respectively) or in women ($p = 0.45$ and 0.58 , respectively). VFX at baseline was significantly associated with the incidence of falls in women (multiple falls 22.2% and 11.3%, single falls 14.4% and 11.4%, in those with and without VFX, respectively, $p = 0.005$), but not in men ($p = 0.06$). OP defined by L2–4 and femoral neck BMD was not associated with the incidence of falls in men and women. Cognitive impairment

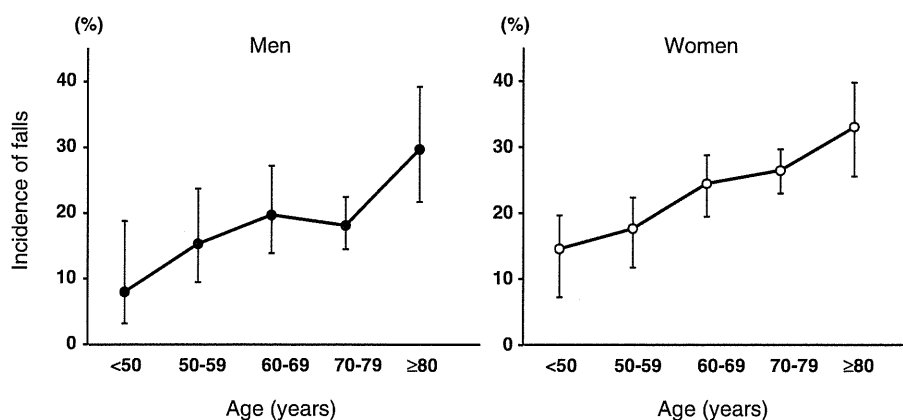


Fig. 1. Incidence rate of falls (error bars represent 95% confidence intervals) by gender and age strata.

Table 3
Comparison of characteristics among non-fallers, single fallers, and multiple fallers in men and women.

	Men				Women			
	Non-fallers	Single fallers	Multiple fallers	p value	Non-fallers	Single fallers	Multiple fallers	p value
Number of participants	373	25	54		680	105	111	
Age (years)	64.4 (11.7)	67.2 (13.2)	67.6 (10.1)	0.10	62.4 (11.6)	66.0 (12.6)	66.7 (11.4)	<0.001
BMI (kg/m ²)	23.4 (3.1)	24.6 (3.9)	23.7 (3.3)	0.16	22.8 (3.5)	22.7 (3.1)	23.8 (3.5)	0.01
Grip strength (kg)	37.0 (median [IQR]) [32.0–43.0]	37.0 (median [IQR]) [30.0–41.5]	35.0 (median [IQR]) [28.8–40.0]	0.08	24.0 (median [IQR]) [20.0–27.0]	23.0 (median [IQR]) [19.5–27.0]	22.0 (median [IQR]) [18.0–26.0]	0.01
6-m walking time (s)	4.5 (median [IQR]) [4.0–6.0]	5.5 (median [IQR]) [4.6–7.3]	6.2 (median [IQR]) [5.0–6.6]	<0.0001	5.0 (median [IQR]) [4.0–6.0]	5.0 (median [IQR]) [4.0–6.5]	5.5 (median [IQR]) [4.0–7.5]	<0.0001
Chair stand time (s)	8.0 (median [IQR]) [7.0–10.0]	11.0 (median [IQR]) [9.0–12.0]	10.0 (median [IQR]) [8.0–13.0]	<0.0001	9.0 (median [IQR]) [7.0–11.0]	9.0 (median [IQR]) [8.0–12.0]	10.0 (median [IQR]) [8.0–12.25]	0.0001
LS BMD	1.05 (0.20)	1.05 (0.20)	1.05 (0.15)	0.99	0.89 (0.18)	0.85 (0.16)	0.86 (0.17)	0.04
Neck BMD	0.75 (0.13)	0.77 (0.12)	0.75 (0.10)	0.79	0.65 (0.13)	0.61 (0.11)	0.63 (0.11)	0.003

Values are the means (standard deviation), except where indicated.

One-way analysis of variance was used to determine the differences in age, height, weight and BMI among non-fallers, single fallers, and multiple fallers.

Kruskal–Wallis test was used to determine the differences in grip strength, 6-m walking time and chair stand time among non-fallers, single fallers, and multiple fallers.

The chi square test was used to determine the differences in the prevalence of cognitive impairment among non-fallers, single fallers, and multiple fallers.

BMI: body mass index, LS: lumbar spondylosis, BMD: bone mineral density.

was associated with the incidence of falls in men (multiple falls 31.3% and 10.9%, single falls 18.8% and 5.1%, in those with and without cognitive impairment, respectively, $p=0.002$), but not in women ($p=0.19$).

In men, multinomial logistic regression analysis after adjusting for age and BMI showed that a longer 6-m walking time, longer chair stand time, and previous falls were risk factors for falls, but grip strength, bone and joint diseases, and cognitive impairment were not

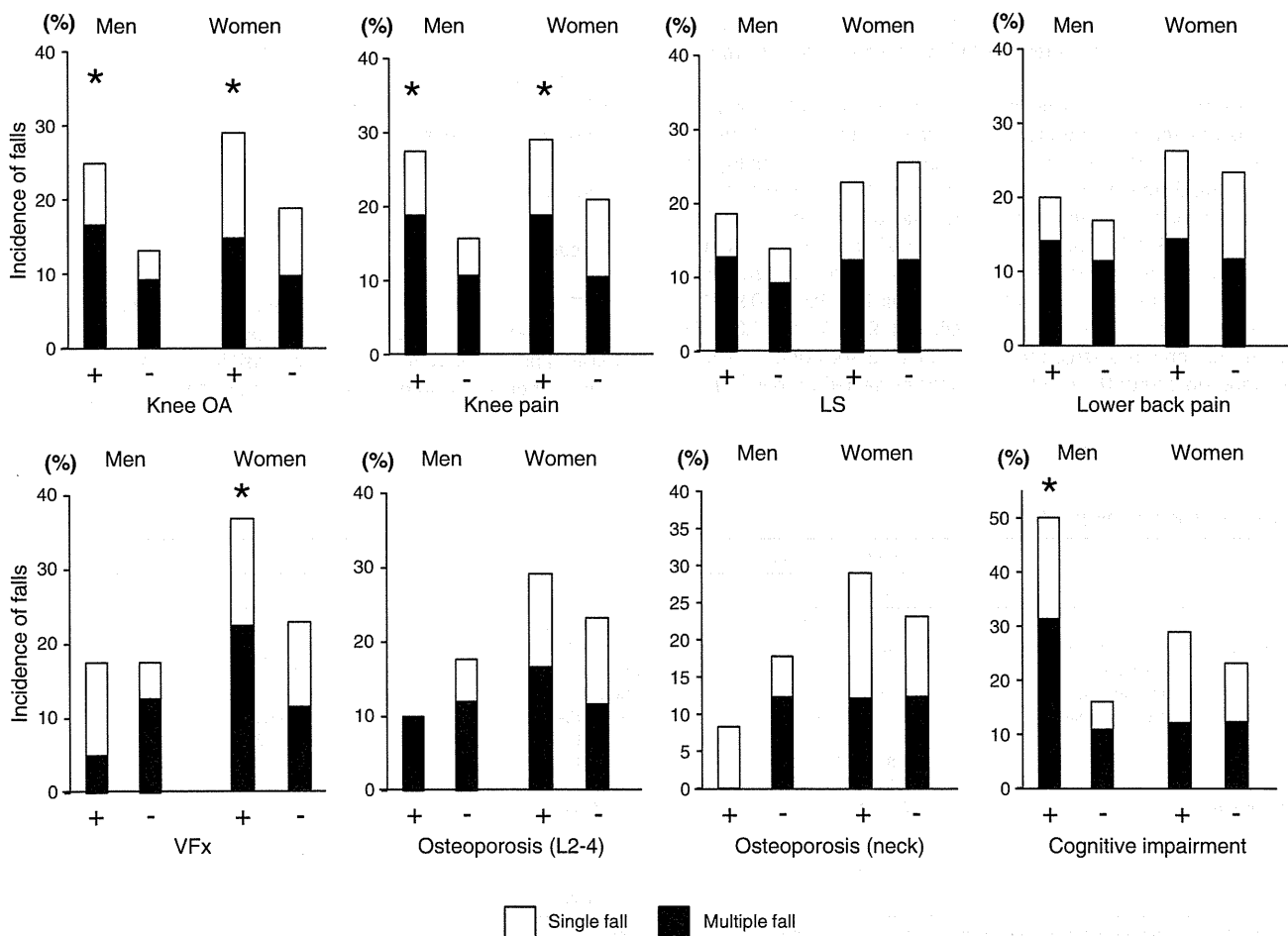


Fig. 2. Incidence of single and multiple falls by bone and joint diseases and cognitive impairment. * $p < 0.05$ vs. participants without each disease or pain, respectively, according to the chi square test. OA, osteoarthritis; LS, lumbar spondylosis; VFx, vertebral fracture.

Table 4
Risk factors for single and multiple falls in men.

	Crude OR (95% CI)		Adjusted OR (95% CI)	
	Single falls	Multiple falls	Single falls	Multiple falls
Grip strength (5 kg increase)	0.90 (0.71–1.14)	0.84 (0.71–0.99)	1.14 (1.01–1.29)	0.88 (0.72–1.08)
6-m walking time (1 s increase)	1.12 (0.98–1.27)	1.13 (1.03–1.26)	1.11 (0.95–1.25)	1.11 (1.01–1.23)
Chair stand time (1 s increase)	1.17 (1.03–1.32)	1.21 (1.11–1.33)	1.15 (1.00–1.32)	1.21 (1.09–1.33)
LS BMD (0.1 mg/cm ² increase)	1.00 (0.80–1.22)	1.00 (0.86–1.16)	0.92 (0.73–1.15)	0.97 (0.83–1.13)
Neck BMD (0.1 mg/cm ² increase)	1.10 (0.81–1.47)	0.98 (0.78–1.21)	1.07 (0.73–1.51)	1.01 (0.77–1.30)
Knee OA	2.44 (1.09–5.56)	2.08 (1.18–3.70)	2.07 (0.84–5.21)	1.77 (0.95–3.33)
Knee pain	2.04 (0.72–5.09)	2.05 (0.99–4.00)	1.65 (0.57–4.21)	1.78 (0.85–3.55)
VFx	2.58 (0.82–6.85)	0.40 (0.06–1.36)	2.48 (0.75–7.04)	0.32 (0.05–1.13)
Cognitive impairment	6.19 (1.29–23.1)	4.83 (1.41–15.1)	13.48 (0.98–178.64)	3.17 (0.44–21.99)
<i>Previous falls</i>				
Single fall	–	–	–	3.52 (1.07–9.97)
Multiple falls	1.18 (0.25–4.61)	9.54 (3.15–30.08)	–	12.6 (5.80–27.97)

Multinomial logistic regression analysis was used to calculate the crude odds ratio (OR) and 95% confidence interval (CI) compared with non-fallers.

Adjusted OR was calculated using multinomial logistic regression analysis after adjusting for age and body mass index (BMI).

OA: osteoarthritis, VFx: vertebral fracture, BMD: bone mineral density, LS: lumbar spondylosis.

Radiographic knee OA was defined as Kellgren Lawrence grade 3 or 4.

(Table 4). Previous falls were significantly associated with the incidence of multiple falls. In women, multinomial logistic regression analysis after adjusting for age and BMI showed that a longer 6-m walking time was a risk factor for multiple, but not single falls (Table 5). Chair stand time also tended to be associated with the incidence of single and multiple falls. Regarding bone and joint diseases, knee pain was a risk factor for single and multiple falls. VFx also tended to be associated with multiple falls, but radiographic knee OA was not associated with falls. Cognitive impairment was a risk factor for multiple falls, but not for single falls. A history of previous falls was a risk factor for multiple, but not single falls.

To determine the independent association of each physical performance parameter with the incidence of falls, multinomial logistic regression analysis was performed with age, BMI, 6-m walking time, and chair stand time as explanatory variables. We found that a longer chair stand time was an independent risk factor for multiple falls (OR 1.18, 95% CI 1.06–1.32), but a longer 6-m walking time was not (OR 1.05, 95% CI 0.93–1.16). In women, a longer 6-m walking time tended to be associated with the incidence of multiple falls (OR 1.09, 95% CI 0.98–1.22), but a longer chair stand time was not (OR 1.01, 95% CI 0.94–1.07). After adjusting for previous falls, the independent association of a longer chair stand time with the incidence of falls remained in men (OR 1.15,

95% CI 1.02–1.30), and the independent association of a longer 6-m walking time with the incidence of falls remained in women (OR 1.12, 95% CI 1.00–1.25). In addition, knee pain and cognitive impairment in women were also significantly associated with falls, and VFx tended to be associated with falls with multinomial logistic regression analysis after adjusting for age and BMI. Thus, to determine the independent association of physical performance, bone and joint diseases, and cognitive impairment, multinomial logistic regression analysis was used with age, BMI, 6-m walking time, knee pain, VFx, and cognitive impairment as explanatory variables. We found that a longer 6-m walking time was an independent risk factor for multiple falls (OR 1.08, 95% CI 1.00–1.18), but the significant association of knee pain, VFx, and cognitive impairment with the incidence of falls disappeared (OR 1.47, 95% CI 0.91–2.35, OR 1.52, 95% CI 0.80–2.81, and OR 1.16, 95% CI 0.35–3.24, respectively).

Discussion

The present study is the first longitudinal population-based cohort study to examine whether physical performance, bone and joint diseases, and cognitive impairment are risk factors for single and multiple falls in men and women. We found gender differences in risk factors for

Table 5
Risk factors for single and multiple falls in women.

	Crude OR (95% CI)		Adjusted OR (95% CI)	
	Single falls	Multiple falls	Single falls	Multiple falls
Grip strength (5 kg increase)	0.84 (0.70–0.99)	0.81 (0.68–0.95)	0.94 (0.77–1.11)	0.91 (0.75–1.08)
6-m walking time (1 s increase)	1.10 (1.01–1.19)	1.16 (1.08–1.25)	1.04 (0.94–1.14)	1.11 (1.02–1.20)
Chair stand time (1 s increase)	1.07 (1.02–1.12)	1.07 (1.03–1.12)	1.04 (0.99–1.10)	1.04 (0.99–1.09)
LS BMD (0.1 mg/cm ² increase)	0.88 (0.78–1.00)	0.90 (0.80–1.01)	0.96 (0.83–1.11)	0.92 (0.80–1.06)
Neck BMD (0.1 mg/cm ² increase)	0.75 (0.63–0.90)	0.85 (0.72–1.01)	0.79 (0.62–1.01)	0.87 (0.69–1.10)
Knee OA	1.79 (1.18–2.78)	1.75 (1.16–2.63)	1.52 (0.94–2.50)	1.12 (0.79–1.82)
Knee pain	1.83 (1.17–2.83)	2.22 (1.44–3.37)	1.62 (1.00–2.60)	1.60 (1.00–2.54)
VFx	1.54 (0.78–2.85)	2.40 (1.35–4.12)	1.15 (0.57–2.20)	1.81 (0.98–3.24)
Cognitive impairment	0.42 (0.02–2.12)	2.12 (0.68–5.60)	0.73 (0.19–2.61)	4.95 (1.50–16.08)
<i>Previous falls</i>				
Single fall	0.55 (0.16–1.74)	1.51 (0.33–5.41)	0.70 (0.30–1.43)	2.48 (1.40–4.28)
Multiple falls	0.86 (0.39–1.81)	8.55 (3.80–19.20)	1.06 (0.35–2.62)	6.93 (3.76–12.72)

Multinomial logistic regression analysis was used to calculate the crude odds ratio (OR) and 95% confidence interval (CI) compared with non-fallers.

Adjusted OR was calculated using multinomial logistic regression analysis after adjusting for age and body mass index (BMI).

OA: osteoarthritis, VFx: vertebral fracture, BMD: bone mineral density, LS: lumbar spondylosis.

Radiographic knee OA was defined as Kellgren Lawrence grade 3 or 4.

falls. Regarding physical performance, a longer chair stand time was an independent risk factor for falls in men, whereas a longer 6-m walking time was an independent risk factor for falls in women. Knee pain, VFX, and cognitive impairment were associated with falls in women, but not in men.

The present study is a population-based longitudinal study to determine whether bone and joint diseases are risk factors for falls in Japanese men and women. After adjusting for age and BMI, knee pain was a risk factor for falls in women, but not in men. The sex differences regarding the association of knee pain with falls may be partly explained by the weaker quadriceps muscles in women, which is known to be an independent risk factor for falls [16]. Muscle strength is higher in men than in women in all decades [39], which may obscure the association of knee pain with falls. In addition, given the insignificant association of radiographic knee OA with falls, falls may occur due to symptoms such as pain rather than radiographic changes in the knee itself. Our study and other previous cross-sectional studies also suggested that knee pain is significantly associated with falls [11]. In other words, falls may be preventable when pain is relieved by medical care, even if patients have radiographic knee OA.

In the present study, LS and lower back pain were not associated with falls, whereas VFX was associated with falls. Lower BMD was not associated with falls in the present study, and thus, radiographic changes but not OP may be associated with falls. Studies of patients with VFX have reported increased kyphosis angles [16,17], which is an independent risk factor for injurious falls [40]. Previous studies [41,42] have demonstrated that people with kyphosis have greater balance abnormalities as assessed by computerized dynamic posturography. Specifically, they reported that women with OP-related kyphosis had greater mediolateral displacement and increased mediolateral velocity compared to controls [42]. In addition, lateral spontaneous sway amplitude has been reported to be the single best predictor of future risk of falls [43]. These observations may partly explain the association between VFX and falls.

In the present study, after adjusting for age and BMI, both a longer 6-m walking time and a longer chair stand time were associated with falls in men and women. A previous study also showed that slower walking speed is a risk factor for falls [44], although men and women were not separately analyzed in the study. To determine the independent association of the 6-m walking time and chair stand time, we further used multinomial logistic regression analysis with age, BMI, 6-m walking time, and chair stand time as explanatory factors, and found that in men, a longer chair stand time was an independent risk factor for multiple falls, but a longer 6-m walking time was not. In women, a longer 6-m walking time was associated with the incidence of multiple falls, whereas a longer chair stand time was not. This indicates that slower walking speed may more strongly affect the risk of falling in women than in men, whereas a longer chair stand time may more strongly affect the risk of falling in men than in women. The walking time and chair stand time can be easily and quickly measured in clinical and research settings without requiring monitoring devices or extensive training. The present study may indicate that walking time is a simple and quick option for measuring the risk of falling, particularly in women, and measuring the chair stand time is a simple and quick option for estimating the risk of falling, particularly in men.

The present study has several limitations. First, our participants lived in the community, and thus, our findings may not apply to elderly persons residing in institutions. Second, we did not include other anatomical locations of weight-bearing OA such as hip OA in the analysis, although this disorder also affects falls [45]. However, the prevalence of KL=3 or 4 hip OA is 1.4% and 3.5% in Japanese men and women [46], respectively, which is lower than that of KL=3 or 4 knee OA (12.2% and 21.0% in men and women, respectively) in the present study. Thus, it is possible that hip OA would not strongly affect the results of the present study. Third, non-responders were older, had

lower physical performance and higher prevalence of knee pain, which were risk factors for falls. This means that the incidence of falls in the present study may have been underestimated. Fourth, the accuracy and reliability of recall of falls over the past 3 years was not assessed in the present study. Previous studies have shown that 13–32% of elderly subjects with confirmed falls did not recall falling over a 12-month period [47], even when excluding subjects with cognitive impairment. Therefore, the incidence of falls may be underestimated, particularly in older subjects and those with cognitive impairment. In addition, individuals are more likely to recall a fall that resulted in injury, which may have influenced the results of this study.

Conclusion

The present longitudinal analysis using a large-scale population from the ROAD study revealed gender differences in risk factors for falls. A longer walking time was a risk factor for falls in women, whereas a longer chair stand time was a risk factor for falls in men. Knee pain and VFX were risk factors for falls in women, but not in men. Further studies, along with continued longitudinal surveys in the ROAD study, will help elucidate the background of bone and joint diseases and their relationship with falls.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.bone.2012.10.020>.

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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 [m²]) 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).

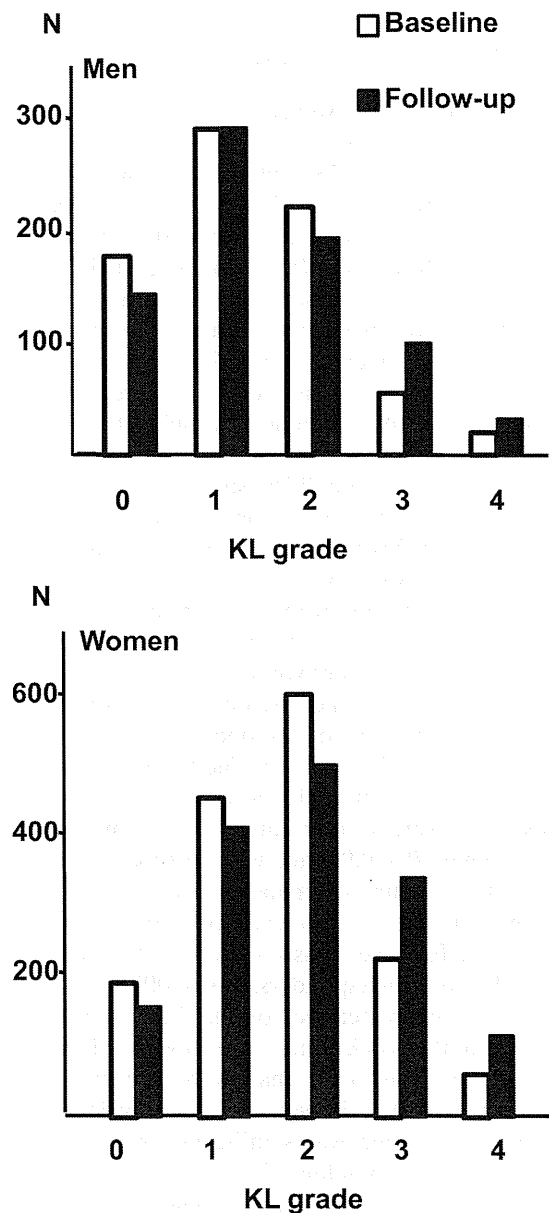


Figure 1. Number (N) of male and female subjects by Kellgren/Lawrence (K/L) grade at baseline and followup.