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.

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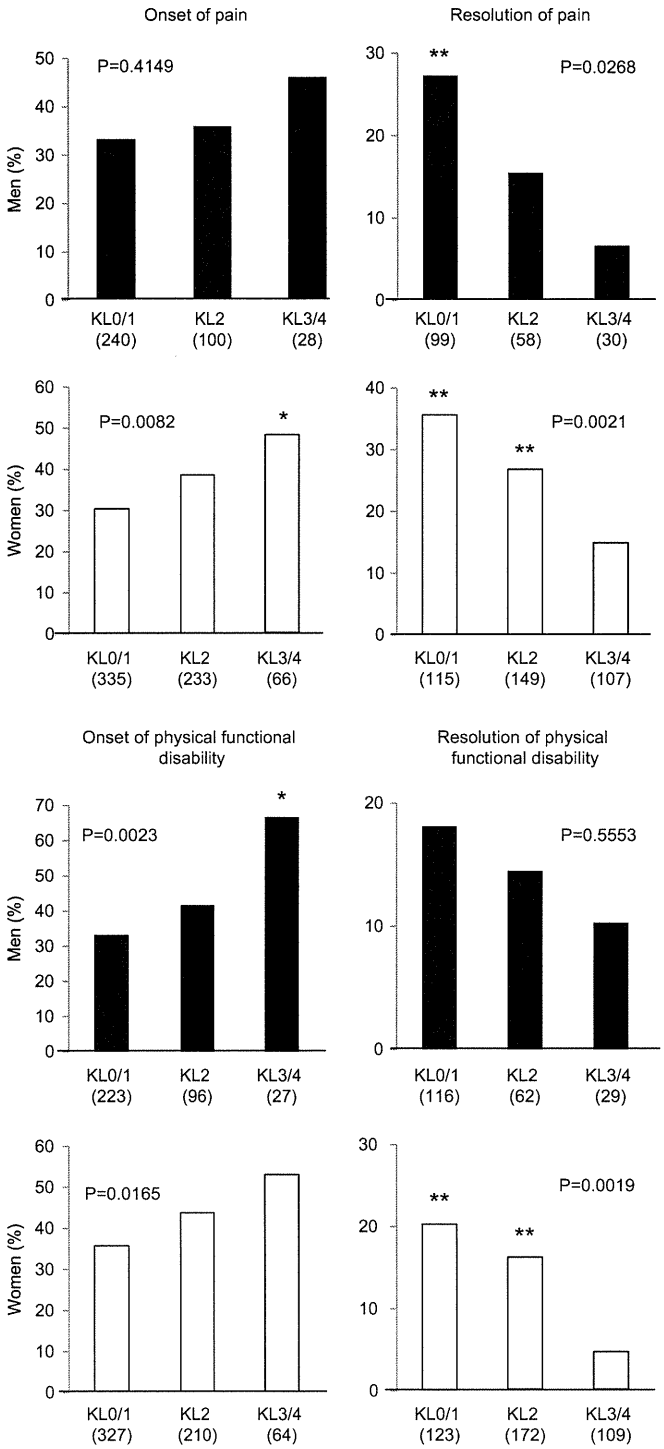

Figure 1. Onset and resolution rate of pain and physical functional disability according to Kellgren Lawrence (KL) grade in men and women. The number of subjects in each subgroup is shown in brackets. Chi-square test was used to determine the association of KL grade with onset of pain and physical functional 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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Supplementary material available online

Supplementary Tables 1–4.

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ORIGINAL ARTICLE

Prevalence, incidence and progression of lumbar spondylosis by gender and age strata

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Abstract

Objectives. To identify the prevalence, incidence and progression of radiographic lumbar spondylosis (LS).

Methods. From the Adult Health Study conducted by the Radiation Effects Research Foundation, 1,204 participants aged 44–85 years who had lumbar spine radiographs in 1990–1992 were reexamined in 1998–2000 (mean 7.9-year interval). The radiographic severity of LS was determined by Kellgren/Lawrence (KL) grading.

Results. In the overall population, the prevalence of radiographic KL ≥ 2 and ≥ 3 LS was 52.9% and 23.6%, respectively. KL ≥ 2 LS was more prevalent in men, whereas KL ≥ 3 LS was more prevalent in women. During the 8-year follow-up, the incidence of KL ≥ 2 LS in men and women was 65.5% and 46.6%, that of KL ≥ 3 LS was 27.3% and 29.5%, that of progressive LS was 31.3% and 34.0%, and multilevel LS was 44.9% and 33.4%, respectively. Body–mass index was a risk factor for both KL ≥ 2 and KL ≥ 3 LS, after adjusting for age and sex.

Conclusions. The present longitudinal study revealed the prevalence, incidence and progression of radiographic LS. Prevalence and incidence of KL ≥ 2 LS was higher in men than women, while, those of KL ≥ 3 were similar between men and women.

Keywords

Incidence, Lumbar spine, Prevalence, Progression, Spondylosis

History

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Introduction

Lumbar spondylosis (LS), characterized by disc degeneration and osteophytosis [1,2], is a major public health issue in most countries and causes chronic disability among the elderly [1,3–8]. Despite the urgent need for strategies to prevent and treat this condition, epidemiologic data on LS are sparse. Past studies reported wide ranged prevalence of radiographic LS from 40% to 85% based on the limited number of study subjects in a clinical setting [9–17]. This variability may be due to the differences in age, communities, sample sizes, imaging modality and ethnic variations, yet the disorder burden remains unclear. Further, there are few studies regarding the incidence or progression of LS [7,12,15,18,19].

Plain radiography is considered the gold standard as a method that is non-invasive, inexpensive, convenient, simple and fast to use in assessing osteoarthritis (OA) severity. The most popular grading system for radiographic severity of OA is the Kellgren/Lawrence (KL) system, which is classified into five grade (0–4) scales; KL ≥ 2 is the conventional standard for diagnosis [20]. For LS, KL Grade 2 is defined as osteophyte formation and KL Grade 3 is defined as osteophyte formation along with disc-space narrowing. Hence, to assess osteophyte formation alone and disc-space narrowing with or without osteophyte formation, the prevalence and incidence of KL ≥ 2 LS as well as that of KL ≥ 3 LS is needed.

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In the present study, we analyzed the prevalence, incidence and progression of LS according to gender and age strata in Japan.

Materials and methods

Subjects

The Adult Health Study (AHS) was established by the Radiation Effects Research Foundation in 1958 to document the late health effects of radiation exposure among atomic-bomb survivors in Hiroshima and Nagasaki, and study subjects have been followed through biennial medical examinations. The participation rate has been over 70% throughout this period. More detail concerning recruitment and examination of participants was reported elsewhere [21].

Among AHS subjects, 1,297 subjects (363 men and 934 women) aged 44–85 years underwent radiographic examinations of the lumbar spine in Hiroshima between 1990 and 1992 (baseline). Of those 1,297 subjects, 1,204 (92.8%) subjects participated in the follow-up study between 1998 and 2000. All participants provided written informed consent, and the study was conducted with the approval of ethical committees of the Radiation Effects Research Foundation. Anthropometric measurements included height, weight and body–mass index (BMI; weight [kg]/height [m^2]) was calculated. We used individual radiation dose estimates from the Radiation Effects Research Foundation's Dosimetry System 2002 (DS02) [22].

Radiographic assessments

Plain radiographs of the lumbar spine were taken in the lateral position to assess radiographic LS. The severity of LS was

Table 1. Characteristics of participants.

	Men					Women				
	Overall	<50	50–59	60–69	≥70	Overall	<50	50–59	60–69	≥70
No. of subjects	363	56	83	158	66	934	129	217	414	174
Age, years	61.2 ± 9.4	46.4 ± 1.3	55.8 ± 3.3	63.2 ± 2.6	75.5 ± 4.1	61.6 ± 8.9	46.5 ± 1.3	55.6 ± 3.0	64.2 ± 2.8	74.2 ± 3.2
Height, cm	163.2 ± 5.8	166.6 ± 6.3	163.9 ± 5.6	163.0 ± 5.3	159.9 ± 5.2	150.7 ± 5.6*	153.4 ± 5.0*	151.9 ± 5.5*	150.7 ± 5.3*	147.3 ± 5.1*
Weight, kg	59.9 ± 8.6	61.6 ± 7.7	61.9 ± 9.1	60.1 ± 8.4	55.6 ± 7.6	52.4 ± 8.7*	54.2 ± 8.5*	54.5 ± 9.0*	52.1 ± 8.3*	49.3 ± 8.6*
BMI, kg/m^2	22.5 ± 2.8	22.2 ± 2.7	23.0 ± 2.9	22.6 ± 2.7	21.7 ± 2.8	23.1 ± 3.5*	23.1 ± 3.6	23.6 ± 3.5	22.9 ± 3.4	22.7 ± 3.6*

Data are mean ± standard deviation.
BMI, body–mass index.
*$p < 0.05$ vs. men in the corresponding group by non-paired Student's t test.

determined according to the KL grading [20] at each intervertebral level from L1/2 to L5/S1 by a well-experienced orthopedists (S.M.), who was masked to the patients' backgrounds. The KL scale defines radiographic OA in five categories: KL Grade 0, no radiographic features of OA; KL Grade 1, minimal osteophytosis only; KL Grade 2, definite osteophytosis with some sclerosis of the anterior part of the vertebral plate; KL Grade 3, marked osteophytosis and sclerosis of the vertebral plates with slight narrowing of the disc space and KL Grade 4, large osteophytes, marked sclerosis of the vertebral plates and marked narrowing of the disc space. To evaluate the intra-observer variability of the KL grading, 100 randomly selected radiographs of the lumbar spine were scored by the same observer more than a month after the first reading. A further 100 radiographs were scored by two experienced orthopedic surgeons. They used the same radiographic atlas for inter-observer variability. The intra- and inter-observer variabilities were evaluated by kappa analysis. These variabilities in the KL grading on lumbar radiographs have been shown to be sufficient for assessment (0.84 and 0.76, respectively).

For the purposes of this study, we defined four LS outcomes. First, a subject could have incident KL≥2 radiographic LS if all vertebral interspaces had < Grade 2 disease at baseline, and if at least one vertebral interspace had ≥ Grade 2 disease at follow-up. Second, a subject could have incident KL≥3 radiographic LS if all vertebral interspaces had < Grade 3 disease at baseline, and if at least one vertebral interspace had Grade≥3 at follow-up. Third, progressive LS was defined as KL≥2 LS at baseline and an increase by at least one grade in the affected vertebral interspace at follow-up. Fourth, multilevel LS was defined as KL≥2 grade at two or more interspaces. A subject could have incident multilevel LS if the subject had less than two interspaces with KL≥2 LS at baseline, and if he or she had two or more interspaces with KL≥2 at follow-up.

Statistical analysis

We used the chi-square test to compare the prevalence and incidence with radiographic LS between men and women. Incidence was calculated as follows: the number of subjects with LS at follow-up among those without LS at baseline divided by the number of subjects without LS at baseline. The association of variables such as age, BMI and gender with the prevalence and incidence of radiographic LS was evaluated by multiple logistic regression analysis. Data analyses were performed using SAS version 9.0 (SAS Institute Inc., Cary, NC).

Results

Characteristics of the 1,297 participants at baseline are shown in Table 1. The mean age of those participating in the follow-up study was 69.1 ± 9.0 years. The interval between baseline examination and follow-up was 7.9 ± 1.1 years.

The prevalence of KL≥2 LS in the overall population and subgroups classified by gender and age strata at baseline is shown in Table 2. The prevalence was significantly higher at all interspaces and at the most severe space in men compared with women in the overall population. The prevalence of multilevel LS was also significantly higher in men than in women. Logistic regression analysis showed that the prevalence of KL≥2 LS at all interspaces as well as at the most severe level, and multilevel spondylosis was significantly associated with age in men and women. In men, the prevalence was highest at L3/4 at almost all age strata, whereas in women, the prevalence was highest at L4/5.

In contrast to KL≥2 LS, the prevalence of KL≥3 LS was significantly higher at all interspaces and at the most severe space in women than men in the overall population (Table 3). The prevalence of multilevel LS was also higher in women than in men. Logistic regression analysis showed that the prevalence of KL≥3 LS at all interspaces as well as at the most severe level, and

Table 2. Number (percentage) of participants with KL≥2 LS at each vertebral interspace as well as the most severe space, and multilevel KL≥2 LS according to gender and age strata at baseline.

Age at baseline	L1/2	L2/3	L3/4	L4/5	L5/S	Severest	Multilevel
Overall	231 (17.8)	370 (28.5)	381 (29.4)	413 (31.8)	180 (13.9)	697 (53.8)	430 (33.2)
Men	102 (28.1)	138 (38.0)	157 (43.2)	140 (38.6)	52 (14.3)	246 (67.8)	167 (46.0)
<50	5 (8.9)	12 (21.4)	15 (26.8)	9 (16.1)	4 (7.1)	22 (39.3)	11 (19.6)
50–59	18 (21.7)	17 (20.5)	25 (30.1)	27 (32.5)	6 (7.2)	48 (57.8)	29 (34.9)
60–69	50 (31.6)	71 (44.9)	76 (48.1)	64 (40.5)	25 (15.8)	118 (74.7)	80 (50.6)
≥70	29 (43.9)	38 (57.6)	41 (62.1)	40 (60.6)	17 (25.8)	58 (87.9)	47 (71.2)
Women	129 (13.8)*	232 (24.8)*	224 (24.0)*	273 (29.2)*	128 (13.7)*	451 (48.3)*	263 (28.2)*
<50	3 (2.3)	9 (7.0)	7 (5.4)	15 (11.6)	6 (4.7)	29 (22.5)	9 (7.0)
50–59	16 (7.4)	32 (14.7)	39 (18.0)	47 (21.7)	26 (12.0)	88 (40.6)	35 (16.1)
60–69	59 (14.3)	121 (29.2)	111 (26.8)	129 (31.2)	61 (14.8)	215 (51.9)	136 (32.9)
≥70	51 (29.3)	70 (40.2)	67 (38.5)	82 (47.1)	35 (20.1)	119 (68.4)	83 (47.7)

Multilevel LS was defined as KL grade≥2 at two or more interspaces.
*$p < 0.05$ vs. men by chi-square test in the overall population.

Table 3. Number (percentage) of participants with KL ≥ 3 LS at each vertebral interspace as well as the most severe space, and multilevel KL ≥ 3 LS according to gender and age strata at baseline.

Age at baseline	L1/2	L2/3	L3/4	L4/5	L5/S	Severest	Multilevel
Overall	30 (2.3)	75 (5.8)	105 (8.1)	236 (18.2)	110 (8.5)	320 (24.7)	141 (10.9)
Men	6 (1.7)	12 (3.3)	19 (5.2)	41 (11.3)	14 (3.9)	58 (16.0)	22 (6.1)
< 50	0 (0.0)	0 (0.0)	2 (3.6)	3 (5.4)	1 (1.8)	4 (7.1)	1 (1.8)
50–59	1 (1.2)	1 (1.2)	1 (1.2)	4 (4.8)	1 (1.2)	6 (7.2)	2 (2.4)
60–69	1 (6.3)	6 (3.8)	8 (5.1)	18 (11.4)	6 (3.8)	27 (17.1)	10 (6.3)
≥ 70	4 (6.1)	5 (7.6)	8 (12.1)	16 (24.2)	6 (9.1)	21 (31.8)	9 (13.6)
Women	24 (2.6)	63 (6.7)*	86 (9.2)*	195 (20.9)*	96 (10.3)*	262 (28.1)*	119 (12.8)*
< 50	0 (0.0)	2 (1.6)	2 (1.6)	10 (7.8)	5 (3.9)	16 (12.4)	3 (2.3)
50–59	1 (0.5)	7 (3.2)	12 (5.5)	30 (13.8)	19 (8.8)	47 (21.7)	14 (6.5)
60–69	10 (2.4)	23 (5.6)	38 (9.2)	88 (21.3)	43 (10.4)	116 (28.0)	55 (13.3)
≥ 70	13 (7.5)	30 (17.3)	34 (19.7)	66 (38.2)	29 (16.8)	82 (47.4)	46 (26.6)

Multilevel LS was defined as KL grade ≥ 3 at two or more interspaces.
*$p < 0.05$ (chi-square test) vs. men in the overall population.

multilevel spondylosis was significantly associated with age in men and women. The prevalence was low at L1/2 and the highest at L4/5 among all interspaces in men and women.

Table 4 shows the incidence of KL ≥ 2 and ≥ 3 LS in the overall population and subgroups classified by gender and age strata. The incidence of KL ≥ 2 LS was significantly higher in men than in women. Logistic regression analysis showed that the incidence of KL ≥ 2 LS was significantly associated with age in men and women. The incidence of KL ≥ 3 LS was significantly higher in women. When the incidence was compared among generations, the incidence of KL ≥ 3 radiographic LS tended to increase with age after the 50s in men and women, whereas that of KL ≥ 2 radiographic LS was not much different between the 40s and 50s.

We also examined progressive and multilevel LS (Table 4). Among subjects with KL = 2 LS at baseline, 31% subjects had KL = 3 LS and 9% subjects had KL = 4 LS at follow-up. Among subjects with KL = 3 LS at baseline, 31% subjects had KL = 4 LS at follow-up. The progression of LS was not associated with gender or age strata. The incidence of multilevel LS was higher in men than in women, and tended to increase with age in men and women.

We next analyzed the independent association of age, gender and BMI with the prevalence of LS by multiple logistic regression analysis (Table 5). Age and BMI were associated with an increased prevalence of KL ≥ 2 LS as well as KL ≥ 3 at the most severe space and multilevel LS. Female gender was associated with decreased prevalence for KL ≥ 2 LS at the most severe space and that of multilevel LS; it was also associated with increased prevalence for KL ≥ 3 LS.

We also analyzed the independent association of age, gender and BMI with the incidence of LS by multiple logistic regression analysis (Table 6). Age and BMI were associated with increased risk for the incidence of KL ≥ 2, KL ≥ 3 and multilevel LS, but not for progressive LS. Female gender was associated with decreased incidence for KL ≥ 2 and multilevel LS, whereas there was no significant association of gender with KL ≥ 3 and progressive LS.

No significant relationship was found between atomic-bomb radiation and prevalence and incidence of KL ≥ 2, KL ≥ 3 and multilevel LS.

Discussion

The present study revealed the prevalence of radiographic KL ≥ 2 and KL ≥ 3 LS in men and women. Although prevalence of KL ≥ 2 LS was more frequent in men than in women, KL ≥ 3 LS was more prevalent in women. Given an 8-year follow-up, we also revealed the incidence of KL ≥ 2 and KL ≥ 3 LS as well as progressive LS and multilevel LS in men and women.

Most previous epidemiologic studies on LS focused on middle-aged or younger populations, reporting the prevalence to be 40–85% [9,11–13,15,16]. This variability may be due to the differences in age, communities, sample sizes and ethnic variations. In terms of ethnic variations, we reported a different prevalence of LS in Japan and the United Kingdom in a small-scale comparative study [14], whereas our previous study of an elderly Japanese population showed a prevalence of 84.1% and 70.7% in men and women, respectively [23], which is similar to the prevalence seen in this study among subjects in their 70s.

Table 4. Incidence of KL ≥ 2 and ≥ 3 LS according to gender and age strata.

	KL ≥ 2		KL ≥ 3		Progressive LS		Multilevel LS	
Age at baseline	No. at risk	Cumulative incidence	No. at risk	Cumulative incidence	No. at risk	Cumulative incidence	No. at risk	Cumulative incidence
Overall	567	285 (50.3)	920	265 (28.8)	696	230 (33.0)	866	312 (36.0)
Men	110	72 (65.5)	286	78 (27.3)	246	77 (31.3)	196	88 (44.9)
< 50	33	18 (54.6)	49	8 (16.3)	22	8 (36.4)	45	14 (31.1)
50–59	33	20 (60.6)	74	15 (20.3)	48	11 (22.9)	54	24 (44.4)
60–69	37	28 (75.7)	125	43 (34.4)†	118	40 (33.9)	78	42 (53.8)
≥ 70	7	6 (85.7)	45	12 (26.7)	58	18 (31.0)	19	8 (42.1)
Women	457	213 (46.6)*	634	187 (29.5)	450	153 (34.0)	670	224 (33.4)
< 50	94	35 (37.2)	105	19 (18.1)	29	6 (20.7)	120	22 (18.3)
50–59	122	43 (35.3)	162	35 (21.6)	88	32 (36.4)	182	51 (28.0)
60–69	193	106 (54.9)†	288	93 (32.3)	215	79 (36.7)	277	110 (39.7)†
≥ 70	48	29 (60.4)†	91	40 (44.0)	118	36 (30.5)	91	41 (45.1)†

*$p < 0.05$ (chi-square test) vs. men in the overall population.
†$p < 0.05$ vs. the corresponding gender at < 50 years by logistic regression analysis.

Table 5. Association of age, BMI and gender with prevalence of radiographic lumbar spondylosis at baseline examination.

	Radiographic LS				Multilevel radiographic LS			
	KL≥2		KL≥3		KL≥2		KL≥3	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Age, years	1.08	1.07–1.10	1.08	1.06–1.09	1.08	1.07–1.10	1.1	1.07–1.12
BMI, kg/m^2	1.08	1.05–1.12	1.08	1.04–1.12	1.08	1.05–1.12	1.05	1.00–1.11
Women (vs. men)	0.36	0.27–0.47	1.99	1.44–2.78	0.36	0.28–0.48	2.27	1.42–3.79

BMI, body–mass index; LS, lumbar spondylosis; OR, odds ratio; CI, confidence interval.
Radiographic spondylosis was determined at the severest level among L1/2-L5/S1.
The odds ratios were calculated by logistic regression analysis.

Interestingly, KL≥2 LS was more prevalent in men than in women, whereas KL≥3 LS was more prevalent in women. We and others have reported that osteophytosis of the lumbar spine was more common in men than in women [12,14,23], while disc-space narrowing was more prevalent in women [14]. Based on the definition of KL grading [20], the discrepancy may be due to distinct etiologic mechanisms between osteophyte formation and disc-space narrowing. A cross-sectional study that investigated the extent, prevalence and distribution of spinal LS in women also showed that osteophytosis and disc-space narrowing were significantly correlated, but each predicted only 19% of the variation in the other [16]. Further clinical and basic research will disclose the distinct backgrounds of these two representative OA features.

We also investigated the age-specific prevalence of LS. Although KL≥2 LS tended to increase with age in men and women, significant differences were not detected in the prevalence of KL≥3 between the 40s and the 50s in men. In fact, the incident of KL≥3 was quite low in the 40s, indicating that the incidence of disc space narrowing was low during middle age.

Most previous studies regarding LS have been cross-sectional, so incidence has not been clarified. The present study was a longitudinal study that assessed incidence and natural history of LS. In this study, KL≥2 LS occurred at rates of 65.5% and 46.6% after 8-year follow-up, respectively. The only longitudinal study using KL grade reported that 45% of women deteriorated after 8.7 years follow-up [7], but deterioration was defined as an increase in KL grade at any level, which was a different definition from our study, so strict comparisons are limited. Considering the definition of KL grade, the incidence of KL≥2 LS may represent osteophytosis. We also found that the incidence of LS was higher in men than in women at all ages and increased with age after the 50s, but was not much different between the 40s and 50s in men and women. In this study, among subjects with incident KL≥2 LS, the percentage of those with KL≥3 LS was extremely high in the 70s compared with other generations. This finding may indicate that at middle age, LS progresses slowly in subjects without LS at baseline, but it progresses faster in the elderly.

This study also clarified that the incidence of KL≥3 LS was similar between men and women. Considering the definition of KL grade, the incidence of KL≥3 LS may represent the occurrence of disc space narrowing. A longitudinal study regarding disc space narrowing of the lumbar spine has been performed [15], but it focused only the progression of disease and not on its incidence. Unlike KL≥2 LS, the incidence of KL≥3 was similar in the 40s, 50s and 60s, and was higher in women than in men at age 70 years or older. When compared among generations, the incidence was similar in the 40s and 50s and increased in the 60s in men and women. In the 70s, the incidence further increased in women, but in men, was similar to the incidence in the 60s. Elderly men generally retire from their occupations around 60–70 years of age, whereas women continue to do household chores even after the age of 70, which may partly explain the increase of incidence after age 70 in women.

We also analyzed the progression of LS. The rate of progressive LS was similar in men and women (4.5% and 4.6% per year, respectively), and was not associated with age, despite the fact that the incidence of KL≥3 LS tended to increase with age. This finding may be due to the fact that the percentage of subjects with KL≥3 LS was extremely high in the 70s compared with other generations among those with incident KL≥2 LS, as mentioned above, which could indicate that in subjects without LS, the incidence of disc space narrowing was associated with age, but not in subjects with osteophytosis, especially in men.

There are several limitations to the present study. First, the study subjects may be biased as persons who received radiographs in both 1990–1992 and 1998–2000. In addition, this study investigated participants who lived independently, and not those who lived in institutional settings. Therefore, the calculated prevalence or incidence may be underestimated. Second, because the KL system emphasizes osteophytosis, it is unclear how to handle LS with disc-space narrowing but no osteophytosis. We are developing a computer-aided diagnostic program that enables measurement of major features of LS, including disc-space narrowing and osteophytosis, on plain radiographs. Furthermore, participants were atomic bomb survivors and thus not representative of the general Japanese population, although we adjusted for radiation, and there are no indications from earlier studies of this cohort that radiation affected BMD and fracture.

In summary, the present longitudinal study revealed the prevalence of radiographic KL≥2 and≥3 LS was 52.9% and 23.6%, respectively. KL≥2 LS was more prevalent in men, whereas KL≥3 LS was more prevalent in women. During the 8-year follow-up, the incidence of KL≥2 LS in men and women was

Table 6. Association of age, BMI and gender with incidence of radiographic lumbar spondylosis.

	KL≥2		KL≥3		Progressive LS		Multilevel LS	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Age, years	1.05	1.03–1.07	1.05	1.04–1.07	1	0.98–1.02	1.06	1.04–1.08
BMI, kg/m^2	1.07	1.02–1.07	1.06	1.01–1.11	1	0.95–1.05	1.02	0.98–1.07
Women (vs. men)	0.37	0.23–0.58	1.09	0.80–1.51	1.08	0.76–1.52	0.5	0.35–0.71

BMI, body–mass index; LS, lumbar spondylosis; OR, odds ratio; CI, confidence interval.
Radiographic spondylosis was determined at the severest level among L1/2-L5/S1.
The odds ratios were calculated by logistic regression analysis.

65.5% and 46.6%, that of KL ≥ 3 LS was 27.3% and 29.5%, respectively. The incidence of KL ≥ 2 was higher in men than women, while, that of KL ≥ 3 was similar between men and women, indicating that different mechanisms might influence osteophytosis and disc space narrowing.

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Conflict of Interest

None.

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ORIGINAL ARTICLE

Association of dietary intake with joint space narrowing and osteophytosis at the knee in Japanese men and women: the ROAD study

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Abstract

Objective. The objective of the present study is to identify dietary nutrients associated with joint space narrowing (JSN) and osteophytosis at the knee in a population-based cohort of the Research on Osteoarthritis/osteoporosis Against Disability (ROAD) study.

Methods. From the baseline survey of the ROAD study, 827 participants (305 men and 522 women) in a rural cohort were analyzed. Dietary nutrient intakes for the last month were assessed by a self-administered brief diet history questionnaire. Minimum joint space width (mJSW) and osteophyte area (OPA) in the medial compartment of the knee were measured using a knee osteoarthritis (OA) computer-aided diagnostic system.

Results. In men, there were no associations of dietary nutrient intakes with mJSW or OPA. In women, vitamins K, B1, B2, B6, and C were associated with mJSW after adjustment for age, body mass index, and total energy ($p < 0.05$). Vitamins E, K, B1, B2, niacin, and B6 were significantly associated with OPA ($p < 0.05$) in women. Vitamins K, B and C may have a protective role against knee OA in women and might lead to disease-modifying treatments.

Conclusions. The present study revealed that low dietary intake of vitamins K, B, and C are associated with JSN and osteophytosis in women.

Keywords

Osteoarthritis, Knee, Diet, Cohort studies, Epidemiology

History

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Introduction

Knee osteoarthritis (OA), characterized by pathological features including joint space narrowing (JSN) and osteophytosis, is a major public health issue causing chronic pain and disability in the elderly in most developed countries [1]. The prevalence of radiographic knee OA is high in Japan [2], with 25,300,000 subjects 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]. Despite the urgent need for strategies for the prevention and treatment of this condition, there have been few established risk factors for knee OA except for age, female sex, obesity, previous injury, and occupational activities [5].

Current recommendations for OA include a combination of nonpharmacological interventions and pharmacological treatments [6]. However, considering that nonsteroidal anti-inflammatory drugs (NSAIDs), which may have serious adverse effects with long-term use, remain among the most widely prescribed drugs for OA [7], there is a need for safe and effective alternative strategies for prevention and treatment of this disease. Such strategies could come from dietary nutrition, because dietary factors are modifiable.

There have been several epidemiologic studies on the relationship between nutritional factors and OA [8–15]. Our previous study showed that dietary vitamin K intake was associated with the prevalence of knee OA [14], but disease was defined according to a categorical grade such as the Kellgren–Lawrence (KL) grade [16]. In the Framingham Study, the association of nutrition with JSN and osteophytosis was separately analyzed [8, 9, 12, 13] in Caucasians, but they were also defined by categorical grades. Categorical methods are statistically less powerful than continuous methods. Thus, the association between nutrition and knee OA might have been underestimated in previous studies.

To overcome these problems, joint space width or osteophyte area should be evaluated using a fully automatic system. To the best of our knowledge, there have been no population-based studies to separately measure joint space width or osteophyte area to clarify the association of dietary nutrient intake with JSN and osteophytosis. In the present study, we measured medial minimum joint space width (mJSW) and osteophyte area (OPA) at the knee in the large-scale population-based cohort study called Research on Osteoarthritis/osteoporosis Against Disability (ROAD). The

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purpose of the present study is to clarify which nutritional factors were associated with JSN and osteophytosis.

Materials and methods

Subjects

The ROAD study is a nationwide prospective study designed to establish epidemiologic indices for evaluation of clinical evidence for the development of a disease-modifying treatment for bone and joint diseases (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 [2, 3, 17]; 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) ranging in age from 23 to 95 years (mean, 70.3 years), who were recruited from resident registration listings in three communities: an urban region in Itabashi, Tokyo; a mountainous region in Hidakagawa, Wakayama; and a coastal region in Taiji, Wakayama.

Residents of these regions were recruited from the resident registration list of the relevant region. Participants in the urban region were recruited from a randomly selected cohort from the Itabashi-ward residents' registration database [18]. 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.

From the baseline data of 855 subjects aged ≥40 years in the mountainous cohort, we excluded 3 individuals who had undergone knee surgeries. In addition we excluded 18 individuals who had lateral knee OA, defined as being present when a knee had KL grade ≥2 and lateral JSN score ≥1 on a 0–3 scale according to the Osteoarthritis Research Society International (OARSI) atlas [19]. We also excluded 4 who did not complete questionnaires regarding dietary nutrition, and 3 whose radiographic conditions were insufficient for measuring JSN and osteophyte area. Thus, a total of 827 participants (305 men and 522 women) were analyzed in the present study.

Dietary assessment

For the dietary survey, we used a self-administered brief diet history questionnaire (BDHQ) and investigated dietary nutrient intakes for the previous month. A questionnaire was given to each participant with detailed explanation to fill out at home, and was reviewed by well-trained interviewers when the participants visited the clinic. The BDHQ is a 4-page, structured questionnaire that inquires about the consumption frequency of 56 food and beverage items, with specified serving sizes described in terms of a natural portion or the standard weight and volume measurement of servings commonly consumed in general Japanese populations. The BDHQ was developed based on a comprehensive (16-page) version of a validated self-administered diet history questionnaire [20], and is now widely used for dietary survey in Japan [14, 21]. Estimates of dietary intake for the 56 food and beverage items, energy, and selected nutrients were calculated using an ad hoc computer algorithm for the BDHQ, which was based on the Standard Tables of Food Composition in Japan. In the present study, dietary intake levels of total energy and 15 nutrient factors (animal protein, vegetable protein, animal fat, vegetable fat, carbohydrate, vitamin B1, 2, 6, and 12, niacin, vitamins C, D, E, K, and salt) were analyzed.

Radiographic assessment

All participants had radiographic examination of both knees using an anterior–posterior view with weight-bearing and foot map positioning. The beam was positioned parallel to the floor with no angle and aimed at the joint space. To visualize the joint space properly and to make the patella centralized over the lower end of the femur, we used fluoroscopic guidance with an anterior–posterior X-ray beam. The images were downloaded into digital imaging and communication in medicine (DICOM) format files. mJSW (mm) in the medial compartment and OPA (mm^2) at the medial tibia were measured by the KOACAD system, and the knee with lower mJSW was defined as the designated knee of each participant. The KOACAD system has been described in detail elsewhere [22–24], and is summarized here only briefly. The KOACAD system can quantify the major features of knee OA on standard radiographs and allows objective, accurate, simple, and easy assessment of the structural severity of knee OA in general clinical practice. This system was programmed to measure mJSW in the medial and lateral compartments and OPA at the medial tibia using digitized knee radiographs. Initially, correction for radiographic magnification was performed based on the image size of a rectangular metal plate. Next, to determine the region of interest (ROI), the center of the tibiofemoral joint was determined as follows: A vertical neighborhood difference filter that vertically scanned digital images to detect the margins of the tibial and femoral condyles was applied to identify points with high absolute values for differences of scale. Then, the center of all points was calculated and defined as the center of the tibiofemoral joint. Finally, a 480 × 200 pixel rectangle around the center was defined as the ROI. Within the ROI, the outline of the femoral condyle was designated as the upper rim of the joint space by vertical filtering with a 3 × 3 square neighborhood difference filter. Both ends of the upper rim were determined using a Canny filter to remove the noise associated with lines, and vertical lines from the ends were designated as the outside rims of the joint space. Outlines of anterior and posterior margins of the tibial plateau were drawn similarly to that of the femoral condyle, and the middle line between the two outlines was designated as the lower rim of the joint space (Fig. 1a). A straight regression line for the lower rim outline was then drawn, and the intersection of the lower rim outline and the regression line was designated as the inside rim. Medial and lateral joint space areas were determined as areas surrounded by the upper, lower, inside, and outside rims as defined above. Medial and lateral mJSWs were further determined as the minimum vertical distances in the respective joint space area (Fig. 1b). To measure the OPA, medial and lateral outlines of the femur and tibia were drawn. Inflection points for these outlines were then calculated. The medial outline of the tibia from the inflection point was drawn upward to the joint level, and the area that was medially prominent over the smoothly extended outline was designated as the OPA (Fig. 1c). We examined the reproducibility of mJSW and OPA measured on radiographs taken at 2-week intervals for 20 individuals; the reproducibility of both mJSW and OPA were high [intraclass correlation coefficient (ICC) = 0.86 and 0.99, respectively] [22]. In addition, we measured mJSW and OPA by KOACAD more than twice on 1979 radiographs, and confirmed that all parameters were unchanged independent of observer or time measured (all ICC = 1.0) [22]. We have previously published reference values of joint space width and osteophyte area by gender and age strata in Japan using the KOACAD system [25].

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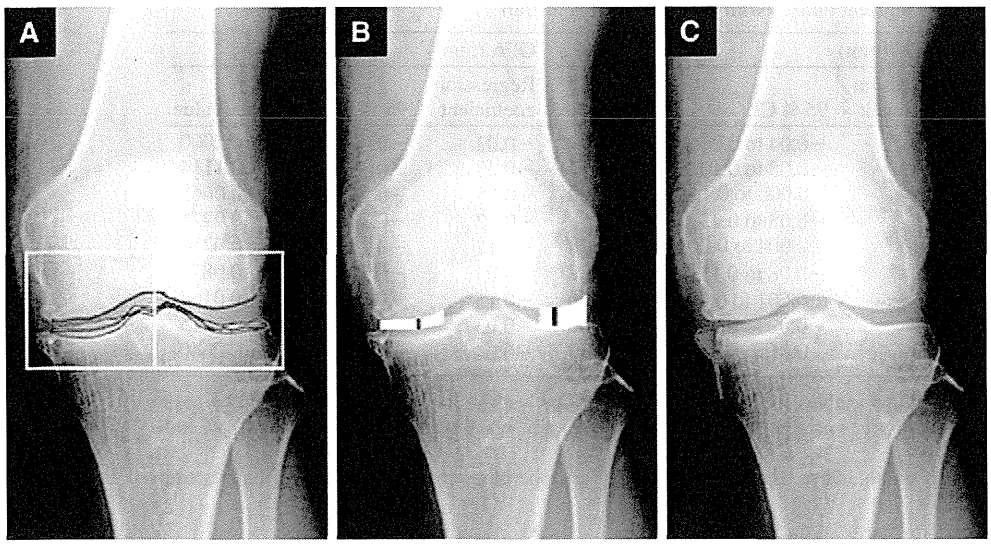

Fig 1. Schema of image processing by KOACAD (cited from Ref. [28]). (a) Outlines of anterior and posterior margins of the tibial plateau. The *middle line* between the two outlines is defined as the lower rim of the joint space. (b) Medial and lateral minimum joint space widths were defined as the minimum vertical distances in the joint space area. (c) Osteophyte area (*red area*) that is medially prominent over the smoothly extended outline of the tibia

Statistical analysis

Differences in age, height, weight, and body mass index (BMI) were examined by nonpaired Student's *t* test. mJSW, OPA, total energy, and dietary nutrient intakes between men and women were examined by Wilcoxon rank-sum test. The distribution of mJSW, OPA, total energy, and dietary nutrient intakes were not normal, thus we applied log transformation to these variables, and multiple regression analysis after adjustment for age, BMI, gender, and total energy was used to determine the association of dietary nutrient intakes with mJSW and OPA in the overall population. Furthermore, multiple regression analysis after adjustment for age, BMI, and total energy was used to determine the association of dietary nutrient intakes with mJSW and OPA in men and women. Data analyses were performed using SAS version 9.0 (SAS Institute Inc., Cary, NC). *p*-Value <0.05 was considered significant.

Results

Characteristics of 827 participants are presented in Table 1. There were no significant differences in BMI between men and women. mJSW was significantly wider in men than women, and OPA was significantly smaller in men than women. Total energy and almost all of dietary nutrient intakes except for vitamins K and C were significantly higher in men than women ($p < 0.01$), whereas vitamin C intake was significantly lower in men than women ($p < 0.0001$) (Table 2). Vitamin K intake was not significantly different between men and women ($p = 0.07$).

Table 1. Characteristics of participants

	Overall	Men	Women	*p* Value
No. of participants	827	305	522	
Age (years)	69.2 ± 9.3	69.6 ± 8.7	68.9 ± 9.6	0.29
Height (cm)	163.0 ± 9.2	161.3 ± 6.7	148.1 ± 6.6	<0.0001
Weight (kg)	54.0 ± 10.2	60.0 ± 10.2	50.5 ± 8.5	<0.0001
BMI (kg/m^2)	23.0 ± 3.2	23.0 ± 3.0	23.0 ± 3.4	0.86
mJSW (mm)	2.43 ± 1.11	2.91 ± 1.01	2.15 ± 1.07	<0.0001
OPA (mm^2)	3.72 ± 8.33	1.72 ± 4.20	4.88 ± 9.79	<0.0001

Data are mean ± standard deviation (SD). Nonpaired Student's *t* test was used to compare age, height, and BMI between men and women. Wilcoxon rank-sum test was used to compare mJSW and OPA between men and women

BMI body mass index, *mJSW* minimum joint space width, *OPA* osteophyte area

We next analyzed the association of dietary nutrient intakes with mJSW and OPA. Overall, after adjustment for age, BMI, gender, and total energy, mJSW was not associated with vitamins D, E, B1 or niacin, but was significantly associated with vitamins K ($R = 0.344$, $p = 0.03$), B2 ($R = 0.343$, $p = 0.04$), and C ($R = 0.345$, $p = 0.02$) (Table 3). OPA was not significantly associated with vitamins D, E, K, B12, C or niacin, but was significantly associated with vitamins B1 ($R = 0.421$, $p = 0.03$), B2 ($R = 0.421$, $p = 0.03$), and B6 ($R = 0.422$, $p = 0.02$) (Table 3). When analyzed in men and women separately, in men, multiple regression analysis after adjustment for age, BMI, and total energy showed that mJSW and OPA were not significantly associated with any nutritional factors (Table 4). In contrast, in women, mJSW was significantly associated with vitamins K ($R = 0.283$, $p = 0.01$), B1 ($R = 0.271$, $p = 0.04$), B2 ($R = 0.270$, $p = 0.04$), B6 ($R = 0.273$, $p = 0.01$), and C ($R = 0.281$, $p = 0.01$) (Table 5), while OPA was significantly associated with vitamins E ($R = 0.426$, $p = 0.04$), K ($R = 0.427$, $p = 0.03$), B1 ($R = 0.436$,

Table 2. Dietary nutrient intakes in men and women

	Overall	Men	Women
Total energy, MJ/day	7.6 (6.3–9.3)	9.5 (8.1–12.1)	6.9* (6.0–7.9)
Dietary nutrients			
Vitamin D, μg/day	17.7 (11.5–25.8)	20.7 (13.3–30.5)	16.4* (10.7–24.2)
Vitamin E, mgα-TE/day	6.9 (5.4–8.8)	7.4 (5.6–9.6)	6.7* (5.3–8.3)
Vitamin K, μg/day	211.0 (146.6–287.9)	224.4 (150.2–313.5)	202.9 (145.3–281.0)
Vitamin B1, mg/day	0.71 (0.58–0.86)	0.79 (0.64–0.97)	0.67* (0.56–0.80)
Vitamin B2, mg/day	0.97 (0.76–1.19)	1.07 (0.82–1.34)	0.92* (0.73–1.12)
Niacin, mgNE/day	14.9 (11.6–19.2)	17.9 (13.9–22.7)	13.6* (10.4–17.1)
Vitamin B6, mg/day	1.1 (0.9–1.4)	1.3 (1.0–1.6)	1.03* (0.86–1.26)
Vitamin B12, μg/day	9.8 (6.8–13.5)	11.0 (7.7–15.8)	8.8* (6.3–12.0)
Vitamin C, mg/day	101.7 (78.3–133.4)	94.0 (71.7–122.0)	108.1* (82.6–137.3)

Values are median (interquartile range)

TE tocopherol equivalent, *NE* niacin equivalent

*$p < 0.01$ versus men by Wilcoxon rank-sum test

Table 3. Association of dietary nutrient intakes with mJSW and OPA overall

	mJSW (mm)			OPA (mm^2)		
	Regression coefficient	95 % CI	*p*-Value	Regression coefficient	95 % CI	*p* Value
Vitamin D, μg/day	0.006	−0.04 to 0.06	0.8044	−0.03	−0.09 to 0.02	0.2000
Vitamin E, mgα-TE/day	0.01	−0.08 to 0.10	0.7613	−0.08	−0.17 to 0.02	0.1114
Vitamin K, μg/day	0.06	0.006 to 0.11*	0.0309	−0.05	−0.11 to 0.004	0.0665
Vitamin B1, mg/day	0.09	−0.05 to 0.23	0.2058	−0.17	−0.32 to 0.02*	0.0271
Vitamin B2, mg/day	0.10	0.004 to 0.20*	0.0418	−0.12	−0.22 to 0.01*	0.0254
Niacin, mgNE/day	0.02	−0.08 to 0.13	0.6422	−0.09	−0.20 to 0.01	0.0877
Vitamin B6, mg/day	0.12	−0.001 to 0.24	0.0526	−0.15	−0.28 to 0.03*	0.0164
Vitamin B12, μg/day	0.04	−0.02 to 0.09	0.2066	−0.03	−0.09 to 0.02	0.2515
Vitamin C, mg/day	0.09	0.01 to 0.16*	0.0179	−0.04	−0.12 to 0.03	0.2640

Log transformation was applied to variables, and multiple regression analysis after adjustment for age, body mass index, gender, and total energy was used to determine the association of nutritional factors with mJSW and OPA

mJSW minimum joint space width, *OPA* osteophyte area, *TE* tocopherol equivalent, *NE* niacin equivalent, *CI* confidence interval

$p = 0.002$), B2 ($R = 0.435$, $p = 0.003$), niacin ($R = 0.428$, $p = 0.02$), and B6 ($R = 0.433$, $p = 0.01$) (Table 5).

Discussion

This is the first population-based cohort study of the relationship between dietary nutrient intakes and JSN and osteophytosis separately in Japanese men and women. In the overall population, vitamins K, B2, and C were significantly associated with mJSW, while vitamins B1, B2, and B6 were significantly associated with OPA. When analyzed in men and women separately, we observed that there were no associations of dietary nutrient intakes with mJSW or OPA in men. In contrast, in women, vitamins K, B1, B2, and B6 were associated with both mJSW and OPA. Vitamin C was associated with mJSW, but not with OPA. Previous studies have already shown that vitamins K and C were associated with knee OA; however, the knee OA was defined by KL grade or other categorical methods in almost all studies [8–15]. KL grade is the most conventional system to grade radiographic severity of knee OA, but in this categorical system, JSN and osteophyte formation are not assessed separately, thus one cannot clarify whether osteophytosis and JSN have distinct risk factors. In addition, a recent cross-sectional study showed that osteophytosis was unrelated to JSN on plain radiographs [26]. Furthermore, our study on an experimental mouse model for OA identified a cartilage-specific molecule, carminerin, that regulates osteophytosis without affecting joint cartilage destruction during OA progression [27, 28]. In addition, there were distinct effects on quality of life (QOL) for JSN and osteophytosis [26]. Such accumulating evidence indicates that JSN and osteophytosis may have distinct etiologic mechanisms and their progression may be neither constant nor proportional. Thus, to examine factors associated with knee OA, these two OA features should be separately assessed. Furthermore, because categorical methods are statistically less powerful than continuous methods, the association between nutrition and knee OA might have been underestimated in previous studies. This study is the first to report that vitamins K, B1, B2, and B6 are significantly associated with both mJSW and OPA, and that vitamin C is significantly associated with mJSW in women. The association of dietary factors with knee OA may be weaker than for gender or obesity, but they are easily modifiable; therefore, these results may contribute to prevent incidence or progression of knee OA, although it is not completely clear what modifications of vitamin intake would be required to achieve clinically meaningful change in mJSW and OPA.

Vitamin K includes vitamin K1, or phylloquinone, which is contained in green leafy vegetables, and vitamin K2, or menaquinone, which is synthesized by bacteria and abundantly contained in a traditional Japanese fermented soybean food called *natto* [29]. Our previous study showed that dietary vitamin K intake was inversely associated with prevalence of knee OA defined by KL grade [14]. However, because of the different etiology that

Table 4. Association of dietary nutrient intakes with mJSW and OPA in men

	mJSW (mm)			OPA (mm^2)		
	Regression coefficient	95 % CI	*p* Value	Regression coefficient	95 % CI	*p* Value
Vitamin D, μg/day	−0.02	−0.10 to 0.06	0.5804	0.04	−0.03 to 0.11	0.2710
Vitamin E, mgα-TE/day	−0.01	−0.14 to 0.11	0.8501	0.03	−0.09 to 0.14	0.6567
Vitamin K, μg/day	0.02	−0.06 to 0.09	0.6626	−0.01	−0.08 to 0.06	0.7939
Vitamin B1, mg/day	−0.01	−0.21 to 0.19	0.8995	0.08	−0.11 to 0.26	0.4275
Vitamin B2, mg/day	0.07	−0.08 to 0.22	0.3515	0.05	−0.09 to 0.19	0.4772
Niacin, mgNE/day	−0.03	−0.18 to 0.12	0.7149	0.06	−0.08 to 0.20	0.4127
Vitamin B6, mg/day	0.04	−0.13 to 0.22	0.6214	−0.005	−0.17 to 0.16	0.9554
Vitamin B12, μg/day	−0.004	−0.09 to 0.09	0.9345	0.06	−0.03 to 0.14	0.1816
Vitamin C, mg/day	0.03	−0.03 to 0.14	0.5079	0.01	−0.08 to 0.11	0.8113

Log transformation was applied to variables, and multiple regression analysis after adjustment for age, body mass index, and total energy was used to determine the association of nutritional factors with mJSW and OPA

mJSW minimum joint space width, *OPA* osteophyte area, *TE* tocopherol equivalent, *NE* niacin equivalent, *CI* confidence interval

Table 5. Association of dietary nutrient intakes with mJSW and OPA in women

	mJSW (mm)			OPA (mm^2)		
	Regression coefficient	95 % CI	*p* Value	Regression coefficient	95 % CI	*p* Value
Vitamin D, μg/day	0.03	−0.03 to 0.09	0.3550	−0.07	−0.14 to 0.004	0.0631
Vitamin E, mgα-TE/day	0.05	−0.08 to 0.18	0.4234	−0.15	−0.29 to −0.008*	0.0383
Vitamin K, μg/day	0.11	0.03 to 0.19*	0.0062	−0.10	−0.18 to −0.009*	0.0302
Vitamin B1, mg/day	0.21	0.01 to 0.41*	0.0366	−0.35	−0.56 to −0.13*	0.0020
Vitamin B2, mg/day	0.13	0.006 to 0.26*	0.0411	−0.22	−0.37 to −0.08*	0.0025
Niacin, mgNE/day	0.08	−0.06 to 0.21	0.2819	−0.18	−0.33 to −0.03*	0.0195
Vitamin B6, mg/day	0.18	0.02 to 0.34*	0.0261	−0.25	−0.42 to −0.07*	0.0053
Vitamin B12, μg/day	0.07	−0.005 to 0.14	0.0679	−0.07	−0.16 to 0.006	0.0699
Vitamin C, mg/day	0.13	0.04 to 0.23*	0.0077	−0.09	−0.20 to 0.02	0.1139

Log transformation was applied to variables, and multiple regression analysis after adjustment for age, body mass index, and total energy was used to determine the association of nutritional factors with mJSW and OPA

mJSW minimum joint space width, *OPA* osteophyte area, *TE* tocopherol equivalent, *NE* niacin equivalent, *CI* confidence interval

may exist between JSN and osteophytosis, these two OA features should be assessed separately to examine factors associated with knee OA. However, the association of these two features with vitamin K cannot be separately analyzed by KL grade. The Framingham Study showed that plasma levels of phylloquinone were inversely associated with osteophytosis in the knee [12], but no population-based study has determined the association of dietary vitamin K intake with mJSW width and OPA separately. In the present study, vitamin K was associated with both JSN and osteophytosis in women, although the results for vitamin K were of borderline significance after adjusting for additional potential confounders, particularly regarding OPA. Several basic studies have shown that vitamin K plays an important role in cartilage metabolism, as an inhibitor of extracellular matrix calcification as well as a promoter of cell survival and proliferation [30–38]. In addition, warfarin, a vitamin K-antagonist anticoagulant, is known to cause warfarin embryopathy characterized by abnormal calcification and decreased growth of cartilage [37, 38]. Habitual low dietary vitamin K intake may exert an inhibitory effect on the vitamin K-dependent MGP and Gas6 functions and modulate the pathogenesis of OA by influencing the process of osteophytosis and cartilage destruction.

Several previous studies have shown that vitamin C intake was inversely associated with knee OA [9, 15], but no population-based study has analyzed the association of vitamin C intake with mJSW and OPA at the same time. In the present study, vitamin C was associated with narrower mJSW in women, but not with OPA. This finding may indicate that vitamin C intake is more strongly associated with JSN than with osteophytosis in women. Damage caused by free radicals has long been thought to be pathogenic, and free radicals play an important role in the progression of many chronic diseases, including OA [9, 11, 39–42]. Vitamin C is an antioxidant, which may partly explain the effect of vitamin C on JSN. This may lead to the logical possibility of using vitamin C supplementation for primary prevention or as a therapeutic intervention for OA.

There have been no studies regarding the association of dietary vitamin B intake with knee OA. In the present study, we found that vitamins B1, B2, and B6 were significantly associated with mJSW in women. Vitamin B is closely involved in the metabolism of homocysteine [43], which has recently been seen to play a role in osteoporosis-related bone damage, and may be linked to its involvement in collagen formation. Homocysteine inhibits the synthesis of insoluble collagen fibrils in vitro by interfering with normal cross-linking [44]. From the perspective of cartilage homeostasis, these changes in matrix organization interfere with chondrocyte-mediated mineralization, potentially altering the function and properties of calcified cartilage [45]. This may be due to homocysteine-mediated inhibition of lysil oxidase, which catalyzes the cross-linking of collagen molecules, a function necessary for its mineralization in bone tissue [46].

In the present study, we found gender differences regarding the association of dietary nutrient intakes with mJSW and OPA. In women, vitamins B and K were significantly associated with both mJSW and OPA, and vitamin C was significantly associated with mJSW, whereas in men, no dietary factors were significantly associated with mJSW or OPA. This difference may be partly explained by muscle strength in men. Because men are known to have greater muscle strength than women at all ages, and muscle strength has a protective effect on knee OA [47–49], it might be that the greater muscle strength obscures the effects of dietary nutrient intakes on knees in men.

There are several limitations to the present study. First, this was a cross-sectional study of baseline data, and thus no causal relationship can be determined. Second, in the present study, we used self-reported measures for dietary assessments; these measurements are prone to bias and measurement error. In addition, the dietary survey in this study investigated dietary habits only for the previous month, which did not necessarily reflect a long habit of several years, despite the fact that OA is a slowly progressing chronic disease. This dietary survey also investigated whether participants had changed their dietary habits. Those who answered "yes" accounted for 9.6 %, whereas 90.4 % of participants answered that they had not changed their dietary habits. Although it is likely that dietary habits in middle-aged and elderly people are usually quite different from those in children and young adults, there is a possibility that most participants in this study had not changed their dietary habits for several years or for a longer time, which may have affected the disease process of OA. Furthermore, the dietary survey in the present study was conducted from autumn to winter although there are four seasons in Japan and diets may vary with the season. Therefore, the present study could suffer from some bias for the effect of season on the nutritional quality of diets. Third, nutritional factors cannot be assumed to be joint location specific, and osteophytes may even be more pronounced in the contralateral tibiofemoral compartment [50]; however, at present, the KOACAD system can only measure medial osteophytes at the tibia. We are now developing a KOACAD system to measure osteophytes at other sites; thus, we may be able to clarify the association between osteophytes at other sites and QOL in the near future. Finally, we clarified the association of vitamins B, C, and K with mJSW and OPA, but did not determine what changes in intake of these vitamins would be needed to achieve clinically meaningful change in mJSW and OPA, because we

have not yet clarified what changes in mJSW and OPA are clinically meaningful. In addition, this is a cross-sectional study, thus causal relationships of vitamins B, C, and K with mJSW and OPA cannot be clarified.

In conclusion, the present cross-sectional study using a population-based cohort revealed that low dietary intakes of vitamins K, B1, B2, and B6 are associated with both JSN and osteophytosis in women. Vitamin C intake was associated with JSN in women, but not with osteophytosis. Further studies, along with longitudinal data from the ROAD study, will elucidate the environmental background of OA and help clarify clinical evidence regarding the development of disease-modifying treatments.

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Conflict of interest

None.

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Associations between radiographic lumbar spinal stenosis and clinical symptoms in the general population: the Wakayama Spine Study

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SUMMARY

Objective: Many asymptomatic individuals have radiographic lumbar spinal stenosis (LSS), but the prevalence of symptoms among individuals with radiographic LSS has not yet been established. The purpose of this study was to clarify the association between radiographic LSS and clinical symptoms in the general population.

Methods: In this cross-sectional study, data from 938 participants (308 men, 630 women; mean age, 66.3 years; range, 40–93 years) were analyzed. The severity of radiographic LSS, including central stenosis, lateral stenosis, and foraminal stenosis, was assessed by mobile magnetic resonance imaging and rated qualitatively. Assessment of clinical symptoms was based on the definition of symptomatic LSS in the North American Spine Society guideline.

Results: We found that 77.9% of participants had more than moderate central stenosis and 30.4% had severe central stenosis. Logistic regression analysis after adjustment for age, sex, body mass index, and severity of radiographic LSS showed that severe central stenosis was related to clinical symptoms. However, only 17.5% of the participants with severe central stenosis were symptomatic.

Conclusion: Although radiographic LSS was common in our cohort, which resembled the general Japanese population, symptomatic persons were relatively uncommon.

Introduction

Radiographic lumbar spinal stenosis (LSS) is defined as a narrowing of the lumbar canal with encroachment of neural structures by surrounding bone and soft tissue[1]. Symptomatic LSS, which requires both the presence of clinical symptoms and radiographic LSS[2], is usually associated with impaired walking and other disabilities in the elderly[1,3] and is the most frequent indication for spinal surgery in patients older than 65 years[4]. Because of the high number of elderly persons in Japan, there is an urgent need for evidence-based data regarding radiographic LSS occurring as a result of degenerative changes. However, little information is available regarding the epidemiology of radiographic LSS. This is because previous studies on radiographic LSS have not included subjects who were part of the general population[5–7]. Furthermore, for radiographic LSS to be diagnosed, the detection of minute changes of the intervertebral discs and ligaments using a tool like magnetic resonance imaging (MRI) is essential[8,9], but to the best of our knowledge, no studies of radiographic LSS among the general population have been performed using MRI.

LSS symptoms include a range of possible clinical presentations resulting from dilatation of the intrinsic vessels of the nerve roots[10]. However, inconsistent with this observation, severe radiographic LSS is often present in asymptomatic patients[7], and little is known of the prevalence of symptoms among individuals with radiographic LSS. Previous studies have reported on the relationship between radiographic LSS and quality of life, function, and pain due to symptoms in symptomatic patients[11–14]. To the best of our knowledge, there has been no study on the association between radiographic LSS and clinical symptoms among the general population, which includes both symptomatic and asymptomatic individuals.

In this study, we aimed to determine the prevalence of radiographic LSS assessed by MRI and its association with clinical symptoms using mobile MRI in a population-based cohort.

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Methods

Participants

The present study, entitled The Wakayama Spine Study, assessed a subcohort drawn from Research on Osteoarthritis/Osteoporosis Against Disability (ROAD), which is a large-scale, prospective study of bone and joint diseases among population-based cohorts established in several communities throughout Japan. As the detailed profile of the ROAD study is described elsewhere, only a brief summary is provided here[15–18]. A database including baseline clinical and genetic information relating to 3,040 inhabitants (1,061 men, 1,979 women) with a mean age of 70.6 years (range, 23–95 years) has been created. We recruited individuals listed in 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 that included 400 items covering lifestyle information, and they underwent anthropometric measurements and assessments of physical performance. Blood and urine samples were collected for biochemical and genetic examinations.

The ROAD study team made a second visit to the mountainous region of Hidakagawa and the coastal region of Taiji between 2008 and 2010. Of the inhabitants who participated in this second visit, 1,063 volunteers were recruited for MRI. Fifty-two of these declined to attend the examination, and the remaining 1,011 were registered in the Wakayama Spine Study. All participants provided their written, informed consent for the MRI examination. Participants who had sensitive implanted devices (such as a pacemaker) or other disqualifiers were excluded. In total, 977 participants underwent lumbar spine MRI. Ten participants who had undergone a previous lumbar operation for LSS were excluded, and 29 participants who were younger than 40 years were excluded because LSS is a degenerative disease. Thus, MRI results were available for 938 participants (308 men and 630 women) with an age range of 40–93 years (mean, 68.3 years for men and 66.9 years for women).

Similar to the baseline study, the second ROAD study included an interviewer-administered questionnaire that included 400 items that covered lifestyle information such as smoking habits, alcohol consumption, family history, past history, physical activity, reproductive variables, and health-related quality of life. Anthropometric measurements included height, weight, bilateral grip strength, and body mass index (BMI) (kg/m^2). Co-morbidities were defined according to blood data (diabetes: HbA1c $> 6.5\%$[19], hyperuricemia: uric acid > 7.0 mg/dL[20], hyperlipidemia: high-density lipoprotein cholesterol < 40 mg/dL[21]). The ankle-brachial index (ABI) of all participants was measured using PWV/ABI (OMRON Co., Kyoto, Japan).

MRI

All participants underwent total spinal MRI with a mobile MRI unit (Excelart 1.5 T; Toshiba, Tokyo, Japan) on the same day as the examination. MRI exclusion criteria included the presence of a cardiac pacemaker, claustrophobia, or other reasons. 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]: 4,000 ms/echo, echo time [TE]: 120 ms, field of view [FOV]: 300 mm × 320 mm) and axial T2-weighted FSE (TR: 4,000 ms/echo, TE: 120 ms, FOV: 180 mm × 180 mm). Sagittal images were taken of the entire spine, but axial images were taken at each lumbar intervertebral level (L1/2–L5/S1) parallel to the vertebral endplates.

Qualitative ratings

The severity of radiographic LSS was qualitatively assessed after all examinations were completed. An experienced orthopedic surgeon (YI) without knowledge of the participants' symptom status examined the images, which were provided on films. The features assessed included the severity of central, lateral recess, and foraminal stenosis, rated on a four-grade scale. We used Fardon and Millette's[22] definition of lateral recess: a recess extending from the medial edge of the facet to the edge of the neuroforamen. We also applied the classification included in a general guideline[2] in which mild stenosis was defined as narrowing of one-third of the normal area or less, moderate stenosis as narrowing of between one- and two-thirds, and severe stenosis as narrowing of more than two-thirds of the area. Central stenosis and lateral recess stenosis were rated on the axial images and foraminal stenosis on the sagittal images. For lateral and foraminal stenosis, the rating for the side with the worst score was used. To evaluate the intraobserver variability of the severity rating, 50 randomly selected lumbar MRI films were scored by the same observer more than 1 month after the first reading. Fifty other lumbar MRI films were also scored by two experienced orthopedic surgeons (YI & KN) to determine the interobserver variability. The intraobserver variabilities in severity rating were confirmed by kappa analysis to be sufficient for the assessment of central, lateral, and foraminal stenosis (0.82, 0.71, and 0.66, respectively); interobserver variability was also sufficient (0.77, 0.66, and 0.66, respectively).

Assessment of clinical symptoms

An experienced orthopedic surgeon (YI) took the medical history and performed the physical examination of all the participants. The history included information about the presence of lower back pain, buttock pain, and leg pain; areas of pain or other discomfort; the presence of intermittent claudication (IC) and its distance; and items on a modified Zurich Claudication Questionnaire[23] (except six items about satisfaction and a history of lumbar surgery for symptomatic LSS). Physical examination included assessments to determine whether any symptoms could be induced by lumbar extension or were improved or induced by lumbar flexion, floor finger distance (cm), and peripheral circulation (good or poor); a straight-leg raising test; manual muscle testing of both the upper and lower extremities; tendon reflex testing for both the upper and lower extremities; and Babinski reflex testing. In addition, an MRI study of the entire spine was performed for all participants on the same day as the physical examination.

Assessment of clinical symptoms in the present study was based on the LSS definition in the North American Spine Society (NASS) guideline[24] and required one or more of the following symptoms: pain, numbness and neurological deficits in the lower extremities and buttocks, and bladder/bowel dysfunction. In addition, the above symptoms were required to be induced or exacerbated by walking or prolonged standing and relieved by lumbar flexion, sitting, and recumbency.

Statistical analysis

All statistical analyses were performed using JMP, version 8 (SAS Institute Japan; Tokyo, Japan). Differences between men and women in age, height, weight, and BMI were examined using non-paired Student's t test., co-morbidities, and clinical symptoms were compared between men and women with the chi-square test. The chi-square test was also used to determine the association between radiographic LSS and age stratum. Logistic regression analysis was performed stratified for sex to determine the effect of age and BMI