

BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email info.bmjopen@bmj.com

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-049157
Article Type:	Original research
Date Submitted by the Author:	20-Jan-2021
Complete List of Authors:	Shimoto, Kyohei; Kyushu University, Artificial Joints and Biomaterials, Faculty of Medical Science; Kyushu University Faculty of Medicine Graduate School of Medical Science, Orthopaedic Surgery Babazono, Akira; Kyushu University Faculty of Medicine Graduate School of Medical Science, Health Care Administration and Management Harano, Yumi; Kyushu University Faculty of Medicine Graduate School of Medical Science, Health Care Administration and Management; Saga Prefecture Medical Center Koseikan Fujita, Takako; Kyushu University Faculty of Medicine Graduate School of Medical Science, Health Care Administration and Management; Kyushu University, Department of Health Sciences, Faculty of Medical Sciences Jiang, Peng; Kyushu University Faculty of Medicine Graduate School of Medical Science, Health Care Administration and Management Kim, Sung-A; Kyushu University Faculty of Medicine Graduate School of Medical Science, Health Care Administration and Management Nakashima, Yasuharu; Kyushu University Faculty of Medicine Graduate School of Medical Science, Orthopedic Surgery
Keywords:	Adult orthopaedics < ORTHOPAEDIC & TRAUMA SURGERY, EPIDEMIOLOGY, PUBLIC HEALTH

SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

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.

Authors

1. Kyohei Shiimoto, MD, PhD

(1)Department of Artificial Joints and Biomaterials, Faculty of Medical Science, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka, 812-8582, Japan

(2)Department of Orthopedic Surgery, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

E-mail address: k-shio@ortho.med.kyushu-u.ac.jp

2. Akira Babazono, MD, PhD

Department of Health Care Administration and Management, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan.

E-mail address: babazono@hcam.med.kyushu-u.ac.jp

3. Yumi Harano, MD. PhD

(1)Department of Health Care Administration and Management, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan.

(2)Department of General Internal Medicine, Saga Medical Center Koseikan, Saga, Japan.

E-mail address: usagino3toqtaro@gmail.com

4. Takako Fujita, MPH

(1)Department of Health Care Administration and Management, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan.

(2)Department of Health Sciences, Faculty of Medical Sciences, Kyushu University, Fukuoka, Japan.

E-mail address: takacooking@gmail.com

5. Peng Jiang, PhD

Department of Health Care Administration and Management, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan.

E-mail address: jiang21peng@163.com

6. Sung-a Kim, MPH

Department of Health Care Administration and Management, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan.

E-mail address: kj61444@naver.com

1
2
3
4
5
6 7. Yasuharu Nakashima, MD, PhD

7 Department of Orthopedic Surgery, Graduate School of Medical Sciences, Kyushu
8 University, Fukuoka, Japan

9 E-mail address: yasunaka@med.kyushu-u.ac.jp
10
11
12
13
14

15 Please address all correspondence to:

16 Kyohei Shiimoto, M.D., Ph.D.

17 Department of Orthopedic Surgery, Kyushu University

18 3-1-1 Maidashi, Higashi-ku, Fukuoka, Japan 812-8582

19 TEL: +81-92-642-5487 FAX: +81-92-642-5507

20 E-mail: k-shio@ortho.med.kyushu-u.ac.jp
21
22
23
24

25 Words counts: Main text 3,464 words, 5 tables and 2 figures; Abstract 286 words
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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/m², normal: 18.5–24.9 kg/m², high: > 25.0 kg/m²) 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

1
2
3
4
5
6 higher in low BMI regardless of sex ($P < .05$). Multivariate Cox proportional hazards models
7
8
9 showed that low BMI was a significant risk factor only in men for vertebral fractures and in both
10
11
12 men and women for hip fractures ($P < .05$).
13
14

15 **Conclusion:** Low BMI was associated with fractures in the elderly population, but there was a
16
17
18 sex difference in the effect for vertebral fractures.
19
20

21 **Trial registration:** This study was approved by the Kyushu University Institutional Review
22
23
24 Board for Clinical Research (Approval No. 20209).
25
26
27
28
29

30 **Keywords:** body mass index (BMI), sex differences, fracture, claim data, elderly people
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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 populations¹⁻³. 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 society⁹. Particularly in Japan, where the elderly population is growing rapidly, the economic burden of these fractures is immense and is an important public health issue¹⁰. 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 fractures¹³⁻¹⁵. From a public health perspective, high BMI, such as obesity, is associated with increased morbidity of diabetes, cardiovascular disease¹⁶, and is generally associated with increased mortality. However, a paradox has also been reported, such as a higher mortality rate in the elderly

1
2
3
4
5
6 with a lower BMI¹⁷⁻¹⁹. In recent years, such a paradox has been reported in fractures as well. Low
7
8
9 BMI is a recognized risk factor for vertebral and hip fracture, and in recent years, high BMI has
10
11
12 been reported to reduce the risk of hip fracture²⁰. Johansson et al.¹⁴ reported that the association
13
14
15 between BMI and fracture risk is complex and differs across skeletal sites; thus, the relationship
16
17
18 between BMI and fracture risk is still controversial. Gender and race may also influence the
19
20
21 relationship between BMI and fractures. Some have reported that the impact of BMI on fractures
22
23
24 varies by gender. It is not yet well known whether the impact of BMI on fractures varies by gender,
25
26
27 especially in Japanese.
28

29
30 In this study, using the healthcare claims database of Fukuoka Prefecture, the following
31
32
33 questions were addressed: (1) What is the incidence of vertebral and hip fractures among the
34
35
36 Japanese elderly? (2) Is there a relationship between BMI and fracture risk and is there a
37
38
39 difference between men and women?
40

41 42 43 44 45 **Materials and Methods**

46 47 48 *Study design and Data source*

49
50
51 This was a retrospective cohort study approved by our institutional review board. We
52
53
54 used data from the healthcare claims database and master database of the Fukuoka Prefecture
55
56
57 Wide-Area Association of Latter-stage Elderly Healthcare between 1 April 2010 and 31 March
58
59
60

1
2
3
4
5
6 2018. This public health insurance is open to people over the age of 75 years and those aged 65-
7
8
9 74 years with disabilities, and the majority of people over the age of 75 years have this insurance.
10
11
12 The majority of the insured have long-term eligibility once they were enrolled; therefore, few
13
14
15 subjects are lost to follow-up. The databases included data for the International Classification of
16
17
18 Diseases 10th Revision (ICD-10) codes; date of diagnosis, medical procedures, such as surgery;
19
20
21 date of admission; and death. The majority of the databases are computer-administered.
22
23
24 According to a report by the Japanese Ministry of Health, Labour and Welfare, the penetration
25
26
27 rate of computer-administered claims databases was 98.6% as of April 2015 ²¹. Elderly people
28
29
30 over the age of 75 years who have this health insurance are eligible for medical examination. We
31
32
33 also used data from the 2010 health examination, which included subjects' height, weight, BMI,
34
35
36 smoking and alcohol drinking.
37

38 39 *Subjects*

40
41
42 Our target population was people with Fukuoka Prefecture Wide-Area Association of
43
44
45 Latter-stage Elderly Healthcare insurance who met the following criteria: (1) People who
46
47
48 underwent the 2010 health examination; (2) age \geq 75 years at the health examination; (3) data
49
50
51 related to smoking and alcohol consumption at the time of health examination are available; and
52
53
54 (4) no history of vertebral and hip fracture before the health examination. The history of these
55
56
57 fractures were investigated using the medical interview at the health examination and using
58
59
60

1
2
3
4
5
6 healthcare claims database.

7
8
9 *Outcomes (vertebral and hip fracture incidence)*

10
11
12 We identified patients with vertebral (ICD-10 code = S22.0-1, S32) and hip (ICD-10 code
13 = S72.0-2) fracture diagnosed between the date of the medical examination and 31 March 2018
14
15 in the medical database and investigated the cumulative fracture incidence. We also investigated
16
17 the time to each primary fracture.
18
19
20
21
22

23
24 *Comparison by BMI category*

25
26
27 Subjects were divided into three groups according to BMI category as follows: low (<
28 18.5 kg/m²), normal (18.5–24.9 kg/m²), and high (> 25.0 kg/m²). Subjects' demographics and the
29
30 incidence of vertebral and hip fractures were compared between the BMI categories.
31
32
33
34

35
36 *Risk factors for vertebral and hip fractures*

37
38
39 We examined age, BMI, alcohol drinking, smoking, comorbidities and osteoporosis as
40
41 risk factors for each fracture by gender. Age was categorized into three groups: 75–79 years, 80–
42
43 84 years, and ≥ 85 years. Smoking and drinking were defined as those who reported habitual
44
45 consumption in the health questionnaire. The Charlson Comorbidity Index (CCI) was used as an
46
47 indicator of patient's comorbidities²². CCI was calculated at the health examination using the
48
49 ICD-10 codes²³ and was divided into four groups: low (0), medium (1–2), high (3–4), and very
50
51 high (≥ 5). Osteoporosis was identified using the ICD-10 codes (M80, M81, M82).
52
53
54
55
56
57
58
59
60

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 \pm 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

1
2
3
4
5
6 data on their drinking and smoking, and 514 people with a history of fracture, and included 24,691
7
8
9 people in this study. Subjects' demographic data are shown in **Table 1**. The mean observation
10
11
12 period was 6.9 years, and 5,409 people died during the observation period. There was a
13
14
15 significantly higher proportion of older age and low BMI groups in women compared to men (P
16
17
18 $< .0001$). Men had significantly higher CCI, smoking, and drinking rates than women ($P < .0001$).
19
20
21 The prevalence of osteoporosis was significantly higher in women ($P < .0001$). **Table 2** shows
22
23
24 the prevalence of the comorbidities used to calculate the CCIs.
25
26

27 *Vertebral and hip fracture rate*

28
29
30 Vertebral and hip fractures occurred in 4,153 (16.8%) and 1,543 (6.5%) of the subjects,
31
32
33 respectively, during the study period. Vertebral fractures occurred in 1,082 (10%) men and 3,071
34
35
36 (22.2%) women, hip fractures occurred in 314 (2.9%) men and 1,229 (8.9%) women, and the
37
38
39 incidence of both fractures was significantly higher in women ($P < .0001$). The incidence of
40
41
42 vertebral fracture was 1500.4 in men and 3159.2 in women per 100,000 person-years, respectively.
43
44
45 The incidence of hip fracture was 435.4 in men and 1264.3 in women per 100,000 person-years,
46
47
48 respectively.
49

50 *Comparison by BMI category*

51
52
53 A comparison of subjects' demographics by BMI category is shown in **Table 3**. Low
54
55
56 BMI was present in a significantly higher proportion of people aged ≥ 85 years, women, and
57
58
59
60

1
2
3
4
5
6 smoking, than in the other two BMI groups ($P < .0001$). There was a significantly lower rate of
7
8
9 alcohol drinking with low BMI ($P < .0001$). High BMI was associated with a significantly higher
10
11
12 CCI than the other two BMI groups ($P < .01$).
13
14

15
16 The cumulative incidence of vertebral fracture in each BMI groups (low/normal/high) at
17
18 the final follow-up estimated using the Kaplan–Meier curve was 14.7% / 10.4% / 9.0% in men
19
20 and 24.9% / 23.0% / 21.9% in women, respectively, and was significantly higher with low BMI
21
22 in both sexes (all $P < .05$) (**Fig.1**). Similarly, the cumulative incidence of hip fracture was 6.3% /
23
24 2.9% / 2.4% in men and 14.1% / 9.0% / 8.1% in women, respectively, and was significantly higher
25
26 with low BMI in both sexes (all $P < .0001$) (**Fig.2**).
27
28
29
30
31
32

33 *Risk factors of vertebral and hip fractures*

34
35

36 In univariate analysis, older age, low BMI, higher CCI, and osteoporosis were significant
37
38 risk factors for vertebral fracture in both men and women (**Table 4**). Multivariate analysis showed
39
40 that older age, higher CCI, and osteoporosis were risk factors for vertebral fracture in both men
41
42 and women, but low BMI was a significant risk factor only in men (**Table 4**).
43
44
45
46
47

48 In univariate analysis, older age, higher CCI, and osteoporosis were significant risk
49
50 factors for hip fracture in both men and women, and smoking was also a significant risk factor in
51
52 men (**Table 5**). Multivariate analysis showed that older age and higher CCI were significant risk
53
54 factors for hip fracture in both men and women, smoking was a significant risk factor only in
55
56
57
58
59
60

1
2
3
4
5
6 men, and osteoporosis was a significant risk factor only in women (**Table 5**). Alcohol drinking
7
8
9 had a significant protective effect on hip fractures in men.
10
11
12
13
14

15 **Discussion**

16
17
18 In this study, we evaluated cumulative incidence of vertebral and hip fractures in the
19
20 elderly during an average of 6.9 years using healthcare claims database in Fukuoka Prefecture.
21
22 Elderly people with Fukuoka Prefecture Wide-Area Association of Latter-stage Elderly
23
24 Healthcare insurance rarely drop out of the program, and the health insurance covers most elderly
25
26 people aged ≥ 75 years who live in this area. Therefore, the strength of this study is that there
27
28 were almost no dropouts other than because of death, and that we were able to investigate the
29
30 occurrence of fractures regardless of the medical institution where the diagnosis was made.
31
32 Previous studies reported that the incidence of vertebral fracture at age ≥ 60 years was 13–18%
33
34 ²⁴⁻²⁶. Tamaki et al. found in a 3-year retrospective cohort study that the incidence of hip fracture
35
36 in people aged 80–84 years was 366 and 880 per 10,000, for men and women, respectively ²⁷.
37
38 We found that the incidence of vertebral and hip fracture was 17% (1500 and 3164 per 100,000,
39
40 for men and women) and 7% (435 and 1264 per 100,000, for men and women), respectively, in
41
42 our study. The incidence rates in the present study were equivalent to those in previous cohort
43
44 studies and did not appear to be unevenly distributed by region ²⁴⁻²⁷.
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7 Our study using this large cohort data demonstrated that the vertebral and hip fracture
8
9 incidence was higher in the low BMI group (BMI < 18.5 kg/m²) by the Kaplan-Meier curve. As
10
11 many previous studies reported, low BMI has long been considered an important risk factor for
12
13 fractures. Generally, lower BMI is associated with lower BMD, and Lloyd et al. reported that
14
15 every unit increase in BMI was associated with an increase of 0.0082 g/cm in BMD²⁸. Although
16
17 low BMI is generally considered a risk factor for fragility fractures, several reports have shown
18
19 that the relationship between BMI and fracture risk may differ by gender and skeletal site, and
20
21 that the relationship is complex^{13, 14}. In this study, we investigated the effect of BMI on fractures,
22
23 stratified by gender. We found that low BMI was a risk factor for hip fractures regardless of
24
25 gender, and for vertebral fractures, low BMI was a risk factor only in men. Kaze et al.¹⁵ reported
26
27 in their meta-analysis that the inverse association between BMI and risk for vertebral fracture in
28
29 men but not in women. Several previous studies have shown that low BMI is consistently
30
31 associated with the risk of hip fracture, regardless of gender^{14, 29}. Johansson et al.¹⁴ found that
32
33 the relationship between BMI and osteoporotic fractures depended on the site of the fracture,
34
35 although their study was only on women. In this study, we similarly suggested that the effect of
36
37 BMI varies by fracture site in women. Several reports have been said that abdominal fat may
38
39 affect bone independently of total body fat, and that there are sex differences in fat distribution,
40
41 which may be a possible reason for the sex differences in the effect of BMI on fracture^{30, 31}.
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6 However, the reasons for the site-specific gender effects, as shown in this study, are not yet well
7
8
9 understood. Another possible explanation could be that BMI as a measure of adiposity has been
10
11
12 shown to be less valid in the elderly due to age-related changes in body composition ³². However,
13
14
15 in this study, only the elderly were included, not the middle-aged or other groups of both men and
16
17
18 women, and this effect is considered to be small.
19

20
21 Not only is low BMI considered a risk factor for fracture, but the preventive effect of high
22
23
24 BMI on fracture has recently been discussed. some reports suggest that obesity has a protective
25
26
27 effect on fractures because of higher BMD and reduced impact of falls as a result of increased
28
29
30 soft-tissue padding ^{33, 34}. However, it has not been proven that obesity is protective against all
31
32
33 fractures, and the relationship between obesity and fracture has been reported to be fracture site-
34
35
36 specific ^{35, 36}. Although there were some reports of sex differences in the preventive effect of BMI
37
38
39 on fractures ^{29, 37}, the results were mixed and the preventive effect of BMI on fractures is still
40
41
42 unclear. We found that obesity had no protective effect on vertebral and hip fractures, regardless
43
44
45 of gender, even after adjusting for confounding factors such as age and comorbidity. Therefore,
46
47
48 the effect of obesity on fracture prevention may be poor in the elderly Asian population.
49

50
51 Further research is still needed to determine whether high BMI has a protective effect on
52
53
54 fractures in the elderly population. However, even if some fracture sites are affected by sex
55
56
57 differences, low BMI in the elderly is state of easy fracture, and may greatly impact QOL in the
58
59
60

1
2
3
4
5
6 future. BMI can be easily measured at the health examination, and screening for fracture risk by
7
8
9 BMI is very useful in terms of health care costs for the healthy life span of the elderly. Prolonged
10
11
12 healthy life expectancy of the elderly is expected with the additional assessment of exercise
13
14
15 function, further assessment of fracture risk by measuring BMD, and fracture prevention in the
16
17
18 elderly with low BMI at the health examination.
19

20
21 Using the Cox proportional hazards model, we found the other factors besides BMI that
22
23
24 influence vertebral and hip fractures. First, for both fractures, older age and higher CCI increased
25
26
27 the risk of fracture. Although it is a well-known finding that the incidence of fragility fractures
28
29
30 increases with age, the effect of aging was more prevalent in hip fractures. This may be related to
31
32
33 the decline in physical function and increased risk of falling with age. Comorbidities such as
34
35
36 chronic kidney disease, diabetes, and dementia are associated with increased risk of fragility
37
38
39 fractures, and it is useful to evaluate the presence of comorbidities and investigate their
40
41
42 contribution to the risk of fractures³⁸⁻⁴⁰. CCI was originally used to assess the risk of
43
44
45 comorbidities for death, but patients at high risk of death with a high CCI may also be at higher
46
47
48 risk of fragility fractures. The present study stratified CCI and assessed the risk of fracture and
49
50
51 showed that a higher CCI was associated with a higher fracture risk. Therefore, CCI may be useful
52
53
54 in assessing fracture risk as well as mortality risk in the elderly.
55
56

57 Secondly, health-related behaviors such as smoking and alcohol drinking are also well-
58
59
60

1
2
3
4
5
6 established risk factors for fragility fractures^{41, 42}, in this study, smoking was a risk factor in hip
7
8
9 fractures in men. Iconaru et al. reported that smoking was a significant risk factor for only hip
10
11
12 fractures among fragility fractures⁴³, and the effect of smoking on fracture may also be site-
13
14
15 specific. The lack of effect of smoking in women may be related to the extremely low smoking
16
17
18 rate (15% in men and 2% in women) in older women. The results of the present study showed
19
20
21 that drinking had a protective effect on hip fractures in men. Several reports state that light to
22
23
24 moderate alcohol consumption decrease age-related bone loss, and that heavy alcohol
25
26
27 consumption is associated with elevated hip fracture risk, while light alcohol consumption is
28
29
30 inversely related to fracture risk^{42, 44}. We did not assessed the amount of alcohol consumed in this
31
32
33 study and cannot discuss the effect of alcohol consumption on fracture risk.

34
35
36 Finally, the coexistence of osteoporosis is an important factor in osteoporotic fractures,
37
38
39 and the results of this study showed that osteoporosis affected vertebral fractures in both men and
40
41
42 women, but only hip fractures in women. One reason for this may be the difference in the
43
44
45 pathogenesis of osteoporosis, in which women, unlike men, experience two phases of bone loss:
46
47
48 menopausal bone loss and age-related bone loss. Another possible explanation is that the
49
50
51 prevalence of osteoporosis at the time of physical examination was quite low in the men in this
52
53
54 study.

55
56
57 This study has several limitations. First, we used a retrospective design and data from a
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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 age²⁷, 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

1
2
3
4
5
6 In this large retrospective cohort study during a mean observation period of about 7 years
7
8
9 in patients aged ≥ 75 years, vertebral and hip fractures occurred in 17% and 7%, respectively. The
10
11
12 incidence of both fractures was higher in the low BMI population. After adjustment for possible
13
14
15 confounders, low BMI was a risk factor for vertebral fracture only in men, and there were sex
16
17
18 differences in the effect of BMI. Low BMI was a risk factor for hip fracture in both men and
19
20
21 women, and low BMI is likely to remain important in the elderly population. Evaluating elderly
22
23
24 with low BMI at health examinations and providing therapeutic interventions may help prevent
25
26
27 subsequent fractures and improve healthy life expectancy.
28

30 **Acknowledgment**

31
32
33 The authors would like to thank Fukuoka Prefecture Wide-Area Association of Latter-Stage
34
35
36 Elderly Healthcare for providing health claims database and master data.
37

39 **Author Contribution**

40
41
42 KS led the study design, extracted and analyzed the data, conducted the literature, and wrote the
43
44
45 manuscript. AB and YN contributed to the study design, analysis and manuscript revision. TH,
46
47
48 TF, PJ and SK contributed to data analysis and manuscript review. All authors read and approved
49
50
51 the final version of the manuscript.
52

54 **Funding**

55
56
57 No funding was received for this study.
58
59
60

Conflicts of interest

Kyohei Shiimoto. 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.

Open access

References

1. Cummings SR, Kelsey JL, Nevitt MC, et al. Epidemiology of osteoporosis and osteoporotic fractures. *Epidemiol Rev* 1985;7:178-208. doi: 10.1093/oxfordjournals.epirev.a036281
2. Gullberg B, Johnell O, Kanis JA. World-wide projections for hip fracture. *Osteoporos Int* 1997;7(5):407-13. doi: 10.1007/pl00004148
3. Schousboe JT. Epidemiology of Vertebral Fractures. *J Clin Densitom* 2016;19(1):8-22. doi: 10.1016/j.jocd.2015.08.004
4. Alexiou KI, Roushias A, Varitimidis SE, et al. Quality of life and psychological consequences in elderly patients after a hip fracture: a review. *Clin Interv Aging* 2018;13:143-50. doi: 10.2147/CIA.S150067
5. Ciubean AD, Ungur RA, Irsay L, et al. Health-related quality of life in Romanian postmenopausal women with osteoporosis and fragility fractures. *Clin Interv Aging* 2018;13:2465-72. doi: 10.2147/CIA.S190440
6. Svedbom A, Borgstrom F, Hernlund E, et al. Quality of life for up to 18 months after low-energy hip, vertebral, and distal forearm fractures-results from the ICUROS. *Osteoporos Int* 2018;29(3):557-66. doi: 10.1007/s00198-017-4317-4
7. Farahmand BY, Michaelsson K, Ahlbom A, et al. Survival after hip fracture. *Osteoporos Int* 2005;16(12):1583-90. doi: 10.1007/s00198-005-2024-z

- 1
2
3
4
5
6
7 8. Lau E, Ong K, Kurtz S, et al. Mortality following the diagnosis of a vertebral compression
8
9 fracture in the Medicare population. *J Bone Joint Surg Am* 2008;90(7):1479-86. doi:
10 10.2106/JBJS.G.00675
11
12
13
14
15 9. Borgstrom F, Karlsson L, Ortsater G, et al. Fragility fractures in Europe: burden, management
16 and opportunities. *Arch Osteoporos* 2020;15(1):59. doi: 10.1007/s11657-020-0706-y
17
18
19
20
21 10. Taguchi Y, Inoue Y, Kido T, et al. Treatment costs and cost drivers among osteoporotic
22 fracture patients in Japan: a retrospective database analysis. *Arch Osteoporos* 2018;13(1):45.
23
24
25
26
27
28
29
30
31 11. Kanis JA, Johnell O, Oden A, et al. Long-term risk of osteoporotic fracture in Malmo.
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
- 10.1007/s11657-018-0456-2
- Osteoporos Int 2000;11(8):669-74. doi: 10.1007/s001980070064
- 2013;68(10):1236-42. doi: 10.1093/gerona/glt092
- Osteoporos Int 2005;16(11):1330-8. doi: 10.1007/s00198-005-1863-y
- J Gerontol A Biol Sci Med Sci
- J Bone Miner Res 2014;29(1):223-33. doi: 10.1002/jbmr.2017
- Osteoporos Int 2018;29(1):31-39. doi: 10.1007/s00198-017-

1
2
3
4
5
6 4294-7
7
8

- 9 16. Bastien M, Poirier P, Lemieux I, et al. Overview of epidemiology and contribution of obesity
10 to cardiovascular disease. *Prog Cardiovasc Dis* 2014;56(4):369-81. doi:
11
12 10.1016/j.pcad.2013.10.016
13
14
15
16
17 17. Hainer V, Aldhoon-Hainerova I. Obesity paradox does exist. *Diabetes Care* 2013;36 Suppl
18 2:S276-81. doi: 10.2337/dcS13-2023
19
20
21
22
23 18. Lee SH, Kim DH, Park JH, et al. Association between body mass index and mortality in the
24 Korean elderly: A nationwide cohort study. *PLoS One* 2018;13(11):e0207508. doi:
25
26 10.1371/journal.pone.0207508
27
28
29
30
31 19. Modig K, Erdefelt A, Mellner C, et al. "Obesity Paradox" Holds True for Patients with Hip
32 Fracture: A Registry-Based Cohort Study. *J Bone Joint Surg Am* 2019;101(10):888-95. doi:
33
34 10.2106/JBJS.18.01249
35
36
37
38
39 20. Tang X, Liu G, Kang J, et al. Obesity and risk of hip fracture in adults: a meta-analysis of
40 prospective cohort studies. *PLoS One* 2013;8(4):e55077. doi: 10.1371/journal.pone.0055077
41
42
43
44
45
46
47
48 21. Ministry of Health Law. Japanese government report: Computer-administered claims
49 penetration rate; 2015.
50
51
52
53
54 22. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity
55 in longitudinal studies: development and validation. *J Chronic Dis* 1987;40(5):373-83. doi:
56
57
58
59
60

- 1
2
3
4
5
6 10.1016/0021-9681(87)90171-8
7
8
9
10 23. Sundararajan V, Henderson T, Perry C, et al. New ICD-10 version of the Charlson
11
12 comorbidity index predicted in-hospital mortality. *J Clin Epidemiol* 2004;57(12):1288-94.
13
14
15 doi: 10.1016/j.jclinepi.2004.03.012
16
17
18 24. Spector TD, McCloskey EV, Doyle DV, et al. Prevalence of vertebral fracture in women and
19
20 the relationship with bone density and symptoms: the Chingford Study. *J Bone Miner Res*
21
22 1993;8(7):817-22. doi: 10.1002/jbmr.5650080707
23
24
25
26
27 25. Kitazawa A, Kushida K, Yamazaki K, et al. Prevalence of vertebral fractures in a population-
28
29 based sample in Japan. *J Bone Miner Metab* 2001;19(2):115-8. doi: 10.1007/s007740170049
30
31
32
33 26. Yoshimura N, Kinoshita H, Oka H, et al. Cumulative incidence and changes in the prevalence
34
35 of vertebral fractures in a rural Japanese community: a 10-year follow-up of the Miyama
36
37 cohort. *Archives of Osteoporosis* 2006;1(1-2):43-49. doi: 10.1007/s11657-006-0007-0
38
39
40
41
42 27. Tamaki J, Fujimori K, Ikehara S, et al. Estimates of hip fracture incidence in Japan using the
43
44 National Health Insurance Claim Database in 2012-2015. *Osteoporos Int* 2019;30(5):975-
45
46 83. doi: 10.1007/s00198-019-04844-8
47
48
49
50
51 28. Lloyd JT, Alley DE, Hawkes WG, et al. Body mass index is positively associated with bone
52
53 mineral density in US older adults. *Arch Osteoporos* 2014;9:175. doi: 10.1007/s11657-014-
54
55 0175-2
56
57
58
59
60

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
29. Sogaard AJ, Holvik K, Omsland TK, et al. Age and Sex Differences in Body Mass Index as a Predictor of Hip Fracture: A NOREPOS Study. *Am J Epidemiol* 2016;184(7):510-19. doi: 10.1093/aje/kww011
30. Fini M, Salamanna F, Veronesi F, et al. Role of obesity , alcohol and smoking on bone health. *Front Biosci (Elite Ed)* 2012;4:2586-606. doi: 10.2741/e575
31. Ng AC, Melton LJ, 3rd, Atkinson EJ, et al. Relationship of adiposity to bone volumetric density and microstructure in men and women across the adult lifespan. *Bone* 2013;55(1):119-25. doi: 10.1016/j.bone.2013.02.006
32. Villareal DT, Apovian CM, Kushner RF, et al. Obesity in older adults: technical review and position statement of the American Society for Nutrition and NAASO, The Obesity Society. *Am J Clin Nutr* 2005;82(5):923-34. doi: 10.1093/ajcn/82.5.923
33. Felson DT, Zhang Y, Hannan MT, et al. Effects of weight and body mass index on bone mineral density in men and women: the Framingham study. *J Bone Miner Res* 1993;8(5):567-73. doi: 10.1002/jbmr.5650080507
34. Bouxsein ML, Szulc P, Munoz F, et al. Contribution of trochanteric soft tissues to fall force estimates, the factor of risk, and prediction of hip fracture risk. *J Bone Miner Res* 2007;22(6):825-31. doi: 10.1359/jbmr.070309
35. Premaor MO, Pilbrow L, Tonkin C, et al. Obesity and fractures in postmenopausal women. *J*

- 1
2
3
4
5
6 Bone Miner Res 2010;25(2):292-7. doi: 10.1359/jbmr.091004
7
8
9
10 36. Compston JE, Watts NB, Chapurlat R, et al. Obesity is not protective against fracture in
11
12 postmenopausal women: GLOW. Am J Med 2011;124(11):1043-50. doi:
13
14 10.1016/j.amjmed.2011.06.013
15
16
17
18 37. Kim SH, Yi SW, Yi JJ, et al. Association Between Body Mass Index and the Risk of Hip
19
20 Fracture by Sex and Age: A Prospective Cohort Study. J Bone Miner Res 2018;33(9):1603-
21
22 11. doi: 10.1002/jbmr.3464
23
24
25
26
27 38. Holmberg AH, Johnell O, Nilsson PM, et al. Risk factors for fragility fracture in middle age.
28
29 A prospective population-based study of 33,000 men and women. Osteoporos Int
30
31 2006;17(7):1065-77. doi: 10.1007/s00198-006-0137-7
32
33
34
35
36 39. Amouzougan A, Lafaie L, Marotte H, et al. High prevalence of dementia in women with
37
38 osteoporosis. Joint Bone Spine 2017;84(5):611-14. doi: 10.1016/j.jbspin.2016.08.002
39
40
41
42 40. Kazama JJ. Chronic kidney disease and fragility fracture. Clin Exp Nephrol 2017;21(Suppl
43
44 1):46-52. doi: 10.1007/s10157-016-1368-3
45
46
47
48 41. Kanis JA, Johnell O, Oden A, et al. Smoking and fracture risk: a meta-analysis. Osteoporos
49
50 Int 2005;16(2):155-62. doi: 10.1007/s00198-004-1640-3
51
52
53
54 42. Zhang X, Yu Z, Yu M, et al. Alcohol consumption and hip fracture risk. Osteoporos Int
55
56 2015;26(2):531-42. doi: 10.1007/s00198-014-2879-y
57
58
59
60

- 1
2
3
4
5
6
7 43. Iconaru L, Moreau M, Kinnard V, et al. Does the Prediction Accuracy of Osteoporotic
8
9 Fractures by BMD and Clinical Risk Factors Vary With Fracture Site? JBMR Plus
10
11
12 2019;3(12):e10238. doi: 10.1002/jbm4.10238
13
14
15 44. Gaddini GW, Turner RT, Grant KA, et al. Alcohol: A Simple Nutrient with Complex Actions
16
17
18 on Bone in the Adult Skeleton. Alcohol Clin Exp Res 2016;40(4):657-71. doi:
19
20
21 10.1111/acer.13000
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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).

For peer review only

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	High 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)/ 75-79/ 80-84/ 85≤	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 = 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 = reference	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)
	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 (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		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 ($P < .05$).

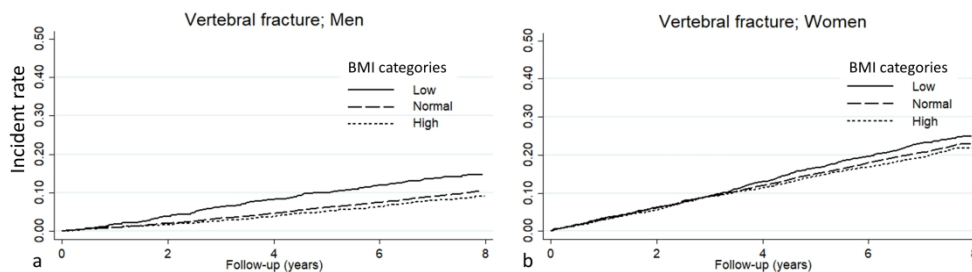
Table 5.

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 = 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 = reference	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)*
	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

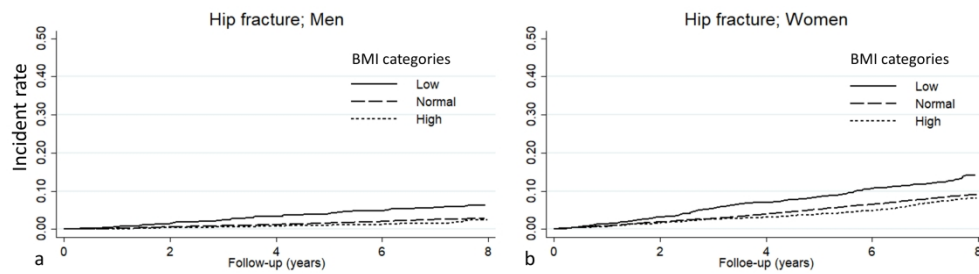
* Statistically significant ($P < .05$).



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

299x86mm (300 x 300 DPI)



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 (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	9
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	7, 8 Table 1 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 (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	11 Table 4, 5 8 Table 3
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.

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-049157.R1
Article Type:	Original research
Date Submitted by the Author:	29-Aug-2021
Complete List of Authors:	Shiomoto, Kyohei; Kyushu University, Artificial Joints and Biomaterials, Faculty of Medical Science; Kyushu University Faculty of Medicine Graduate School of Medical Science, Orthopaedic Surgery Babazono, Akira; Kyushu University Faculty of Medicine Graduate School of Medical Science, Health Care Administration and Management Harano, Yumi; Kyushu University Faculty of Medicine Graduate School of Medical Science, Health Care Administration and Management; Saga Prefecture Medical Center Koseikan Fujita, Takako; Kyushu University Faculty of Medicine Graduate School of Medical Science, Health Care Administration and Management; Kyushu University, Department of Health Sciences, Faculty of Medical Sciences Jiang, Peng; Kyushu University Faculty of Medicine Graduate School of Medical Science, Health Care Administration and Management Kim, Sung-A; Kyushu University Faculty of Medicine Graduate School of Medical Science, Health Care Administration and Management Nakashima, Yasuharu; Kyushu University Faculty of Medicine Graduate School of Medical Science, Orthopedic Surgery
Primary Subject Heading:	Public health
Secondary Subject Heading:	Public health
Keywords:	Adult orthopaedics < ORTHOPAEDIC & TRAUMA SURGERY, EPIDEMIOLOGY, PUBLIC HEALTH

SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

1
2
3
4
5
6 **1 Title Page**

7 2 Original research article

8 3 **Effect of body mass index on vertebral and hip fractures in Older people and**
9 4 **Differences according to sex: A retrospective Japanese cohort study.**

10 5
11 6 **Authors**

12 7 1. Kyohei Shiimoto, MD, PhD

13 8 (1)Department of Artificial Joints and Biomaterials, Faculty of Medical Science, Kyushu
14 9 University, 3-1-1 Maidashi, Higashi-ku, Fukuoka, 812-8582, Japan

15 10 (2)Department of Orthopedic Surgery, Graduate School of Medical Sciences, Kyushu
16 11 University, Fukuoka, Japan

17 12 E-mail address: k-shio@ortho.med.kyushu-u.ac.jp

18 13 2. Akira Babazono, MD, PhD

19 14 Department of Health Care Administration and Management, Graduate School of Medical
20 15 Sciences, Kyushu University, Fukuoka, Japan.

21 16 E-mail address: babazono@hcam.med.kyushu-u.ac.jp

22 17 3. Yumi Harano, MD. PhD

23 18 (1)Department of Health Care Administration and Management, Graduate School of Medical
24 19 Sciences, Kyushu University, Fukuoka, Japan.

25 20 (2)Department of General Internal Medicine, Saga Medical Center Koseikan, Saga, Japan.

26 21 E-mail address: usagino3toqtaro@gmail.com

27 22 4. Takako Fujita, MPH

28 23 (1)Department of Health Care Administration and Management, Graduate School of Medical
29 24 Sciences, Kyushu University, Fukuoka, Japan.

30 25 (2)Department of Health Sciences, Faculty of Medical Sciences, Kyushu University,
31 26 Fukuoka, Japan.

32 27 E-mail address: takacooking@gmail.com

33 28 5. Peng Jiang, PhD

34 29 Department of Health Care Administration and Management, Graduate School of Medical
35 30 Sciences, Kyushu University, Fukuoka, Japan.

36 31 E-mail address: jiang21peng@163.com

37 32 6. Sung-a Kim, MPH

38 33 Department of Health Care Administration and Management, Graduate School of Medical
39 34 Sciences, Kyushu University, Fukuoka, Japan.

40 35 E-mail address: kj61444@naver.com

41 36 7. Yasuharu Nakashima, MD, PhD

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1 Department of Orthopedic Surgery, Graduate School of Medical Sciences, Kyushu
2 University, Fukuoka, Japan
3 E-mail address: yasunaka@med.kyushu-u.ac.jp

6 Please address all correspondence to:
7 Kyohei Shiimoto, M.D., Ph.D.
8 Department of Orthopedic Surgery, Kyushu University
9 3-1-1 Maidashi, Higashi-ku, Fukuoka, Japan 812-8582
10 TEL: +81-92-642-5487 FAX: +81-92-642-5507
11 E-mail: k-shio@ortho.med.kyushu-u.ac.jp

13 Words counts: Main text 4,088 words, 4 tables, 3 figures, and 2 appendices; Abstract 300 words

Peer review only

1
2
3
4
5
6 **Abstract**
7

8
9 **Objectives:** The purpose of this study was to investigate the incidence of vertebral and hip
10
11
12
13 fractures in the older people and to clarify the relationship between these fractures and body mass
14
15
16 index (BMI) along with the impact of sex differences.

17
18 **Design:** This was a retrospective cohort study.
19

20
21 **Setting:** We used administrative claims data between April 2010 and March 2018.
22

23
24 **Participants:** Older people aged ≥ 75 years who underwent health examinations in 2010 and were
25
26
27
28 living in the Fukuoka Prefecture, Japan were included in the study. A total of 24,691 subjects
29
30
31 were included; the mean age was 79.4 ± 4.3 years, 10,853 males and 13,838 females, and an the
32
33
34 mean duration of observation was 6.9 ± 1.6 years.

35
36 **Primary and secondary outcome measures:** We estimated the incidence of vertebral and hip
37
38
39
40 fractures by BMI category (underweight: $<18.5\text{kg/m}^2$, normal weight: $18.5\text{--}24.9\text{kg/m}^2$, overweight
41
42
43 and obese: $>25.0\text{kg/m}^2$) using a Kaplan–Meier curve in males and females and determined fracture
44
45
46 risk by sex using Cox proportional hazards regression analyses.

47
48 **Results:** The incidence of vertebral and hip fractures was 16.8% and 6.5%, respectively. The
49
50
51
52 incidence rate of vertebral and hip fracture at the last observation (8 years) in each BMI groups
53
54
55 (underweight/normal weight/overweight and obese) estimated using the Kaplan–Meier curve was
56
57
58 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
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

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

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

9
10 **Keywords:** body mass index (BMI), sex differences, fracture, claim data, older people

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1 **Strengths and limitations of this study**

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

3 **2.** We followed up participants for approximately 7 years.

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

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

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

11

1 Introduction

2 Vertebral and hip fractures are the major fractures that occur in the older people. The
3 incidence of these fragility fractures appears to be increasing in many countries because of the
4 increasing size of populations¹⁻³. Both vertebral and hip fractures cause pain and dysfunction and
5 decrease quality of life (QOL)⁴⁻⁶. It is well known that there is a high mortality rate after hip
6 fracture, but there are also reports of increased mortality after vertebral fractures^{7,8}. Consequently,
7 among fragility fractures, vertebral and hip fractures greatly impact healthy life expectancy and
8 longevity. In Japan, where the ageing population is rapidly increasing, the economic burden of
9 these fractures is immeasurable and has become an important public health issue^{9,10}. Therefore,
10 in order to prevent these fractures in the older people, it is very important to understand what are
11 the risk factors.

12 Previous studies reported several risk factors for vertebral and hip fractures, with the most
13 important risk being age, sex, history of past fractures, and low bone mineral density (BMD)^{11,12}.
14 FRAX, which is known as a fracture prediction tool, also uses these factors, smoking, and alcohol
15 consumption as fracture risks¹³. The prevalence of osteoporosis is also high in the elderly, and
16 the coexistence of osteoporosis has a significant impact on fractures¹⁴. Body mass index (BMI)
17 is another well-documented risk factor that it is closely related to fragility fractures¹⁵⁻¹⁷.
18 Underweight has been recognized as a risk factor for vertebral and hip fractures, and a cohort

1 study in Japan reported underweight as a preventable risk factor for hip fracture¹⁸. On the other
2 hand, Johansson et al.¹⁶ reported that the association between BMI and fracture risk is complex
3 and differs across skeletal sites; thus, the relationship between BMI and fracture risk is still
4 controversial. Previous study has shown that the effect of BMI on hip fracture varies with age¹⁹.
5 Sex and race may also influence the relationship between BMI and fractures. Although BMD
6 varies by race, there was a report that even after excluding the effects of BMD, there was a
7 difference in fracture risk by race^{20,21}. Some studies reported that the impact of BMI on fractures
8 varies by sex^{16,22}; however, there is no consensus regarding this, especially in Japanese.

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

14 **Materials and Methods**

15 *Study design and data source*

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

1
2
3
4
5
6
7 1 2018. This public health insurance is open to people over the age of 75 years and those aged 65-
8
9 2 74 years with disabilities, and the majority of people over the age of 75 years have this insurance.
10
11
12 3 The total population of Fukuoka Prefecture is about 5.1 million, the 9th largest in Japan, and about
13
14
15 4 520,000 older people are covered by this insurance. Most of the insured have long-term eligibility
16
17
18 5 once they are enrolled; therefore, few participants were lost to follow-up except for death. The
19
20
21 6 databases included data for the International Classification of Diseases 10th Revision (ICD-10)
22
23
24 7 codes; date of diagnosis, medical procedures, such as surgery, date of admission, and death. The
25
26
27 8 database are mostly computer-administered. According to a report by the Japanese Ministry of
28
29
30 9 Health, Labour and Welfare, the penetration rate of computer-administered claims databases was
31
32
33 10 98.6% as of April 2015²³. Older people aged 75 and over who are enrolled in this health insurance
34
35
36 11 and who do not have regular hospital visits for lifestyle-related diseases are eligible for medical
37
38
39 12 examination. We also used data from the 2010 health examination, which included participants'
40
41
42 13 height, weight, BMI, smoking and alcohol drinking.

44 45 14 *Participants*

46
47
48 15 Our target population was people who held Fukuoka Prefecture Wide-Area Association
49
50
51 16 of Latter-stage Elderly Healthcare insurance and who met the following criteria: (1) People who
52
53
54 17 underwent the 2010 health examination; (2) age \geq 75 years at the health examination; (3) data
55
56
57 18 related to smoking and alcohol consumption at the time of health examination were available; and
58
59
60

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

4 *Follow-up duration*

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

8 *Outcomes (vertebral and hip fracture incidence)*

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

13 *Comparison by BMI category*

14 The BMI classification in the general WHO is widely used in Japan, and we used the
15 following cut points. Participants were divided into three groups according to BMI category as
16 follows: underweight ($< 18.5 \text{ kg/m}^2$), normal weight ($18.5\text{--}24.9 \text{ kg/m}^2$), and overweight and obese
17 ($> 25.0 \text{ kg/m}^2$). Participants' demographics and the incidence of vertebral and hip fractures were
18 compared between the BMI categories.

1 *Risk factors for vertebral and hip fractures*

2 We examined age, BMI, alcohol drinking, smoking, comorbidities, and osteoporosis as
3 risk factors for each fracture by sex. Age was categorized into three groups: 75–79 years, 80–84
4 years, and ≥ 85 years. We divided the subjects into two groups: those with smoking and drinking
5 habits and those without. The Charlson Comorbidity Index (CCI) was used as an indicator of each
6 participant's comorbidities²⁴. CCI was calculated at the health examination using the ICD-10
7 codes²⁵ and was divided into four groups: low (0), medium (1–2), high (3–4), and very high (\geq
8 5). Osteoporosis was identified using the ICD-10 codes (M80, M81, M82). Incidentally, the
9 diagnostic criteria for osteoporosis in Japan are 1) BMD value less than 70% of Young adult mean
10 (YAM), 2) history of vertebral fracture or proximal femur fracture, or 3) history of fragility
11 fracture other than vertebral fracture or proximal femur fracture at less than 80% of YAM.

12 *Participant and public Involvement*

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

14 *Statistical analysis*

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

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

9 **Results**

10 *Participants*

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

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

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

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

7 *Vertebral and hip fracture rate*

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

16 *Comparison by BMI category*

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

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

5 The incidence rate of vertebral and hip fracture in each BMI groups (underweight/normal
6 weight/overweight and obese) at the final follow-up estimated using the Kaplan–Meier curve was
7 21.5% / 17.3% / 16.1% and 11.4% / 6.2% / 5.5%, respectively (all $P < .0001$) (**Fig.1**). By sex, he
8 incidence rate of vertebral fracture in each BMI groups was 14.7% / 10.4% / 9.0% in males and
9 24.9% / 23.0% / 21.9% in females, respectively, and was significantly higher with underweight
10 group in both sexes (all $P < .05$) (**Fig.2**). Similarly, the incidence rate of hip fracture was 6.3% /
11 2.9% / 2.4% in males and 14.1% / 9.0% / 8.1% in females, respectively, and was significantly
12 higher with underweight group in both sexes (all $P < .0001$) (**Fig.3**).

13 *Risk factors of vertebral and hip fractures*

14 In univariate analysis, the HRs for age, BMI, alcohol, smoking, CCI, and osteoporosis for
15 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 /
16 1.5 in females, respectively. The HRs for age, BMI, alcohol, smoking, CCI, and osteoporosis for
17 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
18 females, respectively. Older age, underweight, higher CCI, and osteoporosis were significant risk

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

4 In multivariate analysis, the adjusted HRs for age, BMI, alcohol, smoking, CCI, and
5 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 /
6 1.0 / 1.2 / 1.8 / 1.4 in females, respectively. The adjusted HRs for age, BMI, alcohol, smoking,
7 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 /
8 1.4 / 0.9 / 1.1 / 2.7 / 1.1 in females, respectively. Older age, higher CCI, and osteoporosis were
9 significant risk factors for hip fracture in both males and females, and smoking was also a
10 significant risk factor in males (**Table 4**). Multivariate analysis showed that older age and higher
11 CCI were significant risk factors for hip fracture in both males and females, smoking was a
12 significant risk factor only in males, and osteoporosis was a significant risk factor only in females
13 (**Table 4**). Alcohol drinking had a significant protective effect on hip fractures in males.

14 15 **Discussion**

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

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

12 Using this large cohort data, our study demonstrated that the vertebral and hip fracture
13 incidence was higher in the underweight group (BMI < 18.5 kg/m²) according to the Kaplan-
14 Meier curve. As many previous studies reported, underweight has long been considered an
15 important risk factor for fractures. Generally, lower BMI is associated with lower BMD, and
16 Lloyd et al. reported that every unit increase in BMI is associated with an increase of 0.0082 g/cm
17 in BMD ³⁰. Although underweight is generally considered a risk factor for fragility fractures,
18 several reports have shown that the relationship between BMI and fracture risk may differ by sex

1 and skeletal site, and that the relationship is complex^{15 16}. In the current study, we investigated
2 the effect of BMI on fractures, stratified by sex. We found that underweight was a risk factor for
3 hip fractures regardless of sex, and for vertebral fractures, underweight was a risk factor only in
4 males. Kaze et al.¹⁷ reported in their meta-analysis that an inverse association between BMI and
5 risk for vertebral fracture is present in males but not in females. Several previous studies have
6 shown that underweight is consistently associated with the risk of hip fracture, regardless of sex
7^{16 31}. Johansson et al.¹⁶ found that the relationship between BMI and osteoporotic fractures
8 depended on the site of the fracture, although their study was conducted only on females. In this
9 study, we similarly suggested that the effect of BMI varied by fracture site in females. Several
10 reports have indicated that abdominal fat may affect bone independently of total body fat, and
11 that there are sex differences in fat distribution, which may be a possible reason for the sex
12 differences in the effect of BMI on fracture^{32 33}. However, the reasons for the site-specific sex
13 effects, as shown in this study, are not yet well understood. Another possible explanation could
14 be that BMI as a measure of adiposity has been shown to be less valid in the older people owing
15 to age-related changes in body composition³⁴. However, in this study, only the older people were
16 included, not the middle-aged or other groups of both males and females, and this effect is
17 considered to be small.

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

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

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

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

1 influenced vertebral and hip fractures. The comparison of HRs suggested that age and CCI may
2 have a greater effect on fracture than BMI. First, for both types of fractures, older age and higher
3 CCI increased the risk of fracture. Although it is a well-known finding that the incidence of
4 fragility fractures increases with age, the effect of aging was more prevalent in hip fractures.
5 Tamaki et al.²⁹ reported a marked increase in fracture risk after the age of 80, indicating that the
6 very older people are at extremely high risk of fracture. This may be related to the decline in
7 physical function and increased risk of falling with age. Comorbidities such as chronic kidney
8 disease, diabetes, and dementia are associated with increased risk of fragility fractures, and it is
9 useful to evaluate the presence of comorbidities and investigate their contribution to the risk of
10 fractures⁴⁰⁻⁴². CCI was originally used to assess the risk of comorbidities for death, but patients
11 at high risk of death with a high CCI may also be at higher risk of fragility fractures. The present
12 study stratified CCI and assessed the risk of fracture and showed that a higher CCI was associated
13 with a higher fracture risk. Therefore, CCI may be useful in assessing fracture risk as well as
14 mortality risk in the older people.

15 Secondly, health-related behaviors such as smoking and alcohol drinking are also well-
16 established risk factors for fragility fractures^{43 44}, in this study, smoking was a risk factor in hip
17 fractures in men. Iconaru et al. reported that smoking was a significant risk factor for only hip
18 fractures among fragility fractures⁴⁵, and the effect of smoking on fracture may also be site-

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

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

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

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

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

2 3 **Conclusion**

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

11 **Acknowledgments**

12 The authors would like to thank the Fukuoka Prefecture Wide-Area Association of Latter-Stage
13 Elderly Healthcare for allowing access to the health claims database and master data.

14 **Author Contribution**

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

1 approved the final version of the manuscript.

2 **Funding**

3 No funding was received for this study.

4 **Conflicts of interest**

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

8 **Patient consent for publication**

9 Not required.

10 **Ethics approval**

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

13 **Provenance and peer review**

14 Not commissioned, externally peer reviewed.

15 **Data sharing statement**

16 No additional data are available.

17 **Open access**

1 **References**

- 2 1. Cummings SR, Kelsey JL, Nevitt MC, et al. Epidemiology of osteoporosis and osteoporotic
3 fractures. *Epidemiol Rev* 1985;7:178-208. doi: 10.1093/oxfordjournals.epirev.a036281
- 4 2. Gullberg B, Johnell O, Kanis JA. World-wide projections for hip fracture. *Osteoporos Int*
5 1997;7(5):407-13. doi: 10.1007/pl00004148
- 6 3. Schousboe JT. Epidemiology of Vertebral Fractures. *J Clin Densitom* 2016;19(1):8-22. doi:
7 10.1016/j.jocd.2015.08.004
- 8 4. Alexiou KI, Roushias A, Varitimidis SE, et al. Quality of life and psychological consequences
9 in elderly patients after a hip fracture: a review. *Clin Interv Aging* 2018;13:143-50. doi:
10 10.2147/CIA.S150067
- 11 5. Ciubean AD, Ungur RA, Irsay L, et al. Health-related quality of life in Romanian
12 postmenopausal women with osteoporosis and fragility fractures. *Clin Interv Aging*
13 2018;13:2465-72. doi: 10.2147/CIA.S190440
- 14 6. Svedbom A, Borgstrom F, Hernlund E, et al. Quality of life for up to 18 months after low-energy
15 hip, vertebral, and distal forearm fractures-results from the ICUROS. *Osteoporos Int*
16 2018;29(3):557-66. doi: 10.1007/s00198-017-4317-4
- 17 7. Farahmand BY, Michaelsson K, Ahlbom A, et al. Survival after hip fracture. *Osteoporos Int*
18 2005;16(12):1583-90. doi: 10.1007/s00198-005-2024-z

- 1
2
3
4
5
6 1 8. Lau E, Ong K, Kurtz S, et al. Mortality following the diagnosis of a vertebral compression
7
8
9 2 fracture in the Medicare population. *J Bone Joint Surg Am* 2008;90(7):1479-86. doi:
10
11 3 10.2106/JBJS.G.00675
12
13
14
15 4 9. Borgstrom F, Karlsson L, Ortsater G, et al. Fragility fractures in Europe: burden, management
16
17
18 5 and opportunities. *Arch Osteoporos* 2020;15(1):59. doi: 10.1007/s11657-020-0706-y
19
20
21 6 10. Taguchi Y, Inoue Y, Kido T, et al. Treatment costs and cost drivers among osteoporotic
22
23
24 7 fracture patients in Japan: a retrospective database analysis. *Arch Osteoporos* 2018;13(1):45. doi:
25
26
27 8 10.1007/s11657-018-0456-2
28
29
30 9 11. Kanis JA, Johnell O, Oden A, et al. Long-term risk of osteoporotic fracture in Malmo.
31
32
33 10 *Osteoporos Int* 2000;11(8):669-74. doi: 10.1007/s001980070064
34
35
36 11 12. Ensrud KE. Epidemiology of fracture risk with advancing age. *J Gerontol A Biol Sci Med Sci*
37
38
39 12 2013;68(10):1236-42. doi: 10.1093/gerona/glt092
40
41
42 13 13. Kanis JA, Johnell O, Oden A, et al. FRAX and the assessment of fracture probability in men
43
44
45 14 and women from the UK. *Osteoporos Int* 2008;19(4):385-97. doi: 10.1007/s00198-007-0543-5
46
47
48 15 14. Lane NE. Epidemiology, etiology, and diagnosis of osteoporosis. *Am J Obstet Gynecol*
49
50
51 16 2006;194(2 Suppl):S3-11. doi: 10.1016/j.ajog.2005.08.047
52
53
54 17 15. De Laet C, Kanis JA, Oden A, et al. Body mass index as a predictor of fracture risk: a meta-
55
56
57 18 analysis. *Osteoporos Int* 2005;16(11):1330-8. doi: 10.1007/s00198-005-1863-y
58
59
60

- 1
2
3
4
5
6 1 16. Johansson H, Kanis JA, Oden A, et al. A meta-analysis of the association of fracture risk and
7
8
9 2 body mass index in women. *J Bone Miner Res* 2014;29(1):223-33. doi: 10.1002/jbmr.2017
10
11
12 3 17. Kaze AD, Rosen HN, Paik JM. A meta-analysis of the association between body mass index
13
14
15 4 and risk of vertebral fracture. *Osteoporos Int* 2018;29(1):31-39. doi: 10.1007/s00198-017-4294-
16
17
18 5 7
19
20
21 6 18. Fujiwara S, Kasagi F, Yamada M, et al. Risk factors for hip fracture in a Japanese cohort. *J*
22
23
24 7 *Bone Miner Res* 1997;12(7):998-1004. doi: 10.1359/jbmr.1997.12.7.998
25
26
27 8 19. Rikkonen T, Sund R, Sirola J, et al. Obesity is associated with early hip fracture risk in
28
29
30 9 postmenopausal women: a 25-year follow-up. *Osteoporos Int* 2021;32(4):769-77. doi:
31
32
33 10 10.1007/s00198-020-05665-w
34
35
36 11 20. Siris ES, Miller PD, Barrett-Connor E, et al. Identification and fracture outcomes of
37
38
39 12 undiagnosed low bone mineral density in postmenopausal women: results from the National
40
41
42 13 Osteoporosis Risk Assessment. *JAMA* 2001;286(22):2815-22. doi: 10.1001/jama.286.22.2815
43
44
45 14 21. Robbins J, Aragaki AK, Kooperberg C, et al. Factors associated with 5-year risk of hip fracture
46
47
48 15 in postmenopausal women. *JAMA* 2007;298(20):2389-98. doi: 10.1001/jama.298.20.2389
49
50
51 16 22. Xiang BY, Huang W, Zhou GQ, et al. Body mass index and the risk of low bone mass-related
52
53
54 17 fractures in women compared with men: A PRISMA-compliant meta-analysis of prospective
55
56
57 18 cohort studies. *Medicine (Baltimore)* 2017;96(12):e5290. doi: 10.1097/MD.0000000000005290
58
59
60

- 1
2
3
4
5
6 1 23. Welfare. MoHLA. Japanese government report: Computer-administered claims penetration
7
8
9 2 rate. 2015
10
11
12 3 24. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity
13
14
15 4 in longitudinal studies: development and validation. *J Chronic Dis* 1987;40(5):373-83. doi:
16
17
18 5 10.1016/0021-9681(87)90171-8
19
20
21 6 25. Sundararajan V, Henderson T, Perry C, et al. New ICD-10 version of the Charlson
22
23
24 7 comorbidity index predicted in-hospital mortality. *J Clin Epidemiol* 2004;57(12):1288-94. doi:
25
26
27 8 10.1016/j.jclinepi.2004.03.012
28
29
30 9 26. Spector TD, McCloskey EV, Doyle DV, et al. Prevalence of vertebral fracture in women and
31
32
33 10 the relationship with bone density and symptoms: the Chingford Study. *J Bone Miner Res*
34
35
36 11 1993;8(7):817-22. doi: 10.1002/jbmr.5650080707
37
38
39 12 27. Kitazawa A, Kushida K, Yamazaki K, et al. Prevalence of vertebral fractures in a population-
40
41
42 13 based sample in Japan. *J Bone Miner Metab* 2001;19(2):115-8. doi: 10.1007/s007740170049
43
44
45 14 28. Yoshimura N, Kinoshita H, Oka H, et al. Cumulative incidence and changes in the prevalence
46
47
48 15 of vertebral fractures in a rural Japanese community: a 10-year follow-up of the Miyama cohort.
49
50
51 16 *Archives of Osteoporosis* 2006;1(1-2):43-49. doi: 10.1007/s11657-006-0007-0
52
53
54 17 29. Tamaki J, Fujimori K, Ikehara S, et al. Estimates of hip fracture incidence in Japan using the
55
56
57 18 National Health Insurance Claim Database in 2012-2015. *Osteoporos Int* 2019;30(5):975-83. doi:
58
59
60

- 1 10.1007/s00198-019-04844-8
- 2
- 3
- 4
- 5
- 6 1 10.1007/s00198-019-04844-8
- 7
- 8
- 9 2 30. Lloyd JT, Alley DE, Hawkes WG, et al. Body mass index is positively associated with bone
- 10
- 11
- 12 3 mineral density in US older adults. Arch Osteoporos 2014;9:175. doi: 10.1007/s11657-014-0175-
- 13
- 14
- 15 4 2
- 16
- 17
- 18 5 31. Sogaard AJ, Holvik K, Omsland TK, et al. Age and Sex Differences in Body Mass Index as
- 19
- 20
- 21 6 a Predictor of Hip Fracture: A NOREPOS Study. Am J Epidemiol 2016;184(7):510-19. doi:
- 22
- 23
- 24 7 10.1093/aje/kww011
- 25
- 26
- 27 8 32. Fini M, Salamanna F, Veronesi F, et al. Role of obesity , alcohol and smoking on bone health.
- 28
- 29
- 30 9 Front Biosci (Elite Ed) 2012;4:2586-606. doi: 10.2741/e575
- 31
- 32
- 33 10 33. Ng AC, Melton LJ, 3rd, Atkinson EJ, et al. Relationship of adiposity to bone volumetric
- 34
- 35
- 36 11 density and microstructure in men and women across the adult lifespan. Bone 2013;55(1):119-
- 37
- 38
- 39 12 25. doi: 10.1016/j.bone.2013.02.006
- 40
- 41
- 42 13 34. Villareal DT, Apovian CM, Kushner RF, et al. Obesity in older adults: technical review and
- 43
- 44
- 45 14 position statement of the American Society for Nutrition and NAASO, The Obesity Society. Am
- 46
- 47
- 48 15 J Clin Nutr 2005;82(5):923-34. doi: 10.1093/ajcn/82.5.923
- 49
- 50
- 51 16 35. Felson DT, Zhang Y, Hannan MT, et al. Effects of weight and body mass index on bone
- 52
- 53
- 54 17 mineral density in men and women: the Framingham study. J Bone Miner Res 1993;8(5):567-73.
- 55
- 56
- 57 18 doi: 10.1002/jbmr.5650080507
- 58
- 59
- 60

- 1
2
3
4
5
6 1 36. Bouxsein ML, Szulc P, Munoz F, et al. Contribution of trochanteric soft tissues to fall force
7
8
9 2 estimates, the factor of risk, and prediction of hip fracture risk. *J Bone Miner Res* 2007;22(6):825-
10
11
12 3 31. doi: 10.1359/jbmr.070309
13
14
15 4 37. Premaor MO, Pilbrow L, Tonkin C, et al. Obesity and fractures in postmenopausal women. *J*
16
17
18 5 *Bone Miner Res* 2010;25(2):292-7. doi: 10.1359/jbmr.091004
19
20
21 6 38. Compston JE, Watts NB, Chapurlat R, et al. Obesity is not protective against fracture in
22
23
24 7 postmenopausal women: GLOW. *Am J Med* 2011;124(11):1043-50. doi:
25
26
27 8 10.1016/j.amjmed.2011.06.013
28
29
30 9 39. Kim SH, Yi SW, Yi JJ, et al. Association Between Body Mass Index and the Risk of Hip
31
32
33 10 Fracture by Sex and Age: A Prospective Cohort Study. *J Bone Miner Res* 2018;33(9):1603-11.
34
35
36 11 doi: 10.1002/jbmr.3464
37
38
39 12 40. Holmberg AH, Johnell O, Nilsson PM, et al. Risk factors for fragility fracture in middle age.
40
41
42 13 A prospective population-based study of 33,000 men and women. *Osteoporos Int*
43
44
45 14 2006;17(7):1065-77. doi: 10.1007/s00198-006-0137-7
46
47
48 15 41. Amouzougan A, Lafaie L, Marotte H, et al. High prevalence of dementia in women with
49
50
51 16 osteoporosis. *Joint Bone Spine* 2017;84(5):611-14. doi: 10.1016/j.jbspin.2016.08.002
52
53
54 17 42. Kazama JJ. Chronic kidney disease and fragility fracture. *Clin Exp Nephrol* 2017;21(Suppl
55
56
57 18 1):46-52. doi: 10.1007/s10157-016-1368-3
58
59
60

- 1
2
3
4
5
6
7 43. Kanis JA, Johnell O, Oden A, et al. Smoking and fracture risk: a meta-analysis. *Osteoporos*
8
9
10 2 Int 2005;16(2):155-62. doi: 10.1007/s00198-004-1640-3
11
12
13 44. Zhang X, Yu Z, Yu M, et al. Alcohol consumption and hip fracture risk. *Osteoporos Int*
14
15 4 2015;26(2):531-42. doi: 10.1007/s00198-014-2879-y
16
17
18 45. Iconaru L, Moreau M, Kinnard V, et al. Does the Prediction Accuracy of Osteoporotic
19
20
21 6 Fractures by BMD and Clinical Risk Factors Vary With Fracture Site? *JBMR Plus*
22
23
24 7 2019;3(12):e10238. doi: 10.1002/jbm4.10238
25
26
27 46. Gaddini GW, Turner RT, Grant KA, et al. Alcohol: A Simple Nutrient with Complex Actions
28
29
30 9 on Bone in the Adult Skeleton. *Alcohol Clin Exp Res* 2016;40(4):657-71. doi:
31
32
33 10 10.1111/acer.13000
34
35

36 11

37 12
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1 **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)

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

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

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

4

For peer review only

Table 2.

Comparison of subjects' demographics between BMI categories.

Parameters	BMI categories		
	Underweight n = 2,684	Normal weight n = 17,667	Overweight and Obese 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)/ 75–79/ 80–84/ 85≤	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

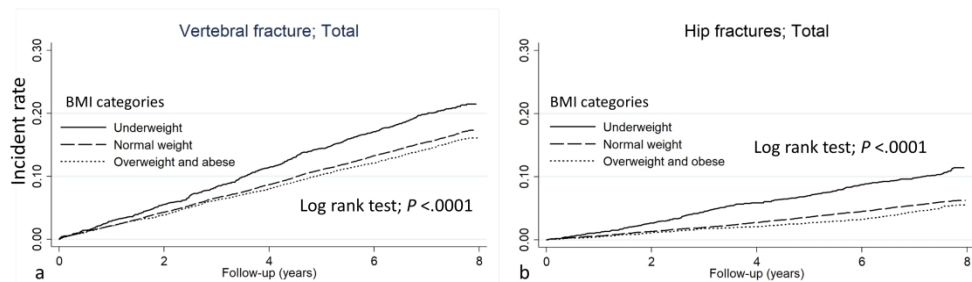
The Kaplan-Meier curve shows the incidence of vertebral fractures in a) males and b) females compared by BMI category. The solid line represents underweight, the dashed line represents normal weight, and the dotted line represents overweight and obese.

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.

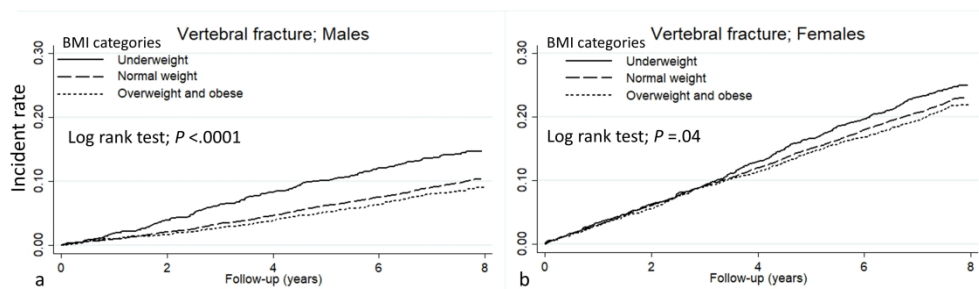
BMI: body mass index



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.

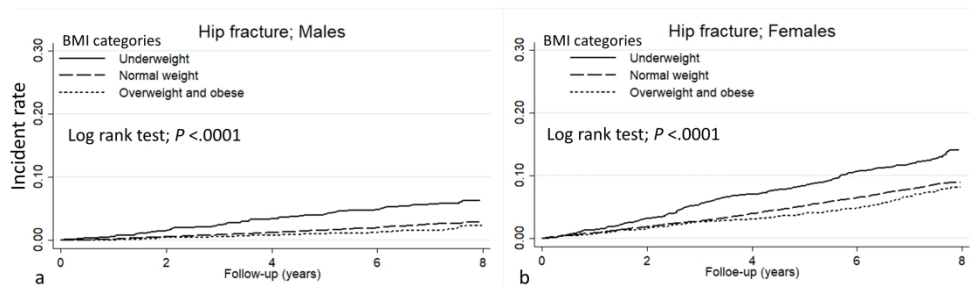
BMI: body mass index

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 (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	9
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	7, 8 Table 1 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 (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	11 Table 4, 5 8 Table 3
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.

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-049157.R2
Article Type:	Original research
Date Submitted by the Author:	10-Oct-2021
Complete List of Authors:	Shiomoto, Kyohei; Kyushu University, Artificial Joints and Biomaterials, Faculty of Medical Science; Kyushu University Faculty of Medicine Graduate School of Medical Science, Orthopaedic Surgery Babazono, Akira; Kyushu University Faculty of Medicine Graduate School of Medical Science, Health Care Administration and Management Harano, Yumi; Kyushu University Faculty of Medicine Graduate School of Medical Science, Health Care Administration and Management; Saga Prefecture Medical Center Koseikan Fujita, Takako; Kyushu University Faculty of Medicine Graduate School of Medical Science, Health Care Administration and Management; Kyushu University, Department of Health Sciences, Faculty of Medical Sciences Jiang, Peng; Kyushu University Faculty of Medicine Graduate School of Medical Science, Health Care Administration and Management Kim, Sung-A; Kyushu University Faculty of Medicine Graduate School of Medical Science, Health Care Administration and Management Nakashima, Yasuharu; Kyushu University Faculty of Medicine Graduate School of Medical Science, Orthopedic Surgery
Primary Subject Heading:	Public health
Secondary Subject Heading:	Public health
Keywords:	Adult orthopaedics < ORTHOPAEDIC & TRAUMA SURGERY, EPIDEMIOLOGY, PUBLIC HEALTH

SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

1
2
3
4
5
6 **1 Title Page**

7 2 Original research article

8 3 **Effect of body mass index on vertebral and hip fractures in Older people and**
9 4 **Differences according to sex: A retrospective Japanese cohort study.**

10 5
11 6 **Authors**

12 7 1. Kyohei Shiimoto, MD, PhD

13 8 (1)Department of Artificial Joints and Biomaterials, Faculty of Medical Science, Kyushu
14 9 University, 3-1-1 Maidashi, Higashi-ku, Fukuoka, 812-8582, Japan

15 10 (2)Department of Orthopedic Surgery, Graduate School of Medical Sciences, Kyushu
16 11 University, Fukuoka, Japan

17 12 E-mail address: k-shio@ortho.med.kyushu-u.ac.jp

18 13 2. Akira Babazono, MD, PhD

19 14 Department of Health Care Administration and Management, Graduate School of Medical
20 15 Sciences, Kyushu University, Fukuoka, Japan.

21 16 E-mail address: babazono@hcam.med.kyushu-u.ac.jp

22 17 3. Yumi Harano, MD. PhD

23 18 (1)Department of Health Care Administration and Management, Graduate School of Medical
24 19 Sciences, Kyushu University, Fukuoka, Japan.

25 20 (2)Department of General Internal Medicine, Saga Medical Center Koseikan, Saga, Japan.

26 21 E-mail address: usagino3toqtaro@gmail.com

27 22 4. Takako Fujita, MPH

28 23 (1)Department of Health Care Administration and Management, Graduate School of Medical
29 24 Sciences, Kyushu University, Fukuoka, Japan.

30 25 (2)Department of Health Sciences, Faculty of Medical Sciences, Kyushu University,
31 26 Fukuoka, Japan.

32 27 E-mail address: takacooking@gmail.com

33 28 5. Peng Jiang, PhD

34 29 Department of Health Care Administration and Management, Graduate School of Medical
35 30 Sciences, Kyushu University, Fukuoka, Japan.

36 31 E-mail address: jiang21peng@163.com

37 32 6. Sung-a Kim, MPH

38 33 Department of Health Care Administration and Management, Graduate School of Medical
39 34 Sciences, Kyushu University, Fukuoka, Japan.

40 35 E-mail address: kj61444@naver.com

41 36 7. Yasuharu Nakashima, MD, PhD

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1 Department of Orthopedic Surgery, Graduate School of Medical Sciences, Kyushu
2 University, Fukuoka, Japan
3 E-mail address: yasunaka@med.kyushu-u.ac.jp

4
5
6 Please address all correspondence to:
7 Kyohei Shiomoto, M.D., Ph.D.
8 Department of Orthopedic Surgery, Kyushu University
9 3-1-1 Maidashi, Higashi-ku, Fukuoka, Japan 812-8582
10 TEL: +81-92-642-5487 FAX: +81-92-642-5507
11 E-mail: k-shio@ortho.med.kyushu-u.ac.jp

12
13 Words counts: Main text 4,127 words, 4 tables, 3 figures, and 2 appendices; Abstract 300 words
14

Peer review only

1
2
3
4
5
6 **Abstract**

7
8
9 **Objectives:** The purpose of this study was to investigate the incidence of vertebral and hip
10
11
12
13 fractures in the older people and to clarify the relationship between these fractures and body mass
14
15
16 index (BMI) along with the impact of sex differences.

17
18 **Design:** This was a retrospective cohort study.

19
20
21 **Setting:** We used administrative claims data between April 2010 and March 2018.

22
23
24 **Participants:** Older people aged ≥ 75 years who underwent health examinations in 2010 and were
25
26
27
28 living in the Fukuoka Prefecture, Japan were included in the study. A total of 24,691 participants
29
30
31 were included; the mean age was 79.4 ± 4.3 years, 10,853 males and 13,838 females, and an the
32
33
34 mean duration of observation was 6.9 ± 1.6 years.

35
36
37 **Primary and secondary outcome measures:** We estimated the incidence of vertebral and hip
38
39
40 fractures by BMI category (underweight: $< 18.5 \text{ kg/m}^2$, normal weight: $18.5\text{--}24.9 \text{ kg/m}^2$, overweight
41
42
43 and obese: $\geq 25.0 \text{ kg/m}^2$) using a Kaplan–Meier curve in males and females and determined fracture
44
45
46 risk by sex using Cox proportional hazards regression analyses.

47
48
49 **Results:** The incidence of vertebral and hip fractures was 16.8% and 6.5%, respectively. The
50
51
52 cumulative incidence of vertebral and hip fracture at the last observation (8 years) in each BMI
53
54
55 groups (underweight/normal weight/overweight and obese) estimated using the Kaplan–Meier
56
57
58 curve was 14.7%/10.4%/9.0% in males and 24.9%/23.0%/21.9% in females, and
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1 6.3%/2.9%/2.4% in males and 14.1%/9.0%/8.1% in females, respectively, and both fractures were
2 significantly higher in underweight groups regardless of sex. Multivariable Cox proportional
3 hazards models showed that underweight was a significant risk factor only in males for vertebral
4 fractures and in both males and females for hip fractures.

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

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

9
10 **Keywords:** body mass index (BMI), sex differences, fracture, claim data, older people
11
12

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1 **Strengths and limitations of this study**

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

3 2. We followed up participants for approximately 7 years.

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

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

8 5. This study has several limitations; bone mineral density (BMD), a factor closely related to
9 fracture, could not be assessed in this study, and although we assessed osteoporosis
10 comorbidity, we could not assess treatment status.
11

1 Introduction

2 Vertebral and hip fractures are the major fractures that occur in the older people. The
3 incidence of these fragility fractures appears to be increasing in many countries because of the
4 increasing size of populations¹⁻³. Gullberg et al. reported that the incidence of hip fractures in the
5 world was estimated to nearly double, from 2.6 million hip fractures in 2025 to 4.5 million in
6 2050, with a particularly marked increase in Asia². Both vertebral and hip fractures cause pain
7 and dysfunction and decrease quality of life (QOL)⁴⁻⁶. It is well known that there is a high
8 mortality rate after hip fracture, but there are also reports of increased mortality after vertebral
9 fractures^{7,8}. Consequently, among fragility fractures, vertebral and hip fractures greatly impact
10 healthy life expectancy and longevity. In Japan, where the ageing population is rapidly increasing,
11 the economic burden of these fractures is immeasurable and has become an important public
12 health issue^{9,10}. Therefore, in order to prevent these fractures in the older people, it is very
13 important to understand what are the risk factors.

14 Previous studies reported several risk factors for vertebral and hip fractures, with the most
15 important risk being age, sex, history of past fractures, and low bone mineral density (BMD)¹¹,
16¹². FRAX, which is known as a fracture prediction tool, also uses these factors, smoking, and
17 alcohol consumption as fracture risks¹³. The prevalence of osteoporosis is also high in the elderly,
18 and the coexistence of osteoporosis has a significant impact on fractures¹⁴. Body mass index

1 (BMI) is another well-documented risk factor that it is closely related to fragility fractures¹⁵⁻¹⁷.
2 Underweight has been recognized as a risk factor for vertebral and hip fractures, and a cohort
3 study in Japan reported underweight as a preventable risk factor for hip fracture¹⁸. On the other
4 hand, Johansson et al.¹⁶ reported that the association between BMI and fracture risk is complex
5 and differs across skeletal sites; thus, the relationship between BMI and fracture risk is still
6 controversial. Previous study has shown that the effect of BMI on hip fracture varies with age¹⁹.
7 Sex and race may also influence the relationship between BMI and fractures. Although BMD
8 varies by race, there was a report that even after excluding the effects of BMD, there was a
9 difference in fracture risk by race^{20,21}. Some studies reported that the impact of BMI on fractures
10 varies by sex^{16,22}; however, there is no consensus regarding this, especially in Japanese.

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

15 16 **Materials and Methods**

17 *Study design and data source*

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

1 used data from the healthcare claims database and master database of the Fukuoka Prefecture
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1 used data from the healthcare claims database and master database of the Fukuoka Prefecture
2 Wide-Area Association of Latter-stage Elderly Healthcare between 1 April 2010 and 31 March
3 2018. This public health insurance is open to people over the age of 75 years and those aged 65-
4 74 years with disabilities, and the majority of people over the age of 75 years have this insurance.
5 The total population of Fukuoka Prefecture is about 5.1 million, the 9th largest in Japan, and about
6 520,000 older people are covered by this insurance. Most of the insured have long-term eligibility
7 once they are enrolled; therefore, few participants were lost to follow-up except for death. The
8 databases included data for the International Classification of Diseases 10th Revision (ICD-10)
9 codes; date of diagnosis, medical procedures, such as surgery, date of admission, and death. The
10 database are mostly computer-administered. According to a report by the Japanese Ministry of
11 Health, Labour and Welfare, the penetration rate of computer-administered claims databases was
12 98.6% as of April 2015²³. Older people aged 75 and over who are enrolled in this health insurance
13 and who do not have regular hospital visits for lifestyle-related diseases are eligible for medical
14 examination. We also used data from the 2010 health examination, which included participants'
15 height, weight, BMI, smoking and use of alcohol.

16 *Participants*

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

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

6 *Follow-up duration*

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

10 *Outcomes (vertebral and hip fracture incidence)*

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

17 *Comparison by BMI category*

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

1 following cut points. Participants were divided into three groups according to BMI category as
2 follows: underweight ($< 18.5 \text{ kg/m}^2$), normal weight ($18.5\text{--}24.9 \text{ kg/m}^2$), and overweight and obese
3 ($\geq 25.0 \text{ kg/m}^2$). Participants' demographics and the incidence of vertebral and hip fractures were
4 compared between the BMI categories.

5 *Risk factors for vertebral and hip fractures*

6 We examined age, BMI, use of alcohol, smoking, comorbidities, and osteoporosis as risk
7 factors for each fracture by sex. BMI was divided into three categories as described above, and
8 the fracture risk of "underweight" and "overweight and obese" was examined using normal as the
9 reference. Age was categorized into three groups: 75–79 years, 80–84 years, and ≥ 85 years.
10 Smoking and use of alcohol were divided into two groups, habitual and non-habitual, and were
11 used as separate risk factors. The Charlson Comorbidity Index (CCI) was used as an indicator of
12 each participant's comorbidities²⁴. CCI was calculated at the health examination using the ICD-
13 10 codes²⁵ and was divided into four groups: low (0), medium (1–2), high (3–4), and very high
14 (≥ 5). Osteoporosis was identified using the ICD-10 codes (M80, M81, M82). Incidentally, the
15 diagnostic criteria for osteoporosis in Japan are 1) BMD value less than 70% of Young adult mean
16 (YAM), 2) history of vertebral fracture or proximal femur fracture, or 3) history of fragility
17 fracture other than vertebral fracture or proximal femur fracture at less than 80% of YAM.

18 *Participant and public Involvement*

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

2 *Statistical analysis*

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

15 **Results**

16 *Participants*

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

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

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

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

13 *Vertebral and hip fracture rate*

14 Vertebral and hip fractures occurred in 4,153 (16.8%) and 1,543 (6.5%) of the participants,
15 respectively, during the study period. Vertebral fractures occurred in 1,082 (10%) males and 3,071
16 (22.2%) females, hip fractures occurred in 314 (2.9%) males and 1,229 (8.9%) females, and the
17 incidence of both fractures was significantly higher in females ($P < .0001$). The incidence of
18 vertebral fracture was 150 in males and 315.9 in females per 10,000 person-years, respectively.

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

4 *Comparison by BMI category*

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

11 The cumulative incidence of vertebral and hip fracture in each BMI groups
12 (underweight/normal weight/overweight and obese) at the final follow-up estimated using the
13 Kaplan–Meier curve was 21.5% / 17.3% / 16.1% and 11.4% / 6.2% / 5.5%, respectively (all P
14 $< .0001$) (**Fig.1**). By sex, the cumulative incidence of vertebral fracture in each BMI groups was
15 14.7% / 10.4% / 9.0% in males and 24.9% / 23.0% / 21.9% in females, respectively, and was
16 significantly higher with underweight group in both sexes (all $P < .05$) (**Fig.2**). Similarly, the
17 cumulative incidence of hip fracture was 6.3% / 2.9% / 2.4% in males and 14.1% / 9.0% / 8.1%
18 in females, respectively, and was significantly higher with underweight group in both sexes (all

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1 $P < .0001$ (**Fig.3**).

2 *Risk factors of vertebral and hip fractures*

3 In univariate analysis, the HRs (95%CI) for age, BMI, alcohol, smoking, CCI, and
4 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-
5 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
6 (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,
7 alcohol, smoking, CCI, and osteoporosis for the hip fracture were 3.9 (2.9-5.2) / 2.2 (1.7-3.0) /
8 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)
9 / 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,
10 underweight, higher CCI, and osteoporosis were significant risk factors for vertebral fracture in
11 both males and females (**Table 3**). Multivariable analysis showed that older age, higher CCI, and
12 osteoporosis were risk factors for vertebral fracture in both males and females, but underweight
13 was a significant risk factor only in males (**Table 3**).

14 In multivariable analysis, the adjusted HRs for age, BMI, alcohol, smoking, CCI, and
15 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-
16 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
17 (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,
18 alcohol, smoking, CCI, and osteoporosis for the hip fracture were 3.2 (2.4-4.3) / 1.7 (1.3-2.4) /

1 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)
2 / 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,
3 higher CCI, and osteoporosis were significant risk factors for hip fracture in both males and
4 females, and smoking was also a significant risk factor in males (**Table 4**). Multivariable analysis
5 showed that older age and higher CCI were significant risk factors for hip fracture in both males
6 and females, smoking was a significant risk factor only in males, and osteoporosis was a
7 significant risk factor only in females (**Table 4**). Use of alcohol had a significant protective effect
8 on hip fractures in males.

9 **Discussion**

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

1 26-28. Tamaki et al. found in a three-year retrospective cohort study that the incidence of hip
2 fracture in people aged 80–84 years was 36.6 and 88 per 10,000, for males and females,
3 respectively²⁹. We found that the incidence of vertebral and hip fracture was 17% (150 and 316.4
4 per 10,000, for males and females) and 7% (43.5 and 126.4 per 10,000, for males and females),
5 respectively, in our study. The incidence rates in the present study were equivalent to those in
6 previous cohort studies and did not appear to be unevenly distributed by region²⁶⁻²⁹.

7 Using this large cohort data, our study demonstrated that the vertebral and hip fracture
8 incidence was higher in the underweight group (BMI < 18.5 kg/m²) according to the Kaplan-
9 Meier curve. As many previous studies reported, underweight has long been considered an
10 important risk factor for fractures. Generally, lower BMI is associated with lower BMD, and
11 Lloyd et al. reported that every unit increase in BMI is associated with an increase of 0.0082 g/cm
12 in BMD³⁰. De Laet et al.¹⁵ also reported that low BMI was a significant risk factor for fracture,
13 even after adjusting for BMD, and that low BMI was associated with an increased relative risk,
14 especially for hip fracture. In the present study, underweight was also associated with higher HR
15 for hip fracture than vertebral fracture, suggesting that underweight may have a particular impact
16 on hip fracture among fragility fractures. Although underweight is generally considered a risk
17 factor for fragility fractures, several reports have shown that the relationship between BMI and
18 fracture risk may differ by sex and skeletal site, and that the relationship is complex^{15, 16}. In the

1 current study, we investigated the effect of BMI on fractures, stratified by sex. We found that
2 underweight was a risk factor for hip fractures regardless of sex, and for vertebral fractures,
3 underweight was a risk factor only in males. Kaze et al.¹⁷ reported in their meta-analysis that an
4 inverse association between BMI and risk for vertebral fracture is present in males but not in
5 females. Several previous studies have shown that underweight is consistently associated with the
6 risk of hip fracture, regardless of sex^{16,31}. Johansson et al.¹⁶ found that the relationship between
7 BMI and osteoporotic fractures depended on the site of the fracture, although their study was
8 conducted only on females. In this study, we similarly suggested that the effect of BMI varied by
9 fracture site in females. Several reports have indicated that abdominal fat may affect bone
10 independently of total body fat, and that there are sex differences in fat distribution, which may
11 be a possible reason for the sex differences in the effect of BMI on fracture^{32,33}. However, the
12 reasons for the site-specific sex effects, as shown in this study, are not yet well understood.
13 Another possible explanation could be that BMI as a measure of adiposity has been shown to be
14 less valid in the older people owing to age-related changes in body composition³⁴. However, in
15 this study, only the older people were included, not the middle-aged or other groups of both males
16 and females, and this effect is considered to be small.

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

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

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

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

1 have a greater effect on fracture than BMI. First, for both types of fractures, older age and higher
2 CCI increased the risk of fracture. Although it is a well-known finding that the incidence of
3 fragility fractures increases with age, the effect of aging was more prevalent in hip fractures.
4 Tamaki et al.²⁹ reported a marked increase in fracture risk after the age of 80, indicating that the
5 very older people are at extremely high risk of fracture. This may be related to the decline in
6 physical function and increased risk of falling with age. Comorbidities such as chronic kidney
7 disease, diabetes, and dementia are associated with increased risk of fragility fractures, and it is
8 useful to evaluate the presence of comorbidities and investigate their contribution to the risk of
9 fractures⁴⁰⁻⁴². CCI was originally used to assess the risk of comorbidities for death, but patients
10 at high risk of death with a high CCI may also be at higher risk of fragility fractures. The present
11 study stratified CCI and assessed the risk of fracture and showed that a higher CCI was associated
12 with a higher fracture risk. Therefore, CCI may be useful in assessing fracture risk as well as
13 mortality risk in the older people.

14 Secondly, health-related behaviors such as smoking and use of alcohol are also well-
15 established risk factors for fragility fractures^{43, 44}, in this study, smoking was a risk factor in hip
16 fractures in men. Iconaru et al. reported that smoking was a significant risk factor for only hip
17 fractures among fragility fractures⁴⁵, and the effect of smoking on fracture may also be site-
18 specific. The lack of effect of smoking in females may be related to the extremely low rate of

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

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

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

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

1

2 **Conclusion**

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

10 **Acknowledgments**

11 The authors would like to thank the Fukuoka Prefecture Wide-Area Association of Latter-Stage
12 Elderly Healthcare for allowing access to the health claims database and master data.

13 **Author Contribution**

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

1
2
3
4
5
6 **1 Funding**
7

8
9 2 No funding was received for this study.
10

11 **3 Conflicts of interest**
12

13
14 4 All authors have no conflicts of interest.
15

16
17 **5 Patient consent for publication**
18

19
20 6 Not required.
21

22
23 **7 Ethics approval**
24

25
26 8 This study was approved by the Kyushu University Institutional Review Board for Clinical
27

28
29 9 Research (Approval No. 20209).
30

31
32 **10 Provenance and peer review**
33

34
35 11 Not commissioned, externally peer reviewed.
36

37
38 **12 Data sharing statement**
39

40
41 13 No additional data are available.
42

43
44 **14 Open access**
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1 **References**

- 2 1. Cummings SR, Kelsey JL, Nevitt MC, et al. Epidemiology of osteoporosis and osteoporotic
3 fractures. *Epidemiol Rev* 1985;7:178-208. doi: 10.1093/oxfordjournals.epirev.a036281
- 4 2. Gullberg B, Johnell O, Kanis JA. World-wide projections for hip fracture. *Osteoporos Int*
5 1997;7(5):407-13. doi: 10.1007/pl00004148
- 6 3. Schousboe JT. Epidemiology of Vertebral Fractures. *J Clin Densitom* 2016;19(1):8-22. doi:
7 10.1016/j.jocd.2015.08.004
- 8 4. Alexiou KI, Roushias A, Varitimidis SE, et al. Quality of life and psychological consequences
9 in elderly patients after a hip fracture: a review. *Clin Interv Aging* 2018;13:143-50. doi:
10 10.2147/CIA.S150067
- 11 5. Ciubean AD, Ungur RA, Irsay L, et al. Health-related quality of life in Romanian
12 postmenopausal women with osteoporosis and fragility fractures. *Clin Interv Aging*
13 2018;13:2465-72. doi: 10.2147/CIA.S190440
- 14 6. Svedbom A, Borgstrom F, Hernlund E, et al. Quality of life for up to 18 months after low-energy
15 hip, vertebral, and distal forearm fractures-results from the ICUROS. *Osteoporos Int*
16 2018;29(3):557-66. doi: 10.1007/s00198-017-4317-4
- 17 7. Farahmand BY, Michaelsson K, Ahlbom A, et al. Survival after hip fracture. *Osteoporos Int*
18 2005;16(12):1583-90. doi: 10.1007/s00198-005-2024-z

- 1
2
3
4
5
6
7 1 8. Lau E, Ong K, Kurtz S, et al. Mortality following the diagnosis of a vertebral compression
8
9 2 fracture in the Medicare population. *J Bone Joint Surg Am* 2008;90(7):1479-86. doi:
10 11
12 3 10.2106/JBJS.G.00675
13
14
15 4 9. Borgstrom F, Karlsson L, Ortsater G, et al. Fragility fractures in Europe: burden, management
16
17 5 and opportunities. *Arch Osteoporos* 2020;15(1):59. doi: 10.1007/s11657-020-0706-y
18
19
20
21 6 10. Taguchi Y, Inoue Y, Kido T, et al. Treatment costs and cost drivers among osteoporotic
22
23 7 fracture patients in Japan: a retrospective database analysis. *Arch Osteoporos* 2018;13(1):45. doi:
24
25 8 10.1007/s11657-018-0456-2
26
27
28
29
30 9 11. Kanis JA, Johnell O, Oden A, et al. Long-term risk of osteoporotic fracture in Malmo.
31
32 10 *Osteoporos Int* 2000;11(8):669-74. doi: 10.1007/s001980070064
33
34
35
36 11 12. Ensrud KE. Epidemiology of fracture risk with advancing age. *J Gerontol A Biol Sci Med Sci*
37
38 12 2013;68(10):1236-42. doi: 10.1093/gerona/glt092
39
40
41
42 13 13. Kanis JA, Johnell O, Oden A, et al. FRAX and the assessment of fracture probability in men
43
44 14 and women from the UK. *Osteoporos Int* 2008;19(4):385-97. doi: 10.1007/s00198-007-0543-5
45
46
47
48 15 14. Lane NE. Epidemiology, etiology, and diagnosis of osteoporosis. *Am J Obstet Gynecol*
49
50 16 2006;194(2 Suppl):S3-11. doi: 10.1016/j.ajog.2005.08.047
51
52
53
54 17 15. De Laet C, Kanis JA, Oden A, et al. Body mass index as a predictor of fracture risk: a meta-
55
56 18 analysis. *Osteoporos Int* 2005;16(11):1330-8. doi: 10.1007/s00198-005-1863-y
57
58
59
60

- 1
2
3
4
5
6 1 16. Johansson H, Kanis JA, Oden A, et al. A meta-analysis of the association of fracture risk and
7
8
9 2 body mass index in women. *J Bone Miner Res* 2014;29(1):223-33. doi: 10.1002/jbmr.2017
10
11
12 3 17. Kaze AD, Rosen HN, Paik JM. A meta-analysis of the association between body mass index
13
14
15 4 and risk of vertebral fracture. *Osteoporos Int* 2018;29(1):31-39. doi: 10.1007/s00198-017-4294-
16
17
18 5 7
19
20
21 6 18. Fujiwara S, Kasagi F, Yamada M, et al. Risk factors for hip fracture in a Japanese cohort. *J*
22
23
24 7 *Bone Miner Res* 1997;12(7):998-1004. doi: 10.1359/jbmr.1997.12.7.998
25
26
27 8 19. Rikkonen T, Sund R, Sirola J, et al. Obesity is associated with early hip fracture risk in
28
29
30 9 postmenopausal women: a 25-year follow-up. *Osteoporos Int* 2021;32(4):769-77. doi:
31
32
33 10 10.1007/s00198-020-05665-w
34
35
36 11 20. Siris ES, Miller PD, Barrett-Connor E, et al. Identification and fracture outcomes of
37
38
39 12 undiagnosed low bone mineral density in postmenopausal women: results from the National
40
41
42 13 Osteoporosis Risk Assessment. *JAMA* 2001;286(22):2815-22. doi: 10.1001/jama.286.22.2815
43
44
45 14 21. Robbins J, Aragaki AK, Kooperberg C, et al. Factors associated with 5-year risk of hip fracture
46
47
48 15 in postmenopausal women. *JAMA* 2007;298(20):2389-98. doi: 10.1001/jama.298.20.2389
49
50
51 16 22. Xiang BY, Huang W, Zhou GQ, et al. Body mass index and the risk of low bone mass-related
52
53
54 17 fractures in women compared with men: A PRISMA-compliant meta-analysis of prospective
55
56
57 18 cohort studies. *Medicine (Baltimore)* 2017;96(12):e5290. doi: 10.1097/MD.0000000000005290
58
59
60

- 1
2
3
4
5
6
7 1 23. Welfare. MoHLA. Japanese government report: Computer-administered claims penetration
8
9 2 rate. 2015
10
11
12 3 24. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity
13
14 4 in longitudinal studies: development and validation. *J Chronic Dis* 1987;40(5):373-83. doi:
15
16 5 10.1016/0021-9681(87)90171-8
17
18
19 6 25. Sundararajan V, Henderson T, Perry C, et al. New ICD-10 version of the Charlson
20
21 7 comorbidity index predicted in-hospital mortality. *J Clin Epidemiol* 2004;57(12):1288-94. doi:
22
23 8 10.1016/j.jclinepi.2004.03.012
24
25
26
27 9 26. Spector TD, McCloskey EV, Doyle DV, et al. Prevalence of vertebral fracture in women and
28
29 10 the relationship with bone density and symptoms: the Chingford Study. *J Bone Miner Res*
30
31 11 1993;8(7):817-22. doi: 10.1002/jbmr.5650080707
32
33
34 12 27. Kitazawa A, Kushida K, Yamazaki K, et al. Prevalence of vertebral fractures in a population-
35
36 13 based sample in Japan. *J Bone Miner Metab* 2001;19(2):115-8. doi: 10.1007/s007740170049
37
38
39 14 28. Yoshimura N, Kinoshita H, Oka H, et al. Cumulative incidence and changes in the prevalence
40
41 15 of vertebral fractures in a rural Japanese community: a 10-year follow-up of the Miyama cohort.
42
43 16 *Archives of Osteoporosis* 2006;1(1-2):43-49. doi: 10.1007/s11657-006-0007-0
44
45
46 17 29. Tamaki J, Fujimori K, Ikehara S, et al. Estimates of hip fracture incidence in Japan using the
47
48 18 National Health Insurance Claim Database in 2012-2015. *Osteoporos Int* 2019;30(5):975-83. doi:
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3
4
5
6 1 10.1007/s00198-019-04844-8
7
8
9 2 30. Lloyd JT, Alley DE, Hawkes WG, et al. Body mass index is positively associated with bone
10
11
12 3 mineral density in US older adults. Arch Osteoporos 2014;9:175. doi: 10.1007/s11657-014-0175-
13
14
15 4 2
16
17
18 5 31. Sogaard AJ, Holvik K, Omsland TK, et al. Age and Sex Differences in Body Mass Index as
19
20
21 6 a Predictor of Hip Fracture: A NOREPOS Study. Am J Epidemiol 2016;184(7):510-19. doi:
22
23
24 7 10.1093/aje/kww011
25
26
27 8 32. Fini M, Salamanna F, Veronesi F, et al. Role of obesity , alcohol and smoking on bone health.
28
29
30 9 Front Biosci (Elite Ed) 2012;4:2586-606. doi: 10.2741/e575
31
32
33 10 33. Ng AC, Melton LJ, 3rd, Atkinson EJ, et al. Relationship of adiposity to bone volumetric
34
35
36 11 density and microstructure in men and women across the adult lifespan. Bone 2013;55(1):119-
37
38
39 12 25. doi: 10.1016/j.bone.2013.02.006
40
41
42 13 34. Villareal DT, Apovian CM, Kushner RF, et al. Obesity in older adults: technical review and
43
44
45 14 position statement of the American Society for Nutrition and NAASO, The Obesity Society. Am
46
47
48 15 J Clin Nutr 2005;82(5):923-34. doi: 10.1093/ajcn/82.5.923
49
50
51 16 35. Felson DT, Zhang Y, Hannan MT, et al. Effects of weight and body mass index on bone
52
53
54 17 mineral density in men and women: the Framingham study. J Bone Miner Res 1993;8(5):567-73.
55
56
57 18 doi: 10.1002/jbmr.5650080507
58
59
60

- 1
2
3
4
5
6
7 1 36. Bouxsein ML, Szulc P, Munoz F, et al. Contribution of trochanteric soft tissues to fall force
8
9 2 estimates, the factor of risk, and prediction of hip fracture risk. *J Bone Miner Res* 2007;22(6):825-
10
11
12 3 31. doi: 10.1359/jbmr.070309
13
14
15 4 37. Premaor MO, Pilbrow L, Tonkin C, et al. Obesity and fractures in postmenopausal women. *J*
16
17
18 5 *Bone Miner Res* 2010;25(2):292-7. doi: 10.1359/jbmr.091004
19
20
21 6 38. Compston JE, Watts NB, Chapurlat R, et al. Obesity is not protective against fracture in
22
23
24 7 postmenopausal women: GLOW. *Am J Med* 2011;124(11):1043-50. doi:
25
26
27 8 10.1016/j.amjmed.2011.06.013
28
29
30 9 39. Kim SH, Yi SW, Yi JJ, et al. Association Between Body Mass Index and the Risk of Hip
31
32
33 10 Fracture by Sex and Age: A Prospective Cohort Study. *J Bone Miner Res* 2018;33(9):1603-11.
34
35
36 11 doi: 10.1002/jbmr.3464
37
38
39 12 40. Holmberg AH, Johnell O, Nilsson PM, et al. Risk factors for fragility fracture in middle age.
40
41
42 13 A prospective population-based study of 33,000 men and women. *Osteoporos Int*
43
44
45 14 2006;17(7):1065-77. doi: 10.1007/s00198-006-0137-7
46
47
48 15 41. Amouzougan A, Lafaie L, Marotte H, et al. High prevalence of dementia in women with
49
50
51 16 osteoporosis. *Joint Bone Spine* 2017;84(5):611-14. doi: 10.1016/j.jbspin.2016.08.002
52
53
54 17 42. Kazama JJ. Chronic kidney disease and fragility fracture. *Clin Exp Nephrol* 2017;21(Suppl
55
56
57 18 1):46-52. doi: 10.1007/s10157-016-1368-3
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1 43. Kanis JA, Johnell O, Oden A, et al. Smoking and fracture risk: a meta-analysis. *Osteoporos*
2 *Int* 2005;16(2):155-62. doi: 10.1007/s00198-004-1640-3

3 44. Zhang X, Yu Z, Yu M, et al. Alcohol consumption and hip fracture risk. *Osteoporos Int*
4 2015;26(2):531-42. doi: 10.1007/s00198-014-2879-y

5 45. Iconaru L, Moreau M, Kinnard V, et al. Does the Prediction Accuracy of Osteoporotic
6 Fractures by BMD and Clinical Risk Factors Vary With Fracture Site? *JBMR Plus*
7 2019;3(12):e10238. doi: 10.1002/jbm4.10238

8 46. Gaddini GW, Turner RT, Grant KA, et al. Alcohol: A Simple Nutrient with Complex Actions
9 on Bone in the Adult Skeleton. *Alcohol Clin Exp Res* 2016;40(4):657-71. doi:
10 10.1111/acer.13000

1 **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)

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

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

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

4

For peer review only

Table 2.

Comparison of participants' demographics between BMI categories.

Parameters	BMI categories		
	Underweight n = 2,684	Normal weight n = 17,667	Overweight and Obese 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)/ 75–79/ 80–84/ 85≤	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)
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)*
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

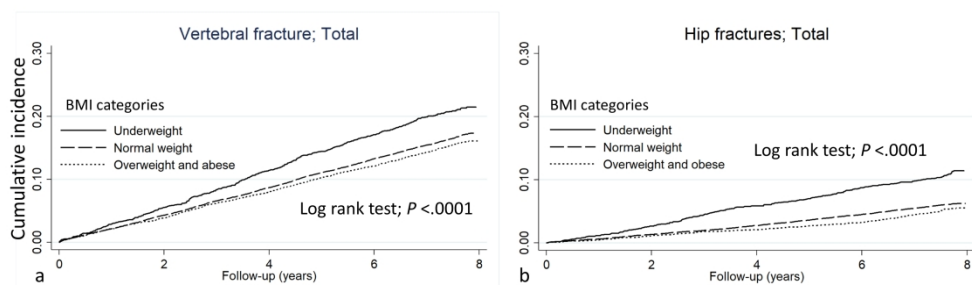


Image 1: Figure. 1

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)

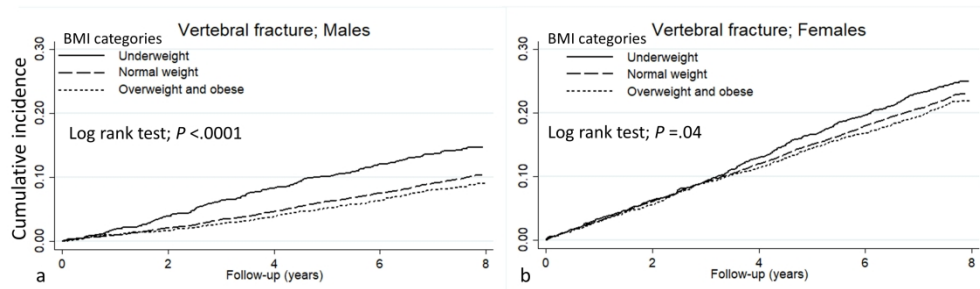


Image 2: Figure. 2

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)

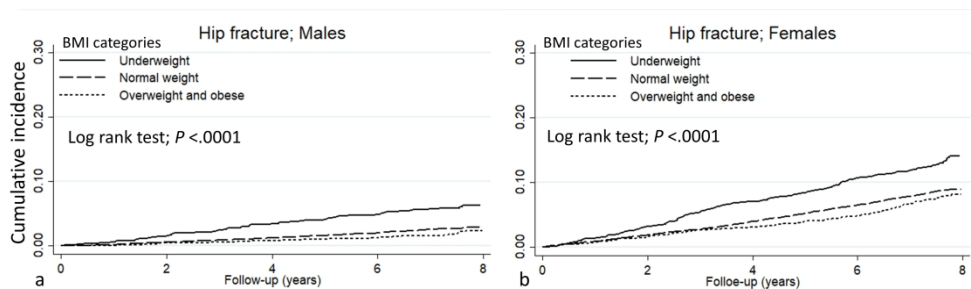


Image 3: Figure. 3

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 (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	11
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (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 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 (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	12 Table 3, 4 9 Table 2
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.