ORIGINAL ARTICLE

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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

Table 3. Details of Incident Fractures by Cohort

Cohort[a]	Person-years	Incident fracture				
		Osteoporotic	Hip	Distal forearm	Tibia/fibula	Humerus/elbow
AHS	6,928	78	25	32	–	14
APOSS	34,588	236	7	113	–	47
CaMos	38,016	618	90	220	18	109
DOES	9,892	339	94	100	25	48
ECOSAP	14,811	282	52	108	–	49
EPIC-Norfolk	47,973	172	82	73	–	–
EPIDOS	25,714	1,056	311	312	–	237
EVOS/EPOS	20,945	520	30	153	36	43
GBG I	9,191	255	198	–	–	–
GBG II	87,577	887	116	443	31	98
GOS	7,315	143	32	34	9	15
Manitoba	232,076	2,855	536	1,070	–	770
Miyama	3,423	51	7	11	1	5
MsOs HK	6,975	96	21	43	–	8
OFELY	7,290	132	20	50	1	17
OPUS	12,019	113	13	68	–	28
OSTPRE	30,568	259	8	192	–	24
PERF	38,991	561	58	353	–	78
Rochester	5,318	219	42	39	16	20
Rotterdam	23,977	550	156	221	37	84
SEMOF	19,639	534	80	184	20	104
Sheffield	8,235	292	91	106	14	37
SOF	115,810	3,211	1,269	967	159	735
THIN	852,566	8,343	1,953	–	–	–
WHI	596,434	8,478	1,166	3,318	1,553	1,385
Totals	2,256,271	30,280	6,457	8,210	1,920	3,955
Age at fracture (years), mean (SD)		72.7 (10.4)	79.5 (8.8)	71.0 (9.6)	69.6 (8.5)	73.6 (9.7)

– = site of fracture not given.

[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.

women were overweight or obese (56%), with 22.1% being obese (Table 4). Approximately 7700 women (1.9%) were underweight. There was a weak but significant negative correlation between age and BMI ($p < 0.001$; $r = -0.01$; 95% CI, −0.01 to −0.01). For example, in women aged 55 to 59 years, 1.3% of women were underweight and the proportion increased progressively with age, so that 5.8% of women aged 85 to 89 years were underweight. Conversely, the prevalence of obesity decreased with age from 25.3% in the age group 55 to 59 years to 10.9% between the ages of 85 and 89 years. There was a significant positive correlation between BMI and BMD ($p < 0.001$; $r = 0.33$; 95% CI, 0.32–0.33). In underweight women, the mean BMD femoral neck *Z*-score was −0.89 and for the obese II category it was 0.67 (Table 4).

BMI and risk of fracture

A total of 30,280 osteoporotic fractures were reported during follow-up (Table 3). A minority (19%) of all osteoporotic fractures occurred in obese women (Table 5) and the observed number was lower than expected (5798 versus 6691, respectively) if BMI was assumed to exert no influence on fracture risk. Thus obesity was a protective factor for osteoporotic fractures as a whole. Similar results were found when hip fracture or distal forearm

Table 4. Baseline Characteristics by BMI Category

	Underweight (BMI <18.5)	Normal (BMI 18.5–24.9)	Overweight (BMI 25.0–29.9)	Obese I (BMI 30.0–34.9)	Obese II (BMI ≥35.0)
Subjects (*n*)	7,699	166,087	136,873	58,919	29,032
Age (years)	65.7 (14.0)	62.2 (11.6)	63.6 (10.7)	63.2 (10.1)	61.2 (9.3)
BMI (kg/m^2)	17.2 (1.3)	22.5 (1.6)	27.2 (1.4)	32.0 (1.4)	39.3 (4.5)
Femoral neck BMD (*Z*-score)	−0.89 (0.97)	−0.25 (0.93)	0.12 (0.94)	0.41 (0.96)	0.67 (1.0)
Subjects with BMD values (*n*)	2,309	46,796	37,741	15,051	6,370

Values are mean (SD).

BMI = body mass index (kg/m^2); BMD = bone mineral density.

Table 5. Number of Fractures According to Fracture Outcome and Category of Baseline BMI

	BMI categories[a]					Obese versus non-obese		
Fracture outcome	Underweight (1.9%)	Normal (41.7%)	Overweight (34.3%)	Obese I (14.8%)	Obese II (7.3%)	HR	95% CI	*p*
Osteoporotic	806 (575)	13,293 (12,627)	10,383 (10,386)	4119 (4481)	1679 (2210)	0.85	0.82–0.88	<0.001
Hip	320 (123)	3257 (2693)	2062 (2215)	628 (956)	190 (471)	0.63	0.59–0.68	<0.001
Distal forearm	126 (150)	3424 (3424)	2990 (2816)	1202 (1215)	468 (599)	0.81	0.76–0.86	<0.001
Tibia/fibula	10 (36)	608 (801)	704 (659)	361 (284)	237 (140)	1.04	0.94–1.14	>0.30
Humerus/elbow	76 (75)	1452 (1649)	1399 (1357)	694 (585)	334 (289)	1.21	1.11–1.31	<0.001

Values are the number of fractures in each BMI category and in parentheses are the expected number of fractures according to the percentage of women in each BMI category.

BMI = body mass index; HR = hazard ratio; CI = confidence interval.

[a]BMI categories (kg/m^2): Underweight, BMI <18.5; Normal, BMI 18.5–24.9; Overweight, BMI 25.0–29.9; Obese I, BMI 30.0–34.9; Obese II, BMI ≥35.0. Percentages are the proportion of women in each BMI category.

fractures were considered individually (Table 5). In contrast, the observed incidence of lower leg fractures was not reduced, and the risk of upper arm fractures was higher than expected in obese women.

When BMI was used as a continuous variable, there was a significant association between BMI and fracture risk ($p < 0.001$). In the case of all osteoporotic fractures, the HR per unit increase of BMI was 0.98 (95% CI, 0.98–0.98) and for hip fracture it was 0.93 (95% CI, 0.92–0.94). The HR was not, however, uniform across BMI; low BMI was associated with a greater risk than would be predicted from a uniform HR and, conversely, a high BMI contributed less to fracture prevention than expected. Thus, when studying the relationship in more detail with spline functions, the function was steeper below a BMI of 25 kg/m^2 than above this value (Fig. 1). When a woman with a BMI of 15 kg/m^2 was compared with a woman with a BMI of 25 kg/m^2 using piecewise linear functions, the HR was 1.5 (95% CI, 1.4–1.6) for osteoporotic fracture and 2.9 (95% CI, 2.6–3.3) for hip fracture (Table 6). By contrast, if a woman with a BMI of 25 kg/m^2 was compared to one with a BMI of 35 kg/m^2, the HR was 0.9 (95% CI: 0.9–0.9) for osteoporotic fracture and 0.7 (95% CI = 0.6–0.8) for hip fracture.

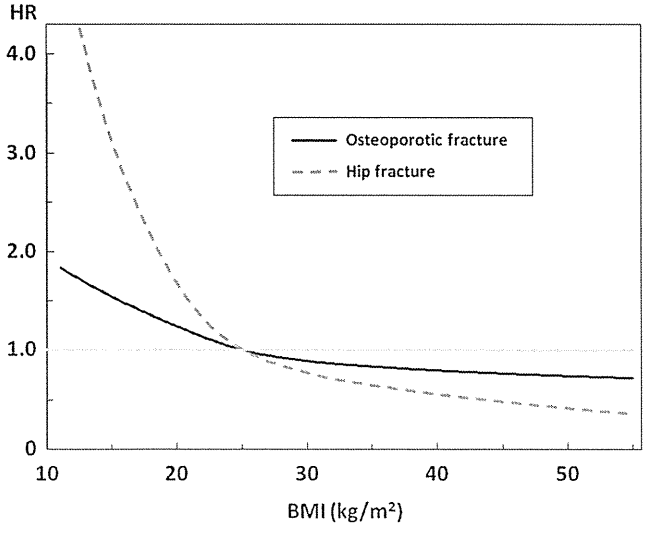

Fig. 1. Relationship between BMI and risk of fracture (HR versus BMI 25 kg/m^2) for osteoporotic fracture (solid line) and hip fracture (dashed line), adjusted for age and time since baseline. BMI = body mass index; HR = hazard ratio.

The use of BMI as a continuous variable also confirmed the different patterns between fracture sites. In the case of upper arm fractures, a BMI of 35 kg/m^2 conferred a significantly higher risk than a BMI of 25 kg/m^2, whereas a BMI of 15 kg/m^2 had a similar risk to that at 25 kg/m^2 (Table 6). The lower BMI was associated with a significant reduction in lower leg fractures, whereas the risk was similar at 25 and 35 kg/m^2 (Table 6).

Adjustment for BMD

When the association between BMI and hip fracture risk was adjusted for BMD, the association was weaker than in the absence of BMD but was still significantly negative. The HR was 0.99 per 1 kg/m^2 increase (95% CI, 0.98–0.99; $p = 0.0014$). When the relationship was examined with spline functions, the relationship was much flatter with BMD adjustment (Fig. 2) than without (Fig. 1). Not withstanding, the risk of hip fracture with low BMI was greater than the protective effect of a high BMI. Thus, a BMI of 15 kg/m^2 had an HR of 1.4 (95% CI, 1.2–1.7) compared to a BMI of 25 kg/m^2 (Table 6), but a BMI of 35 kg/m^2 conferred no greater hip protection than a BMI of 25 kg/m^2 (HR = 1.0; 95% CI, 0.9–1.2).

Interestingly, the association between BMI and osteoporotic fracture risk was weaker but inverted when adjusted for BMD, so that a higher BMI was now associated with a small but significant increase in fracture risk (HR per 1-unit increase in BMI = 1.01; 95% CI, 1.01–1.02; $p < 0.001$). For example, the HR for all osteoporotic fracture was 1.16 (95% CI, 1.09–1.23) when comparing a BMI of 35 kg/m^2 with a BMI of 25 kg/m^2; at a BMI of 15 kg/m^2, the risk was reduced. Thus, for all osteoporotic fractures a higher BMI was, if anything, a modest albeit significant risk factor following adjustment for BMD. A similar pattern was observed for distal forearm fractures. The association of high BMI with increased fracture risk following adjustment for BMD was most marked for upper arm fractures (Table 6). For lower leg fractures, fracture risk was increased and decreased at high and low BMIs, respectively, compared to 25 kg/m^2 (Table 6).

Table 6. HRs for Fracture and 95% CIs Comparing a BMI of 25 kg/m^2 With BMIs of 15 kg/m^2 and 35 kg/m^2, Respectively, According to Different Fracture Outcomes

	Not adjusted for BMD		Adjusted for BMD	
Fracture outcome	BMI 15 versus 25	BMI 35 versus 25	BMI 15 versus 25	BMI 35 versus 25
Osteoporotic	1.54 (1.44–1.64)	0.87 (0.85–0.90)	0.89 (0.80–0.99)	1.16 (1.09–1.23)
Hip	2.88 (2.56–3.25)	0.68 (0.62–0.75)	1.41 (1.16–1.72)	0.99 (0.86–1.15)
Distal forearm	1.05 (0.91–1.20)	0.76 (0.71–0.81)	0.72 (0.60–0.86)	0.97 (0.87–1.07)
Tibia/fibula	0.64 (0.45–0.89)	1.03 (0.94–1.14)	0.34 (0.16–0.74)	1.14 (0.87–1.49)
Humerus/elbow	1.13 (0.92–1.37)	1.18 (1.04–1.27)	0.70 (0.54–0.90)	1.60 (1.42–1.80)

Values are HR (95% CI), adjusted for age and time since baseline.
HR = hazard ratio; CI = confidence interval; BMI = body mass index; BMD = bone mineral density.

Interactions with BMI

There was a significant interaction between age and BMI for osteoporotic fracture ($p < 0.001$). This age interaction was significant both below and above a BMI of 25 kg/m^2 ($p = 0.042$ and $p < 0.001$, respectively). Thus, when BMI was set at 15 kg/m^2 and compared with a BMI of 25 kg/m^2 using piecewise linear functions, the HR was 1.4 at the age of 50 years and 1.7 at the age of 80 years, suggesting that low BMI was a stronger risk factor for osteoporotic fractures in elderly women. The same age-BMI interaction was true for BMI greater than 25 kg/m^2, in that high BMI was a stronger protective factor for elderly women. A significant interaction between age and BMI was seen for hip fracture below a BMI of 25 kg/m^2 ($p < 0.001$), but not for BMI above 25 kg/m^2 ($p = 0.058$). Thus, when BMI, set at 15 kg/m^2, was compared with a BMI of 25 kg/m^2 using piecewise linear functions, the HR was 9.2 at the age of 50 years and 3.1 at the age of 80 years, indicating that low BMI was a stronger risk factor for hip fracture in younger women than in elderly women.

Because there was a significant correlation between BMD and BMI, and BMD affected the relationship between BMI and the risk of fracture, the interaction between BMI and BMD was investigated with both linear and cubic models. No such interactions were found, indicating that the correlation between BMI and fracture risk did not change for different values of BMD. There were also no significant interactions between BMI and time since baseline; ie, the predictive value of BMI did not change with time ($p > 0.20$ for both osteoporotic and hip fracture outcomes).

When women allocated to treatments for osteoporosis in the WHI cohort were included, the results were similar. So, too, were the results when the analysis was confined to population-based cohorts.

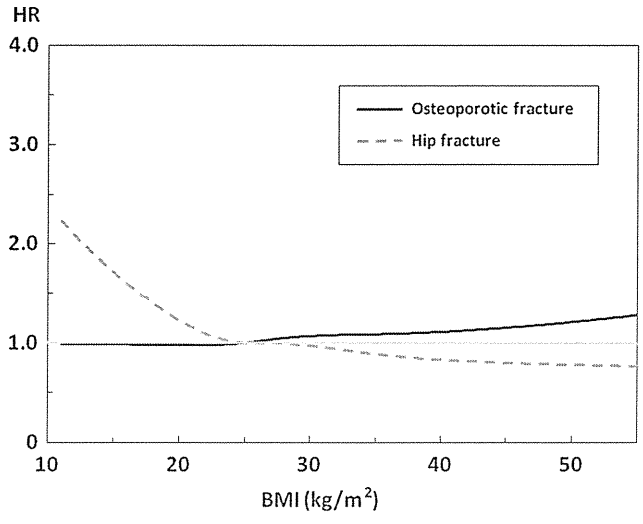

Fig. 2. Relationship between BMI and risk of fracture (HR versus BMI 25 kg/m^2) for osteoporotic fracture (solid line) and hip fracture (dashed line), adjusted for age, time since baseline, and BMD. BMI = body mass index; HR = hazard ratio; BMD = bone mineral density.

Discussion

The principal finding of the present meta-analysis of predominantly prospective population-based cohorts of women is the significant association between BMI at baseline and future osteoporotic fracture, in that a low BMI was a significant risk factor for all osteoporotic fractures, including hip and forearm fractures. These finding are very consistent with an earlier but smaller meta-analysis,[11] though it should be acknowledged that 11% of the women over a shorter time appeared in both meta-analyses. As previously reported in that study, a high BMI was a protective risk factor for osteoporotic fracture, including hip fracture, but a high BMI was weaker as a protective factor than low BMI was as a risk factor. An important conclusion is that obesity itself is not a risk factor for osteoporotic fracture, hip fracture, or forearm fracture. As also seen in the earlier analysis,[11] the association between BMI and fracture risk was dependent on BMD. In the subset of women in whom femoral neck BMD was measured, the association of BMI with hip fracture risk was attenuated and was not evident for all osteoporotic fractures combined. It should be noted that the HRs with and without adjustment for BMD are not strictly comparable; a minority of women (27%) had a BMD test and there was a significant cohort bias in the proportion of women with a BMD test. With this caveat, the results are consistent with the earlier meta-analysis.

Our results also suggest that the association between BMI and risk of future fracture is site-specific. Whereas low BMI was a risk factor for all osteoporotic fractures, a low BMI was a protective factor for lower leg fracture. In this regard, several of the cohorts did not adequately distinguish fractures of the lower leg that are associated with low BMD (eg, proximal tibial fractures) from ankle fractures which are not regarded as being associated with osteoporosis.[52] Exclusion of these cohorts from the analysis still

showed a similar pattern of association of lower leg fractures with BMI (data not shown). In the present study, a high BMI was a significant risk factor for humerus fractures and this persisted after adjustment for BMD. The finding is consistent with a recent short-term (1 year) prospective analysis in 832,775 Spanish women aged 50 years or more visiting general practitioners (SIDIAP),[16] in which a protective effect of obesity was found on future hip fracture and forearm fracture (relative risk [RR] = 0.49; 95% CI, 0.44–0.55, and RR = 0.83; 95% CI, 0.75–0.91, respectively), but obese women were at significantly higher risk of future proximal humeral fracture than the rest of the study population (RR = 1.28; 95% CI, 1.04–1.58). These findings are also consistent with an earlier report that obese women had a higher prevalence of a prior humeral fracture (odds ratio [OR] = 3.48; 95% CI, 0.18–6.68).[56] The reasons for the site-specific association between high BMI and humeral fracture risk are not known, though it may conceivably reflect a different pattern of falling or a greater load upon bones in the upper extremity in falls among the obese population. Moreover, a different padding effect of the soft tissues in different skeletal regions may produce diverse energy dissipation after trauma and, therefore, a different protection of the underlying bone.

Our results are at first sight at variance with the conclusions of Compston and colleagues,[15] who state that that obesity is not protective against fracture in postmenopausal women. That study, however, included a large number of non-adjudicated ankle and tibial fractures. Ankle fractures are not generally regarded as being associated with osteoporosis[51,56] and, as implied above, the accuracy of a self-reported distinction between ankle and other lower leg fractures is questionable. In their report, ankle fractures were significantly more frequent in obese compared with non-obese women. Given that the incidence of forearm, hip, pelvic, upper leg, and spine fractures was higher in underweight women than in obese women, their report is not inconsistent with our findings. Moreover, the present study also found a protective effect of low BMI for future lower leg fracture.

The question arises whether our findings have implications for the Fracture Risk Assessment Tool (FRAX®), which predicts the probability of a hip and a major fracture based on clinical risk factors such as sex, age, BMI, previous fracture, family history, glucocorticoid use, smoking, alcohol use, and secondary osteoporosis.[57] BMI is used as a continuous variable in FRAX, and BMD can be optionally entered into the model. Data from the meta-analysis of De Laet and colleagues[11] were used in the construct of FRAX. The association between BMI and the risk of hip fracture and other osteoporotic fractures in the present study is nearly identical to that described by De Laet and colleagues[11] in the absence of BMD. After adjustment for BMD, the risk of hip fracture associated with low BMI was attenuated in the same way as that described.[11] In the case of osteoporotic fractures, we have shown a slight though significant increase in risk with increasing BMI (see Table 6). This finding is consistent with the earlier meta-analysis, though the increase in risk was not statistically significant because of the smaller sample size. These considerations indicate that modifications of the FRAX algorithm are not warranted based on the present analysis; a view consistent with a recent report from the SOF study that FRAX is of value predicting fractures in obese women, particularly when used with BMD.[58]

The present study has several limitations, some of which we have discussed. These include the limited sampling frame for BMD measurements, inaccuracies in the estimate of BMD in the presence of a high fat mass, and uncertainties in the coding of some fractures. With regard to the first limitation, our results were similar when HRs not adjusted for BMD were calculated in those 27% of women in whom BMD was measured. The different settings of the cohorts are also a limitation, but that would weaken, not strengthen, an association between BMI and fracture. Conversely, the different settings increase the generalizability of our findings. The greatest limitation is that the present analysis is confined to women. Several lines of evidence suggest that the relationship between BMI and fracture risk may differ in men.[11,59]

A limitation in the understanding of possible mechanisms is that we have not been able to examine all potential confounding factors (eg, smoking, previous fracture, alcohol, comorbidities). Of possible relevance is the association of type 2 diabetes with high BMI. In a recent large clinical database in Manitoba, Canada, individuals with diabetes had a BMI approximately 3 kg/m^2 higher than those without diabetes.[60] Of particular interest, diabetes was associated with a 60% increased risk for major osteoporotic fracture when adjusted for clinical risk factors for fracture including BMI and BMD (HR = 1.61; 95% CI, 1.42–1.83). Thus, the higher risk for osteoporotic fracture for obese women (BMI 35 kg/m^2 versus 25 kg/m^2) in this report could be related in part to diabetes. Diabetic status was recorded in the present analysis for only 9% of women. In the women that had information on diabetes, the prevalence of diabetes was 3.4% in women with a normal BMI and 6.7% in obese women (data not shown). The small size of the available sample meant that we were unable to examine the impact of diabetes on the relationship between BMI and future fracture risk in more detail. The age interactions, the result with and without BMD and some of the fracture-specific findings might suggest an important role for low physical function and frailty in explaining these associations; but, as was the case for diabetes, we were unable to examine this further.

With these caveats, we conclude that low BMI remains an important clinical risk factor for hip and all osteoporotic fractures combined and that obesity in women is associated with a significant, albeit modest, reduction in fracture risk. In contrast, obese postmenopausal women appear to be at higher risk for humeral fractures than those with normal BMI. Moreover, after adjustment for BMD there is a slight increase in osteoporotic fracture risk with increasing BMI.

Disclosures

All authors state that they have no conflicts of interest.

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Authors' roles: Study design: HJ, AO, JAK, and EMC. Study conduct: HJ, AO, JAK, and EMC. Data collection: RDC, CC, SRC, ADP, JAE, SF, CCG, DG, DH, KTK, MAK, HK, AZL, EL, WBL, DM, LJM, TWON, JAP, MCZ, FR, JCP, DMR, TvS, and NY. Data analysis: HJ. Data interpretation: HJ, AO, JAK, and EMC. Drafting manuscript: HJ, JAK, and EMC. Revising manuscript content: HJ, AO, JAK, EMC, RDC, CC, SRC, ADP, JAE, SF, CCG, DG, DH, KTK, MAK, HK, AZL, EL, WBL, DM, LJM, TWON, JAP, MCZ, FR, JCP, DMR, TvS, and NY. Approving final version of manuscript: HJ, AO, JAK, EMC, RDC, CC, SRC, ADP, JAE, SF, DG, CCG, DH, KTK, MAK, HK, AZL, EL, WBL, DM, LJM, TWON, JAP, MCZ, FR, JCP, DMR, TvS, and NY. HJ takes responsibility for the integrity of the data analysis.

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Independent Association of Joint Space Narrowing and Osteophyte Formation at the Knee With Health-Related Quality of Life in Japan

A Cross-Sectional Study

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Objective. **To clarify the individual associations of joint space narrowing (JSN) and osteophytosis at the knee with quality of life (QOL) in Japanese men and women using a large-scale population-based cohort from the Research on Osteoarthritis Against Disability (ROAD) study.**

Methods. **The associations of minimum joint space width (JSW) and osteophyte area in the medial compartment of the knee with QOL parameters, such as the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), were examined. Minimum JSW and osteophyte area in the medial compartment of the knee were measured using a computer-aided system for the diagnosis of knee osteoarthritis.**

Results. **Of the 3,040 participants in the ROAD study, the present study included 2,039 participants age 40 years or older who completed the questionnaires (741 men and 1,298 women with a mean ± SD age of 68.6 ± 10.9 years). Multiple regression analysis after adjustment for age and body mass index showed that minimum JSW was significantly associated with scores on the pain domains of the WOMAC in men and women, while osteophyte area was significantly associated with scores on the physical function domains of the WOMAC in men and women.**

Conclusion. **The findings of this cross-sectional study using a large-scale population from the ROAD study indicate that JSN and osteophytosis are independently associated with QOL.**

Knee osteoarthritis (OA) is a major public health issue that causes chronic pain and disability (1–3). The prevalence of radiographic knee OA is high in Japan (4), with 25,300,000 persons age 40 years and older estimated to have radiographic knee OA (5). According to the recent National Livelihood Survey of the Ministry of Health, Labor, and Welfare of Japan, OA is ranked fourth among diseases that cause disabilities that subsequently require support with activities of daily living (6).

Knee OA is characterized by the pathologic features of joint space narrowing (JSN) and osteophytosis, but there is some controversy regarding whether osteophytosis affects knee symptoms or quality of life

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Patents for the Knee Osteoarthritis Computer-Aided Diagnosis (KOACAD) system are held by the University of Tokyo.

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(QOL). Nevertheless, researchers examining the hand and hip have argued that the separate radiographic features should be recorded and may be more meaningful than overall composite scores such as the Kellgren/Lawrence (K/L) scale (7). Furthermore, a previous study showed that osteophytes were well correlated with knee symptoms and performed better as a primary diagnostic feature than JSN in cross-sectional epidemiologic studies of knee OA (8). However, most conventional systems for grading radiographic severity have consisted of categorical grades, such as the K/L scale (9), which is unable to individually assess JSN and osteophytosis. Several studies have shown that knee OA had a strong effect on QOL (10–13), but in those studies, knee OA was defined by categorical grades such as the K/L grade or the American College of Rheumatology grade (14), total knee arthroplasty, and self-questionnaire.

A radiographic atlas of individual features published by the OA Research Society International in 1995 (15) and revised in 2007 (16) allows JSN and osteophyte formation to be evaluated separately. However, the grading is still limited in reproducibility and sensitivity due to the subjective judgment of individual observers and the categorical classification into 4 grades (0–3). To overcome this problem, joint space width (JSW) and osteophyte area should be evaluated using a fully automatic system. To the best of our knowledge, no population-based studies have been conducted to separately measure JSW or osteophyte area in order to clarify the associations of JSN with QOL and of osteophytosis with QOL, despite the fact that the associations between these major features of knee OA and QOL are likely to be different.

Differences between the sexes have also been observed in knee OA. The prevalence of knee OA is higher in women than in men (4), and the association of knee pain with knee OA also differs by sex (4). Thus, the impact of JSN on QOL and of osteophytosis on QOL may also differ between the sexes. However, to the best of our knowledge, no population-based studies have been conducted to assess the associations of JSN and osteophytosis with QOL in men and women separately.

The objective of this study was therefore to separately clarify the association between JSN and QOL and the association between osteophytosis and QOL in Japanese men and women in a large-scale, population-based cohort from the Research on Osteoarthritis Against Disability (ROAD) study. A fully automatic system was used to measure JSW and osteophyte area. QOL was measured using disease-specific scales for knee OA, such as the Western Ontario and McMaster Universities OA Index (WOMAC).

SUBJECTS AND METHODS

Participants. The ROAD study is a nationwide prospective study designed to establish epidemiologic indexes for the evaluation of clinical evidence for the development of a disease-modifying treatment for bone and joint diseases (with OA and osteoporosis as the representative bone and joint diseases). It consists of population-based cohorts in several communities in Japan. The ROAD study has been described in detail previously (4,5,17). To date, we have completed the creation of a baseline database including clinical and genetic information for 3,040 participants (1,061 men and 1,979 women) ranging in age from 23 to 95 years (mean 70.6 years), who were recruited from resident registration listings in 3 communities: an urban region in Itabashi, Tokyo; a mountainous region in Hidakagawa, Wakayama; and a seacoast 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. Height, weight, and body mass index (BMI) (weight [kg]/height [m^2]) were measured. Among the 2,995 participants in the ROAD study who were age 40 years or older, 2,222 (74.2%) completed the WOMAC. The 2,222 participants who completed the WOMAC were younger than those who did not (mean age 68.9 years for those who completed the WOMAC versus 75.9 years for those who did not; $P < 0.0001$). These 2,222 participants were also less likely to be women (63.8% of those who completed the WOMAC versus 68.3% of those who did not; $P < 0.05$), and were less likely to have knee OA than the subjects who did not complete the WOMAC (54.1% versus 60.4%; $P < 0.01$). Of the 2,222 subjects, 183 subjects with lateral knee OA or total knee arthroplasty were excluded. Therefore, a total of 2,039 participants (741 men and 1,298 women) age 40 years or older (mean ± SD 68.6 ± 10.9 years) who had completed the WOMAC were included in the present study.

Radiographic assessment. Radiographic examinations of both knees of all participants, using an anteroposterior view with weight-bearing and foot map positioning, were performed by experienced radiologic technicians. 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 center the patella over the lower end of the femur, we used fluoroscopic guidance with an anteroposterior x-ray beam, and the images were downloaded into Digital Imaging and Communication in Medicine (DICOM) format files. Knee radiographs were read by a single experienced orthopedist (SM), who was blinded with regard to participant clinical status, using the K/L radiographic atlas for overall knee radiographic grades (9), and knee OA was defined as a K/L grade of 2 or severe. Minimum JSW in the medial compartment and osteophyte area at the medial tibia were measured by the Knee Osteoarthritis Computer-Aided Diagnosis (KOACAD) system, and for each subject the knee with the lower minimum JSW was defined as the designated knee. The KOACAD system is a fully automatic system that can quantify the major features of knee OA

on standard radiographs and allows for objective, accurate, and simple assessment of the structural severity of knee OA in general clinical practice. This system was programmed to measure minimum JSW in the medial and lateral compartments and osteophyte area at the medial tibia using digitized knee radiographs. The KOACAD system has been described in detail previously (18). The KOACAD system was applied to the DICOM data by the experienced orthopedist who developed this system (HO), and the reliability of measurement is good (18). Lateral knee OA was defined as a K/L grade of ≥2 with lower lateral minimum JSW than medial minimum JSW.

QOL instrument. To carry out the QOL assessment, we used the WOMAC. The WOMAC, a 24-item OA-specific index, consists of 3 domains: pain, stiffness, and physical function. Each of these 24 items is graded on either a 5-point Likert scale (scores of 0–4) or a 100-mm visual analog scale (19,20). 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 been validated (21).

Statistical analysis. Differences in age, height, weight, BMI, minimum JSW, osteophyte area, and QOL measurements between men and women were examined using Student's unpaired *t*-test. Associations of minimum JSW and osteophyte area with scores on the pain and physical function domains of the WOMAC were determined using multiple regression analysis without adjustment. To assess independent associations of minimum JSW and osteophyte area with QOL, multiple regression analysis was used with age, BMI, minimum JSW, and osteophyte area as independent variables. Data analysis was performed using SAS, version 9.0.

RESULTS

The characteristics of the 2,039 participants in the present study are shown in Table 1. The minimum JSW was significantly lower and osteophyte area was significantly higher in women than in men. Scores on all domains of the WOMAC were significantly lower (indicating better status) in men than in women. Osteophyte area was only moderately associated with minimum JSW on linear regression analysis ($R^2 = 0.173$, $P < 0.05$).

Linear regression analysis without adjustment showed that minimum JSW and osteophyte area were significantly associated with scores on the pain and physical function domains of the WOMAC in the overall population as well as in men and women analyzed separately (Table 2). To determine the independent associations of minimum JSW and osteophyte area with scores on the pain and physical function domains of the WOMAC, we used multiple regression analysis with age, sex, BMI, minimum JSW, and osteophyte area as independent variables in the overall population (Table 2). Minimum JSW and osteophyte area were independently associated with scores on the pain and physical function domains of the WOMAC (β coefficients −0.16 and 0.11 for the association of pain domain score with minimum JSW and osteophyte area, respectively, and β coefficients −0.13 and 0.16 for the association of physical function domain score with minimum JSW and osteophyte area, respectively).

When men and women were analyzed separately (Table 2), in men, minimum JSW was independently associated with the pain domain scores (β coefficient −0.13), but not with the physical function domain scores (β coefficient 0.07) of the WOMAC, while osteophyte area was independently associated with the physical function domain scores (β coefficient 0.14), but not with the pain domain scores (β coefficient −0.07) of the WOMAC. In women, both minimum JSW and osteophyte area were independently associated with scores on the pain and physical function domains of the WOMAC, and the absolute values of the beta values for minimum JSW for scores on the pain domains of the WOMAC

Table 1. Characteristics of the subjects*

	Overall population (n = 2,039)	Men (n = 741)	Women (n = 1,298)
Age, years	68.6 ± 10.9	69.7 ± 10.5	67.9 ± 11.2†
Height, cm	154.7 ± 8.9	162.8 ± 6.5	150.1 ± 6.5†
Weight, kg	55.1 ± 10.4	61.4 ± 10.2	51.5 ± 8.6†
BMI, kg/m^2	22.9 ± 3.3	23.1 ± 3.1	22.8 ± 3.4†
Minimum JSW, mm	2.61 ± 0.98	2.97 ± 0.92	2.40 ± 0.96†
Osteophyte area, mm^2	2.99 ± 8.68	1.28 ± 4.46	3.98 ± 10.25†
Radiographic knee OA, %	50.2	39.0	56.8
WOMAC			
Pain	1.35 ± 2.42	1.10 ± 2.12	1.50 ± 2.57†
Stiffness	0.72 ± 1.25	0.63 ± 1.10	0.77 ± 1.33†
Function	3.99 ± 7.84	3.24 ± 6.69	4.42 ± 8.41†

* Except where indicated otherwise, values are the mean ± SD. BMI = body mass index; JSW = joint space width; OA = osteoarthritis; WOMAC = Western Ontario and McMaster Universities OA Index.
† $P < 0.05$ versus men, by Student's unpaired *t*-test.

Table 2. Associations of minimum JSW and osteophyte area with WOMAC domain scores*

	Pain				Physical function			
	Crude regression coefficient (95% CI)	*P*	Adjusted regression coefficient (95% CI)†	*P*	Crude regression coefficient (95% CI)	*P*	Adjusted regression coefficient (95% CI)†	*P*
Overall population								
Minimum JSW	−0.71 (−0.81, −0.60)	<0.0001	−0.37 (−0.48, −0.25)	<0.0001	−2.33 (−2.66, −1.99)	<0.0001	−0.97 (−1.34, −0.59)	<0.0001
Osteophyte area	0.07 (0.05, 0.08)	<0.0001	0.03 (0.02, 0.04)	<0.0001	0.25 (0.21, 0.29)	<0.0001	0.14 (0.10, 0.18)	<0.0001
Men								
Minimum JSW	−0.47 (−0.64, −0.31)	<0.0001	−0.29 (−0.47, −0.11)	0.002	−1.34 (−1.86, −0.82)	<0.0001	−0.48 (−1.04, 0.08)	0.10
Osteophyte area	0.07 (0.04, 0.11)	<0.0001	0.03 (−0.005, 0.07)	0.09	0.30 (0.19, 0.41)	<0.0001	0.20 (0.09, 0.32)	0.0005
Women								
Minimum JSW	−0.83 (−0.97, −0.69)	<0.0001	−0.41 (−0.57, −0.25)	<0.0001	−2.89 (−3.35, −2.43)	<0.0001	−1.22 (−1.72, −0.72)	<0.0001
Osteophyte area	0.06 (0.05, 0.08)	<0.0001	0.03 (0.01, 0.04)	0.0001	0.24 (0.20, 0.29)	<0.0001	0.12 (0.08, 0.17)	<0.0001

* WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; 95% CI = 95% confidence interval.
† Calculated by multiple regression analysis with age, sex, body mass index, minimum joint space width (JSW), and osteophyte area as the independent variables in the overall population and with age, body mass index, minimum JSW, and osteophyte area as the independent variables in the groups of men and women only.

were larger than those for osteophyte area (−0.15 and 0.11, respectively), while the absolute values of the beta values for minimum JSW for scores on the physical function domains of the WOMAC were smaller than those for osteophyte area (−0.14 and 0.15, respectively).

When the analysis was restricted to the partici-

Table 3. Associations of minimum JSW and osteophyte area with WOMAC domain scores in the subjects with knee OA*

	Pain				Physical function			
	Crude regression coefficient (95% CI)	*P*	Adjusted regression coefficient (95% CI)†	*P*	Crude regression coefficient (95% CI)	*P*	Adjusted regression coefficient (95% CI)†	*P*
Overall population								
Minimum JSW	−0.81 (−0.97, −0.65)	<0.0001	−0.51 (−0.69, −0.33)	<0.0001	−2.77 (−3.32, −2.22)	<0.0001	−1.46 (−2.05, −0.87)	<0.0001
Osteophyte area	0.06 (0.04, 0.07)	<0.0001	0.03 (0.01, 0.04)	0.0007	0.22 (0.18, 0.27)	<0.0001	0.12 (0.07, 0.17)	<0.0001
Men								
Minimum JSW	−0.59 (−0.86, −0.31)	<0.0001	−0.42 (−0.72, −0.11)	0.009	−1.95 (−2.81, −1.08)	<0.0001	−0.97 (−1.97, −0.01)	0.05
Osteophyte area	0.07 (0.02, 0.11)	0.003	0.02 (−0.02, 0.07)	0.40	0.34 (0.21, 0.48)	<0.0001	0.24 (0.10, 0.39)	0.001
Women								
Minimum JSW	−0.89 (−1.09, −0.68)	<0.0001	−0.56 (−0.78, −0.34)	<0.0001	−3.00 (−3.71, −2.29)	<0.0001	−1.61 (−2.35, −0.88)	<0.0001
Osteophyte area	0.05 (0.04, 0.07)	<0.0001	0.03 (0.01, 0.04)	0.002	0.20 (0.15, 0.26)	<0.0001	0.11 (0.05, 0.16)	0.0001

* Knee osteoarthritis (OA) was defined as a Kellgren/Lawrence grade of ≥2. WOMAC = Western Ontario and McMaster Universities OA Index; 95% CI = 95% confidence interval.
† Calculated by multiple regression analysis with age, sex, body mass index, minimum joint space width (JSW), and osteophyte area as the independent variables in the overall population and with age, body mass index, minimum JSW, and osteophyte area as the independent variables in the groups of men and women only.

pants with knee OA, the results were almost the same (Table 3). In men with knee OA, minimum JSW was independently associated with pain domain scores (β coefficient -0.17), but not with physical function domain scores (β coefficient 0.05). In women with knee OA, both minimum JSW and osteophyte area were independently associated with physical function domain scores, but the beta value for minimum JSW for physical function domain scores was smaller than that for osteophyte area (-0.12 and 0.20, respectively).

DISCUSSION

This is the first study to separately examine the associations of JSN and osteophytosis with QOL, measured by a disease-specific scale such as WOMAC, using a large-scale population-based Japanese cohort. In addition, JSN and osteophytosis were estimated not by categorical grade but by continuous values such as minimum JSW and osteophyte area at the knee. In the present study, JSN as well as osteophytosis was independently associated with QOL.

The present study showed that both JSN and osteophytosis reduce QOL. Osteophytosis appears to begin with the activation of periosteal layers, with initial generation of chondrophytes and subsequent calcification to real osteophytes. The process is probably an adaptive reaction of the joint in order to cope with joint instability, and thus osteophyte area may indicate the severity of joint instability (22), which might lead to loss of QOL. When men and women were analyzed separately, minimum JSW was significantly associated with scores on the WOMAC pain domain but not the WOMAC physical function domain in men, while osteophyte area was associated with scores on the physical function domain but not the pain domain. According to the methodology of the WOMAC, pain domains estimate the severity of pain, indicating that JSN may be strongly associated with pain. In contrast, physical function domains assess difficulties in activities of daily living, indicating that osteophytosis may be mainly associated with activities of daily living, particularly in men.

Our findings also indicated differences between the sexes in the associations of JSN and osteophytosis with QOL. Minimum JSW was significantly associated with scores on the physical function domains of the WOMAC in women, but not in men. Similarly, osteophyte area was associated with scores on the pain domains of the WOMAC in women, but not in men. These differences may indicate that JSN and osteophytosis were more strongly associated with loss of QOL in women than in men. Our previous study also showed that the odds ratio of knee pain for K/L grade 3 or 4 knee OA was approximately twice as high in women as in men (4). This may be partly explained by the lower muscle mass in women than in men. Previous reports have shown that muscle mass is also associated with QOL (23,24). In men, muscular strength may obscure the associations of JSN and osteophytosis with QOL loss; thus, these were not associated with some QOL parameters in men.

The present study has several limitations. First, this is a large-scale, population-based study, with a cross-sectional study of baseline data. Thus, causal relationships could not be determined. The ROAD study is a longitudinal survey, so further progress may help elucidate any causal relationships. Second, we did not include other weight-bearing forms of OA, such as hip OA, in the analysis, although this disorder may also affect QOL. However, the prevalence of K/L grade 3 or 4 hip OA is 1.4% and 3.5% in Japanese men and women (25), respectively, which is lower than the prevalence of K/L grade 3 or 4 knee OA (13.5% and 24.6% in Japanese men and women, respectively) (4). Thus, it is possible that including hip OA would not strongly affect the results of the present study. Third, the QOL questionnaire was completed by 74.2% of all participants age 40 years or older in the ROAD study. Participants who completed the questionnaire were younger and more likely to have knee OA than the participants who did not complete the questionnaire, and thus the participants included in this study may have had better QOL than those who did not complete the questionnaire, and our results may have overestimated QOL. Fourth, although osteophytes may be even more pronounced in the contralateral tibiofemoral compartment (26), at present the KOACAD system can only measure medial osteophytes at the tibia. We are now developing the 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.

In conclusion, the present cross-sectional study using a large-scale population from the ROAD study revealed that JSN and osteophytosis are independently associated with QOL. Further studies, along with continued longitudinal surveys in the ROAD study, will help clarify the mechanisms of JSN and osteophytosis at the knee, and their relationship with QOL.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Muraki had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Muraki, Oka, Akune, En-yo, M. Yoshida, Suzuki, H. Yoshida, Ishibashi, Tokimura, Yamamoto, Nakamura, Kawaguchi, Yoshimura.

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Association of occupational activity with joint space narrowing and osteophytosis in the medial compartment of the knee: the ROAD study (*OAC5914R2*)

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SUMMARY

Objective: We investigated the association of occupational activity with joint space narrowing and osteophytosis at the knee separately in Japanese subjects using a large-scale population-based cohort of the Research on Osteoarthritis Against Disability (ROAD).

Methods: From the baseline survey of the ROAD study, 1,402 participants (512 men and 890 women) living in mountainous and seacoast communities were analyzed. Information collected included a lifetime occupational history and details of specific workplace physical activities. To estimate the severity of joint space narrowing and osteophytosis at the knee, 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 diagnosis system.

Results: For women, agricultural, forestry, and fishery workers had significantly lower mJSW values compared with clerical workers or technical experts, whereas OPA did not differ significantly among job titles in men or women. For occupational activities, kneeling and squatting were associated with lower mJSW as well as higher OPA. Walking and heavy lifting were associated with lower mJSW, but not with OPA.

Conclusion: This cross-sectional study using a population-based cohort suggests that an occupational activity that includes kneeling and squatting appears to have a greater effect on knee OA.

Introduction

Knee osteoarthritis (OA), which causes cartilage degeneration and osteophyte formation at joints in the limbs, is a major public health issue causing chronic disability in the elderly in developed countries[1–3]. The prevalence of knee OA is high in the elderly in Japan[4] and 25,300,000 subjects aged 40 years and older are estimated to experience radiographic knee OA[5]. Further, 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 regard to activities of daily living[6].

Established risk factors for knee OA in Caucasians include older age, female sex, evidence of OA in other joints, obesity, and previous injury or surgery of the knee[7–11]. Evidence is accumulating in Caucasians that the disease is more common in people who have performed heavy physical work[12–17], particularly in those whose jobs have involved kneeling or squatting[18–24]. We also showed that occupational activities that included sitting, standing, walking, climbing, and heavy lifting had a significant association with moderate knee OA, and kneeling and squatting were associated with severe knee OA[25]. However, in our and other studies regarding occupational risks for knee OA, the disease was defined according to the Kellgren–Lawrence (KL) grade[26] or whether subjects had undergone total knee arthroplasty. KL grade is the most conventional system to grade radiographic severity of knee OA, but in this categorical system, joint space narrowing and osteophyte formation are not assessed separately. In addition, because the KL system emphasizes osteophytosis, it is unclear how to handle knee OA with joint space narrowing but no osteophytosis. Further, we have already reported that occupational activities of

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kneeling and squatting were significantly associated with KL ≥3 knee OA, but not with KL ≥2 knee OA[25]. Considering the definition of the KL grade[26], this difference may suggest distinct risk factors between osteophytosis and joint space narrowing. However, we cannot clarify whether osteophytosis and joint space narrowing have distinct risk factors, because osteophytosis and joint space narrowing are not separately defined according to the KL grade. In addition, a recent cross-sectional study has shown that osteophytosis was unrelated not only to joint space narrowing on plain radiographs, but also to cartilage loss measured by quantitative magnetic resonance imaging[27]. Furthermore, our study on an experimental mouse model for OA has identified a cartilage-specific molecule, carminerin, that regulates osteophytosis without affecting joint cartilage destruction during OA progression[28,29]. This accumulating evidence has indicated that joint space narrowing 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 assessed separately. However, to the best of our knowledge, there are no large population-based studies that investigate occupational factors associated with joint space narrowing and osteophyte formation separately.

In the present study, we measured medial minimum joint space width (mJSW) and osteophyte area (OPA) in the large-scale population-based cohort study called the Research on Osteoarthritis Against Disability (ROAD). The purpose of the present study was to investigate the association of job title and occupational activity with joint space narrowing and osteophytosis at the knee separately, and to clarify which kinds of occupational activities were associated with joint space narrowing and osteophytosis. Furthermore, we aimed to clarify whether the association of each occupational activity with joint space width and OPA was different.

Subjects and methods

Subjects

The ROAD study is a nationwide prospective study to establish epidemiologic indexes for evaluation of clinical evidence for the development of a disease-modifying treatment for bone and joint diseases (with OA and osteoporosis as the representative bone and joint diseases) consisting of population-based cohorts in several communities in Japan. As a detailed profile of the ROAD study has been described in detail elsewhere[4,5,30,31], only a brief summary is provided here. To date, we have completed creation of a baseline database including clinical and genetic information on 3,040 inhabitants (1,061 men and 1,979 women) ranging in age from 23 to 95 years (mean, 70.6 years) who were recruited from listings of resident registrations in three communities: an urban region in Itabashi, Tokyo; a mountainous region in Hidakagawa, Wakayama; and a seacoast region in Taiji, Wakayama. All participants provided written informed consent, and the study was conducted with the approval of ethics committees of the University of Tokyo and the Tokyo Metropolitan Institute of Gerontology. Information collected about job title and occupational activity included a lifetime occupational history with details of seven types of specific workplace physical activities: sitting on a chair, kneeling, squatting, standing, walking, climbing, and heavy lifting. Participants were asked whether they engaged in the following activities: sitting on a chair for ≥2 h/day, kneeling for ≥1 h/day, squatting for ≥1 h/day, standing for ≥2 h/day, walking for ≥3 km/day, climbing up slopes or steps for ≥1 h/day, and lifting loads weighing ≥10 kg ≥1 time/week. Information on these activities was obtained for the principal job, defined as the job at which the participant had worked longest. These definitions were chosen to be similar to definitions used in previous studies of occupations and OA[22,23,25]. Anthropometric measurements included height and weight, and body mass index (BMI; weight [kg]/height^2 [m^2]) was calculated. From baseline data of all participants, the present study analyzed 1,402 participants (512 men and 890 women) aged ≥50 years living in mountainous and seacoast cohorts, after excluding 69 subjects with lateral knee OA.

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 in the medial compartment and OPA at the medial tibia were measured by the KOACAD (knee osteoarthritis computer-aided diagnosis) system, and a knee with the lower mJSW was defined as the designated knee of a participant. The KOACAD system has been described in detail elsewhere[32], 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 difference of scale, and then the center of all points was calculated, that was defined as the center of the tibiofemoral joint, and a 480 × 200 pixels of rectangle with the center was decided as the ROI (Supplementary Figure). Within the ROI, the outline of the femoral condyle was designated as the upper rim of the joint space by vertical filtering with the 3 × 3 square neighborhood difference filter. The both ends of the upper rim were determined using a Canny's 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. 1(A)]. 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. 1(B)]. 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. 1(C)]. We have previously published reference values of joint space width and OPA by gender and age strata in Japan using the KOACAD system[33].

Statistical analysis

The differences of age, height, weight, BMI, mJSW, and OPA at the designated knee between men and women were examined by

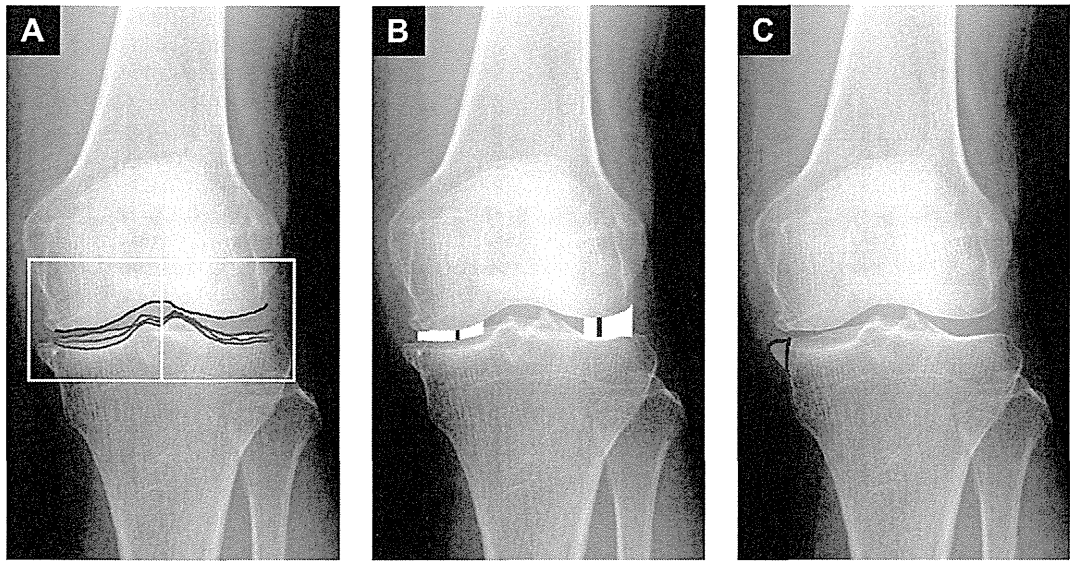

Fig. 1. Schema of image processing by KOACAD (cited from reference number[9]). (A). Outlines of anterior and posterior margins of the tibial plateau. The middle line between the two outlines is defined as the lower rim of the joint space. (B). Medial and lateral mJSWs were defined as the minimum vertical distances in the joint space area. (C). OPA (red area) that is medially prominent over the smoothly extended outline of the tibia.

the non-paired Student's *t*-test. The percentage of each occupational activity was compared between men and women by chi-square test. To determine the association of job title with mJSW and OPA, the Tukey Honestly Significant Differences (HSD) test was used after adjustment for age, gender, and BMI in the overall population and after adjustment for age and BMI in men and women. To determine the association of mJSW and OPA with each occupational activity separately after adjustment for age, gender, and BMI in the overall population, multiple regression analyses were used with age, gender, BMI, and each occupational activity as independent variables in the overall populations. Further, to determine the association of mJSW and OPA with each occupational activity separately after adjustment for age and BMI in men and women, multiple regression analyses were used with age, BMI, and each occupational activity as independent variables. Next, to determine the independent association of occupational activities with mJSW, multiple regression analysis was used with age, gender, BMI, and all significantly associated occupational activities in the overall subjects, and with age, BMI and all significantly associated occupational activities in men and women, as explanatory variables, statistical analyses were performed using SAS version 9.0 (SAS Institute Inc., Cary, NC).

Results

Characteristics of the 1,402 participants aged ≥50 in the mountainous and seacoast cohorts of the ROAD study are shown in Table I. mJSW was significantly lower in women than in men, whereas OPA was significantly higher in women compared with men. OPA was moderately associated with mJSW ($R^2 = 0.21$, $P < 0.05$) by linear regression analysis. When we analyzed the association of height with mJSW, the R^2 was 0.027 and 0.076 in men and women, respectively ($P < 0.05$). With regards to OPA, the R^2 was 0.01 and 0.006 in men and women, respectively ($P < 0.05$).

There was great diversity in job titles of study participants (Table II). Although a substantial proportion included clerical workers and technical experts, there were many agricultural, forestry, and fishery workers. Among various occupational activities, agricultural, forestry, and fishery workers had the highest rates of kneeling, squatting, standing, walking, climbing, and lifting weights, and the lowest rates for sitting on a chair, whereas clerical workers and technical experts had the lowest rates for the former activities and the highest rates for the latter activity (Fig. 2).

Table I
Characteristics of participants

	Overall	Men	Women
Number of subjects	1,402	512	890
Age, years	68.2 ± 9.2	68.9 ± 9.1	67.7 ± 9.2*
Height, cm	154.4 ± 9.3	162.4 ± 6.9	149.9 ± 7.2*
Weight, kg	55.3 ± 10.5	61.0 ± 10.3	52.0 ± 9.1*
BMI, kg/m^2	23.1 ± 3.4	23.1 ± 3.1	23.1 ± 3.5
mJSW, mm	2.5 ± 1.1	2.9 ± 1.0	2.3 ± 1.1*
OPA, mm^2	3.0 ± 7.9	1.4 ± 4.4	3.9 ± 9.3*

Values are mean ± SD except where indicated.
mJSW, minimum joint space width.
* $P < 0.05$ vs men by non-paired *t* test.

Table II
Number (percentage) of participants with job title and occupational activity reported as the principal job

	Overall	Men	Women
Job titles, *n* (%)			
Clerical workers/technical experts	350 (25.0)	164 (32.0)	186 (20.9)
Agricultural/forestry/fishery workers	299 (21.3)	158 (30.9)	141 (15.8)
Factory/construction workers	148 (10.6)	67 (13.1)	81 (9.1)
Shop assistants/managers	124 (8.8)	24 (4.7)	100 (11.2)
Housekeepers	118 (8.4)	0 (0.0)	118 (13.3)
Teachers	80 (5.7)	40 (7.8)	40 (4.5)
Dressmakers	46 (3.3)	1 (0.2)	45 (5.1)
Clinical workers	40 (2.9)	1 (0.2)	39 (4.4)
Hairdressers	17 (1.2)	6 (1.2)	11 (1.2)
Others (cook, taxi driver, etc.)	70 (5.0)	21 (4.1)	49 (5.5)
No answer	110 (7.8)	30 (5.9)	80 (9.0)
Occupational activities, n (%)			
Sitting on a chair ≥2 h/day	629 (44.9)	247 (48.2)	382 (42.9)
Kneeling ≥1 h/day	280 (20.0)	92 (18.0)	188 (21.1)
Squatting ≥1 h/day	368 (26.2)	127 (24.8)	241 (27.1)
Standing ≥2 h/day	1,179 (84.0)	439 (85.7)	740 (83.1)
Walking ≥3 km/day	638 (45.5)	255 (49.8)	383 (43.0)
Climbing ≥1 h/day	325 (23.2)	175 (34.2)	150 (16.9)*
Lifting weights ≥10 kg ≥1 time/week	750 (53.5)	336 (65.6)	414 (46.5)*

* $P < 0.05$ vs men by chi-square test.