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Title Page

Original research article

Effect of body mass index on vertebral and hip fractures in elderly people and its sex differences: A retrospective Japanese cohort study.

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Abstract

Objectives: The purpose of this study was to investigate the incidence of vertebral and hip fractures in the elderly and to clarify the relationship between these fractures and body mass index (BMI) and the impact of sex differences.

Design: This was a retrospective cohort study.

Setting: We used administrative claims data from April 2010 and 31 March 2018.

Participants: Elderly people living in Fukuoka Prefecture, Japan who underwent health examination in 2010 and aged ≥75 years at the time of health examination were included in the study.

Primary and secondary outcome measures: We estimated the incidence of vertebral and hip fractures by BMI category (low: < 18.5 kg/m^2, normal: 18.5–24.9 kg/m^2, high: > 25.0 kg/m^2) using a Kaplan–Meier curve in men and women and determined fracture risk by gender using Cox proportional hazards regression analyses.

Results: A total of 24,691 people were included; the mean duration of observation was 6.9 years. The incidence of vertebral and hip fractures was 16.8% and 6.5%, respectively. The cumulative incidence of vertebral and hip fracture in each BMI groups estimated using the Kaplan–Meier curve was 14.7%/10.4%/9.0% in men and 24.9%/23.0%/21.9% in women, and 6.3%/2.9%/2.4% in men and 14.1%/9.0%/8.1% in women, respectively, and both fractures were significantly

higher in low BMI regardless of sex ($P < .05$). Multivariate Cox proportional hazards models showed that low BMI was a significant risk factor only in men for vertebral fractures and in both men and women for hip fractures ($P < .05$).

Conclusion: Low BMI was associated with fractures in the elderly population, but there was a sex difference in the effect for vertebral fractures.

Trial registration: This study was approved by the Kyushu University Institutional Review Board for Clinical Research (Approval No. 20209).

Keywords: body mass index (BMI), sex differences, fracture, claim data, elderly people

Strengths and limitations of this study

1. This was a retrospective cohort study including 24,691 elderly peoples.

2. We followed up participants for approximately 7 years.

3. We investigated the incidence of vertebral fractures and hip fractures in the elderly and evaluated the relationship between BMI and fractures and differences by gender.

4. We evaluated the relationship between BMI and fracture by adjusting for major factors such as age, smoking, and osteoporosis, as well as comorbidity using the Charlson Comorbidity Index.

5. This study has several limitations; BMD, a factor closely related to fracture, could not be assessed in this study, and although we assessed osteoporosis comorbidity, we could not assess treatment status.

Introduction

Vertebral and hip fractures are the major fractures in the elderly. The incidence of these fragility fractures appear to be increasing in many countries because of increasing elderly populations [1-3]. Both vertebral and hip fractures cause pain and dysfunction and decrease quality of life (QOL) [4-6]. It is well known that there is a high mortality rate after hip fracture, but there are also reports of increased mortality after vertebral fractures [7, 8]. Consequently, among fragility fractures, vertebral and femoral fractures are very important for healthy life expectancy and longevity. Furthermore, the costs associated with these fractures are diverse, including treatment and care costs, and are largely related to the increased economic burden on society [9]. Particularly in Japan, where the elderly population is growing rapidly, the economic burden of these fractures is immense and is an important public health issue [10]. Therefore, to prevent these fractures in the elderly, it is very important to understand what are the risks factors.

Previous studies reported several risk factors for vertebral and hip fractures, and the most important risk factors are age, sex, history of past fractures, and low bone mineral density (BMD) [11, 12]. Body mass index (BMI) is a well-documented that it is closely related to fragility fractures [13-15]. From a public health perspective, high BMI, such as obesity, is associated with increased morbidity of diabetes, cardiovascular disease [16], and is generally associated with increased mortality. However, a paradox has also been reported, such as a higher mortality rate in the elderly

with a lower BMI [17-19]. In recent years, such a paradox has been reported in fractures as well. Low BMI is a recognized risk factor for vertebral and hip fracture, and in recent years, high BMI has been reported to reduce the risk of hip fracture [20]. Johansson et al. [14] reported that the association between BMI and fracture risk is complex and differs across skeletal sites; thus, the relationship between BMI and fracture risk is still controversial. Gender and race may also influence the relationship between BMI and fractures. Some have reported that the impact of BMI on fractures varies by gender. It is not yet well known whether the impact of BMI on fractures varies by gender, especially in Japanese.

In this study, using the healthcare claims database of Fukuoka Prefecture, the following questions were addressed: (1) What is the incidence of vertebral and hip fractures among the Japanese elderly? (2) Is there a relationship between BMI and fracture risk and is there a difference between men and women?

Materials and Methods

Study design and Data source

This was a retrospective cohort study approved by our institutional review board. We used data from the healthcare claims database and master database of the Fukuoka Prefecture Wide-Area Association of Latter-stage Elderly Healthcare between 1 April 2010 and 31 March

2018. This public health insurance is open to people over the age of 75 years and those aged 65-74 years with disabilities, and the majority of people over the age of 75 years have this insurance. The majority of the insured have long-term eligibility once they were enrolled; therefore, few subjects are lost to follow-up. The databases included data for the International Classification of Diseases 10th Revision (ICD-10) codes; date of diagnosis, medical procedures, such as surgery; date of admission; and death. The majority of the databases are computer-administered. According to a report by the Japanese Ministry of Health, Labour and Welfare, the penetration rate of computer-administered claims databases was 98.6% as of April 2015 [21]. Elderly people over the age of 75 years who have this health insurance are eligible for medical examination. We also used data from the 2010 health examination, which included subjects' height, weight, BMI, smoking and alcohol drinking.

Subjects

Our target population was people with Fukuoka Prefecture Wide-Area Association of Latter-stage Elderly Healthcare insurance who met the following criteria: (1) People who underwent the 2010 health examination; (2) age ≥ 75 years at the health examination; (3) data related to smoking and alcohol consumption at the time of health examination are available; and (4) no history of vertebral and hip fracture before the health examination. The history of these fractures were investigated using the medical interview at the health examination and using

healthcare claims database.

Outcomes (vertebral and hip fracture incidence)

We identified patients with vertebral (ICD-10 code = S22.0-1, S32) and hip (ICD-10 code = S72.0-2) fracture diagnosed between the date of the medical examination and 31 March 2018 in the medical database and investigated the cumulative fracture incidence. We also investigated the time to each primary fracture.

Comparison by BMI category

Subjects were divided into three groups according to BMI category as follows: low (< 18.5 kg/m^2), normal (18.5–24.9 kg/m^2), and high (> 25.0 kg/m^2). Subjects' demographics and the incidence of vertebral and hip fractures were compared between the BMI categories.

Risk factors for vertebral and hip fractures

We examined age, BMI, alcohol drinking, smoking, comorbidities and osteoporosis as risk factors for each fracture by gender. Age was categorized into three groups: 75–79 years, 80–84 years, and ≥ 85 years. Smoking and drinking were defined as those who reported habitual consumption in the health questionnaire. The Charlson Comorbidity Index (CCI) was used as an indicator of patient's comorbidities [22]. CCI was calculated at the health examination using the ICD-10 codes [23] and was divided into four groups: low (0), medium (1–2), high (3–4), and very high (≥ 5). Osteoporosis was identified using the ICD-10 codes (M80, M81, M82).

Patient and Public Involvement

We used administrative claims data and did not involve patients in this study.

Statistical analysis

Statistical analyses were performed using Stata software, version 14 (Stata Corp, College station, TX). Differences among three the BMI groups were analyzed using the Steel-Dwass test and the chi-square test. We estimated the incidence of vertebral and hip fractures by BMI category using a Kaplan–Meier curve in men and women, and differences between groups were tested for statistical significance using the log-rank test in men and women. To examine the risk factors for vertebral and hip fracture by gender, Cox proportional hazards regression analyses were performed using the following factors: age, BMI, alcohol drinking, smoking, osteoporosis and CCI. Statistical significance was set as $P < .05$. Continuous values were expressed as mean ± standard deviation.

Results

Subjects

Of the people with Fukuoka Prefecture Wide-Area Association of Latter-stage Elderly Healthcare insurance, 26,005 underwent the 2010 health examination. We excluded 1,314 people: 691 people younger than 75 years at the time of the health examination, 109 people had missing

data on their drinking and smoking, and 514 people with a history of fracture, and included 24,691 people in this study. Subjects' demographic data are shown in **Table 1**. The mean observation period was 6.9 years, and 5,409 people died during the observation period. There was a significantly higher proportion of older age and low BMI groups in women compared to men ($P < .0001$). Men had significantly higher CCI, smoking, and drinking rates than women ($P < .0001$). The prevalence of osteoporosis was significantly higher in women ($P < .0001$). **Table 2** shows the prevalence of the comorbidities used to calculate the CCIs.

Vertebral and hip fracture rate

Vertebral and hip fractures occurred in 4,153 (16.8%) and 1,543 (6.5%) of the subjects, respectively, during the study period. Vertebral fractures occurred in 1,082 (10%) men and 3,071 (22.2%) women, hip fractures occurred in 314 (2.9%) men and 1,229 (8.9%) women, and the incidence of both fractures was significantly higher in women ($P < .0001$). The incidence of vertebral fracture was 1500.4 in men and 3159.2 in women per 100,000 person-years, respectively. The incidence of hip fracture was 435.4 in men and 1264.3 in women per 100,000 person-years, respectively.

Comparison by BMI category

A comparison of subjects' demographics by BMI category is shown in **Table 3**. Low BMI was present in a significantly higher proportion of people aged ≥ 85 years, women, and

smoking, than in the other two BMI groups ($P < .0001$). There was a significantly lower rate of alcohol drinking with low BMI ($P < .0001$). High BMI was associated with a significantly higher CCI than the other two BMI groups ($P < .01$).

The cumulative incidence of vertebral fracture in each BMI groups (low/normal/high) at the final follow-up estimated using the Kaplan–Meier curve was 14.7% / 10.4% / 9.0% in men and 24.9% / 23.0% / 21.9% in women, respectively, and was significantly higher with low BMI in both sexes (all $P < .05$) (**Fig.1**). Similarly, the cumulative incidence of hip fracture was 6.3% / 2.9% / 2.4% in men and 14.1% / 9.0% / 8.1% in women, respectively, and was significantly higher with low BMI in both sexes (all $P < .0001$) (**Fig.2**).

Risk factors of vertebral and hip fractures

In univariate analysis, older age, low BMI, higher CCI, and osteoporosis were significant risk factors for vertebral fracture in both men and women (**Table 4**). Multivariate analysis showed that older age, higher CCI, and osteoporosis were risk factors for vertebral fracture in both men and women, but low BMI was a significant risk factor only in men (**Table 4**).

In univariate analysis, older age, higher CCI, and osteoporosis were significant risk factors for hip fracture in both men and women, and smoking was also a significant risk factor in men (**Table 5**). Multivariate analysis showed that older age and higher CCI were significant risk factors for hip fracture in both men and women, smoking was a significant risk factor only in

men, and osteoporosis was a significant risk factor only in women (**Table 5**). Alcohol drinking had a significant protective effect on hip fractures in men.

Discussion

In this study, we evaluated cumulative incidence of vertebral and hip fractures in the elderly during an average of 6.9 years using healthcare claims database in Fukuoka Prefecture. Elderly people with Fukuoka Prefecture Wide-Area Association of Latter-stage Elderly Healthcare insurance rarely drop out of the program, and the health insurance covers most elderly people aged ≥ 75 years who live in this area. Therefore, the strength of this study is that there were almost no dropouts other than because of death, and that we were able to investigate the occurrence of fractures regardless of the medical institution where the diagnosis was made. Previous studies reported that the incidence of vertebral fracture at age ≥ 60 years was 13–18% [24-26]. Tamaki et al. found in a 3-year retrospective cohort study that the incidence of hip fracture in people aged 80–84 years was 366 and 880 per 10,0000, for men and women, respectively [27]. We found that the incidence of vertebral and hip fracture was 17% (1500 and 3164 per 100,000, for men and women) and 7% (435 and 1264 per 100,000, for men and women), respectively, in our study. The incidence rates in the present study were equivalent to those in previous cohort studies and did not appear to be unevenly distributed by region [24-27].

Our study using this large cohort data demonstrated that the vertebral and hip fracture incidence was higher in the low BMI group (BMI < 18.5 kg/m^2) by the Kaplan-Meier curve. As many previous studies reported, low BMI has long been considered an important risk factor for fractures. Generally, lower BMI is associated with lower BMD, and Lloyd et al. reported that every unit increase in BMI was associated with an increase of 0.0082 g/cm in BMD [28]. Although low BMI is generally considered a risk factor for fragility fractures, several reports have shown that the relationship between BMI and fracture risk may differ by gender and skeletal site, and that the relationship is complex [13, 14]. In this study, we investigated the effect of BMI on fractures, stratified by gender. We found that low BMI was a risk factor for hip fractures regardless of gender, and for vertebral fractures, low BMI was a risk factor only in men. Kaze et al.[15] reported in their meta-analysis that the inverse association between BMI and risk for vertebral fracture in men but not in women. Several previous studies have shown that low BMI is consistently associated with the risk of hip fracture, regardless of gender [14, 29]. Johansson et al. [14] found that the relationship between BMI and osteoporotic fractures depended on the site of the fracture, although their study was only on women. In this study, we similarly suggested that the effect of BMI varies by fracture site in women. Several reports have been said that abdominal fat may affect bone independently of total body fat, and that there are sex differences in fat distribution, which may be a possible reason for the sex differences in the effect of BMI on fracture [30, 31].

However, the reasons for the site-specific gender effects, as shown in this study, are not yet well understood. Another possible explanation could be that BMI as a measure of adiposity has been shown to be less valid in the elderly due to age-related changes in body composition [32]. However, in this study, only the elderly were included, not the middle-aged or other groups of both men and women, and this effect is considered to be small.

Not only is low BMI considered a risk factor for fracture, but the preventive effect of high BMI on fracture has recently been discussed. some reports suggest that obesity has a protective effect on fractures because of higher BMD and reduced impact of falls as a result of increased soft-tissue padding 33, 34. However, it has not been proven that obesity is protective against all fractures, and the relationship between obesity and fracture has been reported to be fracture site-specific [35, 36]. Although there were some reports of sex differences in the preventive effect of BMI on fractures 29, 37, the results were mixed and the preventive effect of BMI on fractures is still unclear. We found that obesity had no protective effect on vertebral and hip fractures, regardless of gender, even after adjusting for confounding factors such as age and comorbidity. Therefore, the effect of obesity on fracture prevention may be poor in the elderly Asian population.

Further research is still needed to determine whether high BMI has a protective effect on fractures in the elderly population. However, even if some fracture sites are affected by sex differences, low BMI in the elderly is state of easy fracture, and may greatly impact QOL in the

future. BMI can be easily measured at the health examination, and screening for fracture risk by BMI is very useful in terms of health care costs for the healthy life span of the elderly. Prolonged healthy life expectancy of the elderly is expected with the additional assessment of exercise function, further assessment of fracture risk by measuring BMD, and fracture prevention in the elderly with low BMI at the health examination.

Using the Cox proportional hazards model, we found the other factors besides BMI that influence vertebral and hip fractures. First, for both fractures, older age and higher CCI increased the risk of fracture. Although it is a well-known finding that the incidence of fragility fractures increases with age, the effect of aging was more prevalent in hip fractures. This may be related to the decline in physical function and increased risk of falling with age. Comorbidities such as chronic kidney disease, diabetes, and dementia are associated with increased risk of fragility fractures, and it is useful to evaluate the presence of comorbidities and investigate their contribution to the risk of fractures [38-40]. CCI was originally used to assess the risk of comorbidities for death, but patients at high risk of death with a high CCI may also be at higher risk of fragility fractures. The present study stratified CCI and assessed the risk of fracture and showed that a higher CCI was associated with a higher fracture risk. Therefore, CCI may be useful in assessing fracture risk as well as mortality risk in the elderly.

Secondly, health-related behaviors such as smoking and alcohol drinking are also well-

established risk factors for fragility fractures [41, 42], in this study, smoking was a risk factor in hip fractures in men. Iconaru et al. reported that smoking was a significant risk factor for only hip fractures among fragility fractures [43], and the effect of smoking on fracture may also be site-specific. The lack of effect of smoking in women may be related to the extremely low smoking rate (15% in men and 2% in women) in older women. The results of the present study showed that drinking had a protective effect on hip fractures in men. Several reports state that light to moderate alcohol consumption decrease age-related bone loss, and that heavy alcohol consumption is associated with elevated hip fracture risk, while light alcohol consumption is inversely related to fracture risk [42, 44]. We did not assessed the amount of alcohol consumed in this study and cannot discuss the effect of alcohol consumption on fracture risk.

Finally, the coexistence of osteoporosis is an important factor in osteoporotic fractures, and the results of this study showed that osteoporosis affected vertebral fractures in both men and women, but only hip fractures in women. One reason for this may be the difference in the pathogenesis of osteoporosis, in which women, unlike men, experience two phases of bone loss: menopausal bone loss and age-related bone loss. Another possible explanation is that the prevalence of osteoporosis at the time of physical examination was quite low in the men in this study.

This study has several limitations. First, we used a retrospective design and data from a

claims database and medical examination, which did not include BMD values. Therefore, it is not possible to say whether BMI is a risk factor for fractures independent of BMD. However, this does not change the fact that BMI is a simpler and more useful tool for fracture evaluation. Second, the claims and medical examination data used in this study were derived from public insurance covering people aged ≥ 75 years, and the results may differ for younger populations, such as those in middle age. However, the fracture prevalence increases sharply in those over 70 years of age [27], and we believe that the evaluation used in this study is useful in other vulnerable population. One of the strengths of our study is that the follow-up rate for people aged ≥ 75 years who are covered by the insurance is extremely high. Third, this study referred to osteoporosis using ICD-10 codes, but failed to mention drug treatment. In this study, only the presence or absence of osteoporosis, which may play a major role, was included as a risk factor because it is difficult to unify the effect of drug treatment, since there is a wide range of drugs used to treat osteoporosis and the effect varies depending on the duration of treatment. Finally, this study was performed exclusively in Japan, where ethnic diversity is limited. Compared to the Japanese, Western populations have a relatively high BMI, and our findings may not be generalizable to other populations.

Conclusion

In this large retrospective cohort study during a mean observation period of about 7 years in patients aged ≥ 75 years, vertebral and hip fractures occurred in 17% and 7%, respectively. The incidence of both fractures was higher in the low BMI population. After adjustment for possible confounders, low BMI was a risk factor for vertebral fracture only in men, and there were sex differences in the effect of BMI. Low BMI was a risk factor for hip fracture in both men and women, and low BMI is likely to remain important in the elderly population. Evaluating elderly with low BMI at health examinations and providing therapeutic interventions may help prevent subsequent fractures and improve healthy life expectancy.

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Author Contribution

KS led the study design, extracted and analyzed the data, conducted the literature, and wrote the manuscript. AB and YN contributed to the study design, analysis and manuscript revision. TH, TF, PJ and SK contributed to data analysis and manuscript review. All authors read and approved the final version of the manuscript.

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Conflicts of interest

Kyohei Shiomoto. outside the current study declares grants from Kyocera. Akira Babazono, Yumi Harano, Takako Fujita, Peng Jiang, Sung-a Kim, and Yasuharu Nakashima declare that they have no conflict of interest.

Patient consent for publication

Not required.

Ethics approval

This study was approved by the Kyushu University Institutional Review Board for Clinical Research (Approval No. 20209).

Provenance and peer review

Not commissioned; externally peer reviewed.

Data sharing statement

No additional data are available.

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Figure Legends

Image 1: Figure. 1

The Kaplan-Meier curve shows the incidence of vertebral fractures in a) men and b) women compared by BMI category. The solid line represents low BMI, the dashed line represents normal BMI, and the dotted line represents high BMI.

BMI: body mass index

Image 2: Figure. 2

The Kaplan-Meier curve shows the incidence of hip fracture in a) men and b) women compared by BMI category. The solid line represents low BMI, the dashed line represents normal BMI, and the dotted line represents high BMI.

BMI: body mass index

Table 1. Patient's demographic data

Parameters	Total N = 24,691	Men N = 10,853	Women N = 13,838
Age at examination (years old)	79.4 ± 4.3 (75–103)	79.2 ± 4.0 (75–101)*	79.4 ± 4.3 (75–103)
Age categories, n (%)			
75-79	14,932 (60.5)	6,757 (62.3)*	8,175 (59.1)
80-84	6,554 (26.5)	2,892 (26.6)*	3,662 (26.5)
85≤	3,205 (13.0)	1,204 (11.1)*	2,001 (14.5)
Gender; male/female, n (%)	10,853 (44.0) : 13,838 (56.0)		
BMI (kg/m^2)	22.2 ± 3.1 (11.6–54.2)	22.4 ± 2.9 (13–54.2)*	22.0 ± 3.2 (11.6–43)
BMI categories			
Low (BMI < 18.5)	2,684 (10.9)	910 (8.4)*	1,774 (12.8)
Normal (18.5 ≤ BMI < 25)	17,997 (71.6)	7,980 (73.5)	9,687 (70.0)
High (25 ≤ BMI)	4,340 (17.6)	1,963 (18.1)	2,377 (17.1)
CCI	1.7 ± 1.7 (0–11)	1.9 ± 1.8 (0–11)	1.5 ± 1.5 (0–10)
CCI categories, n (%)			
Low	4,710 (19.1)	1,907 (17.6)*	2,803 (20.3)
Medium	12,982 (52.6)	5,226 (48.2)	7,756 (56.1)
High	5,331 (21.6)	2,772 (25.1)	2,609 (18.9)
Very high	1,668 (6.8)	998 (9.2)	670 (4.8)
Smoking, n (%)	1,891 (7.7)	1,586 (14.6)*	305 (2.2)

Alcohol drinking, n (%)	9,444 (38.2)	6,447 (59.4)*	2,997 (21.7)
Osteoporosis, n (%)	3,969 (16.1)	374 (3.4)*	3,595 (26.0)
Follow-up duration (year)	6.9 ± 1.6 (0.1–8.0)	6.6 ± 1.8 (0.1–8.0)*	7.0 ± 1.4 (0.1–8.0)

Continuous values are expressed as mean ± standard deviation (range).

BMI: body mass index, CCI: Charlson comorbidity index.

* Significantly different between men and women ($P < .05$).

Table 2. Prevalence of the comorbidities used to calculate the CCI

	Total N = 24,691, n (%)	Men N = 10,853, n (%)	Women N = 13,838, n (%)
Acute myocardial infraction	130 (0.5)	91 (0.8)*	39 (0.3)
Congestive heart failure	972 (3.9)	448 (4.1)	524 (3.8)
Peripheral vascular disease	3,365 (13.6)	1,593 (14.7)*	1,772 (12.8)
Cerebral vascular disease	10,922 (44.2)	4,679 (43.1)*	6,243 (45.1)
Dementia	633 (2.6)	224 (2.1)*	409 (3.0)
Pulmonary disease	2,735 (11.1)	1,343 (12.4)*	1,392 (10.1)
Connective tissue disorder	1,672 (6.7)	711 (6.6)	961 (6.9)
Peptic ulcer	1,979 (8.0)	928 (8.6)*	1,051 (7.6)
Mild liver disease	1,725 (7.0)	912 (8.4)*	813 (5.9)
Diabetes without complications	1,273 (5.2)	724 (6.7)*	549 (4.0)
Diabetes with complications	1,013 (4.1)	583 (5.4)*	430 (3.1)
Paraplegia	715 (2.9)	376 (3.5)*	339 (2.5)
Renal disease	3,564 (14.4)	1,794 (16.5)*	1,770 (12.8)
Cancer	2,832 (11.5)	1,876 (17.1)*	972 (7.0)
Metastatic cancer	100 (0.4)	68 (0.6)*	32 (0.2)
Sever liver disease	13 (0.1)	8 (0.07)	5 (0.04)
HIV	0 (0)	0 (0)	0 (0)

CCI: Charlson comorbidity index, HIV: human immunodeficiency virus

* Significantly different between men and women ($P < .05$).

Table 3.

Comparison of subjects' demographics between BMI categories.

Parameters	BMI categories		
	Low N = 2,684	Normal N = 17,667	Low N = 4,340
Age at examination (years old)	80.8 ± 4.8 (75–103)[a, b]	79.4 ± 4.2 (75–103)[c]	78.9 ± 4.0 (75–99)
Age categories, n (%) 75-79/ 80-84/ 85≤	1,291 (48.1)/ 828 (30.8)/ 565 (21.1)[a, b]	10,775 (60.9)/ 4,691 (26.6)/ 2,201 (12.5)[c]	2,866 (66.1)/ 1,035 (23.8)/ 439 (10.1)
Sex; men/women, n (%)	910 (33.9)/ 1,774 (66.1)[a, b]	7,980 (45.2)/ 9,687 (54.8)	1,963 (45.2)/ 2,377 (54.8)
BMI (kg/m^2)	17.2 ± 1.0 (11.6–18.4)[a, b]	21.8 ± 1.7 (18.5–24.9)[c]	26.9 ± 1.9 (25–54.2)
CCI	1.6 ± 1.6 (0–10)[b]	1.7 ± 1.7 (0–11)[c]	1.9 ± 1.8 (0–10)
CCI categories, n (%) Low (=0)/ Medium (=1-2)/ High (=3-4)/ Very high (≥ 5)	 481 (17.9)/ 1,426 (53.1)/ 574 (21.4)/ 203 (7.6)[b]	 3,425 (19.4)/ 9.349 (52.9)/ 3,759 (21.3)/ 1,134 (6.4)[c]	 804 (18.5)/ 2,207 (50.9)/ 998 (23.0)/ 331 (7.6)
Smoking, n (%)	266 (9.9)[a, b]	1,346 (7.6)[c]	279 (6.4)
Alcohol drinking, n (%)	786 (29.3)[a, b]	6,939 (39.3)	1,719 (39.6)
Osteoporosis, n (%)	537 (20)[a, b]	2,806 (15.9)	626 (14.4)
Follow-up duration (year)	6.4 ± 2.0 (0.1–8.0)[a, b]	6.9 ± 1.5 (0.1–8.0)[c]	7.1 ± 1.3 (0.1–8.0)

Continuous values are expressed as mean ± standard deviation (range). BMI: body mass index, CCI: Charlson comorbidity index

a; $P < .05$ for significantly different between low BMI and normal BMI.

b; $P < .05$ for significantly different between low BMI and high BMI.

c; $P < .05$ for significantly different between normal BMI and high BMI.

Table 4.

Cox proportional hazards analysis of the risk factors for vertebral fracture.

Factor		Univariate HR (95% CI)		Adjusted HR (95% CI)	
		Men	Women	Men	Women
Age categories	75–79	1.55 (1.35–1.78)*	1.25 (1.15–1.36)*	1.45 (1.26–1.66)*	1.20 (1.10–1.30)*
< 75 = reference	85<	2.37 (2.02–2.78)*	1.34 (1.21–1.47)*	2.13 (1.81–2.51)*	1.24 (1.12–1.37)*
BMI categories	Low	1.51 (1.26–1.82)*	1.11 (1.00–1.23)*	1.33 (1.10–1.61)*	1.07 (0.96–1.19)
normal = reference	High	0.87 (0.73–1.02)	0.95 (0.86–1.04)	0.91 (0.77–1.08)	0.95 (0.86–1.05)
Alcohol drinking		0.96 (0.85–1.09)	0.93 (0.85–1.02)	1.06 (0.94–1.19)	0.97 (0.89–1.06)
Smoking		0.92 (0.77–1.10)	1.13 (0.90–1.42)	0.93 (0.78–1.11)	1.17 (0.93–1.46)
CCI categories	Medium	1.83 (1.48–2.26)*	1.48 (1.34–1.65)*	1.74 (1.40–2.15)*	1.42 (1.28–1.57)*
(low = reference)	High	2.33 (1.87–2.91)*	1.82 (1.62–2.05)*	2.10 (1.68–2.62)*	1.67 (1.48–1.89)*
	Very high	2.83 (2.19–3.64)*	2.04 (1.72–2.42)*	2.52 (1.95–3.25)*	1.81 (1.52–2.14)*
Osteoporosis		2.24 (1.77–2.83)*	1.49 (1.38–1.61)*	1.83 (1.44–2.32)*	1.39 (1.29–1.50)*

HR: hazard ratio, CI: confidence interval, BMI: body mass index, CCI: Charlson comorbidity index

* Statistically significant ($P < .05$).

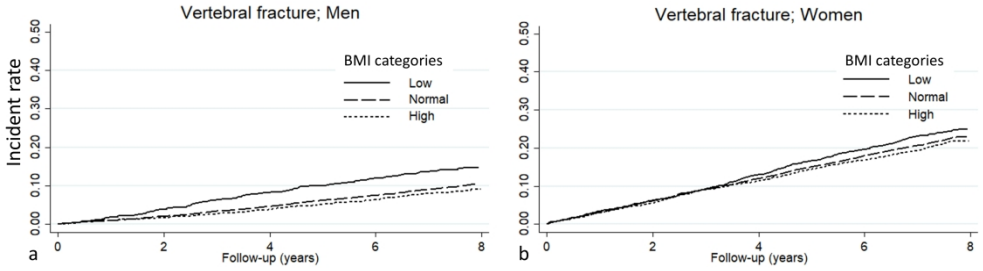
Table 5.

Cox proportional hazards analysis of the risk factors for hip fracture.

Factor		Univariate HR (95% CI)		Adjusted HR (95% CI)	
		Men	Women	Men	Women
Age categories	75–79	2.16 (1.67–2.79)*	2.26 (1.98–2.59)*	1.93 (1.49–2.50)*	2.14 (1.87–2.45)*
< 75 = reference	85<	3.89 (2.94–5.16)*	4.03 (3.51–4.63)*	3.21 (2.41–4.29)*	3.66 (3.18–4.21)*
BMI categories	Low	2.24 (1.66–3.00)*	1.57 (1.36–1.82)*	1.74 (1.29–2.35)*	1.36 (1.17–1.57)*
normal = reference	High	0.74 (0.53–1.03)	0.88 (0.75–1.03)	0.81 (0.58–1.14)	0.89 (0.75–1.04)
Alcohol drinking		0.68 (0.55–0.85)*	0.80 (0.69–0.93)*	0.79 (0.55–0.97)*	0.92 (0.80–1.06)
Smoking		1.38 (1.04–1.83)*	1.07 (0.74–1.55)	1.37 (1.03–1.82)*	1.13 (0.78–1.63)
CCI categories (low = reference)	Medium	2.40 (1.53–3.75)*	1.95 (1.62–2.34)*	2.20 (1.41–3.45)*	1.79 (1.49–2.16)*
	High	3.36 (2.12–5.33)*	2.39(1.95–2.93)*	2.87 (1.81–4.55)*	2.01 (1.64–2.48)*
	Very high	3.78 (2.26–6.32)*	3.38 (2.61–4.38)*	3.28 (1.96–5.49)*	2.73 (2.10–3.54)*
Osteoporosis		1.63 (1.00–2.66)*	1.29 (1.15–1.46)*	1.20 (0.73–1.97)	1.10 (0.98–1.25)*

HR: hazard ratio, CI: confidence interval, BMI: body mass index, CCI: Charlson comorbidity index

* Statistically significant ($P < .05$).



The Kaplan-Meier curve shows the incidence of vertebral fractures in a) men and b) women compared by BMI category. The solid line represents low BMI, the dashed line represents normal BMI, and the dotted line represents high BMI.
BMI: body mass index

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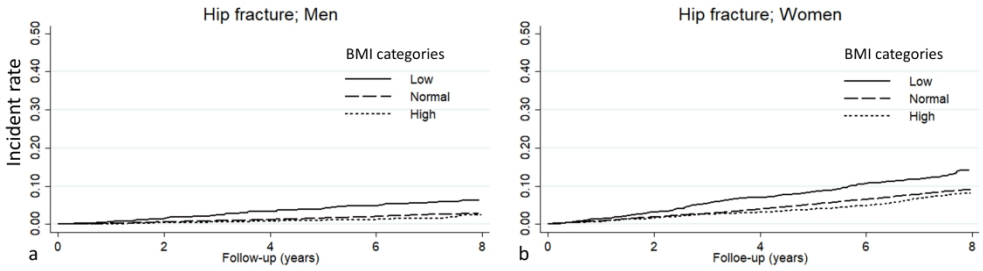

The Kaplan-Meier curve shows the incidence of hip fracture in a) men and b) women compared by BMI category. The solid line represents low BMI, the dashed line represents normal BMI, and the dotted line represents high BMI.
BMI: body mass index

299x86mm (300 x 300 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1, 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5, 6
Objectives	3	State specific objectives, including any prespecified hypotheses	5, 6
Methods			
Study design	4	Present key elements of study design early in the paper	6, 7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6, 7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7,8
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8, 9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8, 9
Bias	9	Describe any efforts to address potential sources of bias	8, 9
Study size	10	Explain how the study size was arrived at	9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8, 9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9
		(*b*) Describe any methods used to examine subgroups and interactions	8, 9
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7, 8 Table 1
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	9, 10 Table 1
Outcome data	15*	Report numbers of outcome events or summary measures over time	11, Fig1, 2
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11 Table 4, 5
		(*b*) Report category boundaries when continuous variables were categorized	8 Table 3
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Table 3, 4, 5
Discussion			
Key results	18	Summarise key results with reference to study objectives	12, 13,14, 15
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12, 13
Generalisability	21	Discuss the generalisability (external validity) of the study results	16, 17, 18
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Effect of body mass index on vertebral and hip fractures in Older people and Differences according to sex: A retrospective Japanese cohort study.

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Title Page

Original research article

Effect of body mass index on vertebral and hip fractures in Older people and Differences according to sex: A retrospective Japanese cohort study.

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Abstract

Objectives: The purpose of this study was to investigate the incidence of vertebral and hip fractures in the older people and to clarify the relationship between these fractures and body mass index (BMI) along with the impact of sex differences.

Design: This was a retrospective cohort study.

Setting: We used administrative claims data between April 2010 and March 2018.

Participants: Older people aged ≥75 years who underwent health examinations in 2010 and were living in the Fukuoka Prefecture, Japan were included in the study. A total of 24,691 subjects were included; the mean age was 79.4 ± 4.3 years, 10,853 males and 13,838 females, and an the mean duration of observation was 6.9 ± 1.6 years.

Primary and secondary outcome measures: We estimated the incidence of vertebral and hip fractures by BMI category (underweight:<18.5kg/m^2, normal weight:18.5–24.9kg/m^2, overweight and obese:>25.0kg/m^2) using a Kaplan–Meier curve in males and females and determined fracture risk by sex using Cox proportional hazards regression analyses.

Results: The incidence of vertebral and hip fractures was 16.8% and 6.5%, respectively. The incidence rate of vertebral and hip fracture at the last observation (8 years) in each BMI groups (underweight/normal weight/overweight and obese) estimated using the Kaplan–Meier curve was 14.7%/10.4%/9.0% in males and 24.9%/23.0%/21.9% in females, and 6.3%/2.9%/2.4% in males

and 14.1%/9.0%/8.1% in females, respectively, and both fractures were significantly higher in underweight groups regardless of sex. Multivariate Cox proportional hazards models showed that underweight was a significant risk factor only in males for vertebral fractures and in both males and females for hip fractures.

Conclusion: Underweight was associated with fractures in the ageing population, but there was a sex difference in the effect for vertebral fractures.

Trial registration: This study was approved by the Kyushu University Institutional Review Board for Clinical Research (Approval No. 20209).

Keywords: body mass index (BMI), sex differences, fracture, claim data, older people

Strengths and limitations of this study

1. This was a retrospective cohort study including 24,691 older peoples.

2. We followed up participants for approximately 7 years.

3. We investigated the incidence of vertebral fractures and hip fractures in the older people and evaluated the relationship between BMI and fractures and differences by sex.

4. We evaluated the relationship between BMI and fracture by adjusting for major factors such as age, smoking, and osteoporosis, as well as comorbidity using the Charlson Comorbidity Index.

5. This study has several limitations; bone mineral density (BMD), a factor closely related to fracture, could not be assessed in this study, and although we assessed osteoporosis comorbidity, we could not assess treatment status.

Introduction

Vertebral and hip fractures are the major fractures that occur in the older people. The incidence of these fragility fractures appears to be increasing in many countries because of the increasing size of populations [1-3]. Both vertebral and hip fractures cause pain and dysfunction and decrease quality of life (QOL) [4-6]. It is well known that there is a high mortality rate after hip fracture, but there are also reports of increased mortality after vertebral fractures [7 8]. Consequently, among fragility fractures, vertebral and hip fractures greatly impact healthy life expectancy and longevity. In Japan, where the ageing population is rapidly increasing, the economic burden of these fractures is immeasurable and has become an important public health issue [9 10]. Therefore, in order to prevent these fractures in the older people, it is very important to understand what are the risk factors.

Previous studies reported several risk factors for vertebral and hip fractures, with the most important risk being age, sex, history of past fractures, and low bone mineral density (BMD) [11 12]. FRAX, which is known as a fracture prediction tool, also uses these factors, smoking, and alcohol consumption as fracture risks [13]. The prevalence of osteoporosis is also high in the elderly, and the coexistence of osteoporosis has a significant impact on fractures [14]. Body mass index (BMI) is another well-documented risk factor that it is closely related to fragility fractures [15-17]. Underweight has been recognized as a risk factor for vertebral and hip fractures, and a cohort

study in Japan reported underweight as a preventable risk factor for hip fracture [18]. On the other hand, Johansson et al. [16] reported that the association between BMI and fracture risk is complex and differs across skeletal sites; thus, the relationship between BMI and fracture risk is still controversial. Previous study has shown that the effect of BMI on hip fracture varies with age [19]. Sex and race may also influence the relationship between BMI and fractures. Although BMD varies by race, there was a report that even after excluding the effects of BMD, there was a difference in fracture risk by race [20 21]. Some studies reported that the impact of BMI on fractures varies by sex [16 22]; however, there is no consensus regarding this, especially in Japanese.

In this study, using the healthcare claims database of the Fukuoka Prefecture, the following questions were addressed: (1) What is the incidence of vertebral and hip fractures in the older people who live in Fukuoka Prefecture? (2) Is there a relationship between BMI and fracture risk and is there a difference between males and females?

Materials and Methods

Study design and data source

This was a retrospective cohort study approved by our Institutional Review Board. We used data from the healthcare claims database and master database of the Fukuoka Prefecture Wide-Area Association of Latter-stage Elderly Healthcare between 1 April 2010 and 31 March

2018. This public health insurance is open to people over the age of 75 years and those aged 65-74 years with disabilities, and the majority of people over the age of 75 years have this insurance. The total population of Fukuoka Prefecture is about 5.1 million, the 9th largest in Japan, and about 520,000 older people are covered by this insurance. Most of the insured have long-term eligibility once they are enrolled; therefore, few participants were lost to follow-up except for death. The databases included data for the International Classification of Diseases 10th Revision (ICD-10) codes; date of diagnosis, medical procedures, such as surgery, date of admission, and death. The database are mostly computer-administered. According to a report by the Japanese Ministry of Health, Labour and Welfare, the penetration rate of computer-administered claims databases was 98.6% as of April 2015 [23]. Older people aged 75 and over who are enrolled in this health insurance and who do not have regular hospital visits for lifestyle-related diseases are eligible for medical examination. We also used data from the 2010 health examination, which included participants' height, weight, BMI, smoking and alcohol drinking.

Participants

Our target population was people who held Fukuoka Prefecture Wide-Area Association of Latter-stage Elderly Healthcare insurance and who met the following criteria: (1) People who underwent the 2010 health examination; (2) age ≥ 75 years at the health examination; (3) data related to smoking and alcohol consumption at the time of health examination were available; and

(4) no history of vertebral or hip fracture before the health examination. Fracture history was investigated using self-reports at the time of the health examination and the medical claims database to determine if there were any fractures prior to the health examination.

Follow-up duration

The follow-up duration was defined as from the date of the participant's 2010 health examination to the date of death or until March 2018. There was a slight discrepancy because participants did not have a consistent date for their health examination.

Outcomes (vertebral and hip fracture incidence)

We identified patients with vertebral (ICD-10 code = S22.0-1, S32) and hip (ICD-10 code = S72.0-2) fractures diagnosed between the date of the medical examination and 31 March 2018 in the medical database and investigated the cumulative fracture incidence. We also investigated the time to each primary fracture. A second fracture at the same site was not included.

Comparison by BMI category

The BMI classification in the general WHO is widely used in Japan, and we used the following cut points. Participants were divided into three groups according to BMI category as follows: underweight (< 18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), and overweight and obese (> 25.0 kg/m^2). Participants' demographics and the incidence of vertebral and hip fractures were compared between the BMI categories.

Risk factors for vertebral and hip fractures

We examined age, BMI, alcohol drinking, smoking, comorbidities, and osteoporosis as risk factors for each fracture by sex. Age was categorized into three groups: 75–79 years, 80–84 years, and ≥ 85 years. We divided the subjects into two groups: those with smoking and drinking habits and those without. The Charlson Comorbidity Index (CCI) was used as an indicator of each participant's comorbidities [24]. CCI was calculated at the health examination using the ICD-10 codes [25] and was divided into four groups: low (0), medium (1–2), high (3–4), and very high (≥ 5). Osteoporosis was identified using the ICD-10 codes (M80, M81, M82). Incidentally, the diagnostic criteria for osteoporosis in Japan are 1) BMD value less than 70% of Young adult mean (YAM), 2) history of vertebral fracture or proximal femur fracture, or 3) history of fragility fracture other than vertebral fracture or proximal femur fracture at less than 80% of YAM.

Participant and public Involvement

We used administrative claims data and did not involve participants in this study.

Statistical analysis

Statistical analyses were performed using Stata software, version 14 (Stata Corp, College Station, TX). All continuous variables were examined for normality with the Shapiro-Wilk test. Since all continuous variables were non-normal, the Wilcoxon signed-rank test was used for two-group comparisons and the Steel-Dwass test was used for three-group comparisons. For

qualitative variables, the chi-square test was used. We estimated the incidence proportion of vertebral and hip fractures by BMI category using a Kaplan–Meier curve in males and females, and differences between groups were tested for statistical significance using the log-rank test in males and females. To examine the risk factors for vertebral and hip fracture by sex, Cox proportional hazards regression analyses were performed using the following factors: age, BMI, alcohol drinking, smoking, osteoporosis and CCI. All risk factors were used as categorical variables. Statistical significance was set as $P < .05$. Continuous values were expressed as mean ± standard deviation.

Results

Participants

Of the people who held Fukuoka Prefecture Wide-Area Association of Latter-stage Elderly Healthcare insurance, 26,005 underwent the 2010 health examination. We excluded 1,314 people: 691 people were younger than 75 years at the time of the health examination, 109 people had missing data related to their drinking and smoking, and 514 people had a history of fracture; therefore, 24,691 participants were included in this study. Participants' demographic data are shown in **Table 1**. The mean observation period was 6.9 years, and 5,409 people died during this period. There was a significantly higher proportion of older age and underweight groups in females compared to males ($P < .0001$). Males had significantly higher CCI, smoking, and

drinking rates than females ($P < .0001$). The prevalence of osteoporosis was significantly higher in females ($P < .0001$). **Appendix 1** shows the prevalence of the comorbidities used to calculate the CCIs.

Comparison of patients lost to follow-up due to death vs. those that remained alive

Those that died during follow-up were older, more male, had lower BMI, higher CCI, and more smokers than those that survived (all $P < .0001$). Details are shown in **Appendix 2**.

Vertebral and hip fracture rate

Vertebral and hip fractures occurred in 4,153 (16.8%) and 1,543 (6.5%) of the participants, respectively, during the study period. Vertebral fractures occurred in 1,082 (10%) males and 3,071 (22.2%) females, hip fractures occurred in 314 (2.9%) males and 1,229 (8.9%) females, and the incidence of both fractures was significantly higher in females ($P < .0001$). The incidence of vertebral fracture was 150 in males and 315.9 in females per 10,000 person-years, respectively. The incidence of hip fracture was 43.5 in males and 126.4 in females per 10,000 person-years, respectively. A total of 520 participants had both vertebral and hip fractures, with a significantly higher number of females ($P < .0001$).

Comparison by BMI category

A comparison of participants' demographics by BMI category is shown in **Table 2**. Underweight group was present in a significantly higher proportion of people aged ≥ 85 years, in

females, and in those who smoked, than in the other two BMI groups ($P < .0001$). There was a significantly lower proportion of alcohol drinking with underweight group ($P < .0001$). Overweight and obese group was associated with a significantly higher CCI than the other two BMI groups ($P < .01$).

The incidence rate of vertebral and hip fracture in each BMI groups (underweight/normal weight/overweight and obese) at the final follow-up estimated using the Kaplan–Meier curve was 21.5% / 17.3% / 16.1% and 11.4% / 6.2% / 5.5%, respectively (all $P < .0001$) (**Fig.1**). By sex, he incidence rate of vertebral fracture in each BMI groups was 14.7% / 10.4% / 9.0% in males and 24.9% / 23.0% / 21.9% in females, respectively, and was significantly higher with underweight group in both sexes (all $P < .05$) (**Fig.2**). Similarly, the incidence rate of hip fracture was 6.3% / 2.9% / 2.4% in males and 14.1% / 9.0% / 8.1% in females, respectively, and was significantly higher with underweight group in both sexes (all $P < .0001$) (**Fig.3**).

Risk factors of vertebral and hip fractures

In univariate analysis, the HRs for age, BMI, alcohol, smoking, CCI, and osteoporosis for the vertebral fracture were 2.4 / 1.5 / 1.0 / 0.9 / 2.8 / 2.2 in males, and 1.3 / 1.1 / 0.9 / 1.1 / 2.0 / 1.5 in females, respectively. The HRs for age, BMI, alcohol, smoking, CCI, and osteoporosis for the hip fracture were 2.2 / 2.2 / 0.7 / 1.4 / 3.8 / 1.6 in males, and 3.2 / 1.7 / 0.8 / 1.4 / 3.3 / 1.2 in females, respectively. Older age, underweight, higher CCI, and osteoporosis were significant risk

factors for vertebral fracture in both males and females (**Table 3**). Multivariate analysis showed that older age, higher CCI, and osteoporosis were risk factors for vertebral fracture in both males and females, but underweight was a significant risk factor only in males (**Table 3**).

In multivariate analysis, the adjusted HRs for age, BMI, alcohol, smoking, CCI, and osteoporosis for the vertebral fracture were 2.1 / 1.3 / 1.1 / 0.9 / 2.5 / 1.8 in males, and 1.2 / 1.1 / 1.0 / 1.2 / 1.8 / 1.4 in females, respectively. The adjusted HRs for age, BMI, alcohol, smoking, CCI, and osteoporosis for the hip fracture were 3.2 / 1.7 / 0.8 / 1.4 / 3.3 / 1.2 in males, and 3.7 / 1.4 / 0.9 / 1.1 / 2.7 / 1.1 in females, respectively. Older age, higher CCI, and osteoporosis were significant risk factors for hip fracture in both males and females, and smoking was also a significant risk factor in males (**Table 4**). Multivariate analysis showed that older age and higher CCI were significant risk factors for hip fracture in both males and females, smoking was a significant risk factor only in males, and osteoporosis was a significant risk factor only in females (**Table 4**). Alcohol drinking had a significant protective effect on hip fractures in males.

Discussion

In this study, we evaluated the cumulative incidence of vertebral and hip fractures in the older people over an average of 6.9 years using the healthcare claims database in the Fukuoka Prefecture. Older people holding the Fukuoka Prefecture Wide-Area Association of Latter-stage

Elderly Healthcare insurance rarely drop out of the program, and the health insurance covers most older people aged ≥ 75 years who live in this area. Therefore, the strength of this study is that there were almost no dropouts other than because of death, and that we were able to investigate the occurrence of fractures regardless of the medical institution where the diagnosis was made. Previous studies reported that the incidence of vertebral fracture at age ≥ 60 years was 13–18% [26-28]. Tamaki et al. found in a three-year retrospective cohort study that the incidence of hip fracture in people aged 80–84 years was 36.6 and 88 per 10,0000, for males and females, respectively [29]. We found that the incidence of vertebral and hip fracture was 17% (150 and 316.4 per 10,000, for males and females) and 7% (43.5 and 126.4 per 10,000, for males and females), respectively, in our study. The incidence rates in the present study were equivalent to those in previous cohort studies and did not appear to be unevenly distributed by region [26-29].

Using this large cohort data, our study demonstrated that the vertebral and hip fracture incidence was higher in the underweight group (BMI < 18.5 kg/m^2) according to the Kaplan-Meier curve. As many previous studies reported, underweight has long been considered an important risk factor for fractures. Generally, lower BMI is associated with lower BMD, and Lloyd et al. reported that every unit increase in BMI is associated with an increase of 0.0082 g/cm in BMD [30]. Although underweight is generally considered a risk factor for fragility fractures, several reports have shown that the relationship between BMI and fracture risk may differ by sex

and skeletal site, and that the relationship is complex [15 16]. In the current study, we investigated the effect of BMI on fractures, stratified by sex. We found that underweight was a risk factor for hip fractures regardless of sex, and for vertebral fractures, underweight was a risk factor only in males. Kaze et al. [17] reported in their meta-analysis that an inverse association between BMI and risk for vertebral fracture in present in males but not in females. Several previous studies have shown that underweight is consistently associated with the risk of hip fracture, regardless of sex [16 31]. Johansson et al. [16] found that the relationship between BMI and osteoporotic fractures depended on the site of the fracture, although their study was conducted only on females. In this study, we similarly suggested that the effect of BMI varied by fracture site in females. Several reports have indicated that abdominal fat may affect bone independently of total body fat, and that there are sex differences in fat distribution, which may be a possible reason for the sex differences in the effect of BMI on fracture [32 33]. However, the reasons for the site-specific sex effects, as shown in this study, are not yet well understood. Another possible explanation could be that BMI as a measure of adiposity has been shown to be less valid in the older people owing to age-related changes in body composition [34]. However, in this study, only the older people were included, not the middle-aged or other groups of both males and females, and this effect is considered to be small.

Not only is low BMI considered a risk factor for fracture, but a preventive effect of high

BMI on fracture has recently been discussed. Some reports suggest that obesity has a protective effect on fractures because of higher BMD and reduced impact of falls as a result of increased soft-tissue padding [35 36]. However, it has not been proven that obesity is protective against all fractures, and the relationship between obesity and fracture has been reported to be fracture site-specific [37 38]. Although there are some reports of sex differences in the preventive effect of BMI on fractures [31 39], the results are mixed and the preventive effect of BMI on fractures is still unclear. We found that obesity had no protective effect on vertebral and hip fractures, regardless of sex, even after adjusting for confounding factors such as age and comorbidity. Therefore, the effect of obesity on fracture prevention may be poor in the ageing Asian population.

Further research is still needed to determine whether high BMI has a protective effect on fractures in the ageing population. However, underweight in the older people is consistently associated with a higher risk of fracture, which can have a greatly impact QOL in the future. BMI can be easily measured at a health examination, and screening for fracture risk according to BMI is effective in terms of health care costs for the healthy life span of the older people. Prolonged healthy life expectancy of the older people is associated with; the additional assessment of exercise function, further assessment of fracture risk by measuring BMD, and fracture prevention in the older people with underweight at the health examinations.

Using the Cox proportional hazards model, we found other factors besides BMI that

influenced vertebral and hip fractures. The comparison of HRs suggested that age and CCI may have a greater effect on fracture than BMI. First, for both types of fractures, older age and higher CCI increased the risk of fracture. Although it is a well-known finding that the incidence of fragility fractures increases with age, the effect of aging was more prevalent in hip fractures. Tamaki et al. [29] reported a marked increase in fracture risk after the age of 80, indicating that the very older people are at extremely high risk of fracture. This may be related to the decline in physical function and increased risk of falling with age. Comorbidities such as chronic kidney disease, diabetes, and dementia are associated with increased risk of fragility fractures, and it is useful to evaluate the presence of comorbidities and investigate their contribution to the risk of fractures [40-42]. CCI was originally used to assess the risk of comorbidities for death, but patients at high risk of death with a high CCI may also be at higher risk of fragility fractures. The present study stratified CCI and assessed the risk of fracture and showed that a higher CCI was associated with a higher fracture risk. Therefore, CCI may be useful in assessing fracture risk as well as mortality risk in the older people.

Secondly, health-related behaviors such as smoking and alcohol drinking are also well-established risk factors for fragility fractures [43 44], in this study, smoking was a risk factor in hip fractures in men. Iconaru et al. reported that smoking was a significant risk factor for only hip fractures among fragility fractures [45], and the effect of smoking on fracture may also be site-

specific. The lack of effect of smoking in females may be related to the extremely low rate of smoking (15% in males and 2% in females) in older females. The results of the present study showed that alcohol drinking had a protective effect on hip fractures in males. Several reports state that light to moderate alcohol consumption decrease age-related bone loss, and that heavy alcohol consumption is associated with elevated hip fracture risk, while light alcohol consumption is inversely related to fracture risk [44 46]. We did not assess the amount of alcohol consumed in this study and therefore are unable to discuss the effect of alcohol consumption on fracture risk.

Finally, the coexistence of osteoporosis is an important factor in osteoporotic fractures. The results of this study showed that osteoporosis affected vertebral fractures in both males and females, but only hip fractures in females. One reason for this may be the difference in the pathogenesis of osteoporosis, in which females, unlike males, experience two phases of bone loss: menopausal bone loss and age-related bone loss. Another possible explanation is that the prevalence of osteoporosis at the time of physical examination was quite low in the males in this study.

This study has several limitations. First, we used a retrospective design and data from a claims database and medical examination, which did not include BMD values. Therefore, it is not possible to say whether BMI is a risk factor for fractures independent of BMD. However, this does not change the fact that BMI is a simpler and more useful tool for fracture evaluation. Second,

the claims and medical examination data used in this study were derived from public insurance covering people aged ≥ 75 years, and the results may differ for younger populations, such as those in middle age. However, the fracture prevalence increases sharply in those over 70 years of age [29], and we believe that the evaluation used in this study is useful in other vulnerable population. One of the strengths of our study was that the follow-up rate for people aged ≥ 75 years who were covered by the insurance was extremely high. Third, since the fracture occurrence was extracted from the medical claims data using ICD-10 codes, asymptomatic vertebral fractures could not be extracted, and there is a concern that the number of vertebral fractures may have been underestimated. In addition, we were not able to obtain detailed information on the actual occurrence, for example, whether it was a fall or a traffic accident. Fragility fractures, which are the main focus of this study, are commonly caused by low-energy trauma. Therefore, the limitation is that some fractures from high energy trauma may be included in the study. Forth, this study referred to osteoporosis using ICD-10 codes, but failed to mention drug treatment. The coexistence of osteoporosis influences the occurrence of fractures, but the effect may vary greatly depending on the type of drug, the duration of medication, and other circumstances of osteoporosis treatment. This study was not able to investigate osteoporosis treatment and could not address the effect of osteoporosis treatment. Finally, this study was performed exclusively in Japan, where ethnic diversity is limited. Compared to the Japanese, Western populations have a

relatively high BMI, and our findings may not be generalizable to other populations.

Conclusion

The incidence of both fractures was higher in the underweight population. After adjustment for possible confounders, underweight was a risk factor for vertebral fracture only in males, and there were sex differences in the effect of BMI. Underweight was a risk factor for hip fracture in both males and females, and underweight is likely to remain important in the ageing population. Evaluating older people with underweight at health examinations and providing therapeutic interventions may help prevent subsequent fractures and improve healthy life expectancy.

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Author Contribution

Kyohei Shiomoto led the study design, extracted and analyzed the data, conducted the literature search, and wrote the manuscript. Akira Babazono and Yasuharu Nakashima contributed to the study design, analysis and manuscript revision. Yumi Harano, Takako Fujita, Peng Jiang and Sung-a Kim contributed to data analysis and reviewed the manuscript. All authors read and

approved the final version of the manuscript.

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Conflicts of interest

Kyohei Shiomoto. outside the current study declares grants from Kyocera. Akira Babazono, Yumi Harano, Takako Fujita, Peng Jiang, Sung-a Kim, and Yasuharu Nakashima declare that they have no conflicts of interest.

Patient consent for publication

Not required.

Ethics approval

This study was approved by the Kyushu University Institutional Review Board for Clinical Research (Approval No. 20209).

Provenance and peer review

Not commissioned, externally peer reviewed.

Data sharing statement

No additional data are available.

Open access

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Table 1. Patient's demographic data

Parameters	**Total** n = 24,691	**Males** n = 10,853	**Females** n = 13,838
Age at examination (years old)	79.4 ± 4.3 (75–103)	79.2 ± 4.0 (75–101)*	79.4 ± 4.3 (75–103)
Age categories, n (%)			
75–79	14,932 (60.5)	6,757 (62.3)*	8,175 (59.1)
80–84	6,554 (26.5)	2,892 (26.6)*	3,662 (26.5)
85≤	3,205 (13.0)	1,204 (11.1)*	2,001 (14.5)
BMI (kg/m^2)	22.2 ± 3.1 (11.6–54.2)	22.4 ± 2.9 (13–54.2)*	22.0 ± 3.2 (11.6–43)
BMI categories			
Underweight (BMI < 18.5)	2,684 (10.9)	910 (8.4)*	1,774 (12.8)
Normal weight (18.5 ≤ BMI < 25)	17,997 (71.6)	7,980 (73.5)	9,687 (70.0)
Overweight and obese (25 ≤ BMI)	4,340 (17.6)	1,963 (18.1)	2,377 (17.1)
CCI	1.7 ± 1.7 (0–11)	1.9 ± 1.8 (0–11)	1.5 ± 1.5 (0–10)
CCI categories, n (%)			
Low (0)	4,710 (19.1)	1,907 (17.6)*	2,803 (20.3)
Medium (1–2)	12,982 (52.6)	5,226 (48.2)	7,756 (56.1)
High (3–4)	5,331 (21.6)	2,772 (25.1)	2,609 (18.9)
Very high (≥ 5)	1,668 (6.8)	998 (9.2)	670 (4.8)
Smoking (yes), n (%)	1,891 (7.7)	1,586 (14.6)*	305 (2.2)
Alcohol drinking (yes), n (%)	9,444 (38.2)	6,447 (59.4)*	2,997 (21.7)

Osteoporosis, n (%)	3,969 (16.1)	374 (3.4)*	3,595 (26.0)
Follow-up duration (year)	6.9 ± 1.6 (0.1–8.0)	6.6 ± 1.8 (0.1–8.0)*	7.0 ± 1.4 (0.1–8.0)

Continuous values are expressed as mean ± standard deviation (range).

BMI: body mass index, CCI: Charlson comorbidity index.

* Significantly different between males and females ($P < .05$).

Table 2.

Comparison of subjects' demographics between BMI categories.

Parameters	BMI categories		
	Underweight	**Normal weight**	**Overweight and Obese**
	n = 2,684	n = 17,667	n = 4,340
Age at examination (years old)	80.8 ± 4.8 (75–103)[a, b]	79.4 ± 4.2 (75–103)[c]	78.9 ± 4.0 (75–99)
Age categories, n (%) 75–79/ 80–84/ 85≤	1,291 (48.1)/ 828 (30.8)/ 565 (21.1)[a, b]	10,775 (60.9)/ 4,691 (26.6)/ 2,201 (12.5)[c]	2,866 (66.1)/ 1,035 (23.8)/ 439 (10.1)
Sex; males/females, n (%)	910 (33.9)/ 1,774 (66.1)[a, b]	7,980 (45.2)/ 9,687 (54.8)	1,963 (45.2)/ 2,377 (54.8)
BMI (kg/m^2)	17.2 ± 1.0 (11.6–18.4)[a, b]	21.8 ± 1.7 (18.5–24.9)[c]	26.9 ± 1.9 (25–54.2)
CCI	1.6 ± 1.6 (0–10)[b]	1.7 ± 1.7 (0–11)[c]	1.9 ± 1.8 (0–10)
CCI categories, n (%)			
Low (=0)/ Medium (=1–2)/ High (=3–4)/ Very high (≥ 5)	481 (17.9)/ 1,426 (53.1)/ 574 (21.4)/ 203 (7.6)[b]	3,425 (19.4)/ 9.349 (52.9)/ 3,759 (21.3)/ 1,134 (6.4)[c]	804 (18.5)/ 2,207 (50.9)/ 998 (23.0)/ 331 (7.6)
Smoking (yes), n (%)	266 (9.9)[a, b]	1,346 (7.6)[c]	279 (6.4)
Alcohol drinking (yes), n (%)	786 (29.3)[a, b]	6,939 (39.3)	1,719 (39.6)
Osteoporosis, n (%)	537 (20)[a, b]	2,806 (15.9)	626 (14.4)
Follow-up duration (year)	6.4 ± 2.0 (0.1–8.0)[a, b]	6.9 ± 1.5 (0.1–8.0)[c]	7.1 ± 1.3 (0.1–8.0)

Continuous values are expressed as mean ± standard deviation (range). BMI: body mass index, CCI: Charlson comorbidity index

a; $P < .05$ for significantly different between underweight and normal weight.

b; $P < .05$ for significantly different between underweight and overweight and obese.

c; $P < .05$ for significantly different between normal weight and over.

Table 3.

Cox proportional hazards analysis of the risk factors for vertebral fracture. Age, BMI, alcohol drinking, smoking, CCI, and osteoporosis were used as covariates.

Factor		Univariate HR (95% CI)		Adjusted HR (95% CI)	
		Males	**Females**	**Males**	**Females**
Age categories < 75 = reference	75–79	1.55 (1.35–1.78)*	1.25 (1.15–1.36)*	1.45 (1.26–1.66)*	1.20 (1.10–1.30)*
	85<	2.37 (2.02–2.78)*	1.34 (1.21–1.47)*	2.13 (1.81–2.51)*	1.24 (1.12–1.37)*
BMI categories normal weight = reference	Underweight	1.51 (1.26–1.82)*	1.11 (1.00–1.23)*	1.33 (1.10–1.61)*	1.07 (0.96–1.19)
	Overweight and obese	0.87 (0.73–1.02)	0.95 (0.86–1.04)	0.91 (0.77–1.08)	0.95 (0.86–1.05)
Alcohol drinking No = reference	Yes	0.96 (0.85–1.09)	0.93 (0.85–1.02)	1.06 (0.94–1.19)	0.97 (0.89–1.06)
Smoking No = reference	Yes	0.92 (0.77–1.10)	1.13 (0.90–1.42)	0.93 (0.78–1.11)	1.17 (0.93–1.46)
CCI categories (low = reference)	Medium	1.83 (1.48–2.26)*	1.48 (1.34–1.65)*	1.74 (1.40–2.15)*	1.42 (1.28–1.57)*
	High	2.33 (1.87–2.91)*	1.82 (1.62–2.05)*	2.10 (1.68–2.62)*	1.67 (1.48–1.89)*
	Very high	2.83 (2.19–3.64)*	2.04 (1.72–2.42)*	2.52 (1.95–3.25)*	1.81 (1.52–2.14)*
Osteoporosis No = reference	Yes	2.24 (1.77–2.83)*	1.49 (1.38–1.61)*	1.83 (1.44–2.32)*	1.39 (1.29–1.50)*

HR: hazard ratio, CI: confidence interval, BMI: body mass index, CCI: Charlson comorbidity index

* Statistically significant difference compared to reference ($P < .05$).

Table 4.

Cox proportional hazards analysis of the risk factors for hip fracture. Age, BMI, alcohol drinking, smoking, CCI, and osteoporosis were used as covariates.

Factor		Univariate HR (95% CI)		Adjusted HR (95% CI)	
		Males	**Females**	**Males**	**Females**
Age categories < 75 = reference	75–79	2.16 (1.67–2.79)*	2.26 (1.98–2.59)*	1.93 (1.49–2.50)*	2.14 (1.87–2.45)*
	85<	3.89 (2.94–5.16)*	4.03 (3.51–4.63)*	3.21 (2.41–4.29)*	3.66 (3.18–4.21)*
BMI categories normal weight = reference	Underweight	2.24 (1.66–3.00)*	1.57 (1.36–1.82)*	1.74 (1.29–2.35)*	1.36 (1.17–1.57)*
	Overweight and obese	0.74 (0.53–1.03)	0.88 (0.75–1.03)	0.81 (0.58–1.14)	0.89 (0.75–1.04)
Alcohol drinking No = reference	Yes	0.68 (0.55–0.85)*	0.80 (0.69–0.93)*	0.79 (0.55–0.97)*	0.92 (0.80–1.06)
Smoking No = reference	Yes	1.38 (1.04–1.83)*	1.07 (0.74–1.55)	1.37 (1.03–1.82)*	1.13 (0.78–1.63)
CCI categories (low = reference)	Medium	2.40 (1.53–3.75)*	1.95 (1.62–2.34)*	2.20 (1.41–3.45)*	1.79 (1.49–2.16)*
	High	3.36 (2.12–5.33)*	2.39(1.95–2.93)*	2.87 (1.81–4.55)*	2.01 (1.64–2.48)*
	Very high	3.78 (2.26–6.32)*	3.38 (2.61–4.38)*	3.28 (1.96–5.49)*	2.73 (2.10–3.54)*
Osteoporosis No = reference	Yes	1.63 (1.00–2.66)*	1.29 (1.15–1.46)*	1.20 (0.73–1.97)	1.10 (0.98–1.25)*

HR: hazard ratio, CI: confidence interval, BMI: body mass index, CCI: Charlson comorbidity index

* Statistically significant difference compared to reference ($P < .05$).

Figure Legends

Image 1: Figure. 1

The Kaplan-Meier curve shows the incidence of a) vertebral fractures and b) hip fracture compared by BMI category. The solid line represents underweight, the dashed line represents normal weight, and the dotted line represents overweight and obese.

BMI: body mass index

Image 2: Figure. 2

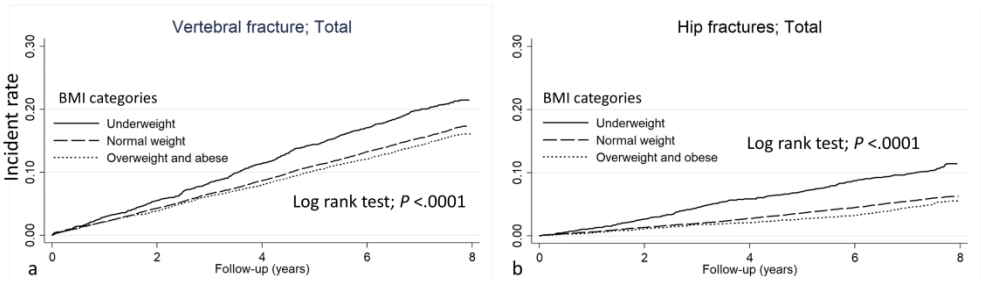
The Kaplan-Meier curve shows the incidence of vertebral fractures in a) males and b) females compared by BMI category. The solid line represents underweight, the dashed line represents normal weight, and the dotted line represents overweight and obese.

BMI: body mass index

Image 3: Figure. 3

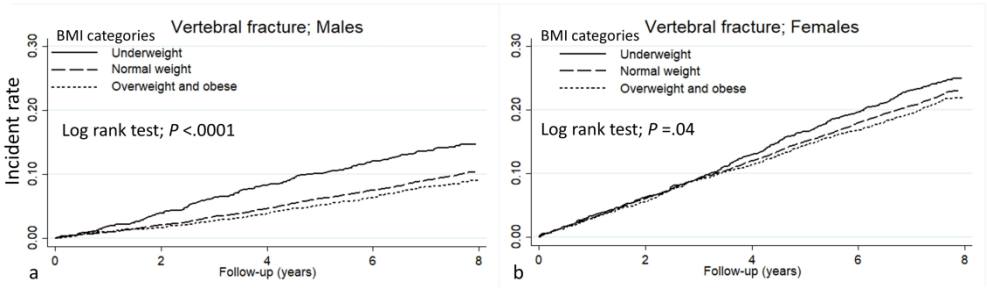
The Kaplan-Meier curve shows the incidence of hip fracture in a) males and b) females compared by BMI category. The solid line represents underweight, the dashed line represents normal weight, and the dotted line represents overweight and obese.

BMI: body mass index



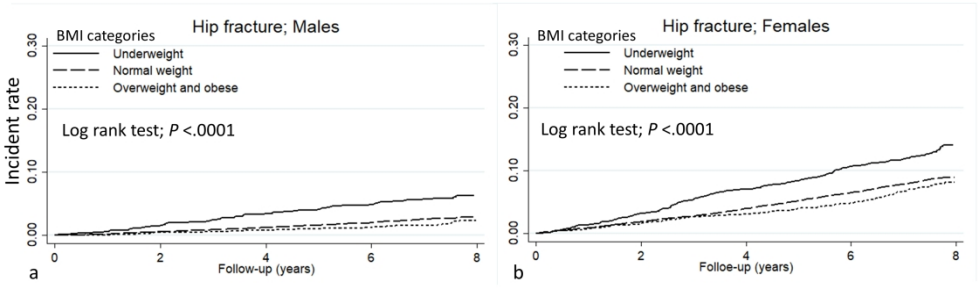
The Kaplan-Meier curve shows the incidence of a) vertebral fractures and b) hip fracture compared by BMI category. The solid line represents underweight, the dashed line represents normal weight, and the dotted line represents overweight and obese.
BMI: body mass index

299x86mm (300 x 300 DPI)



The Kaplan-Meier curve shows the incidence of vertebral fractures in a) males and b) females compared by BMI category. The solid line represents underweight, the dashed line represents normal weight, and the dotted line represents overweight and obese.
BMI: body mass index

299x86mm (300 x 300 DPI)



The Kaplan-Meier curve shows the incidence of hip fracture in a) males and b) females compared by BMI category. The solid line represents underweight, the dashed line represents normal weight, and the dotted line represents overweight and obese.
BMI: body mass index

299x86mm (300 x 300 DPI)

Appendix 1. Prevalence of the comorbidities used to calculate the CCI

	Total n = 24,691, n (%)	Males n = 10,853, n (%)	Females n = 13,838, n (%)
Acute myocardial infraction	130 (0.5)	91 (0.8)*	39 (0.3)
Congestive heart failure	972 (3.9)	448 (4.1)	524 (3.8)
Peripheral vascular disease	3,365 (13.6)	1,593 (14.7)*	1,772 (12.8)
Cerebral vascular disease	10,922 (44.2)	4,679 (43.1)*	6,243 (45.1)
Dementia	633 (2.6)	224 (2.1)*	409 (3.0)
Pulmonary disease	2,735 (11.1)	1,343 (12.4)*	1,392 (10.1)
Connective tissue disorder	1,672 (6.7)	711 (6.6)	961 (6.9)
Peptic ulcer	1,979 (8.0)	928 (8.6)*	1,051 (7.6)
Mild liver disease	1,725 (7.0)	912 (8.4)*	813 (5.9)
Diabetes without complications	1,273 (5.2)	724 (6.7)*	549 (4.0)
Diabetes with complications	1,013 (4.1)	583 (5.4)*	430 (3.1)
Paraplegia	715 (2.9)	376 (3.5)*	339 (2.5)
Renal disease	3,564 (14.4)	1,794 (16.5)*	1,770 (12.8)
Cancer	2,832 (11.5)	1,876 (17.1)*	972 (7.0)
Metastatic cancer	100 (0.4)	68 (0.6)*	32 (0.2)
Sever liver disease	13 (0.1)	8 (0.07)	5 (0.04)
HIV	0 (0)	0 (0)	0 (0)

CCI: Charlson comorbidity index, HIV: human immunodeficiency virus

* Significantly different between males and females ($P < .05$).

Appendix. 2 Alive vs. death among participants

Parameters	Alive n = 19,282	Death n = 5,409
Age at examination (years old)	78.7 ± 3.6 (75–99)*	82.1 ± 5.3 (75–103)
Age categories, n (%)		
75–79	12,898 (66.9)*	2,034 (37.6)
80–84	4,820 (25.0)*	1,734 (32.1)
85≤	1,564 (8.1)*	1,641 (30.3)
Sex; male/female, n (%)	7,795 (40.4) / 11,487 (59.6)*	3,058 (56.5) / 2,351 (43.5)
BMI (kg/m^2)	22.4 ± 3.0 (11.6–54.2)*	21.5 ± 3.2 (12.5–39.6)
BMI categories		
Underweight (BMI < 18.5)	1,761 (9.1)*	923 (17.1)
Normal weight (18.5 ≤ BMI < 25)	13,896 (72.1)	3,771 (69/7)
Overweight and Obese (25 ≤ BMI)	3,625 (18.8)	715 (13.2)
CCI	1.5 ± 1.6 (0–11)	2.3 ± 1.9 (0–10)
CCI categories, n (%)		
Low	4,134 (21.4)*	576 (10.7)
Medium	10,530 (54.6)	2,452 (45.3)
High	3,627 (18.8)	1,704 (31.5)
Very high	991 (5.1)	677 (12.5)
Smoking, n (%)	1,279 (6.6)*	612 (11.3)
Alcohol drinking, n (%)	7,442 (38.6)*	2,002 (37.0)
Osteoporosis, n (%)	3,126 (16.2)	843 (15.6)
Follow-up duration (year)	7.5 ± 0.3 (0.1–8.0)*	4.5 ± 2.0 (0.1–7.9)

Continuous values are expressed as mean ± standard deviation (range). BMI: body mass index, CCI: Charlson comorbidity index

* Significantly different between alive and death (P < .05).

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1, 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5, 6
Objectives	3	State specific objectives, including any prespecified hypotheses	5, 6
Methods			
Study design	4	Present key elements of study design early in the paper	6, 7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6, 7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7,8
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8, 9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8, 9
Bias	9	Describe any efforts to address potential sources of bias	8, 9
Study size	10	Explain how the study size was arrived at	9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8, 9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9
		(*b*) Describe any methods used to examine subgroups and interactions	8, 9
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7, 8 Table 1
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	9, 10 Table 1
Outcome data	15*	Report numbers of outcome events or summary measures over time	11, Fig1, 2
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11 Table 4, 5
		(*b*) Report category boundaries when continuous variables were categorized	8 Table 3
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Table 3, 4, 5
Discussion			
Key results	18	Summarise key results with reference to study objectives	12, 13,14, 15
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12, 13
Generalisability	21	Discuss the generalisability (external validity) of the study results	16, 17, 18
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Effect of body mass index on vertebral and hip fractures in Older people and Differences according to sex: A retrospective Japanese cohort study.

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Title Page

Original research article

Effect of body mass index on vertebral and hip fractures in Older people and Differences according to sex: A retrospective Japanese cohort study.

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Abstract

Objectives: The purpose of this study was to investigate the incidence of vertebral and hip fractures in the older people and to clarify the relationship between these fractures and body mass index (BMI) along with the impact of sex differences.

Design: This was a retrospective cohort study.

Setting: We used administrative claims data between April 2010 and March 2018.

Participants: Older people aged ≥75 years who underwent health examinations in 2010 and were living in the Fukuoka Prefecture, Japan were included in the study. A total of 24,691 participants were included; the mean age was 79.4 ± 4.3 years, 10,853 males and 13,838 females, and an the mean duration of observation was 6.9 ± 1.6 years.

Primary and secondary outcome measures: We estimated the incidence of vertebral and hip fractures by BMI category (underweight:<18.5kg/m^2, normal weight:18.5–24.9kg/m^2, overweight and obese:≥25.0kg/m^2) using a Kaplan–Meier curve in males and females and determined fracture risk by sex using Cox proportional hazards regression analyses.

Results: The incidence of vertebral and hip fractures was 16.8% and 6.5%, respectively. The cumulative incidence of vertebral and hip fracture at the last observation (8 years) in each BMI groups (underweight/normal weight/overweight and obese) estimated using the Kaplan–Meier curve was 14.7%/10.4%/9.0% in males and 24.9%/23.0%/21.9% in females, and

6.3%/2.9%/2.4% in males and 14.1%/9.0%/8.1% in females, respectively, and both fractures were significantly higher in underweight groups regardless of sex. Multivariable Cox proportional hazards models showed that underweight was a significant risk factor only in males for vertebral fractures and in both males and females for hip fractures.

Conclusion: Underweight was associated with fractures in the ageing population, but there was a sex difference in the effect for vertebral fractures.

Trial registration: This study was approved by the Kyushu University Institutional Review Board for Clinical Research (Approval No. 20209).

Keywords: body mass index (BMI), sex differences, fracture, claim data, older people

Strengths and limitations of this study

1. This was a retrospective cohort study including 24,691 older peoples.

2. We followed up participants for approximately 7 years.

3. We investigated the incidence of vertebral fractures and hip fractures in the older people and evaluated the relationship between BMI and fractures and differences by sex.

4. We evaluated the relationship between BMI and fracture by adjusting for major factors such as age, smoking, and osteoporosis, as well as comorbidity using the Charlson Comorbidity Index.

5. This study has several limitations; bone mineral density (BMD), a factor closely related to fracture, could not be assessed in this study, and although we assessed osteoporosis comorbidity, we could not assess treatment status.

Introduction

Vertebral and hip fractures are the major fractures that occur in the older people. The incidence of these fragility fractures appears to be increasing in many countries because of the increasing size of populations [1-3]. Gullberg et al. reported that the incidence of hip fractures in the world was estimated to nearly double, from 2.6 million hip fractures in 2025 to 4.5 million in 2050, with a particularly marked increase in Asia [2]. Both vertebral and hip fractures cause pain and dysfunction and decrease quality of life (QOL) [4-6]. It is well known that there is a high mortality rate after hip fracture, but there are also reports of increased mortality after vertebral fractures [7, 8]. Consequently, among fragility fractures, vertebral and hip fractures greatly impact healthy life expectancy and longevity. In Japan, where the ageing population is rapidly increasing, the economic burden of these fractures is immeasurable and has become an important public health issue [9, 10]. Therefore, in order to prevent these fractures in the older people, it is very important to understand what are the risk factors.

Previous studies reported several risk factors for vertebral and hip fractures, with the most important risk being age, sex, history of past fractures, and low bone mineral density (BMD) [11, 12]. FRAX, which is known as a fracture prediction tool, also uses these factors, smoking, and alcohol consumption as fracture risks [13]. The prevalence of osteoporosis is also high in the elderly, and the coexistence of osteoporosis has a significant impact on fractures [14]. Body mass index

(BMI) is another well-documented risk factor that it is closely related to fragility fractures [15-17]. Underweight has been recognized as a risk factor for vertebral and hip fractures, and a cohort study in Japan reported underweight as a preventable risk factor for hip fracture [18]. On the other hand, Johansson et al. [16] reported that the association between BMI and fracture risk is complex and differs across skeletal sites; thus, the relationship between BMI and fracture risk is still controversial. Previous study has shown that the effect of BMI on hip fracture varies with age [19]. Sex and race may also influence the relationship between BMI and fractures. Although BMD varies by race, there was a report that even after excluding the effects of BMD, there was a difference in fracture risk by race [20, 21]. Some studies reported that the impact of BMI on fractures varies by sex [16, 22]; however, there is no consensus regarding this, especially in Japanese.

In this study, using the healthcare claims database of the Fukuoka Prefecture, the following questions were addressed: (1) What is the incidence of vertebral and hip fractures in the older people who live in Fukuoka Prefecture? (2) Is there a relationship between BMI and fracture risk and is there a difference between males and females?

Materials and Methods

Study design and data source

This was a retrospective cohort study approved by our Institutional Review Board. We

used data from the healthcare claims database and master database of the Fukuoka Prefecture Wide-Area Association of Latter-stage Elderly Healthcare between 1 April 2010 and 31 March 2018. This public health insurance is open to people over the age of 75 years and those aged 65-74 years with disabilities, and the majority of people over the age of 75 years have this insurance. The total population of Fukuoka Prefecture is about 5.1 million, the 9th largest in Japan, and about 520,000 older people are covered by this insurance. Most of the insured have long-term eligibility once they are enrolled; therefore, few participants were lost to follow-up except for death. The databases included data for the International Classification of Diseases 10th Revision (ICD-10) codes; date of diagnosis, medical procedures, such as surgery, date of admission, and death. The database are mostly computer-administered. According to a report by the Japanese Ministry of Health, Labour and Welfare, the penetration rate of computer-administered claims databases was 98.6% as of April 2015 [23]. Older people aged 75 and over who are enrolled in this health insurance and who do not have regular hospital visits for lifestyle-related diseases are eligible for medical examination. We also used data from the 2010 health examination, which included participants' height, weight, BMI, smoking and use of alcohol.

Participants

Our target population was people who held Fukuoka Prefecture Wide-Area Association of Latter-stage Elderly Healthcare insurance and who met the following criteria: (1) People who

underwent the 2010 health examination; (2) age ≥ 75 years at the health examination; (3) data related to smoking and alcohol consumption at the time of health examination were available; and (4) no history of vertebral or hip fracture before the health examination. Fracture history was investigated using self-reports at the time of the health examination and the medical claims database to determine if there were any fractures prior to the health examination.

Follow-up duration

The follow-up duration was defined as from the date of the participant's 2010 health examination to the date of death or until March 2018. There was a slight discrepancy because participants did not have a consistent date for their health examination.

Outcomes (vertebral and hip fracture incidence)

We identified patients with vertebral (ICD-10 code = S22.0-1, S32) and hip (ICD-10 code = S72.0-2) fractures diagnosed between the date of the medical examination and 31 March 2018 in the medical database and investigated the cumulative fracture incidence. We also investigated the time to each primary fracture. A second fracture at the same site was not included. Participants who died during the follow-up period were also included as fracture patients if they had a fracture before death.

Comparison by BMI category

The BMI classification in the general WHO is widely used in Japan, and we used the

following cut points. Participants were divided into three groups according to BMI category as follows: underweight (< 18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), and overweight and obese (≥ 25.0 kg/m^2). Participants' demographics and the incidence of vertebral and hip fractures were compared between the BMI categories.

Risk factors for vertebral and hip fractures

We examined age, BMI, use of alcohol, smoking, comorbidities, and osteoporosis as risk factors for each fracture by sex. BMI was divided into three categories as described above, and the fracture risk of "underweight" and "overweight and obese" was examined using normal as the reference. Age was categorized into three groups: 75–79 years, 80–84 years, and ≥ 85 years. Smoking and use of alcohol were divided into two groups, habitual and non-habitual, and were used as separate risk factors. The Charlson Comorbidity Index (CCI) was used as an indicator of each participant's comorbidities [24]. CCI was calculated at the health examination using the ICD-10 codes [25] and was divided into four groups: low (0), medium (1–2), high (3–4), and very high (≥ 5). Osteoporosis was identified using the ICD-10 codes (M80, M81, M82). Incidentally, the diagnostic criteria for osteoporosis in Japan are 1) BMD value less than 70% of Young adult mean (YAM), 2) history of vertebral fracture or proximal femur fracture, or 3) history of fragility fracture other than vertebral fracture or proximal femur fracture at less than 80% of YAM.

Participant and public Involvement

We used administrative claims data and did not involve participants in this study.

Statistical analysis

Statistical analyses were performed using Stata software, version 14 (Stata Corp, College Station, TX). All continuous variables were examined for normality with the Shapiro-Wilk test. Since all continuous variables were non-normal, the Wilcoxon signed-rank test was used for two-group comparisons and the Steel-Dwass test was used for three-group comparisons. For qualitative variables, the chi-square test was used. We estimated the incidence proportion of vertebral and hip fractures by BMI category using a Kaplan–Meier curve in males and females, and differences between groups were tested for statistical significance using the log-rank test in males and females. To examine the risk factors for vertebral and hip fracture by sex, Cox proportional hazards regression analyses were performed using the following factors: age, BMI, use of alcohol, smoking, osteoporosis and CCI. All risk factors were used as categorical variables. Statistical significance was set as $P < .05$. Continuous values were expressed as mean ± standard deviation.

Results

Participants

Of the people who held Fukuoka Prefecture Wide-Area Association of Latter-stage Elderly Healthcare insurance, 26,005 underwent the 2010 health examination. We excluded 1,314

people: 691 people were younger than 75 years at the time of the health examination, 109 people had missing data related to their drinking and smoking, and 514 people had a history of fracture; therefore, 24,691 participants were included in this study. Participants' demographic data are shown in **Table 1**. The mean observation period was 6.9 years, and 5,409 people died during this period. There was a significantly higher proportion of older age and underweight groups in females compared to males ($P < .0001$). Males had significantly higher CCI, smoking, and use of alcohol than females ($P < .0001$). The prevalence of osteoporosis was significantly higher in females ($P < .0001$). **Appendix 1** shows the prevalence of the comorbidities used to calculate the CCIs.

Comparison of patients lost to follow-up due to death vs. those that remained alive

Those that died during follow-up were older, more male, had lower BMI, higher CCI, and more smokers than those that survived (all $P < .0001$). Details are shown in **Appendix 2**.

Vertebral and hip fracture rate

Vertebral and hip fractures occurred in 4,153 (16.8%) and 1,543 (6.5%) of the participants, respectively, during the study period. Vertebral fractures occurred in 1,082 (10%) males and 3,071 (22.2%) females, hip fractures occurred in 314 (2.9%) males and 1,229 (8.9%) females, and the incidence of both fractures was significantly higher in females ($P < .0001$). The incidence of vertebral fracture was 150 in males and 315.9 in females per 10,000 person-years, respectively.

The incidence of hip fracture was 43.5 in males and 126.4 in females per 10,000 person-years, respectively. A total of 520 participants had both vertebral and hip fractures, with a significantly higher number of females ($P < .0001$).

Comparison by BMI category

A comparison of participants' demographics by BMI category is shown in **Table 2**. Underweight group was present in a significantly higher proportion of people aged ≥ 85 years, in females, and in those who smoked, than in the other two BMI groups ($P < .0001$). There was a significantly lower proportion of use of alcohol with underweight group ($P < .0001$). Overweight and obese group was associated with a significantly higher CCI than the other two BMI groups ($P < .01$).

The cumulative incidence of vertebral and hip fracture in each BMI groups (underweight/normal weight/overweight and obese) at the final follow-up estimated using the Kaplan–Meier curve was 21.5% / 17.3% / 16.1% and 11.4% / 6.2% / 5.5%, respectively (all $P < .0001$) (**Fig.1**). By sex, the cumulative incidence of vertebral fracture in each BMI groups was 14.7% / 10.4% / 9.0% in males and 24.9% / 23.0% / 21.9% in females, respectively, and was significantly higher with underweight group in both sexes (all $P < .05$) (**Fig.2**). Similarly, the cumulative incidence of hip fracture was 6.3% / 2.9% / 2.4% in males and 14.1% / 9.0% / 8.1% in females, respectively, and was significantly higher with underweight group in both sexes (all

$P < .0001$) (**Fig.3**).

Risk factors of vertebral and hip fractures

In univariate analysis, the HRs (95%CI) for age, BMI, alcohol, smoking, CCI, and osteoporosis for the vertebral fracture were 2.4 (2.0-2.8) / 1.5 (1.3-1.8) / 1.0 (0.9-1.1) / 0.9 (0.8-1.1) / 2.8 (2.2-3.6) / 2.2 (1.8-2.8) in males, and 1.3 (1.2-1.5) / 1.1 (1.0-1.2) / 0.9 (0.9-1.0) / 1.1 (0.9-1.4) / 2.0 (1.7-2.4) / 1.5 (1.4-1.6) in females, respectively. The HRs (95%CI) for age, BMI, alcohol, smoking, CCI, and osteoporosis for the hip fracture were 3.9 (2.9-5.2) / 2.2 (1.7-3.0) / 0.7 (0.6-0.9) / 1.4 (1.0-1.8) / 3.8 (2.3-6.3) / 1.6 (1.0-2.7) in males, and 4.0 (3.5-4.6) / 1.6 (1.4-1.8) / 0.8 (0.7-0.9) / 1.1 (0.7-1.6) / 3.4 (2.6-4.4) / 1.3 (1.2-1.5) in females, respectively. Older age, underweight, higher CCI, and osteoporosis were significant risk factors for vertebral fracture in both males and females (**Table 3**). Multivariable analysis showed that older age, higher CCI, and osteoporosis were risk factors for vertebral fracture in both males and females, but underweight was a significant risk factor only in males (**Table 3**).

In multivariable analysis, the adjusted HRs for age, BMI, alcohol, smoking, CCI, and osteoporosis for the vertebral fracture were 2.1 (1.8-2.5) / 1.3 (1.1-1.6) / 1.1 (0.9-1.2) / 0.9 (0.8-1.1) / 2.5 (2.0-3.3) / 1.8 (1.4-2.3) in males, and 1.2 (1.1-1.4) / 1.1 (1.0-1.2) / 1.0 (0.9-1.1) / 1.2 (0.9-1.5) / 1.8 (1.5-2.1) / 1.4 (1.3-1.5) in females, respectively. The adjusted HRs for age, BMI, alcohol, smoking, CCI, and osteoporosis for the hip fracture were 3.2 (2.4-4.3) / 1.7 (1.3-2.4) /

0.8 (0.6-1.1) / 1.4 (1.0-1.8) / 3.3 (2.0-5.5) / 1.2 (0.7-2.0) in males, and 3.7 (3.2-4.2) / 1.4 (1.2-1.6) / 0.9 (0.8-1.1) / 1.1 (0.8-1.6) / 2.7 (2.1-3.5) / 1.1 (1.0-1.3) in females, respectively. Older age, higher CCI, and osteoporosis were significant risk factors for hip fracture in both males and females, and smoking was also a significant risk factor in males (**Table 4**). Multivariable analysis showed that older age and higher CCI were significant risk factors for hip fracture in both males and females, smoking was a significant risk factor only in males, and osteoporosis was a significant risk factor only in females (**Table 4**). Use of alcohol had a significant protective effect on hip fractures in males.

Discussion

In this study, we evaluated the cumulative incidence of vertebral and hip fractures in the older people over an average of 6.9 years using the healthcare claims database in the Fukuoka Prefecture. Older people holding the Fukuoka Prefecture Wide-Area Association of Latter-stage Elderly Healthcare insurance rarely drop out of the program, and the health insurance covers most older people aged ≥ 75 years who live in this area. Therefore, the strength of this study is that there were almost no dropouts other than because of death, and that we were able to investigate the occurrence of fractures regardless of the medical institution where the diagnosis was made. Previous studies reported that the incidence of vertebral fracture at age ≥ 60 years was 13–18%

[26-28]. Tamaki et al. found in a three-year retrospective cohort study that the incidence of hip fracture in people aged 80–84 years was 36.6 and 88 per 10,0000, for males and females, respectively [29]. We found that the incidence of vertebral and hip fracture was 17% (150 and 316.4 per 10,000, for males and females) and 7% (43.5 and 126.4 per 10,000, for males and females), respectively, in our study. The incidence rates in the present study were equivalent to those in previous cohort studies and did not appear to be unevenly distributed by region [26-29].

Using this large cohort data, our study demonstrated that the vertebral and hip fracture incidence was higher in the underweight group (BMI < 18.5 kg/m^2) according to the Kaplan-Meier curve. As many previous studies reported, underweight has long been considered an important risk factor for fractures. Generally, lower BMI is associated with lower BMD, and Lloyd et al. reported that every unit increase in BMI is associated with an increase of 0.0082 g/cm in BMD30 [30]. De Laet et al. [15] also reported that low BMI was a significant risk factor for fracture, even after adjusting for BMD, and that low BMI was associated with an increased relative risk, especially for hip fracture. In the present study, underweight was also associated with higher HR for hip fracture than vertebral fracture, suggesting that underweight may have a particular impact on hip fracture among fragility fractures. Although underweight is generally considered a risk factor for fragility fractures, several reports have shown that the relationship between BMI and fracture risk may differ by sex and skeletal site, and that the relationship is complex [15, 16]. In the

current study, we investigated the effect of BMI on fractures, stratified by sex. We found that underweight was a risk factor for hip fractures regardless of sex, and for vertebral fractures, underweight was a risk factor only in males. Kaze et al. [17] reported in their meta-analysis that an inverse association between BMI and risk for vertebral fracture in present in males but not in females. Several previous studies have shown that underweight is consistently associated with the risk of hip fracture, regardless of sex [16, 31]. Johansson et al. [16] found that the relationship between BMI and osteoporotic fractures depended on the site of the fracture, although their study was conducted only on females. In this study, we similarly suggested that the effect of BMI varied by fracture site in females. Several reports have indicated that abdominal fat may affect bone independently of total body fat, and that there are sex differences in fat distribution, which may be a possible reason for the sex differences in the effect of BMI on fracture [32, 33]. However, the reasons for the site-specific sex effects, as shown in this study, are not yet well understood. Another possible explanation could be that BMI as a measure of adiposity has been shown to be less valid in the older people owing to age-related changes in body composition [34]. However, in this study, only the older people were included, not the middle-aged or other groups of both males and females, and this effect is considered to be small.

Not only is low BMI considered a risk factor for fracture, but a preventive effect of high BMI on fracture has recently been discussed. Some reports suggest that obesity has a protective

effect on fractures because of higher BMD and reduced impact of falls as a result of increased soft-tissue padding [35, 36]. However, it has not been proven that obesity is protective against all fractures, and the relationship between obesity and fracture has been reported to be fracture site-specific [37, 38]. Although there are some reports of sex differences in the preventive effect of BMI on fractures [31, 39], the results are mixed and the preventive effect of BMI on fractures is still unclear. We found that obesity had no protective effect on vertebral and hip fractures, regardless of sex, even after adjusting for confounding factors such as age and comorbidity. Therefore, the effect of obesity on fracture prevention may be poor in the ageing Asian population.

Further research is still needed to determine whether high BMI has a protective effect on fractures in the ageing population. However, underweight in the older people is consistently associated with a higher risk of fracture, which can have a greatly impact QOL in the future. BMI can be easily measured at a health examination, and screening for fracture risk according to BMI is effective in terms of health care costs for the healthy life span of the older people. Prolonged healthy life expectancy of the older people is associated with; the additional assessment of exercise function, further assessment of fracture risk by measuring BMD, and fracture prevention in the older people with underweight at the health examinations.

Using the Cox proportional hazards model, we found other factors besides BMI that influenced vertebral and hip fractures. The comparison of HRs suggested that age and CCI may

have a greater effect on fracture than BMI. First, for both types of fractures, older age and higher CCI increased the risk of fracture. Although it is a well-known finding that the incidence of fragility fractures increases with age, the effect of aging was more prevalent in hip fractures. Tamaki et al. [29] reported a marked increase in fracture risk after the age of 80, indicating that the very older people are at extremely high risk of fracture. This may be related to the decline in physical function and increased risk of falling with age. Comorbidities such as chronic kidney disease, diabetes, and dementia are associated with increased risk of fragility fractures, and it is useful to evaluate the presence of comorbidities and investigate their contribution to the risk of fractures [40-42]. CCI was originally used to assess the risk of comorbidities for death, but patients at high risk of death with a high CCI may also be at higher risk of fragility fractures. The present study stratified CCI and assessed the risk of fracture and showed that a higher CCI was associated with a higher fracture risk. Therefore, CCI may be useful in assessing fracture risk as well as mortality risk in the older people.

Secondly, health-related behaviors such as smoking and use of alcohol are also well-established risk factors for fragility fractures [43, 44], in this study, smoking was a risk factor in hip fractures in men. Iconaru et al. reported that smoking was a significant risk factor for only hip fractures among fragility fractures [45], and the effect of smoking on fracture may also be site-specific. The lack of effect of smoking in females may be related to the extremely low rate of

smoking (15% in males and 2% in females) in older females. The results of the present study showed that use of alcohol had a protective effect on hip fractures in males. Several reports state that light to moderate alcohol consumption decrease age-related bone loss, and that heavy alcohol consumption is associated with elevated hip fracture risk, while light alcohol consumption is inversely related to fracture risk [44, 46]. We did not assess the amount of alcohol consumed in this study and therefore are unable to discuss the effect of alcohol consumption on fracture risk.

Finally, the coexistence of osteoporosis is an important factor in osteoporotic fractures. The results of this study showed that osteoporosis affected vertebral fractures in both males and females, but only hip fractures in females. One reason for this may be the difference in the pathogenesis of osteoporosis, in which females, unlike males, experience two phases of bone loss: menopausal bone loss and age-related bone loss. Another possible explanation is that the prevalence of osteoporosis at the time of physical examination was quite low in the males in this study.

This study has several limitations. First, we used a retrospective design and data from a claims database and medical examination, which did not include BMD values. Therefore, it is not possible to say whether BMI is a risk factor for fractures independent of BMD. However, this does not change the fact that BMI is a simpler and more useful tool for fracture evaluation. Second, the claims and medical examination data used in this study were derived from public insurance

covering people aged ≥ 75 years, and the results may differ for younger populations, such as those in middle age. However, the fracture prevalence increases sharply in those over 70 years of age [29], and we believe that the evaluation used in this study is useful in other vulnerable population. One of the strengths of our study was that the follow-up rate for people aged ≥ 75 years who were covered by the insurance was extremely high. Third, since the fracture occurrence was extracted from the medical claims data using ICD-10 codes, asymptomatic vertebral fractures could not be extracted, and there is a concern that the number of vertebral fractures may have been underestimated. In addition, we were not able to obtain detailed information on the actual occurrence, for example, whether it was a fall or a traffic accident. Fragility fractures, which are the main focus of this study, are commonly caused by low-energy trauma. Therefore, the limitation is that some fractures from high energy trauma may be included in the study. Forth, this study referred to osteoporosis using ICD-10 codes, but failed to mention drug treatment. The coexistence of osteoporosis influences the occurrence of fractures, but the effect may vary greatly depending on the type of drug, the duration of medication, and other circumstances of osteoporosis treatment. This study was not able to investigate osteoporosis treatment and could not address the effect of osteoporosis treatment. Finally, this study was performed exclusively in Japan, where ethnic diversity is limited. Compared to the Japanese, Western populations have a relatively high BMI, and our findings may not be generalizable to other populations.

Conclusion

The incidence of both fractures was higher in the underweight population. After adjustment for possible confounders, underweight was a risk factor for vertebral fracture only in males, and there were sex differences in the effect of BMI. Underweight was a risk factor for hip fracture in both males and females, and underweight is likely to remain important in the ageing population. Evaluating older people with underweight at health examinations and providing therapeutic interventions may help prevent subsequent fractures and improve healthy life expectancy.

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Author Contribution

Kyohei Shiomoto led the study design, extracted and analyzed the data, conducted the literature search, and wrote the manuscript. Akira Babazono and Yasuharu Nakashima contributed to the study design, analysis and manuscript revision. Yumi Harano, Takako Fujita, Peng Jiang and Sung-a Kim contributed to data analysis and reviewed the manuscript. All authors read and approved the final version of the manuscript.

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Conflicts of interest

All authors have no conflicts of interest.

Patient consent for publication

Not required.

Ethics approval

This study was approved by the Kyushu University Institutional Review Board for Clinical Research (Approval No. 20209).

Provenance and peer review

Not commissioned, externally peer reviewed.

Data sharing statement

No additional data are available.

Open access

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Table 1. Patient's demographic data

Parameters	**Total** n = 24,691	**Males** n = 10,853	**Females** n = 13,838
Age at examination (years old)	79.4 ± 4.3 (75–103)	79.2 ± 4.0 (75–101)*	79.4 ± 4.3 (75–103)
Age categories, n (%)			
75–79	14,932 (60.5)	6,757 (62.3)*	8,175 (59.1)
80–84	6,554 (26.5)	2,892 (26.6)*	3,662 (26.5)
85≤	3,205 (13.0)	1,204 (11.1)*	2,001 (14.5)
BMI (kg/m^2)	22.2 ± 3.1 (11.6–54.2)	22.4 ± 2.9 (13–54.2)*	22.0 ± 3.2 (11.6–43)
BMI categories			
Underweight (BMI < 18.5)	2,684 (10.9)	910 (8.4)*	1,774 (12.8)
Normal weight (18.5 ≤ BMI < 25)	17,997 (71.6)	7,980 (73.5)	9,687 (70.0)
Overweight and obese (25 ≤ BMI)	4,340 (17.6)	1,963 (18.1)	2,377 (17.1)
CCI	1.7 ± 1.7 (0–11)	1.9 ± 1.8 (0–11)	1.5 ± 1.5 (0–10)
CCI categories, n (%)			
Low (0)	4,710 (19.1)	1,907 (17.6)*	2,803 (20.3)
Medium (1–2)	12,982 (52.6)	5,226 (48.2)	7,756 (56.1)
High (3–4)	5,331 (21.6)	2,772 (25.1)	2,609 (18.9)
Very high (≥ 5)	1,668 (6.8)	998 (9.2)	670 (4.8)
Smoking (yes), n (%)	1,891 (7.7)	1,586 (14.6)*	305 (2.2)
Use of alcohol (yes), n (%)	9,444 (38.2)	6,447 (59.4)*	2,997 (21.7)

Osteoporosis, n (%)	3,969 (16.1)	374 (3.4)*	3,595 (26.0)
Follow-up duration (year)	6.9 ± 1.6 (0.1–8.0)	6.6 ± 1.8 (0.1–8.0)*	7.0 ± 1.4 (0.1–8.0)

Continuous values are expressed as mean ± standard deviation (range).

BMI: body mass index, CCI: Charlson comorbidity index.

* Significantly different between males and females ($P < .05$).

Table 2.

Comparison of participants' demographics between BMI categories.

Parameters	BMI categories		
	Underweight	**Normal weight**	**Overweight and Obese**
	n = 2,684	n = 17,667	n = 4,340
Age at examination (years old)	80.8 ± 4.8 (75–103)[a, b]	79.4 ± 4.2 (75–103)[c]	78.9 ± 4.0 (75–99)
Age categories, n (%)	1,291 (48.1)/ 828 (30.8)/	10,775 (60.9)/ 4,691 (26.6)/	2,866 (66.1)/ 1,035 (23.8)/ 439
75–79/ 80–84/ 85≤	565 (21.1)[a, b]	2,201 (12.5)[c]	(10.1)
Sex; males/females, n (%)	910 (33.9)/ 1,774 (66.1)[a, b]	7,980 (45.2)/ 9,687 (54.8)	1,963 (45.2)/ 2,377 (54.8)
BMI (kg/m^2)	17.2 ± 1.0 (11.6–18.4)[a, b]	21.8 ± 1.7 (18.5–24.9)[c]	26.9 ± 1.9 (25–54.2)
CCI	1.6 ± 1.6 (0–10)[b]	1.7 ± 1.7 (0–11)[c]	1.9 ± 1.8 (0–10)
CCI categories, n (%)			
Low (=0)/ Medium (=1–2)/	481 (17.9)/ 1,426 (53.1)/	3,425 (19.4)/ 9.349 (52.9)/ 3,759	804 (18.5)/ 2,207 (50.9)/
High (=3–4)/ Very high (≥ 5)	574 (21.4)/ 203 (7.6)[b]	(21.3)/ 1,134 (6.4)[c]	998 (23.0)/ 331 (7.6)
Smoking (yes), n (%)	266 (9.9)[a, b]	1,346 (7.6)[c]	279 (6.4)
Use of alcohol (yes), n (%)	786 (29.3)[a, b]	6,939 (39.3)	1,719 (39.6)
Osteoporosis, n (%)	537 (20)[a, b]	2,806 (15.9)	626 (14.4)
Follow-up duration (year)	6.4 ± 2.0 (0.1–8.0)[a, b]	6.9 ± 1.5 (0.1–8.0)[c]	7.1 ± 1.3 (0.1–8.0)

Continuous values are expressed as mean ± standard deviation (range). BMI: body mass index, CCI: Charlson comorbidity index

a; $P < .05$ for significantly different between underweight and normal weight.

b; $P < .05$ for significantly different between underweight and overweight and obese.

c; $P < .05$ for significantly different between normal weight and over.

Table 3.

Cox proportional hazards analysis of the risk factors for vertebral fracture. Age, BMI, use of alcohol , smoking, CCI, and osteoporosis were used as covariates.

Factor		Univariate HR (95% CI)		Adjusted HR (95% CI)	
		Males	**Females**	**Males**	**Females**
Age categories < 75 = reference	75–79	1.55 (1.35–1.78)*	1.25 (1.15–1.36)*	1.45 (1.26–1.66)*	1.20 (1.10–1.30)*
	85<	2.37 (2.02–2.78)*	1.34 (1.21–1.47)*	2.13 (1.81–2.51)*	1.24 (1.12–1.37)*
BMI categories normal weight = reference	Underweight	1.51 (1.26–1.82)*	1.11 (1.00–1.23)*	1.33 (1.10–1.61)*	1.07 (0.96–1.19)
	Overweight and obese	0.87 (0.73–1.02)	0.95 (0.86–1.04)	0.91 (0.77–1.08)	0.95 (0.86–1.05)
Use of alcohol No = reference	Yes	0.96 (0.85–1.09)	0.93 (0.85–1.02)	1.06 (0.94–1.19)	0.97 (0.89–1.06)
Smoking No = reference	Yes	0.92 (0.77–1.10)	1.13 (0.90–1.42)	0.93 (0.78–1.11)	1.17 (0.93–1.46)
CCI categories (low = reference)	Medium	1.83 (1.48–2.26)*	1.48 (1.34–1.65)*	1.74 (1.40–2.15)*	1.42 (1.28–1.57)*
	High	2.33 (1.87–2.91)*	1.82 (1.62–2.05)*	2.10 (1.68–2.62)*	1.67 (1.48–1.89)*
	Very high	2.83 (2.19–3.64)*	2.04 (1.72–2.42)*	2.52 (1.95–3.25)*	1.81 (1.52–2.14)*
Osteoporosis No = reference	Yes	2.24 (1.77–2.83)*	1.49 (1.38–1.61)*	1.83 (1.44–2.32)*	1.39 (1.29–1.50)*

HR: hazard ratio, CI: confidence interval, BMI: body mass index, CCI: Charlson comorbidity index

* Statistically significant difference compared to reference ($P < .05$).

Table 4.

Cox proportional hazards analysis of the risk factors for hip fracture. Age, BMI, use of alcohol , smoking, CCI, and osteoporosis were used as covariates.

Factor		Univariate HR (95% CI)		Adjusted HR (95% CI)	
		Males	**Females**	**Males**	**Females**
Age categories < 75 = reference	75–79	2.16 (1.67–2.79)*	2.26 (1.98–2.59)*	1.93 (1.49–2.50)*	2.14 (1.87–2.45)*
	85<	3.89 (2.94–5.16)*	4.03 (3.51–4.63)*	3.21 (2.41–4.29)*	3.66 (3.18–4.21)*
BMI categories normal weight = reference	Underweight	2.24 (1.66–3.00)*	1.57 (1.36–1.82)*	1.74 (1.29–2.35)*	1.36 (1.17–1.57)*
	Overweight and obese	0.74 (0.53–1.03)	0.88 (0.75–1.03)	0.81 (0.58–1.14)	0.89 (0.75–1.04)
Use of alcohol No = reference	Yes	0.68 (0.55–0.85)*	0.80 (0.69–0.93)*	0.79 (0.55–0.97)*	0.92 (0.80–1.06)
Smoking No = reference	Yes	1.38 (1.04–1.83)*	1.07 (0.74–1.55)	1.37 (1.03–1.82)*	1.13 (0.78–1.63)
CCI categories (low = reference)	Medium	2.40 (1.53–3.75)*	1.95 (1.62–2.34)*	2.20 (1.41–3.45)*	1.79 (1.49–2.16)*
	High	3.36 (2.12–5.33)*	2.39(1.95–2.93)*	2.87 (1.81–4.55)*	2.01 (1.64–2.48)*
	Very high	3.78 (2.26–6.32)*	3.38 (2.61–4.38)*	3.28 (1.96–5.49)*	2.73 (2.10–3.54)*
Osteoporosis No = reference	Yes	1.63 (1.00–2.66)*	1.29 (1.15–1.46)*	1.20 (0.73–1.97)	1.10 (0.98–1.25)*

HR: hazard ratio, CI: confidence interval, BMI: body mass index, CCI: Charlson comorbidity index

* Statistically significant difference compared to reference ($P < .05$).

Figure Legends

Image 1: Figure. 1

The Kaplan-Meier curve shows the incidence of a) vertebral fractures and b) hip fracture compared by BMI category. The solid line represents underweight, the dashed line represents normal weight, and the dotted line represents overweight and obese.

BMI: body mass index

Image 2: Figure. 2

The Kaplan-Meier curve shows the incidence of vertebral fractures in a) males and b) females compared by BMI category. The solid line represents underweight, the dashed line represents normal weight, and the dotted line represents overweight and obese.

BMI: body mass index

Image 3: Figure. 3

The Kaplan-Meier curve shows the incidence of hip fracture in a) males and b) females compared by BMI category. The solid line represents underweight, the dashed line represents normal weight, and the dotted line represents overweight and obese.

BMI: body mass index

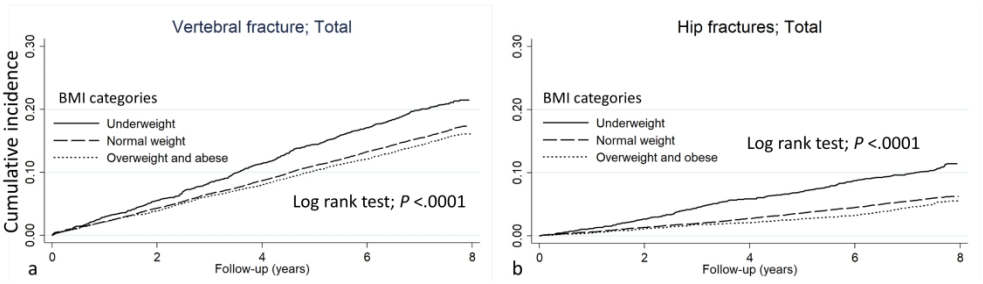

Image 1: Figure. 1

The Kaplan-Meier curve shows the incidence of a) vertebral fractures and b) hip fracture compared by BMI category. The solid line represents underweight, the dashed line represents normal weight, and the dotted line represents overweight and obese.

BMI: body mass index

299x86mm (300 x 300 DPI)

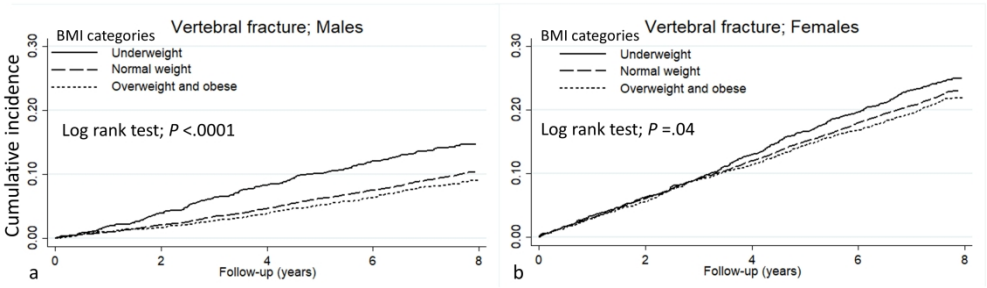

Image 2: Figure. 2
The Kaplan-Meier curve shows the incidence of vertebral fractures in a) males and b) females compared by BMI category. The solid line represents underweight, the dashed line represents normal weight, and the dotted line represents overweight and obese.
BMI: body mass index

299x86mm (300 x 300 DPI)

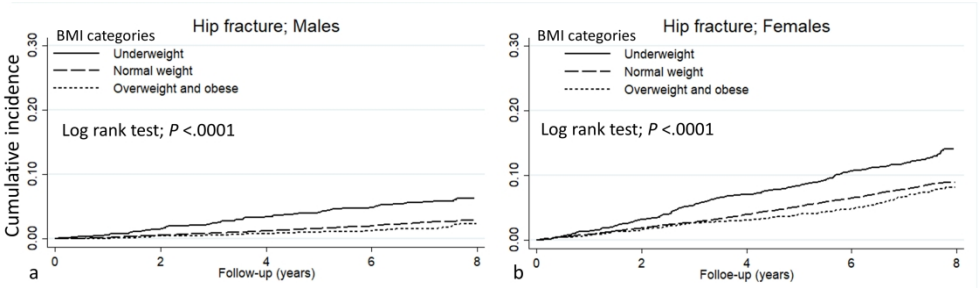

Image 3: Figure. 3
The Kaplan-Meier curve shows the incidence of hip fracture in a) males and b) females compared by BMI category. The solid line represents underweight, the dashed line represents normal weight, and the dotted line represents overweight and obese.
BMI: body mass index

299x86mm (300 x 300 DPI)

Appendix 1. Prevalence of the comorbidities used to calculate the CCI

	Total n = 24,691, n (%)	Males n = 10,853, n (%)	Females n = 13,838, n (%)
Acute myocardial infraction	130 (0.5)	91 (0.8)*	39 (0.3)
Congestive heart failure	972 (3.9)	448 (4.1)	524 (3.8)
Peripheral vascular disease	3,365 (13.6)	1,593 (14.7)*	1,772 (12.8)
Cerebral vascular disease	10,922 (44.2)	4,679 (43.1)*	6,243 (45.1)
Dementia	633 (2.6)	224 (2.1)*	409 (3.0)
Pulmonary disease	2,735 (11.1)	1,343 (12.4)*	1,392 (10.1)
Connective tissue disorder	1,672 (6.7)	711 (6.6)	961 (6.9)
Peptic ulcer	1,979 (8.0)	928 (8.6)*	1,051 (7.6)
Mild liver disease	1,725 (7.0)	912 (8.4)*	813 (5.9)
Diabetes without complications	1,273 (5.2)	724 (6.7)*	549 (4.0)
Diabetes with complications	1,013 (4.1)	583 (5.4)*	430 (3.1)
Paraplegia	715 (2.9)	376 (3.5)*	339 (2.5)
Renal disease	3,564 (14.4)	1,794 (16.5)*	1,770 (12.8)
Cancer	2,832 (11.5)	1,876 (17.1)*	972 (7.0)
Metastatic cancer	100 (0.4)	68 (0.6)*	32 (0.2)
Sever liver disease	13 (0.1)	8 (0.07)	5 (0.04)
HIV	0 (0)	0 (0)	0 (0)

CCI: Charlson comorbidity index, HIV: human immunodeficiency virus

* Significantly different between males and females ($P < .05$).

Appendix. 2 Alive vs. death among participants

Parameters	Alive n = 19,282	Death n = 5,409
Age at examination (years old)	78.7 ± 3.6 (75–99)*	82.1 ± 5.3 (75–103)
Age categories, n (%)		
75–79	12,898 (66.9)*	2,034 (37.6)
80–84	4,820 (25.0)*	1,734 (32.1)
85≤	1,564 (8.1)*	1,641 (30.3)
Sex; male/female, n (%)	7,795 (40.4) / 11,487 (59.6)*	3,058 (56.5) / 2,351 (43.5)
BMI (kg/m^2)	22.4 ± 3.0 (11.6–54.2)*	21.5 ± 3.2 (12.5–39.6)
BMI categories		
Underweight (BMI < 18.5)	1,761 (9.1)*	923 (17.1)
Normal weight (18.5 ≤ BMI < 25)	13,896 (72.1)	3,771 (69/7)
Overweight and Obese (25 ≤ BMI)	3,625 (18.8)	715 (13.2)
CCI	1.5 ± 1.6 (0–11)	2.3 ± 1.9 (0–10)
CCI categories, n (%)		
Low	4,134 (21.4)*	576 (10.7)
Medium	10,530 (54.6)	2,452 (45.3)
High	3,627 (18.8)	1,704 (31.5)
Very high	991 (5.1)	677 (12.5)
Smoking, n (%)	1,279 (6.6)*	612 (11.3)
Use of alcohol, n (%)	7,442 (38.6)*	2,002 (37.0)
Osteoporosis, n (%)	3,126 (16.2)	843 (15.6)
Follow-up duration (year)	7.5 ± 0.3 (0.1–8.0)*	4.5 ± 2.0 (0.1–7.9)

Continuous values are expressed as mean ± standard deviation (range). BMI: body mass index, CCI: Charlson comorbidity index

* Significantly different between alive and death (P < .05).

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-4
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3, 4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6, 7
Objectives	3	State specific objectives, including any prespecified hypotheses	6, 7
Methods			
Study design	4	Present key elements of study design early in the paper	7, 8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7, 8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	8, 9
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9, 10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	9, 10
Bias	9	Describe any efforts to address potential sources of bias	9, 10
Study size	10	Explain how the study size was arrived at	10
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9, 10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10
		(*b*) Describe any methods used to examine subgroups and interactions	9, 10
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	11
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11 Table 1
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	11 Table 1
Outcome data	15*	Report numbers of outcome events or summary measures over time	12, Fig1, 2, 3
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	12 Table 3, 4
		(*b*) Report category boundaries when continuous variables were categorized	9 Table 2
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Table 3, 4
Discussion			
Key results	18	Summarise key results with reference to study objectives	14, 15
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13,14
Generalisability	21	Discuss the generalisability (external validity) of the study results	19-21
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	22

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.