Table III
Baseline risk factors for incident radiographic LS.

		KL≥2					KL≥3				
		No (%)	Crude OR	95% CI	Adjusted OR	95% CI	No (%)	Crude OR	95% CI	Adjusted OR	95% CI
Age, years			1.05	1.03–1.06	1.05	1.03–1.06		1.05	1.04–1.07	1.05	1.03–1.06
BMI, kg/m^2			1.07	1.02–1.12	1.07	1.02–1.13		1.01	0.97–1.06		
Gender											
Men		76/152 (50.0)	1.00	Reference	1.00	Reference	66/431 (15.3)	1.00	Reference	1.00	Reference
Women		198/575 (34.4)	0.53	0.37–0.76	0.50	0.34-0.72	200/845 (23.7)	1.71	1.27–2.34	2.19	1.54–3.17
Low back pain	No	223/607 (36.7)	1.00	Reference			219/1078 (20.3)	1.00	Reference		
	Yes	51/120 (42.5)	1.27	0.85–1.89			47/198 (23.7)	1.22	0.85–1.74		
Smoking	No	244/661 (36.9)	1.00	Reference			246/1136 (21.7)	1.00	Reference	1.00	Reference
	Yes	30/66 (45.5)	1.42	0.85–2.37			20/140 (14.3)	0.60	0.36–0.97	1.01	0.58–1.69
Alcohol	No	184/476 (38.7)	1.00	Reference			185/774 (23.9)	1.00	Reference	1.00	Reference
	Yes	90/251 (35.9)	0.89	0.64–1.22			81/502 (16.1)	0.61	0.46–0.82	0.87	0.63–1.20
KL grade											
KL=0 or 1								1.00	Reference	1.00	Reference
KL=2								1.66	1.27–2.19	1.67	1.24–2.25

The adjusted ORs were calculated by multiple logistic regression analysis after adjustment for all other significant variables without adjustment. We did not include KL grade in the analysis of incident KL≥2 LS, because all subjects had KL=0 or 1.

women. The incidence of lower back pain increased as the number of KL≥3 vertebral interspaces increased in women, whereas the incidence was similar in men with 0, 1 and 2 KL≥3 vertebral interspaces, and having 3 or more KL≥3 vertebral interspaces suddenly increased the incidence of lower back pain.

There were several limitations in this study. First, we did not read the X-rays for osteophytes and joint space narrowing scored separately. Furthermore, in the KL classification, atrophic and degenerative features of LS, which likely have different aetiology, were combined; thus, the differences in associations with pain between these features may have been obscured. We are developing a computer-aided diagnostic program to enable fully automated measurements of the major features of LS, including disc space narrowing and osteophytosis on plain radiographs. The second limitation of our study was that a single orthopaedist read both films in pairs without being blinded to baseline and follow-up status. This may likely have caused the reader to over-read progression (i.e., inflate sensitivity) and therefore confer bias. This may be one reason for the higher incidence of LS in the present study compared with other studies. Third, we used only plain radiography to assess LS, although computed tomography (CT)/MRI is standard practice for evaluating nonspecific lower back pain in many countries. In addition, plain films can be affected by scoliosis, positioning and multiple other factors, which may have affected our results. Fourth, although experienced orthopaedists asked all participants the question regarding lower back pain based on previous studies[3,8], we defined lower back pain as present or absent, rather than as a continuous validated measure of pain, such as assessed by the Oswestry Disability Index[25]. Categorical methods are statistically less powerful than continuous methods. In addition, severity of lower back pain was not assessed in the present study. The association between lower back pain and other variables might have been underestimated in the present study. Furthermore, although the psychosocial dimension is an important factor for lower back pain[26], we did not include this in our analysis. Fifth, in the follow-up study, the responders was younger, more likely to be women and less likely to have LS at baseline compared with the nonresponders, which may have affected the results in the present study, because age, gender and KL grade were found to be associated with incident LS 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 LS in Japan. Gender seems to be distinctly associated with incident KL≥2 and KL≥3 LS, indicating that different

Table IV
Baseline risk factors for progressive LS and incident lower back pain

		Progressive LS					Lower back pain				
		No (%)	Crude OR	95% CI	Adjusted OR	95% CI	No (%)	Crude OR	95% CI	Adjusted OR	95% CI
Age, years			1.05	1.04–1.07	1.05	1.04–1.07		1.00	0.99–1.01	1.00	0.99–1.01
BMI, kg/m^2			1.01	0.98–1.05				1.01	0.98–1.04	1.01	0.98–1.04
Gender											
Men		123/599 (20.5)	1.00	Reference	1.00	Reference	178/630 (28.3)	1.00	Reference	1.00	Reference
Women		255/931 (27.4)	1.46	1.14–1.87	1.44	1.10–1.91	380/1219 (31.2)	1.15	0.93–1.42	1.12	0.90–1.39
Low back pain	No	302/1225 (24.7)	1.00	Reference							
	Yes	76/305 (24.9)	1.01	0.76–1.35							
Smoking	No	348/1385 (25.1)	1.00	Reference			503/1677 (30.0)	1.00	Reference		
	Yes	30/145 (20.7)	0.78	0.50–1.17			55/172 (32.0)	1.10	0.78–1.53		
Alcohol	No	253/958 (26.4)	1.00	Reference			360/1162 (31.0)	1.00	Reference		
	Yes	125/572 (21.9)	0.78	0.61–0.99			198/687 (28.8)	0.90	0.73–1.11		
KL grade											
KL=0 or 1							177/607 (29.2)	1.00	Reference	1.00	Reference
KL=2		103/549 (18.8)	1.00	Reference			118/471 (25.1)	0.81	0.62–1.06	0.86	0.64–1.14
KL≥3		275/981 (28.0)	1.69	1.31–2.18			263/771 (34.1)	1.26	1.00–1.58	1.32	1.03–1.69

The adjusted ORs were calculated by multiple logistic regression analysis after adjustment for all other significant variables without adjustment. We did not include KL grade in the analysis of incident KL≥2 LS, because all subjects had KL=0 or 1.

Table V
Association of KL ≥ 3 LS at baseline with incident lower back pain by each vertebral interspace and the severest space in 1,849 subjects with no lower back pain at baseline

		L1/2		L2/3		L3/4		L4/5		L5/S		The severest	
		No. (%)	OR (95% CI)	No.(%)	OR (95% CI)	No. (%)	OR (95% CI)	No. (%)	OR (95% CI)	No. (%)	OR (95% CI)	No. (%)	OR (95% CI)
Men	KL < 3	154/552 (27.9)	1.00	142/528 (26.9)	1.00	136/512 (26.6)	1.00	117/424 (27.6)	1.00	130/496 (26.2)	1.00	98/368 (26.6)	1.00
$N = 630$	KL ≥ 3	24/78 (30.8)	1.20 (0.70–2.01)	36/102 (35.3)	1.57 (0.98–2.48)	42/118 (35.6)	1.62 (1.04–2.50)	61/206 (29.6)	1.15 (0.79–1.67)	48/134 (35.8)	1.65 (1.09–2.49)	80/262 (30.5)	1.26 (0.88–1.81)
Women	KL < 3	331/1,083 (30.6)	1.00	298/1,007 (29.6)	1.00	284/960(29.6)	1.00	236/828 (28.5)	1.00	284/971 (29.3)	1.00	197/710 (27.8)	1.00
$N = 1,219$	KL ≥ 3	49/136 (36.0)	1.28 (0.87–1.87)	82/212 (38.7)	1.52 (1.11–2.10)	96/259 (37.1)	1.43 (1.06–1.92)	144/391 (36.8)	1.50 (1.15–1.97)	96/248 (38.7)	1.56 (1.15–2.10)	183/509 (36.0)	1.51 (1.16–1.95)

Multiple logistic regression analysis after adjustment for age was used to calculate OR and 95% CI.

mechanisms might influence the initiation of osteophytosis and joint space narrowing. Lower back pain was not significantly associated with incident radiographic LS, whereas radiographic severe LS was a risk factor for incident lower back pain. Further progress, along with continued longitudinal surveys of the ROAD study, will elucidate the environmental and genetic background of LS.

Author contributions

All authors have made substantial contributions to all three of sections (1), (2) and (3) below;

(1) The conception and design of the study, or acquisition of data, or analysis and interpretation of data
(2) Drafting the article or revising it critically for important intellectual content
(3) Final approval of the version to be submitted

Conflicts of interest

There are no conflicts of interest.

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Supplementary material

Supplementary data related to this article can be found online at doi:10.1016/j.joca.2012.03.009

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Prevalence of symptomatic lumbar spinal stenosis and its association with physical performance in a population-based cohort in Japan: the Wakayama Spine Study

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SUMMARY

Objective: The purpose of this study was to investigate the prevalence of symptomatic lumbar spinal stenosis (LSS) and to clarify the association between symptomatic LSS and physical performance using magnetic resonance imaging (MRI) in a population-based cohort.
Design: This cross-sectional study was performed as a part of the Research on Osteoarthritis/osteoporosis Against Disability (ROAD) in Japan and 1,009 subjects (335 men, 674 women, mean age 66.3 years, age range 21–97 years) were analyzed. An experienced orthopedic surgeon obtained the medical history and performed the physical testing for all participants. Symptomatic LSS diagnostic criteria required the presence of both symptoms and radiographic LSS findings. A 6-m walking time, chair standing time, and one-leg standing time were obtained from all participants.
Results: The prevalence of symptomatic LSS was 9.3% (95% confidence interval [CI]: 7.7–11.3) overall, 10.1% (CI: 7.4–13.8) in men and 8.9% (CI: 7.0–11.3) in women. There was a difference in the prevalence with increasing age by gender. The LSS prevalence showed little difference with age greater than 70 years for men, but the LSS prevalence for women was higher with increasing age. Among physical performance measures, 6-m walking time at a maximal pace was significantly associated with symptomatic LSS ($P = 0.03$).
Conclusion: The prevalence of symptomatic LSS was approximately 10% in a cohort resembling the general Japanese population. A 6-m walking time at a maximal pace was a more sensitive index than walking at a usual pace in assessing decreased physical performance associated with symptomatic LSS.

Introduction

Symptomatic lumbar spinal stenosis (LSS) is usually associated with impaired walking and other disabilities in the elderly. Symptomatic LSS has been shown to be the most frequent indication for spinal surgery in patients more than 65 years old[1,2]. However, little is known about the prevalence of symptomatic LSS in the general population. This is because the subjects in previous symptomatic LSS studies were limited to patients who visited the hospital[3,4]. Hence, people with minor symptomatic LSS who did not visit the hospital were not included in those studies. Furthermore, an examination that can capture minute changes of the intervertebral discs and ligaments using a tool like magnetic resonance imaging (MRI) is essential for the diagnosis of symptomatic LSS. This is because the definition of stenosis includes a morphological element. Many previous studies have reported the utility of MRI[5,6], but, to our knowledge, there have been no population-based cohort studies of symptomatic LSS using MRI.

It is well-known that the principal symptoms for LSS are sciatica and intermittent claudication (IC)[1,2]. Although most patients with MRI evidence of radiographic LSS are asymptomatic[7,8], when symptoms are present, severe symptoms are probably associated with poor physical performance. There have been few reports concerning physical performance of patients with symptomatic LSS[9,10]. According to a previous report concerning walking ability of

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subjects with three different degenerative musculoskeletal disorders (knee osteoarthritis, hip osteoarthritis, and symptomatic LSS) who were scheduled for either joint replacement or spinal decompression surgery, walking ability was limited in all three groups compared to healthy controls[9]. However, patients with symptomatic LSS showed the greatest restrictions in walking ability. In another report regarding subjects with symptomatic LSS in an orthopedic clinical practice, subjects in the healthy group showed greater functional mobility than those in the symptomatic LSS group[10]. The subjects included in the previous studies had enough symptoms to have visited the hospital, however, the association of physical performance measures with symptomatic LSS in subjects with minor symptoms who do not visit the hospital has not been well characterized. Although there may be a latent diminished physical functioning in symptomatic LSS with even minor radiographic changes and symptoms, there have been no population-based studies on symptomatic LSS that have included people with minor signs and symptoms of LSS.

Symptomatic LSS in this study was diagnosed by the presence of both clinical symptoms and radiographic LSS findings consistent with the clinical presentation. The aim of the present study was to clarify the prevalence of symptomatic LSS by gender and age strata using a population-based cohort. In addition, the association of symptomatic LSS with physical performance measures (walking speed, chair standing time, and one-leg standing time) was evaluated.

Methods

Participants

The present study, entitled "the Wakayama Spine Study: population-based cohort", was a population-based study for degenerative spinal disease and performed in a subcohort of the large-scale population-based cohort study called Research on Osteoarthritis/osteoporosis Against Disability (ROAD). ROAD is a nationwide, prospective study of bone and joint diseases consisting of population-based cohorts established in several communities in Japan. As a detailed profile of the ROAD study has already been described elsewhere, only a brief summary is provided here[11–14]. To date, creation of a baseline database including 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) has been completed. Participants were recruited from listings of resident registrations in three communities: an urban region in Itabashi, Tokyo; a mountainous region in Hidakagawa, Wakayama; and a coastal region in Taiji, Wakayama. All participants provided written informed consent, and the study was conducted with the approval of ethical committees of the University of Tokyo and the Tokyo Metropolitan Institute of Gerontology. Participants completed an interviewer-administered questionnaire of 400 items that included lifestyle information, underwent anthropometric measurements, and physical performance measures were recorded. A second visit of the ROAD study to the mountainous region of Hidakagawa and the seacoast region of Taiji was performed between 2008 and 2010. From inhabitants participating in the second visit of the ROAD study, 1,063 volunteers were recruited to undergo MRI examinations. Fifty-two of the 1,063 volunteers declined the MRI examination, therefore, 1,011 were registered in the present study. All participants provided another written informed consent for the MRI examination. Among those 1,011 participants, two participants with LSS symptoms for whom MRI was contraindicated (due to presence of a pacemaker) were excluded, because a final diagnosis of symptomatic LSS could not be made (Fig. 1). Thus, 1,009 participants (335 men and 674 women,

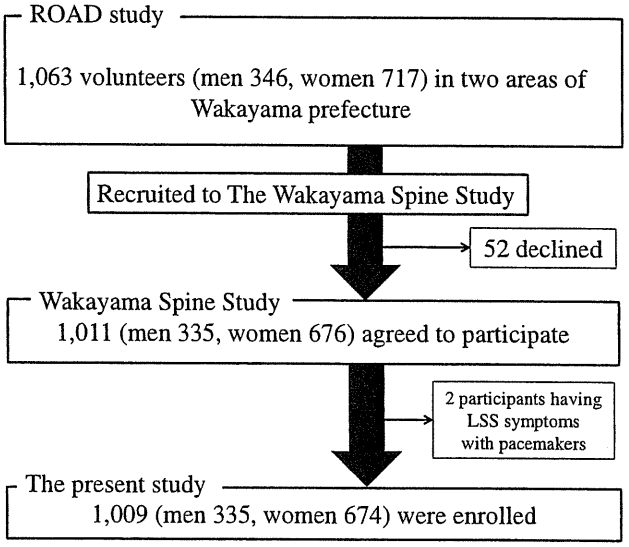

Fig. 1. Flow diagram depicting participants recruited to the Wakayama Spine Study from the ROAD study.

mean age 66.3 years, age range of 21–97 years) were analyzed in the present study. Similar to the baseline study, participants in the second visit of the ROAD study completed an interviewer-administered questionnaire of 400 items that included lifestyle information such as smoking habits, alcohol consumption, family history, past history, physical activity, reproductive variables, and health-related quality of life (QOL). Anthropometric measurements included height, weight, bilateral grip strength, and body mass index (BMI) (weight [kg]/height^2 [m^2]). The ankle-brachial index (ABI) was measured using PWV/ABI (OMRON Co., Kyoto, Japan) for all participants. A timed 6-m walk at the participant's usual pace in a hallway was recorded to measure physical performance. Similarly, 6-m walking time at a maximal pace was measured[15–18]. The time taken for five consecutive chair rises without the use of hands was also recorded[18–20]. One-leg standing time with each leg was measured using a stopwatch (upper limit, 60 s) and the time adopted was the mean value of both legs[21,22].

MRI

A mobile MRI (Excelart 1.5 T, Toshiba, Tokyo, Japan) unit was used in the present study, and total spinal MRI was performed for all participants on the same day as the examination. MRI exclusion criteria included presence of a cardiac pacemaker, claustrophobia, or other contraindications. The participants were positioned in supine during the MRI, and those with rounded backs used triangular pillows under their head and knees. The imaging protocol included sagittal T2-weighted fast spin echo (FSE) (repetition time (TR): 4,000 ms/echo, echo time (TE): 120 ms, field of view (FOV): 300 × 320 mm), and axial T2-weighted FSE (TR: 4,000 ms/echo, TE: 120 ms, FOV: 180 × 180 mm). Sagittal images were taken for the entire spine, but axial images were done at each lumbar intervertebral level (L1/2–L5/S1) parallel to the vertebral endplates.

Symptomatic LSS diagnosis

An experienced orthopedic surgeon (YI) consistently took the medical history and performed the physical testing for all the participants in this study. The history included information on the

presence of low back, buttock and leg pain, the area of pain or other discomfort, the presence of IC and its distance, and a modified Zurich Claudication Questionnaire[23] (excepting six items about satisfaction and a history of lumbar surgery for symptomatic LSS). Physical examinations included symptoms induced by lumbar extension, symptoms improved or induced with lumbar flexion, floor finger distance (cm), peripheral circulation (good or poor), a straight leg raising test, manual muscle testing of both upper and lower extremities, tendon reflex testing for both upper and lower extremities, and Babinski reflex testing. In addition, the MRI study of the entire spine was performed on all participants on the same day as the physical examination.

The diagnostic criteria for symptomatic LSS used in the present study were based on the LSS definition from the North American Spine Society (NASS) guideline, which requires presentation of both LSS symptoms and radiographic signs of LSS[24]. The orthopedic surgeon (YI) made the diagnosis of symptomatic LSS using this definition. The diagnosis for LSS symptoms required one or more of the following symptoms: pain, numbness and neurological deficits in the lower extremities and buttocks, and bladder/bowel dysfunction. The symptom characteristics should be induced or exacerbated with walking or prolonged standing and relieved with lumbar flexion, sitting and recumbency. The severity of radiographic LSS was assessed by qualitative measurements, which were performed by a well-experienced orthopedic surgeon (YI) and images were provided on films. The features assessed for LSS included severity of central, lateral recess, and foraminal stenosis, rated as four grades: none, mild, moderate and severe. The lateral recess was defined, as per Fardon and Millette[25], as extending from the medial edge of the facet to the edge of the neural foramen. We applied the general guideline classification of a[26] mild stenosis as narrowing of the normal area by one-third or less, moderate stenosis as narrowing between one-third and two-thirds, and severe stenosis as narrowing of more than two-thirds. Central and lateral recess stenosis was rated on the axial images and foraminal stenosis on the sagittal images. We used the most severe side for the rating of lateral and foraminal stenosis at each level. The same observer scored 50 randomly selected lumbar MRI films more than 1 month after the first reading to evaluate the intraobserver variability of the severity rating. Two experienced orthopedic surgeons also scored 50 different lumbar MRI films (YI & KN) for interobserver variability. The intraobserver variability was confirmed by a kappa analysis which dichotomized radiographic LSS severity as no/mild stenosis vs moderate/severe stenosis, and showed sufficient reliability for assessment of central, lateral and foraminal stenosis (0.77, 0.70 and 0.65, respectively). Interobserver variability was also sufficient for assessment using the kappa analysis (0.71, 0.65 and 0.65, respectively).

Radiographic LSS also required the severity to be more than moderate and the radiographic finding needs to be consistent with the symptoms as outlined above. An experienced orthopedic surgeon (YI) made the final diagnosis of symptomatic LSS using this definition, which requires presentation of both LSS symptoms and radiographic LSS findings. There were no participants with LSS symptoms due to tumor, inflammatory, or traumatic pathologies.

Statistical analysis

All statistical analyses were performed using JMP version 8 (SAS Institute Japan, Tokyo, Japan). Differences in age, height, weight, BMI, 6-m walking time at a usual pace, 6-m walking time at a maximal pace, chair standing time, and one-leg standing time between men and women were examined by the non-paired Student's *t*-test. The non-paired Student's *t*-test was also used to compare age between participants with and without symptomatic LSS. The prevalence of symptomatic LSS was also compared between men and women by the chi-square test. Differences in physical performance measures (6-m walking time at a usual pace, 6-m walking time at a maximal pace, chair standing time, and one-leg standing time) between participants with and without symptomatic LSS were examined by the non-paired Student's *t*-test. Furthermore, logistic regression analysis was used to estimate the odds ratios (ORs) of physical performance measures (6-m walking time at a usual pace, 6-m walking time at a maximal pace, chair standing time, and one-leg standing time) for symptomatic LSS after adjustment for age, gender and BMI.

Results

Table I shows the characteristics of 1,009 participants (335 men and 674 women, mean age 66.3 years, age range of 21–97 years) including age, anthropometric measurements, and physical performance in the present study. Two-thirds of the 1,009 participants were women. Mean age was not significantly different between men and women. BMI was significantly lower in women than in men ($P = 0.005$). Physical performance measures of the 6-m walking time at a usual pace and at a maximal pace were significantly shorter in men than in women ($P < 0.05$ for both), while chair standing time and one-leg standing time were not significantly different between men and women.

The prevalence of radiographic LSS findings was much greater than the prevalence of symptomatic LSS for the participants in this study. The percentage of participants with moderate or severe radiographic central stenosis was 76.5% (95% confidence interval [CI]: 73.7–79.0) in total, while the prevalence of symptomatic LSS was 9.3% (95% CI: 7.7–11.3) in total, 10.1% (CI: 7.4–13.8) in men, and 8.9% (CI: 7.0–11.3) in women. There was no significant difference between men and women ($P = 0.52$). The prevalence in men less than 39 years, 40–49, 50–59, 60–69, 70–79, and 80 years and older was 0%, 3.8% (CI: 0.7–18.9), 9.8% (CI: 4.6–19.8), 11.8% (CI: 6.1–21.5), 11.7% (CI: 6.7–19.8), and 10.7% (CI: 5.6–19.7), respectively, while that in women was 0%, 1.4% (CI: 0.2–7.3), 5.7% (CI: 2.8–11.3), 9.3% (5.7–14.8), 11.9% (CI: 7.9–17.5), and 13.3% (CI: 8.4–20.6), respectively (Fig. 2). The prevalence of both genders

Table I
Characteristics of participants

	Total	Men	Women	*P* value for gender
No. of participants	1009	335	674	
Age group (years)				
≦39	30	11	19	–
40–49	100	26	74	–
50–59	184	61	123	–
60–69	229	68	161	–
70–79	271	94	177	–
≧80	195	75	120	–
Demographic characteristics				
Age, years	66.3 ± 13.6	67.3 ± 13.8	65.9 ± 13.4	0.11
Height, cm	155.9 ± 9.4	164.5 ± 7.1	151.6 ± 7.2	<0.0001
Weight, kg	56.8 ± 11.5	64.4 ± 11.7	53.1 ± 9.4	<0.0001
BMI, kg/m^2	23.3 ± 3.6	23.7 ± 3.5	23.1 ± 3.6	0.005
Physical performance				
Six-meter walking time at a usual pace, s	5.7 ± 2.2	5.5 ± 1.5	5.8 ± 2.4	0.04
Six-meter walking time at a maximal pace, s	3.9 ± 1.4	3.6 ± 1.1	4.0 ± 1.6	<0.0001
Chair standing time, s	8.9 ± 4.0	8.8 ± 3.4	8.9 ± 4.2	0.61
One-leg standing time, s	36.0 ± 23.7	35.7 ± 24.0	36.1 ± 23.6	0.82

Non-paired *t*-test was used to determine differences in demographic characteristics and measurements of physical performance between men and women. Values are the means ± standard deviation.

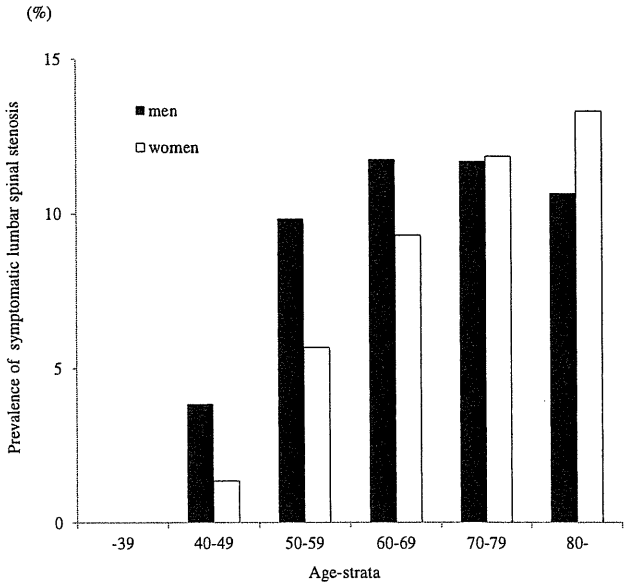

Fig. 2. Prevalence of symptomatic LSS classified by age and gender among 1,009 participants from a community cohort in Japan.

increased until reaching the 60–69 year old age group in which the prevalence in men was higher than that of women. However, the prevalence for women was higher than that of men after age 70. The prevalence of symptomatic LSS in men demonstrated little difference between age groups 60–69 years to over 80 years, but the prevalence for women became significantly higher with increasing aging ($P = 0.036$).

Fifty-five (58.5%) of 94 participants defined as having symptomatic LSS had IC. Five of these 55 participants presented with an ABI < 0.9. However, these five participants also had symptomatic LSS and their leg symptoms were positionally dependent. In this study, there were fifty neurogenic IC cases. There were five cases of unspecified IC, which was caused by both neurogenic and vascular claudication.

Table II shows the physical performance measures in participants with and without symptomatic LSS. In the overall population, 6-m walking time at a usual pace, 6-m walking time at a maximal pace, chair standing time, and one-leg standing time were significantly worse in participants with symptomatic LSS than those without symptomatic LSS ($P < 0.01$ for all). When analyzed in men and women separately, the results were similar to those overall, although the significant differences disappeared in some physical performance measures in men. The significant differences of 6-m walking time at a usual pace in both genders and one-leg standing time in men disappeared after a Bonferroni adjustment. Logistic regression analysis after adjustment for age, gender and BMI showed that 6-m walking time at a maximal pace was significantly associated with symptomatic LSS (OR: 1.17, 95% CI: 1.01–1.34). The physical performance measures of 6-m walking time at a usual pace, chair standing time, and one-leg standing time were not significantly associated with symptomatic LSS (OR: 1.04, 95% CI: 0.94–1.13, OR: 1.03, 95% CI: 0.97–1.09 and OR: 1.00, 95% CI: 0.98–1.01, respectively).

Discussion

The present study is the first to clarify the prevalence of symptomatic LSS by gender and age strata and the association of symptomatic LSS with physical performance measures using a population-based cohort. The prevalence of symptomatic LSS was found to be 9.3% in the general Japanese population, 10.1% in men, 8.9% in women, and there were no significant differences between genders. Interestingly, although the prevalence in women was higher with increasing age, the prevalence in men was the highest at 60–69 years, and little difference in prevalence was seen in men aged 60–69 years to 80 years or older. The prevalence of radiographic LSS was much greater than the prevalence of symptomatic LSS, with only a small proportion of participants with radiographic LSS actually showing symptoms suggestive of the clinical syndrome. The 6-m walking time at a maximal pace was significantly associated with symptomatic LSS, while the 6-m walking time at a usual pace was not.

We have identified no previous studies of symptomatic LSS prevalence. Johnsson[4] reported that the incidence of symptomatic LSS was 50/million person-years in southern Sweden in a study of patients who consulted the orthopedic department in two cities. However, as the author of that report described, the incidence of symptomatic LSS could be underestimated, because the studies did not include patients with minor symptoms who did not visit the hospital. This study is the first to clarify the prevalence of symptomatic LSS using a population-based cohort study.

Reported differences in prevalence of symptomatic LSS between men and women are mixed[27–29]. Verbiest reported a preponderance of symptomatic LSS in men as compared to women among his patients diagnosed by clinical symptoms and myelography[28]. However, Getty reported an equal gender distribution of symptomatic LSS prevalence in a series in which subjects were treated surgically for symptomatic LSS[29]. It is important to note that the subjects in those studies were patients who visited hospitals. In the present study, differences in the prevalence of symptomatic LSS between men and women in the general population were clarified. The prevalence of symptomatic LSS in men was slightly higher than in women, but there was no significant difference between genders. There was a difference in distribution of symptomatic LSS between men and women. The prevalence in women was higher with increasing age, but that in men was the highest at 60–69 years and

Table II
Measurements of each physical performance in participants with and without symptomatic LSS

	Total			Men			Women		
	LSS	Non-LSS	*P* value	LSS	Non-LSS	*P* value	LSS	Non-LSS	*P* value
Number of participants	94	915		34	301		60	614	
Physical performance									
Six-meter walking time at a usual pace, s	6.3 ± 2.7	5.6 ± 2.1	0.003	6.0 ± 1.6	5.4 ± 1.5	0.03	6.5 ± 3.1	5.7 ± 2.3	0.02
Six-meter walking time at a maximal pace, s	4.5 ± 2.1	3.8 ± 1.3	<0.0001	3.9 ± 1.1	3.6 ± 1.1	0.09	4.8 ± 2.4	3.9 ± 1.5	<0.0001
Chair standing time, s	10.1 ± 4.0	8.8 ± 3.9	0.002	9.7 ± 2.8	8.7 ± 3.4	0.10	10.3 ± 4.6	8.8 ± 4.1	0.008
One-leg standing time, s	27.9 ± 23.5	36.8 ± 23.6	0.0005	27.7 ± 25.4	36.7 ± 23.7	0.04	28.0 ± 22.6	36.9 ± 23.5	0.006

Values are the means ± standard deviation.
Non-paired *t*-test was used to determine differences in measurements of physical performance between LSS and non-LSS.

little different in men aged 60–69 years to 80 years and older. The prevalence of lumbar spondylosis (LS) diagnosed as Kellgren/Lawrence (KL) grade two or greater (defined as osteophyte formation with and without disc space narrowing) was found to be significantly higher in men than in women[30]. The prevalence of LS in women was found to be higher with increasing age, while that in men found little difference over 60 years[13]. Interestingly, these distribution patterns are similar to the prevalence of symptomatic LSS in the present study. Anatomical LSS arises from degenerative LS, and facet osteoarthritis and/or hypertrophy, which is associated with narrowing of the space available for the neural elements[1]. This may be one reason for the similarity between LS and symptomatic LSS prevalence.

The present study was the first to show that, among the general population, 6-m walking time at a maximal pace was significantly associated with symptomatic LSS, while 6-m walking time at a usual pace was not. This may mean that participants with symptomatic LSS appeared to have no disadvantage concerning activities of daily living compared to those without symptomatic LSS. However, when requiring greater functional reserve, such as 6-m walking time at a maximal pace, differences between participants with and without symptomatic LSS appeared. This is also the first study to indicate that tasks requiring greater functional reserve, such as walking at a maximal speed, could be a more sensitive index in assessment of decreased physical performance due to symptomatic LSS.

There are several limitations in the present study. First, although the present study included more than 1,000 participants, these participants may not represent the general population as they were recruited from only two areas. However, anthropometric measurements were compared between participants and the general Japanese population, and no significant differences were found in BMI (men: 23.71 (3.41) and 23.95 (2.64), $P = 0.33$, women: 23.06 (3.42) and 23.50 (3.69), $P = 0.07$)[31]. In addition, the proportion of current smokers and current drinkers (those who regularly smoked or drank more than one drink/month) in the general Japanese population was compared with that in the study population. Proportions of current smokers and drinkers in men and that of current drinkers in women were significantly higher in the general Japanese population than in the study population, but there were no significant differences in that of current smokers in women (smokers: men, 32.6% in the Japanese population, 25.2% in study participants, $P = 0.015$; women, 4.9% in the Japanese population, 4.1% in study participants, $P = 0.50$; drinkers: men, 73.9% in the Japanese population, 56.8% in study participants, $P < 0.0001$; women, 28.1% in the Japanese population, 18.8% in study participants, $P < 0.0001$), suggesting that it is likely that the participants (both men and women) had healthier lifestyles than the general Japanese population. Second, this is a cross-sectional study, so any causal relationship between symptomatic LSS and physical performance cannot be clarified. The Wakayama Spine Study is a longitudinal survey, so further progress will help to elucidate any causal relationships. Thirds, total walking distance/duration was not measured, and this metric for walking would likely have been of greater relevance to symptomatic LSS than speed of walking. In addition, this study only represents the Japanese population, hence, prevalence in other countries may be quite different.

In conclusion, the present study clarified that the prevalence of symptomatic LSS was about 10% in a cohort resembling the Japanese general population. There was a difference in the prevalence of symptomatic LSS distribution by age strata between men and women. The 6-m walking time at a maximal pace was a more sensitive index for assessing decreased physical performance due to LSS than the 6-m walking time at a usual pace. Further longitudinal surveys of the Wakayama Spine Study will help to further clarify the incidence and risk factors for symptomatic LSS.

Author contributions

All authors worked collectively to develop the protocols and methods described in this paper. YI, SM, KN, NO, HO, TA, and NY were principal investigators responsible for the fieldwork in the Wakayama Spine Study. YI and SM performed the statistical analysis. YI, HY, SM, KN, HH, HO, TA, MY, and NY contributed to the analysis and interpretation of results. YI wrote the report. All authors read and approved the final report.

Role of the funding source

The study sponsors played no role in the study design, the collection, analysis, and interpretation of data, writing of the report, or the decision to submit the paper for publication. The corresponding author had full access to all the data and had the final decision to submit for publication.

Conflict of interest

The authors declare that we have no conflicts of interest.

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ORIGINAL ARTICLE

Ethnic difference of clinical vertebral fracture risk

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Abstract
Summary Vertebral fractures are the most common osteoporotic fractures. Data on the vertebral fracture risk in Asia remain sparse. This study observed that Hong Kong Chinese and Japanese populations have a less dramatic increase in hip fracture rates associated with age than Caucasians, but the vertebral fracture rates were higher, resulting in a high vertebral-to-hip fracture ratio. As a result, estimation of the absolute fracture risk for Asians may need to be readjusted for the higher clinical vertebral fracture rate.

Introduction Vertebral fractures are the most common osteoporotic fractures. Data on the vertebral fracture risk in Asia remain sparse. The aim of this study was to report the incidence of clinical vertebral fractures among the Chinese and to compare the vertebral-to-hip fracture risk to other ethnic groups.

Methods Four thousand, three hundred eighty-six community-dwelling Southern Chinese subjects (2,302 women and 1,810 men) aged 50 or above were recruited in the Hong Kong Osteoporosis Study since 1995. Baseline demographic characteristics and medical history were obtained. Subjects were followed annually for fracture outcomes with a structured questionnaire and verified by the computerized patient information system of the Hospital Authority of the Hong Kong Government. Only non-traumatic incident hip fractures and clinical vertebral fractures that received medical attention were included in the analysis. The incidence rates of clinical vertebral fractures and hip fractures were determined and compared to the published data of Swedish Caucasian and Japanese populations.

Results The mean age at baseline was 62±8.2 years for women and 68±10.3 years for men. The average duration of follow-up was 4.0±2.8 (range, 1 to 14) years for a total of 14,733 person-years for the whole cohort. The incidence rate for vertebral fracture was 194/100,000 person-years in men and 508/100,000 person-years in women, respectively. For subjects above the age of 65, the clinical vertebral fracture and hip fracture rates were 299/100,000 and 332/100,000 person-years, respectively, in men, and 594/100,000 and 379/100,000 person-years, respectively, in women. Hong Kong Chinese and Japanese populations

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have a less dramatic increase in hip fracture rates associated with age than Caucasians. At the age of 65 or above, the hip fracture rates for Asian (Hong Kong Chinese and Japanese) men and women were less than half of that in Caucasians, but the vertebral fracture rate was higher in Asians, resulting in a high vertebral-to-hip fracture ratio.
Conclusions The incidences of vertebral and hip fractures, as well as the vertebral-to-hip fracture ratios vary in Asians and Caucasians. Estimation of the absolute fracture risk for Asians may need to be readjusted for the higher clinical vertebral fracture rate.

Keywords Asian · Chinese · Fracture incidence · Osteoporosis · Vertebral fracture

Introduction

Osteoporosis is a disease associated with decreased bone mass and bone strength and leads to increased fracture risk. Osteoporosis has become a major public health concern in the past decade due to the high prevalence and health care costs associated with it. Vertebral fractures, despite being the most common osteoporotic fracture, accounting for nearly 50% of all osteoporotic fractures, have received little attention compared to hip fractures. Data on the epidemiology of vertebral fractures in Asia remain sparse [1]. It has been shown that both symptomatic and asymptomatic vertebral fractures are predictors of future osteoporotic fractures [2] and are associated with physical deformity, as well as reduced mobility and quality of life [3, 4], and increased mortality [5, 6].

Unfortunately, obtaining accurate information on vertebral fracture is made difficult by the variable presentation of symptoms and the lack of a gold standard for the definition of vertebral fracture. Although vertebral fractures typically present with back pain, height loss and kyphosis, up to 75% of vertebral fractures were not diagnosed clinically due to the absence of specific symptoms in some cases and the difficulty in determining the cause of these physical symptoms [7]. Numerous methods were developed to help objectively identify morphometric vertebral fractures. The more important ones include the quantitative methods of measuring vertebral body height on radiographs [8, 9], as well as the semi-quantitative method proposed by Genant et al. [10]. These assessments use different cut-offs to define the presence of a vertebral fracture, and the reference for comparison of vertebral height could either be the individual's adjacent vertebral body or the mean of a reference population. These variations affected the sensitivity and specificity of the assessments resulting in high false-negative and false-positive rates and also created a considerable discordance of results in assessing the prevalence and incidence of vertebral fractures [11–13]. Also, vertebral fractures can also be confused with normal variants in vertebral shape or other end-plate deformities caused by other diseases Therefore, the exclusion of other vertebral deformities in order to make a correct diagnosis of vertebral fracture can only be accomplished by visual inspection and expert interpretation of the radiograph [14].

The lack of a gold standard for a definition of vertebral fracture makes it difficult to assess the true incidence of vertebral fractures. Previous cross-sectional and retrospective studies have suggested a similar prevalence of vertebral fracture in Asians and Caucasians [15–19] despite their lower hip fracture rates [20]. The World Health Organization (WHO) developed fracture risk assessment algorithms (FRAX®) to provide 10-year probabilities of hip fracture and major osteoporotic fracture (clinical spine, hip, humerus and forearm) based on a clinical risk factor profile and country-specific fracture and death incidence. The most complete models available are from the UK, Sweden, Japan and the US since the epidemiology of the relevant fractures is established [21]. However, the FRAX® models for some other countries (France, Spain, Italy, Turkey, Mainland China Hong Kong, etc.) are based on hip fracture risk alone due to the lack of ethnic-specific data and use assumptions, i.e. the site of fracture ratios observed from the Swedish population, to derive the relevant risk functions for other major fractures including vertebral fractures [22]. The objectives of this study were (1) to report the incidence rates of clinical vertebral and hip fractures in a prospective cohort of Chinese men and women, (2) to compare the clinical vertebral and hip fracture rates with those of other ethnic groups, and (3) to evaluate whether a fracture prediction model that assumes a universal spine-to-hip fracture ratio may be biased.

Methods

Hong Kong

This is the first prospective study of clinical vertebral fracture in an Asian population and is a part of the prospective Hong Kong Osteoporosis Study in which community-dwelling Southern Chinese men and women aged 50 or above were recruited from health fairs held in various districts in Hong Kong since 1995 [19, 23]. Baseline demographic data including anthropometric measurements, low-trauma fracture history after the age of 45 years, age at menopause and the use of hormone replacement therapy, medical history and symptoms associated with clinical vertebral fractures were obtained using a structured questionnaire at baseline. Subjects with conditions associated with vertebral deformity, including

osteomalacia, Paget's disease, Scheuermann's disease, hyperparathyroidism, renal bone disease and malignancy with bone metastasis, were excluded. Information on symptoms associated with vertebral fractures was also collected, including difficulty in bending forward, kyphosis (occiput-to-wall >0 cm and/or gap between the costal margin and iliac crest <3 fingerbreadths), low back pain and height loss more than 2 cm since the age of 25 years. These data were collected from interviews conducted by a trained research assistant.

All subjects were followed annually via telephone interviews using a structured questionnaire for assessment of the clinical outcome of incident fractures, falls, hospitalization, use of anti-osteoporotic medications, living status and functional status. Subjects who commenced anti-osteoporosis medication prior to the occurrence of a primary fracture were excluded. Medical history and incident fractures were verified with the computerized patient information system of the Hospital Authority of the Hong Kong Government. For this study, only non-traumatic incident hip fractures and clinical vertebral fractures were included in the analysis. Hip fractures were defined as having a diagnosis coded as International Classification of Disease, Tenth Revision (ICD-10) S72.0-S72.2 (fracture of the femoral neck, intertrochanteric, trochanteric, or subtrochanteric), and clinical vertebral fractures were identified in subjects who received medical attention from a physician with a diagnosis coded as ICD-10S22.0-S22.1 (fracture of the thoracic vertebra/multiple thoracic vertebrae), S32.0 or S32.7 (fracture of the lumbar vertebra/multiple lumbar vertebrae). Pathological fractures or fractures caused by traffic accidents or falls from standing heights were excluded. The study was approved by the Institutional Review Board of the University of Hong Kong and the Hong Kong West Clusters Hospital of the Hospital Authority.

Japan

The hip and clinical vertebral fracture incidence rates for the Japanese were obtained from previously published data used to develop the Japanese version of FRAX® [24]. The hip fracture incidence rate was based on data from a census study in Tottori Prefecture, Japan, in 1994 [25]. The incidence of vertebral fracture was based on data obtained from the Adult Health Study in Hiroshima, Japan [26]. Participants were followed through biennial medical examination including radiology assessments since the establishment of the study in 1958. A total of 2,613 subjects (763 men and 1,593 women) who attended at least two follow-up examinations in 1994 to 2000 were included in the analysis. An incident morphometric vertebral fracture was diagnosed by lateral and posterior–anterior chest and spinal X-rays using the semi-quantitative assessment [12], in which a decrease of at least 20% in height of any vertebral body from initial reading to the end of the study was defined as a morphometric vertebral fracture. Since the incidence of clinical vertebral fracture was not known in Japan, the ratio of clinical fracture to morphometric fracture incidence was assumed to be the same in Japan as it was for Sweden when the Japanese version of FRAX® was developed, i.e. 30% of morphometric vertebral fractures were assumed as clinical fractures [24, 27].

Sweden

The incidence rates of hip and clinical vertebral fractures for Swedish Caucasians were also obtained from a previously published study by Kanis et al., in which all incident fractures, including hip fractures (1991) and clinical vertebral fractures (1993 and 1994) were identified from files at the Department of Diagnostic Radiology in Malmo, Sweden, for the relevant year. Only vertebral fractures that came to clinical attention were captured, and subjects who previously sustained a fracture of the same type were excluded from analysis. The annual incidences of hip and clinical vertebral fractures were calculated for men and women by age [28].

Statistical analyses

Baseline characteristics of the Chinese subjects are expressed in means±SD for continuous variables and in percentage for categorical variables. Time to incident hip or vertebral fractures was calculated according to the date of X-ray reports or physician's consultations when the diagnosis was made. The average follow-up period for all subjects was 4.0±2.8 (range, 1 to 14) years, with a total follow-up of 14,733 patient-years. Subjects who had received anti-osteoporosis medication after sustaining a fracture during the follow-up period or those who deceased at the time of analysis were analysed up to their time of treatment initiation or last contact time point. Incidence rates were reported as rate per 100,000 person-years. The incidence rates of vertebral and hip fractures were compared to the published data from Japan and Sweden. Vertebral-to-hip fracture ratios were used to demonstrate the proportion of vertebral fractures in relation to hip fractures in different populations.

Results

A total of 4,116 Southern Chinese subjects (2,302 women and 1,810 men) aged 50 or above were included in the analysis. The mean age at baseline was 62±8.2 years for

women and 68±10.3 years for men. Of the women, 37.2% and 63.4% of men were above the age of 65 years. Baseline demographic information and characteristics are shown in Table 1. Of the men, 55.5% and 72.1% of women reported having difficulty bending forward, kyphosis, low back pain and/or height loss >2 cm since the age of 25. However, only 2.7% of men and 5.5% of women reported a history of past clinical vertebral fracture.

Two hundred and sixty-seven subjects had died at the time of analysis (77 women and 190 men), and 353 patients (333 women and 19 men) received anti-osteoporosis medication after sustaining a fracture during the follow-up period. The data for these subjects were analysed up to their last contact time point or time of treatment initiation, respectively. During the follow-up period, 57 clinical vertebral fractures and 34 incident hip fractures were reported (11 vertebral fractures and 10 new hip fractures in men; 46 vertebral fractures and 24 new hip fractures in women). The incidence for vertebral fractures was 194 per 100,000 person-years in men and 508 per 100,000 in women (overall female/male ratio=2.6:1), and the incidence for hip fractures was 176 per 100,000 person-years in men and 265 per 100,000 person-years in women (female/male ratio=1.5:1). Table 2 shows the incidence rates of clinical vertebral and hip fractures according to sex and age groups. Both clinical vertebral and hip fracture incidences increased exponentially with increasing age in both sexes. Men aged 50–55 years had a fracture incidence of 50 per 100,000 person-years for the vertebra and 10 per 100,000 for the hip versus men aged 85 years and above who have a vertebral fracture incidence of 954 per 100,000 person-years and a hip fracture incidence of 477 per 100,000 person-years. Similarly, incidences of vertebral and hip fracture increase from 219 and 16 per 100,000 person-years in women 50 years of age to 2,689 and 1,377 per 100,000 person-years, respectively, at age 85. Overall, men older than 65 years have a vertebral fracture incidence of 299 per 100,000 person-years and hip fracture incidence of 332 per 100,000 person-years, and the overall incidence of vertebral and hip fractures for women older than 65 years were 594 per 100,000 person-years and 379 per 100,000 person-years, respectively.

The fracture incidence of Chinese subjects was compared to those of the Swedish and Japanese populations. The incidence rates of hip fractures in Caucasian men and women rose exponentially with age, whereas the rise was near linear for vertebral fractures. In contrast, for Asian women in Hong Kong and Japan, the incidence rate for vertebral fractures rose exponentially with age, whereas the rise was near linear for hip fractures. In Asian men, both the incidence rates of vertebral and hip fractures rose near linearly with age. The hip fracture incidences in Hong Kong men and women were similar to those of Japan but much lower than those of the Caucasian population in Sweden. For example, the hip fracture rates for Hong Kong men and women aged 65 to 69 years old were only 49% and 33%, respectively, of those of the Caucasian men and women in the same age group. However, the incidence of vertebral fractures in Asian men was similar to that of Caucasian men; and Asian women have a much higher

Table 1 Clinical characteristic of the study population (Mean±SD)

	Men (n=1,810)	Women (n=2,302)
Years of follow-up (mean±SD (range))	3.5±2.9 (1–14)	4.7±2.6 (1–14)
Age (year)	68±10.3 (50–99)	62±8.2 (50–91)
Height (cm)	164.6±6.5	152.7±6.0
Weight (kg)	62.9±10.3	55.3±9.1
Body mass index (kg/m^2)	28.1±8.4	23.7±3.7
Number of postmenopausal women	–	2,229 (96%)
Age at menopause (year)	–	49.5±4.0
Current or history of hormone replacement therapy	–	217 (9.4%)
Difficulty bending forward	185 (10.2%)	365 (15.8%)
Kyphosis	78 (4.3%)	126 (5.5%)
Low back pain	510 (28.2%)	1,336 (58.0%)
Height loss >2 cm since 25 years old	442 (24.4%)	854 (37.1%)
Have at least one of the above symptoms	1,004 (55.5%)	1,660 (72.1%)
History of clinical vertebral fracture	48 (2.7%)	126 (5.5%)
History of hip fracture	24 (1.7%)	31 (1.3%)
Incident clinical vertebral fracture at follow-up	11 (0.6%)	46 (2.0%)
Incident hip fracture at follow-up	10 (0.6%)	24 (1.0%)

Table 2 Incidence (per 100,000 person-years) of hip and clinical vertebral fracture according to sex and age groups

Fracture site and age group	Men	Women	F/M
Hip			
50–54	10	16	1.6
55–59	21	31	1.5
60–64	46	57	1.2
65–69	99	103	1.0
70–74	215	273	1.3
75–79	348	527	1.5
80–84	602	1,059	1.8
85+	477	1,377	2.9
Vertebral			
50–54	50	219	4.4
55–59	111	313	2.8
60–64	165	516	3.1
65–69	95	564	5.9
70–74	226	874	3.9
75–79	450	1,205	2.7
80–84	594	2,119	3.6
85+	954	2,689	2.8

vertebral fracture incidence than Caucasian women (Fig. 1a and b). Among older women aged 80 or above, the incidence of vertebral fracture in Asians almost doubled to that of Swedish Caucasian women.

The spine-to-hip fracture ratios also differed between different Asians and Caucasians. Although vertebral fractures occur with a higher incidence earlier in life than hip fractures in both Asians and Caucasians, Asians have a much higher spine-to-hip fracture ratio than Caucasians, meaning vertebral fractures have a higher proportion to hip fractures in Asians than in Caucasians, especially among subjects younger than 65 years (Table 3).

Discussion

Vertebral fractures are the most common type of osteoporotic fractures, and they are well known as an independent predictor of future osteoporotic fractures, including both vertebral and non-vertebral fractures [22]. However, reports about the incidence of vertebral fracture are scant because of the discrepancies in the definition of vertebral fracture and the difficulties in recognizing them clinically. A

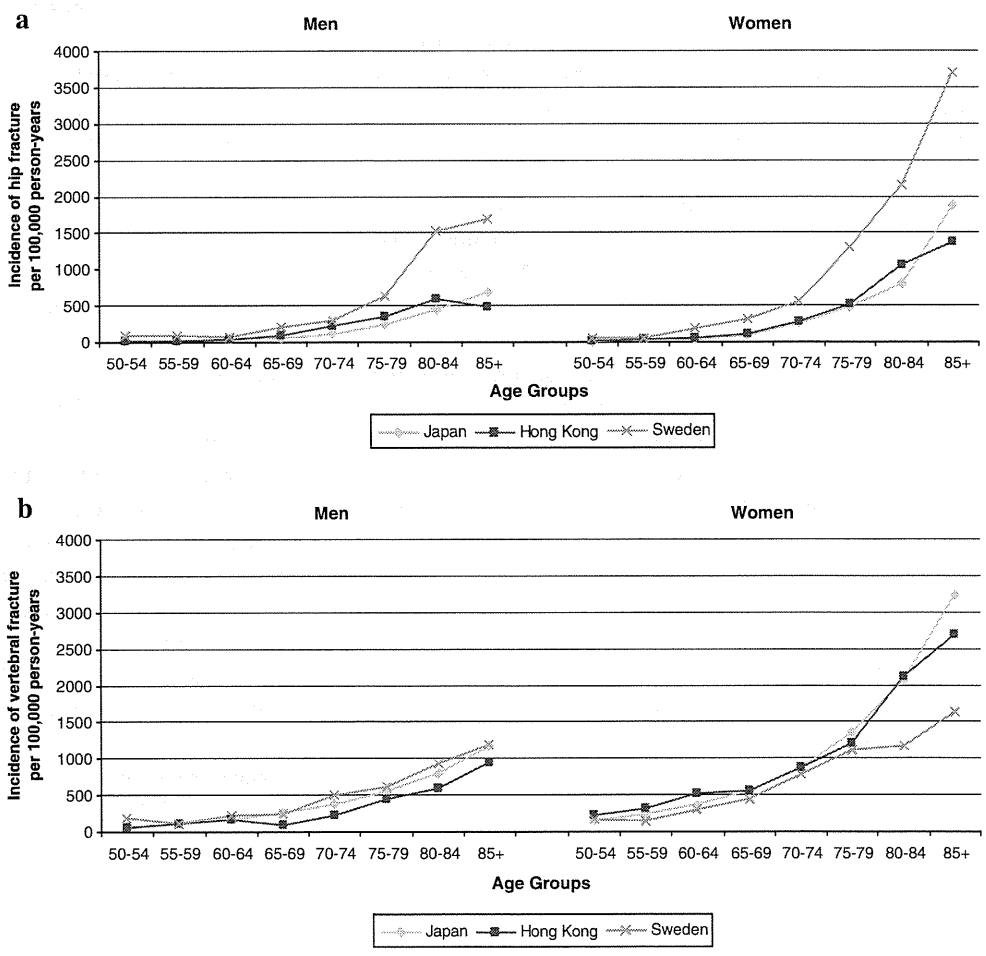

Fig. 1 Age-specific incidence rates (per 100,000 person-years) in Hong Kong compared to Japanese and Swedish Caucasians for hip fracture (**a**) and clinical vertebral fracture (**b**)

Table 3 Age- and sex-specific clinical vertebral-to-hip fracture ratio in Hong Kong compared to Japanese and Swedish Caucasians

	Men			Women		
Age group	Japan [24]	Hong Kong	Sweden [28]	Japan [24]	Hong Kong	Sweden [28]
50–54	3.9	5.0	2.2	N/A[a]	13.7	2.6
55–59	7.1	5.3	1.4	4.7	10.1	2.9
60–64	2.8	3.6	3.2	8.9	9.1	1.6
65–69	4.1	1.0	1.2	6.3	5.5	1.4
70–74	3.5	1.1	1.7	3.4	3.2	1.4
75–79	2.3	1.3	1.0	2.8	2.3	0.8
80–84	1.8	1.0	0.6	2.6	2.0	0.5
85+	1.7	2.0	0.7	1.7	1.1	0.4

[a] Clinical vertebral-to-hip fracture ratio for Japanese women aged 50–54 was not available since the hip fracture incidence for this group was zero

previous study has shown that the postmenopausal women in Hong Kong, Beijing and Taiwan have a similar prevalence of morphometric vertebral fracture as Caucasian women in the USA and Europe (about 25% in all regions), in contrast to the marked worldwide variations in the prevalence of hip fractures [21]. The present study further confirmed that, although the risk of hip fractures in Asians was low, Asian men do have a vertebral fracture risk similar to Caucasian men, and Asian women have an even higher clinical vertebral fracture risk than Caucasian women.

The observed ethnic differences in fracture incidences may be due to the fact that hip fracture risk was affected by fall risk, whereas the risk of vertebral fracture mostly depends on bone strength [13]. Despite the low hip fracture rate in our population, Hong Kong women had a higher prevalence of osteoporosis (bone mineral density T-score≤ -2.5 at any one site in reference to ethnic-specific peak young mean according to the ISCD recommendation) than US Caucasian women (35.8% vs. 20%, respectively) [29, 30] and a similar prevalence of about 6% in Hong Kong and US Caucasian men [31]. In view of the ethnic differences, it is important to obtain accurate information on population fracture risk to characterize the absolute fracture risk of individual subjects. At present, information on the risk of clinical vertebral fracture in Asians is lacking, and the WHO fracture risk assessment algorithms (FRAX®) estimated population-specific absolute major osteoporotic fracture risks based on the assumption that the ratio of hip-to-vertebral fracture is the same as that observed in Swedish populations to provide. However, our study demonstrated the variations of the spine-to-hip fracture ratios between ethnic groups; thus, a fracture prediction model that assumes a universal spine-to-hip fracture ratio may be biased.

Our previous prospective study on Southern Chinese men over 50 years old has shown that the FRAX® algorithm seemed to overestimate the 10-year major osteoporotic fracture risk in subjects with low fracture risk, but underestimated the risk for high-risk groups [29]. Results from the current study raise a concern that a model that presumes a ratio of vertebral fractures to hip fractures in a Swedish population might underestimate the risk of vertebral fractures in Asians, resulting in a general underestimation of the absolute risk of major osteoporotic fracture.

Strengths of this study include the use of a community-based population to investigate the incidence rate of clinical vertebral fractures. All clinical vertebral fractures and hip fractures were confirmed by the medical record. A major limitation of the present study is that the comparisons to incidence rate of clinical vertebral fracture to other ethnic groups were based on published literatures, and the data among Asian countries are scanty. Japan is the only country in Asia that reported the incidence rate on morphometric vertebral fractures based on a radiographic survey in a community-based population. Also, the Japanese data used for comparison came from the early 1990s, and there has been some evidence that hip fracture rates are increasing in Asians [20]. The impact on the change in epidemiology of fracture in Asians has not been evaluated. Another drawback of the present study is that only the incidences of clinical vertebral fractures were reported due to the lack of a common definition of morphometric vertebral fractures in other publications. Furthermore, the sample size and the number of fractures recorded in the men's cohort were small, and this study may have underestimated the fracture rates in the general male population.

In conclusion, this study demonstrated that while the hip fracture incidence in Asians is lower than in Caucasians, the incidence of clinical vertebral fractures was at least as high in Asians as in Caucasians.

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Conflicts of interest None.

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ORIGINAL ARTICLE

JBMR

Height Loss Starting in Middle Age Predicts Increased Mortality in the Elderly

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ABSTRACT

The purpose of this study was to determine the mortality risk among Japanese men and women with height loss starting in middle age, taking into account lifestyle and physical factors. A total of 2498 subjects (755 men and 1743 women) aged 47 to 91 years old underwent physical examinations during the period 1994 to 1995. Those individuals were followed for mortality status through 2003. Mortality risk was estimated using an age-stratified Cox proportional hazards model. In addition to sex, adjustment factors such as radiation dose, lifestyle, and physical factors measured at the baseline—including smoking status, alcohol intake, total cholesterol, blood pressure, and diagnosed diseases—were used for analysis of total mortality and mortality from each cause of death. There were a total of 302 all-cause deaths, 46 coronary heart disease and stroke deaths, 58 respiratory deaths including 45 pneumonia deaths, and 132 cancer deaths during the follow-up period. Participants were followed for 20,787 person-years after baseline. Prior history of vertebral deformity and hip fracture were not associated with mortality risk. However, more than 2 cm of height loss starting in middle age showed a significant association with all-cause mortality among the study participants (HR = 1.76, 95% CI 1.31 to 2.38, $p = 0.0002$), after adjustment was made for sex, attained age, atomic-bomb radiation exposure, and lifestyle and physical factors. Such height loss also was significantly associated with death due to coronary heart disease or stroke (HR = 3.35, 95% CI 1.63 to 6.86, $p = 0.0010$), as well as respiratory-disease death (HR = 2.52, 95% CI 1.25 to 5.22, $p = 0.0130$), but not cancer death. Continuous HL also was associated with all-cause mortality and CHD- or stroke-caused mortality. Association between height loss and mortality was still significant, even after excluding persons with vertebral deformity. Height loss of more than 2 cm starting in middle age was an independent risk factor for cardiovascular and respiratory-disease mortality among the elderly, even after adjusting for potential risk factors. © 2012 American Society for Bone and Mineral Research.

KEY WORDS: HEIGHT LOSS; MORTALITY; VERTEBRAL DEFORMITY; CORONARY HEART DISEASE; RESPIRATORY DISEASE

Introduction

Many studies have shown increased fracture risk[1–3] and mortality[4–8] after clinical vertebral fracture. Even subjects with no clinical fracture and little pain but with vertebral deformity detected by X-ray showed slightly increased mortality.[9] Other studies, however, showed no evidence of increased mortality among elderly with vertebral fracture.[10] Increased mortality after hip fracture was observed in several studies.[7,11,12]

Kyphosis and height loss are thought to result mainly from underlying vertebral fractures, but have not yet gained much clinical interest other than as markers for osteoporosis.[13–18] Height loss, however, not only could be caused by vertebral fracture, but also to some extent by intervertebral disk degeneration that decreases disk height; osteoarthritic conditions of the spine, hip, or knee, various inflammatory and structural/congenital spinal deformities; and weakness of the back muscles.[19,20] Our previous report showed that height loss and vertebral deformity significantly and independently affected quality of life (QOL) in the elderly, and height loss aggravated QOL more significantly than did vertebral deformity in all domains, even with different effect patterns between height loss and vertebral deformity.[21] The mechanism behind such decreased height loss–associated QOL remains uncertain. Recent reports have suggested that hyperkyphotic posture or marked height loss might predict future fracture risk[22] and mortality.[23–25]

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In the present study, we assessed whether height loss starting in middle age affects all-cause and specific-cause mortality, after taking into account vertebral deformity and hip fracture in Japanese men and women.

Materials and Methods

Data source

Study participants comprised cohort members of the Adult Health Study (AHS), which was established to investigate late health effects of radiation exposure among atomic-bomb survivors in Hiroshima and Nagasaki. The original AHS cohort was comprised of about 20,000 atomic-bomb survivors and their controls selected from residents of Hiroshima and Nagasaki, based on the 1950 national census. Since 1958, the AHS cohort members have been followed through biennial health examinations, including physical examinations; measurements of height, body weight, and blood pressure; and chest X-rays. The health study participants were interviewed by nurses to obtain disease histories and lifestyle information, such as smoking status and alcohol intake. Participation rates in the study were around 70% to 80% throughout the follow-up period. Further information about the cohort and details of the health examinations are available elsewhere.[26–28]

Subjects of this study numbered a total of 2498 individuals (755 men and 1743 women) aged 47 to 91 years old, undergoing physical examinations in Hiroshima during the health study's 1994 to 1995 examination cycle (Fig. 1). Measurements of height, using a stadiometer, were available for all subjects at each examination since 1962. Participants were measured without shoes, with their heels, buttocks, and back against an upright board. The participants with hyperkyphosis were instructed to stand straight and stretch the muscles in their backs as much as possible. We defined height loss starting in middle age (HL) as the difference between a participant's average height in their 40s and height measured in 1994 to 1995. We calculated average height based on from two to five measurements at ages in the 40s for each participant. If a participant did not have data on average height in the 40s, we then defined HL as the difference between his or her average height in the 50s and height measured in 1994 to 1995 (those for whom height in their 50s was used: 12.5%). We also defined marked HL as a difference of more than 2 cm based on results from receiver operating characteristic (ROC) analysis for mortality.

The subjects underwent bone mineral density (BMD) measurements at the spine (L1-4, anteroposterior direction) and the total hip using dual X-ray absorptiometry (DXA, QDR-2000 [Hologic Inc, Waltham, MA, USA]) at the time of the examinations in 1994 1995. Morphometric vertebral deformity was diagnosed by lateral and posterior-anterior chest and spinal X-ray examinations. An experienced radiologist diagnosed vertebral deformity using semi-quantitative procedures.[29,30] We defined "prevalent vertebral deformity" as vertebral deformity at thoracic and lumbar vertebrae diagnosed during the 1994 to 1995 examination cycle, that is, prevalent cases in 1994 to 1995. Diagnosis of hip fracture was based on history-taking by a physician. Pathologic fractures or fractures due to traffic accidents or falls from heights were excluded.

The study follow-up of all participants began in the 1994 to 1995 examination cycle. The accumulation of each participant's person-years of risk ended at the date of death, or the date of the last examination before December 2003. Mortality follow-up was conducted through checks of the vital status of cohort members using the Japanese family registration system. We were thus able to completely follow the mortality status of the cohort members.

Statistical Methods

The rates of many diseases increase as some power of age, so a simple linear adjustment factor would undercontrol for age effects. To avoid this bias, we used an age-stratified Cox proportional hazard analysis, whereby people are assigned to an age stratum reflecting their age at baseline according to five-year age intervals. After confirming the assumption that hazard ratios were proportional, we used an age-stratified Cox proportional

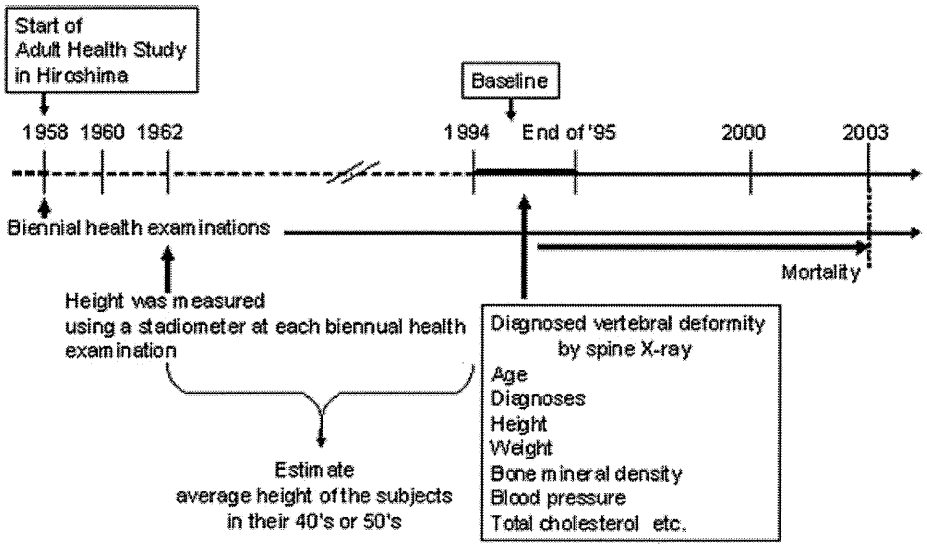

Fig. 1. Timeline of the study.

hazards model to assess the multivariate-adjusted hazard ratio (HR) for mortality. Fitted as categorical variables in the adjustment were assessments obtained at the 1994 to 1995 baseline: prevalent vertebral deformity (yes/no), prevalent hip fracture (yes/no), smoking status (never, current, former smoker, and unknown), alcohol intake (never, current occasional, current often, former drinker, and unknown), preexisting hypertension (yes/no), preexisting hyperlipidemia (yes/no), preexisting diabetes (yes/no), preexisting cardiovascular disease (yes/no), preexisting cancer (yes/no), marked HL (HL $\geq$ 2 cm/HL $<$ 2 cm). Weight, height, body mass index (BMI: calculated as weight in kilograms divided by height in meters squared), systolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol, BMD at baseline, radiation dose, and HL were fitted as continuous variables. For each risk factor, we first evaluated all-cause mortality using an univariate model. We then conducted evaluation with multivariate model, including variables found to be significantly associated with all-cause mortality. We obtained a final model after removing non-significant terms. As a result, we included such variables as sex, preexisting cancer, preexisting cardiovascular disease (CVD), preexisting diabetes, radiation dose, marked HL, smoking status, and alcohol intake in the model. We also evaluated mortalities caused by coronary heart disease (CHD) or stroke, respiratory disease, pneumonia, and cancer. In the same procedure, we analyzed participants excluding 191 participants with prevalent vertebral deformities. We used individual radiation dose estimates on the Radiation Effects Research Foundation's Dosimetry System 2002 (DS02).[31]

For the mortality analysis, we used the PHREG procedure in SAS program (SAS version 9.1, SAS Institute Inc, Cary, NC, USA), with stratification by 5-year intervals of baseline age, for estimation of the parameters and testing. With consideration for parameter distributions, we tested differences between the alive group and the death group using Student's *t*-tests for continuous variables and χ^2 tests for categorical variables. A value of $p < 0.05$ was used for determination of statistical significance.

Ethical considerations

The present study was carried out in accordance with such national regulations as the *Ethical Guidelines Concerning Epidemiological Studies* (Ministry of Education, Culture, Sports, Science and Technology [MEXT], and Ministry of Health, Labour and Welfare [MHLW]). The study was approved by the Research Protocol Committee and the Human Investigation Committee at the Radiation Effects Research Foundation. At the time of the health examinations, informed consent was obtained from the participants. All participants provided written consent for all aspects of the examinations.

Results

Characteristics of the participants taken at baseline are shown in Table 1. In men, mean ages $\pm$ 1 standard deviation (SD) in the 1994 to 1995 examination period for the alive group were 61.2 $\pm$ 8.9 years, and 70.3 $\pm$ 9.1 years for the death group, ranging from 47 to 91 years. In women, mean ages were 64.7 $\pm$ 9.1 years and 73.5 $\pm$ 8.9 years, respectively, ranging from 47 to 91 years. Mean age of the "death" group was significantly higher than that of the "alive" group. Mean height loss starting in middle age was 0.83 cm for men and 1.85 cm for women. Figure 2 shows HL distribution by sex. We used $\geq$ 2 cm as the cut-off value through the sensitivity analysis, and compared the death group with the alive group. Twenty-one men and 170 women had prevalent vertebral fracture, and 12 men and 44 women had prior history of hip fracture in the 1994 to 1995 examination period. Prevalence of diseases at baseline is presented in Table 1. The proportion of individuals with cancer and CVD appeared to be higher in the death group than in the alive group in both men and women. The proportion of individuals with hypertension appeared to be higher in the death group than in the alive group in women. Approximately 90% of women were postmenopausal with an average age at menopause of 47.7 years.

Through December 2003, there were 302 all-cause deaths, 46 CHD and stroke deaths, 58 respiratory-disease deaths including 45 pneumonia deaths, and 132 cancer deaths. Mean follow-up was 8.3 years (Table 2). Participants were followed for 20,787 person-years after baseline. The death rate was 14.5 per 1000 person-years.

Multivariate adjustments were made for variables including physical and lifestyle factors, as described in "Methods," which were further adjusted for estimation of mortality risk (Table 3). After these adjustments, mortality hazard ratio for the marked HL was 1.76 (95% CI, 1.31to 2.38), $p = 0.0002$.

Mortality risk also was analyzed for specific causes of death. Adjusted mortality risk results are presented in Table 4. When causes of death were classified, increased mortality risk for marked HL was observed in CHD- or stroke-caused death (HR = 3.35, 95% CI 1.63 to 6.86, $p = 0.0010$) and respiratory disease-caused death (HR = 2.52, 95% CI 1.25 to 5.22, $p = 0.0130$), but not cancer-caused death ($p = 0.3143$). No significant increase in mortality from cancer was observed. With significance, continuous HL also was associated with all-cause mortality (HR = 1.08 per 1 cm HL increase, 95% CI 1.03 to 1.14, $p = 0.0034$) and CHD- or stroke-caused death (HR = 1.11, per 1 cm HL increase, 95% CI 1.00 to 1.23, $p = 0.0465$). Previous history of vertebral deformity and hip fracture were not associated with all-cause mortality risk (Table 4).

The hazard ratios for marked HL were reduced only slightly when the 191 prevalent cases of vertebral deformity were excluded (eg, HR of 1.65, rather than 1.76 for all-cause mortality) (analyses not shown).

Discussion

HL and mortality

This is the first study to show that HL of more than 2 cm increased the risk of all-cause death, CHD- or stroke- and respiratory disease-caused death, but not cancer death, with vertebral fracture assessed simultaneously. Furthermore, the present study showed that HL treated as a continuous variable was

Table 1. Baseline (1994–1995) Characteristics of Study Population by Sex and Vital Status

	Men		Women	
Variable	Alive	Dead	Alive	Dead
Number of subjects	627	128	1569	174
Age (years)	61.2 (8.9)	70.3 (9.1)**	64.7 (9.1)	73.5 (8.9)**
Height (cm)	163.9 (6.0)	161.5 (6.3)**	150.7 (5.7)	147.6 (6.4)**
Weight (kg)	61.4 (8.8)	58.2 (9.2)**	52.8 (8.7)	48.6 (9.3)**
BMI (kg/m^2)	22.8 (2.9)	22.3 (3.0)	23.2 (3.6)	22.3 (3.9)**
height at 40s or 50s (cm)[a]	164.5 (5.8)	162.9 (5.8)**	152.3 (5.2)	150.9 (5.4)**
HL (cm)	0.69 (1.01)	1.50 (1.46)**	1.69 (1.94)	3.34(2.76)**
marked HL (%)	67 (10.7)	42 (32.8)**	556 (35.4)	127 (73.0)**
BMD (g/cm2)				
Spine (L1-4)	0.960 (0.155)	0.972 (0.164)	0.796 (0.154)	0.739 (0.148)**
Total hip	0.739 (0.115)	0.709 (0.109)**	0.626 (0.107)	0.571 (0.093)**
Prevalent hip fracture	7 (1.1%)	5 (3.9%)*	34 (2.2%)	10 (5.8%)**
Prevalent vertebral deformity	15 (2.4%)	6 (4.7%)	138 (8.8%)	32 (18.4%)**
SBP	131.8 (20.3)	136.3 (22.1)*	130.7 (21.1)	136.4 (21.4)**
DBP	80.8 (11.4)	77.3 (15.2)**	77.3 (11.4)	76.4 (12.5)
Total cholesterol	203.2 (34.0)	202.0 (36.7)	221.3 (34.6)	211.1 (42.6)**
Diagnosed disease				
Hypertension	185 (32.9%)	37 (39.0%)	390 (27.7%)	50 (40.7%)**
Hyperlipidemia	44 (7.8%)	6 (6.3%)	194 (13.8%)	15 (12.2%)
Diabetes	96 (15.3%)	28 (21.9%)	162 (10.3%)	23 (13.2%)
CVD	288 (45.9%)	78 (60.9%)**	660 (42.1%)	113 (64.9%)**
Cancer	40 (6.4%)	18 (14.1%)*	153 (9.8%)	33 (19.0%)**
Alcohol intake				
Never	105 (16.7%)	27 (21.1%)	769 (49.0%)	102 (58.6%)*
Current occasional	107 (17.1%)	29 (22.7%)	256(16.3%)	31 (17.8%)
Current often	262 (41.8%)	31 (24.2%)**	113 (7.2%)	9 (5.2%)
Former	14 (2.2%)	8 (6.2%)*	13 (0.8%)	5 (2.9%)*
Unknown	139 (22.2%)	33 (25.8%)	418 (26.7%)	27 (15.5%)**
Smoking status				
Never	88 (15.6%)	9 (11.7%)	920 (64.5%)	67 (58.6%)
Current	210 (33.5%)	42 (32.8%)	104 (6.6%)	11 (6.3%)
Former	167 (26.6%)	35 (27.4%)	47 (3.0%)	6 (3.5%)
Unknown	152 (24.3%)	36 (28.1%)	406 (25.9%)	55 (31.6%)*
Radiation dose (Gy)	0.382 (0.634)	0.432 (0.608)	0.297 (0.514)	0.407 (0.568)

HL, historical height loss starting in middle age; BMI, body mass index; BMD, bone mineral density; SBP, systolic blood pressure; DBP, diastolic blood pressure; CVD, cardiovascular disease.

Mean (SD).

With consideration for parameter distributions, we tested difference between death or alive using *t*-test for height, weight, BMI, height at 40s or 50s, marked HL, BMD, SBP, DBP, total cholesterol, radiation dose, using a Wilcoxon test for age, and using χ^2-test for prevalence of hip fracture, prevalence of vertebral deformity, alcohol intake, smoking status, and diagnosed diseases.

[a]Longitudinal data of height are available for all study participants of the cohort since 1962. We defined height loss starting in middle age (HL) as the difference between a participant's average height in his or her 40s and height measured in 1994 to 1995.

*$p < 0.05$.

**$p < 0.01$.

associated with significantly increased risk of all-cause mortality and CHD- or stroke-caused mortality.

Our previous report[21] showed that height loss and vertebral deformity affected QOL significantly and independently in the elderly. Even after excluding individuals with vertebral deformity, height loss was associated with decreased QOL. Furthermore, it is observed that factors other than vertebral deformity, such as intervertebral disk degeneration and osteoarthritic conditions, also caused height loss. In the present study, we observed association between mortality and height loss starting in middle age, but not prevalent vertebral deformity. The presence of certain adverse health conditions, for example poor muscle strength, possibly causing height loss may be implicated.

Wannamethee et al. followed 4213 men measured for height at ages 40 to 59 and again 20 years later, observing 760 deaths occurring after six more years. In the aforementioned study, Wannamethee et al. described how osteoporotic disease complicated by vertebral fractures was not likely to explain