BMJ open accessible medical research

# Does mild cognitive impairment affect the occurrence of radiographic knee osteoarthritis? A 3-year follow-up in the ROAD study

Noriko Yoshimura,[1] Shigeyuki Muraki,[2] Hiroyuki Oka,[1] Hiroshi Kawaguchi,[3] Kozo Nakamura,[4] Sakae Tanaka,[3] Toru Akune[2]

**To cite:** Yoshimura N, Muraki S, Oka H, *et al.* Does mild cognitive impairment affect the occurrence of radiographic knee osteoarthritis? A 3-year follow-up in the ROAD study. *BMJ Open* 2012;**2**:e001520. doi:10.1136/bmjopen-2012-001520

► Prepublication history for this paper are available online. To view these files please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2012-001520).

Received 25 May 2012
Accepted 11 October 2012



For numbered affiliations see end of article.

**Correspondence to**
Noriko Yoshimura;
yoshimuran-ort@h.u-tokyo.ac.jp

## ABSTRACT

**Objective:** To determine whether mild cognitive impairment (MCI) increases the risk of occurrence or progression of radiographic knee osteoarthritis (KOA) in a general population.

**Design:** Population-based cohort study.

**Setting:** Residents in mountain and seaside areas of Wakayama Prefecture, Japan.

**Participants:** 1690 participants (596 men, 1094 women; mean age 65.2 years old) were enrolled from the large-scale cohort for the Research on Osteoarthritis (OA)/osteoporosis Against Disability (ROAD) study initiated in 2005 to investigate epidemiological features of OA in Japan. Of these, 1384 individuals (81.9%; 466 men, 918 women) completed the second survey including knee radiography 3 years later.

**Primary outcome measures:** Radiographic KOA was defined as Kellgren-Lawrence (KL) grade ≥ 2 using paired x-ray films. Incidence of KOA during follow-up defined on radiographs as KL grade ≥2, progression of KOA defined as a higher KL grade (either knee) at follow-up compared with baseline. MCI defined as a summary mini-mental state examination (MMSE) score ≤23. Associations between MCI and incidence or progression of KOA were analysed.

**Results:** The annual cumulative incidence of KOA was 3.3%; for progression of OA it was 8.0%. On logistic regression analysis adjusted for age, gender, regional differences, body mass index, grip strength (worse side), smoking, alcohol consumption, regular exercise and history of knee injury, baseline MMSE summary score was significantly associated with the incidence of KOA (+1 MMSE score; OR 0.83, p=0.010). Baseline MCI was also significantly associated with the incidence of KOA (vs non-occurrence of KOA; OR 4.90, p=0.027). There was no significant association between MMSE scores, the presence of MCI and progression of KOA (+1 MMSE score; OR 0.96, p=0.232; vs non-progression of KOA; OR 1.38, p=0.416).

**Conclusions:** MCI significantly increases the risk of incident radiographic KOA, but not the progression of KOA.

## ARTICLE SUMMARY

### Article focus

- Both cognitive impairment and osteoarthritis (OA) are top-ranked causes of disability requiring support, but there have been no previous reports on the association between cognitive impairment and OA.
- We aimed to investigate the association between mild cognitive impairment (MCI) and the occurrence and progression of radiographic knee osteoarthritis (KOA) among men and women who participated in the Research on Osteoarthritis/osteoporosis against Disability (ROAD) study.

### Key messages

- Of 1690 participants at the baseline, 1384 individuals (81.9%; 466 men, 918 women) completed the second survey including knee radiography 3 years later.
- The annual cumulative incidence of radiographic KOA in these 1384 participants was 3.3%; for progression of KOA, it was 8.0%.
- The prevalence of MCI in the 1384 participants defined as summary mini-mental state examination score ≤23 was 4.5%.
- Baseline mini-mental state examination (MMSE) summary score was significantly associated with the incidence of radiographic KOA after adjustment for confounders (+1 score; OR0.83, p=0.010). Baseline MCI was also significantly associated with the incidence of radiographic KOA (vs non-occurrence of KOA; OR 4.90, p=0.027). There was no significant association between MMSE scores, the presence of MCI and the progression of radiographic KOA (+1 score; OR 0.96, p=0.232; vs non-progression of KOA; OR 1.38, p=0.416).

## INTRODUCTION

Plural chronic diseases have a high prevalence in the elderly population. In the USA, about 77% of older adults have two or more chronic illnesses, and these can lead to

## ARTICLE SUMMARY

### Strengths and limitations of this study

- The present study includes a population-based design of a cohort, large number of participants with KOA, and a 3-year follow-up with a high participation rate of 81.9%.
- Substantial amount of detailed information, including an interviewer-administered questionnaire, dietary assessment, anthropometric measurements, neuromuscular function assessment, biochemical measurements, medical history, radiographic assessment and bone mineral density measurement, was collected at both the baseline and the second visit.
- We used KL grade ≥2 for the diagnosis of radiographic KOA, but the KL scale is a categorical index, and it might be impossible to evaluate the minimum joint space and osteophytosis separately.
- We used only the MMSE to diagnose MCI, and were unable to perform additional examinations such as MRI to improve the accuracy of the diagnosis.
- The small proportion of the population with MCI at risk of KOA onset detection might raise a bias in the results of the study.

severe and immediate disabilities.[1] According to the recent national livelihood survey by the Japanese Ministry of Health, Labour and Welfare, the leading causes of disability requiring support and long-term care were cardiovascular disease (CVD) followed by dementia, cognitive impairment, senility and osteoarthritis (OA).[2]

It is important to establish associations among these diseases causing disability, in order to reduce the risk of disability. In terms of CVD and dementia, the existence of vascular dementia, for example, indicates that there are links between CVD and dementia, and cardiovascular and metabolic risk factors such as hypertension and diabetes may play a role in the pathogenesis of Alzheimer's disease as well as in the development of vascular dementia.[3–6] Association between metabolic syndrome and risk of developing cognitive impairment has been demonstrated in older women, with a 23% age-adjusted increase in the risk of developing cognitive impairment in the number of components of metabolic syndrome.[7] Higher total cholesterol and low-density lipoprotein, and history of diabetes have been associated with faster cognitive decline in patients with incident Alzheimer's disease.[8]

However, as per our knowledge, there have been no previous reports on the association between OA and dementia. Mild cognitive impairment (MCI), a transitional state associated with memory impairment, has been associated with an increased risk of progression of Alzheimer's disease.[9 10] We aimed to investigate the association between MCI and the occurrence and progression of radiographic knee osteoarthritis (KOA) among men and women who participated in the Research on Osteoarthritis/Osteoporosis Against Disability (ROAD) study.

## PARTICIPANTS AND METHODS

### Participants

Our analysis was based on data collected from cohorts established in 2005 for the ROAD study. Details of the cohort have been reported elsewhere.[11 12] In brief, we created a baseline database in 2005–2007, which included clinical and genetic information for 3040 residents of Japan (1061 men, 1979 women). Participants were recruited from resident registration listings in three communities, each with different characteristics, namely an urban region in Itabashi, Tokyo; a mountainous region in Hidakagawa, Wakayama; and a coastal region in Taiji, Wakayama.

For the present study, we enrolled 1690 participants (596 men, 1094 women) residing in the mountainous and coastal areas, where the mental test was performed at baseline. Participants provided written informed consent, and the study was conducted with the approval of the ethics committees of the University of Tokyo (approval number 1264).

### Baseline procedures

Participants completed an interviewer-administered questionnaire comprising 400 items. These included lifestyle-related questions to obtain information about main occupation; smoking habits (0: exsmoker or never smoked, 1: current smoker); alcohol consumption (0: exdrinker or never drank, 1: current drinker); alcohol consumption; physical activity including cycling every day in the past 12 months (0: no, 1: yes); regular exercise, that is, football, tennis, baseball, golf or other sports after graduation from school (0: no, 1: yes); and medical history including history of knee injury (0: no, 1: yes).

Anthropometric measurements included height, weight, body mass index (BMI) calculated as weight (kg)/height ($m^2$) and grip strength of both hands. Experienced orthopaedic surgeons (SM and HO) collected medical information about pain, swelling and the range of motion in the knee.

All participants underwent a radiographic examination of both knees using an anteroposterior view with weight-bearing and foot map positioning. Fluoroscopic guidance with a horizontal anteroposterior x-ray beam was used to properly visualise the joint space.

Cognitive functioning was measured using the mini-mental state examination (MMSE).[13] This is a 30-item cognitive screening test that measures orientation, registration, short-term memory, attention and concentration, language and constructional capacity. The test–retest reliability of the original version of the MMSE is 0.83,[13] and the criterion validity is 0.66–0.79 with the Wechsler Adult Intelligence Scale, 0.83 with the Short Portable Mental Status Questionnaire and 0.88 with the Cognitive Capacity Screening Examination.[14 15] We used the validated Japanese version of the MMSE.[16] Summary scores from the MMSE were used to measure cognitive

functioning and the criterion for MCI was a summary score ≤23.

### Three-year follow-up and definition of the occurrence and progression of radiographic Knee osteoarthritis

In 2008–2010, the 1690 participants were invited to attend the 3-year follow-up of the second ROAD survey, which involved a repeat of the baseline examinations. Knee radiographs obtained at baseline and follow-up were read in pairs without knowledge of the participant's clinical status by a single well-experienced orthopaedist (SM), and the Kellgren/Lawrence (K/L) grade was defined using the K/L radiographic atlas for overall knee radiographic grades.[17] To evaluate the intraobserver variability of the K/L grading, 100 randomly selected radiographs of the knee were scored by the same observer 1 month after the first reading. One hundred other radiographs were also scored by two experienced orthopaedic surgeons (SM and HO) using the same atlas for interobserver variability. The intravariabilities and intervariabilities evaluated for K/L grade (0–4) were confirmed by kappa analysis to be sufficient for assessment (κ=0.86 and 0.80, respectively). When a different grade was assigned to each knee, the participant was classified by the higher grade. A participant with a KL grade ≥2 was defined as having radiographic KOA. A new case of radiographic KOA was identified if the KL grade at baseline had been <2 for both knees, and if one or both knees were assigned grade ≥2 at follow-up. A higher KL grade for either knee at follow-up compared with the baseline was defined as progression of OA.

### Statistical analysis

Statistical analyses were performed using STATA statistical software (STATA Corp, College Station, Texas, USA). Differences in proportions were compared using the $\chi^2$ test. Differences in continuous variables were tested for significance using analysis of variance (ANOVA) for multiple groups or Scheffé's least significant difference test for pairs of groups. To test the association between occurrence or progression of radiographic KOA and the presence of MCI after adjustment for confounding factors, we performed two types of multivariate logistic regression analysis. For both, we entered the occurrence or progression of OA over 3 years (1: yes, 0: no) as the dependent variable, and the MMSE summary score or presence of MCI (1: presence, 0: absence) as the independent variable. In model 1, the analysis was performed after adjusting for age, gender, regional differences and BMI. In model 2, we adjusted for potential risk factors that had previously been identified in this cohort as significantly associated with the presence of KOA,,[9 18] namely age, gender, regional differences, BMI, grip strength (kg) on the worse side, smoking, alcohol consumption, regular exercise and history of knee injuries. All p values and 95% CI of two-sided analysis are presented.

## RESULTS

### Eligible participants

Of the all 1690 participants in the baseline survey performed in the mountainous and coastal regions, 251 individuals (14.9%; 104 men, 147 women) did not attend the 3-year follow-up. Among them, 40 (27 men, 13 women) had died, 97 (32 men, 65 women) did not attend follow-up due to bad health, 16 (5 men, 11 women) had moved away, 51 (24 men, 27 women) declined the invitation to attend the second survey, 8 (4 men, 4 women) were absent and 39 (12 men, 27 women) did not participate for other reasons. In addition, 55 participants in the second survey (3.3%; 26 men, 29 women) did not complete all the follow-up examinations, including the interviewer-administered questionnaire, anthropometric measurements, radiographic examination and blood tests. Thus, our analysis was based on the remaining 1384 subjects (81.9%; 466 men, 918 women) who completed all examinations at both the baseline and follow-up (figure 1).

### Prevalence of MCI and its baseline characteristics

The prevalence of MCI and baseline characteristics of the 1384 participants are shown in table 1. Based on the MMSE summary score, 75 participants (30 men, 45 women) were diagnosed with MCI (prevalence, 4.5%; men, 5.1%, women, 4.2%). The prevalence of MCI was significantly higher in the older age groups (trend, p<0.001). The mean MMSE summary score was significantly lower in participants with MCI than in those without (21.2 vs 28.5). Participants with MCI tended to reside in mountainous areas, and they had significantly lower weight, height and grip strength; drank less alcohol and exercised less compared with those without MCI (table 1). In addition, the prevalence of radiographic KOA classified by presence of MCI was compared in table 1. In total, 75.7% of patients in the MCI group were observed to have KOA, which was

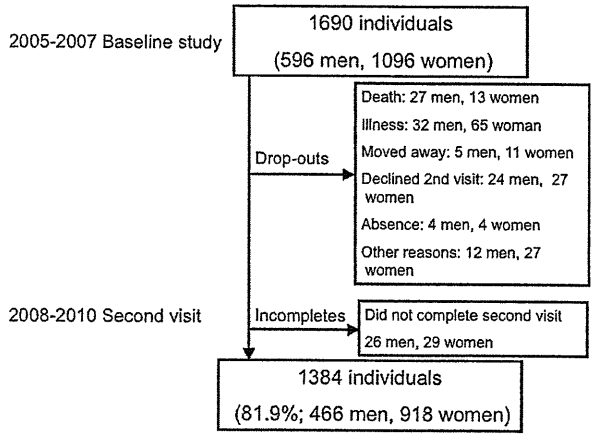



**Figure 1** Flow diagram for participation in the baseline and follow-up Research on Osteoarthritis/osteoporosis Against Disability surveys.

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

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

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

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

### Occurrence of radiographic KOA in participants with and without MCI

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

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

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

### Progression of radiographic KOA with and without MCI

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

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

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

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

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

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

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

| Occurrence of KOA | Total | | | Men | | | Women | | |
|---|---|---|---|---|---|---|---|---|---|
| | KOA (–) (n=657) | KOA (+) (n=71) | p Value | KOA (–) (n=272) | KOA (+) (n=18) | p Value | KOA (–) (n=385) | KOA (+) (n=53) | p Value |
| Number of subjects classified by age-strata (cumulative incidence, %/year) | | | | | | | | | |
| ≤39 (year) | 38 | 0 (0.0) | | 10 | 0 (0.0) | | 28 | 0 (0.0) | |
| 40–49 | 118 | 1 (0.3) | | 36 | 0 (0.0) | | 82 | 1 (0.4) | |
| 50–59 | 201 | 15 (2.3) | <0.001*** | 77 | 0 (0.0) | 0.009** | 124 | (3.6) | <0.001*** |
| 60–69 | 177 | 27 (4.4) | | 76 | 11 (4.2) | | 101 | (4.6) | |
| 70–79 | 108 | 23 (5.9) | | 62 | 6 (2.9) | | 46 | 17 (9.0) | |
| ≥80 | 15 | 5 (8.3) | | 11 | 1 (2.8) | | 4 | 4 (16.7) | |
| Mean values (SDs) for MMSE summary score and prevalence of MCI | | | | | | | | | |
| MMSE summary score | 29.1 (1.6) | 28.0 (2.3) | <0.0001*** | 28.8 (1.9) | 27.3 (2.7) | 0.0017** | 29.3 (1.3) | 28.2 (2.1) | <0.0001*** |
| Prevalence of MCI (%) | 7/654 (1.1) | 4/71 (5.6) | 0.003** | 6/270 (2.2) | 2/18 (11.1) | 0.026* | 1/384 (0.3) | 2/53 (3.8) | 0.004* |
| Mean values (SDs) for age, anthropometric factors and neuromuscular function | | | | | | | | | |
| Age (year) | 58.2 (11.8) | 67.3 (8.2) | <0.0001*** | 61.0 (11.8) | 70.0 (6.1) | 0.0021** | 56.4 (11.4) | 66.4 (8.7) | <0.0001*** |
| Height (cm) | 158.8 (8.6) | 153.9 (7.6) | <0.0001*** | 165.6 (7.0) | 162.0 (5.0) | 0.0360* | 154.0 (6.0) | 151.2 (6.2) | 0.0018** |
| Weight (kg) | 56.8 (11.0) | 56.0 (8.8) | 0.5560 | 63.7 (11.0) | 63.7 (9.2) | 0.9859 | 51.9 (8.1) | 53.4 (7.1) | 0.2051 |
| BMI (kg/m$^2$) | 22.4 (3.2) | 23.6 (2.9) | 0.0035** | 23.2 (3.2) | 24.2 (3.1) | 0.1709 | 21.9 (3.1) | 23.4 (2.8) | 0.0012** |
| Grip strength (better side) (kg) | 31.3 (9.9) | 26.7 (8.1) | 0.0002*** | 39.4 (8.8) | 35.9 (7.1) | 0.0996 | 25.6 (6.0) | 23.5 (5.6) | 0.0171* |
| Grip strength (worse side) (kg) | 28.0 (9.6) | 23.0 (8.5) | <0.0001*** | 35.9 (9.0) | 30.7 (11.0) | 0.0188* | 22.5 (5.1) | 20.4 (5.5) | 0.0065** |
| Percentage of selected characteristics, % | | | | | | | | | |
| Residing in a coastal area | 70.8 | 56.3 | 0.012* | 66.9 | 55.6 | 0.324 | 73.5 | 56.6 | 0.011* |
| Current smoking habit (more than once a month) | 16.9 | 7.1 | 0.034* | 34.2 | 27.8 | 0.577 | 4.7 | 0.0 | 0.110 |
| Current alcohol consumption (more than once a month) | 47.9 | 35.2 | 0.041* | 70.0 | 61.1 | 0.428 | 32.5 | 26.4 | 0.375 |
| Regular exercise after graduation from school | 19.9 | 7.0 | 0.008** | 37.5 | 27.8 | 0.408 | 7.5 | 0.0 | 0.039* |
| Past injury of either knee | 1.8 | 5.6 | 0.038* | 0.4 | 5.6 | 0.010* | 2.9 | 5.7 | 0.277 |

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

BMI, body mass index; KOA, knee osteoarthritis; KOA(–), non-occurrence of KOA; KOA(+), occurrence of KOA; n, number of subjects.

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

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

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

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

| Progression of KOA Women | Total | | | Men | | | Women | | |
|---|---|---|---|---|---|---|---|---|---|
| | Progression | | | Progression | | | Progression | | |
| | (–) (n=985) | (+) (n=311) | p Value | (–) (n=359) | (+) (n=86) | p Value | (–) (n=626) | (+) (n=225) | p Value |
| Number of subjects classified by age-strata (Proportion of progression, %/year) | | | | | | | | | |
| ≤39 (year) | 37 | 2 (1.7) | | 9 | 1 (3.3) | | 28 | 1 (1.1) | |
| 40–49 | 128 | 7 (1.7) | | 38 | 2 (1.7) | | 90 | 5 (1.8) | |
| 50–59 | 248 | 44 (5.0) | <0.001*** | 89 | 8 (2.8) | <0.001*** | 159 | 36 (6.2) | <0.001*** |
| 60–69 | 292 | 105 (8.2) | | 101 | | | 191 | 79 (9.8) | |
| 70–79 | 241 | 115 (10.8) | | 105 | 38 (8.9) | | 136 | 77 (12.1) | |
| ≥80 | 39 | 38 (16.5) | | 17 | 11 (13.1) | | 22 | 27 (18.4) | |
| Mean values (SDs) for MMSE summary score and prevalence of MCI | | | | | | | | | |
| MMSE summary score | 28.7 (1.8) | 28.0 (2.2) | <0.0001*** | 28.5 (1.9) | 27.9 (2.3) | 0.0056** | 28.8 (1.8) | 28.1 (2.1) | <0.0001*** |
| Prevalence of MCI (%) | 18/980 (1.8) | 14/295 (4.5) | 0.008** | 9/357 (2.5) | 5/85 (5.9) | 0.112 | 9/623 (1.4) | 9/224 (4.0) | 0.022* |
| Mean values (SDs) for age, anthropometric factors and neuromuscular function | | | | | | | | | |
| Age (year) | 61.6 (11.9) | 68.7 (9.3) | <0.0001*** | 63.3 (11.8) | 70.0 (9.4) | <0.0001*** | 60.7 (11.9) | 68.2 (9.3) | <0.0001*** |
| Height (cm) | 156.7 (8.9) | 153.1 (8.6) | <0.0001*** | 164.6 (7.1) | 161.8 (6.2) | 0.0010** | 152.2 (6.4) | 149.7 (6.9) | <0.0001*** |
| Weight (kg) | 56.0 (10.9) | 55.6 (9.9) | 0.5496 | 63.1 (10.9) | 62.8 (10.2) | 0.8520 | 52.0 (8.6) | 52.9 (8.4) | 0.1883 |
| BMI (kg/m$^2$) | 22.7 (3.3) | 23.6 (3.1) | <0.0001*** | 23.2 (3.2) | 23.9 (3.1) | 0.0643 | 22.4 (3.3) | 23.5 (3.1) | <0.0001*** |
| Grip strength (better side) (kg) | 29.3 (9.7) | 25.7 (8.0) | <0.0001*** | 38.1 (8.7) | 34.4 (7.2) | 0.0003*** | 24.3 (6.0) | 22.4 (5.3) | <0.0001*** |
| Grip strength (worse side) (kg) | 26.0 (9.4) | 22.5 (7.9) | <0.0001*** | 34.6 (8.8) | 30.1 (8.7) | <0.0001*** | 21.1 (5.3) | 19.6 (5.2) | 0.0003*** |
| Percentage of selected characteristics (%) | | | | | | | | | |
| Residing in a coastal area | 57.9 | 42.1 | <0.001*** | 53.8 | 44.2 | 0.110 | 60.4 | 41.3 | <0.001*** |
| Current smoking habit (more than once a month) | 14.1 | 8.6 | 0.013* | 31.2 | 24.4 | 0.220 | 4.1 | 2.3 | 0.222 |
| Current alcohol consumption (more than once a month) | 44.4 | 32.5 | <0.001*** | 72.1 | 57.0 | 0.006** | 28.6 | 23.1 | 0.114 |
| Regular exercise after graduation from school | 18.1 | 8.0 | <0.001*** | 39.6 | 23.3 | 0.005** | 5.8 | 2.2 | 0.034* |
| Past injury of either knee | 2.0 | 3.2 | 0.226 | 1.1 | 3.5 | 0.112 | 2.6 | 3.1 | 0.660 |

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

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

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

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

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

## DISCUSSION

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

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

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

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

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

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

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

On the contrary, the strengths of the present study include a population-based design of a cohort, large number of participants with KOA, and a 3-year follow-up with a high participation rate of 81.9%. Substantial amount of detailed information, including an interviewer-administered questionnaire, dietary assessment, anthropometric measurements, neuromuscular function assessment, biochemical measurements, medical history, radiographic assessment and bone mineral density measurement, was collected at both the baseline and the second visit.

## CONCLUSION

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

**Author affiliations**
[1]Department of Joint Disease Research, 22nd Century Medical and Research Center, the University of Tokyo, Tokyo, Japan
[2]Department of Clinical Motor System Medicine, 22nd Century Medical and Research Center, the University of Tokyo, Tokyo, Japan
[3]Department of Orthopaedic Surgery, Sensory and Motor System Medicine, Graduate School of Medicine, the University of Tokyo, Tokyo, Japan
[4]National Rehabilitation Center for Persons with Disabilities, Saitama, Japan

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

**Contributors** NY conceptualised the study, was primarily responsible for developing the protocol, and acts as the guarantor for this study. SM, HO and TA conducted data collection and x-ray assessment. All authors reviewed the protocol and contributed to interpretation of the results. All authors were involved in drafting the article and approved the final version submitted for publication. All authors had full access to all of the data in the study and take responsibility for the integrity and accuracy of the data analyses.

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

**Competing interests** None.

**Ethics approval** Ethics approval was provided by the institutional review board at the University of Tokyo (approval number 1264).

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data sharing statement** No additional data are available.

## REFERENCES

1. National Council of Aging. Fact Sheet: Chronic Disease Self-Management. http://www.ncoa.org/assets/files/pdf/NCOA-Chronic-Desease.pdf (accessed 12 Nov 2012).
2. Ministry of Health, Labour and Welfare. The outline of the results of National Livelihood Survey 2010. (http://www.mhlw.go.jp/toukei/saikin/hw/k-tyosa/l^tyousa10/4-2.html. (accessed 12 Nov 2012)
3. Launer LJ. Demonstrating the case that AD is a vascular disease: epidemiologic evidence. *Ageing Res Rev* 2002;1:61–77.
4. Kalmijn S, Feskens EJ, Launer LJ, *et al.* Glucose intolerance, hyperinsulinaemia and cognitive function in a general population of elderly men. *Diabetologia* 1995;38:1096–102.
5. Gregg EW, Yaffe K, Cauley JA, *et al.* Is diabetes associated with cognitive impairment and cognitive decline among older women? Study of Osteoporotic Fractures Research Group. *Arch Intern Med* 2000;160:174–80.
6. Yaffe K, Barrett-Connor E, Lin F, *et al.* Serum lipoprotein levels, statin use, and cognitive function in older women. *Arch Neurol* 2002;59:378–84.
7. Yaffe K, Weston AL, Blackwell T, *et al.* The metabolic syndrome and development of cognitive impairment among older women. *Arch Neurol* 2009;66:324–8.
8. Helzner EP, Luchsinger JA, Scarmeas N, *et al.* Contribution of vascular risk factors to the progression in Alzheimer disease. *Arch Neurol* 2009;66:343–8.
9. Ninomiya T, Ohara T, Hirakawa Y, *et al.* Midlife and late-life blood pressure and dementia in Japanese elderly: the Hisayama study. *Hypertension* 2011;58:22–8.
10. Petersen RC, Smith GE, Waring SC, *et al.* Mild cognitive impairment: clinical characterization and outcome. *Arch Neurol* 1999;56:303–8.
11. Yoshimura N, Muraki S, Oka H, *et al.* Prevalence of knee osteoarthritis, lumbar spondylosis and osteoporosis in Japanese men and women: the research on osteoarthritis/osteoporosis against disability study. *J Bone Miner Metab* 2009;27:620–8.
12. Yoshimura N, Muraki S, Oka H, *et al.* Cohort profile: research on Osteoarthritis/Osteoporosis Against Disability (ROAD) study. *Int J Epidemiol* 2010;39:988–95.
13. Folstein MF, Folstein SE, McHugh PR. Mini-Mental State. A practical method for grading the cognitive state of patients for the clinician. *J Psychiatric Res* 1975;12:189–98.
14. Anthony JC, LeResche L, Niaz U, *et al.* Limits of the 'Mini-Mental State' as a screening test for dementia and delirium among hospital patients. *Psychological Med* 1982;12:397–408.
15. Foreman MD. Reliability and validity of mental status questionnaires in elderly hospitalized patients. *Nursing Res* 1987;36:216–20.
16. Mori E, Mitsuya Y, Yamadori A. Usefulness of the Japanese version mini-mental state examination for the neurological patients. *Jpn J Neuropsychol* 1985;33:228–35.
17. Kellgren JH, Lawrence JS eds. *The epidemiology of chronic rheumatism: atlas of standard radiographs of arthritis.* Oxford: Blackwell Scientific, 1963.
18. Muraki S, Akune T, Oka H, *et al.* Association of radiographic and symptomatic knee osteoarthritis with health-related quality of life in a population-based cohort study in Japan: the ROAD study. *Osteoarthritis Cartilage* 2010;18:1227–34.
19. McGeer EG, McGeer PL. Brain inflammation in Alzheimer disease and the therapeutic implications. *Curr Pharm Des* 1999;5:821–36.
20. Zandi PP, Anthony JC, Hayden KM, *et al.* Reduced incidence of AD with NSAID but not H2 receptor antagonists: the Cache County Study. *Neurology* 2002;59:880–6.
21. Pottie P, Presle N, Terlain B, *et al.* Obesity and osteoarthritis: more complex than predicted! *Ann Rheum Dis* 2006;65:1403–5.
22. Kalmijn S, Feskens EJ, Launer LJ, *et al.* Glucose intolerance, hyperinsulinaemia and cognitive function in a general population of elderly men. *Diabetologia* 1995;38:1096–102.

23. Gregg EW, Yaffe K, Cauley JA, *et al.* Is diabetes associated with cognitive impairment and cognitive decline among older women? Study of Osteoporotic Fractures Research Group. *Arch Intern Med* 2000;160: 174–80.
24. Yaffe K, Barrett-Connor E, Lin F, *et al.* Serum lipoprotein levels, statin use, and cognitive function in older women. *Arch Neurol* 2002;59:378–84.
25. Yoshimura N, Muraki S, Oka H, *et al.* Accumulation of metabolic risk factors such as overweight, hypertension, dyslipidaemia, and impaired glucose tolerance raises the risk of occurrence and progression of knee osteoarthritis: a 3-year follow-up of the ROAD study. *Osteoarthritis Cartilage* 2012;20:1217–26.
26. Oka H, Muraki S, Akune T, *et al.* Fully automatic quantification of knee osteoarthritis severity on plain radiographs. *Osteoarthritis Cartilage* 2008;16:1300–6.

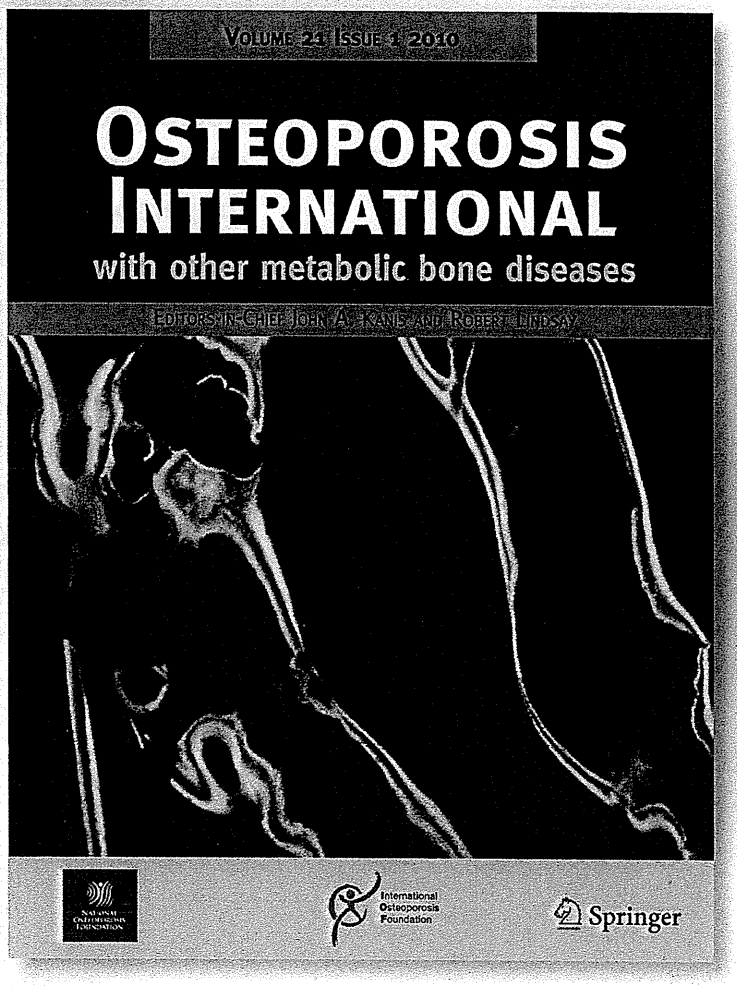
# *Physical performance, bone and joint diseases, and incidence of falls in Japanese men and women: a longitudinal cohort study*

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

**Osteoporosis International**
With other metabolic bone diseases

ISSN 0937-941X

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




Springer

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

ORIGINAL ARTICLE

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

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

Received: 20 October 2011 / Accepted: 27 February 2012


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

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

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

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

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

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

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

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

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

## Introduction

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

Published online: 21 March 2012

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

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

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

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

## Methods

### Subjects

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

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

### 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]/height$^2$ [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 ± 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±11.3 | 69.4±11.1 | 68.1±11.4* |
| Height (cm) | 154.7±8.8 | 163.2±6.6 | 150.4±6.3* |
| Weight (kg) | 55.5±10.2 | 62.2±9.9 | 52.0±8.5* |
| BMI (kg/m$^2$) | 23.1±3.3 | 23.3±3.0 | 23.0±3.4* |
| Grip strength (kg) | 26.3±9.3 | 34.5±8.8 | 22.1±6.2* |
| Walking speed (m/s) | 1.24±0.34 | 1.26±0.35 | 1.23±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 ± 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

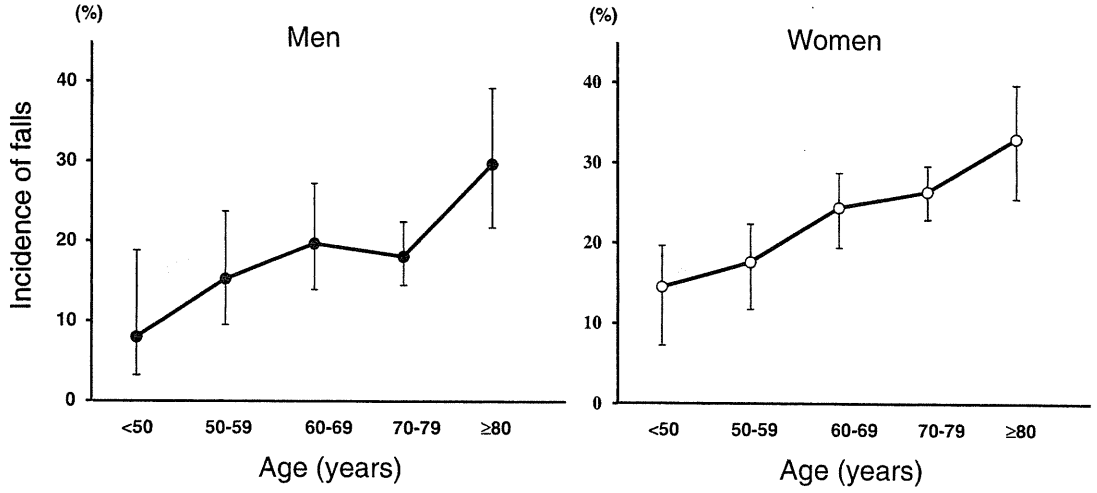



**Fig. 1** Incidence rate of falls (95 % CI) by gender and age

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 | *p* value | Nonfallers | Fallers | *p* 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

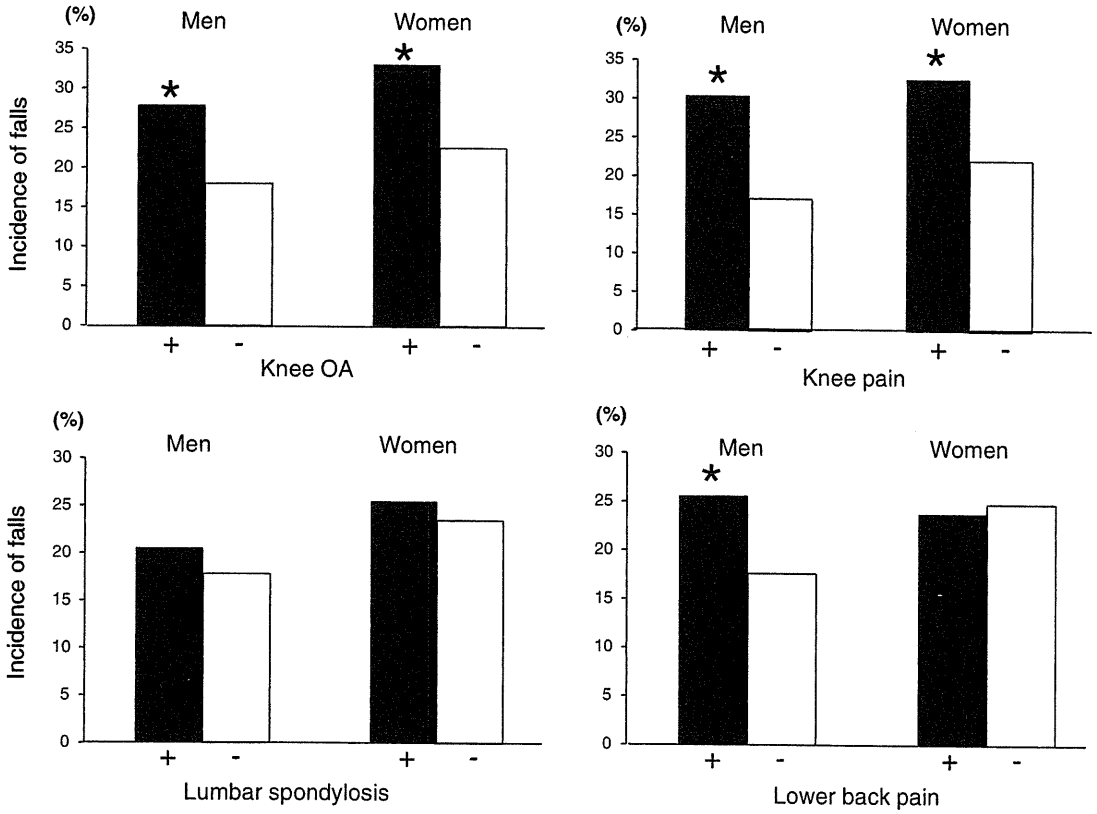



**Fig. 2** Incidence of falls by knee OA, knee pain, LS, and lower back pain. *$p<0.05$ vs. subjects without knee OA, LS, knee pain, and lower back pain, respectively, by chi-square test

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 $OR_1$ was calculated using multiple logistic regression analysis after adjustment for age and BMI. Adjusted $OR_2$ 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