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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

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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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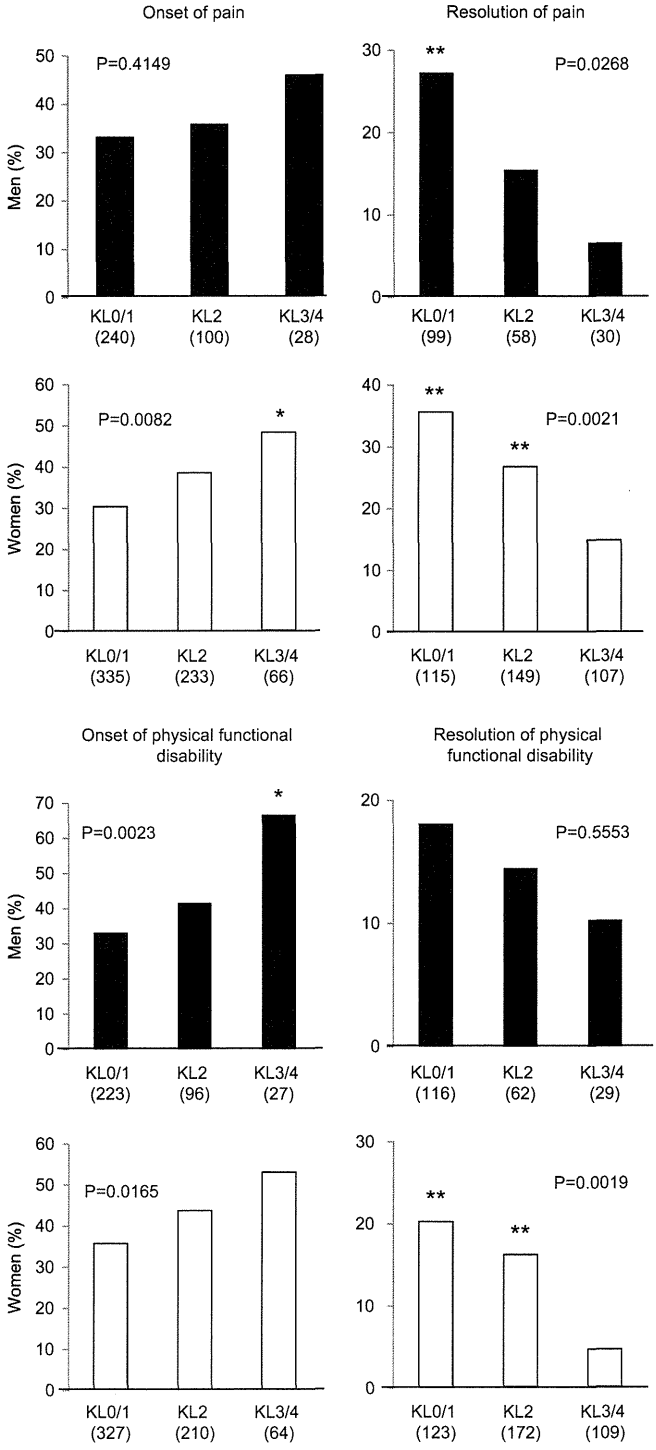

Figure 1. Onset and resolution rate of pain and physical functional disability according to Kellgren Lawrence (KL) grade in men and women. The number of subjects in each subgroup is shown in brackets. Chi-square test was used to determine the association of KL grade with onset of pain and physical functional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

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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.

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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.

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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.

References

1. Sharma L, Kapoor D. Epidemiology of osteoarthritis. In: Moskowitz RW, Altman RD, Hochberg MC, Buckwalter JA, Goldberg VM, editors. Osteoarthritis: Diagnosis and Medical/Surgical Management. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2007. pp. 3–26.
2. Muraki S, Oka H, Akune T, Mabuchi A, En-yo Y, Yoshida M, et al. Prevalence of radiographic knee osteoarthritis and its association with knee pain in the elderly of Japanese population-based cohorts: The ROAD study. Osteoarthritis Cartilage. 2009;17(9):1137–43.
3. Yoshimura N, Muraki S, Oka H, Mabuchi A, En-yo Y, Yoshida M, et al. Prevalence of knee osteoarthritis, lumbar spondylosis and osteoporosis in Japanese men and women: The Research on Osteoarthritis/osteoporosis Against Disability (ROAD). J Bone Miner Metab. 2009;27(5):620–8.
4. Ministry of Health, Labour and Welfare. The outline of the results of National Livelihood Survey 2007. August 2013. Available at http://www.mhlw.go.jp/toukei/list/20-19-1.html.
5. Linaker CH, Walker-Bone K, Palmer K, Cooper C. Frequency and impact of regional musculoskeletal disorders. Baillieres Clin Rheumatol. 1999;13(2):197–215.
6. Duncan R, Peat G, Thomas E, Hay E, McCall I, Croft P. Symptoms and radiographic osteoarthritis: not as discordant as they are made out to be? Ann Rheum Dis. 2007;66(1):86–91.
7. Hannan MT, Felson DT, Pincus T. Analysis of the discordance between radiographic changes and knee pain in osteoarthritis of the knee. J Rheumatol. 2000;27(6):1513–7.
8. Neogi T, Felson D, Niu J, Nevitt M, Lewis CE, Aliabadi P, et al. Association between radiographic features of knee osteoarthritis and pain: results from two cohort studies. BMJ. 2009;339:b2844.
9. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol. 1988;15(12):1833–40.
10. Thumboo J, Chew LH, Soh CH. Validation of the Western Ontario and McMaster University osteoarthritis index in Asians with osteoarthritis in Singapore. Osteoarthritis Cartilage. 2001;9(5):440–6.
11. Woo J, Lau E, Lee P, Kwok T, Lau WC, Chan C, et al. Impact of osteoarthritis on quality of life in a Hong Kong Chinese population. J Rheumatol 2004;31(12):2433–8.
12. Dillon CF, Rasch EK, Gu Q, Hirsch R. Prevalence of knee osteoarthritis in the United States: arthritis data from the Third National Health and Nutrition Examination Survey 1991-94. J Rheumatol. 2006;33(11):2271–9.
13. Jordan JM, Helmick CG, Renner JB, Luta G, Dragomir AD, Woodard J, et al. Prevalence of knee symptoms and radiographic and symptomatic knee osteoarthritis in African Americans and Caucasians: the Johnston County Osteoarthritis Project. J Rheumatol. 2007;34(1):172–80.
14. Yoshida S, Aoyagi K, Felson DT, Aliabadi P, Shindo H, Takemoto T. Comparison of the prevalence of radiographic osteoarthritis of the knee and hand between Japan and the United States. J Rheumatol. 2002;29(7):1454–8.
15. Roubenoff R. Sarcopenia: a major modifiable cause of frailty in the elderly. J Nutr Health Aging. 2000;4(3):4140–2.
16. Bohannon RW. Hand-grip dynamometry predicts future outcomes in aging adults. J Geriatr Phys Ther. 2008;31(1):3–10.
17. Sirola J, Rikkonen T, Tuppurainen M, Jurvelin JS, Kroger H. Association of grip strength change with menopausal bone loss and related fractures: a population based follow-up study. Calcif Tissue Int. 2006;78(4):218–26.
18. Kerr A, Syddall HE, Cooper C, Turner GF, Briggs RS, Sayer AA. Does admission grip strength predict length of stay in hospitalised older patients? Age Ageing 2006;35(1):82–4.
19. Wind AE, Takken T, Helders PJ, Engelbert RH. Is grip strength a predictor for total muscle strength in healthy children, adolescents, and young adults? Eur J Pediatr. 2010;169(3):281–7.
20. Yoshimura N, Muraki S, Oka H, Kawaguchi H, Nakamura K, Akune T. Cohort profile: Research on osteoarthritis/osteoporosis against disability (ROAD) study. Int J Epidemiol. 2010;39:988–95.
21. Kellgren JH, Lawrence JS (eds.). The Epidemiology of Chronic Rheumatism: Atlas of Standard Radiographs of Arthritis. Oxford, England: Blackwell Scientific; 1963.
22. Barr S, Bellamy N, Buchanan WW, Chalmers A, Ford PM, Kean WF, et al. A comparative study of signal versus aggregate methods of outcome measurement based on the WOMAC Osteoarthritis Index. J Rheumatol 1994;21(11):2106–12.
23. Hashimoto H, Hanyu T, Sledge CB, Lingard EA. Validation of a Japanese patient-derived outcome scale for assessing total knee arthroplasty: comparison with Western Ontario and McMaster Universities osteoarthritis index (WOMAC). J Orthop Sci. 2003;8(3):288–93.
24. Muraki S, Akune T, Oka H, Ishimoto Y, Nagata K, Yoshida M, et al. Incidence and risk factors for radiographic knee osteoarthritis and knee pain in Japanese men and women: a longitudinal population-based cohort study. Arthritis Rheum. 2012;64(5):1447–56.
25. Soni A, Kiran A, Hart DJ, Leyland KM, Goulston L, Cooper C, et al. Prevalence of reported knee pain over twelve years in a community-based cohort. Arthritis Rheum 2012;64(4):1145–52.
26. Saito T, Koshino T. Distribution of neuropeptides in synovium of the knee with osteoarthritis. Clin Orthop Relat Res. 2000;376:172–82.

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27. Bollet AJ. Edema of the bone marrow can cause pain in osteoarthritis and other diseases of bone and joints. Ann Intern Med. 2001;134(7):591–3.
28. Teichtahl AJ, Wluka AE, Morris ME, Davis SR, Cicuttini FM. The relationship between the knee adduction moment and knee pain in middle-aged women without radiographic osteoarthritis. J Rheumatol. 2006;33(9):1845–8.
29. Thorp LE, Sumner DR, Wimmer MA, Block JA. Relationship between pain and medial knee joint loading in mild radiographic knee osteoarthritis. Arthritis Rheum. 2007;57(7):1254–60.
30. Felson DT, Niu J, Guermazi A, Roemer F, Aliabadi P, Clancy M, et al. Correlation of the development of knee pain with enlarging bone marrow lesions on magnetic resonance imaging. Arthritis Rheum. 2007;56(9):2986–92.

Supplementary material available online

Supplementary Tables 1-4.

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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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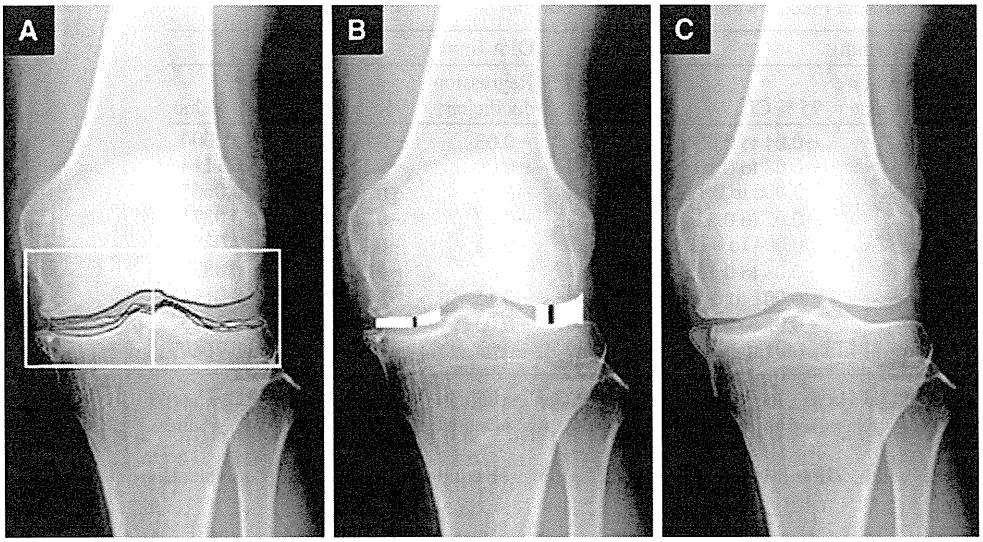

Fig 1. Schema of image processing by KOACAD (cited from Ref. [28]). (a) Outlines of anterior and posterior margins of the tibial plateau. The *middle line* between the two outlines is defined as the lower rim of the joint space. (b) Medial and lateral minimum joint space widths were defined as the minimum 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

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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

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$p = 0.002$), 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

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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

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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.

References

1. Sharma L, Kapoor D. Epidemiology of osteoarthritis. In: Moskowitz RW, Altman RD, Hochberg MC, Buckwalter JA, Goldberg VM. Osteoarthritis: diagnosis and medical/surgical management. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2007. p. 3–26.
2. Muraki S, Oka H, Akune T, Mabuchi A, En-yo Y, Yoshida M, et al. Prevalence of radiographic knee osteoarthritis and its association with knee pain in the elderly of Japanese population-based cohorts: the ROAD study. Osteoarthr Cartil. 2009;17:1137–43.
3. Yoshimura N, Muraki S, Oka H, Mabuchi A, En-yo Y, Yoshida M, et al. Prevalence of knee osteoarthritis, lumbar spondylosis and osteoporosis in Japanese men and women: the Research on Osteoarthritis/osteoporosis Against Disability (ROAD). J Bone Miner Metab. 2009;27:620–8.
4. Ministry of Health, Labour and Welfare. The outline of the results of National Livelihood Survey 2007. http://www.mhlw.go.jp/toukei/list/20-19-1.html. Accessed 1 Oct 2012.
5. Blagojevic M, Jinks C, Jeffery A, Jordan KP. Risk factors for onset of osteoarthritis of the knee in older adults: a systematic review and meta-analysis. Osteoarthr Cartil. 2010;18:24–33.
6. Zhang W, Moskowitz RW, Nuki G, Abramson S, Altman RD, Arden N, et al. OARSI recommendations for the management of hip and knee osteoarthritis, part I: critical appraisal of existing treatment guidelines and systematic review of current research evidence. Osteoarthr Cartil. 2007;15:981–1000.
7. Simon LS, Strand V. The pharmacologic treatment of osteoarthritis. In: Moskowitz RW, Altman RD, Hochberg MC, Buckwalter JA, Goldberg VM. Osteoarthritis: diagnosis and medical/surgical management. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2007. p. 267–86.
8. McAlindon TE, Felson DT, Zhang Y, Hannan MT, Aliabadi P, Weissman B, et al. Relation of dietary intake and serum levels of vitamin D to progression of osteoarthritis of the knee among participants in the Framingham Study. Ann Intern Med. 1996;125:353–9.
9. McAlindon TE, Jacques P, Zhang Y, Hannan MT, Aliabadi P, Weissman B, et al. Do antioxidant micronutrients protect against the development and progression of knee osteoarthritis?. Arthritis Rheum. 1996;39:648–56.
10. McAlindon TE, Biggee BA. Nutritional factors and osteoarthritis: recent developments. Curr Opin Rheumatol. 2005;17:647–52.
11. Ameye LG, Chee WS. Osteoarthritis and nutrition. From nutraceuticals to functional foods: a systematic review of the scientific evidence. Arthritis Res Ther. 2006;8:R127.
12. Neogi T, Booth SL, Zhang YQ, Jacques PF, Terkeltaub R, Aliabadi P, et al. Low vitamin K status is associated with osteoarthritis in the hand and knee. Arthritis Rheum. 2006;54:1255–61.
13. Felson DT, Niu J, Clancy M, Aliabadi P, Sack B, Guermazi A, et al. Low levels of vitamin D and worsening of knee osteoarthritis: results of two longitudinal studies. Arthritis Rheum. 2007;56:129–36.
14. Oka H, Akune T, Muraki S, En-yo Y, Yoshida M, Saika A, et al. Low dietary vitamin K intake is associated with radiographic knee osteoarthritis in the Japanese elderly: dietary survey in a population-based cohort of the ROAD study. J Orthop Sci. 2009;14:687–92.
15. Peregoy J, Wilder FV. The effects of vitamin C supplementation on incident and progressive knee osteoarthritis: a longitudinal study. Pub Health Nutr. 2010;14:709–15.
16. Kellgren JH, Lawrence JS. The epidemiology of chronic rheumatism: atlas of standard radiographs of arthritis. Oxford: Blackwell Scientific; 1963.
17. Yoshimura N, Muraki S, Oka H, Kawaguchi H, Nakamura K, Akune T. Cohort profile: Research on Osteoarthritis/osteoporosis Against Disability (ROAD) Study. Int J Epidemiol. 2010;39:988–95.
18. Shimada H, Lord SR, Yoshida H, Kim H, Suzuki T. Predictors of cessation of regular leisure-time physical activity in community-dwelling elderly people. Gerontology. 2007;53:293–7.
19. Altman RD, Gold GE. Atlas of individual radiographic features in osteoarthritis, revised. Osteoarthr Cartil. 2007;15 Suppl A:A1–56.
20. Sasaki S, Yanagibori R, Amano K. Self-administered diet history questionnaire developed for health education: a relative validation of the test-version by comparison with 3-day diet record in women. J Epidemiol. 1998;8:203–15.
21. Murakami K, Mizoue T, Sasaki S, Ohta M, Sato M, Matsushita Y, et al. Dietary intake of folate, other B vitamins, and omega-3 polyunsaturated fatty acids in relation to depressive symptoms in Japanese adults. Nutrition. 2008;24:140–7.
22. Oka H, Muraki S, Akune T, Mabuchi A, Suzuki T, Yoshida H, et al. Fully automatic quantification of knee osteoarthritis severity on plain radiographs. Osteoarthr Cartil. 2008;16:1300–6.
23. Muraki S, Oka H, Akune T, En-yo Y, Yoshida M, Nakamura K, et al. Association of occupational activity with joint space narrowing and osteophytosis in the medial compartment of the knee: the ROAD study. Osteoarthr Cartil. 2011;19:840–6.
24. Muraki S, Oka H, Akune T, En-yo Y, Yoshida M, Suzuki T, et al. Independent association of joint space narrowing and osteophyte formation at the knee with health-related quality of life in Japan: a cross-sectional study. Arthritis Rheum. 2011;63:3859–64.
25. Oka H, Muraki S, Akune T, Nakamura K, Kawaguchi H, Yoshimura N. Normal and threshold values of joint space width, joint space area, osteophyte area and fibro-tibial angle using a computer-assisted measuring system (KOACAD) to evaluate knee osteoarthritis: the ROAD study. J Orthop Sci. 2010;15:781–9.
26. Muraki S, Oka H, Akune T, En-yo Y, Yoshida M, Suzuki T, et al. Independent association of joint space narrowing and osteophyte formation at the knee with health-related quality of life in Japan: a cross-sectional study. Arthritis Rheum. 2011;63:3859–64.
27. Yamada T, Kawano H, Koshizuka Y, Fukuda T, Yoshimura K, Kamekura S, et al. Carminerin contributes to chondrocyte calcification during endochondral ossification. Nat Med. 2006;12:665–70.
28. Kamekura S, Kawasaki Y, Hoshi K, Shimoaka T, Chikuda H, Maruyama Z, et al. Contribution of runt-related transcription factor 2 to the pathogenesis of osteoarthritis in mice after induction of knee joint instability. Arthritis Rheum. 2006;54:2462–70.
29. Kaneki M, Hodges SJ, Hosoi T, Fujiwara S, Lyons A, Crean SJ, et al. Japanese fermented soybean food as the major determinant of the large geographic difference in circulating levels of vitamin K2: possible implications for hip-fracture risk. Nutrition. 2001;17:315–21.
30. Furie B, Bouchard BA, Furie BC. Vitamin K-dependent biosynthesis of gamma-carboxyglutamic acid. Blood. 1999;93:1798–808.
31. Schneider C, King RM, Philipson L. Genes specifically expressed at growth arrest of mammalian cells. Cell. 1988;54:787–93.
32. Loeser RF, Varnum BC, Carlson CS, Goldring MB, Liu ET, Sadiev S, et al. Human chondrocyte expression of growth-arrest-specific gene 6 and the tyrosine kinase receptor axl: potential role in autocrine signaling in cartilage. Arthritis Rheum. 1997;40:1455–65.
33. Hafizi S, Dahlbäck B. Gas6 and protein S. Vitamin K-dependent ligands for the Axl receptor tyrosine kinase subfamily. FEBS J. 2006;273:5231–44.

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34. Luo G, D'Souza R, Hogue D, Karsenty G. The matrix Gla protein gene is a marker of the chondrogenesis cell lineage during mouse development. J Bone Miner Res. 1995;10:325–34.
35. Munroe PB, Olgunturk RO, Fryns JP, Van Maldergem L, Ziereisen F, Yuksel B, et al. Mutations in the gene encoding the human matrix Gla protein cause Keutel syndrome. Nat Genet. 1999;21:142–4.
36. Luo G, Ducy P, McKee MD, Pinero GJ, Loyer E, Behringer RR, et al. Spontaneous calcification of arteries and cartilage in mice lacking matrix GLA protein. Nature. 1997;386:78–81.
37. Pauli RM, Lian JB, Mosher DF, Suttie JW. Association of congenital deficiency of multiple vitamin K-dependent coagulation factors and the phenotype of the warfarin embryopathy: clues to the mechanism of teratogenicity of coumarin derivatives. Am J Hum Genet. 1987;41:566–83.
38. Howe AM, Lipson AH, de Silva M, Ouvrier R, Webster WS. Severe cervical dysplasia and nasal cartilage calcification following prenatal warfarin exposure. Am J Med Genet. 1997;71:391–6.
39. Felson D, Zhang Y. An update on the epidemiology of knee and hip osteoarthritis with a view to prevention. Arthritis Rheum. 1998;41:1343–55.
40. Canter PH, Wider B, Ernst E. The antioxidant vitamins A, C, E and selenium in the treatment of arthritis: a systematic review of randomized clinical trials. Rheumatology. 2007;46:1223–33.
41. Kurz B, Jost B, Schünke M. Dietary vitamins and selenium diminish the development of mechanically induced osteoarthritis and increase the expression of antioxidative enzymes in the knee joint of STR/1N mice. Osteoarthr Cartil. 2002;10:119–26.
42. Sowers M, Lachance L. Vitamins and arthritis—the roles of vitamins A, C, D, and E. Rheum Dis Clin North Am. 1999;25:315–32.
43. Selhub J, Jacques PF, Wilson PW, Rush D, Rosenberg IH. Vitamin status and intake as primary determinants of homocysteinemia in an elderly population. JAMA. 1993;270:2693–8.
44. Kang AH, Trelstad RL. A collagen defect in homocystinuria. J Clin Invest. 1973;52:2571–8.
45. Khan M, Yamauchi M, Srisawasdi S, Stiner D, Doty S, Paschalis EP, et al. Homocysteine decreases chondrocyte-mediated matrix mineralization in differentiating chick limb-bud mesenchymal cell micro-mass cultures. Bone. 2001;28:387–98.
46. Lubec B, Fang-Kircher S, Lubec T, Blom HJ, Boers GH. Evidence for McKusick's hypothesis of deficient collagen cross-linking in patients with homocystinuria. Biochim Biophys Acta. 1996;1315: 159–62.
47. Sinaki M, Nwaogwugwu NC, Phillips BE, Mokri MP. Effect of gender, age, and anthropometry on axial and appendicular muscle strength. Am J Phys Med Rehabil. 2001;80:330–8.
48. McAlindon TE, Cooper C, Kirwan JR, Dieppe PA. Determinants of disability in osteoarthritis of the knee. Ann Rheum Dis. 1993;52: 258–62.
49. O'Reilly SC, Jones A, Muir KR, Doherty M. Quadriceps weakness in knee osteoarthritis: the effect on pain and disability. Ann Rheum Dis. 1998;57:588–94.
50. Felson DT, Gale DR, Elon Gale M, Niu J, Hunter DJ, Goggins J, et al. Osteophytes and progression of knee osteoarthritis. Rheumatology (Oxford). 2005;44:100–4.

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A Meta-Analysis of the Association of Fracture Risk and Body Mass Index in Women

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ABSTRACT

Several recent studies suggest that obesity may be a risk factor for fracture. The aim of this study was to investigate the association between body mass index (BMI) and future fracture risk at different skeletal sites. In prospective cohorts from more than 25 countries, baseline data on BMI were available in 398,610 women with an average age of 63 (range, 20–105) years and follow up of 2.2 million person-years during which 30,280 osteoporotic fractures (6457 hip fractures) occurred. Femoral neck BMD was measured in 108,267 of these women. Obesity (BMI $\geq$ 30 kg/m^2) was present in 22%. A majority of osteoporotic fractures (81%) and hip fractures (87%) arose in non-obese women. Compared to a BMI of 25 kg/m^2, the hazard ratio (HR) for osteoporotic fracture at a BMI of 35 kg/m^2 was 0.87 (95% confidence interval [CI], 0.85–0.90). When adjusted for bone mineral density (BMD), however, the same comparison showed that the HR for osteoporotic fracture was increased (HR, 1.16; 95% CI, 1.09–1.23). Low BMI is a risk factor for hip and all osteoporotic

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fracture, but is a protective factor for lower leg fracture, whereas high BMI is a risk factor for upper arm (humerus and elbow) fracture. When adjusted for BMD, low BMI remained a risk factor for hip fracture but was protective for osteoporotic fracture, tibia and fibula fracture, distal forearm fracture, and upper arm fracture. When adjusted for BMD, high BMI remained a risk factor for upper arm fracture but was also a risk factor for all osteoporotic fractures. The association between BMI and fracture risk is complex, differs across skeletal sites, and is modified by the interaction between BMI and BMD. At a population level, high BMI remains a protective factor for most sites of fragility fracture. The contribution of increasing population rates of obesity to apparent decreases in fracture rates should be explored. © 2014 American Society for Bone and Mineral Research.

KEY WORDS: BMI; FRACTURE RISK; POPULATION STUDIES; POISSON REGRESSION MODEL; WOMEN; OBESITY

Introduction

Fractures are an important cause of morbidity in the population, especially in women. Hip fractures in particular are a major cause of pain, loss of function, and increased mortality, and are associated with very high costs to society.[1–3] Because fracture incidence increases with age, the burden from fracture is predicted to increase in the future due to an increase in the elderly population.[3–5]

In addition to low bone mineral density (BMD), many risk factors for fragility fractures have been identified.[2,6,7] Strong risk factors include a prior fragility fracture, a family history of fracture, exposure to glucocorticoids, and low body mass index (BMI).[8–11] Low BMI has been considered a risk factor for fracture, and obesity has been considered a protective factor for fracture,[11–13] but this association has recently been challenged.[14,15] Compston and colleagues[15] reported that obesity was not protective against fracture in postmenopausal women and, indeed, was associated with an increased risk of ankle and upper leg fractures. Similarly, Prieto-Alhambra and colleagues[16] concluded that obesity, though protective against hip and pelvis fracture, was associated with an increase in risk for proximal humerus fractures. In a recent review, Nielson and colleagues[17] stated that the importance of fractures occurring in the overweight and obese elderly may have been lost in the message that being underweight increases the risk of fracture.

The aim of this study was to investigate the association between BMI and future fracture risk at different skeletal sites in 25 international prospective cohorts comprising almost 400,000 women.

Subjects and Methods

Cohorts studied

We used baseline and follow-up data from 25 prospective cohorts, the majority of which were population based (20/25). Details of each of the cohorts are published elsewhere, but are summarized briefly below and in Tables 1, 2, and 3.

The Adult Health Study (AHS) at the Radiation Effects Research Foundation was established in 1958 to document the late health effects of radiation exposure among atomic bomb survivors in Hiroshima and Nagasaki, Japan. The original AHS cohort consisted of about 15,000 atomic bomb survivors and 5000 controls selected from residents in Hiroshima and Nagasaki using the 1950 national census supplementary schedules and the Atomic Bomb Survivors Survey. AHS subjects have been followed through biennial medical examinations since 1958.[18,19] In the Aberdeen Prospective Osteoporosis Screening Study from the UK (APOSS),[20] women were randomly selected from a community-based register and invited to participate in a population-based screening program for osteoporotic fracture risk. The Canadian Multicentre Osteoporosis study (CaMos) is an ongoing prospective age-stratified cohort of men and women ages 25 to 80+ randomly selected from regional residential telephone listings. The sampling frame was a 50-km radius around nine study centers in seven provinces, and participants are representative of 41% of the population of Canada.[21] The Dubbo Osteoporosis Epidemiology Study (DOES) is a population-based study from Dubbo, Australia.[22] The Ecografía Osea en Atención Primaria (ECOSAP) study was a referral population recruited in 58 primary care center throughout Spain, regardless of the reason for consultation.[23] The Norfolk cohort of the European Prospective Investigation into Cancer (EPIC-Norfolk) comprises men and women aged 40 to 79 years who were resident in Norfolk, UK, at the time of recruitment and were recruited from general practice listings.[24] The Epidemiologie de l'osteoporose (EPIDOS) study comprises a population-based cohort from five French centers (Amiens, Lyon, Montpellier, Paris, and Toulouse)[25]: women were recruited through mailings using large population-based listings such as voter registration rolls. The European Vertebral Osteoporosis Study (EVOS) comprised age- and sex-stratified random samples from 36 centers in 19 European countries.[26] Equal numbers of men and women were drawn in each center within six 5-year age bands (50–74 and 75+ years). BMD was measured in 13 centers. This sample provided the framework for the European Prospective Osteoporosis Study (EPOS), in which repeated assessment was undertaken in 29 of the centers.[27,28] The Gothenburg I subjects were drawn randomly from the population register in Gothenburg, Sweden, by the date of birth to provide cohorts aged 70, 76, 79, and 85 years at the time of investigation.[29] The Gothenburg II study comprised a randomly drawn population that attended for mammography screening.[30] The Geelong Osteoporosis Study (GOS) is an age-stratified sample of women drawn randomly from the electoral roll of Geelong and surrounding districts in south eastern Australia.[31] The Manitoba cohort is a referral population of all women attending for BMD measurements in the Province of Manitoba, Canada, where health services are provided to residents through a single public healthcare system.[32] The Miyama study is a population-based cohort drawn from inhabitants born in Miyama, Japan, between 1910 and 1949.[33] Of 1543 inhabitants, an age-stratified sample of 400 men and women was drawn by birth decade. The MsOS study is a cohort study on osteoporosis in a convenience sample of ambulant Asian women recruited from the community in Hong Kong.[34] The Os des Femmes de Lyon (OFELY) cohort comprised an age-stratified female cohort randomly selected from the regional section of a large health insurance company (Mutuelle Generale d'Education Nationale, Lyon, France).[35] The Osteoporosis and Ultrasound Study (OPUS) comprises five age-stratified population-based female cohorts drawn from different European centers (Sheffield and Aberdeen in the UK; Berlin and Kiel in Germany; and Paris in France).[36] The Kuopio osteoporosis

Table 1. Cohorts Studied

Cohort	Year for baseline	Bone densitometry	Fracture report
AHS	1958 (BMD: 1994)	DXA FN, Hologic QDR 2000	Spinal radiographs and self-report
APOSS	1990–1994	DXA left FN, Norland (Cooper Surgical)	Self-report, computer reports from radiologists, hospital record, primary care physicians' record
CaMos	1996–1997	DXA FN, Hologic QDR and Lunar DPX Alpha phantom-calibrated across centers and machines	Self-report. Radiographic or medical report verification of incident fractures was obtained when information was available.
DOES	1989	DXA FN, GE-Lunar, DPX and Prodigy	Radiologists' report
ECOSAP[a]	2000–2001	QUS right calcaneus, Sahara (Hologic)	Self-report, confirmed by investigator by X-ray or radiological or surgical reports
EPIC-Norfolk[b]	1997–2000	–	Hospital record linkage
EPIDOS	1992–1993	DXA FN, Lunar DPX	Self-report, family, or physician
EVOS/EPOS	1989	DXA FN, cross-calibrated using European Spine Phantom	Self-reported fractures were confirmed where possible by radiograph, attending physicians or subject interview
GBG I	1985–1993	Dual photon absorptiometry right heel	Radiology departments servicing the region
GBG II[a]	1992–1997	Distal forearm, Osteometer DTX-200	Radiology departments servicing the region
GOS	1994–1997	DXA FN, Lunar DPX-L	Radiographically confirmed from hospital records
Manitoba[a]	1990–2007	DXA FN, Lunar DPX or Lunar prodigy	Ascertained using ICD codes, where two or more hospitals or physicians ICD fracture codes had to be present to confirm a fracture. Site-specific orthopedic intervention codes for hip and forearm fractures.
Miyama	1989–1990	DXA FN, Lunar DPX	Self-report, confirmed by X-ray
MsOs HK[a]	2001	DXA FN, Hologic QDR-4, 500-W	Self-report, confirmed by X-ray or medical record
OFELY	1992–1993	DXA FN, Hologic QDR 2000	Radiography, X-rays, surgical reports
OPUS	1999–2001	DXA FN, Hologic QDR 4500 or Lunar Expert	Spinal radiograph; verification of non-vertebral incident fractures when information was available.
OSTPRE	1989	DXA FN, Lunar DPX	Self-report
PERF	1977–1997	DXA FN, Hologic QDR-2000	Spinal radiographs and self-report
Rochester	1980	DXA FN, Hologic QDR 2000 and dual-photon absorptiometry cross-calibrated to DXA	Self-report combined with review of the in-patient and outpatient medical records of all local care providers
Rotterdam	1990–1993	DXA FN, Lunar DPX-L	Automatic link with general practitioner computer systems and hospital admission data. Validated by two independent research physicians.
SEMOF	1997–1999	DXA FN, Hologic QDR 4500	Questionnaire and confirmed from medical records
Sheffield	1993–1999	DXA FN, Hologic QDR 4500	Self-report at home visits
SOF[a]	1986–1988 (BMD: 1990–1991)	DXA FN, Hologic QDR 1000	Telephone or correspondence and confirmed from X-ray reports
THIN	1995–2004	–	General practitioners' records

(*Continued*)

Table 1. *(Continued)*

Cohort	Year for baseline	Bone densitometry	Fracture report
WHI[a]	1990	DXA FN, Hologic 2000	Hip fractures by medical records and adjudicated at a central facility. Other fractures were adjudicated locally (clinical trials) and by self report (observational study for patients without BMD).

AHS = Adult Health Study; BMD = bone mineral density; DXA = dual-energy X-ray absorptiometry; FN = femoral neck; QDR = quantitative digital radiography; APOSS = Aberdeen Prospective Osteoporosis Screening Study; CaMos = Canadian Multicentre Osteoporosis study; DOES = Dubbo Osteoporosis Epidemiology Study; ECOSAP = Ecografía Osea en Atención Primaria; QUS = quantitative ultrasound; EPIC-Norfolk = Norfolk cohort of the European Prospective Investigation into Cancer; EPIDOS = Epidemiologie de l'osteoporose; EVOS = European Vertebral Osteoporosis Study; EPOS = European Prospective Osteoporosis Study; GBG I = Gothenburg I; GBG II = Gothenburg II; GOS = Geelong Osteoporosis Study; Manitoba = Province of Manitoba, Canada; ICD = International Classification of Diseases; Miyama = Miyama, Japan; MsOs HK = osteoporosis in Asian women in Hong Kong; OFELY = Os des Femmes de Lyon; OPUS = Osteoporosis and Ultrasound Study; OSTPRE = osteoporosis risk factor and prevention, Kuopio, Finland; PERF = Prospective Epidemiological Risk Factors; Rochester = two random population samples of women, Minnesota, USA; Rotterdam = ongoing study in Ommoord district, Rotterdam, the Netherlands; SEMOF = Swiss Evaluation of the Methods of Measurement of Osteoporotic Fracture Risk; Sheffield = women ≥75 in Sheffield, UK; THIN = The Health Improvement Network; WHI = Women's Health Initiative.

[a]Denotes that the cohort was not population-based.

[b]EPIC Norfolk collected QUS data on approximately 15,000 men and women between 1997 and 2000; fractures were ascertained by hospital record linkage.

risk factor and prevention (OSTPRE) study in Finland comprised a postal inquiry sent to all 14,220 women who were residents of Kuopio province.[37] The Prospective Epidemiological Risk Factors (PERF) study was a population-based cohort in Copenhagen, Denmark.[38] The survey invited women to participate in screening for various placebo-controlled clinical trials and epidemiological studies in Copenhagen. The Rochester cohort was recruited from two random population samples of women from Minnesota, USA, stratified by decade of age.[39,40] The Rotterdam Study is an ongoing prospective cohort study that aimed to examine and follow all residents aged 55 years and older living in Ommoord, a district of Rotterdam, the Netherlands.[41–43] The Swiss Evaluation of the Methods of Measurement of Osteoporotic Fracture Risk (SEMOF) study is a prospective multicenter study (10 centers in Switzerland).[44] Women were randomly selected from an address register. The Sheffield cohort comprised women aged 75 years or more selected randomly from the population of Sheffield, UK, and surrounding districts, identified from general practitioner listings. The women willing to participate and meeting inclusion criteria were randomly allocated to treatment with placebo or the bisphosphonate, clodronate, to study its effects on fracture risk. The subjects for this study comprised 2171 women allocated to treatment with placebo only.[45,46] The Study of Osteoporotic Fractures (SOF) is a multicenter cohort study of risk factors for osteoporosis and fracture.[47] Participants were ambulatory white women selected by convenience and recruited at four clinical centers from the United States (Baltimore, MD; Minneapolis, MN; Pittsburgh, PA; and Portland, OR, USA). The Health Improvement Network (THIN) research database was derived from computerized records of a sample of general practitioners in the UK, similar to the General Practice Research Database.[48] The study population comprised all women aged 50 years or more. The Women's Health Initiative (WHI) study comprises three overlapping randomized controlled studies and an observational study in a convenience sample of postmenopausal women.[49,50] The trials comprised dietary modification (low-fat diet) ($n = 48{,}836$), hormone replacement therapy (HRT) in women with or without a uterus ($n = 27{,}347$), and supplementation with calcium and vitamin D ($n = 36{,}282$). The total sample size was 161,808. For this analysis women taking bone active medication (HRT, bisphosphonates, and calcitonin) were excluded, leaving a sample size of 81,377.

Measurements

Height and weight were measured using standard techniques in all cohorts. BMI was calculated as weight in kilograms divided by height squared in meters and used as a continuous variable or categorized according to the WHO criteria[51]: underweight (BMI < 18.5 kg/m^2); normal (18.5–24.9 kg/m^2); overweight (25.0–29.9 kg/m^2); obese I (30.0–34.9 kg/m^2); and obese II (≥35.0 kg/m^2). BMD was assessed in 27% of the women using several different techniques summarized in Table 1 and converted to standardized cohort-specific *Z*-scores. The proportion of women with BMD measurement varied by cohorts from 0% to 100% (Table 2).

For fracture outcomes, we used information on fractures only at sites considered to be associated with osteoporosis[52]; ie, fractures of the spine, coccyx, ribs, pelvis, humerus, forearm, elbow, hip, other femoral, tibia and fibula, clavicle, scapula, and sternum. Fractures of the skull, face, hands and fingers, feet and toes, ankle, and patella were excluded. In addition to "osteoporotic fractures," incident hip, distal forearm, lower leg (tibia and/or fibula), and upper arm (humerus and/or elbow) were considered separately.

Statistical methods

Correlation tests between BMI and other variables used nonparametric Pitman's permutation test; Pearson correlation coefficients were also calculated.

The association between BMI and the risk of fracture was examined using an extension of the Poisson regression model[53] in each cohort. The observation period of each participant was divided in intervals of 1 month. The first fracture per person was counted for each relevant outcome. Covariates included current age and time since start of follow-up, and analyses were performed with and without adjustment for BMD. Interactions between BMD and BMI were also studied. The β-coefficients from each cohort were weighted according to the variance, and then

Table 2. Details of Cohorts Studied

Cohort[a]	Subjects (*n*)	Length of follow-up (years), mean (maximum)	Age (years), mean (range)	BMI (kg/m^2) mean (SD)	BMD (*n*)[b]
AHS	1,810	3.8 (6.8)	66 (47–95)	23.1 (3.6)	1,797
APOSS	5,110	7.0 (12.3)	48 (44–56)	25.5 (4.6)	5,102
CaMos	6,315	6.0 (8.6)	63 (25–103)	26.9 (5.2)	5,719
DOES	1,270	7.8 (13.6)	71 (57–94)	25.4 (4.6)	1,259
ECOSAP	5,128	2.9 (4.5)	72 (65-100)	29.2 (4.7)	–
EPIC-Norfolk	8,856	5.4 (6.9)	62 (42–81)	26.6 (4.4)	–
EPIDOS	7,593	3.4 (5.0)	80 (70-100)	25.4 (4.2)	7,560
EVOS/EPOS	9,013	3.0 (5.9)	64 (41–93)	27.2 (4.6)	2,761
GBG I	1,158	7.9 (16.3)	79 (69–85)	25.3 (4.2)	947
GBG II	7,065	12.4 (16.2)	59 (21–89)	24.6 (3.6)	7,056
GOS	1,863	6.3 (10.9)	63 (35–95)	26.8 (5.3)	1,805
Manitoba	43,860	5.3 (18.4)	62 (40–102)	26.6 (5.4)	43,186
Miyama	400	8.6 (13.0)	59 (40–79)	22.1 (2.8)	400
MsOs HK	2,000	3.5 (5.3)	73 (65–98)	23.9 (3.5)	2,000
OFELY	668	10.9 (14.2)	62 (50–89)	24.0 (3.5)	663
OPUS	2,881	6.0 (8.2)	61 (20–81)	26.3 (4.6)	2,836
OSTPRE	3,058	10.0 (10.0)	52 (47–57)	26.1 (4.3)	1,743
PERF	5,433	7.2 (24.0)	63 (44–81)	25.5 (3.9)	2,305
Rochester	655	8.1 (19.0)	58 (21–94)	25.5 (4.9)	650
Rotterdam	4,068	5.9 (9.4)	70 (55–99)	26.7 (4.1)	3,325
SEMOF	7,062	2.8 (4.9)	75 (70–91)	25.9 (4.3)	908
Sheffield	2,170	3.8 (5.8)	80 (74–96)	26.7 (4.5)	2,150
SOF	9,704	11.9 (20.6)	72 (65–99)	26.4 (4.6)	7,963
THIN	180,093	4.7 (13.9)	60 (50–105)	26.0 (5.1)	–
WHI	81,377	7.4 (11.2)	64 (49–79)	28.6 (6.2)	6,132
Totals	398,610	5.7 (24.0)	63 (20–105)	26.6 (5.4)	108,267

BMI = body mass index; BMD = bone mineral density.

[a]The cohort abbreviations are defined in detail in the Cohorts studied section of Subjects and Methods, and are defined in brief in the footnotes for Table 1.

[b]Subjects with BMD data available.

merged to determine the weighted mean of the coefficient and its SD. The associations between BMI and risk of fracture were described as the hazard ratio (HR) for fracture per 1-unit change in BMI together with 95% confidence intervals (CIs).

Heterogeneity between cohorts was tested by means of the I^2 statistic.[54] Heterogeneity was found for the osteoporotic fracture outcome ($I^2 = 75\%$; 95% CI, 63% to 83%) and the hip fracture outcome ($I^2 = 86\%$; 95% CI, 81% to 90%). When the interaction between BMI and current age was included, there was no significant heterogeneity between cohorts for BMI ($I^2 = 14\%$; 95% CI, 0% to 48%) for the outcome of osteoporotic fracture. For the outcome of hip fracture there was a moderate heterogeneity between cohorts for BMI ($I^2 = 61\%$; 95% CI, 39% to 75%). Because we had a moderate heterogeneity for the outcome of hip fracture even when including an interaction with age, we performed both a fixed and a random effect model when merging the result from the different cohorts. Overall the weighted β-coefficient describing the association between BMI and the outcome of osteoporotic fracture was −0.0215 when using a fixed-effect model and −0.0210 when using a random effect model (with a SD describing the variance between cohorts of 0.013), resulting in the same HR per 1-unit of 0.98. When describing the association between BMI and the outcome of hip fracture the β-coefficient was −0.0740 when using a fixed-effect model and −0.0719 when using a random effect model (with a SD of 0.014) resulting in the same HR per 1-unit of 0.93. Because the estimates were so similar, we used the fixed-effect model to present the results.

In order to study the association between BMI and fracture risk in more detail, a spline Poisson regression model was fitted using cohort specific knots at the 10th, 50th, and 90th percentiles of BMI, as recommended by Harrell.[55] The splines were second order functions between the breakpoints and linear functions at the tails, resulting in a smooth curve. When the comparisons between two points at the curve was done, a piecewise linear model with knot at BMI = 25 kg/m^2 were used to study the relationship between BMI and the risk of fracture.

In sensitivity analyses, we repeated the calculations (1) in those cohorts that were population-based (see Table 1); (2) in cohorts without excluding women that received treatments for osteoporosis; and (3) using a random-effect rather than a fixed-effect model.

Results

The cohorts comprised 398,610 women aged 20 to 105 years with an average age of 63 years, who were followed for approximately 2.26 million person-years (Tables 2 and 3). During an average follow-up of 5.7 years 30,280 osteoporotic fractures were documented, of which 6457 were at the hip (Table 3). The mean BMI was 26.6 kg/m^2 and approximately one-half of the