Ⅳ．研究成果の刊行物・別刷

ARTHRITIS & RHEUMATISM
Vol. 64, No. 5, May 2012, pp 1447–1456
DOI 10.1002/art.33508

Incidence and Risk Factors for Radiographic Knee Osteoarthritis and Knee Pain in Japanese Men and Women

A Longitudinal Population-Based Cohort Study

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Objective. **To examine the incidence and progression of radiographic knee osteoarthritis (OA) and the incidence of knee pain, and their risk factors in Japan, using the large-scale population of the nationwide cohort study ROAD (Research on Osteoarthritis/osteoporosis Against Disability).**

Methods. **Subjects from the ROAD study who had been recruited in 2005–2007 were followed up with knee radiography 3 years later. A total of 2,262 paired radiographs (74.4% of the original sample) were scored using the Kellgren/Lawrence (K/L) grading system, and the incidence and progression rate of knee OA was examined. The incidence rate of knee pain was also examined. In addition, risk factors were tested for their association with incident and progressive radiographic knee OA and incident knee pain.**

Results. **Given the ~3.3-year followup, the rate of incident K/L grade ≥2 radiographic knee OA was 6.9% and 11.9% in men and women, respectively, while that of K/L grade ≥3 knee OA was 8.4% and 13.9% in men and women, respectively. The rate of progressive knee OA was 17.8% and 22.3% in men and women, respectively. The incident rate of knee pain was 21.2% and 27.3% in men and women, respectively. Female sex was a risk factor for incident K/L grade ≥2 knee OA, but was not associated with incident K/L grade ≥3 knee OA or progressive knee OA. Knee pain was a risk factor for incident and progressive knee OA. Previous knee injury was a risk factor for knee pain but not for radiographic knee OA.**

Conclusion. **The present longitudinal study revealed a high incidence of radiographic knee OA in Japan.**

Knee osteoarthritis (OA), characterized by pathologic features including joint space narrowing 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 ages ≥40 years estimated to experience radiographic knee OA (3). According to the recent National Livelihood Survey of the Ministry of Health, Labor, and Welfare in Japan, OA is ranked fourth among diseases that cause

Supported by grants-in-aid for Scientific Research (S19109007, B20390182, C20591737, C20591774), for Young Scientists (A18689031), and for Exploratory Research (19659305) from the Japanese Ministry of Education, Culture, Sports, Science, and Technology; grants H17-Men-eki-009, H18-Choujyu-037, H20-Choujyu-009, and H21-Chouju-Wakate-011 from the Ministry of Health, Labor, and Welfare; research funding from the Japanese Orthopaedic Association (JOA-Subsidized Science Project Research 2006-1 and 2010-2); and grant 166 from the Japan Orthopaedics and Traumatology Foundation.

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Submitted for publication February 8, 2011; accepted in revised form November 22, 2011.

disabilities that subsequently require support with activities of daily living (4). Despite the urgent need of strategies for the prevention and treatment of this condition, there have only been a few studies of rates of incidence and progression of knee OA (5–9). Furthermore, to the best of our knowledge, there has been no study of the incidence or progression of knee OA in Asians, although large differences in prevalence of knee OA exist among the different races (2,10,11).

Previous studies that investigated risk factors for knee OA (12–23) showed that obesity, previous knee injury, female sex, muscle strength, occupational activities, and older age were risk factors for knee OA mainly in Caucasians. However, in addition to the differences in prevalence among different ethnic groups, anthropometric measurements and environmental situations varied substantially in different countries. Thus, findings in Caucasians cannot be applied to different ethnic groups. Few population-based cohort studies have examined risk factors for knee OA in Asians.

The principal clinical symptom of knee OA is knee pain (24). Ours and other previous studies have demonstrated that the impact of knee pain on quality of life is disproportionate to the radiographic changes themselves in the knee (25,26). Several cross-sectional studies have investigated the factors associated with knee pain (25,27), but in most of those studies, radiographic findings were not included in the analysis, although radiographic severity of knee OA is an important factor for knee pain (2). Furthermore, there have been few longitudinal studies of the incidence of knee pain that include radiographic findings in the analysis.

The objective of the present study was to clarify the incidence and progression rate of radiographic knee OA as well as the incidence of knee pain in Japanese men and women using the large-scale, population-based cohort study known as the Research on Osteoarthritis/osteoporosis Against Disability (ROAD). In addition, we examined the risk factors for the incidence and progression of knee OA as well as for the incidence of knee pain.

SUBJECTS AND METHODS

Subjects. The ROAD study was a nationwide prospective study of bone and joint diseases (with osteoarthritis 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 (2,3,28), a brief summary is provided here. In 2005–2007, we created a baseline database that included the clinical and genetic information for 3,040 inhabitants (1,061 men, 1,979 women) in the age range of 23–95 years (mean 70.6 years), recruited from listings of resident registrations in 3 communities: an urban region in Itabashi, Tokyo; a mountainous region in Hidakagawa, Wakayama; and a coastal region in Taiji, Wakayama. Participants in the urban region were recruited from a randomly selected cohort from the Itabashi-ward residents' registration database (29). 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 2 areas were 56.7% and 31.7%, respectively. The inclusion criteria, apart from residence in the communities mentioned above, were the ability to walk to the survey site, report data, and understand and sign an informed consent form. 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 Geriatric Medical Center.

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. Anthropometric measurements included height and weight, from which the body mass index (BMI) (weight [kg]/height [m^2]) was calculated. Grip strength was measured on bilateral sides using a TOEI LIGHT handgrip dynamometer, and the better measurement was used to represent maximum muscle strength. Furthermore, all participants were interviewed by well-experienced orthopedists regarding pain in both knees, who asked "Have you experienced right knee pain on most days in the past month, in addition to now?" and "Have you experienced left knee pain on most days in the past month, in addition to now?" Subjects who answered "yes" were defined as having knee pain.

In 2008–2010, we attempted to trace and review all 3,040 subjects; they were invited to attend a followup interview and undergo repeat radiography. The interviews, which included questions about current knee pain, were conducted by the same trained orthopedists who undertook the baseline study in 2005–2007. Anthropometric measurements also included height, weight, and grip strength at followup.

Radiographic assessment. All participants underwent radiographic examination of both knees using an anteroposterior view with weight-bearing and foot map positioning. Fluoroscopic guidance with a horizontal anteroposterior x-ray beam was used to properly visualize the joint space. Knee radiographs at baseline and followup were read in pairs without knowledge of the participant's clinical status by a single well-experienced orthopedist (SM), and the Kellgren/Lawrence (K/L) grade was defined using the K/L radiographic atlas for overall knee radiographic grades (30). In the K/L 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 K/L grading, 100 randomly selected radiographs of the knee were scored by the same observer >1 month after the first reading. One hundred other radiographs were also scored by 2 experienced orthopedic surgeons (SM and HO) using the same atlas for interobserver variability. The intra- and intervariabilities evaluated for K/L grade (0–4) were confirmed by kappa

Table 1. Baseline characteristics of the participants*

	Overall (n = 2,262)	Men (n = 763)	Women (n = 1,499)
Age, years	68.7 ± 11.3	69.6 ± 11.1	68.2 ± 11.4†
Height, cm	154.6 ± 8.8	163.1 ± 6.6	150.3 ± 6.4†
Weight, kg	55.4 ± 10.2	62.2 ± 9.9	51.9 ± 8.4†
BMI, kg/m^2	23.1 ± 3.3	23.3 ± 3.0	23.0 ± 3.4†
Grip strength, kg	26.2 ± 9.2	34.3 ± 8.8	22.1 ± 6.2†
OA prevalence, no. (%)			
K/L grade ≥1	1,898 (83.9)	586 (76.8)	1,312 (87.5)‡
K/L grade ≥2	1,164 (51.5)	296 (38.8)	868 (57.9)‡
K/L grade ≥3	355 (15.7)	75 (9.8)	280 (18.7)‡
Knee pain, no. (%)	478 (21.1)	111 (14.6)	367 (24.5)‡
Previous knee injury, no. (%)	217 (9.6)	52 (6.8)	165 (11.0)‡
Smoking, no. (%)	212 (9.4)	165 (21.6)	47 (3.1)‡
Alcohol, no. (%)	831 (36.7)	483 (63.3)	348 (23.2)‡

* Except where indicated otherwise, values are the mean ± SD. BMI = body mass index; OA = osteoarthritis; K/L = Kellgren/Lawrence.
† $P < 0.05$ versus men, by Student's unpaired *t*-test.
‡ $P < 0.05$ versus men, by chi-square test.

analysis to be sufficient for assessment ($\kappa = 0.86$ and $\kappa = 0.80$, respectively).

For the purposes of this study, we defined 4 knee OA outcomes. First, a subject was defined as having incident K/L grade ≥1 radiographic knee OA if both knees had less than grade 1 disease at baseline and if at least one knee had grade 1 or higher disease at followup. Second, a subject was defined as having incident K/L grade ≥2 radiographic knee OA if both knees had less than grade 2 disease at baseline and if at least one knee had grade 2 or higher disease at followup. Third, incident K/L grade ≥3 radiographic knee OA was defined as less than grade 3 disease in both knees at baseline and grade 3 or higher disease in at least one knee at followup. Fourth, progressive knee OA was defined as K/L grade 2 and K/L grade 3 knee OA at baseline (because K/L grade 4 knee OA cannot progress) and an increase by at least 1 grade in the affected knee at followup.

Statistical analysis. Odds ratios (ORs) and 95% confidence intervals (95% CIs) are provided. The differences in age, height, weight, BMI, and grip strength between men and women were examined using Student's unpaired *t*-test. To compare the prevalence of radiographic knee OA and knee pain between men and women, we performed the chi-square test. A logistic regression analysis was used to determine the association of incident radiographic knee OA, progressive knee OA, and incident knee pain with age in men and women. To determine risk factors for incident knee OA and progressive knee OA, a univariate generalized estimating equation (GEE) logistic regression analysis was used. Furthermore, to determine independent risk factors, multiple GEE logistic regression analysis was used with significant risk factors in a univariate GEE logistic regression analysis model as independent variables. Incident knee pain was defined as no knee pain in both knees at baseline and knee pain in at least one knee at followup. To determine risk factors for incident knee pain, a univariate GEE logistic regression analysis was used. Furthermore, to determine independent risk factors, multiple GEE logistic regression analysis was used with significant risk factors in a univariate logistic regression analysis model in addition to regions as independent variables. When we analyzed risk factors for incident knee OA, progressive knee OA, and incident knee pain, K/L grade at baseline, knee pain at baseline, and previous knee injury were defined for the knee which had the incident OA, progressive OA, and incident pain, respectively. Data analyses were performed using SAS software, version 9.0 (SAS Institute).

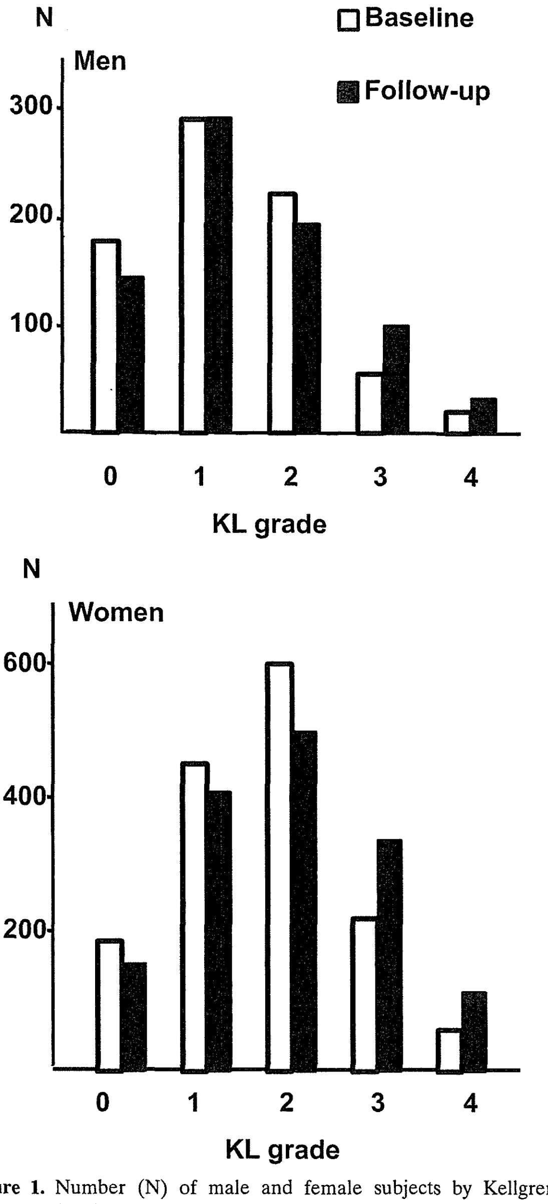

Figure 1. Number (N) of male and female subjects by Kellgren/Lawrence (K/L) grade at baseline and followup.

Table 2. Incidence of radiographic knee OA, progressive knee OA, and knee pain according to sex*

	K/L grade ≥1		K/L grade ≥2		K/L grade ≥3		Progressive knee OA		Knee pain	
	No. at risk	Cumulative incidence, no. (%)	No. at risk	Cumulative incidence, no. (%)	No. at risk	Cumulative incidence, no. (%)	No. at risk	Cumulative incidence, no. (%)	No. at risk	Cumulative incidence, no. (%)
Overall	364	70 (19.2)	1,098	107 (9.7)	1,907	228 (12.0)	1,084	229 (21.1)	1,784	447 (25.1)
Men	177	35 (19.8)	467	32 (6.9)	688	58 (8.4)	276	49 (17.8)	652	138 (21.2)
Women	187	35 (18.7)	631	75 (11.9)†	1,219	169 (13.9)†	808	180 (22.3)	1,132	309 (27.3)†

* See Table 1 for definitions.
† $P < 0.05$ versus men, by chi-square test.

RESULTS

Of the 3,040 subjects in the baseline study in 2005–2007, 125 (4.1%) had died by the time of the review 3 years later, 123 (4.0%) did not participate in the followup study due to bad health, 69 (2.3%) had moved away, 83 (2.7%) declined the invitation to attend the followup study, and 155 (5.1%) did not participate in the followup study for other reasons. Among the 2,485 subjects who did participate in the followup study, 175 (5.8%) did not undergo plain radiography and 18 (0.6%) provided incomplete pain questionnaires; these were excluded. We also excluded 30 subjects (1.0%) who underwent total knee arthroplasty before the followup study, leaving a total of 2,262 subjects (74.4%) (763 men and 1,499 women) from whom paired radiographs and complete pain histories were obtained. Their mean ± SD age at followup was 72.2 ± 11.4 years. The mean ± SD duration of followup between initial and second radiographs was 3.3 ± 0.6 years. Those participating in the followup study were younger than those who did not survive or who did not participate for other reasons (mean age 68.6 years for responders versus 75.1 years for nonresponders; $P < 0.0001$). The followup study participants also were more likely to be women (66.3% of responders were women and 61.8% of nonresponders were women; $P = 0.03$) and were less likely to have knee OA at the baseline examination than either those who did not survive to followup or those who did not participate for other reasons (51.5% of responders versus 60.9% of nonresponders; $P < 0.0001$).

The characteristics of the 2,262 participants at baseline in the ROAD study are shown in Table 1. Men were significantly older than women, while BMI was higher in men than in women. The prevalence of knee OA and knee pain was significantly higher in women than in men at baseline. The proportion of previous knee injuries was also higher in women than in men. The number of subjects with each K/L grade at baseline and at followup is shown in Figure 1.

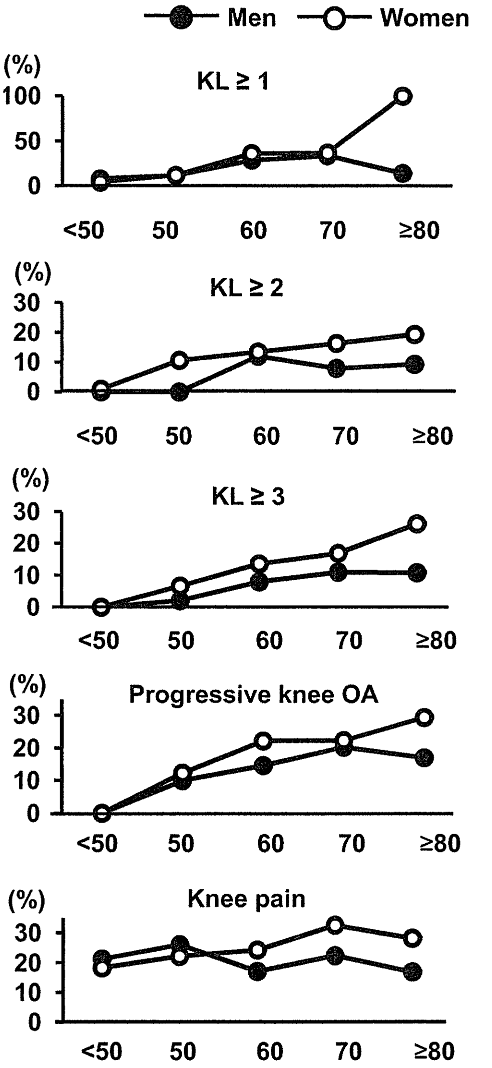

Figure 2. Percentage of subjects with incident radiographic knee osteoarthritis (OA) (Kellgren/Lawrence [K/L] grade ≥1, ≥2, or ≥3), progressive knee OA, and incident knee pain in each age stratum (<50 years, 50–59 years, 60–69 years, 70–79 years, and ≥80 years).

Table 3. Risk factors for incident radiographic knee osteoarthritis*

	K/L grade ≥2			K/L grade ≥3		
	No./total no. (%) of subjects	Crude OR (95% CI)	Adjusted OR (95% CI)	No./total no. (%) of subjects	Crude OR (95% CI)	Adjusted OR (95% CI)
Age (+5 years)	–	1.26 (1.15–1.39)	1.31 (1.15–1.49)	–	1.33 (1.23–1.44)	1.25 (1.13–1.39)
BMI (+5 kg/m^2)	–	2.00 (1.49–2.69)	2.43 (1.76–3.39)	–	1.67 (1.36–2.04)	1.68 (1.35–2.11)
Grip strength (+1 kg)	–	0.96 (0.94–0.98)	1.01 (0.97–1.04)	–	0.95 (0.94–0.97)	1.00 (0.97–1.02)
Sex						
Men	32/467 (6.9)	Referent	Referent	58/688 (8.4)	Referent	Referent
Women	75/631 (11.9)	1.83 (1.20–2.86)	2.76 (1.50–5.18)	169/1,219 (13.9)	1.75 (1.28–2.41)	1.42 (0.88–2.29)
K/L grade at baseline						
0	–	Referent	Referent	–	Referent	Referent
1	–	4.11 (2.33–7.83)	2.48 (1.35–4.87)	–	1.91 (0.69–5.43)	1.29 (0.45–3.80)
2	–	–	–	–	5.69 (2.38–14.30)	5.94 (1.07–35.83)
Knee pain at baseline						
No	–	Referent	–	–	Referent	Referent
Yes	–	0.91 (0.32–2.24)	–	–	3.77 (2.44–5.73)	2.53 (1.59–4.00)
Previous knee injury						
No	–	Referent	–	–	Referent	–
Yes	–	4.08 (0.66–18.8)	–	–	1.24 (0.45–3.11)	–
Smoking						
No	99/958 (10.3)	Referent	–	213/1,713 (12.4)	Referent	Referent
Yes	8/140 (5.7)	0.53 (0.23–1.04)	–	14/194 (7.2)	0.55 (0.30–0.93)	1.07 (0.55–1.94)
Alcohol use						
No	68/627 (10.9)	Referent	–	158/1,171 (13.5)	Referent	Referent
Yes	39/471 (8.3)	0.74 (0.49–1.12)	–	69/736 (9.4)	0.66 (0.49–0.89)	0.96 (0.67–1.36)

* Adjusted odds ratios (ORs) were calculated by multiple generalized estimating equation logistic regression analysis after adjustment for all other variables in addition to regions. We show all variables we analyzed in the present study. K/L = Kellgren/Lawrence; 95% CI = 95% confidence interval; BMI = body mass index.

Table 2 shows the rates of incident and progressive knee OA and incident knee pain in the overall population and subgroups classified by sex. The incidences of K/L grade ≥2 and K/L grade ≥3 knee OA and knee pain were significantly higher in women than in men, while there were no significant differences in the incidence of K/L grade ≥1 knee OA and the progression of knee OA between men and women. The incidence and progression rate of knee OA tended to increase with age in men and women (for 5-year increase: K/L grade ≥1, OR 1.22 [95% CI 1.06–1.43] and OR 1.52 [95% CI 1.29–1.84], respectively; K/L grade ≥2, OR 1.35 [95% CI 1.12–1.67] and OR 1.29 [95% CI 1.15–1.45], respectively; K/L grade ≥3, OR 1.34 [95% CI 1.15–1.58] and OR 1.35 [95% CI 1.24–1.49], respectively; progressive knee OA, OR 1.15 [95% CI 0.95–1.42] and OR 1.15 [95% CI 1.0–1.28], respectively) (Figure 2). Interestingly, the incidence rate of knee pain was age-dependent in women (OR 1.10 [95% CI 1.04–1.17]), while it was not age-dependent in men (OR 0.97 [95% CI 0.90–1.06]). Furthermore, in subjects age <60 years, the incidence of knee pain was similar between women and men (OR 1.12 [95% CI 0.88–1.42]), while in subjects age >60 years, the incidence of knee pain was significantly higher in women than in men (OR 0.78 [95% CI 0.68–0.88]) (Figure 2).

Table 3 shows the baseline risk factors for incident radiographic knee OA. Univariate logistic regression analysis showed that age, BMI, grip strength, sex, and K/L grade were associated with incident K/L grade ≥2 knee OA. Age, BMI, grip strength, sex, K/L grade, knee pain at baseline, previous knee injury, smoking, and alcohol consumption were associated with incident K/L grade ≥3 knee OA. We then determined independent risk factors using a multiple logistic regression analysis that included the above significant factors in the univariate model in addition to regions as independent variables. The results showed that age and BMI were risk factors for incident K/L grade ≥2 and incident K/L grade ≥3 knee OA. Female sex was a risk factor for incident K/L grade ≥2 knee OA, while being female was not significantly associated with incident K/L grade ≥3 knee OA. A more severe K/L grade at baseline was strongly associated with incident K/L grade ≥2 and incident K/L grade ≥3 knee OA. Knee pain at baseline was significantly associated with incident K/L grade ≥3 knee OA.

Univariate logistic regression analysis showed

Table 4. Risk factors for progressive knee OA and incident knee pain*

	Progressive knee OA			Knee pain		
	No./total no. (%) of subjects	Crude OR (95% CI)	Adjusted OR (95% CI)	No./total no. (%) of subjects	Crude OR (95% CI)	Adjusted OR (95% CI)
Age (+5 years)	–	1.14 (1.04–1.25)	1.17 (1.05–1.30)	–	1.05 (1.01–1.10)	1.01 (0.95–1.07)
BMI (+5 kg/m^2)	–	1.47 (1.20–1.80)	1.43 (1.16–1.77)	–	1.60 (1.37–1.88)	1.54 (1.30–1.82)
Grip strength (+1 kg)	–	0.98 (0.96–1.00)	0.99 (0.96–1.01)	–	0.98 (0.97–1.00)	1.00 (0.98–1.02)
Sex						
Men	49/276 (17.8)	Referent	–	138/652 (21.2)	Referent	Referent
Women	180/808 (22.3)	1.33 (0.94–1.90)	–	309/1,132 (27.3)	1.40 (1.11–1.76)	1.32 (0.94–1.84)
K/L grade at baseline						
0 and 1	–	–	–	–	Referent	Referent
2	–	–	–	–	1.89 (0.80–4.49)	1.58 (0.65–3.85)
3 and 4	–	–	–	–	3.17 (1.95–5.17)	2.54 (1.52–4.24)
Knee pain at baseline						
No	–	Referent	Referent	–	–	–
Yes	–	2.87 (1.99–4.14)	2.63 (1.81–3.81)	–	–	–
Previous knee injury						
No	–	Referent	–	–	Referent	Referent
Yes	–	0.79 (0.31–1.86)	–	–	3.09 (1.34–7.23)	2.91 (1.26–6.82)
Smoking						
No	219/1,016 (21.6)	Referent	–	411/1,603 (25.6)	Referent	–
Yes	10/68 (14.7)	0.63 (0.30–1.19)	–	36/181 (19.9)	0.72 (0.49–1.04)	–
Alcohol use						
No	168/746 (22.4)	Referent	–	281/1,093 (25.7)	Referent	–
Yes	61/338 (18.1)	0.76 (0.54–1.04)	–	166/691 (24.0)	0.91 (0.73–1.14)	–

* Adjusted ORs were calculated by multiple generalized estimating equation logistic regression analysis after adjustment for all other variables in addition to regions. We show all variables we analyzed in the present study. OA = osteoarthritis (see Table 3 for other definitions).

that age, BMI, grip strength, and knee pain at baseline were associated with progressive knee OA. We then included age, BMI, grip strength, and knee pain at baseline in addition to regions as independent variables in a multiple logistic regression analysis to determine independent risk factors (Table 4). Age and BMI at baseline were risk factors, but their adjusted ORs for progressive knee OA were lower than those for incident K/L grade ≥2 knee OA (Table 4). Knee pain was significantly associated with progressive knee OA.

We further investigated risk factors for incident knee pain (Table 4). Univariate logistic regression analysis showed that age, BMI, grip strength, sex, K/L grade, and previous knee injury were associated with incident knee pain. To determine independent risk factors for knee pain, multiple logistic regression analysis was used with age, BMI, grip strength, sex, K/L grade, and previous knee injury in addition to regions as independent variables. BMI was significantly associated with incident knee pain, but female sex was not associated with incident knee pain. Subjects with K/L grade ≥3 knee OA at baseline had an ~2.5-fold increased risk for incidence of knee pain compared with K/L grade 0 and K/L grade 1 knees. Previous knee injury was also significantly associated with incident knee pain.

DISCUSSION

This is the first population-based study to examine the incidence and progression of knee OA and risk factors for incident and progressive knee OA among Japanese men and women. We also examined the incident rate of knee pain and its risk factors. The present study showed high rates of incident knee OA, progressive knee OA, and incident knee pain.

Few population-based studies have examined incident radiographic knee OA (6–9). In the Framingham Osteoarthritis Study (6), given the ~8.1-year followup, the incident rate of K/L grade ≥2 knee OA was 11.1% and 18.1% (1.4% and 2.2% per year) in Caucasian men and women, respectively. A population-based study in the UK (18) showed that given the ~5.1-year followup, the incident rate of K/L grade ≥2 knee OA was 18.5% (2.3% per year), but men and women were not separated in the analysis. In the present study, the incidence of K/L grade ≥2 OA was 2.0% and 3.7% per year in men and women, respectively, which is a little higher than that in previous epidemiologic studies in the US and Europe (6,8), implying that the incidence is higher among Japanese than in Caucasians. This is compatible with our findings regarding prevalence of K/L grade ≥2 knee OA in our previous study (2), which showed that the prevalence of K/L grade ≥2 knee OA was much higher in Japanese people than in Caucasians (10,11).

For incident K/L grade ≥3 knee OA, to the best of our knowledge no population-based studies have been previously reported. In the Chingford Study (7), knee OA was not defined according to K/L grade but according to osteophytosis and joint space narrowing. The Chingford Study showed that given the ~4-year followup, the incidence of joint space narrowing was 12.6% (3.2% per year) in women, which may be comparable to our results for incident K/L grade ≥3 knee OA, considering the K/L grade definition; however, a closer comparison provides quite limited accuracy.

In the present study, the incident rate of K/L grade ≥3 knee OA was 4.1% per year in Japanese women, which was also a little higher than that seen in Caucasian women. However, this higher incident rate of K/L grade ≥3 may be partly explained by the definition of K/L grade ≥3 knee OA, because by considering any knees that start at K/L grade <3 as eligible for this outcome, we combined incident (e.g., knees starting at K/L grade 0–1) and progressive (knees starting at K/L grade 2) disease. In the present study, we also examined progression of knee OA, and we found that the progression rate of knee OA was 5.2% and 6.3% per year in Japanese men and women, respectively, which was also higher than that in other studies in the US and the UK (2.2–3.9%) (6,8). The higher incidence of radiographic knee OA in Japan could also be due to lifestyle factors, because the traditional Japanese lifestyle includes sitting on the heels on a mat and using Japanese-style lavatories, requiring squatting and kneeling, which are associated with knee OA (31–33). These positions may cause mechanical stress to the knee joint and possibly lead to the acceleration of OA.

Although the rate of incident radiographic knee OA and progressive knee OA increased with age in both sexes, that of knee pain was age-dependent in women but not in men. This may be due to the fact that elderly men generally retire from their occupations at age ~60–70 years, and thus the load on the knees may be lighter in men age >60 years compared with those age <60 years, whereas women must often continue to do household chores even after age 70 years, and thus the load on the knees may not be lighter in women age >70 years compared with those age <70 years.

The present study also showed that age and BMI are risk factors for incident radiographic knee OA, consistent with findings of previous epidemiologic studies (5,7,8). Previous studies have shown that obesity is a strong risk factor for incident knee OA (34), possibly due to the accumulation of mechanical stress on the knee joint. More severe K/L grade was also a risk factor for incident radiographic knee OA in the present study, which is also consistent with findings of previous studies (7,8). Female sex was also a strong risk factor for incident K/L grade ≥2 knee OA, as in previous studies (6,8), possibly implicating the involvement of muscle strength to compensate for mechanical stress, as women are known to have less muscle strength than men in all decades of life (35). However, female sex was not a significant risk factor for incident K/L grade ≥3 knee OA or progressive knee OA. Furthermore, age and BMI at baseline were risk factors for progressive knee OA, but their ORs for progressive knee OA were lower than those for incident K/L grade ≥2 knee OA.

This discordance between the determinants of incidence of K/L grade ≥2 and K/L grade ≥3 knee OA or between those of incidence and progression of knee OA using K/L grade suggests that different mechanisms might influence the initiation of osteophytosis (the principal abnormality in K/L grade 2 disease) and joint space narrowing (the principal abnormality in K/L grade 3 disease). However, since K/L grade was defined by a categorical method, which is comparably insensitive to change, this discordance might simply be a function of the scoring system. Nevertheless, there is also accumulating evidence from previous studies that osteophytosis and joint space narrowing have distinct etiologic mechanisms. A recent cross-sectional study has shown that osteophytosis is unrelated not only to joint space narrowing on plain radiographs, but also to cartilage loss measured by quantitative magnetic resonance imaging (36). Furthermore, our study of an experimental mouse model of OA has identified a cartilage-specific molecule, carminerin, that regulates osteophytosis without affecting joint cartilage destruction during OA progression (37,38). Our most recent findings have implications for our understanding of the pathogenesis of knee OA, as well as for preventive strategies.

In the present study, knee pain was a risk factor for incident K/L grade ≥3 knee OA and progressive knee OA. Subjects with knee pain may tend not to go out or exercise because of the pain, which may lead to lower quadriceps strength. This may be one of the reasons why knee pain is a risk factor for incident and progressive knee OA, as quadriceps weakness has been previously associated with radiographic knee OA (39).

For incidence of knee pain, age was not a risk factor after adjustment for BMI, sex, and K/L grade at baseline. Knee pain occurrence may be mainly due to environmental factors rather than individual factors. As described above, elderly men generally retire from their occupations at ages 60–70 years, and thus the load on the knees may be lighter in men age <60 years compared with those age >60 years, which may partly explain the lack of significant association between age and incidence of knee pain. BMI was a risk factor for incident knee pain even after adjustment for K/L grade at baseline, indicating that obesity is a strong risk factor not only for incident radiographic knee OA but also for incident knee pain. In addition, knee OA at baseline was a risk factor for knee pain, but the ORs for knee pain of K/L grade 2 knee OA and K/L grades 3 and 4 knee OA were just 1.6 and 2.5, respectively. In fact, the proportion of subjects with knee pain of those with K/L grade 2 knee OA and K/L grades 3 and 4 knee OA was just 28.0% and 47.1%, respectively, indicating that ~70% of subjects with K/L grade 2 knee OA who had no knee pain at baseline and ~50% of subjects with K/L grades 3 and 4 knee OA who had no knee pain at baseline also had no knee pain after 3 years.

Previous cross-sectional studies have also demonstrated that correlation of knee pain with radiographic severity of knee OA is not as strong as one would expect (2,40–42), most likely because knee pain may arise from a variety of structures other than joint cartilage, such as the menisci, synovium, ligaments, bursae, bone, and bone marrow (43–47). Hence, comprehensive mechanistic studies of knee pain taking various tissues in and around the knee joint into consideration will be needed to elucidate the relationship between radiographic OA and symptomatic OA.

We were unable to detect an association between knee injury and incident OA in the present study. Other cross-sectional studies of OA prevalence have observed strong association with previous knee injury (48), while the incidence data from the Zoetermeer Study, Framingham Study, and Chingford Study (5–7) also showed a slight increase in risk with interim knee injury but were based on small numbers; no significant association with past knee injury was seen in those groups. In the present study, K/L grade ≥2 knee OA in subjects with previous knee injury was not significantly associated with previous knee injury, which suggests that the association of incident radiographic knee OA with previous knee injury may be weak, although the number of subjects with incident K/L grade ≥2 knee OA who had previous knee injury was just 12. Thus, the small number may partly explain the lack of statistical significance. The present study showed that previous knee injury is a risk factor for incident knee pain. As mentioned above, the correlation of knee pain with radiographic severity of knee OA is not as strong as expected (2,40–42), as knee pain may arise from a variety of structures other than joint cartilage, such as menisci, synovium, ligaments, bursae, bone, and the bone marrow (43–47), and these tissues may have been damaged by a previous knee injury, which may lead to the incident knee pain.

We were unable to detect an association between smoking/drinking alcohol and incident knee OA or knee pain. The association between smoking and incident knee OA is controversial. The Zoetermeer Study showed that smoking has no association with incident knee OA (5), while incidence data from the Framingham Study showed that smoking protects against incident knee OA (49). We were also unable to show any effect of physical activity in this incidence study. However, the numbers and power were too low to examine this group and to confirm or exclude such effects on incidence.

The present study has several limitations. First, the radiographic investigators did not have readers calibrate their readings to those from other studies. Although we reported a higher incidence of radiographic knee OA than in previous studies, differences in radiographic acquisition, scoring techniques, and methodology across studies limit strict comparisons between our results and previous reports. Differences across studies in the thresholds used by readers to define osteophytes may have had a substantial impact on their incidence. The high incidence of knee OA in our study compared to that in other populations may be due to such differences. Second, our analysis did not include patellofemoral joint radiographs, which would likely increase the concordance between radiographic knee OA and its pain. Third, we defined knee pain as present or absent, rather than as a continuous measure such as the Western Ontario and McMaster Universities Osteoarthritis Index (50) or visual analog scale score. Categorical methods are statistically less powerful than continuous methods. Thus, the association between knee pain and other variables might have been underestimated in the present study.

In conclusion, the present longitudinal study, using a large-scale population from the ROAD study, revealed a high incidence of radiographic knee OA in Japan compared with previous studies. Age, BMI, and female sex influence incidence more than radiographic progression of knee OA, indicating that different mechanisms might influence the initiation of osteophytosis and joint space narrowing. Knee pain was a risk factor for radiographic knee OA. Knee injury was not significantly associated with radiographic knee OA, but was a risk factor for incident knee pain. Further progress, along with continued longitudinal surveys within the ROAD study, will elucidate the environmental and genetic backgrounds of knee OA.

ACKNOWLEDGMENTS

The authors thank Drs. Seizo Yamamoto, Hideaki Ishibashi, and Yorito Anamizu and members of the Department of Orthopedics, and Mr. Yuji Kutsuma and other members of the Department of Radiology at Tokyo Metropolitan Geriatric Medical Center; Mrs. Tomoko Takijiri and other members of the Public Office in Hidakagawa, Japan; and Mrs. Tamako Tsutsumi, Mrs. Kanami Maeda, and other members of the Public Office in Taiji, Japan, for their assistance in the location and scheduling of participants for examinations.

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, Akune, Oka, Ishimoto, Nagata, Yoshida, Tokimura, Nakamura, Kawaguchi, Yoshimura.

Acquisition of data. Muraki, Akune, Oka, Ishimoto, Nagata, Yoshimura.

Analysis and interpretation of data. Muraki, Akune, Oka, Yoshimura.

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Original Research

Prevalence of vertebral fracture in Asian men and women: Comparison between Hong Kong, Thailand, Indonesia and Japan

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ARTICLE INFO

Article history:
Received 14 December 2010
Received in revised form
31 January 2012
Accepted 12 March 2012
Available online 5 May 2012

Keywords:
Vertebral fracture
Asia
Elderly
Quality of life

SUMMARY

Objectives: Little is known about the prevalence of vertebral fracture among Asians. This study investigated the prevalence of radiographically defined vertebral fracture, and identified associated risk factors in the aged population of four Asian countries.

Study design: In total, 1588 males and females aged ≥65 years were recruited from Hong Kong, Thailand, Indonesia and Japan.

Methods: Standard X-rays for the spine were taken and vertebral heights were measured. Vertebral fracture was defined as a reduction of >3 standard deviations in vertebral height ratio. Bone mineral density (BMD) of the hip was measured by dual energy X-ray absorptiometry, and anthropometric measurements were taken in Hong Kong and Japan. Other relevant data were entered in a standard questionnaire.

Results: The prevalence of vertebral fracture for both males and females was highest in Japan for younger (65–74 years) and older (≥75 years) age groups (36.6% and 37.6% for males; 18.8% and 28.7% for females). Lower hip BMD was associated with vertebral fracture in both sexes. Older age, lower quality of life score on Short Form-12 (physical), past longest occupation as a farmer, and history of cataract were significantly associated with vertebral fracture in females. However, smoking did not appear to be an important risk factor for vertebral fracture.

Conclusions: Radiographic assessments for vertebral fracture were performed in all four Asian countries. The prevalence of vertebral fracture was highest in Japan. Lower hip BMD, poorer physical condition and past longest occupation as a farmer were associated with vertebral fracture.

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doi:10.1016/j.puhe.2012.03.002

Introduction

Osteoporosis is a condition characterized by low bone mass and micro-architectural deterioration of bone tissues causing increased bone fragility and susceptibility to fracture. The disease is becoming a major health problem in Asia where a rapidly increasing aged population will be accompanied by increasing incidence of hip fracture.[1] In Hong Kong, for instance, over the last two decades, the number of cases of hip fracture has increased two-fold due to the increase in the ageing population. Of every 1000 people who are aged ≥80 years, one man and two women will have a fractured hip each year.[2] The age-adjusted rate in Hong Kong is comparable to that in Singapore and higher than that in Japan. It has been projected that over half of all hip fractures in the world will occur in Asia by 2050.[1]

While there are many data on the prevalence and risk factors for hip fracture, little is known of the prevalence and risk factors for vertebral fracture in Asia. In a study by Lau *et al.*, the prevalence of vertebral fracture was estimated to be 29% in women in Hong Kong.[3] Vertebral deformity, back pain and psychological problems were associated symptoms in elderly Chinese women, and the use of analgesics was common in men. Overseas studies have demonstrated associations between vertebral fracture and back pain, disability and the need for healthcare support.[4–6] The survival rate of elderly people who had experienced a clinical vertebral fracture was found to be lower than that of elderly people who had not experienced a fracture.[7] Women with severe vertebral deformities were found to have a consistently higher risk of back pain and height loss. In addition, genetic and lifestyle factors may influence vertebral fracture. However, the risk factors for Asian men are still unclear.

The aim of this study was to investigate the prevalence of radiographically defined vertebral fracture, and to identify underlying risk factors associated with vertebral fracture in the aged population in four Asian countries (Hong Kong, Thailand, Indonesia and Japan). Existing data from Beijing, China were used for comparison.

Methods

Subjects

In total, 1588 subjects were recruited from Hong Kong, Thailand, Indonesia and Japan. Each country was required to recruit 400 ambulatory community-dwelling subjects (200 males and 200 females), half of whom were aged 65–74 years and the other half were aged ≥75 years. They all were ethnic Asians. Subjects were recruited in community centres (recreation centres for group activities, social support and public information) for the elderly. Recruitment notices were placed at these centres explaining the purpose and procedures of this study in different districts, including urban and rural areas. Moreover, community activities and community advertisements were used to enhance the representativeness of the whole region.

Radiographs and digitization

Radiographic films of the lateral thoracic and lumbar spine were taken with a tube-to-film distance of 100 cm, with thoracic films centred at T8 and lumbar films centred at L3. The radiographs were evaluated by morphometry using a backlight translucent digitizing table (GTCO, Rockville, MD, USA) and cursor. Six points were marked on the radiographs with a wax pencil for each vertebral body T4–L4, and the X,Y co-ordinates for each point were recorded on an electronic grid with a resolution of 0.1 mm. In total, 120 and 68 subjects lacked T4 and T5, respectively. Standardized procedures were adopted. The six points corresponded to the four corners of the vertebral body and the midpoints of the end plates[8] (Fig. 1). Vertebral height ratios (VHR) were calculated [anterior to posterior (Ha/Hp), middle to posterior (Hm/Hp) and posterior above to posterior below (Hp/Hp−1 and Hp/Hp+1)]. Prevalent vertebral fracture was defined as a reduction of >3 standard deviations (SD) among any one of the VHRs.[6,8] Mean (SD) VHRs are shown in Table 1. X-ray films for Hong Kong, Thailand and Indonesia were measured in Hong Kong by three trained members of staff, all with >10 years of experience and trained by the radiologist-in-charge with standardized procedures. Fifteen films were selected at random for reliability analysis. Whereas X-ray films from Japan were measured in Japan, 30 were selected at random and sent to Hong Kong for reliability analysis. The analysis was performed by two members of staff (one from Hong Kong and one from Japan).

Questionnaire

Subjects were interviewed using a standardized and structured questionnaire in Hong Kong, Thailand and Indonesia by trained staff. Data collected included demographic information, Mini-Mental Status Examination score, medical history, fall history, smoking habit, alcohol consumption, Physical Activity Screening for Elderly score, quality of life,

Fig. 1 – Measurement of vertebral height. Hp, posterior height; Hm, mid-body height; Ha, anterior height.

Table 1 – Adjusted means[a] and standard deviations (SD) of vertebral height ratios in Chinese male and female subjects.

Level	Ha/Hp		Hm/Hp		Hp/Hp−1		Hp/Hp+1	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Male[b]								
T4	0.87	0.06	0.91	0.04	–	–	1.00	0.06
T5	0.87	0.07	0.92	0.04	1.00	0.06	0.98	0.06
T6	0.87	0.07	0.92	0.04	1.03	0.06	0.98	0.06
T7	0.86	0.07	0.92	0.04	1.02	0.06	1.00	0.06
T8	0.89	0.07	0.93	0.04	1.00	0.06	0.98	0.06
T9	0.91	0.07	0.94	0.04	1.02	0.06	0.95	0.06
T10	0.92	0.07	0.94	0.04	1.05	0.06	0.91	0.06
T11	0.86	0.08	0.91	0.05	1.10	0.07	0.93	0.05
T12	0.84	0.07	0.90	0.04	1.08	0.06	0.95	0.05
L1	0.84	0.06	0.89	0.04	1.06	0.05	1.01	0.04
L2	0.88	0.06	0.91	0.03	1.00	0.04	1.01	0.04
L3	0.92	0.06	0.94	0.04	0.99	0.04	1.06	0.05
L4	0.97	0.07	1.00	0.05	0.95	0.04	–	–
Female[c]								
T4	0.90	0.08	0.92	0.06	–	–	0.99	0.09
T5	0.88	0.08	0.91	0.06	1.03	0.09	0.99	0.07
T6	0.86	0.07	0.91	0.05	1.03	0.07	0.99	0.07
T7	0.86	0.08	0.91	0.05	1.02	0.07	0.99	0.06
T8	0.88	0.07	0.92	0.05	1.01	0.06	0.99	0.06
T9	0.92	0.08	0.94	0.05	1.01	0.06	0.97	0.06
T10	0.92	0.08	0.94	0.05	1.04	0.07	0.95	0.06
T11	0.87	0.08	0.91	0.05	1.06	0.07	0.94	0.06
T12	0.86	0.09	0.90	0.06	1.07	0.07	0.96	0.07
L1	0.87	0.08	0.89	0.05	1.05	0.08	1.00	0.05
L2	0.93	0.08	0.91	0.05	1.01	0.06	1.01	0.06
L3	0.98	0.08	0.95	0.06	0.99	0.06	1.04	0.07
L4	1.02	0.10	1.01	0.07	0.96	0.07	–	–

Ha/Hp, anterior height of vertebrae/posterior height of vertebrae; Hm/Hp, middle height of vertebrae/posterior height of vertebrae; Hp/Hp−1, posterior height of vertebrae/posterior height of vertebrae above; Hp/Hp+1, posterior height of vertebrae/posterior height of vertebrae below.

a Adjusted means were estimated as the mode on the log-frequency curve after trimming 5% of the values from each end of the distribution. The adjusted SDs were estimated by quantile–quantile plot after 10% of values were trimmed from each end of the distribution.

b Data used by Lau et al.[30]

c Data published by Lau et al.[3]

fracture history, back pain and musculoskeletal symptoms, medications, diet history, Geriatric Depression Scale score, and past longest occupation in their life.

Dual X-ray densitometry and anthropometric measurement

Bone mineral density (BMD), height and weight were measured in Hong Kong and Japan. Hip and spine BMD were measured by dual energy X-ray absorptiometry (DXA) using a Hologic QDR-4500W densitometer (Hologic, Waltham, MA, USA). The same type of DXA machine was used in both Hong Kong and Japan. The coefficient of variation (CV) in the laboratory was 0.7% and 0.9% for hip and spine, respectively. Height was measured using a Holtain Harpenden stadiometer (Holtain Ltd., Crosswell, UK), and weight was measured using the Physician Beam Balance Scale (Healthometer, IL, USA) with subjects wearing a light gown.

Study flow

The study started in Hong Kong, Indonesia and Thailand. Radiographs and questionnaires were performed in these three countries. Japan joined the study at a later date; radiographs, BMD and anthropometric measurements were conducted but no questionnaire was used. As different information was collected from the four countries, the results are shown in three parts. First, the prevalence of vertebral fracture was compared between the four countries. Second, lifestyle and medical risk factors for vertebral fracture were analysed for Hong Kong, Indonesia and Thailand. Finally, anthropometric factors in Japan were compared with those for Hong Kong.

Statistical analysis

Inter-rater reliability of each parameter was assessed using the intraclass correlation coefficient (ICC). The prevalence of deformity was calculated based on the number of individuals with at least one vertebral deformity, and this was compared between countries using Chi-squared test. Data were analysed separately by sex. Continuous variables were compared between the countries using t-test or analysis of variance, while categorical variables were compared using Chi-squared test. Logistic regression (with adjustment for age) was used to calculate odds ratios (OR) and 95% confidence intervals (CI) of various lifestyle and anthropometric factors for definite vertebral deformity. Significant factors were collated to form the final models. All statistical analyses were performed using SAS Version 9.1 (SAS Institute, Inc., Cary, NC, USA). An α level of 5% was used as the level of significance.

Results

Inter-rater reliabilities of vertebral measurements were fair to good. ICC (3,1) ranged from 0.54 to 0.94 for anterior heights, from 0.70 to 0.96 for middle heights, and from 0.60 to 0.92 for posterior heights among 15 randomly selected subjects from Hong Kong, Thailand and Indonesia. ICC (3,1) ranged from 0.73 to 0.93 for anterior heights, from 0.69 to 0.93 for middle heights, and from 0.76 to 0.95 for posterior heights among 30 Japanese subjects.

Part 1: prevalence of vertebral fracture in four Asian countries

Seven hundred and seventy males (mean age 72.9 years) and 818 females (mean age 72.4 years) were recruited. The prevalence of vertebral fracture in Hong Kong, Indonesia, Thailand and Japan is shown in Table 2. Among males, the prevalence of fracture was highest in Japan (36.6% for age 65–74 years, 37.6% for age ≥75 years); the difference between Japan and the other three countries was significant. The prevalence of fracture was lowest in Hong Kong males (9.2%

Table 2 – Prevalence of vertebral fracture.

	Prevalence of vertebral fracture (%)				P-value of Chi-square
	Hong Kong (H)	Indonesia (I)	Thailand (T)	Japan (J)	
Male					
Age 65–74 years	(n = 98)	(n = 127)	(n = 105)	(n = 101)	
Radiological fracture					
Definite vertebral deformity, <mean − 3 SD	9.2	15.0	17.1	36.6[a,b,c]	<0.0001
Severe vertebral deformity, <mean − 4 SD	3.1	7.1	13.3[a]	20.8[a,b]	0.0003
Reported fracture	0.0	0.0	2.9	–	0.0402
Age ≥75 years	(n = 100)	(n = 40)	(n = 98)	(n = 101)	
Radiological fracture					
Definite vertebral deformity, <mean − 3 SD	18.0	20.0	24.5	37.6[a,b,c]	0.0102
Severe vertebral deformity, <mean − 4 SD	9.0	17.5	20.4[a]	20.8[a]	0.0926
Reported fracture	2.0	0.0	1.0	–	0.6125
Female					
Age 65–74 years	(n = 99)	(n = 170)	(n = 98)	(n = 101)	
Radiological fracture					
Definite vertebral deformity, <mean − 3 SD	2.0	7.6	8.2[a]	18.8[a,b,c]	0.0010
Severe vertebral deformity, <mean − 4 SD	1.0	5.9	6.1	10.9[a]	0.0338
Reported fracture	1.0	0.0	3.0	–	0.2930
Age ≥75 years	(n = 98)	(n = 54)	(n = 97)	(n = 101)	
Radiological fracture					
Definite vertebral deformity, <mean − 3 SD	15.3	13.0	17.5	28.7[a,b]	0.0727
Severe vertebral deformity, <mean − 4 SD	10.2	9.3	15.5	18.8	0.2312
Reported fracture	1.0	0.0	3.0	–	0.2930

SD, standard deviation.
Note: a higher number of reported fractures was significantly associated with a higher number of radiological fractures (Chi-squared = 7.078, P-value = 0.0078).
a P-value < 0.05 comparing Indonesia (I), Thailand (T) or Japan (J) with Hong Kong (H), by Chi-squared test.
b P-value < 0.05 comparing Thailand (T) or Japan (J) with Indonesia (I), by Chi-squared test.
c P-value < 0.05 comparing Japan (J) with Thailand (T), by Chi-squared test.

for age 65–74 years; 18% for age ≥75 years). In females, the prevalence of fracture was also highest in Japan (18.8% for age 65–74 years; 28.7% for age ≥75 years), and was lowest in Hong Kong and Indonesia (2% for age 65–74 years; 13% for age ≥75 years). The reported fracture rates ranged from 0 to 2.97%, which were much lower than radiological fracture rates (0–24.5%) (Table 2). More reported fractures were significantly associated with more radiological fractures (Chi-squared = 7.078, P-value = 0.0078).

Part 2: lifestyle and medical factors of vertebral fracture in Hong Kong, Indonesia and Thailand

Results for Hong Kong, Indonesia and Thailand are shown in Tables 3 and 4. Subjects' characteristics are shown in Table 3. Males and females in Hong Kong had significantly higher quality of life {Short Form[SF]-12 (mental)}; higher prevalence of hypertension, heart disease and myocardial infarction/angina; and lower levels of education compared with Indonesia and Thailand. The percentage of respondents who stated that their longest occupation had been as a farmer was highest in Thailand.

Risk factors of vertebral fracture are shown in Table 4. For males, older age, lower SF-12 (physical) score, and history of stroke were significantly associated with vertebral fracture. For females, older age, lower SF-12 (physical) score, history of cataract, and past longest occupation as a farmer were significantly associated with vertebral fracture. In logistic regression, a lower SF-12 (physical) score (OR 0.68, 95% CI 0.55–0.84) was associated with vertebral fracture among the males. Older age (OR 1.33, 95% CI 1.03–1.71), lower SF-12 (physical) score (OR 0.73, 95% CI 0.56–0.95), history of cataract (OR 2.86, 95% CI 1.48–5.53), and past longest occupation as a farmer (OR 2.47, 95% CI 1.07–5.72) were associated with vertebral fracture in females.

Part 3: anthropometric factors of vertebral fracture in Hong Kong and Japan

To investigate the difference in fracture rate between Japan and Hong Kong, 25 males and 27 females in Japan were selected at random as subsamples to obtain anthropometric factors: weight and height and bone density. Results are shown in Tables 5 and 6. Differences in characteristics between Hong Kong and Japan are shown in Table 5. Subjects in Hong Kong were heavier and taller (marginally in males but significantly in females). The body mass index of Hong Kong females was also significantly higher. Logistic regressions of vertebral fractures are shown in Table 6. Lower hip BMD (OR 1.47, 95% CI 1.001–2.17 per SD reduction) was associated with vertebral fracture in males, while in females, older age (OR 1.9, 95% CI 1.13–3.2), heavier weight (OR 1.6, 95% CI 1.1–2.3) and lower hip BMD (OR 3.23, 95% CI 1.72–6.25 per SD reduction) were associated with vertebral fracture.

Table 3 – Characteristics of subjects by country.

Variable	Male			P-value[a]	Female			P-value[a]
	Mean (SD)/%				Mean (SD)/%			
	Hong Kong ($n = 198$)	Indonesia ($n = 167$)	Thailand ($n = 203$)		Hong Kong ($n = 197$)	Indonesia ($n = 224$)	Thailand ($n = 195$)	
Age	73.7 (5.4)	70.3 (5.1)	73.8 (6.0)	0.9610	73.8 (5.5)	70.3 (5.8)	73.7 (5.5)	0.9078
SF-12 (physical)	49.7 (9.0)	47.2 (10.4)	46.0 (10.9)	**0.0003**	45.3 (9.0)	41.8 (11.6)	43.6 (11.6)	0.1085
SF-12 (mental)	56.4 (5.9)	52.1 (8.1)	53.1 (8.7)	**<0.0001**	55.7 (8.1)	52.3 (8.3)	52.7 (9.1)	**0.0005**
Physical activity (PASE score)	104.8 (49.8)	102.7 (67.9)	93.0 (80.8)	0.0880	81.3 (30.7)	70.8 (42.7)	70.5 (47.6)	**0.0081**
Marital status: married	84.1%	82.4%	81.3%	0.7564	57.7%	62.3%	50.5%	**0.0456**
Education				**<0.0001**				**<0.0001**
Primary or below	53.2%	41.9%	64.5%		76.6%	55.1%	72.9%	
Secondary	33.8%	43.8%	14.2%		18.9%	34.8%	15.1%	
Tertiary or above	12.9%	14.4%	21.3%		4.5%	10.1%	12.0%	
Demented (MMSE < 24)	11.0%	13.4%	15.8%	0.3634	36.3%	22.9%	25.0%	**0.0046**
Diabetes	14.9%	10.5%	11.3%	0.3690	9.0%	14.2%	13.0%	0.2243
Reported osteoporosis	5.0%	1.7%	3.5%	0.2361	9.0%	11.6%	10.0%	0.6492
Stroke	6.0%	2.3%	4.4%	0.2263	3.5%	2.2%	2.0%	0.5768
Hypertension	39.3%	19.2%	22.7%	**<0.0001**	42.3%	26.7%	25.0%	**0.0002**
Heart disease	19.9%	2.3%	4.9%	**<0.0001**	14.4%	3.5%	4.5%	**<0.0001**
Myocardial infarction/ angina	18.4%	1.2%	4.9%	**<0.0001**	11.4%	4.3%	3.5%	**0.0014**
Congestive heart failure	2.5%	0.6%	2.5%	0.3150	3.5%	1.3%	1.0%	0.1328
Chronic obstructive pulmonary disease	15.9%	5.2%	3.0%	**<0.0001**	6.5%	4.3%	1.5%	**0.0424**
Cataracts	33.3%	18.6%	22.2%	**0.0024**	44.8%	23.3%	27.0%	**<0.0001**
Gastrectomy	9.0%	8.1%	11.3%	0.5425	4.0%	14.2%	7.0%	**0.0005**
Cancer	4.5%	0.6%	1.5%	**0.0268**	3.5%	2.2%	1.5%	0.4115
Fall in past 12 months	22.9%	4.1%	21.7%	**<0.0001**	20.9%	14.2%	31.5%	**<0.0001**
Smoker	9.5%	29.2%	19.4%	**<0.0001**	0.5%	1.4%	1.0%	0.6472
Use of alcohol at least 12 times in past 12 months	22.9%	5.5%	36.1%	**<0.0001**	0.5%	0.5%	6.5%	**<0.0001**
Fracture after 50 years of age	6.0%	5.5%	9.4%	0.2739	16.9%	5.6%	7.6%	**0.0002**
Past longest occupation as a farmer	1.0%	14.3%	44.8%	**<0.0001**	3.1%	5.7%	40.0%	**<0.0001**

SF-12, Short Form-12; PASE, physical activity screening for elderly; MMSE, Mini-Mental State Examination.
Bold: P-value < 0.05.
a P-value of Chi-squared for categorical variables or analysis of variance for continuous variables where appropriate.

Discussion

The occurrence of osteoporotic vertebral fracture is particularly common in older postmenopausal Asian women. The common sites involved are T12 and L1 as these levels are, biomechanically, the most vulnerable regiments of the thoracolumbar spine.[9] The first vertebral fracture is an important indicator for subsequent vertebral fracture, and possibly non-vertebral fracture including hip fracture.[10,11] Understanding the prevalence of vertebral fracture and deformity is critical for prevention.

Fracture identification can easily be affected by differences in radiographic methods. Fracture definition and methods of morphological assessment also affect the determination of fracture rates. Degenerative spondylosis and old asymptomatic spinal fractures may lead to spuriously high BMD at the site of involvement, thus diminishing the sensitivity in the prediction of fracture. In this study, all the radiographs were taken according a standardized protocol, and were analysed by trained and experienced assessors to minimize possible observer bias and to acquire more precise and accurate results. The number of reported vertebral fractures was generally lower in both males and females than the number of radiologically determined vertebral fractures in all four countries. As elsewhere, vertebral fractures were often under-reported. Vertebral fractures could also be overlooked when patients present with back pain arising from various spinal conditions.

This study found that the prevalence of vertebral fracture was significantly higher in Japan compared with Hong Kong, Thailand and Indonesia for both sexes. BMD is an important factor,[12,13] but in this study, no difference was noted between Hong Kong and Japan. This may be explained by the smaller body size of Japanese subjects. In a systematic review, Ruyssen-Witrand *et al.*[14] showed that vertebral size was an independent risk factor for vertebral fracture. After controlling for well-known confounding factors such as age, height,

Table 4 – Characteristics in subjects with vertebral fracture and control.

Variable	Unit	Male		Female	
		Age-adjusted model OR (95% CI)	Multivariate model OR (95% CI)	Age-adjusted model OR (95% CI)	Multivariate model OR (95% CI)
Age	5	**1.24 (1.03–1.49)[a]**	1.17 (0.96–1.44)	**1.48 (1.20–1.84)[a]**	**1.33 (1.03–1.71)**
Country					
Hong Kong	–	1	1	1	1
Indonesia	Indonesia/Hong Kong	1.44 (0.79–2.62)	1.28 (0.68–2.40)	1.36 (0.67–2.72)	1.20 (0.53–2.73)
Thailand	Thailand/Hong Kong	1.66 (0.97–2.82)	1.45 (0.84–2.51)	1.58 (0.82–3.05)	1.36 (0.61–2.99)
SF-12 – Physical	10	**0.65 (0.53–0.80)**	**0.68 (0.55–0.84)**	**0.67 (0.53–0.85)**	**0.73 (0.56–0.95)**
SF-12 – Mental	10	0.99 (0.75–1.32)		0.86 (0.64–1.17)	
Physical activity (PASE score)	50	1.00 (0.84–1.19)		0.72 (0.50–1.03)	
Marital status – married	Yes/no	1.78 (0.91–3.46)		0.68 (0.40–1.18)	
Education					
Primary or below	–	1		1	
Secondary	Secondary/primary	0.63 (0.36–1.11)		0.96 (0.48–1.91)	
Tertiary or above	Tertiary/primary	1.02 (0.55–1.90)		0.37 (0.09–1.57)	
Demented (MMSE<24)	Yes/no	1.36 (0.74–2.49)		1.34 (0.76–2.37)	
Diabetes	Yes/no	1.09 (0.56–2.14)		0.67 (0.26–1.75)	
Reported osteoporosis	Yes/no	1.26 (0.41–3.91)		2.01 (0.95–4.24)	
Stroke	Yes/no	**2.61 (1.08–6.31)**	2.32 (0.94–5.71)	1.43 (0.31–6.60)	
Hypertension	Yes/no	1.08 (0.66–1.77)		0.72 (0.39–1.31)	
Heart disease	Yes/no	0.80 (0.36–1.77)		0.94 (0.35–2.53)	
Myocardial infarction/angina	Yes/no	0.94 (0.42–2.08)		0.88 (0.29–2.60)	
Congestive heart failure	Yes/no	1.67 (0.43–6.47)		1.74 (0.37–8.26)	
Chronic obstructive pulmonary disease	Yes/no	1.02 (0.46–2.27)		–	
Cataracts	Yes/no	1.21 (0.73–1.98)		**1.80 (1.05–3.10)**	**2.86 (1.48–5.53)**
Gastrectomy	Yes/no	0.83 (0.38–1.83)		0.72 (0.25–2.09)	
Cancer	Yes/no	–		0.64 (0.08–5.04)	
Fall in past 12 months	Yes/no	0.90 (0.49–1.63)		1.39 (0.76–2.51)	
Smoker	Yes/no	0.62 (0.33–1.20)		–	
Use of alcohol at least 12 times in past 12 months	Yes/no	1.30 (0.78–2.17)		2.12 (0.45–9.95)	
Fracture after 50 years of age	Yes/no	2.00 (0.93–4.31)		1.36 (0.62–2.98)	
Past longest occupation as a farmer	Yes/no	1.19 (0.68–2.08)		2.14 (1.13–4.05)	**2.47 (1.07–5.72)**

SF-12, Short Form-12; PASE, Physical Activity Screening for Elderly; MMSE, Mini-Mental State Examination; OR, odds ratio; CI, confidence interval.
Bold: *P*-value < 0.05.
a Crude OR.

weight and BMD, small vertebral dimensions including area, cross-sectional area and volume were associated with vertebral fracture.[14–16] Moreover, there is a difference in the nutrient intake of these two populations; dietary calcium intake in the Japanese population is less than that of the Hong Kong population (550 mg/day in men and 519 mg/day in women vs 628 mg/day and 569 mg/day for people aged ≥65 years).[17,18] Kobayashi reported that the calcium content of river water in Japan was lower than that in most European countries.[19]

For Asian women, a review of vertebral fracture revealed that the prevalence of vertebral fracture increases steeply with age in Beijing: the prevalence of vertebral fracture in Chinese women aged 50–59 years was 3.9%, compared with 10.5%, 15% and 31.2% at ages 60–69, 70–79 and ≥80 years.[6,20,21] A similar trend has also been observed among Japanese women residing in Japan and Hawaii[22,23]; the rates were slightly higher for those living in Japan (8%, 25%, 38% and 43% for ages 65–70, 70–75, 75–80 and 80–85 years, compared with 5%, 15%, 25% and 27% for those living in Hawaii in 1996), suggesting that environmental factors are more influential than genetic factors.[24] Horikawa *et al.* reported a prevalence of 22.6% for Japanese women aged 65–92 years living in a fishing/farming village located in Nansei-cho in 2001.[25] Data for Japan in the present study showed similar rates. These data are similar to findings among Caucasian women in the USA, where the prevalence of vertebral fracture was 22% for women aged 70–79 years, and 34% for women aged ≥80 years. Hence, observations from the present study suggest that vertebral fracture is as prevalent in Asian women as in Caucasian women.[20]

The prevalence of vertebral fracture among Chinese women in 1996 in Hong Kong was 29% at age 70–79 years.[1,3] The current study found a prevalence of vertebral fracture of 2% at age 65–74 years and 15% at age ≥75 years among Hong Kong Chinese women. The prevalence of vertebral fracture appears to have decreased significantly over the years between these studies. This may reflect a proper

Table 5 – Comparison of characteristics between Hong Kong and Japan.

Variable	Mean (SD)		P-value[a]
	Hong Kong	Japan	
Male	n = 198	n = 25	
Age (years)	73.75 (5.40)	73.28 (4.31)	0.6784
Weight (kg)	61.86 (9.35)	58.34 (6.66)	0.0692
Height (cm)	162.64 (5.75)	160.50 (7.70)	0.0925
Body mass index (kg/m^2)	23.35 (3.13)	22.72 (2.73)	0.3315
Hip BMD (g/cm^2)	0.851 (0.129)	0.823 (0.105)	0.2956
Spine BMD (g/cm^2)	0.950 (0.183)	0.961 (0.151)	0.7742
Female	n = 197	n = 27	
Age (years)	73.76 (5.51)	72.33 (4.67)	0.2012
Weight (kg)	55.01 (9.01)	48.62 (7.98)	0.0006
Height (cm)	151.48 (4.99)	148.61 (6.23)	0.0072
Body mass index (kg/m^2)	23.93 (3.44)	21.98 (3.05)	0.0056
Hip BMD (g/cm^2)	0.697 (0.113)	0.691 (0.112)	0.7654
Spine BMD (g/cm^2)	0.757 (0.141)	0.787 (0.137)	0.3028

BMD, bone mineral density; SD, standard deviation.
a P-value of t-test for continuous or Chi-squared test for categorical variables.

osteoporosis prevention regime, health promotion and raised public awareness of osteoporosis in Hong Kong since 2001. The Hong Kong experience may set an example to other Asian countries for reference in combating osteoporosis.

Lau *et al.*[13] reported that the prevalence of vertebral fracture among Chinese men aged 70–79 years in 1998 in Hong Kong was 16%. The present study shows a similar result; 9.2% and 18% for men aged 65–74 and ≥75 years, respectively.

This study found that both male and female subjects aged ≥75 years with a lower hip BMD have more vertebral fractures. Most vertebral fractures are not caused by direct trauma[26] but are linked with low BMD.[10,12] Previous studies have shown that US women of African descent have the highest bone mass in the spine, while Caucasian women have intermediate values, and Asian women have the lowest values (unadjusted BMD values). An analysis and comparison of different ethnic populations residing in the USA suggested that the BMD of Asian women differed little from that of Caucasian women after adjustment for body size.[27] Unadjusted lumbar spine and femoral neck BMDs were 7–12% and 14–24% higher in African-American women compared with Caucasian, Japanese or Chinese women. Among women of comparable weight of <70 kg, there were no differences in lumbar spine BMD among African-American, Chinese and Japanese women, all of whom have higher BMDs than Caucasians.[20] This study also noted that there were no differences in lumbar spine and hip BMDs between Hong Kong and Japanese women or men. Kung reported that the pattern and magnitude of age-related bone loss in the lumbar spine was similar between female Asian and Caucasian populations.[20] Subjects with a spinal fracture had a spine or hip BMD that was 20–30% lower compared with normal healthy controls. After adjusting for age and body size, each SD reduction in bone density in the Hong Kong Chinese women increased the risk of vertebral fracture approximately two-fold for both spine and femoral neck measurements, whereas in Beijing Chinese women, each SD reduction in BMD at the spine or hip was associated with a 2.5-fold increased risk of vertebral fracture.[20] In the present study, among Hong Kong and Japanese women, each SD reduction in hip BMD was associated with a 3.2-fold increased risk of vertebral fracture after adjustment for age and body size, which is consistent with the previous finding. In men, each SD reduction had a 1.5-fold increased risk, showing less

Table 6 – Logistic regression of vertebral fracture.

Variable	Mean (SD)/frequency (%)		Unit	Adjusted OR (95% CI)
	Control	Vertebral fracture		
Male	n = 187	n = 36		
Age	73.57 (5.27)	74.61 (5.29)	5	1.15 (0.81–1.65)
Country				
Hong Kong	171 (91.4%)	27 (75.0%)	–	1
Japan	16 (8.6%)	9 (25.0%)	Japan/Hong Kong	**3.67 (1.42–9.49)**
Weight (kg)	61.48 (9.17)	60.94 (9.21)	5	1.27 (0.95–1.69)
Height (cm)	162.59 (5.77)	161.07 (7.14)	5	0.77 (0.55–1.09)
Hip BMD (g/cm^2)	0.855 (0.126)	0.816 (0.125)	−0.1	**1.47 (1.001–2.17)**
Female	n = 201	n = 23		
Age	73.09 (5.31)	77.43 (4.81)	5	**1.90 (1.13–3.20)**
Country				
Hong Kong	180 (89.6%)	17 (73.9%)	–	1
Japan	21 (10.5%)	6 (26.1%)	Japan/Hong Kong	**5.99 (1.58–22.68)**
Weight (kg)	54.45 (9.10)	53.42 (9.69)	5	**1.61 (1.11–2.33)**
Height (cm)	151.51 (5.01)	148.55 (6.39)	5	0.68 (0.39–1.17)
Hip BMD (g/cm^2)	0.707 (0.109)	0.608 (0.115)	−0.1	**3.23 (1.72–6.25)**

BMD, bone mineral density; SD, standard deviation; OR, odds ratio; CI, confidence interval.
Bold: P-value < 0.05.

influence than that in women. However, low BMD is still a causal factor of vertebral fracture.[12]

Lifestyle and medical factors are other important determinants of vertebral fracture. Women who had jobs involving heavy physical labour had a lower prevalence of vertebral fracture than women who had had more sedentary jobs. This suggests that strenuous physical activity during young adulthood is protective against vertebral fracture.[6] Gregg *et al.*[28] found that physical activity reduced the risk of hip fracture but not vertebral or wrist fractures. However, in this study, subjects with vertebral fracture had significantly lower SF-12 (physical) scores, which implies that poor physical strength may lead to more vertebral fractures. Stroke is another risk factor for vertebral fracture. Kim *et al.* reported that in the acute stages of stroke, bone loss progressed rapidly. Risks of osteoporosis and vertebral fracture were higher among subjects who had experienced a stroke.[29] People with cataracts were more likely to fall, which increases the risk of fracture.[30] The prevalence of vertebral fracture was higher in farmers. This may be explained by the lower intake of calcium. Kamiyama *et al.* performed a survey in various areas in Japan, and found that calcium intake in three farm villages was lower than that in the city (512, 532 and 601 mg vs 633 mg). The prevalence of osteoporosis was also higher in farm villages.[31]

Subjects from Hong Kong had the highest prevalence of hypertension, heart disease and myocardial infarction/angina, but the association with vertebral fracture was insignificant. This implies that hypertension, heart disease and myocardial infarction/angina are not direct risk factors for vertebral fracture. However, Lau *et al.*[32] reported that hypertension was associated with higher BMD; this may explain the fact that the lowest prevalence of vertebral fracture was seen in Hong Kong.

There were more male smokers in Indonesia. However, smoking in Indonesia did not appear to lead to adverse effects resulting in vertebral fracture. Grazio *et al.*[33] found that current smoking was a risk factor for vertebral fracture, but a study by Bensen *et al.*[34] did not. Similarly, the rate of falls was lowest in Indonesia, but this did not reflect on the prevalence of vertebral fracture, implying that falls are not a strong risk factor for vertebral fracture. This differed from hip fracture, which was always associated with falls and trauma[20] and 90% of cases resulted from falls.[35]

This study was a joint venture between Hong Kong, Thailand, Indonesia and Japan. Radiographic assessments of vertebral fractures were completed carefully in all four countries using the same methodology. As subjects were recruited using community activities and community advertisements, the subjects were members of the general population and hence the results are representative. The percentages of people who worked as farmers in Hong Kong, Indonesia and Thailand were 2.1%, 9.3% and 42.4% in this study, which is close to the population figures: 0.9%, 12.4% and 39%, respectively.[36–38] Unfortunately, the Indonesian and Thai collaborators in this study did not possess a DXA machine; otherwise data correlation between the groups could be more comprehensive. Likewise, the questionnaire was not used in Japan, which influenced the completeness of this study. Moreover, it would be more convincing if a study with a larger sample size was conducted. Despite the obvious limitations, this study provides useful data for prevention planning. Some of these data are similar to the results of previous studies, but some are unique (e.g. strong association between low SF-12 (physical) score and vertebral fracture among Asians; smoking habit was not an important risk factor for vertebral fracture).

Acknowledgements

Ethical approval

The institutional review board at each centre approved the study protocol, and written informed consent was obtained from all participants.

Funding

None declared.

Conflict of interest

None declared.

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