disability remained significant after adjustment. This means that in women without knee OA, pain may occur, but it may disappear more easily. In addition, grip strength was also associated with resolution of physical functional disability after adjustment, indicating that muscle exercises may help make physical functional disability disappear.

The present study showed gender differences in the associations of knee OA with pain and physical functional disability. In women, knee OA was significantly associated with onset of pain and physical functional disability as well as their resolution, whereas in men, there were no significant association of knee OA with onset of pain and resolution of physical functional disability. Our previous cross-sectional study also showed that the odds ratio of knee pain for KL 3/4 knee OA was approximately twice as high in women as in men[2]. These findings may be partly explained by the lower muscle mass in women compared with men. In men, muscular strength may obscure the associations of knee OA with pain and physical functional disability.

In conclusion, the present longitudinal study revealed the onset rate of pain and physical functional disability as well as their resolution rate using WOMAC. In addition, severe knee OA was significantly associated with onset of pain and physical functional disability as well as their resolution, particularly in women. Furthermore, we also clarified that BMI and grip strength were associated with onset of pain and physical functional disability as well as their resolution in women.

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Conflict of interest

None.

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Supplementary material available online

Supplementary Tables 1-4.

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ORIGINAL ARTICLE

Prevalence of hallux valgus and risk factors among Japanese community dwellers

Akinobu Nishimura · Ko Kato · Aki Fukuda · Shigeto Nakazora · Tomomi Yamada · Atsumasa Uchida · Akihiro Sudo

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Abstract
Background To investigate the prevalence and severity of radiographically detected hallux valgus (HV) as well as associated risk factors among Japanese residents of Miyagawa, a mountain village located in the center of Mie Prefecture.
Methods The height, weight and body mass index (BMI) of 403 participants (male $n = 135$, female $n = 268$) recruited from among the residents of Miyagawa Village, Japan aged ≥65 years were measured, and baseline data, including age, sex and medical history were obtained from interviews and questionnaires. Knee osteoarthritis (KOA) was determined from radiographs of the feet and knees, and osteoporosis was determined by measuring bone mineral density. Hallux valgus, defined as angulation of the big toe at the first metatarsophalangeal joint of >20°, was classified as: mild (20°–30°), moderate (30°–40°) or severe (>40°). Risk factors for HV were calculated using multivariate logistic regression analysis that included age, sex, obesity (BMI ≥25), KOA, osteoporosis, Heberden's nodes and low back pain as variables.
Results The overall prevalence of definite radiographic HV was 22.8 % (184/806), and mild, moderate and severe HV was found in 66.3, 27.2 and 6.5 % of the participants, respectively. Hallux valgus was found in at least one foot in 120 (29.8 %) of the participants and the prevalence significantly differed between females with and without HV and KOA (odds ratios: 2.54 and 1.71, respectively).
Conclusions The prevalence of definite radiographic HV was 29.8 %. Female sex and KOA were significantly associated with increased risk for radiographic HV.

A. Nishimura (✉) · A. Fukuda · S. Nakazora · A. Uchida · A. Sudo
Department of Orthopaedic Surgery, Mie University Graduate School of Medicine, 2-174 Edobashi, Tsu, Mie 514-8507, Japan
e-mail: meiten@clin.medic.mie-u.ac.jp

A. Nishimura · K. Kato
Department of Orthopaedics and Sports Medicine, Mie University Graduate School of Medicine, Mie, Japan

T. Yamada
Department of Translational Medical Science, Mie University Graduate School of Medicine, Mie, Japan

Introduction

Hallux valgus (HV) is a common deformity in adults that is characterized by abnormal angulation, rotation and lateral deviation of the big toe at the first metatarsophalangeal joint [1, 2]. Wearing footwear causes individuals with HV pain and difficulty in walking [3], and many such patients require orthosis and/or surgery [4, 5]. Understanding the associated risk factors is very important to prevent HV and determine the ratio of individuals with HV. However, the community prevalence of HV estimated by epidemiological studies varies between 21 and 70 % [6–10]. This variation is partly attributable to differences in study populations and unclear definitions of HV, with the terms "hallux valgus" and "bunion" specifically causing confusion. Most epidemiological HV studies have used a self-check sheet or footprint rather than X-rays to detect HV [11] and very few community-based studies have incorporated such radiographic imaging [12]. We initiated a cohort study in 1997 to investigate the epidemiology of knee osteoarthritis (KOA) [13–15] and osteoporosis [16]. The present study of HV started from the seventh (2009) and eighth (2011) biennial examinations.

The present cross-sectional study investigates the prevalence of radiographic HV and associated risk factors

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among Japanese inhabitants of Miyagawa. Whether having radiographic HV affected their quality of life (QOL) was determined using the Japanese version of the EuroQol 5D (EQ-5D) questionnaire [17, 18].

Materials and methods

Individuals aged ≥65 years were recruited from among the inhabitants of Miyagawa, a mountain village located in the center of the Mie Prefecture, Japan. The population of this village was 3,364 in the year 2012, and 1,522 residents met the age criterion. The study that started in 1997 was designed to determine factors associated with KOA and osteoporosis by analyzing data from a representative sample of a rural elderly population every 2 years. The present study analyzes data from the seventh and eighth biennial examinations in 2009 and 2011, respectively.

The Ethics Committee for Human Research at our institution approved this study, and written informed consent was obtained from all participants before enrollment.

Baseline data were obtained at one-to-one interviews using standard questionnaires designed by orthopedic surgeons. These data included information about age, sex, medical history, cigarette smoking, and health-related QOL determined from the EQ-5D questionnaire. Height and body weight were measured, and body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2) at the baseline assessment. Obesity was defined as BMI >25. Bunions and callosities were identified by palpation. Pain was determined by applying pressure to the bunion. The location of callosities was categorized from maps of the soles of the feet. Heberden's nodes were located by visual inspection and palpation.

The EQ-5D is a standardized, characterized instrument for assessing the course of health processes [17] that was translated into Japanese for the present study. The EQ-5D contains a self-assessment section in which participants provide a description of their health status from the viewpoints of mobility, self-care, daily activities, pain (discomfort and anxiety) and depression. They selected the most appropriate of three statements about each of the five QOL dimensions to indicate their current health status. Each statement represents an increasing degree of severity. The results were coded and converted to utility scores using a table of values [18].

Other medical examinations consisted of radiography of the feet and knees and measurement of bone mineral density (BMD) at the distal third of the non-dominant side radius using dual energy X-ray absorptiometry (DCS-600EX; Aloka, Tokyo, Japan). Osteoporosis was defined as 2.5 standard deviations (SD) of BMD below that of the young adult mean (YAM) of a healthy young adult of the same sex.

Fully extended anteroposterior (AP) radiographs of both knees while standing were scored for radiographic KOA according to the Kellgren Lawrence (K/L) grading system [19]. Confirmed radiographic KOA was defined as a K/L grade of ≥2.

Foot X-rays were taken from participants standing upright with both feet on the cassette as described by Saltzman [20]. The standardized radiographic projection was indicated for weight-bearing views, in which the X-ray beam was inclined at 20° at a distance of 40 in., and centered between the bilateral feet. The hallux valgus angle (HVA), which is formed by the bone axes of the first metatarsal and the first proximal phalanx, and the M1-M2 angle formed by the bone axes of the first and second metatarsals on all radiographs, were consistently measured by the same examiner (AN) [21] and analyzed using Image J version 1.37 software (National Institutes of Health, Bethesda, MD, USA). The HVA value was taken as the mean of three determinations.

Hallux valgus was defined as an HV angle >20°, according to the Japanese Orthopaedic Society criteria and severity was classified as mild (20°–30°), moderate (30°–40°) or severe (>40°) [22].

Statistical analysis

Means ± standard deviations (SD) were calculated for variables unless otherwise noted. Risk factors for HV were determined from multivariate logistic regression analysis that included age, sex, obesity, KOA, osteoporosis, Heberden's nodes and low back pain as variables. The relationship between HVA and the M1-M2 angle was assessed using Pearson's correlation coefficient. The relationship between the severity of HV and of KOA (except total knee arthroplasty) was assessed using the Spearman rank correlation coefficient. Risk factors for HV are summarized as odds ratios (OR) with 95 % confidence intervals (CI). The EQ-5D values for normal feet or for each grade of HV were determined using a one-way ANOVA with Dunnett's post hoc test.

Significance at the level of 5 % was taken for all tests. All data were statistically analyzed using PASW Statistics for Windows version 18 (SPSS Inc, Chicago, IL, USA).

Results

A total of 314 (105 men, 209 women) and 221 (74 men, 147 women) elderly residents participated in the seventh and eighth Miyagawa studies, respectively, of whom 130 participated in both. Two residents declined X-ray examinations, and thus data from 403 (overall mean age: 75.5 ± 6.4 years, range: 65–94 years, female: 75.8 ± 6.6 years, male: 75.4 ± 6.3 years) participants (806 feet) who fulfilled the study criteria were analyzed. None of the participants had a history of surgically treated HV.

Table 1 shows the distribution of HV severity in the 806 feet. The overall prevalence of definite radiographic HV was 22.8 % (184/806), and 11.6 % (28/270) and 41.1 % (156/536) in men and women, respectively. The ratios of residents with mild, moderate and severe HV were 66.3 % (122/184), 27.2 % (50/184) and 6.5 % (12/184), respectively. The HV was bilateral in 64 (15.9 %), unilateral in 56 (13.9 %), and on at least one side in 120 (29.8 %) of the participants.

Figure 1 shows that HVA significantly correlated with the M1-M2 angle (Pearson's correlation coefficient $(r) = 0.762$, $p < 0.001$).

Table 2 shows relationships between each risk factor and the prevalence of HV. The prevalence of females significantly differed between groups with and without HV ($p = 0.003$, OR: 2.54, 95 % CI: 1.38–4.66) and KOA ($p = 0.028$, OR: 1.71, 95 % CI: 1.06–2.76).

The incidences of bunions on normal feet and on feet with mild, moderate and severe HV were 2.7 % (17/622), 28.7 % (35/122), 54.0 % (27/50), and 91.7 % (11/12), respectively (Fig. 2a). The incidences of painful bunions on normal feet and on feet with mild, moderate and severe HV were 0.3 % (2/622), 5.7 % (6/122), 8.0 % (4/50), and 16.7 % (2/12), respectively. The rate of painful bunions on all those with HV was 6.5 % (12/184). The incidences of callosities located on the balls (the first metatarsal head) of both normal feet and on feet with mild, moderate and severe HV were 3.2 % (20/622), 7.4 % (9/122), 2.0 % (1/50), and 0 % (0/12), respectively. On the other hand, the incidences of callosities located on the second, third, and fourth metatarsal heads of normal feet and of feet with mild, moderate and severe HV

Table 1 Distribution of hallux valgus severity

Participants	Normal	Mild	Moderate	Severe
Men	242	22	5	1
Women	380	100	45	11
Total	622	122	50	12

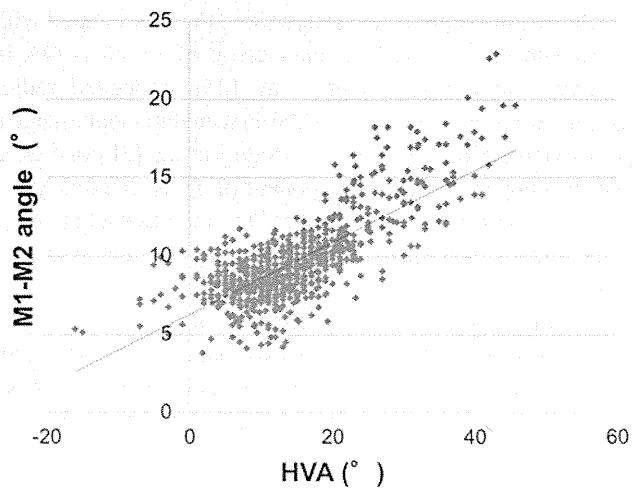

Fig. 1 Relationship between hallux valgus (*HVA*) angle and M1-M2 angle

Table 2 Comparison of individuals with and without radiographic hallux valgus

	HV ($n = 120$)	No HV ($n = 283$)	p	95 % CI	OR
Age (years)	76.1 ± 6.9	75.3 ± 6.1	0.66	0.97–1.05	1.01
Gender	M21; F99	M114; F169	0.003*	1.38–4.66	2.54
Obesity	+30/−90	+81/−282	0.23	0.38–1.22	0.73
KOA	+73/−47	+115/−168	0.03†	1.06–2.76	1.71
Osteoporosis	+66/−54	+123/−160	0.80	0.65–1.74	1.07
Heberden's nodes	+67/−53	+118/−165	0.13	0.90–2.27	1.43
Low back pain	+53/−67	+146/−137	0.10	0.44–1.08	0.68

HV hallux valgus, *KOA* knee osteoarthritis, *CI* confidence interval, *OR* odds ratio. Age is shown as mean ± SD. * $p < 0.01$, † $p < 0.05$

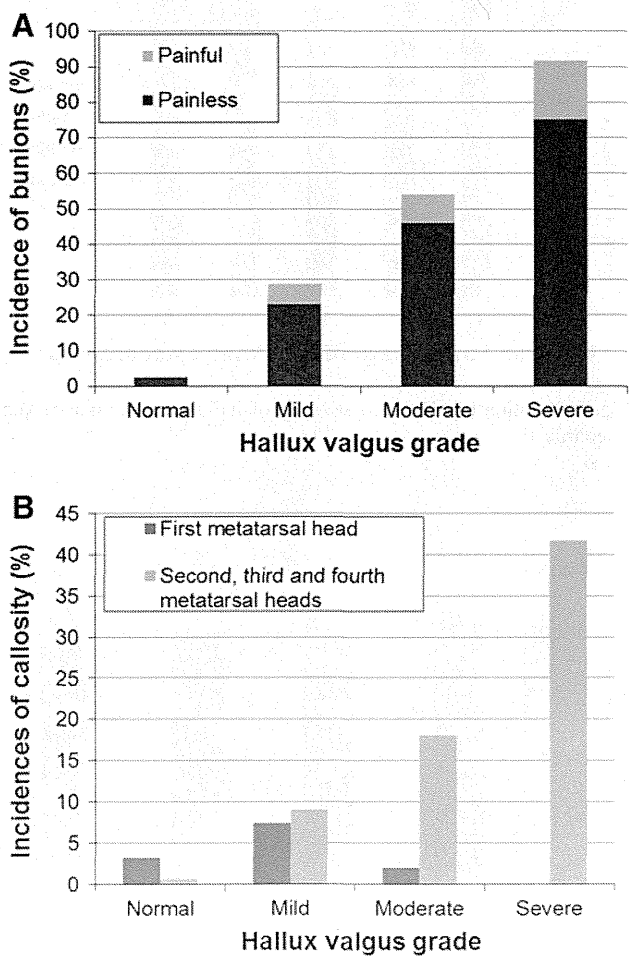

Fig. 2 Incidence of painful (*gray*) and painless (*black*) bunions (**a**) and callosities (**b**)

were 0.6 % (4/622), 9.0 % (11/122), 18.0 % (9/50) and 41.7 % (5/12), respectively (Fig. 2b).

Figure 3 shows that the severity of HV and of KOA significantly correlated ($\rho = 0.228$ and $p < 0.001$).

The EQ-5D utility scores of individuals with normal feet and with mild, moderate and severe HV were 0.855, 0.872, 0.809 and 0.769, respectively, with no significant differences among the groups (Fig. 4).

Discussion

The results of this cross-sectional study indicated a 29.8 % prevalence of radiographic HV among residents in a single village. Roddy et al. [2] reported a 28.4 % prevalence of self-reported HV among 4,249 patients in two general practices. On the other hand, Cho et al. [12] found radiographic HV in 364 (64.7 %) of 563 individuals. The reason for this higher value is their wider definition of radiographic HV as >15°, compared with our definition of >20°. Severe HV (>25°) was also found in 48 (13.2 %) individuals. Given these diagnostic criteria for HV, the prevalence was similar in both studies.

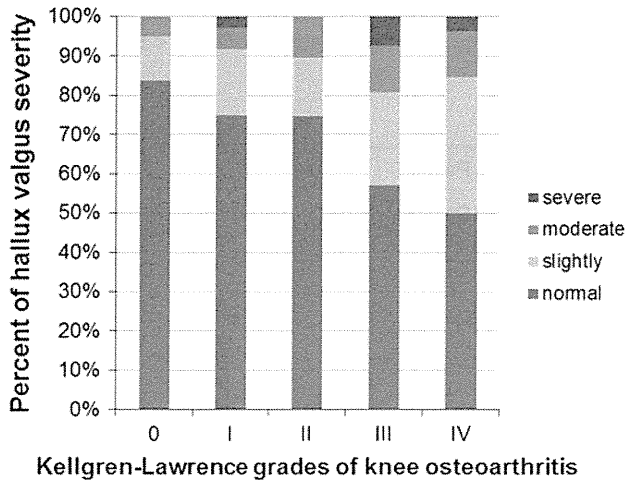

Fig. 3 Relationship between severity of hallux valgus and of knee osteoarthritis

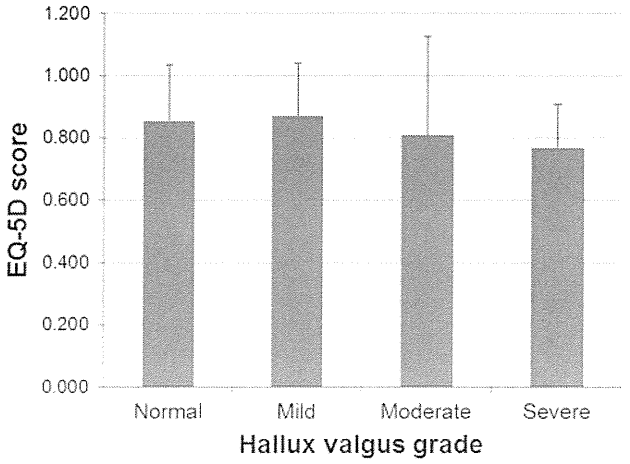

Fig. 4 EQ-5D utility scores of hallux valgus severity. Severity does not significantly differ between groups

Badlissi [11] identified HV in 37.1 % of 784 individuals in a community-based study and found no association with foot pain or function, whereas 9.9 % of individuals studied by Cho et al. [12] reported foot pain. On the other hand, Menz et al. [23] identified foot pain in 20–30 % of community-dwelling elderly individuals. Although foot pain was not assessed in the present study, bunions and callosities, which are the main cause of pain associated with HV, were investigated. The rate of painful bunions on all those with HV in the present study was 6.5 % (12/184), which closely correlated with the severity of HV. The rates of painful bunions and callosities were higher in feet with HV than in normal feet. The locations of callosities changed from the ball of the foot to the second, third and fourth metatarsal heads according to the severity of HV. The likely reason for this is that the load center of the foot moves from the ball of the foot to the second, third and fourth metatarsal heads as HV severity progresses.

Risk factors for HV in some countries have been reported. Our results concurred with the findings of many reports indicating that female sex increases risk for HV [2, 12, 24–26], but contradicted those of Roddy et al. [2], who reported that HV is closely associated with age. However, their study participants were much younger than those in the present study (>30 vs >65 years). Our results suggested that HV is less likely to occur in the elderly. We also found that osteoporosis, which is considered a typical musculoskeletal disease of the elderly, and low back pain, which is associated with osteoporosis, were not associated with HV.

Our results support the notion that HV is associated with knee pain [2, 12, 27], the main cause of which is OA in elderly individuals. Wilder et al. [28] associated radiographically confirmed OA of the first metatarsophalangeal joint with radiographic KOA. Roddy et al. [2] concluded that HV appears to be a component of generalized OA and a likely marker of OA of the first metatarsophalangeal joint. However, the cross-sectional design of their study did not allow confirmation of this relationship ahead of the possibility that HV coexists with OA or that HV is a precursor of OA of the first metatarsophalangeal joint. Other reports [29, 30] show that most patients with HV also have cartilage degeneration of the first metatarsophalangeal joint. Knee OA has a genetic association [34], as well as a phenotypic association with factors such as weight loading (obesity) [12]. A deformity (especially of the varus type) of a person with a genetic background of KOA might proceed

gradually, according to weight loading. On the other hand, valgus stress affects the first MTP joint very little when walking barefoot, but the effect is considerable when wearing shoes, especially those with pointed toes or high heels. Not all people who wear such shoes develop HV, so we believe that those who develop HV have internal factors that are related to KOA. On the other hand, Heberden's nodes that are considered hand OA [31] are thought to indicate a systemic predisposition to generalized OA [32]. However, our data showed that HV is related to KOA, but not to Heberden's nodes. Cicuttini et al. [33] found poor agreement between Heberden's nodes and radiological distal interphalangeal osteophytes in the same finger of the same hand. Heberden's nodes were defined in the present study only by inspection and palpation, and such a relationship might be revealed by X-rays of the hand. Further study is needed to clarify this issue.

Cho et al. [12] associated a high BMI with HV, whereas Roddy et al. [2] and Abhishek et al. [35] did not. The present study supports the latter finding, as an association between HV and BMI >25 (obesity) was not identified. Race, lifestyle or socioeconomic background might be involved in this contradiction.

Abhishek et al. [35] suggested that self-reported HV and big toe pain are associated with an impaired QOL, whereas HV alone is not. They also considered that the influence of HV on QOL could be explained by impaired balance [36] and gait [23]. Cho et al. [12] reported that participants with at least moderate HV (HVA >25°) had impaired general functional status on the physical function domain of the SF-36. They also found even lower general functional status among participants who had HV with foot pain than those without. Both moderate and severe HV tended to be a relatively lower EQ-5D score in the present study, but not significantly with QOL (EQ-5D). We considered only HV angle and not foot pain. This could explain the discrepancy between the previous and present results.

The present study has several potential limitations. We did not question participants about the types of shoes they wore when they were young, and so could not clarify the relationship between HV and type of shoes worn in youth. However, many inhabitants were engaged in forestry and/or agriculture because Miyagawa is a mountain village. Thus, most of them probably wore Japanese tabi socks and/or Japanese zori sandals when they were young. Both tabi socks and zori separate the big toe from the other toes and they do not have a heel. Shoes with pointed toes and high heels are risk factors for HV according to the Japanese guidelines [22]. Thus, people who wore tabi and zori in their youth might be less likely to develop HV, and because the younger generations did not wear tabi and zori even when they were young and often wore high-heeled shoes, the prevalence of HV might increase in the near future as they age. Participants who could visit the hospital were generally healthier than non-participants. The statistical significance of the risk factors might be relatively low. The EQ-5D is a standardized instrument used as a measure of health outcome, so it is not foot-specific like the self-administered foot evaluation questionnaire (SAFE-Q) [37], which might reveal significant differences. This study was cross-sectional and not longitudinal. Only two of the 130 participants who participated in both the seventh and eighth Miyagawa studies were free of HV (HVA <20) at the seventh study but had HV by the eighth (data not shown). Thus, a longitudinal study was impossible at this time. Further investigations of more participants over a longer term are planned, as the study will continue every 2 years.

Conclusion

This cross-sectional epidemiological study identified a 22.8 % prevalence of definite radiographic HV in a rural Japanese village. The ratios of mild, moderate and severe HV were 66.3, 27.2 and 6.5 %, respectively, and 15.9 and 13.9 % of participants had bilateral and unilateral HV, respectively. Furthermore, both female sex and KOA were identified as risk factors for radiographic HV.

Conflict of interest The authors declare that they have no conflict of interest.

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ORIGINAL ARTICLE

Osteoporosis, vertebral fractures and mortality in a Japanese rural community

Akinobu Nishimura[1,2], Koji Akeda[1], Ko Kato[2], Kunihiro Asanuma[1], Tomomi Yamada[3], Atsumasa Uchida[1], and Akihiro Sudo[1]

[1]*Department of Orthopaedic Surgery, Mie University Graduate School of Medicine, Mie, Japan,* [2]*Department of Orthopaedics and Sports Medicine, Mie University Graduate School of Medicine, Mie, Japan, and* [3]*Department of Translational Medical Science, Mie University Graduate School of Medicine, Mie, Japan*

Abstract

Objectives. The present study aims to determine the relationship between osteoporosis (OP), vertebral fracture (VF) and mortality.

Methods. We followed up 1024 residents of Miyagawa village every 2 years for a mean of 8.4 years between 1997 and 2009. The residents were assessed every 2 years. We defined OP as T scores for bone mineral density that were <2.5 standard deviations below peak bone mass. VF was assessed by lateral radiography of the thoracic and lumbar spine. The participants were allocated as follows depending on the presence or absence of OP and VF: with OP and without VF (OP group), with VF and without OP (VF group), with OP and VF (OP + VF group) and without OP and VF (Control group). We determined survival/mortality rates until 2011 by reviewing medical histories and death certificates.

Results. By 2011, 304 participants had died. The respective 5-year survival rates for the OP + VF, OP, VF and Control groups were 80.6%, 93.7%, 87.8% and 94.2%. Mortality rates were significantly worse for the OP + VF group than the Control group (OP + VF Hazard Ratio: 1.89; 95% CI, 1.27–2.77).

Conclusion. Prevention of osteoporotic VF in elderly persons is very important from the viewpoint of increasing life expectancy.

Keywords

Elderly, Epidemiology, Mortality, Osteoporosis, Vertebral fractures

History

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Introduction

Osteoporosis (OP) is characterized by increased bone loss and enhanced bone fragility. Japanese society is rapidly aging. Yoshimura et al. [1] described that about 6.4 and 11 million individuals in Japan have L2–4 and femoral neck OP. Therefore, OP and osteoporotic fractures are major public health problems in this aging society.

Vertebral fractures (VF) are the most common type of osteoporotic fracture, with an estimated annual incidence of 700 000 in the US [2] and 1.4 million in Europe [3]. Elderly persons typically develop VF due to bone fragility caused by OP. However, VF are sometimes caused by high-velocity accidents, such as car crashes or falls from a considerable height. Morphological evaluation by radiography alone cannot easily differentiate whether or not VF result from high-velocity accidents involving osteoporotic bone. However, the possibility that a combination of OP and VF causes osteoporotic VF might be quite high.

Some investigators have reported that low bone mineral density (BMD) is a risk factor for death [4,5]. If OP is independently associated with mortality, increased mortality might be associated with other types of osteoporotic fractures. Many studies have shown that osteoporotic [6–9], particularly hip [10–13], fractures are associated with increased mortality. Several recent studies of VF have also found that mortality is higher in patients with OP than in the general population [6,14–16]. However, Cummings and Melton [17] noted that most VF are subclinical or remain unrecognized without radiographic examination. Haczynski and Jakimiuk [16] also noted only one third of all VF are diagnosed clinically. Many studies have evaluated clinical (symptomatic) VF, but few have described mortality rates based on prevalent, radiographically defined VF [18,19].

We tested the hypothesis that osteoporotic, radiographic VF is associated with an increased risk of death among Japanese community dwellers.

Correspondence to: Akinobu Nishimura, MD, PhD, Department of Orthopaedic Surgery, Mie University Graduate School of Medicine, 2-174 Edobashi, Tsu City, Mie 514-8507, Japan. Tel: +81-59-231-5022. Fax: +81-59-231-5211. E-mail: meiten@clin.medic.mie-u.ac.jp

Materials and methods

This population-based study of the residents of Miyagawa, a rural mountain village located in the center of Mie Prefecture, Japan, began in 1997. The participants were self-recruited, community-dwelling volunteers aged ≥ 65 years, who were assessed every 2 years from 1997 to 2011 at Houtoku Hospital for a total of eight studies. The population of the village in 1997 and 2010 was 4196 and 3490, respectively, when 1463 and 1553 residents, respectively, met the age criterion. This study proceeded at a local hospital, so participants had to arrive by public transportation or by other means, and they also had to understand the purpose of the study. Thus, the participants were generally healthier than non-participants.

Of 1271 residents (806 women and 465 men) who participated in these studies at least once, 1024 (661 women and 363 men) who

were followed up for a mean of 8.4 (1–14) years were included in the study.

The Committee for the Ethics of Human Research at Mie University approved the study protocol, and all participants provided written, informed consent before enrollment.

Baseline data obtained from standard questionnaires administered by orthopedic surgeons included information regarding age, gender and medical history. Body–mass index (BMI) was calculated from height and weight. Other medical examinations comprised radiography of the thoracic and lumbar spine and assessments of BMD at the distal third of the non-dominant side radius using dual energy X-ray absorptiometry (DCS-600EX; Aloka, Tokyo, Japan). We defined OP as T scores of BMD < 2.5 standard deviations (SD) below peak bone mass according to the World Health Organization criteria [20]. Central DXA of the lumbar spine or femoral neck is generally used to diagnose OP. However, many elderly individuals have vertebral deformities. Thus, lumbar DXA tends to show high BMD. Positioning (degree of internal rotation) of the femoral neck for DXA is difficult and thus reproducibility is poor and femoral DXA is unsuitable for longitudinal studies. Therefore, we assessed the participants using radial DXA.

We assessed VF from lateral radiographs of the thoracic and lumbar spine in terms of a wedge, biconcave or crushed appearance according the Japanese Society of Bone and Mineral Research criteria [21].

Based on the baseline OP and VF criteria, the participants were allocated to the following groups: with OP and without VF (OP group), with VF and without OP (VF group), with OP and VF (OP + VF group) and without OP and VF (Control group).

We assessed the survival/mortality rates of the participants until 2011 by reviewing their medical histories and death certificates with the help of local hospital staff. Causes of death were determined from death certificates.

Statistical analysis

Means ± SD were calculated for variables unless otherwise noted. Significant differences in baseline characteristics between the OP and Control groups, between the VF and Control groups, and between the OP + VF and Control groups were determined using t and χ^2 tests. Survival curves for the OP, VF, OP + VF and Control groups were constructed based on the Kaplan–Meier method. We also used Cox proportional hazards analyses to determine age–gender-adjusted mortality (as hazard ratios [HR] and 95% confidence intervals [CI]) among three groups (OP, VF and OP + VF groups) and the Control group. The Control group served as the reference for the Cox proportional hazards analyses. The period of the Cox model was measured in months. The significance level for entry into the model was 0.05. All data were statistically analyzed using PASW Statistics version 18 software (SPSS, Chicago, IL, USA).

Table 1. Baseline physical characteristics of all groups.

	OP + VF $n = 125$	OP $n = 356$	VF $n = 59$	Control $n = 484$
Gender (M/F)	9/116*	33/323*	40/19	281/201
Age (y)	77.1 ± 7.6*	72.2 ± 6.6*	72.1 ± 6.1	70.8 ± 5.6
Height (cm)	143.1 ± 7.6*	147.7 ± 7.0*	154.5 ± 7.4	154.8 ± 7.5
Weight (kg)	46.9 ± 10.0*	49.9 ± 8.4*	55.6 ± 10.1	56.6 ± 8.4
BMI (kg/m^2)	22.8 ± 3.9†	22.8 ± 3.3*	23.2 ± 3.6	23.6 ± 3.0

BMI, body–mass index; F, female; M, male; OP, osteoporosis; VF, vertebral fractures.
*$p < 0.01$ and †$p < 0.05$ versus Control.

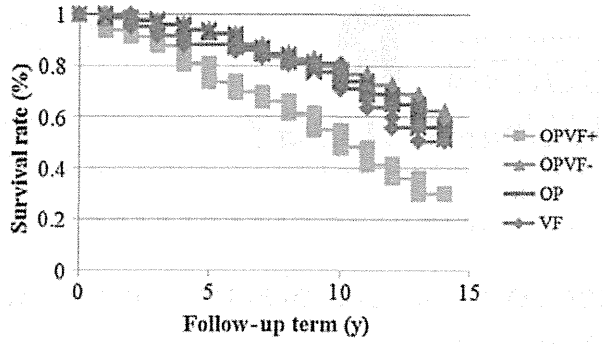

Figure 1. Survival rates for all groups. OP, osteoporosis; VF, vertebral fractures.

Results

The overall mean age of participants was 72.1 ± 6.5 years (average for men and women, 72.4 ± 6.3 and 72.0 ± 6.7, respectively). During a mean follow-up of 8.4 years, 304 participants (29.7%) had died. Table 1 compares the physical characteristics among the four groups. Height, weight and BMI were significantly lower, whereas the ratio of females and age were significantly higher for the OP + VF and OP groups than for the Control group.

Figure 1 shows the Kaplan–Meier survival curves for the four groups. The respective 5- and 10-year survival rates for the OP + VF, OP, VF and Control groups were 80.6%, 93.7%, 87.8% and 94.2% and 54.9%, 77.4%, 80.7% and 79.8%. Table 2 shows the results of the age and gender-adjusted Cox proportional hazards analyses. The mortality was significantly worse for the OP + VF group than for the Control group. The HR for the OP + VF group was 1.89 (95% CI, 1.27–2.77). The mortality rate tended to be worse for the OP group, but the difference did not reach significance.

Table 3 shows the causes of the 304 deaths. Malignant tumors, heart disease, old age, accidents, suicide, other and unknown causes accounted for 24.7%, 18.8%, 3.3%, 3.6%, 2.0%, 12.5% and 8.9%, respectively, of the deaths. These data were similar to the national data for Japan during 2009 [22]. The causes of death did not significantly differ among the four groups.

Discussion

We recognized the combination OP and VF (OP + VF group) as osteoporotic VF, and found that this combination was associated with high mortality rates among a Japanese village community.

Johnell et al. [15] and Cooper et al. [6] reported 5-year survival rates for individuals with VF of 28% in Sweden, and 61% in the USA, respectively. Our rates of all groups were higher than these findings, which might have been due to our study cohort being generally healthier.

Some authors [4,5] have reported that low BMD is a risk factor for death, and that it is probably related to comorbidity in affected patients. Of course, OP predisposes bones to easy breakage and

Table 2. Age and gender-adjusted Cox proportional hazards findings versus Control.

	Alive	Dead	HR	95% CI	DF	P
					3	0.01
Control	360	124	1			
OPVF+	64	61	1.88	1.27–2.77	1	<0.005*
OP	255	101	1.33	0.98–1.81	1	0.07
VF	41	18	0.91	0.55–1.49	1	0.70

95% CI, 95% confidence intervals; HR, hazard ratio; OP, osteoporosis; VF, vertebral fractures.
*$p < 0.005$ versus Control.

Table 3. Causes of death.

	OP + VF $n = 125$	OP $n = 356$	VF $n = 59$	Control $n = 484$	Total $n = 1024$
Malignant tumor	11	21	3	40	75
Heart disease	10	18	3	26	57
Pneumonia	6	17	5	22	50
Brain disease	4	14	2	10	30
Old age	4	5	0	1	10
Accident	2	5	2	2	11
Suicide	2	2	1	1	6
Other	17	9	1	11	38
Unknown	5	10	1	11	27
Total	61	101	18	124	304

OP, osteoporosis; VF, vertebral fractures.

the relationship between OP and subsequent mortality might explain why survival decreases after sustaining osteoporotic fractures such as those of the hip [23]. In fact, a few studies have found that increased mortality is indeed associated with hip fractures [23–25]. Kanis et al. [26] reported that about 23% of deaths involving hip fractures might be causally related to the fracture itself. However, some [27–29] have shown that OP is associated with atherosclerosis, whereas others [30,31] have shown that OP does not increase the risk of mortality associated with fractures but is rather due to cardiovascular disease. The present study found that only OP without VF tended to associate with mortality, but a significant relationship was not identified ($p = 0.07$). Further study is needed to clarify this issue.

In term of causes of death, Kado et al. [14] reported that women with VF were 2- to 3-fold more likely to die of pulmonary causes than those without fractures. They also explained that severe kyphosis was highly predictive of pulmonary death, perhaps because those with underlying lung disease and decreased respiratory reserves might not be able to tolerate restrictive changes in thoracic anatomy resulting from VF. Indeed, Leech et al. [32] described a 9% decrease in predicted forced vital capacity per VF. Our preliminary report [19] associated the number of VF with mortality. Moreover, multiple VF might cause esophageal hiatal hernia and esophagitis [33,34], and restrict physical function, activities of daily living and quality of life [35,36]. Kado et al. [14] and Cooper et al. [6] also associated VF with increased cancer mortality. Thus, previous reports have associated VF with various causes of death. The present study associated the combination of VF and OP with increased mortality, but without relevance to a specific cause of death. Further investigation is needed to clarify the causes of death associated with osteoporotic VF.

Our study has several limitations. First, Miyagawa village is a rural mountain community, and many of the inhabitants are typically engaged in forestry. Thus, whether the present findings reflect the general population of Japan is doubtful. Second, participants who could attend the hospital were generally healthier than non-participants. Third, this investigation was based on a relatively small cohort. Therefore, the statistical significance of the risk factors might be relatively low. Fourth, since VF was evaluated only by radiographic morphometry and not clinically, we could not investigate differences between clinical and morphological VF.

In conclusion, the respective 5-year survival rates for the OP + VF, OP, VF and Control groups were 80.6%, 93.7%, 87.8% and 94.2%. The mortality rate was worse for elderly individuals with than without OP combined with VF (osteoporotic VF). Since osteoporotic VF increased the mortality rate 2-fold, efforts should be directed toward preventing such fractures in elderly populations to decrease mortality rates and increase life expectancy.

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Conflict of interest

None.

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ORIGINAL ARTICLE

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

Helena Johansson,[1,2] John A Kanis,[1] Anders Odén,[1] Eugene McCloskey,[1] Roland D Chapurlat,[3] Claus Christiansen,[4] Steve R Cummings,[5] Adolfo Diez-Perez,[6] John A Eisman,[7,8,9] Saeko Fujiwara,[10] Claus-C Glüer,[11] David Goltzman,[12] Didier Hans,[13] Kay-Tee Khaw,[14] Marc-Antoine Krieg,[15] Heikki Kröger,[16] Andrea Z LaCroix,[17] Edith Lau,[18] William D Leslie,[19] Dan Mellström,[2] L Joseph Melton III,[20] Terence W O'Neill,[21,22] Julie A Pasco,[23] Jerilynn C Prior,[24] David M Reid,[25] Fernando Rivadeneira,[26] Tjerd van Staa,[27] Noriko Yoshimura,[28] and M Carola Zillikens[26]

[1]WHO Collaborating Centre for Metabolic Bone Diseases, University of Sheffield, UK
[2]Centre for Bone and Arthritis Research (CBAR) at the Sahlgrenska Academy, Institute of Medicine, University of Gothenburg, Gothenburg, Sweden
[3]INSERM UMR 1033, Université de Lyon, Hôpital E Herriot, Lyon, France
[4]Center for Clinical and Basic Research, Ballerup, Denmark
[5]San Francisco Coordinating Center, California Pacific Medical Center Research Institute, University of California, San Francisco, CA, USA
[6]Departament de Medicina, Hospital del Mar IMIM-UAB-RETICEF, Barcelona, Spain
[7]Clinical Translation and Advanced Education, Osteoporosis and Bone Biology, Garvan Institute of Medical Research, St Vincent's Hospital, Sydney, Australia
[8]St Vincent's Clinical School, The University of New South Wales, Australia
[9]Clinical Excellence and Research, Sydney School of Medicine, Notre Dame University, Sydney, Australia
[10]Health Management & Promotion Center, Hiroshima Atomic Bomb Casualty Council, Hiroshima, Japan
[11]Sektion Biomedizinische Bildgebung, Klinik für Radiologie, Universitätsklinikum Schleswig-Holstein, Kiel, Germany
[12]Department of Medicine, McGill University, Montreal, Canada
[13]Department of Bone & Joint, Center of Bone Diseases, Lausanne University Hospital, Lausanne, Switzerland
[14]Department of Public Health and Primary Care, University of Cambridge, UK
[15]Department of Musculoskeletal Medicine, CHUV, Lausanne, Switzerland
[16]Department of Orthopaedics and Traumatology, Kuopio University Hospital, Kuopio, Finland
[17]Fred Hutchinson Cancer Research Center, Seattle, USA
[18]Hong Kong Orthopaedic and Osteoporosis Center for Treatment and Research, Hong Kong
[19]Department of Medicine, University of Manitoba, Winnipeg, Canada
[20]Division of Epidemiology, College of Medicine, Mayo Clinic, Rochester, MN, USA
[21]Arthritis and Rheumatism Council (ARC), Epidemiology Research Unit, University of Manchester, Manchester, UK
[22]Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands
[23]School of Medicine, Deakin University, Geelong, Australia
[24]Department of Medicine and Endocrinology, University of British Columbia, Vancouver, Canada
[25]School of Medicine & Dentistry, University of Aberdeen, Aberdeen, UK
[26]Department of Internal Medicine, Erasmus MC Rotterdam, The Netherlands
[27]Clinical Practice Research Datalink, Medicines and Healthcare Products Regulatory Agency, London, UK
[28]Department of Public Health, Wakayama Medical University School of Medicine, Wakayama, Japan

ABSTRACT

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

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Address correspondence to: Helena Johansson, PhD, WHO Collaborating Centre for Metabolic Bone Diseases, University of Sheffield, UK.
E-mail: helena.johansson@mbox319.swipnet.se

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

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

Introduction

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

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

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

Subjects and Methods

Cohorts studied

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

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

Table 1. Cohorts Studied

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

(*Continued*)

Table 1. *(Continued)*

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

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

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

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

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

Measurements

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

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

Statistical methods

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

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

Table 2. *Details of Cohorts Studied*

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

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

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

[b]Subjects with BMD data available.

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

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

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

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

Results

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

Table 3. Details of Incident Fractures by Cohort

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

– = site of fracture not given.

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

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

BMI and risk of fracture

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

Table 4. Baseline Characteristics by BMI Category

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

Values are mean (SD).

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

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

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

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

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

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

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

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

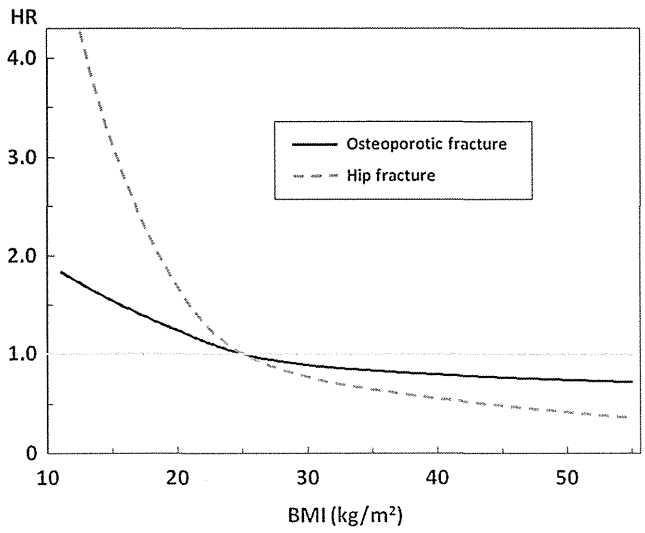

Fig. 1. Relationship between BMI and risk of fracture (HR versus BMI 25 kg/m^2) for osteoporotic fracture (solid line) and hip fracture (dashed line), adjusted for age and time since baseline. BMI = body mass index; HR = hazard ratio.

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

Adjustment for BMD

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

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

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

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

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

Interactions with BMI

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

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

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

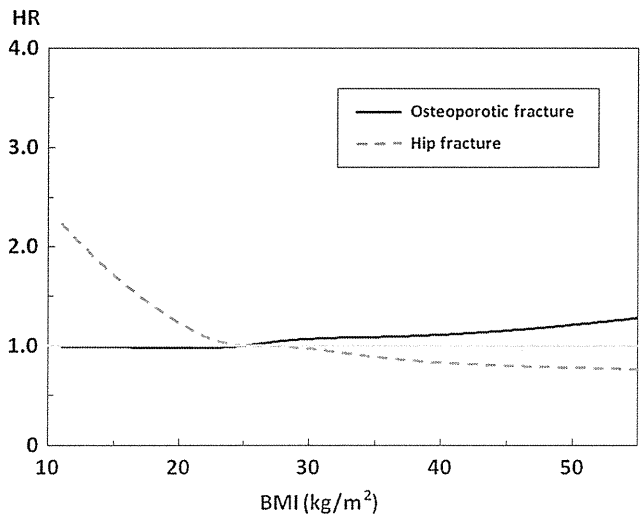

Fig. 2. Relationship between BMI and risk of fracture (HR versus BMI 25 kg/m^2) for osteoporotic fracture (solid line) and hip fracture (dashed line), adjusted for age, time since baseline, and BMD. BMI = body mass index; HR = hazard ratio; BMD = bone mineral density.

Discussion

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

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