Metropolitan Geriatric Hospital. Since gait speed was not measured at Tokyo Metropolitan Geriatric Hospital, 819 individuals who visited this hospital were removed from the present study. Of 1,846 participants, the remaining 1,019 individuals aged ≥65 years who visited the survey site located in Hidakagawa, Taiji, or at the University of Tokyo Hospital and underwent an examination including gait speed assessment were recruited for the present study. Of the 1,019 individuals, 19 were removed because 1 did not undergo handgrip strength measurement and 18 did not undergo skeletal muscle mass measurement. For the present study, we enrolled 1,000 participants (349 men and 651 women aged ≥65 years) from the second visit who completed assessment of handgrip strength, gait speed, and skeletal muscle mass. The mean age of the participants was 75.7 (SD, 5.9) years in men and 74.4 (SD, 6.1) years in women. All participants provided written informed consent, and the study was conducted with approval from the Ethics Committee of the University of Tokyo.

Participants completed an interviewer-administered questionnaire comprising 400 items regarding lifestyle information such as smoking habits, alcohol consumption, and physical activity. An interviewer asked the following question regarding past physical activity: "During the time you were aged 25–50 years, did you ever practice sports or physical exercise sufficient to produce sweating or shortness of breath?" Possible responses were as follows: never, occasionally, <2 hours per week, and ≥2 hours per week. Those who answered "occasionally, <2 hours per week, or ≥2 hours per week" were defined as having exercise habits in middle age. The following question was asked regarding current physical activity: "Do you practice walking more than 30 minutes every day?" Those who answered "yes" were defined as having a current walking habit.

Anthropometric and physical performance measurements

Anthropometric measurements, including height and weight, were obtained, and body mass index (weight [kg]/height [m^2]) was estimated based on the measured height and weight. Grip strength was measured on the right and left sides using a TOEI LIGHT handgrip dynamometer (TOEI LIGHT CO. LTD, Saitama, Japan), and the highest measurement was used to characterize maximum muscle strength. Subjects were defined as having low grip strength if grip strength was <30 kg in men and <20 kg in women, as reported by Lauretani and colleagues [20].

Skeletal muscle mass was measured by bioimpedance analysis [21–25] using the Body Composition Analyzer MC-190 (Tanita Corp., Tokyo, Japan). The protocol was described by Tanimoto and colleagues [10, 12], and the method has been validated [26]. Appendicular skeletal muscle mass (ASM) was derived as the sum of the muscle mass of the arms and the legs. Absolute ASM was converted to an appendicular muscle mass index (SMI) by dividing by height in meters squared (kg/m^2). Subjects were defined as having low skeletal muscle mass if the SMI was <2 SDs of the young adult mean. We used an SMI of <7.0 kg/m^2 in men and <5.8 kg/m^2 in women as cut-off points for low skeletal muscle mass based on the reference data of SMI measured by the MC-190 in 1,719 healthy young Japanese volunteers aged 18–39 years [10].

To measure physical performance, the time taken to walk 6 m at normal walking speed in a hallway was recorded, and usual gait speed was calculated. Subjects were defined as having low gait speed if usual gait speed was ≤0.8 m/s. The time taken for five consecutive chair rises without the use of hands was also recorded. Timing began with the command "Go" and ended when the buttocks contacted the chair on the fifth landing. One-leg standing time with eyes open was measured on both sides, and the best measurement was used. Participants were asked to stand on one leg while continuing to elevate their contralateral limb. Timing commenced when the participant assumed the correct posture and ended when any body part touched a supporting surface.

Statistical analysis

All statistical analyses were performed using STATA statistical software (STATA, College Station, TX). Differences in the values of the parameters between two groups were tested for significance using the nonpaired Student's *t* test and chi-square test. Trends in values were tested using the Jonckheere-Terpstra trend test. Factors associated with sarcopenia were determined using multivariate logistic regression analysis with sarcopenia as the dependent variable; the odds ratio (OR) and 95 % confidence interval were determined after adjusting for age, sex, and BMI. Factors associated with exercise habits in middle age were determined using multivariate linear regression analysis with exercise habits in middle age as the independent variable; the regression coefficient and 95 % CI were determined after adjusting for age, sex, and BMI.

Results

Table 1 shows the characteristics of the participants according to EWGSOP sarcopenia status. Age was significantly greater, while BMI, ASM, and SMI were significantly lesser in those with sarcopenia than in those without sarcopenia in both men and women. In physical performance, chair stand time was significantly greater and one-leg standing time was significantly lesser in those with sarcopenia than in those without sarcopenia in both men and women. The percentage of individuals with exercise habits in middle age was significantly lower in those with sarcopenia than in those without sarcopenia in both men and women.

Table 1 Characteristics of participants according to EWGSOP sarcopenia status

	Men		Women	
	No sarcopenia	Sarcopenia	No sarcopenia	Sarcopenia
No. of subjects	301	48	570	81
Age, years	75.1 (5.8)	79.9 (5.2)*	73.5 (5.6)	80.8 (5.8)*
Height, cm	161.9 (6.0)	158.5 (5.8)*	148.9 (6.4)	145.6 (6.6)*
Weight, kg	61.2 (9.5)	52.9 (6.5)*	52.4 (8.4)	42.6 (6.3)*
BMI, kg/m^2	23.3 (3.0)	21.0 (2.0)*	23.6 (3.3)	20.0 (2.3)*
ASM, kg	19.8 (3.0)	16.0 (1.7)*	13.8 (1.8)	11.4 (1.2)*
SMI, kg/m^2	7.54 (0.90)	6.36 (0.47)*	6.22 (0.66)	5.35 (0.30)*
Grip strength, kg	36.9 (6.8)	28.0 (4.0)*	23.9 (4.6)	16.8 (3.4)*
Usual gait speed, m/s	1.11 (0.25)	0.85 (0.27)*	1.06 (0.28)	0.82 (0.22)*
Chair stand time, s	9.6 (3.7)	11.9 (4.2)*	9.9 (4.2)	13.4 (5.9)*
One-leg standing time, median (IQR), s	31.0 (10.0–60.0)	8.0 (4.0–16.0)*	26.0 (8.0–60.0)	11.0 (5.0–23.0)*
Smoking, %	15.6	16.7	2.3	6.2
Alcohol consumption, %	58.8	45.8	14.7	18.8
Current walking habits, %	56.5	45.0	55.1	56.5
Exercise habits in middle age, %	69.9	46.2†	43.3	26.1†

Except where indicated otherwise, values are mean (SD)

ASM appendicular skeletal muscle mass, *BMI* body mass index, *EWGSOP* European Working Group on Sarcopenia in Older People, *IQR* interquartile range, *SMI* skeletal muscle mass index

*P<.001 vs. no sarcopenia in the same sex group by unpaired Student's t test; †P<.01 vs. no sarcopenia in the same sex group by chi-square test

Figure 1 shows sex- and age-wise distributions of prevalence of sarcopenia (Fig. 1a), low SMI (Fig. 1b), low grip strength (Fig. 1c), and low gait speed (Fig. 1d). The total prevalence of sarcopenia was 13.8 % in men and 12.4 % in women. Prevalence of sarcopenia (number of cases/subjects) in the age strata of 65–69, 70–74, 75–79, 80–84, and ≥85 years was 1.6 % (1/63), 5.7 % (5/88), 17.8 % (19/107), 23.2 % (16/69), and 31.8 % (7/22) in men and 0.6 % (1/163), 5.5 % (10/182), 13.8 % (22/160), 22.9 % (25/109), and 62.2 % (23/37) in women. Prevalence of sarcopenia tended to be significantly higher according to increasing age (P<.001 for trend) in both men and women. Prevalence of low grip strength and low gait speed also tended to be significantly higher according to increasing age (P<.001 for trend) in both men and women. However, the increasing tendency of prevalence of low SMI (P<.001 for trend) was milder compared with that of sarcopenia, low grip strength, and low gait speed.

Then, we determined the factors associated with sarcopenia by logistic regression analysis; the upper part of Table 2 shows the results using sarcopenia as the dependent variable. In the overall population, age (OR, 1.20; 95 % CI, 1.15–1.24) and BMI (OR, 0.68; 95 % CI, 0.63–0.75) were significantly associated with sarcopenia, whereas sex was not. In physical performance, chair stand time (OR, 1.09; 95 % CI, 1.04–1.14) and one-leg standing time (OR, 0.94; 95 % CI, 0.96–0.99) were significantly associated with sarcopenia in the overall population after adjusting for age, sex, and BMI. Current walking habit (OR, 0.69; 95 % CI, 0.42–1.12) was not significantly associated with sarcopenia. However, exercise habit in middle age (OR, 0.53; 95 % CI, 0.31–0.90) was associated with sarcopenia in the overall population after adjusting for age, sex, and BMI, indicating that exercise habit in middle age was significantly associated with low prevalence of sarcopenia in older age. The significance of the association did not change when current walking habit was added as an explanatory variable in this logistic regression model (OR, 0.53; 95 % CI, 0.32–0.90). In addition, we investigated the association of each category—occasionally, <2 h per week, and ≥2 h per week—with sarcopenia using "never" as a reference, in addition to the association of the presence of exercise habits in middle age with sarcopenia. The associated ORs for the three categories were comparable, but they did not reach significance level (occasionally: OR, 0.63; 95 % CI, 0.34–1.17; <2 h per week: OR, 0.30; 95 % CI, 0.09–1.01; ≥2 h per week: OR, 0.49; 95 % CI, 0.22–1.09).

The lower part of Table 2 shows the results of linear regression analysis using SMI, grip strength, gait speed, chair stand time, or one-leg standing time as the dependent variable and exercise habit in middle age as the independent variable. Exercise habit in middle age was significantly associated with grip strength in older age (P<.001), gait speed in older age (P<.001), and one-leg standing time in older age (P=.005) after adjusting for age, sex, and BMI in the overall population. We conducted the same analyses in men and women separately (Tables 3 and 4) and found results similar to those in the overall population. Some sex differences were observed in the present results. Exercise habit in middle age was significantly associated with grip strength and gait speed in older age in both men and women, whereas it was significantly associated with chair stand time and one-leg standing time only in men; however, the sample size of men was smaller than that of women. In the overall population, exercise habit in middle age was not associated with chair stand time.

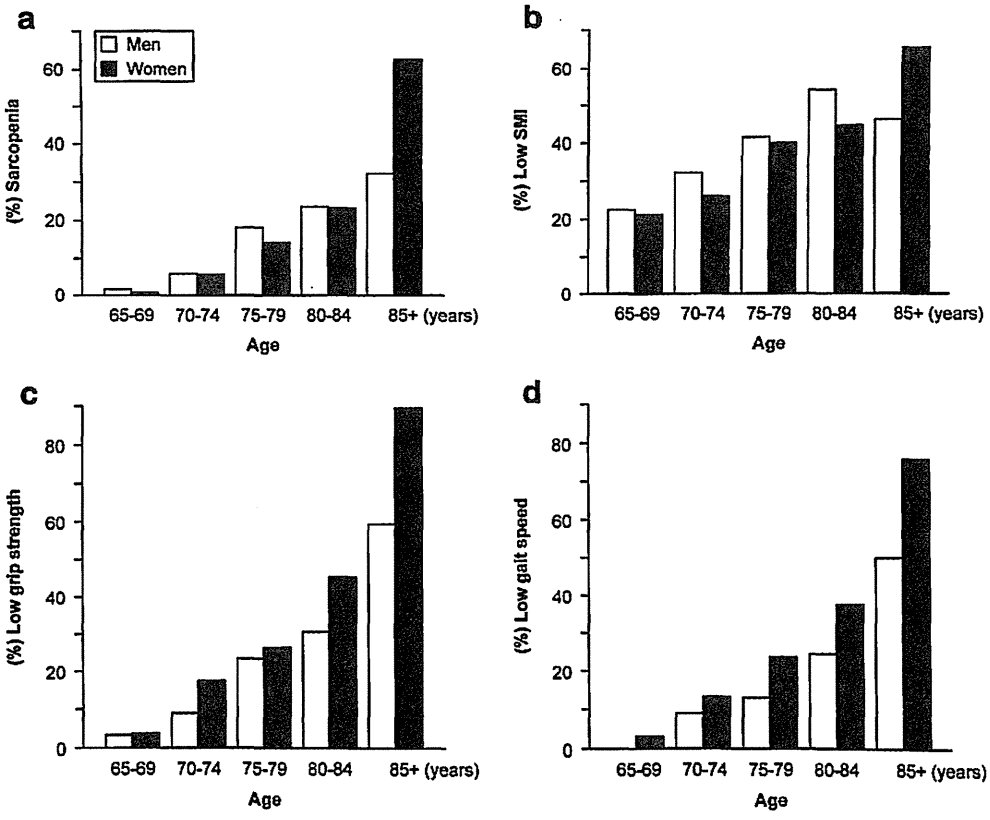

Fig. 1 Percentage of sarcopenia (**a**), low skeletal muscle mass index (*SMI*) (**b**), low grip strength (**c**), and low gait speed (**d**) in men and women in each age stratum (65–69, 70–74, 75–79, 80–85, and ≥85 years). Low SMI was defined as a value of <7.0 kg/m^2 in men and <5.8 kg/m^2 in women. Low grip strength was defined as a value of <30 kg in men and <20 kg in women. Low gait speed was defined as a value of ≤0.8 m/s

Discussion

The present study investigated the prevalence of sarcopenia using the EWGSOP definition in the elderly participants of Japanese population-based cohorts. We determined that age was positively associated with sarcopenia and that BMI was inversely associated, but sex was not. Exercise habit in middle age was associated with increased muscle strength and physical performance and low prevalence of sarcopenia in older age. To the best of our knowledge, this is the first study to show the relationship between exercise habits in middle age and sarcopenia in older age in the elderly participants of population-based cohorts.

Previous studies have reported the prevalence of sarcopenia and its associated factors. For example, Tanimoto and colleagues reported the prevalence of sarcopenia in

Table 2 Factors associated with sarcopenia and exercise habits in middle age in the overall population

Factors associated with sarcopenia	Odds ratio	95 % CI	*P* value
Age (+1 year)	1.20	1.15–1.24	<.001
Sex (women vs. men)	0.98	0.63–1.53	.9
BMI (+1 kg/m^2)	0.68	0.63–0.75	<.001
Chair stand time (+1 s)	1.09[a]	1.04–1.14	.001
One-leg standing time (+1 s)	0.97[a]	0.96–0.99	<.001
Smoking (yes vs. no)	1.86[a]	0.86–4.02	.1
Alcohol consumption (yes vs. no)	1.00[a]	0.60–1.67	.9
Current walking habits (yes vs. no)	0.69[a]	0.42–1.12	.1
Exercise habits in middle age (yes vs. no)	0.53[a]	0.31–0.90	.01
Factors associated with exercise habits in middle age	Regression coefficient	95 % CI	*P* value
SMI	0.09[b]	−0.02–0.19	.1
Grip strength	1.73[c]	1.02–2.44	<.001
Gait speed	0.07[c]	0.04–0.10	<.001
Chair stand time	−0.47[c]	−1.02–0.09	.09
One-leg standing time	4.14[c]	1.26–7.02	.005

BMI body mass index, *CI* confidence interval, *SMI* skeletal muscle mass index

[a] Odds ratio and 95 % CI were calculated by logistic regression analysis after adjusting for age, sex, and BMI

[b] Regression coefficient and 95 % CI were calculated by linear regression analysis after adjusting for age and sex

[c] Regression coefficient and 95 % CI were calculated by linear regression analysis after adjusting for age, sex, and BMI

Table 3 Factors associated with sarcopenia and exercise habits in middle age in men

Factors associated with sarcopenia	Odds ratio	95 % CI	*P* value
Chair stand time (+1 s)	1.09[a]	1.01–1.18	.03
One-leg standing time (+1 s)	0.97[a]	0.95–0.99	.001
Smoking (yes vs. no)	1.49[a]	0.59–3.75	.4
Alcohol consumption (yes vs. no)	0.78[a]	0.40–1.53	.4
Current walking habits (yes vs. no)	0.60[a]	0.28–1.27	.1
Exercise habits in middle age (yes vs. no)	0.48[a]	0.22–1.03	.06
Factors associated with exercise habits in middle age	Regression coefficient	95 % CI	*P* value
SMI	0.16[b]	−0.06 to 0.38	.1
Grip strength	3.17[c]	1.70 to 4.65	<.001
Gait speed	0.10[c]	0.04 to 0.15	.001
Chair stand time	−1.12[c]	−1.95 to −0.28	.009
One-leg standing time	7.81[c]	2.57 to 13.05	.004

CI confidence interval, *SMI* skeletal muscle mass index

[a] Odds ratio and 95 % CI were calculated by logistic regression analysis after adjusting for age and BMI

[b] Regression coefficient and 95 % CI were calculated by linear regression analysis after adjusting for age

[c] Regression coefficient and 95 % CI were calculated by linear regression analysis after adjusting for age and BMI

Japanese community-dwelling elderly individuals based on the EWGSOP definition using bioimpedance analysis (MC-190) [12]. They reported a prevalence of 11.3 % in men and 10.7 % in women [12], which is similar to our results. Although the cut-off value for low SMI was the same in these two studies, the cut-off value used for handgrip strength was different; we used cutoff values of <30 kg in men and <20 kg in women, in accordance with Lauretani and colleagues [20], while they used values of <30.3 kg in men and <19.3 kg in women, based on the lowest quartile of handgrip strength in their study population [12]. In the population of the present study, the lowest quartile of grip strength was 30.5 kg in men and 20.0 kg in women. Considering that these two studies showed similar results, cut-off values of 30 kg in men and 20 kg in women for handgrip strength [20] also may be appropriate for the practical case definition of the EWGSOP algorithm in the Japanese population.

Patel and colleagues reported the prevalence of sarcopenia in Caucasians using the EWGSOP definition, in which low muscle mass is defined as the lowest tertile of lean or fat-free

Table 4 Factors associated with sarcopenia and exercise habits in middle age in women

Factors associated with sarcopenia	Odds ratio	95 % CI	*P* value
Chair stand time (+1 s)	1.08[a]	1.02–1.15	.01
One-leg standing time (+1 s)	0.98[a]	0.96–1.00	.01
Smoking (yes vs. no)	2.44[a]	0.61–9.72	.2
Alcohol consumption (yes vs. no)	1.26[a]	0.58–2.71	.5
Current walking habits (yes vs. no)	0.75[a]	0.39–1.44	.3
Exercise habits in middle age (yes vs. no)	0.55[a]	0.27–1.13	.1
Factors associated with exercise habits in middle age	Regression coefficient	95 % CI	*P* value
SMI	0.06[b]	−0.05 to 0.17	.2
Grip strength	1.03[c]	0.29 to 1.78	.007
Gait speed	0.06[c]	0.01 to 0.10	.01
Chair stand time	−0.12[c]	−0.83 to 0.60	.7
One-leg standing time	2.19[c]	−1.24 to 5.62	.2

CI confidence interval, *SMI* skeletal muscle mass index

[a] Odds ratio and 95 % CI were calculated by logistic regression analysis after adjusting for age and BMI

[b] Regression coefficient and 95 % CI were calculated by linear regression analysis after adjusting for age

[c] Regression coefficient and 95 % CI were calculated by linear regression analysis after adjusting for age and BMI

mass [11]. They recommended use of the lowest tertile of muscle mass as a cut-off value if the reference value of muscle mass in a young healthy population is unavailable. In the population of the present study, the lowest tertile of SMI was 6.92 kg/m^2 in men and 5.80 kg/m^2 in women, which is similar to the cut-off value of <2 SDs of the young adult mean (7.0 kg/m^2 in men and 5.8 kg/m^2 in women) [10]. For evaluating low muscle mass, use of the lowest tertile may be an appropriate alternative method if the reference value of a young healthy population is unavailable.

The present study showed an association between sarcopenia and physical performance, including chair stand time and one-leg standing time, which is consistent with results of previous reports using the EWGSOP definition [11, 13]. However, these were comparisons between sarcopenia and current status of physical performance or exercise habit. Therefore, causal association was unclear whether sarcopenia was caused by decreased physical performance or activity or whether low physical performance or activity was due to sarcopenia. We also revealed that exercise habit in middle age was associated with increased muscle strength and physical performance and low prevalence of sarcopenia in older age. These results suggest that exercise habit in middle age is a protective factor against sarcopenia in older age and effective in maintaining muscle strength and physical performance in older age.

Some sex differences were observed in the present results. Exercise habit in middle age was significantly associated with grip strength and gait speed in older age in both men and women, whereas it was significantly associated with chair stand time and one-leg standing time only in men; however, the sample size of men was smaller than that of women. In the overall population, exercise habit in middle age was not associated with chair stand time; this finding may have been influenced by the fact that the sample size of women was almost twice that of men. The present results suggest that the impact of exercise habit in middle age on physical ability in older age is greater in men than in women.

Since exercise is a modifiable factor, it is a promising finding that exercise habit may be effective in preventing sarcopenia. In the present study, exercise habit was defined as physical activity in the period when the individual was aged 25–50 years, in which subjects practiced sports or physical exercise sufficient to produce sweating or shortness of breath, occasionally or more frequently. Although exercise habit was associated with low prevalence of sarcopenia at the age of ≥65 years, some details remain unclear, including exercise type, intensity, time, and other factors appropriate for prevention of sarcopenia. In addition to the association of the presence of exercise habit in middle age with sarcopenia, we further investigated the association of each category—occasionally, <2 h per week, and ≥2 h per week—with sarcopenia using "never" as a reference. Among the three categories, the analysis could not determine the best frequency and amount of exercise for protection from sarcopenia. The associated ORs for the three categories were comparable, and no dose–response tendency was seen in the relationship between frequency and amount of exercise and prevalence of sarcopenia; the associations also did not reach significance level. The present results suggest that abstaining from exercise during middle age is a risk factor for sarcopenia in older age. Furthermore, the presence of exercise habit in middle age might be much more important than the frequency and amount of exercise. Further studies are necessary to develop intervention programs and to test their effectiveness, along with accumulation of epidemiologic evidence including longitudinal studies.

The present study has several limitations. First, since this was a cross-sectional design, a causal relationship could not be determined. Second, information regarding exercise habits in middle age was obtained by self-report, and there is a possibility of recall bias. Third, the present study included participants who could walk to the survey site and could understand and sign an informed consent form. Since those who did not meet these inclusion criteria were not included in the analyses, the study participants do not truly represent the general population because of health bias. This should be considered when generalizing the results of the present study. Fourth, the results may have been affected by the characteristics of the population, including age and BMI. In the present study, age was positively associated with sarcopenia, whereas BMI was inversely associated with sarcopenia. Therefore, care should be taken when extrapolating the data to other populations with different characteristics, including age and BMI, which may confound the results.

In conclusion, the present study revealed prevalence of sarcopenia in the elderly participants of Japanese population-based cohorts. Exercise habit in middle age was associated with increased muscle strength and physical performance and low prevalence of sarcopenia in older age. These results suggest that exercise habit in middle age is a protective factor against sarcopenia in older age and is effective in maintaining muscle strength and physical performance in older age. Further long-term longitudinal epidemiological studies are necessary to develop effective intervention programs for the prevention and treatment of sarcopenia.

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Conflicts of interest None.

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Prevalence and distribution of intervertebral disc degeneration over the entire spine in a population-based cohort: the Wakayama Spine Study

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SUMMARY

Objectives: The purposes of this study were to investigate the prevalence and distribution of intervertebral disc degeneration (DD) over the entire spine using magnetic resonance imaging (MRI), and to examine the factors and symptoms potentially associated with DD.
Design: This study included 975 participants (324 men, mean age of 67.2 years; 651 women, mean age of 66.0 years) with an age range of 21–97 years in the Wakayama Spine Study. DD on MRI was classified into Pfirrmann's system (grades 4 and 5 indicating DD). We assessed the prevalence of DD at each level in the cervical, thoracic, and lumbar regions and the entire spine, and examined DD-associated factors and symptoms.
Results: The prevalence of DD over the entire spine was 71% in men and 77% in women aged <50 years, and >90% in both men and women aged >50 years. The prevalence of an intervertebral space with DD was highest at C5/6 (men: 51.5%, women: 46%), T6/7 (men: 32.4%, women: 37.7%), and L4/5 (men: 69.1%, women: 75.8%). Age and obesity were associated with the presence of DD in all regions. Low back pain was associated with the presence of DD in the lumbar region.
Conclusion: The current study established the baseline data of DD over the entire spine in a large population of elderly individuals. These data provide the foundation for elucidating the causes and mechanisms of DD.

Introduction

Intervertebral disc degeneration (DD) is thought to be the first step in degenerative spinal changes[1], and is typically followed by the gradual formation of osteophytes, disc narrowing, and spinal stenosis[2,3]. Furthermore, DD is considered to be one of the causes of several symptoms (neck pain or low back pain)[4–7]. Therefore, in terms of developing preventive strategies for spinal disorders, it will be important to obtain fundamental data on DD (prevalence, distribution, associated factors, etc.) in a population-based cohort.

We believe that the analysis of DD over the entire spine would provide more useful data than that of DD in the cervical, thoracic, or lumbar regions, separately. In particular, investigations on the extent of DD in these three regions using whole spine magnetic resonance imaging (MRI) could provide useful data concerning intra-individual factors in the development of DD. Several studies have examined degenerative changes in only cervical and lumbar discs because of the high susceptibility to DD in these regions[8–12]. As well, several previous studies have investigated the aging process of the intervertebral discs in the cervical and lumbar regions using MRI in population-based cohorts[13,14]. However, degenerative changes in the thoracic region and correspondingly over the entire spine are poorly understood, because DD in the thoracic region is considered to be an uncommon problem[15,16]. In particular, the stabilization of the thoracic region by the thoracic cage, which

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reduces the mechanical stress imposed on the intervertebral discs, is believed to reduce the incidence of degenerative diseases in this region[17].

Consistent with the above-mentioned previous studies, a population-based cohort analysis of DD in the different spinal regions using MRI could be used to examine the distribution of DD over the entire spine. However, to our knowledge, no previous studies have performed this type of investigation with a population-based cohort.

From the perspective of discogenic pain, the association between DD and symptoms remains controversial, although several reports have found that DD was a source of low back pain[4,5]. Moreover, reports on the association between the presence of DD in the cervical and thoracic regions and neck pain are rare[6,7]. Further, these studies were not performed with population-based cohorts and did not use whole spine MRI. Thus, no study has assessed neck pain and low back pain within individuals using whole spine MRI. To clarify the points described above, we established a population-based cohort study in which participants underwent whole spine MRI and were examined for symptoms associated with spinal disorders. This is our first report of DD over the entire spine based on a cross-sectional examination of a baseline population.

The aims of this study were to examine (1) the prevalence and distribution of DD over the entire spine using MRI in a population-based cohort, (2) the factors associated with DD (age, gender, and body mass index [BMI]) in the cervical, thoracic, and lumbar regions, and (3) the association between DD and symptoms (neck pain and low back pain).

Methods

Participants

The present study, entitled the Wakayama Spine Study, was performed with a sub-cohort of the second visit of the ROAD (Research on Osteoarthritis/osteoporosis Against Disability) study, which was initiated as a nationwide, prospective study of bone and joint diseases in population-based cohorts; the cohorts were established in three communities with different characteristics (i.e., urban, mountainous, and coastal regions) in Japan. A detailed profile of the ROAD study has already been described elsewhere[18,19]. Here, we briefly summarize the profile of the present study. The second visit of the ROAD study began in 2008 and was completed in 2010. All the participants in the baseline study were invited to participate in the second visit. In addition to the former participants, inhabitants aged 60 years and older in the urban area and those aged 40 years and younger in the mountainous and coastal areas who were willing to participate in the ROAD survey were also included in the second visit (both the mountainous and coastal areas were in Wakayama prefecture). Finally, 2674 individuals (900 men, 1774 women) participated in the second visit of the ROAD study, and comprised 1067 individuals (353 men, 714 women) in the urban area, 742 individuals (265 men, 477 women) in the mountainous area, and 865 individuals (282 men, 583 women) in the coastal area. Among these three communities in the ROAD study, the mountainous and coastal areas from which we invited all 1607 participants (547 men, 1060 women) to the Wakayama Spine Study are located in Wakayama prefecture. Of the 1607 participants, a total of 1011 individuals provided written informed consent and attended the Wakayama Spine Study with MRI examinations[20,21]. Among the 1011 participants, those who had MRI-sensitive implanted devices (e.g., pacemakers) and other disqualifiers were excluded. Consequently, 980 individuals underwent MRI of the whole spine. Furthermore, one participant who had undergone a previous cervical operation and four participants who had undergone a previous posterior lumbar fusion were excluded from the analysis. Finally, whole spine MRI results were available for 975 participants (324 men, 651 women) with an age range of 21–97 years (mean, 67.2 years for men and 66.0 years for women). Table I shows the demographic and baseline characteristics of the 975 participants in the present study.

For the purpose of analysis, the participants were divided into five age groups: (1) under 50 years, (2) 50–59 years, (3) 60–69 years, (4) 70–79 years, and (5) 80 years and over. The anthropometric measurements included height, weight, and BMI (weight [kg]/height^2 [m^2]). BMI was categorized according to the guidelines for Asians proposed by the World Health Organization and was thus defined as follows: underweight, less than 18.5; normal, 18.5–23; overweight, 23–27.5; and obesity, greater than 27.5[22]. Experienced orthopedists also asked all participants the following question regarding neck pain and low back pain: "Have you experienced neck pain on most days during the past month, in addition to now?" and "Have you experienced low back pain on most days during the past month, in addition to now?" Those who answered "yes" were defined as having neck pain or low back pain based on previous studies[23–26].

MRI

A mobile MRI unit (Excelart 1.5 T, Toshiba, Tokyo, Japan) was used in the present study, and whole spine MRI was performed for all participants on the same day as the examination. The participants were supine during the MRI, and those with rounded backs used triangular pillows under their head and knees. The imaging protocol included sagittal T2-weighted fast spin echo (FSE) (repetition time [TR]: 4000 ms/echo, echo time [TE]: 120 ms, field of view [FOV]: 300 × 320 mm), and axial T2-weighted FSE (TR: 4000 ms/echo, TE: 120 ms, FOV: 180 × 180 mm).

Sagittal T2-weighted images were used to assess the intervertebral space from C2/3 to L5/S1. C2/3 to C7/T1, T1/2 to T12/L1, and L1/2 to L5/S1 were defined as the cervical region, thoracic region, and lumbar region, respectively. DD grading was performed by an

Table I
Characteristics of participants

	Overall	Men	Women
No. of participants	**975**	**324**	**651**
Age strata (years)			
<50	125	38	87
50–59	175	59	116
60–69	223	65	158
70–79	261	89	172
≧80	191	73	118
Demographic characteristics			
Age, years	66.4 ± 13.5	67.2 ± 13.9	66.0 ± 13.4
Height, cm	156.4 ± 9.4	164.6 ± 7.2	151.5 ± 7.2
Weight, kg	56.8 ± 11.5	64.5 ± 11.6	53.0 ± 9.4
BMI (kg/m^2)	23.3 ± 3.6	23.6 ± 3.4	23.1 ± 3.7
BMI (WHO-Asian category) (N)			
Underweight	61	16	45
Normal	425	124	300
Overweight	361	139	221
Obesity	128	44	84
Baseline characteristics			
Symptoms (%)			
Neck pain	24.9	19.4	27.7
Low back pain	43	36.7	42.1
Life style (%)			
Smoking	10.7	25.2	4.1
Alcohol consumption	31.4	56.8	18.8

BMI category for Asian was based on World Health Organization (WHO) guidelines defining underweight (<18.5), normal (18.5–23), overweight (23–27.5), and obese (>27.5). Values are the means ± standard deviation.

orthopedist (MT) who was blind to the background of the subjects. The degree of DD on MRI was classified into five grades based on Pfirrmann's classification system[27], with grades 4 and 5 indicating DD. As shown in Fig. 1, the signal intensity for grade 4 was intermediate to hypointense to the cerebrospinal fluid (dark gray), while the structure is inhomogeneous. Meanwhile, for grade 5, the signal intensity is hypointense to the cerebrospinal fluid (black), and the structure is likewise inhomogeneous. In addition, the disc space is collapsed. It has been reported that loss of signal intensity is significantly associated with the morphological level of the DD and is also associated with both the water and proteoglycan content in a disc[28]. Therefore, we used a grading based on signal intensity and disc height. For evaluating intraobserver variability, 100 randomly selected magnetic resonance images of the entire spine were rescored by the same observer (MT) more than 1 month after the first reading. Furthermore, to evaluate interobserver variability, 100 other magnetic resonance images were scored by two orthopedists (MT and RK) using the same classification. The intraobserver and interobserver variability for DD, as evaluated by kappa analysis, was 0.94 and 0.94, respectively.

"Prevalence of DD", which was defined as "the proportion of the number of participants who had DD at each intervertebral space or region or over the entire spine divided by the total number of participants", was used to describe the frequency of the presence of DD. In the analysis, to clarify the associated factors using multiple logistic regression analysis, we entered a variable of prevalence state (1, presence; 0, absence) of DD as a dependent variable.

Statistical analysis

Multiple logistic regression analysis was used to estimate the association between the presence of DD in each region (cervical, thoracic, and lumbar) as dependent variables and the age group, gender, and BMI category as nominal independent variables after adjustment for the age group, gender and BMI category, mutually.

Additionally, multiple logistic regression analysis was used to estimate the association between the presence of neck pain or low back pain and the presence of DD in each region after adjustment for age, gender, and BMI. Furthermore, in cases in which the presence of DD was significantly associated with a symptom, we examined as a sub-analysis the association between the presence of neck pain or low back pain and the number of DD (categorized into "0", "1 or 2", "3 or more" for ready assessment) in each region using multiple logistic regression analysis after adjustment for age, gender, and BMI. All statistical analyses were performed using JMP version 8 (SAS Institute Japan, Tokyo, Japan).

Results

As shown in Table II, the prevalence of DD in the cervical and thoracic regions and over the entire spine increased with the elevation of the age strata in both men and women. For both genders, the prevalence of DD in the lumbar region was also increased with the elevation of the age strata up to the 70-year-old age group but decreased in the 80-year-old age group. Table III

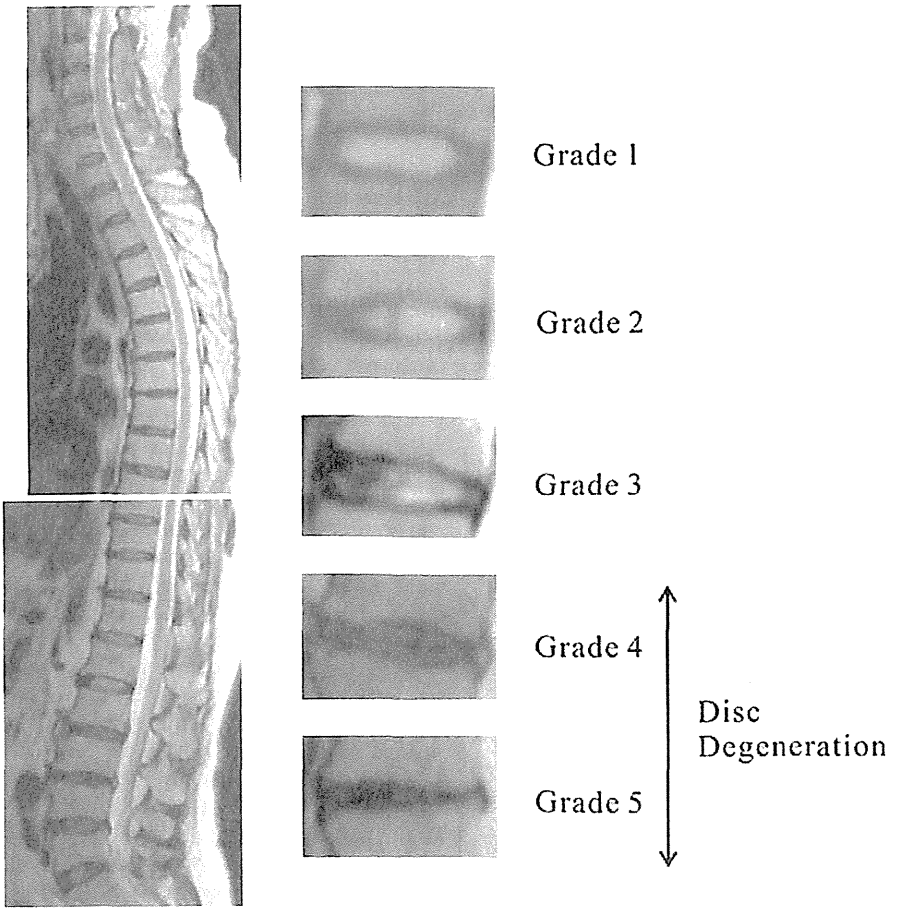

Fig. 1. Mid-sagittal view on T2-weighted images of the whole spine MRI with Pfirrmann classification. The grade is described according to Pfirrmann classification. Grades 4 and 5 were considered degenerated. The signal intensity for grade 4 was intermediate to hypointense to the cerebrospinal fluid (dark gray), while the structure is inhomogeneous. Meanwhile, for grade 5, the signal intensity is hypointense to the cerebrospinal fluid (black), and the structure is also inhomogeneous. Additionally, the disc space is collapsed.

shows the prevalence of intervertebral spaces with DD over the entire spine for the participants in this study. The three highest prevalence levels of DD in the intervertebral spaces in the cervical, thoracic, and lumbar regions were as follows. The prevalence at C5/6 was 51.5% (95% CI: 46.1–56.3) in men and 46% (95% CI: 42.2–49.9) in women, followed by the prevalence at C6/7 of 43.5% in men and 33.3% in women, and at C4/5 of 38.6% in men and 35.8% in women. The prevalence at T6/7 was 32.4% (95% CI: 27.5–37.6) in men and 37.7% (95% CI: 34.1–41.5) in women, followed by the prevalence at T7/8 of 31.8% in men and 36.2% in women, and at T5/6 of 28.4% in men and 35.9% in women. The prevalence at L4/5 was 69.1% (95% CI: 63.9–73.9) in men and 75.8% (95% CI: 72.3–78.9) in women, followed by that at L5/S1 of 66.7% in men and 70.9% in women, and at L3/4 of 59.3% in men and 61.9% in women.

An older age was significantly associated with the presence of DD in each region. Gender was not significantly associated with the presence of DD in each region, although men demonstrated a tendency for a greater number of DD than women in the cervical region. In addition, overweight status (BMI: 23–27.5) was a significantly associated factor in the cervical and thoracic regions, and obesity (BMI: >27.5) was a significantly associated factor in all regions compared with participants of a normal weight (BMI: 18.5–23) (Table IV).

The participants with DD in the cervical region did not significantly differ in terms of the presence of neck pain (OR 0.88, 95% CI: 0.63–1.22, $P = 0.53$). The presence of DD in the thoracic region was not significantly associated with neck pain (OR 0.84, 95% CI: 0.60–1.19, $P = 0.33$) and low back pain (OR 1.08, 95% CI: 0.80–1.47, $P = 0.60$). However, the presence of DD in the lumbar region was significantly associated with low back pain (OR 1.57, 95% CI: 1.02–2.49, $P < 0.05$). Moreover, in a sub-analysis, we investigated the association between low back pain and the number of DD in the lumbar region ("0", "1 or 2", "3 or more"). The presence of low back pain was significantly higher in participants with three or more DD (OR 1.75, 95% CI: 1.11–2.81, $P < 0.05$), but not in those with one or two DD (OR 1.34, 95% CI: 0.84–2.20, $P = 0.22$), as compared with participants without DD.

Discussion

This study is the first to report the prevalence and distribution of DD over the entire spine using whole spine MRI in a population-based cohort. The prevalence of DD over the entire spine and in each of the three spinal regions was higher in older participants. In addition, we noted that the presence of DD was significantly associated with low back pain in the lumbar region but not with neck pain in the cervical region.

Battié *et al.* reviewed the prevalence of DD in the lumbar region and noted that it ranged from 20% to 83%[29]. Consistent with the observations of this review, other reported prevalence levels of DD in the lumbar region have shown wide variation between samples and have often been quite high because the studies had certain drawbacks, including relatively small sample sizes[1,30], narrow age ranges[5,31], and asymptomatic subjects[32]. However, no previous study has assessed the prevalence of DD over the entire spine using whole spine MRI. We noted that the prevalence of DD over the entire spine exceeded 70% in participants less than 50 years of age and was greater than 90% in participants older than 50 years of age.

Little epidemiological data are available concerning DD in the intervertebral space using MRI assessments in a population-based cohort. Matsumoto *et al.*[4] reported that the prevalence of DD in the cervical region was the highest at C5/6 (86% in men and 89% in women over the age of 60 years). In addition, Hanagai *et al.*[33] and Kanayama *et al.*[34] reported that the prevalence of DD in the lumbar region was the highest at L4/5 (67%; mean age 68.4 years) and L5/S1 (49.5%; mean age 39.7 years), respectively. In the present study, the prevalence of DD was the highest at C5/6 (51.5% in men and 46.0% in women) and L4/5 (69.1% in men and 75.8% in women). The prevalence of cervical DD in the previous study by Matsumoto *et al.*[4] was higher than that in the present study. However, the subjects were recruited from volunteers in the hospital rather than a population; thus, the capacity for strict comparisons are limited. Furthermore, few studies have reported age-related DD in the thoracic region. Matsumoto *et al.* reported that the highest prevalence of DD occurred at T7/8 (30.9%; mean age 48.0 y) followed by T6/7 in the thoracic region; however, all 94 participants in this report were asymptomatic[35]. In the present study, we confirmed a high prevalence of DD at T6/7 in the thoracic region. This finding is supported by results from thoracic MRI investigations demonstrating a high prevalence of DD in asymptomatic individuals.

The distribution of prevalence of DD was similar to the alignment of the spine in the sagittal plane, such as cervical lordosis (C3–C7), thoracic kyphosis (T1–T12), and lumbar lordosis (L1–L5)[36]. The high prevalence of DD in the lumbar region can potentially be explained by mechanical stress. Our results support the hypothesis that compressive stress affected DD, since compressive stresses are the highest in the mid-thoracic region of the entire spine[37]. Mechanical stress on the thoracic intervertebral disc is reduced due to stabilization by the thoracic cage, and therefore, the thoracic intervertebral disc may be affected by the detrimental effect of compressive stress caused by posture on the sagittal balance of the spine[38]. This study also provides the first mapping of intervertebral spaces with DD over the entire spine by MRI analysis, which adds to our knowledge of the distribution of prevalence of DD in the cervical, thoracic, and lumbar regions, which has been reported only fragmentarily in previous reports.

Our current results confirmed that age was a significant factor associated with the presence of DD in all three regions. Previous studies reported that the association of DD to factors such as height, weight, and gender was uncertain; however, age, obesity, smoking, and occupation have been suggested to be DD-associated factors[39–42]. The previous studies focused almost entirely on the lumbar region, and the identification of associated factors may be challenging for this region because it is affected to a greater extent by various factors, including mechanical stress. Moreover, it remains unknown what other factors (beyond age) are associated with DD in the cervical and thoracic regions[6,13]. In the present study, overweight and obesity significantly influenced DD in the cervical and thoracic regions (cervical; OR: overweight 1.38 [95% CI 1.00–1.90], obesity 1.60 [95% CI 1.04–2.51], thoracic; OR: overweight 1.64 [95% CI 1.17–2.29], obesity 3.12 [95% CI 1.91–5.19]), and obesity also significantly influenced DD in the lumbar region (OR: 2.56 [95% CI 1.20–6.14]). In a previous study, Samartzis *et al.* reported that DD in the lumbar region was significantly associated with overweight and obesity[39]. However, DD in the cervical and thoracic region did not demonstrate a significant association with BMI, as reported by Okada *et al.*[6] and Matsumoto *et al.*[35]. Of note, the previous studies were

Table II
Prevalence of DD by age strata in men and women

	Entire spine		Cervical		Thoracic		Lumbar	
	Men	Women	Men	Women	Men	Women	Men	Women
Age strata (years)								
<50	71.0	77.0	26.3	27.9	15.7	11.4	55.2	71.2
50–59	91.5	93.1	47.4	49.1	49.1	35.3	86.4	91.3
60–69	98.4	95.5	66.1	54.4	61.5	63.2	96.9	94.3
70–79	95.8	99.4	80.9	72.0	73.0	79.6	96.6	96.5
≧80	93.2	97.4	86.3	85.5	79.4	88.9	82.1	84.5

Values are percentage.

Table III
Prevalence of intervertebral spaces with DD over the entire spine by age strata in men and women

Age strata (years)	C2/3	C3/4	C4/5	C5/6	C6/7	C7/T1	T1/2	T2/3	T3/4	T4/5	T5/6	T6/7	T7/8	T8/9	T9/10	T10/11	T11/12	T12/L1	L1/2	L2/3	L3/4	L4/5	L5/S1
Men																							
Total	28.3	30.2	38.6	51.5	43.5	26.8	20.3	23.4	22.2	24.0	28.4	32.4	31.8	28.7	31.4	25.0	24.0	17.5	30.0	51.5	59.3	69.1	66.7
<50	10.5	10.5	13.1	15.7	13.1	5.2	5.2	7.8	7.8	5.2	10.5	7.8	5.2	2.6	2.6	2.6	0.0	0.0	2.6	10.5	7.8	34.2	47.3
50–59	6.7	11.8	15.2	37.2	27.1	10.1	8.4	6.7	11.8	11.8	16.9	23.7	27.1	16.9	20.3	16.9	13.5	5.1	15.2	35.5	61.0	74.5	50.8
60–69	35.3	36.9	49.2	50.7	40.0	21.0	20.0	24.6	23.0	27.6	27.6	35.3	32.3	36.9	41.5	23.0	24.6	18.4	40.0	60.0	69.0	76.9	75.3
70–79	35.9	35.9	49.4	64.0	51.6	34.8	24.7	26.9	25.8	30.3	33.7	38.2	41.5	35.9	40.4	37.0	31.4	26.9	39.3	69.6	73.0	79.7	79.7
≧80	39.7	42.4	47.9	67.1	65.7	46.5	32.8	39.7	32.8	32.8	41.0	42.4	36.9	35.6	35.6	30.1	35.6	24.6	39.7	56.1	58.9	63.0	65.7
Women																							
Total	21.9	24.8	35.8	46.0	33.3	13.6	15.2	23.1	29.8	31.7	35.9	37.7	36.2	34.2	32.7	28.7	23.8	20.0	31.7	49.7	61.9	75.8	70.9
<50	2.2	3.4	10.3	20.6	10.3	1.1	0.0	1.1	4.5	0.0	1.1	4.5	3.4	5.7	4.5	4.5	1.1	0.0	4.5	12.6	18.3	49.4	56.3
50–59	11.2	9.4	23.2	36.2	23.2	3.4	6.8	12.0	15.5	15.5	16.3	18.1	19.8	12.9	13.7	10.3	6.9	6.9	15.6	35.6	55.6	73.9	70.4
60–69	13.9	20.8	31.0	43.6	29.1	11.3	13.2	18.3	29.7	32.2	37.9	39.8	31.6	32.2	30.3	19.6	15.8	14.5	25.3	55.0	66.4	85.4	75.9
70–79	33.7	34.8	46.5	53.4	42.4	16.2	22.0	34.3	41.2	44.7	50.0	50.0	47.0	45.9	44.7	42.4	34.3	26.1	44.7	64.5	80.2	86.0	81.9
≧80	40.6	46.6	57.6	66.9	52.5	32.2	27.1	40.6	45.7	51.6	57.6	61.0	66.9	61.8	57.6	56.7	52.9	46.1	57.2	62.3	67.5	69.2	58.9

Values are percentage.

conducted with asymptomatic healthy subjects. Therefore, based on our findings, obesity appears to have some influence on the process of DD over the entire spine.

An association between DD in the lumbar region and low back pain was previously demonstrated in a twin study[43]. Moreover, Okada *et al.*[6] reported an association between neck pain and DD in the cervical region, whereas Arana *et al.*[7] found an association between neck pain and DD in the upper thoracic region. Of interest, no agreement has been reached regarding the most appropriate definition of neck pain and low back pain in population cohorts[7]. Nonetheless, we observed a significant association between the presence of DD in the lumbar region and low back pain.

The present study has several limitations. First, it was a cross-sectional study, and therefore, the transition to DD cannot be clarified. Second, the participants included in the present study may not represent the general population, since they were recruited from only two local areas. To confirm whether the participants of the Wakayama Spine Study are representative of the Japanese population, we compared the anthropometric measurements and frequencies of smoking and alcohol consumption between the general Japanese population and the study participants. No significant differences in BMI were observed (men: 24.0 and 23.7, $P = 0.33$; women: 23.5 and 23.1, $P = 0.07$). Further, the proportion of current smokers and those who consumed alcohol (those who regularly smoked or consumed alcohol more than once per month) in men and the proportion of those who consumed alcohol in women were significantly higher in the general Japanese population than in the study population, whereas there was no significant difference in the proportion of current smokers in women (male smokers, 32.6% and 25.2%, $P = 0.015$; female smokers, 4.9% and 4.1%, $P = 0.50$; men who consumed alcohol, 73.9% and 56.8%, $P < 0.0001$; women who consumed alcohol, 28.1% and 18.8%, $P < 0.0001$). These results suggest the likelihood that in this study, participants had healthier lifestyles than those of the general Japanese population[44]. This "healthy" selection bias should be taken into consideration when generalizing the results obtained from the Wakayama Spine Study. Third, the Pfirrmann classification introduced a comprehensive MRI grading system based on the assessment of structure, the distinction of the nucleus and annulus fibrosis, the signal intensity[28], and the height of the intervertebral discs[27]. However, bony endplate alterations, osteophyte changes, spinal stenosis, and disc protrusion are not covered by the Pfirrmann classification. Therefore, it is necessary to perform investigations that include these morphological changes. Finally, the accurate measurement of obesity, such as abdominal obesity and/or body composition, might reveal that obesity has a stronger association with DD; however, the present study examined only BMI as a measurement of obesity. Thus, we plan to examine the girth of the abdomen and body composition using electrical impedance in the assessment of human body composition (the BIA method) in a future study.

In conclusion, this study is the first one to investigate the prevalence of DD over the entire spine in a large population of individuals to establish baseline data for a prospective longitudinal

Table IV
Multiple logistic regression of the association with presence of DD with age, BMI, and gender

	Cervical	Thoracic	Lumbar
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Age group (years)			
<50	1	1	1
50–59 (vs <50)	2.45 (1.5–4.06)**	4.60 (2.53–8.76)***	4.47 (2.44–8.48)***
60–69 (vs <50)	3.62 (2.26–5.91)***	12.0 (6.77–22.7)***	9.95 (5.02–21.3)***
70–79 (vs <50)	7.87 (4.86–12.9)***	24.9 (13.8–47.6)***	15.0 (7.26–34.5)***
≧80 (vs <50)	16.9 (9.68–30.5)***	47.0 (24.5–95.6)***	2.94 (1.71–5.13)**
Men (vs women)	1.20 (0.89–1.64)	0.88 (0.64–1.21)	0.70 (0.45–1.09)
BMI (WHO-Asian category)			
Underweight (vs normal)	0.91 (0.49–1.70)	1.36 (0.71–2.67)	0.81 (0.38–1.84)
Normal	1	1	1
Overweight (vs normal)	1.38 (1.00–1.90)*	1.64 (1.17–2.29)*	1.14 (0.71–1.85)
Obesity (vs normal)	1.60 (1.04–2.51)*	3.12 (1.91–5.19)***	2.56 (1.20–6.14)*

BMI category for Asian was based on World Health Organization (WHO) guidelines defining underweight (<18.5), normal (18.5–23), overweight (23–27.5), and obese (>27.5). OR = odds ratio, CI = confidential interval.
*$P < 0.05$, **$P < 0.001$, ***$P < 0.0001$.

study. The prevalence of intervertebral spaces with DD was the highest at C5/6, T6/7, and L4/5 in the cervical, thoracic, and lumbar regions, respectively. DD in the cervical, thoracic, and lumbar regions was significantly associated with age and obesity. A significant positive association was observed between the presence of DD in the lumbar region and low back pain.

Author contributions

All authors worked collectively to develop the protocols and method described in this paper. MT, NY, SM, HO, YI, KN, NT, and TA were principal investigators responsible for the fieldwork in the Wakayama Spine study. MT and SM performed the statistical analysis. All authors contributed to the analysis and interpretation of results. MT wrote the report. All authors read and approved the final manuscript.

Role of the funding source

The sponsors had no role in study design, data collection, data analysis, data interpretation, or in writing of the report.

Conflict of interest

The authors declare no conflicts of interest.

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ORIGINAL ARTICLE

Association of knee osteoarthritis with onset and resolution of pain and physical functional disability: The ROAD study

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Abstract

Objectives. To examine the onset and resolution of pain and physical functional disability using Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and their association with knee osteoarthritis (OA) in the longitudinal large-scale population of the nationwide cohort study, Research on Osteoarthritis/osteoporosis Against Disability (ROAD).

Methods. Subjects from the ROAD study who had been recruited during 2005–2007 were followed up 3 years later. A total of 1,578 subjects completed the WOMAC questionnaire at baseline and follow up, and the onset and resolution rate of pain and physical functional disability were examined. We also examined the association of onset of pain and physical functional disability and their resolution with severity of knee OA as well as age, body–mass index and grip strength.

Results. After a 3.3-year follow-up, the onset rate of pain was 35.0% and 35.3% in men and women, respectively, and the onset rate of physical functional disability was 38% and 40%, respectively. Resolution rate of pain was 20.3% and 26.2% in men and women, respectively, and resolution rate of physical functional disability was 16% and 14% in men and women, respectively. Knee OA was significantly associated with onset and resolution of pain and physical functional disability in women, but there was no significant association of knee OA with onset of pain and resolution of physical functional disability in men.

Conclusions. The present longitudinal study revealed the onset rate of pain and physical functional disability as well as their resolution, and their association with knee OA.

Keywords

Knee joint, Osteoarthritis, Epidemiology, Longitudinal studies

History

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Introduction

Knee osteoarthritis (OA), characterized by pathological features including joint space narrowing and osteophytosis, is a major public health issue causing chronic pain and disability among the elderly in most developed countries [1]. The prevalence of radiographic knee OA in Japan is high [2], with 25,300,000 subjects aged 40 years and older estimated to experience radiographic knee OA [3]. According to the recent National Livelihood Survey of the Ministry of Health, Labour and Welfare in Japan, OA is ranked fourth among diseases that cause disabilities that subsequently require support with activities of daily living [4].

The principal clinical symptoms of knee OA are pain and physical functional disability [5], but the correlation of these symptoms with radiographic severity of knee OA is controversial [2,6–8]. Thus it would be interesting to determine whether the impact of radiographic knee OA on pain and physical functional disability differs according to the severity of OA. In terms of disease-specific scales for estimating pain and physical functional disability due to knee OA, the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) has been used for Caucasians [9] and Asians [10,11], although these reports were not population-based studies. Furthermore, there is little information on the impact of knee OA on onset of pain and physical functional disability using WOMAC in Japan, although a population survey suggests that the disease pattern differs among races [12–14]. In addition, to the best of our knowledge, although pain and physical functional disability can disappear or improve, there is no information on the impact of knee OA on the resolution of pain and physical functional disability.

Grip strength is a useful marker of muscle function and sarcopenia [15]. There is growing evidence that reduced grip strength is associated with adverse outcomes including morbidity, disability, falls, higher fracture rates, increased length of hospital stay and mortality [16–18]. A previous study also showed that grip strength is related to total muscle strength [19]. Thus, the association of knee OA with pain and physical functional disability may be influenced by grip strength, but again, no studies have examined the association of knee OA and grip strength with onset of pain and disability as well as their resolution simultaneously in the same population using a longitudinal cohort study.

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The objective of the present study was to clarify the onset and resolution rate of pain and physical functional disability using WOMAC in Japanese men and women who were part of the large-scale, longitudinal, population-based cohort study known as the Research on Osteoarthritis/osteoporosis Against Disability (ROAD) study. In addition, we examined the association of body-- mass index (BMI), grip strength and severity of knee OA with onset of pain and physical functional disability as well as their resolution in men and women.

Materials and methods

Subjects

The ROAD study was a nationwide prospective study for bone and joint diseases (with OA 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 [2,3,20], only a brief summary is provided here. During 2005–2007, we created a baseline database that included clinical and genetic information for 3,040 inhabitants (1,061 men; 1,979 women) aged 23–95 years (mean, 70.6 years), recruited from listings of resident registrations in three communities: an urban region in Itabashi, Tokyo; a mountainous region in Hidakagawa, Wakayama; and a coastal region in Taiji, Wakayama. All participants provided written informed consent, and the study was conducted with the approval of the ethics committees of the University of Tokyo and the Tokyo Metropolitan Institute of Gerontology. Participants completed an interviewer-administered questionnaire of 400 items that included lifestyle information such as smoking habit, alcohol consumption, family history, medical history and previous knee injury history. Furthermore, subjects were interviewed by well-experienced orthopedists regarding the treatment for knee OA, such as medication, injections, physical therapy, bracing, etc. between the baseline and follow-up study. Anthropometric measurements included height and weight, from which BMI (weight [kg]/height^2 [m^2]) was calculated. Grip strength was measured on bilateral sides using a TOEI LIGHT handgrip dynamometer (Toei Light Co., Ltd., Saitama, Japan), and the better measurement was used to represent maximum muscle strength. During 2008–2010, we attempted to trace and review all 3,040 subjects; they were invited to attend a follow-up interview. The interviews were conducted by the same trained orthopedists who undertook the baseline study during 2005–2007.

Radiographic assessment

All participants underwent radiographic examination of both knees using an anterior–posterior view with weight-bearing and foot map positioning. Fluoroscopic guidance with a horizontal anterior–posterior X-ray beam was used to properly visualize the joint space. Knee radiographs at baseline and follow-up were read in pairs without knowledge of the participant's clinical status by a single well-experienced orthopedist (S.M.), and the Kellgren Lawrence (KL) grade was defined using the KL radiographic atlas for overall knee radiographic grades [21]. In the KL 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 KL grading, 100 randomly selected radiographs of the knee 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. & H.O.) using the same atlas for interobserver variability. The intra- and inter variabilities evaluated for KL grades (0–4) were confirmed by kappa analysis to be sufficient for assessment (0.86 and 0.80, respectively).

Instruments

The WOMAC, a 24-item OA-specific index, consists of three domains: pain, stiffness and physical function. Each of these 24 items is graded on either a 5-point Likert scale or a 100-mm visual analog scale [22,9]. In the present study, we used the Likert scale (version LK 3.0). The domain score ranges from 0 to 20 for pain, 0 to 8 for stiffness and 0 to 68 for physical function. Japanese versions of the WOMAC have also been validated [23]. In the present study, onset of pain and physical functional disability were defined as WOMAC pain score = 0 at baseline and >0 at follow up and WOMAC physical function score = 0 at baseline and >0 at follow up, respectively. Resolution of pain and physical functional disability were defined as WOMAC pain score >0 at baseline and = 0 at follow up and WOMAC physical function score >0 at baseline and = 0 at follow up, respectively. Worsening pain and physical functional disability were defined as WOMAC pain and physical function at follow up was worse than at baseline, respectively.

Statistical analysis

The differences in age, height, weight, BMI, grip strength, and WOMAC pain and physical function scores at baseline and follow up between men and women were examined using a non-paired Student's t-test. The prevalence of knee OA was compared between men and women using chi-square test. Tukey's honestly significant difference test after adjustment for age and BMI was used to compare WOMAC pain and physical functional score and differences between baseline and follow up among subjects with KL = 0/1, 2 and 3/4. The non-paired Student's t test was used to compare age, BMI and grip strength between subjects with and without onset of pain and physical functional disability as well as those with and without resolution of pain and physical functional disability. Chi-square test was used to compare prevalence of knee OA between subjects with and without onset of pain and physical functional disability as well as those with and without resolution of pain and physical functional disability. Multiple logistic regression analysis after adjustment for age was also used to determine the association of severity of knee OA with onset of pain and physical functional disability as well as their resolution. In addition, to determine independent association of age, BMI, grip strength and knee OA with onset of pain and physical function as well as their resolution, multiple logistic regression analysis was used with significant variables ($p < 0.01$) in univariate analyses as explanatory variables. Data analyses were performed using SAS version 9.0 (SAS Institute Inc., Cary, NC).

Results

Of the 3,040 subjects in the baseline study during 2005–2007, 125 had died by the time of the review held 3 years later, 123 did not participate in the follow-up study due to bad health, 69 had moved away, 83 declined the invitation to attend the follow-up study, and 155 did not participate in the follow-up study for other reasons. Among the 2,485 subjects who did participate in the follow-up study, we excluded 39 subjects who were younger than 40 years at baseline. Those participating in the follow-up study were younger than those who did not survive or who did not participate for other reasons (responders 68.6 years, non-responders 75.1 years; $p < 0.0001$). The follow-up study participants also were more likely to be women (responders 66.3% women, nonresponders 61.8% women; $P = 0.03$) and were more likely to have knee OA at the baseline examination than either those who did not survive to follow-up or those who did not participate for other reasons (responders 51.5%, nonresponders 60.9%; $P < 0.0001$). Among them, 1,578 subjects provided completed WOMAC questionnaires both at baseline and follow up. We also excluded three subjects

Table 1. Characteristics of subjects.

	Overall	Men	Women	p value
N	1558	553	1005	
Age	67.0 ± 11.0	68.1 ± 10.7	66.5 ± 11.0	0.004
Height	155.2 ± 8.9	163.4 ± 6.5	150.8 ± 6.5	<0.0001
Weight	55.5 ± 10.4	62.2 ± 10.2	51.8 ± 8.5	<0.0001
BMI	22.9 ± 3.3	23.2 ± 3.1	22.8 ± 3.3	0.0043
Grip strength	27.2 ± 9.5	35.4 ± 8.7	22.7 ± 6.4	<0.0001
Knee OA (%)	49.3	38.7	55.2	<0.0001
WOMAC at baseline				
Pain	1.12 ± 2.18	1.02 ± 2.05	1.18 ± 2.25	0.157
Physical function	3.03 ± 6.63	2.56 ± 5.71	3.29 ± 7.07	0.0268
WOMAC at follow up				
Pain	1.82 ± 2.83	1.72 ± 2.67	1.88 ± 2.91	0.291
Physical function	5.59 ± 9.7	4.73 ± 8.30	6.06 ± 10.36	0.0061

Knee OA was defined as Kellgren Lawrence grade 2 or worse at baseline.
BMI, body–mass index; OA, osteoarthritis; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

who did not undergo plain radiography at knee and 17 subjects who underwent total knee arthroplasty before the follow-up study, leaving a total of 1,558 subjects (553 men and 1,005 women). The mean duration between baseline and follow up was 3.3 ± 0.6 years.

The characteristics of the 1,578 participants at baseline in the present study are shown in Table 1. Men were significantly older than women, and BMI was significantly higher in men than in women. The prevalence of knee OA was significantly higher in women than in men at baseline. WOMAC pain score was not significantly different between gender, while, physical function score was significantly worse in women than in men at baseline and follow up. The scores of WOMAC pain and physical function scores worsened at follow up compared with those at baseline in men and women ($p < 0.05$).

The scores of WOMAC pain and physical function scores and their differences between baseline and follow up according to the KL grade are shown in Supplementary Table 1 available online at http://informahealthcare.com/doi/abs/10.3109/14397595.2014.883055. In men, differences in WOMAC physical function scores were significantly larger in subjects with KL 3/4 than those with KL 0/1 after adjustment for age and BMI, while differences in WOMAC pain scores were not. In women, after adjustment for age and BMI, differences in WOMAC pain and physical function scores between baseline and follow up were significantly larger in subjects with KL 3/4 than those with KL 0/1.

Among 366 men and 634 women in subjects without pain at baseline, 128 (35.0%) men and 224 (35.3%) women had onset of pain at follow up (Table 2). In men, subjects with onset of pain tended to be older than those without pain, while BMI and grip strength were not significantly different between them. In women, age and BMI were significantly different between subjects with and without onset of pain, and grip strength tended to be higher in subjects with onset of pain than those without pain. Among 346 men and 601 subjects without physical functional disability at baseline, 132 (38.2%) men and 243 (40.4%) women had onset of physical functional disability at follow up (Table 2). Age and BMI were significantly different between subjects with and without onset of physical functional disability in both men and women, and BMI tended to be higher in subjects with onset of physical functional disability than those without it in women only.

We next examined onset of pain and physical functional disability according to KL grade (Figure 1). There were no significant differences in onset of pain among men with KL 0/1 knee, KL 2 knee OA and KL 3/4 knee OA (33.3%, 36.0% and 46.2%, respectively, $p = 0.4149$ by chi-square test), while there were significant differences in onset of pain among women with KL 0/1 knee, KL 2 knee OA and KL 3/4 knee OA (30.4%, 38.6% and 48.5%, respectively, $p = 0.0082$ by chi-square test). Multiple logistic regression analysis after adjustment for age showed that women with KL 3/4 knee OA had significant higher onset of pain compared with those with KL 0/1. There were significant differences in onset of physical functional disability among subjects with KL 0/1 knee OA, KL 2 knee OA and KL 3/4 knee OA in men and women (men 33.2%, 41.7% and 66.7%, respectively, $p = 0.0023$ by chi-square test, women 35.8%, 43.8% and 53.1%, respectively, $p = 0.0165$ by chi-square test). Multiple logistic regression analysis after adjustment for age showed that men with KL 3/4 knee OA had a significant higher onset of physical functional disability compared with those with KL 0/1.

In addition, we examined the association of age, BMI, grip strength and WOMAC pain and physical function scores at baseline with resolution of pain and physical functional disability (Table 3). Among 187 men and 371 women with WOMAC pain at baseline, pain disappeared in 38 (20.3%) men and 97 (26.2%) women at follow up. In men, WOMAC pain score at baseline was significantly different between subjects with resolution of pain and those with continuous pain. BMI tended to be higher in subjects with continuous pain than in those with resolution of pain. In women, age, BMI, grip strength and WOMAC pain score at baseline were significantly different between subjects with resolution of pain and those with continuous pain. Among 207 men and 404 women with physical functional disability at baseline,

Table 2. Age, BMI, grip strength, and WOMAC pain and physical function score according to onset of pain and physical functional disability in subjects without pain and physical functional disability at baseline.

	Pain $N = 1{,}000$			Physical function $N = 947$		
	Continuous no pain	Onset of pain	p value	Continuous no physical functional disability	Onset of physical functional disability	p value
Men						
N	238	128		214	132	
Age	65.3 ± 11.3	67.6 ± 10.8	0.056	63.3 ± 11.0	68.9 ± 10.2	<0.0001
BMI	23.1 ± 3.1	23.1 ± 2.8	0.7981	23.1 ± 3.0	23.0 ± 3.2	0.8946
Grip strength	37.1 ± 8.8	36.6 ± 9.3	0.6531	37.4 ± 8.6	35.9 ± 9.1	0.0149
Women						
N	410	224		358	243	
Age	62.7 ± 11.0	65.4 ± 9.9	0.0017	60.2 ± 10.4	65.7 ± 10.0	<0.0001
BMI	22.0 ± 3.1	22.7 ± 3.1	0.0023	22.2 ± 3.1	22.6 ± 3.1	0.0823
Grip strength	24.2 ± 6.4	23.3 ± 6.5	0.0948	25.3 ± 6.5	22.8 ± 5.3	<0.0001

Values are the means ± standard deviation.
BMI, body mass index; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

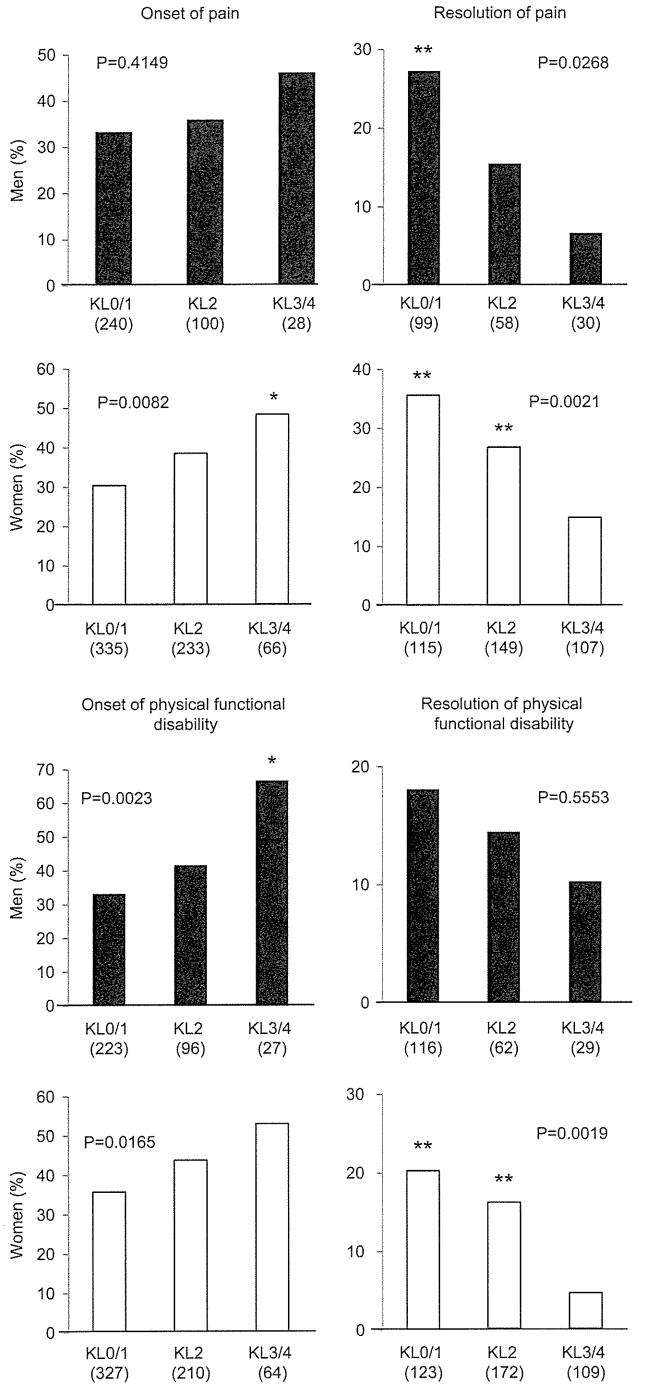

Figure 1. Onset and resolution rate of pain and physical functional disability according to Kellgren Lawrence (KL) grade in men and women. The number of subjects in each subgroup is shown in brackets. Chi-square test was used to determine the association of KL grade with onset of pain and physical functional disability as well as their resolution. *$p < 0.05$ versus KL grade 0/1 by multiple logistic regression analysis after adjustment for age. **$p < 0.05$ versus KL grade 3/4 by multiple logistic regression analysis after adjustment for age.

disability disappeared in 33 (15.9%) men and 58 (14.4%) women at follow up. In men, age and grip strength were significantly different between subjects with resolution of physical functional disability and those with continuous physical functional disability. Age, BMI, grip strength and WOMAC physical function score at baseline were significantly different between subjects with resolution of physical functional disability and those with continuous physical functional disability. In women, age, BMI, grip strength and WOMAC physical function score at baseline were significantly different between subjects with resolution of physical functional disability and those with continuous physical functional disability.

We next examined resolution of pain and physical functional disability according to KL grade (Figure 1). There were significant differences in resolution of pain among subjects with KL 0/1 knee, KL 2 knee OA and KL 3/4 knee OA in men and women (men 27.3%, 15.5% and 6.7%, respectively, $p = 0.0268$ by chi-square test; women 35.7%, 26.8% and 15.0%, respectively, $p = 0.0021$ by chi-square test). Multiple logistic regression analysis after adjustment for age showed that men with KL 3/4 knee OA had a significantly higher onset of pain compared with those with KL 0/1. Regarding resolution of physical functional disability, there were no significant differences among subjects with KL 0/1 knee, KL 2 knee OA and KL 3/4 knee OA in men (18.1%, 14.5% and 10.3%, respectively, $p = 0.5553$ by chi-square test), while there were significant differences subjects with KL 0/1 knee, KL 2 knee OA and KL 3/4 knee OA in women (20.3%, 16.3% and 4.6%, respectively, $p = 0.0019$ by chi-square test). Multiple logistic regression analysis after adjustment for age showed that women with KL 2 and 3/4 knee OA had a significantly higher onset of physical functional disability compared with those with KL 0/1.

To determine the independent association of age, BMI, grip strength and KL grade with onset of pain and physical functional disability, we next used multiple logistic regression analysis with significant variables ($p < 0.01$) by non-paired Student's t test or chi-square test shown in Table 2 and Figure 1 as explanatory variables (Table 4). Regarding onset of pain, there were no significant variables in men; thus, we did not examine the independent association with onset of pain. In women, older age and higher BMI were independently associated with onset of pain. Older age and KL 3/4 knee OA were independent risk factors for onset of physical functional disability in men, whereas older age, higher BMI and weaker grip strength were independent risk factors for onset of physical functional disability in women. The significant association of knee OA with onset of physical functional disability disappeared after adjustment age, BMI and grip strength in women.

We also examined independent associations of age, BMI, grip strength and KL grade with resolution of pain and physical functional disability (Table 5). KL 0/1 knee and lower WOMAC pain score at baseline were significantly associated with resolution of pain in men, whereas lower BMI, higher grip strength and lower WOMAC pain score were significantly associated with resolution of pain in women. Regarding physical function, only age was significantly associated with resolution of physical functional disability in men, whereas higher grip strength, KL 2 knee OA and lower WOMAC physical function score were significantly associated with resolution of physical functional disability in women. KL 01 knee also tended to be associated with resolution of physical functional disability in women. Because treatment for knee OA might affect the resolution of pain and physical functional disability, we further examined the association of treatment for knee OA with the resolution of pain and physical functional disability. Among subjects with pain at baseline, the resolution rate of pain was 36.2% in subjects who underwent treatment for knee OA, and 14.2% in subjects who did not undergo treatment for knee OA. Among subjects with physical functional disability at baseline, the resolution rate of physical functional disability was 19.3% in subjects who underwent treatment for knee OA, while, 7.2% in subjects who did not undergo treatment for knee OA. The resolution rate of pain and physical functional disability was significantly different between subjects who had and had not undergone treatment for knee OA (chi-square test, $p < 0.0001$). Thus, we examined independent associations of age, BMI, grip strength and KL grade with resolution of pain and physical functional disability after adjustment for the treatment for

Table 3. Age, BMI, grip strength, and WOMAC pain and physical function score according to resolution of pain and physical functional disability in subjects with pain and physical functional disability at baseline, respectively.

	Pain $N=558$			Physical function $N=611$		
	Resolution of pain	Continuous pain	p value	Resolution of physical functional disability	Continuous physical functional disability	p value
Men						
N	38	149		33	174	
Age	72.3 ± 8.9	71.9 ± 8.5	0.8	67.9 ± 11.6	73.4 ± 7.6	0.0118
BMI	22.8 ± 3.0	23.7 ± 3.3	0.08	23.4 ± 3.2	23.6 ± 3.2	0.8041
Grip strength	32.6 ± 6.4	32.4 ± 7.5	0.8694	34.9 ± 6.7	31.4 ± 7.3	0.0091
WOMAC at baseline						
Pain	1.82 ± 1.20	3.32 ± 2.69	<0.0001	–	–	–
Physical function	–	–	–	4.85 ± 7.69	7.20 ± 7.58	0.1132
Women						
N	97	274		58	346	
Age	68.1 ± 12.6	72.4 ± 8.6	0.0022	68.1 ± 11.1	73.2 ± 8.2	0.0015
BMI	22.4 ± 3.2	24.0 ± 3.6	<0.0001	22.3 ± 3.2	23.6 ± 3.6	0.0066
Grip strength	22.9 ± 7.2	19.8 ± 4.9	0.0002	23.7 ± 7.4	19.7 ± 5.4	0.0002
WOMAC at baseline						
Pain	1.84 ± 1.18	3.68 ± 2.90	<0.0001	–	–	–
Physical function	–	–	–	3.33 ± 4.32	8.99 ± 9.54	<0.0001

Values are the means ± standard deviation.
BMI, body mass index; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

knee OA. Results were similar to findings without adjustment for treatment of knee OA (Supplementary Table 2 available online at http://informahealthcare.com/doi/abs/10.3109/14397595.2014.883055). In addition, we examined associations of age, BMI, grip strength and severity of knee OA with worsening pain and physical functional disability in subjects with pain and physical functional disability at baseline (Supplementary Table 3 available online at http://informahealthcare.com/doi/abs/10.3109/14397595.2014.883055). Multiple logistic regression analysis showed that weaker grip strength was a risk factor for worsening pain, whereas KL 3/4 knee OA was a risk factor for worsening physical functional disability (Supplementary Table 4 available online at http://informahealthcare.com/doi/abs/10.3109/14397595.2014.883055).

Discussion

This is the first longitudinal population-based study to examine the onset, resolution and worsening of pain and physical functional disability using WOMAC. We also clarified the associations of age, BMI, grip strength and knee OA with the onset, resolution and worsening of pain and physical functional disability.

Our previous study showed that onset of knee pain during 3 years was approximately 20% and 30% in men and women, respectively [24]. The Chingford study also showed that more than 10% women had onset of pain during 2 years [25]. However, in these previous studies, knee pain was defined as present or absent, rather than as an established measure of pain such as WOMAC. In addition, in our previous study, we did not examine resolution of pain. In the present study, we found that 35% of men and women had onset of pain. These values were higher than onset values obtained from questionnaires in our previous study [24], indicating that WOMAC may be more powerful for detecting pain than questionnaires regarding only the presence or absence of pain. We also found that pain disappeared in approximately 20% men and 25% women using WOMAC. The Chingford study previously showed that knee pain disappeared in approximately 40% of Caucasian women during 2 years using a questionnaire on the presence and absence of pain [25], which is higher than the values

Table 4. Association of onset of pain and physical functional disability with age, BMI, grip strength, and KL grade.

	Onset of pain			Onset of physical functional disability		
	Adjusted OR	95% CI	p value	Adjusted OR	95% CI	p value
Men						
Age (+ 1 year)	–	–	–	1.05	1.02–1.08	0.0011
BMI (+ 1kg/m^2)	–	–	–	–	–	–
Grip strength (+ 1kg)	–	–	–	1.01	0.97–1.04	0.628
KL grade						
KL 0/1	–	–	–	1		
KL 2	–	–	–	1.02	0.60–1.72	0.9504
KL 3/4	–	–	–	2.7	1.14–6.69	0.0274
Women						
Age (+ 1 year)	1.02	1.003–1.04	0.023	1.05	1.03–1.07	<0.0001
BMI (+ 1kg/m^2)	1.08	1.03–1.15	0.0047	1.08	1.02–1.14	0.0141
Grip strength (+ 1kg)	0.99	0.96–1.02	0.4977	0.96	0.92–0.99	0.0152
KL grade						
KL 0/1	1			1		
KL 2	1.09	0.74–1.61	0.6593	0.84	0.56–1.25	0.4035
KL 3/4	1.42	0.79–2.55	0.2337	1	0.54–1.82	0.9894

Multiple logistic regression analysis was used with significant variables ($p<0.01$) in univariate models as explanatory variables.
BMI, body mass index; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

found in the present study. This discrepancy between our study and the Chingford study may be partly explained by age differences in addition to different estimations for pain and racial differences, because mean age was 52 years in the Chingford study compared with 67 years in the present study. Furthermore, we first found that approximately 40% men and women had onset of physical functional disability and approximately 15% men and women had resolution of physical functional disability. To our knowledge, no other community-based studies have described longitudinal patterns of physical functional disability, and the present study was the first to clarify the onset and resolution of physical functional disability using WOMAC.

Pain is the principal clinical symptom of knee OA [5], but, although much effort has been devoted to defining knee pain, the correlation with radiographic severity of the knee OA is not as strong as one would expect [2,6–8]. In the present study, we examined onset of pain according to KL grade using WOMAC. In men and women without knee OA (KL 0/1), more than 30% subjects had onset of pain. In addition, 50% of men and women with KL 3/4 knee OA had onset of pain, meaning that 50% did not have onset of pain despite having severe radiographic knee OA. In fact, in the present study, radiographic knee OA was not significantly associated with onset of pain in men, and after adjustment, the significant association of knee OA with onset of pain disappeared in women. These findings indicate that pain may arise from a variety of structures other than joint cartilage, such as menisci, synovium, ligaments, bursae, bone and bone marrow [26–30]. In addition, in the present study, the risk for onset of pain was higher with higher BMI rather than knee OA in women, indicating knee pain may be prevented by reducing obesity.

In the present study, we also examined the association of knee OA with the resolution of pain, and found that around 30% of men and women without knee OA had resolution of knee pain, which was a similar rate to onset of pain, and only 7% of men and 15% of women with severe knee OA had resolution of knee pain. These findings indicate that around 90% of subjects with severe knee OA had continuous knee pain. There were significant associations of resolution of pain with KL grade. Considering the results of onset of pain, severe knee OA may lead to difficulties with resolution of pain rather than onset of pain, particularly in men. In addition, after adjustment, resolution of pain was significantly associated with lower BMI and higher grip strength, which is a useful marker of muscle function and sarcopenia [15], rather than radiographic knee OA, indicating that improvement of obesity and performing muscle exercises may help make pain disappear. In addition, the significant association of BMI and grip strength remained after adjustment for treatment of knee OA, indicating that reducing obesity and performing muscle exercises may be as important as treatment to achieve resolution of pain due to knee OA.

We also found that severe knee OA was a risk factor for physical functional disability, particularly in men, despite the finding that severe knee OA was not significantly associated with onset of pain in men. Severe knee OA was not significantly associated with onset of physical functional disability after adjustment for age in women, despite the finding that severe knee OA was significantly associated with onset of pain. This discrepancy between gender may be partly explained by the idea that women are more susceptible to pain. In fact, our previous study showed that the prevalence of knee pain in women with KL 0/1, 2 and 3/4 knee OA was significantly higher than that in men with KL 0/1, 2 and 3/4 knee OA, respectively[2]. In addition, risk factors for onset of physical functional disability were higher BMI and weaker grip strength rather than knee OA in women in the present study. Grip strength is a useful marker of muscle function and sarcopenia [15]. A previous study also showed that grip strength is related to total muscle [19]. Results in the present study indicate that onset of physical functional disability may be prevented by improvement of obesity and muscle exercises.

In the present study, physical functional disability disappeared in 20% of women without knee OA, whereas physical functional disability disappeared only in 5% of women with severe knee OA. The association of knee OA with resolution of physical functional

Table 5. Association of resolution of pain and physical functional disability with age, BMI, grip strength, and KL grade.

	Resolution of pain			Resolution of physical functional disability		
	Adjusted OR	95% CI	p value	Adjusted OR	95% CI	p value
Men						
Age (+ 1 year)	–	–	–	0.95	0.90–0.9985	0.0443
BMI (+ 1kg/m^2)	0.92	0.80–1.04	0.1994	–	–	–
Grip strength (+ 1kg)	–	–	–	1.02	0.96–1.09	0.526
KL grade						
KL 3/4	1			–	–	–
KL 2	2.37	0.52–16.8	0.3042	–	–	–
KL 0/1	5.18	1.32–34.6	0.0378	–	–	–
WOMAC at baseline						
Pain	0.63	0.46–0.80	0.001	–	–	–
Physical function	–	–	–	–	–	–
Women						
Age (+ 1 year)	0.99	0.96–1.02	0.6031	0.98	0.95–1.02	0.4081
BMI (+ 1kg/m^2)	0.88	0.80–0.96	0.0034	0.93	0.84–1.02	0.1358
Grip strength (+ 1kg)	1.08	1.02–1.14	0.014	1.09	1.02–1.16	0.0123
KL grade						
KL 3/4	1			1		
KL 2	1.34	0.66–2.79	0.4312	3.04	1.15–9.62	0.0362
KL 0/1	1.71	0.79–3.77	0.1797	2.52	0.89–8.34	0.0997
WOMAC at baseline						
Pain	0.66	0.53–0.78	<0.0001	–	–	–
Physical function	–	–	–	0.87	0.78–0.93	0.0009

Multiple logistic regression analysis was used with significant variables ($p<0.01$) in univariate model as explanatory variables.

BMI, body mass index; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; KL, Kellgren Lawrence grade.

disability remained significant after adjustment. This means that in women without knee OA, pain may occur, but it may disappear more easily. In addition, grip strength was also associated with resolution of physical functional disability after adjustment, indicating that muscle exercises may help make physical functional disability disappear.

The present study showed gender differences in the associations of knee OA with pain and physical functional disability. In women, knee OA was significantly associated with onset of pain and physical functional disability as well as their resolution, whereas in men, there were no significant association of knee OA with onset of pain and resolution of physical functional disability. Our previous cross-sectional study also showed that the odds ratio of knee pain for KL 3/4 knee OA was approximately twice as high in women as in men[2]. These findings may be partly explained by the lower muscle mass in women compared with men. In men, muscular strength may obscure the associations of knee OA with pain and physical functional disability.

In conclusion, the present longitudinal study revealed the onset rate of pain and physical functional disability as well as their resolution rate using WOMAC. In addition, severe knee OA was significantly associated with onset of pain and physical functional disability as well as their resolution, particularly in women. Furthermore, we also clarified that BMI and grip strength were associated with onset of pain and physical functional disability as well as their resolution in women.

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Conflict of interest

None.

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