의학박사 학위논문

체중변동성이 골절에 미치는 영향 : 50세 이상 한국 성인을 대상으로 한 인구기반 연구

Impact of weight variability on the risk of fracture : A population based study among Korean over 50

2020년 2월

서울대학교 대학원

의학과 임상의과학 전공

조 유 선

A thesis of the Degree of Doctor of Philosophy

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February 2020

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지도교수 박 상 민

이 논문을 의학박사 학위논문으로 제출함

2019년 10월

서울대학교 대학원

의학과 임상의과학 전공

조 유 선

조유선의 박사 학위 논문을 인준함

2020년 1월

위 원 장 윤 영 호 (인)

부위원장 박 상 민 (인)

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by

Yoosun Cho

A thesis submitted to the Department of Clinical medical sciences in partial fulfillment of the requirements for the Degree of Doctor of Philosophy in clinical medical sciences as Seoul National University College of Medicine

January 2020

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Abstract

Impact of weight variability on the risk of fracture
: A population based study among Korean over 50

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Background: In Korea, the incidence of hip, vertebral, and upper extremity fractures is increasing and mortality related to fractures is higher compared to that of other countries. We aimed to investigate the relationship between variability in body mass index (BMI), and risk of fractures in this large-scale population-based cohort in Korea.

Methods: Within a population-based cohort of 166,932 men and women aged 50 years or older from the National Health Insurance Service- Health Screening Cohort, weight variability from three follow-up examinations during 2002-2007 was categorized into quartiles. The risk of admission from the fractures in hip, spinal, and upper extremity during 2008-2015 according to BMI variability was determined by calculating the hazard ratios (HRs) and 95% confidence intervals (CIs) using Cox proportional hazards regression analysis.

Results: Compared to those within the first quartile (lowest) of weight variability, those within the second, third, and fourth quartile (highest) of weight variability had increased risk of total fractures (aHR 1.07, 95% CI 1.01-1.15; aHR 1.10, 95% CI 1.03-1.17; aHR 1.16 95% CI 1.09-1.23, respectively). Furthermore, the risk of total fractures increased upon greater degrees of weight variability (*p* for trend <0.001). Among individuals who had osteoporosis, those within the greatest weight variability had increased risk of fractures (aHR 1.19, 95% CI 1.07-1.32) compared to those within the first quartile of weight variability. Among individuals without osteoporosis, those within greatest weight variability had increased risk of fractures (aHR 1.14, 95% CI 1.06-1.23). The relationship between BMI variability and fracture seemed to be varied according to the presence of osteoporosis (*p* for interaction=0.003). The risk-increasing effect of weight variability on fracture was preserved regardless of direction of weight change.

Conclusion: Weight variability was associated with increased risk of fracture at hip, spinal, and upper extremity. Weight maintenance, instead of weight fluctuation, may be beneficial in lowering the risk of fracture among over 50 year-old Korean adults.

Keywords : body weight changes; fractures; bone; osteoporosis
Student Number : 2017-35314

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Ⅰ. INTRODUCTION

1. Background

Increasing concern about osteoporosis regarded as another chronic disease in the society, I started off investigation about bone health with this cross-sectional study based on Korean elderly men and women. It was conducted using the fourth (IV) and fifth (V) Korea National Health and Nutrition Examination Survey (KNHANES), a nationwide survey database representing the non-institutionalized civilian population of Korea. KNHANES IV and V were organized by the Korean Ministry of Health and Welfare from 2008 to 2011 and included health surveys along with large-scale whole-body dual energy X-ray absorptiometry (DXA) examinations. As a result, heavy alcohol intake for men was related to low whole body bone mineral density (BMD) and light alcohol intake for women was associated with high whole body, spinal, and total femur BMD (Table 1, 2, 3 and Figure 1). Since prevention of fracture is an ultimate goal for bone health, a longitudinal study assessing risk factors for fragility fracture is imperative and the issue of body weight has been the first step.

Table 1. Characteristics of study participants by alcohol intake

Gender	Men (n= 2,657)				Women (n= 2,080)			
Alcohol intake	0 g/day	1-19 g/day	20-39 g/day	≥ 40 g/day	0 g/day	1-9 g/day	10-19 g/day	≥ 20 g/day
Number of people	489	1,470	540	158	1,329	657	46	48
Age, year								
50-64	55.01	60.54	73.52	71.52	68.98	70.16	77.55	84.62
65-79	44.99	39.46	26.48	28.48	31.02	29.84	22.45	15.38
Body mass index, kg/㎡								
	23.66±2.95	23.76±2.84	24.00±2.85	23.77±3.20	24.45±3.01	24.15±2.95	23.85±3.01	24.59±3.24
Household income								
Lowest third	21.88	25.65	21.11	24.68	29.80	29.53	23.91	35.42
Middle third	50.92	48.10	49.07	50.63	47.18	44.90	47.83	50.00
High third	25.15	25.31	28.33	24.05	21.67	24.20	28.26	14.58
Smoking								
non smoker	18.61	14.01	12.41	10.76	93.60	89.19	86.96	58.33
smoker	55.83	61.63	63.33	72.15	5.35	9.13	10.87	41.67
past smoker	25.56	24.29	24.26	17.09	1.05	1.67	2.17	0.00
Physical activity, MET min^{-1a}								
Low (≤600)	28.22	22.99	20.93	27.22	34.01	27.70	19.57	33.33

Moderate (601~2999)	39.88	42.45	33.89	33.54	38.90	44.29	32.61	31.25
High (≥3000)	31.90	34.22	44.63	39.24	26.64	27.85	47.83	35.42
25-hydroxyvitamin D								
Low (< 20 ng/mL)	50.10	43.74	46.30	42.41	74.77	75.00	50.00	100.00
Normal (≥20ng/mL)	46.63	53.40	51.85	54.43	21.50	23.68	50.00	0.00
Comorbidity[b]								
None	90.80	94.35	94.63	98.73	85.33	84.93	84.78	89.58
1 or more	9.20	5.65	5.37	1.27	14.67	15.07	15.22	10.42
Whole body BMD, g/㎠	1.160±0.117	1.164±0.117	1.163±0.117	1.143±0.119	1.029±0.121	1.046±0.134	1.028±0.129	1.039±0.142
Spinal BMD, g/㎠	0.931±0.164	0.947±0.152	0.953±0.150	0.923±0.144	0.831±0.142	0.842±0.147	0.833±0.158	0.867±0.140
Femur neck BMD, g/㎠	0.738±0.125	0.755±0.115	0.765±0.117	0.748±0.108	0.653±0.106	0.664±0.109	0.663±0.123	0.687±0.099
Total femur BMD, g/㎠	0.916±0.134	0.933±0.125	0.944±0.121	0.926±0.118	0.807±0.113	0.817±0.119	0.815±0.127	0.828±0.113

Acronyms: BMD, bone mass density; MET, metabolic equivalent task
Values are presented as mean±SD for continuous variables or numbers (%) for categorical variables.
[a] Physical activity was calculated according to MET on the International Physical Activity Questionnaire (IPAQ).
[b] Presence of comorbidity was related to bone quality, thyroid disease, liver cirrhosis, chronic kidney disease, or rheumatoid arthritis.

Table 2. Stratified, multivariate-adjusted analyses of whole body BMD by alcohol intake in men compared to the light alcohol intake group.

Alcohol intake	0 g/day	1-19 g/day (ref)	20-39 g/day	≥ 40 g/day
Number of people	489	1,470	540	158
Age, years				
50-64	1.170 (1.154-1.186)	1.179 (1.171-1.188)	1.168 (1.157-1.180)	1.151 (1.128-1.174)*
65-79	1.156 (1.133-1.178)	1.148 (1.136-1.160)	1.159 (1.132-1.187)	1.161 (1.122-1.201)
Body mass index, kg/㎡				
< 24.9	1.148 (1.131-1.165)	1.158 (1.149-1.167)	1.148 (1.134-1.161)	1.130 (1.104-1.156)*
≥ 25.0	1.203 (1.183-1.224)	1.196 (1.184-1.208)	1.197 (1.179-1.214)	1.189 (1.156-1.223)
Smoking				
Never	1.164 (1.144-1.187)	1.184 (1.167-1.202)	1.196 (1.162-1.229)	1.216 (1.150-1.282)
Current or Past smoker	1.170 (1.154-1.185)	1.169 (1.162-1.177)	1.160 (1.149-1.172)	1.144 (1.122-1.165)*
Physical activity, MET min^{-1}				
Low (≤ 600)	1.164 (1.136-1.192)	1.165 (1.149-1.182)	1.177 (1.156-1.197)	1.166 (1.132-1.200)
Moderate or high (≥ 601)	1.168 (1.154-1.183)	1.173 (1.165-1.181)	1.162 (1.150-1.175)	1.144 (1.120-1.169)*
Household income				
Lowest	1.178 (1.137-1.218)	1.158 (1.142-1.173)	1.130 (1.105-1.155)	1.086 (1.033-1.139)*

Middle or high	1.156 (1.141-1.171)	1.169 (1.159-1.179)	1.167 (1.152-1.183)	1.162 (1.137-1.188)
25-hydroxyvitamin D				
Low (< 20 ng/mL)	1.171 (1.152-1.190)	1.169 (1.159-1.179)	1.162 (1.146-1.178)	1.151 (1.122-1.179)
Normal (≥20 ng/mL)	1.162 (1.144-1.180)	1.173 (1.163-1.183)	1.167 (1.152-1.182)	1.150 (1.120-1.180)

BMD, bone mass density; MET, metabolic equivalent task

Adjusted mean (95% confidence interval) calculated by linear regression model analysis adjusted for age, BMI, smoking, physical activity, household income, comorbidity and 25(OH) Vit D level in men.

p value: <0.05 (*), <0.01 (**), <0.001 (***)

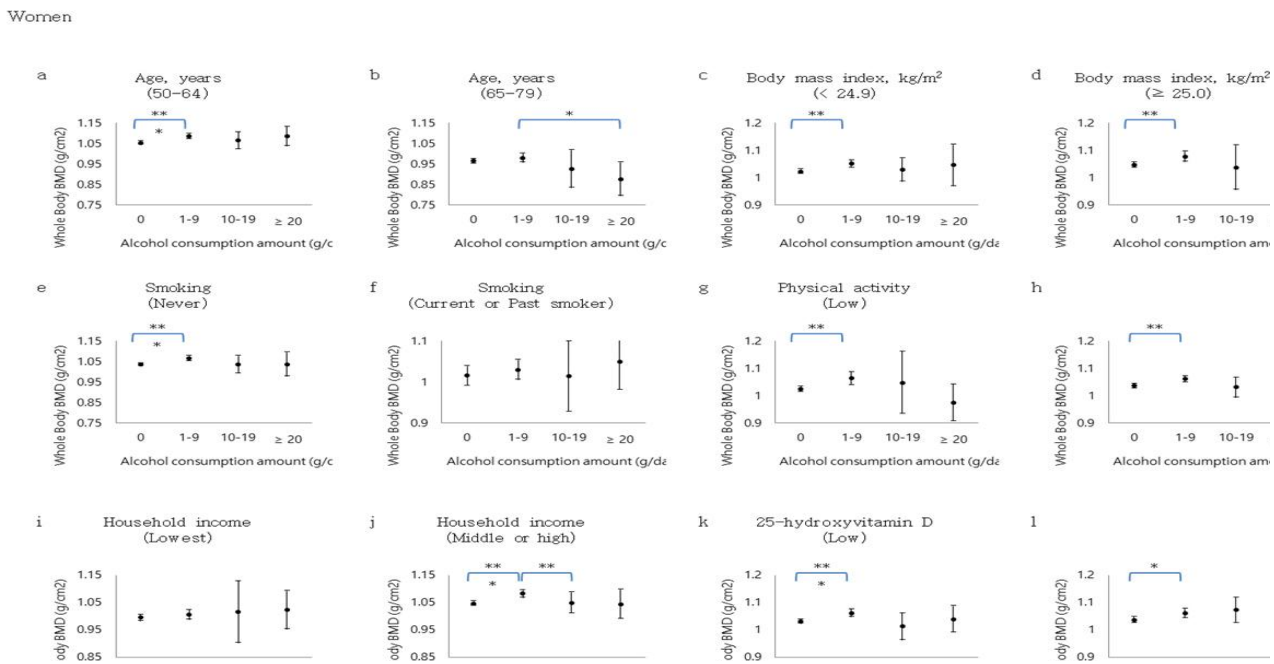
Table 3. Stratified, multivariate-adjusted analyses of whole body BMD by alcohol intake in women compared to the light alcohol intake group.

Alcohol intake	0 g/day	1-9 g/day (ref)	10-19 g/day	≥ 20 g/day
Number of people	1,329	657	46	48
Age, years				
50-64	1.053 (1.046-1.061)***	1.084 (1.072-1.096)	1.059 (1.018-1.100)	1.086 (1.037-1.135)
65-79	0.965 (0.952-0.977)	0.983 (0.960-1.006)	0.934 (0.841-1.028)	0.884 (0.760-1.008)*
Body mass index, kg/㎡				
< 24.9	1.023 (1.015-1.032)**	1.049 (1.036-1.063)	1.025 (0.983-1.067)	1.047 (0.973-1.121)
≥ 25.0	1.049 (1.039-1.060)**	1.081 (1.062-1.099)	1.044 (0.962-1.127)	1.065 (1.013-1.117)
Smoking				
Never	1.036 (1.029-1.043)***	1.066 (1.054-1.077)	1.039 (0.997-1.081)	1.047 (0.982-1.112)
Current or Past smoker	1.018 (0.993-1.043)	1.027 (1.000-1.053)	0.986 (0.901-1.071)	1.050 (0.983-1.117)
Physical activity, MET min^{-1}				
Low (≤ 600)	1.027 (1.016-1.038)**	1.067 (1.045-1.089)	1.055 (0.942-1.168)	0.989 (0.913-1.065)
Moderate or high (≥ 601)	1.036 (1.028-1.045)**	1.060 (1.048-1.072)	1.026 (0.990-1.062)	1.092 (1.041-1.143)
Household income				
Lowest	0.995 (0.983-1.006)	1.006 (0.988-1.024)	1.016 (0.903-1.129)	1.023 (0.953-1.092)

Middle or high	1.047 (1.039-1.055)***	1.082 (1.068-1.095)	1.049 (1.011-1.088)**	1.044 (0.991-1.097)
25-hydroxyvitamin D				
Low (< 20 ng/mL)	1.031 (1.023-1.039)***	1.062 (1.048-1.076)	1.013 (0.963-1.062)	1.039 (0.991-1.088)
Normal (≥20 ng/mL)	1.037 (1.026-1.048)*	1.061 (1.044-1.078)	1.073 (1.027-1.119)	1.068 (0.969-1.168)

BMD, bone mass density; MET, metabolic equivalent task
Adjusted mean (95% confidence interval) calculated by linear regression model analysis adjusted for age, BMI, smoking, physical activity, household income, comorbidity and 25(OH) Vit D level in women.
p value: <0.05 (*), <0.01 (**), <0.001 (***)

Figure 1. The association between alcohol consumption and BMD in both men and women



Adjusted mean values calculated by linear regression model analysis adjusted for age, BMI, smoking, physical activity, household income, comorbidity and 25(OH) Vit D level in (A) men and (B) women.

P value: <0.05 (*), <0.01 (**), <0.001 (***)

BMD, bone mineral density

Admission due to fractures, particularly among older people, is a growing worldwide public health problem. According to this recent review article, there are outstanding variations in hip fracture rates and in the 10-year probability of major osteoporotic fractures in the different countries. It might be due to disparity on geographic-, ethnic-, age- and sex-specific incidence of fracture between countries (1-3). Korea is in moderate to high risk of fracture contributed by increase in urbanization, increase in medical accessibility, and finally increase in survival of older population (1). A previous study predicted that approximately 59.5% of women and 23.8% of men in Korea aged more than 50 years experiences osteoporosis-related fractures (4).

The percentage of hip fracture is rising globally as the population ages. Asian population belongs to the moderate risk countries, and Korean population belongs to the high risk countries for men, and moderate risk countries for women(3). Although today about half of the hip fractures occur in Europe and North America, the steepest increases will be observed in Asia along with Latin America (5). In case of hip fractures, increasing trend in both genders, of 0.7%/year in men and 1.6%/year in women, was reported for South Korea (1). Actually, the radiographic incidence of vertebral fractures is much higher than that of hip fractures, whereas the incidence rate of clinical vertebral fractures is comparable to the rate of clinical vertebral fractures is comparable to the rate of hip fractures in most countries, indicating that the rate of vertebral fractures has become higher than that officially reported in the real world (2). In South Korea, the incidence of vertebral fracture was comparable with those of other countries and the mortality was higher among those with fractures compared to those without fractures (6, 7). The second most common form of osteoporotic fracture in Korea, distal radius fractures, can be a significant risk factor for subsequent osteoporotic fractures in older patients (8). It is well-known that hip or vertebral fracture increase the risk of mortality although other fracture including one at upper extremity is controversial (7, 9-13). However, it is undeniable that any fracture regardless of specific site of it could increase multi-cause morbidity, and loss of functional independence.

2. Previous literature

1) Body weight and fracture

A low body mass index (BMI), being underweight, is a well-known risk factor for future fracture whereas a high BMI appears to be protective (14, 15). However, there is a controversy in the relationship between increased BMI and fracture. Increased BMI was positively associated with a higher risk of upper extremity fractures (16, 17), and the relationship between BMI and risk of fractures after adjustment for BMD was appeared not to be linear, but U-shaped (14). In the aspect of the change of weight, weight loss could increase the risk of hip fracture however that weight gain may reduce the risk of hip fracture (18). However, weight gain (≥5% of body weight over three years) was related to increased incidence rates of upper and lower extremity fractures (19). In this large cohort of older men, most hip and other nonspine fractures occurred in those who were overweight or obese (20), implying increased weight is not always desirable to bone health.

2) Body weight change and fracture

There is a well-studied meta-analysis which suggests that weight loss may be a risk factor for hip fracture and that weight gain may be a protective factor for hip fracture (18). According to this meta-analysis including eight prospective studies, weight loss is more likely a risk factor of hip fracture (RR 1.84, 95% CI 1.45-2.33). In contrast, weight gain can decrease the risk of hip fracture (RR 0.73, 95% CI 0.61-0.89). Among the 45-74 aged Chinese population, Dai et al. provided evidence that substantial weight loss is an important risk factor for osteoporotic hip fractures (21). They used prospective data from the Singapore Chinese Health Study, a population-based cohort of 63,257 Chinese men and women. Weight change was estimated based on the weight difference over an average of 6 years, and grouped as loss ≥ 10 %, loss 5 to <10 %, loss or gain <5 %. Compared to stable weight, weight loss ≥10 % was associated with 39 % increased risk (hazard ratio 1.39; 95% CI 1.14-1.69). Such increased risk with weight loss ≥ 10% was resulted in both genders and age groups at follow-up (≤65 and >65 years) and in those with baseline BMI ≥20 kg/㎡. There was no significant association with weight gain.

3) Body weight variability and fracture

Unlike the association between BMI or change of BMI and fracture, the relationship between BMI variability and fracture has not been well-investigated upon. According to a previous prospective study of middle-aged Norwegians, high weight variability was associated with increased risk of hip fracture (22). This cohort study followed by an average 11.6 years from the third examination with respect to hip fracture was assessed by linear regression in weight change between the three examinations. In both sexes, those with the highest weight variability had an increased risk of fracture (RR 2.07, 95% CI 1.24–3.46 in women, and RR 2.70, 95% CI 1.25–5.86 in men, high vs low quarter of weight variability). High weight variability defined a group with increased risk of hip fracture in this middle-aged cohort. The effect was independent of BMI and a linear trend in weight change. However, it did not include elderly people, a population with the greatest burden of hip fracture. Another study showed that a history of weight cycling had no adverse effect on total femur and total-body bone mineral density in overweight sedentary premenopausal women (23), but it is unclear if these findings would be consistent across other populations, ethnic groups, or age groups. There is lack of study that explored the association between BMI variability and fractures in Asian populations.

II. Purpose

We aimed to investigate the relationship between variability in BMI and risk of fractures in this large-scale population-based cohort study using the Korean National Health Insurance System – National Health Screening Cohort (NHIS-HEALS) database.

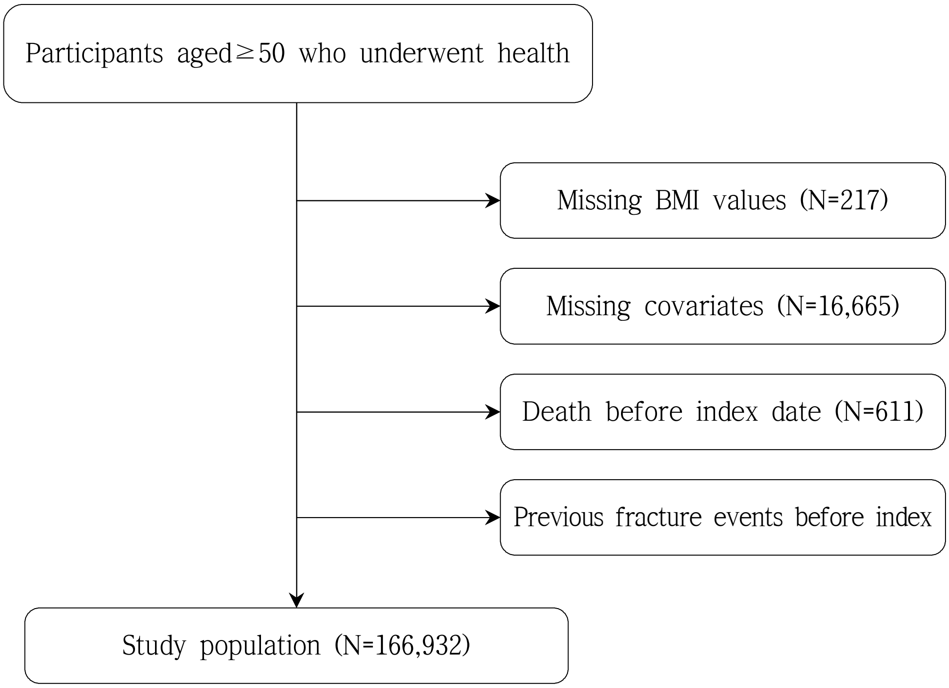
Ⅲ. Methods

1. Study population

The study population was derived from the NHIS-HEALS research database in Korea. All health insurance enrollees are required to undergo health checkups on a biannual basis once they turn 40 years old. The NHIS built a database using a simple random sampling method based on data from health examinations, sociodemographics, hospital use, and death registries. Multiple epidemiological studies ranging across various fields have used this NHIS database, and its validity has been described in detail elsewhere (24, 25).

Among 192,300 men and women aged 50 years or older who underwent health examinations during the first (2002-2003), second (2004-2005), and third (2006-2007) health examination periods, we excluded 217 participants with missing BMI values. Furthermore, 16,665 individuals with missing values on covariates and 611 participants who died before the index date of 1 January 2008 were excluded. Lastly, 7,875 participants who had fractures before the index date were excluded. The final study population consisted of 166,932 men and women (Figure 2). The Seoul National University Hospital Institutional Review Board approved this study (IRB number:E-1901-025-1001) and waived the requirement for informed consent from study participants as the NHIS database is anonymized in adherence to strict confidentiality guidelines.

Figure 2. Study Population



Key variables

BMI values, determined by dividing the weight in kilograms by the height in meters squared, were measured for each of the three health examination periods; the first (2002-2003), second (2004-2005), and third (2006-2007). Then, weight variability was then calculated by the average successive variability (ASV) method (26). In detail, weight variability was determined by calculating the averaged absolute values of the differences in BMI between examinations. Then, the study population was categorized into four groups according to quartiles of weight variability, with the first quartile having the lowest weight variability and the fourth quartile having the highest weight variability.

Hospital admission records from the NHIS-HEALS research database were used to determine hospital admission and causes of admission. Hospital admission from fractures was identified as participants with admission dates between 1 January 2008 and 31 December 2015. Among those with an admission date, the admission due to fractures from the Tenth Revision of International Classification of Diseases (ICD-10) codes by the World Health Organization was identified. Admission from fractures was defined when the cause of admission was due to ICD-10 codes for hip fractures (S72.0, S72.1), spinal fractures (S22.0, S22.1, S32.0, M48.4, M48.5), and upper extremity fractures (S52.5, S52.6, S42.2, S42.3). We clinically defined "spinal fractures" as claims listing an ICD-10 code of S22.0 (fracture of the thoracic spine), S22.1 (multiple fractures of the thoracic spine), S32.0 (fracture of the spinal spine), M48.4 (fatigue fracture of vertebra) and M48.5 (collapsed vertebra, not elsewhere classified (NEC)). These criteria were adopted from previous studies that used nationwide health claims database for identifying fracture outcomes (6, 27-29).

Potential confounding covariates considered were age (continuous, years), sex (categorical, men and women), baseline BMI (continuous, kg/㎡), change in BMI (continuous, kg/㎡), household income (categorical, 1st, 2nd, 3rd, and 4th quartiles), smoking (categorical, never, past, and current smokers), alcohol consumption (categorical, none, <1, 1-2, 3-4, 5, times per week), physical activity (categorical, none, 1-2, 3-4, 5-6, 7, times per week), comorbidity (categorical, Charlson comorbidity index, <4 or ≥4 %) and diagnosis with osteoporosis (categorical, yes or no). We defined the participants who had osteoporosis as those diagnosed with ICD-10 codes for osteoporosis. BMI change or direction of weight change was determined by the difference in BMI values between the third and first health examinations. BMI change or direction of weight change was determined by the difference in BMI values between the third and first health examinations. Household income was determined by the insurance premium. Charlson comorbidity index was determined by assessing major comorbidities during 2002-2007 using an algorithm for calculating the Charlson comorbidity index from claims data from a previous study (30).

Statistical analysis

All participants were followed-up from 1 January 2008 until incidence of a fracture, at the date of death or 31 December 2015, whichever came first. We computed Kaplan-Meier survival curves to evaluate crude survival. Also, we used Schoenfeld residual method to see if the covariates violate cox proportional hazard assumption. The risk of admission from the fractures in hip, spinal, and upper extremity according to BMI variability was determined by calculating the hazard ratios (HRs) and 95% confidence intervals (CIs) using Cox proportional hazards regression analysis. In all analyses, the first quartile of BMI variability, those with the lowest BMI variability was considered the reference group. We conducted stratified subgroup analyses by dividing the participants into subgroups for each covariate and calculating the multivariate-adjusted HRs and 95% CI by Cox proportional hazards regression analyses for each subgroup of age, sex, initial BMI, direction of weight change, and diagnosis with osteoporosis. For sensitivity analyses, the effect of weight variability on fracture adjusting absolute of BMI instead change of BMI was conducted. Additional assessment on the effect of weight variability on fracture according to different weight change patterns; continuous weight gain (gain of weight between every examinations), continuous weight loss (loss of weight between every examinations), and weight fluctuation (other than continuous weight gain or continuous weight loss). Also, another sensitivity analysis with fracture as an admission or at least three clinic visits was conducted.

Statistical significance was defined as a p value of less than 0.05 in a two-sided manner. All data collection and statistical analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC, USA). Finally, the proportional hazard assumption between BMI variability and fracture was validated graphically using Kaplan-Meier survival curves. For covariates, we have checked the validity through Schoenfeld residuals and log-log transformed survival curves.

Ⅳ. Results

1. Baseline characteristics

Table 4, 5 and 6 depict the descriptive characteristics of the study population according to weight variability for total population, men, and women. The number of individuals for the first, second, third, and fourth quartiles of weight variability are 41,798, 416,699, 41,700, and 41,765 participants, respectively. The mean age for the first, second, third, and fourth quartile groups were 59.00, 59.25, 59.73 and 60.66. The mean weight variability values determined by ASV for the first, second, third, and fourth quartile groups were 0.28 kg/㎡, 0.59 kg/㎡, 0.92 kg/㎡, and 1.79 kg/㎡ respectively. The mean initial BMI for the first, second, third, and fourth quartile groups were 23.79 kg/㎡, 23.90 kg/㎡, 24.08 kg/㎡, and 24.54 kg/㎡, respectively. Participants who were female, had lower household income, were never smokers, did not consume alcohol, had osteoporosis, and had more severe comorbidities tended to have greater weight variability.

Table 4. Descriptive characteristics of the study population

		BMI variability				
		First quartile	Second quartile	Third quartile	Fourth quartile	*p* value
Number of participants(%)		41,798 (25.04)	41,669 (24.96)	41,700 (24.98)	41,765 (25.02)	
Age years, mean (SD)		59.00 (7.49)	59.25 (7.54)	59.73 (7.80)	60.66 (8.19)	<0.001
Sex, N (%)						<0.001
	Men	24,801 (59.34)	25,090 (60.21)	23,297 (55.87)	21,192 (50.74)	
	Women	16,997 (40.66)	16,579 (39.79)	18,403 (44.13)	20,573 (49.26)	
BMI Variability (ASV), kg/㎡,mean (SD)		0.28 (0.12)	0.59 (0.08)	0.92 (0.11)	1.79 (1.05)	<0.001
Initial BMI, kg/㎡,mean (SD)		23.79 (2.69)	23.90 (2.70)	24.08 (2.82)	24.54 (3.26)	<0.001
Change in BMI, kg/㎡,mean (SD)		−0.01 (0.50)	−0.01 (0.93)	−0.04 (1.33)	−0.15 (2.45)	<0.001
Household income, N (%)						<0.001
	First quartile	16,171 (38.69)	15,618 (37.48)	14,579 (34.96)	12,930 (30.96)	
	Second quartile	11,990 (28.69)	11,877 (28.50)	12,220 (29.30)	12,294 (29.44)	
	Third quartile	8,251 (19.74)	8,551 (20.52)	8,971 (21.51)	9,674 (23.16)	
	Fourth quartile	5,386 (12.89)	5,623 (13.49)	5,930 (14.22)	6,867 (16.44)	
Smoking, N (%)						<0.001
	Never smoker	30,513 (73.00)	30,109 (72.26)	31,109 (74.60)	31,852 (76.26)	
	Past smoker	3,953 (9.46)	4,037 (9.69)	3,589 (8.61)	3,428 (8.21)	
	Current smoker	7,332 (17.54)	7,523 (18.05)	7,002 (16.79)	6,485 (15.53)	
						<0.001

Alcohol consumption, times per week, N (%)						
	None	24,911 (59.60)	24,807 (59.53)	26,161 (62.74)	27,891 (66.78)	
	<1	5,977 (14.30)	5,908 (14.18)	5,404 (12.96)	4,833 (11.57)	
	1-2	6,856 (16.40)	6,855 (16.45)	6,177 (14.81)	5,363 (12.84)	
	3-4	2,534 (6.06)	2,594 (6.23)	2,421 (5.81)	2,146 (5.14)	
	≥5	1,520 (3.64)	1,505 (3.61)	1,537 (3.69)	1,532 (3.67)	
Physical activity, times per week, N (%)						<0.001
	None	19,217 (45.98)	19,426 (46.62)	20,422 (48.97)	22,147 (53.03)	
	1-2	12,018 (28.75)	11,828 (28.39)	10,967 (26.30)	9,858 (23.60)	
	3-4	5,858 (14.02)	5,662 (13.59)	5,401 (12.95)	4,837 (11.58)	
	5-6	1,502 (3.59)	1,526 (3.66)	1,466 (3.52)	1,467 (3.51)	
	7	3,203 (7.66)	3,227 (7.74)	3,444 (8.26)	3,456 (8.27)	
CCI (%)						<0.001
	<4	38,308 (91.65)	38,061 (91.34)	37,576 (90.11)	36,650 (87.75)	
	≥4	3,490 (8.35)	3,608 (8.66)	4,124 (9.89)	5,115 (12.25)	
Diagnosis with osteoporosis (%)						<0.001
	Yes	3,986 (9.54)	3,913 (9.39)	4,344 (10.42)	4,948 (11.85)	
	No	37,812 (90.46)	37,756 (90.61)	37,356 (89.58)	36,817 (88.15)	

p value calculated by Chi-squared test for categorical variables and analysis of variance for continuous variables

Acronyms: BMI, body mass index; ASV, Average successive variability; SD, standard deviation; N, number of people; CCI, Charlson Comorbidity Index

Table 5. Descriptive characteristics of the study population for men

		BMI variability				
		First quartile	Second quartile	Third quartile	Fourth quartile	*P* value
Number of participants (%)		24,801 (26.28)	25,090 (26.58)	23,297 (24.68)	21,192 (22.45)	
Age years, mean (SD)		58.80 (7.50)	58.95 (7.51)	59.47 (7.78)	60.26 (8.16)	<0.001
BMI Variability (ASV), kg/㎡,mean(SD)		0.27 (0.12)	0.59 (0.08)	0.92 (0.11)	1.76 (1.11)	<0.001
Initial BMI, kg/㎡,mean(SD)		23.78 (2.60)	23.94 (2.64)	24.04 (2.73)	24.33 (3.21)	<0.001
Change in BMI, kg/㎡,mean(SD)		-0.01 (0.49)	-0.01 (0.92)	-0.04 (1.31)	-0.08 (2.51)	<0.001
Household income, N (%)						<0.001
	First quartile	10,663 (42.99)	10,518 (41.92)	9,066 (38.91)	7,352 (34.69)	
	Second quartile	7,068 (28.50)	7,138 (28.45)	6,888 (29.57)	6,322 (29.83)	
	Third quartile	4,366 (17.60)	4,553 (18.15)	4,534 (19.46)	4,499 (21.23)	
	Fourth quartile	2,704 (10.90)	2,881 (11.48)	2,809 (12.06)	3,019 (14.25)	
Smoking, N (%)						0.164
	Never smoker	13,819 (55.72)	13,826 (55.11)	13,036 (55.96)	11,707 (55.24)	
	Past smoker	3,871 (15.61)	3,953 (15.76)	3,485 (14.96)	3,312 (15.63)	
	Current smoker	7,111 (28.67)	7,311 (29.14)	6,776 (29.09)	6,173 (29.13)	
Alcohol consumption, times per week, N (%)						<0.001
	None	10,072 (40.61)	10,367 (41.32)	10,022 (43.02)	9,783 (46.13)	
	<1	4,639 (18.70)	4,557 (18.16)	3,987 (17.11)	3,360 (15.86)	

	1-2	6,220 (25.08)	6,245 (24.89)	5,523 (23.71)	4,606 (21.73)	
	3-4	2,420 (9.76)	2,504 (9.98)	2,324 (9.98)	2,021 (9.54)	
	≥5	1,450 (5.85)	1,417 (5.65)	1,441 (6.19)	1,422 (6.71)	
Physical activity, times per week, N (%)						<0.001
	None	9,982 (40.25)	10,271 (40.94)	9,996 (42.91)	9,743 (45.97)	
	1-2	8,297 (33.45)	8,348 (33.27)	7,168 (30.77)	6,013 (28.37)	
	3-4	3,716 (14.98)	3,655 (14.57)	3,339 (14.33)	2,808 (13.25)	
	5-6	874 (3.52)	919 (3.66)	880 (3.78)	797 (3.76)	
	7	1,932 (7.79)	1,897 (7.56)	1,914 (8.22)	1,831 (8.64)	
CCI (%)						<0.001
	<4	22,920 (92.42)	23,124 (92.16)	21,201 (91.00)	18,818 (88.80)	
	≥4	1,881 (7.58)	1,966 (7.84)	2,096 (9.00)	2,374 (11.20)	
Diagnosis with osteoporosis (%)						<0.001
	Yes	606 (2.44)	694 (2.77)	694 (2.98)	738 (3.48)	
	No	24,195 (97.56)	24,396 (97.23)	22,603 (97.02)	20,454 (96.52)	

p value calculated by Chi-squared test for categorical variables and analysis of variance for continuous variables

Acronyms: BMI, body mass index; ASV, Average successive variability; SD, standard deviation; N, number of people; CCI, Charlson Comorbidity Index

Table 6. Descriptive characteristics of the study population for women

		BMI variability				
		First quartile	Second quartile	Third quartile	Fourth quartile	*P* value
Number of participants (%)		16,997 (23.43)	16,579 (22.85)	18,403 (25.37)	20,573 (28.36)	
Age years, mean (SD)		59.28 (7.48)	59.72 (7.56)	60.06 (7.81)	61.07 (8.20)	<0.001
BMI Variability (ASV), kg/㎡,mean(SD)		0.29 (0.12)	0.59 (0.08)	0.92 (0.11)	1.81 (0.99)	
Initial BMI, kg/㎡, mean(SD)		23.80 (2.81)	23.86 (2.78)	24.14 (2.93)	24.75 (3.30)	
Change in BMI, kg/㎡, mean(SD)		-0.00 (0.51)	-0.01 (0.93)	-0.04 (1.34)	-0.21 (2.38)	
Household income, N (%)						<0.001
	First quartile	5,508 (32.41)	5,100 (30.76)	5,513 (29.96)	5,578 (27.11)	
	Second quartile	4,922 (28.96)	4,739 (28.58)	5,332 (28.97)	5,972 (29.03)	
	Third quartile	3,885 (22.86)	3,998 (24.11)	4,437 (24.11)	5,175 (25.15)	
	Fourth quartile	2,682 (15.78)	2,742 (16.54)	3,121 (16.96)	3,848 (18.70)	
Smoking, N (%)						0.170
	Never smoker	16,694 (98.22)	16,283 (98.21)	18,073 (98.21)	20,145 (97.92)	
	Past smoker	82 (0.48)	84 (0.51)	104 (0.57)	116 (0.56)	
	Current smoker	221 (1.30)	212 (1.28)	226 (1.23)	312 (1.52)	
Alcohol consumption, times per week, N (%)						0.035
	None	14,839 (87.30)	14,440 (87.10)	16,139 (87.70)	18,108 (88.02)	
	<1	1,338 (7.87)	1,351 (8.15)	1,417 (7.70)	1,473 (7.16)	
	1-2	636 (3.74)	610 (3.68)	654 (3.55)	757 (3.68)	

	3-4	114 (0.67)	90 (0.54)	97 (0.53)	125 (0.61)	
	≥5	70 (0.41)	88 (0.53)	96 (0.52)	110 (0.53)	
Physical activity, times per week, N (%)						<0.001
	None	9,235 (54.33)	9,155 (55.22)	10,426 (56.65)	12,404 (60.29)	
	1-2	3,721 (21.89)	3,480 (20.99)	3,799 (20.64)	3,845 (18.69)	
	3-4	2,142 (12.60)	2,007 (12.11)	2,062 (11.20)	2,029 (9.86)	
	5-6	628 (3.69)	607 (3.66)	586 (3.18)	670 (3.26)	
	7	1,271 (7.48)	1,330 (8.02)	1,530 (8.31)	1,625 (7.90)	
CCI (%)						<0.001
	<4	15,388 (90.53)	14,937 (90.10)	16,375 (88.98)	17,832 (86.68)	
	≥4	1,609 (9.47)	1,642 (9.90)	2,028 (11.02)	2,741 (13.32)	
Diagnosis with osteoporosis (%)						<0.001
	Yes	5,876 (34.57)	5,773 (34.82)	6,410 (34.83)	7,525 (36.58)	
	No	11,121 (65.43)	10,806 (65.18)	11,993 (65.17)	13,048 (63.42)	

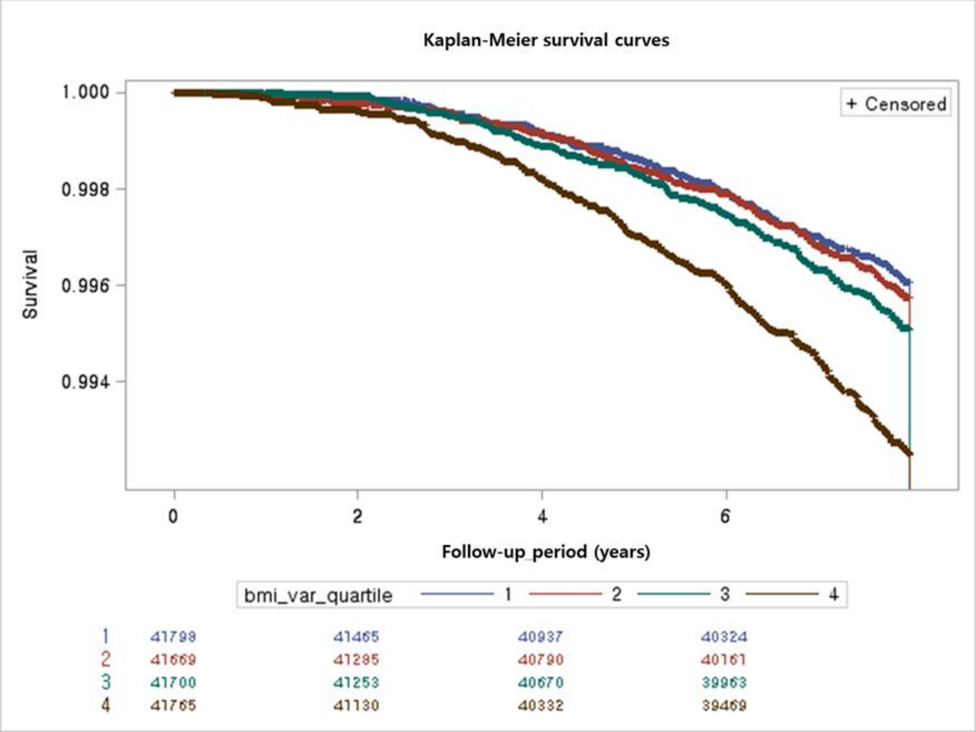
p value calculated by Chi-squared test for categorical variables and analysis of variance for continuous variables

Acronyms: BMI, body mass index; ASV, Average successive variability; SD, standard deviation; N, number of people; CCI, Charlson Comorbidity Index

2. Test for Cox proportional hazards assumption

Kaplan-Meier survival curves until occurrence of the fracture endpoint were presented for the estimation of statistical difference in the survivals among 1st, 2nd, 3rd, and 4th quartile groups. There was a significant difference in survival times between the weight variability groups (Figure3).

Figure 3. Kaplan-Meier survival curves



An important assumption made by the Cox proportional hazards model is the proportional hazards assumption. This assumption states that the hazard ratio for a given covariate remains constant over time.

In the presence of violation of proportionality in Cox proportional hazards model, adding the time-dependent coefficients would allow us to estimate the hazard ratios over time (31). Table 5 depicts the proportionality in Cox proportional hazards model for the covariates. Unfortunately, the comorbidity (presented as Charlson comorbidity index, CCI) appears to violate the proportionality in Cox proportional hazards model through the statistical test (p value <0.05) as well as graphical diagnostic plot (Figure 4). We have therefore demonstrated that log-log function curves for CCI, where the Y-axis represents the log-log transformed survival function estimated using the Cox proportional hazards regression model. The two curves do not cross over in the early period of observation and remain parallel after that. This plot suggests that CCI does not violate the proportional hazards assumption (Figure 5).

Table 7. Test of proportionality of hazards on Schoenfeld residuals

Covariates	Schoenfeld Residual (*p*-value)
Age	0.545
Sex	0.885
Initial BMI	0.146
Change in BMI	0.417
Household Income	0.347
Smoking	0.267
Alcohol consumption	0.664
Physical activity	0.710
CCI	0.002
Diagnosis with osteoporosis	0.630

Figure 4. Schoenfeld residual plot for Charlson Comorbidity Index (CCI)

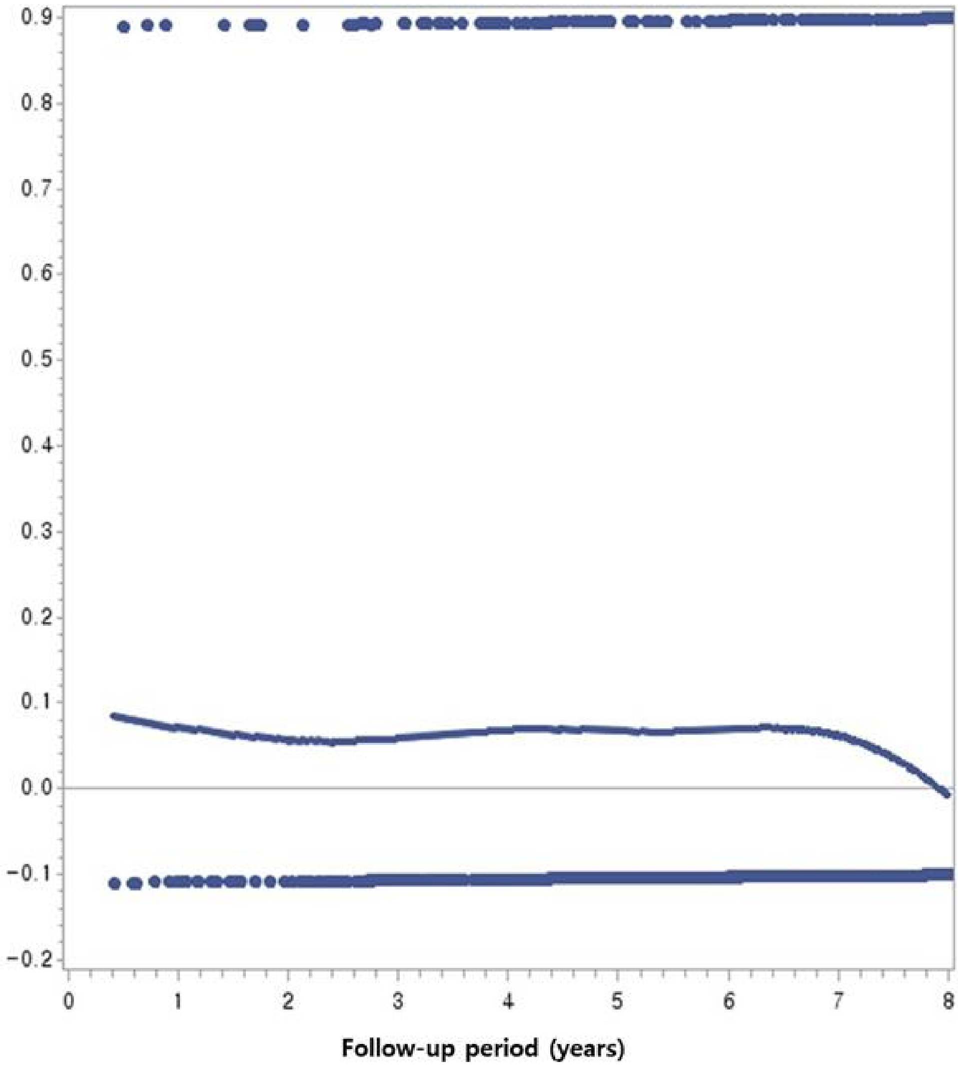
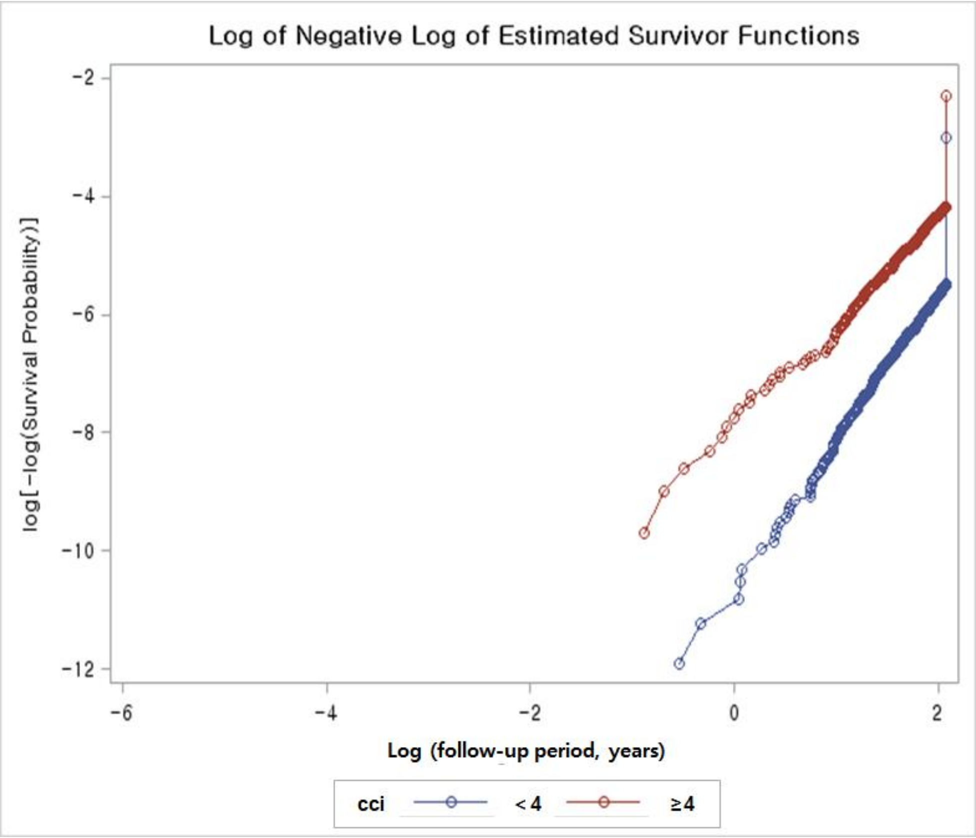


Figure 5. Log-log transformed survival curves for Charlson Comorbidity Index (CCI)



3. Association between weight variability and fracture

Part I. Definition of fracture - admission due to fracture

The impact of weight variability on fractures at three specific sites (hip, spinal, and upper extremity) and sum of the fractures called “total fractures” is shown in Table 8. Compared to those within the first quartile (lowest) of weight variability, those within the second, third and fourth quartile (highest) of weight variability had increased risk of total fractures (aHR 1.07, 95% CI 1.01-1.15; aHR 1.10, 95% CI 1.03-1.17; aHR 1.16 95% CI 1.09-1.23, respectively). Furthermore, the risk of total fractures increased upon greater degrees of weight variability (*p* for trends <0.001). Compared to those within the first quartile of weight variability, those within the second, third, and fourth quartile of weight variability had increased risk of hip fractures (aHR 1.05, 95% CI 0.87-1.26; aHR 1.23, 95% CI 1.04-1.46; aHR 1.23 95% CI 1.04-1.46, respectively). The risk of hip fractures increased upon greater degrees of weight variability (*p* for trends=0.005). Compared to those within the first quartile of weight variability, those within the second, third, and fourth quartile of weight variability had increased risk of spinal fractures (aHR 1.07, 95% CI 0.98-1.17; aHR 1.11, 95% CI 1.02-1.21; aHR 1.17 95% CI 1.08-1.27, respectively). The risk of spinal fractures increased upon greater degrees of weight variability (*p* for trends <0.001). However, in site of upper extremity, those within the greatest weight variability had no significant risk-increasing effect of fractures compared to those within the lowest weight variability (aHR 1.09, 95% CI 0.98-1.21).

Table 8. Hazard ratios for the BMI variability on risk of fracture

	BMI variability (ASV)				*P* for trend
	First quartile	Second quartile	Third quartile	Fourth quartile	
Total fracture					
Events	551	599	617	650	
Person-years	192,585	194,719	179,667	161,333	
aHR (95% CI)	1.00 (ref)	1.07 (0.95-1.20)	1.12 (1.00-1.25)	1.22 (1.09-1.37)	0.001
Hip fracture					
Events	121	107	132	152	
Person-years	192,221	194,389	179,292	160,877	
aHR (95% CI)	1.00 (ref)	0.86 (0.67-1.12)	1.04 (0.81-1.33)	1.14 (0.90-1.45)	0.137
Spinal fracture					
Events	323	344	372	393	
Person-years	191,568	193,570	178,504	160,077	
aHR (95% CI)	1.00 (ref)	1.05 (0.90-1.22)	1.13 (0.97-1.31)	1.20 (1.04-1.40)	0.008
Other fracture					
Events	130	169	135	129	
Person-years	192,100	194,080	179,177	160,837	
aHR (95% CI)	1.00 (ref)	1.28 (1.02-1.61)	1.09 (0.86-1.39)	1.14 (0.89-1.45)	0.601

Hazard ratio calculated by Cox proportional hazards regression.
Fully-adjusted model includes adjustments for age, initial BMI, change in BMI, household income, smoking, alcohol consumption, physical activity, Charlson comorbidity index, and osteoporosis medication
Acronyms: BMI, body mass index; ASV, Average successive variability; aHR, adjusted hazard ratio

Table 9. Hazard ratios for the BMI variability on risk of fracture for men

	BMI variability (ASV)				*P* for trend
	First quartile	Second quartile	Third quartile	Fourth quartile	
Total fracture					
Events	1,735	1,893	2,108	2,521	
Person-years	326,895	325,597	324,617	322,044	
aHR (95% CI)	1.00 (ref)	1.07 (1.01-1.15)	1.10 (1.03-1.17)	1.16 (1.09-1.23)	<0.001
Hip fracture					
Events	222	241	316	384	
Person-years	326,171	324,830	323,613	320,777	
aHR (95% CI)	1.00 (ref)	1.05 (0.87-1.26)	1.23 (1.04-1.46)	1.23 (1.04-1.46)	0.005
Spinal fracture					
Events	973	1,060	1,218	1,514	
Person-years	323,556	321,886	320,342	316,601	
aHR (95% CI)	1.00 (ref)	1.07 (0.98-1.17)	1.11 (1.02-1.21)	1.17 (1.08-1.27)	<0.001
Other fracture					
Events	618	701	690	785	
Person-years	324,582	322,835	322,014	318,888	

Hazard ratio calculated by Cox proportional hazards regression.
Fully-adjusted model includes adjustments for age, initial BMI, change in BMI, household income, smoking, alcohol consumption, physical activity, Charlson comorbidity index, and osteoporosis medication
Acronyms: BMI, body mass index; ASV, Average successive variability; aHR, adjusted hazard ratio

Table 10. Hazard ratios for the BMI variability on risk of fracture for women

	BMI variability (ASV)				*P* for trend
	First quartile	Second quartile	Third quartile	Fourth quartile	
Total fracture					
Events	1,184	1,294	1,491	1,871	
Person-years	134,309	130,878	144,950	160,711	
aHR (95% CI)	1.00 (ref)	1.08 (1.00-1.17)	1.09 (1.01-1.18)	1.14 (1.06-1.22)	0.001
Hip fracture					
Events	101	134	184	232	
Person-years	133,950	130,441	144,321	159,900	
aHR (95% CI)	1.00 (ref)	1.28 (0.99-1.65)	1.45 (1.14-1.85)	1.35 (1.06-1.70)	0.017
Spinal fracture					
Events	650	716	846	1,121	
Person-years	131,988	128,316	141,838	156,524	
aHR (95% CI)	1.00 (ref)	1.08 (0.98-1.21)	1.10 (1.00-1.22)	1.16 (1.06-1.28)	0.003
Other fracture					
Events	488	532	555	656	
Person-years	132,483	128,755	142,837	158,051	
aHR (95% CI)	1.00 (ref)	1.11 (0.98-1.25)	1.03 (0.91-1.17)	1.08 (0.96-1.21)	0.433

Hazard ratio calculated by Cox proportional hazards regression.
Fully-adjusted model includes adjustments for age, initial BMI, change in BMI, household income, smoking, alcohol consumption, physical activity, Charlson comorbidity index, and osteoporosis medication
Acronyms: BMI, body mass index; ASV, Average successive variability; aHR, adjusted hazard ratio

For men (Table 9), compared to those within the first quartile (lowest) of weight variability, those within the second, third and fourth quartile (highest) of weight variability had increased risk of total fractures (aHR 1.07, 95% CI 0.95-1.20; aHR 1.12, 95% CI 1.00-1.25; aHR 1.22 95% CI 1.09-1.37, respectively). Furthermore, the risk of total fractures increased upon greater degrees of weight variability (p for trends=0.001). Compared to those within the first quartile of weight variability, those within the second, third, and fourth quartile of weight variability had increased risk of hip fractures (aHR 0.86, 95% CI 0.67-1.12; aHR 1.04, 95% CI 0.81-1.33; aHR 1.14 95% CI 0.90-1.45, respectively), but without significance. Compared to those within the first quartile of weight variability, those within the second, third, and fourth quartile of weight variability had increased risk of spinal fractures (aHR 1.05, 95% CI 0.90-1.22; aHR 1.13, 95% CI 0.97-1.31; aHR 1.20 95% CI 1.04-1.40, respectively). The risk of spinal fractures increased upon greater degrees of weight variability (p for trends 0.008). Compared to those within the first quartile of weight variability, those within the second, third, fourth quartile of weight variability had increased risk of other fractures (aHR 1.28, 95% CI 1.02-1.61; aHR 1.09, 95% 0.86-1.39; aHR 1.14, 95% CI 0.89-1.45, respectively), but without significance.

For women (Table 10), compared to those within the first quartile (lowest) of weight variability, those within the second, third and fourth quartile (highest) of weight variability had increased risk of total fractures (aHR 1.08, 95% CI 1.00-1.17; aHR 1.09, 95% CI 1.01-1.18; aHR 1.14, 95% CI 1.06-1.22, respectively). Furthermore, the risk of total fractures increased upon greater degrees of weight variability (p

for trends=0.001). Compared to those within the first quartile of weight variability, those within the second, third, and fourth quartile of weight variability had increased risk of hip fractures (aHR 1.28, 95% CI 0.99-1.65; aHR 1.45, 95% CI 1.14-1.85; aHR 1.35 95% CI 1.06-1.70, respectively). The risk of hip fracture increased upon greater digress of weight variability (*p* for trends=0.017). Compared to those within the first quartile of weight variability, those within the second, third, and fourth quartile of weight variability had increased risk of spinal fractures (aHR 1.08, 95% CI 0.98-1.21; aHR 1.10, 95% CI 1.00-1.22; aHR 1.16, 95% CI 1.06-1.28, respectively). The risk of spinal fractures increased upon greater degrees of weight variability (*p* for trends=0.003). Compared to those within the first quartile of weight variability, those within the second, third, fourth quartile of weight variability had increased risk of other fractures (aHR 1.11, 95% CI 0.98-1.25; aHR 1.03, 95% 0.91-1.17; aHR 1.08, 95% CI 0.96-1.21, respectively), but without significance.

Table 11 (Table 12 for men, and Table 13 for women) shows the result from association of weight variability on total fractures according to different adjustment for baseline covariates. Control for relevant covariates in unquestionable of importance in estimating more accurate effect of an exposure on some outcome. However, variables such as initial BMI and change in BMI could be considered as "mediators" in association of weight variability and risk of fracture, not confounders, which results in overadjustment bias. Removing initial BMI and/or change in BMI from the model due to its mediator property was tested in this study with different models; model adjusted including initial BMI and change in BMI; model 2 adjusted including initial BMI only; model 3 not adjusted with initial BMI and change in BMI, but other covariates. Conclusively, there was no change in trends of association between weight variability and fracture according to adjustment status of the covariates, initial BMI and change in BMI. Therefore, there is no evidence for overadjustment bias for the covariates; initial BMI and change in BMI.

Table 11. Hazard ratios for the BMI variability on risk of fracture according to different adjustment for baseline covariates

		BMI variability (ASV)				*P* for trend
		First quartile	Second quartile	Third quartile	Fourth quartile	
Total fracture						
	Events	1,735	1,893	2,108	2,521	
	Person-years	326,895	325,597	324,617	322,044	
Model 1	aHR (95% CI)	1.00 (ref)	1.07 (1.01-1.15)	1.10 (1.03-1.17)	1.16 (1.09-1.23)	<0.001
Model 2	aHR (95% CI)	1.00 (ref)	1.07 (1.01-1.15)	1.10 (1.03-1.17)	1.16 (1.09-1.23)	<0.001
Model 3	aHR (95% CI)	1.00 (ref)	1.07 (1.00-1.14)	1.09 (1.02-1.16)	1.14 (1.07-1.21)	<0.001
Hip fracture						
	Events	222	241	316	384	
	Person-years	326,171	324,830	323,613	320,777	
Model 1	aHR (95% CI)	1.00 (ref)	1.05 (0.87-1.26)	1.23 (1.04-1.46)	1.23 (1.04-1.46)	0.005
Model 2	aHR (95% CI)	1.00 (ref)	1.05 (0.88-1.26)	1.23 (1.04-1.47)	1.25 (1.06-1.48)	0.002
Model 3	aHR (95% CI)	1.00 (ref)	1.05 (0.88-1.26)	1.22 (1.03-1.45)	1.23 (1.03-1.44)	0.006

Spinal fracture						
	Events	973	1,060	1,218	1,514	
	Person-years	323,556	321,886	320,342	316,601	
Model 1	aHR (95% CI)	1.00 (ref)	1.07 (0.98-1.17)	1.11 (1.02-1.21)	1.17 (1.08-1.27)	<0.001
Model 2	aHR (95% CI)	1.00 (ref)	1.07 (0.98-1.17)	1.11 (1.02-1.21)	1.17 (1.08-1.27)	<0.001
Model 3	aHR (95% CI)	1.00 (ref)	1.07 (0.98-1.17)	1.11 (1.02-1.20)	1.16 (1.07-1.26)	<0.001
Other fracture						
	Events	618	701	690	785	
	Person-years	324,582	322,835	322,014	318,888	
Model 1	aHR (95% CI)	1.00 (ref)	1.14 (1.03-1.28)	1.05 (0.94-1.17)	1.09 (0.98-1.21)	0.358
Model 2	aHR (95% CI)	1.00 (ref)	1.14 (1.03-1.28)	1.05 (0.94-1.17)	1.09 (0.98-1.21)	0.356
Model 3	aHR (95% CI)	1.00 (ref)	1.14 (1.03-1.27)	1.04 (0.93-1.16)	1.07 (0.97-1.19)	0.540

Hazard ratio calculated by Cox proportional hazards regression.
Model 1: Fully-adjusted model includes adjustments for age, sex, initial BMI, change in BMI, household income, smoking, alcohol consumption, physical activity, Charlson comorbidity index, and diagnosis with osteoporosis
Model 2: Fully-adjusted model includes adjustments for age, sex, initial BMI, household income, smoking, alcohol consumption, physical activity, Charlson comorbidity index, and diagnosis with osteoporosis
Model 3: Fully-adjusted model includes adjustments for age, sex, household income, smoking, alcohol consumption, physical activity, Charlson comorbidity index, and diagnosis with osteoporosis
Acronyms: BMI, body mass index; ASV, Average successive variability; aHR, adjusted hazard ratio

Table 12. Hazard ratios for the BMI variability on risk of fracture according to different adjustment for baseline covariates for men

		BMI variability (ASV)				*P* for trend
		First quartile	Second quartile	Third quartile	Fourth quartile	
Total fracture						
	Events	551	599	617	650	
	Person-years	192,585	194,719	179,667	161,333	
Model 1	aHR (95% CI)	1.00 (ref)	1.07 (0.95-1.20)	1.12 (1.00-1.25)	1.22 (1.09-1.37)	0.001
Model 2	aHR (95% CI)	1.00 (ref)	1.07 (0.95-1.20)	1.11 (0.99-1.25)	1.21 (1.08-1.36)	0.001
Model 3	aHR (95% CI)	1.00 (ref)	1.06 (0.94-1.19)	1.10 (0.98-1.23)	1.18 (1.05-1.32)	0.004
Hip fracture						
	Events	121	107	132	152	
	Person-years	192,221	194,389	179,292	160,877	
Model 1	aHR (95% CI)	1.00 (ref)	0.86 (0.67-1.12)	1.04 (0.81-1.33)	1.14 (0.90-1.45)	0.137
Model 2	aHR (95% CI)	1.00 (ref)	0.87 (0.67-1.12)	1.04 (0.81-1.33)	1.16 (0.91-1.48)	0.101
Model 3	aHR (95% CI)	1.00 (ref)	0.86 (0.66-1.11)	1.03 (0.79-1.30)	1.11 (0.88-1.42)	0.196

Spinal fracture						
	Events	323	344	372	393	
	Person-years	191,568	193,570	178,504	160,077	
Model 1	aHR (95% CI)	1.00 (ref)	1.05 (0.90-1.22)	1.13 (0.97-1.31)	1.20 (1.04-1.40)	0.008
Model 2	aHR (95% CI)	1.00 (ref)	1.05 (0.90-1.22)	1.13 (0.97-1.31)	1.20 (1.04-1.40)	0.008
Model 3	aHR (95% CI)	1.00 (ref)	1.04 (0.89-1.21)	1.11 (0.96-1.29)	1.17 (1.01-1.36)	0.023
Other fracture						
	Events	130	169	135	129	
	Person-years	192,100	194,080	179,177	160,837	
Model 1	aHR (95% CI)	1.00 (ref)	1.28 (1.02-1.61)	1.09 (0.86-1.39)	1.14 (0.89-1.45)	0.601
Model 2	aHR (95% CI)	1.00 (ref)	1.28 (1.02-1.61)	1.09 (0.86-1.39)	1.14 (0.89-1.45)	0.595
Model 3	aHR (95% CI)	1.00 (ref)	1.28 (1.02-1.61)	1.08 (0.85-1.38)	1.12 (0.88-1.43)	0.675

Hazard ratio calculated by Cox proportional hazards regression.
Model 1: Fully-adjusted model includes adjustments for age, sex, initial BMI, change in BMI, household income, smoking, alcohol consumption, physical activity, Charlson comorbidity index, and diagnosis with osteoporosis
Model 2: Fully-adjusted model includes adjustments for age, sex, initial BMI, household income, smoking, alcohol consumption, physical activity, Charlson comorbidity index, and diagnosis with osteoporosis
Model 3: Fully-adjusted model includes adjustments for age, sex, household income, smoking, alcohol consumption, physical activity, Charlson comorbidity index, and diagnosis with osteoporosis
Acronyms: BMI, body mass index; ASV, Average successive variability; aHR, adjusted hazard ratio

Table 13. Hazard ratios for the BMI variability on risk of fracture according to different adjustment for baseline covariates for women

		BMI variability (ASV)				*P* for trend
		First quartile	Second quartile	Third quartile	Fourth quartile	
Total fracture						
	Events	1,184	1,294	1,491	1,871	
	Person-years	134,309	130,878	144,950	160,711	
Model 1	aHR (95% CI)	1.00 (ref)	1.08 (1.00-1.17)	1.09 (1.01-1.18)	1.14 (1.06-1.22)	0.001
Model 2	aHR (95% CI)	1.00 (ref)	1.08 (1.00-1.17)	1.09 (1.01-1.18)	1.14 (1.06-1.22)	0.001
Model 3	aHR (95% CI)	1.00 (ref)	1.08 (1.00-1.17)	1.09 (1.01-1.17)	1.13 (1.05-1.21)	0.002
Hip fracture						
	Events	101	134	184	232	
	Person-years	133,950	130,441	144,321	159,900	
Model 1	aHR (95% CI)	1.00 (ref)	1.28 (0.99-1.65)	1.45 (1.14-1.85)	1.35 (1.06-1.70)	0.017
Model 2	aHR (95% CI)	1.00 (ref)	1.28 (0.99-1.66)	1.45 (1.14-1.85)	1.36 (1.07-1.72)	0.013
Model 3	aHR (95% CI)	1.00 (ref)	1.28 (0.99-1.66)	1.45 (1.14-1.85)	1.35 (1.07-1.71)	0.016

Spinal fracture						
	Events	650	716	846	1,121	
	Person-years	131,988	128,316	141,838	156,524	
Model 1	aHR (95% CI)	1.00 (ref)	1.08 (0.98-1.21)	1.10 (1.00-1.22)	1.16 (1.06-1.28)	0.003
Model 2	aHR (95% CI)	1.00 (ref)	1.08 (0.98-1.21)	1.11 (1.00-1.22)	1.16 (1.06-1.28)	0.003
Model 3	aHR (95% CI)	1.00 (ref)	1.08 (0.98-1.21)	1.10 (1.00-1.22)	1.16 (1.05-1.28)	0.003
Other fracture						
	Events	488	532	555	656	
	Person-years	132,483	128,755	142,837	158,051	
Model 1	aHR (95% CI)	1.00 (ref)	1.11 (0.98-1.25)	1.03 (0.91-1.17)	1.08 (0.96-1.21)	0.433
Model 2	aHR (95% CI)	1.00 (ref)	1.11 (0.98-1.25)	1.03 (0.92-1.17)	1.08 (0.96-1.21)	0.435
Model 3	aHR (95% CI)	1.00 (ref)	1.11 (0.98-1.25)	1.03 (0.91-1.16)	1.06 (0.94-1.19)	0.620

Hazard ratio calculated by Cox proportional hazards regression.
Model 1: Fully-adjusted model includes adjustments for age, sex, initial BMI, change in BMI, household income, smoking, alcohol consumption, physical activity, Charlson comorbidity index, and diagnosis with osteoporosis
Model 2: Fully-adjusted model includes adjustments for age, sex, initial BMI, household income, smoking, alcohol consumption, physical activity, Charlson comorbidity index, and diagnosis with osteoporosis
Model 3: Fully-adjusted model includes adjustments for age, sex, household income, smoking, alcohol consumption, physical activity, Charlson comorbidity index, and diagnosis with osteoporosis
Acronyms: BMI, body mass index; ASV, Average successive variability; aHR, adjusted hazard ratio

1) Association between weight variability and fracture according to diagnosis of osteoporosis

Table 14 shows the result from a stratified analysis of the effect of weight variability on total fractures according to presence of osteoporosis. Among individuals who had osteoporosis, those within the second, third and fourth quartile of weight variability had increased risk of fractures (aHR 1.12, 95% CI 0.99-1.25; aHR 1.11, 95% CI 0.99-1.24; aHR 1.19, 95% CI 1.07-1.32, respectively) compared to those within the first quartile of weight variability. The risk of fractures increased upon greater degrees of weight variability (*p* for trend=0.003). Among individuals without osteoporosis, those within the second, third, and fourth quartile of weight variability had increased risk of fractures (aHR 1.05, 95% CI 0.97-1.14; aHR 1.09, 95% CI 1.01-1.18; aHR 1.14, 95% CI 1.06-1.23, respectively) compared to those within the first quartile of weight variability. The risk of fractures increased upon greater degrees of weight variability (*p* for trend=0.001). The relationship between BMI variability and fracture was varied across the presence of osteoporosis (*p* for interaction=0.003).

For men, among individuals without osteoporosis, those within the second, third and fourth quartile of weight variability had increased risk of fractures (aHR 1.08, 95% CI 0.96-1.21; aHR 1.13, 95% CI 1.00-1.27; aHR 1.22, 95% CI 1.08-1.37, respectively) compared to those within the first quartile of weight variability. The risk of fractures increased upon greater degrees of weight variability (*p* for trend=0.001). Among individuals who had osteoporosis, those within the fourth quartile of weight variability had increased risk of fractures (aHR 1.17, 95% CI 0.77-1.79, respectively) compared to those within the first quartile of weight variability. The trend was not significant for the risk of fractures increased upon greater degrees of weight variability (*p* for trend=0.416).

For women, among the individuals who had osteoporosis, those within the second, third, and fourth quartile of weight variability had increased risk of fractures (aHR 1.13, 95% CI 1.00-1.27; aHR 1.12, 95% CI 0.99-1.26; aHR 1.20, 95% CI 1.07-1.33, respectively) compared to those within the first quartile of weight variability. The risk of fractures increased upon greater degrees of weight variability (*p* for trend=0.005). Among the individuals without osteoporosis, those within the second, third, and fourth quartile of weight variability had increased risk of fractures (aHR 1.05, 95% CI 0.94-1.16; aHR 1.07, 95% CI 0.97-1.19; aHR 1.10, 95% CI 1.00-1.21, respectively) compared to those within the first quartile of weight variability. The risk of fractures increased upon greater degrees of weight variability with marginal significance (*p* for trend=0.058).

Table 14. Hazard ratios for BMI variability on risk of total fracture among those who had osteoporosis

Diagnosed with osteoporosis		BMI variability (ASV)				*p* for trend	*p* for interaction
		First quartile	Second quartile	Third quartile	Fourth quartile		
Total	Yes, events	538	615	698	931		0.003
	Person-years	50,842	50,679	55,584	63,963		
	aHR (95% CI)	1.00 (ref)	1.12 (0.99-1.25)	1.11 (0.99-1.24)	1.19 (1.07-1.32)	0.003	
	No, events	1,197	1,278	1,410	1,590		
	Person-years	276,053	274,919	269,026	258,081		
	aHR (95% CI)	1.00 (ref)	1.05 (0.97-1.14)	1.09 (1.01-1.18)	1.14 (1.06-1.23)	0.001	
Men	Yes, events	36	40	43	58		
	Person-years	4,514	5,219	5,167	5,367		
	aHR (95% CI)	1.00 (ref)	0.97 (0.62-1.52)	0.99 (0.63-1.54)	1.17 (0.77-1.79)	0.416	
	No, events	515	559	574	592		
	Person-years	188,072	189,500	174,493	155,966		
	aHR (95% CI)	1.00 (ref)	1.08 (0.96-1.21)	1.13 (1.00-1.27)	1.22 (1.08-1.37)	0.001	

Women	Yes, events	502	575	655	873	
	Person-years	46,329	45,460	50,417	58,596	
	aHR (95% CI)	1.00 (ref)	1.13 (1.00-1.27)	1.12 (0.99-1.26)	1.20 (1.07-1.33)	0.005
	No, events	682	719	836	998	
	Person-years	87,981	85,419	94,533	102,115	
	aHR (95% CI)	1.00 (ref)	1.05 (0.94-1.16)	1.07 (0.97-1.19)	1.10 (1.00-1.21)	0.058

Hazard ratio calculated by Cox proportional hazards regression.
Fully-adjusted model includes adjustments for age, sex, initial BMI, change in BMI, household income, smoking, alcohol consumption, physical activity, Charlson comorbidity index, and diagnosis with osteoporosis
Acronyms: BMI, body mass index; ASV, Average successive variability; aHR, adjusted hazard ratio

2) Association between BMI variability on risk of fracture according to different 'weight fluctuation' groups

Table 15, 16, 17, and 18 depict the impact of BMI variability on the risk of total, hip, spinal and upper extremity fracture according to different weight fluctuation groups. Categorized upon the difference in BMI values from the second (2004-2005) to the first (2002-2003) examination period and from the third (2006-2007) to second (2004-2005) examination period, the study population was divided into three groups; weight gain/gain, weight gain/loss or loss/gain (including no change), and weight loss/loss. Among individuals who experienced weight gain repetitively during three examination periods, those within the second, third and fourth quartile of weight variability had increased risk of fractures (aHR 1.06, 95% CI 0.90-1.24; aHR 1.17, 95% CI 1.00-1.37; aHR 1.19, 95% CI 1.00-1.41, respectively) compared to those within the first quartile of weight variability. The risk of fractures increased upon greater degrees of weight variability (*p* for trend=0.019). Among individuals who experienced weight gain/loss or loss/gain, during three examination periods, those within the second, third and fourth quartile of weight variability had increased risk of fractures (aHR 1.04, 95% CI 0.96-1.13; aHR 1.06, 95% CI 0.98-1.14; aHR 1.12, 95% CI 1.04-1.20, respectively) compared to those within the first quartile of weight variability. The risk of fractures increased upon greater degrees of weight variability (*p* for trend=0.003). Among individuals who experienced weight loss repetitively during three examination periods, those within the second, third and fourth quartile of weight variability had increased risk of fractures (aHR 1.24, 95% CI

1.06–1.45; aHR 1.24, 95% CI 1.06–1.46; aHR 1.36, 95% CI 1.15–1.61, respectively) compared to those within the first quartile of weight variability. The risk of fractures increased upon greater degrees of weight variability (*p* for trend=0.001).

For men, among individuals who experienced weight gain repetitively during three examination periods, those within the third and fourth quartile of weight variability had increased risk of fracture (aHR 1.07, 95% CI 0.81–1.41; aHR 1.08, 95% CI 0.80–1.46, respectively) compared to those within the first quartile of weight variability, but the trend was not significant (*p* for trend =0.406). Among individuals who experienced weight gain/loss or loss/gain, during three examination periods, those within the fourth quartile of weight variability had increased risk of fractures (aHR 1.12, 95% CI 1.04–1.20) compared to those within the first quartile of weight variability. The risk of fractures increased upon greater degrees of weight variability (*p* for trend=0.015). Among individuals who experienced weight loss repetitively during three examination periods, those within the second, third and fourth quartile of weight variability had increased risk of fractures (aHR 1.27, 95% CI 0.96–1.68; aHR 1.48, 95% CI 1.11–1.95; aHR 1.47, 95% CI 1.08–2.02, respectively) compared to those within the first quartile of weight variability. The risk of fractures increased upon greater degrees of weight variability (*p* for trend=0.006).

For women, among individuals who experienced weight gain repetitively during three examination periods, those within the second, third and fourth quartile of weight variability had increased risk of fracture (aHR 1.15, 95% CI 0.94–1.40; aHR 1.23, 95% CI 1.01–1.49; aHR 1.26, 95% CI 1.02–1.55, respectively) compared to those within the first quartile of weight variability. The risk of fractures increased upon greater degrees of weight variability (*p* for trend=0.026). Among individuals who experienced weight gain/loss or loss/gain, during three examination periods, those within the second, third and fourth quartile of weight variability had increased risk of fractures (aHR 1.03, 95% CI 0.94-1.14; aHR 1.06, 95% CI 0.97-1.16; aHR 1.09, 95% CI 1.00-1.18, respectively) compared to those within the first quartile of weight variability. The risk of fractures increased upon greater degrees of weight variability (*p* for trend=0.049). Among individuals who experienced weight loss repetitively during three examination periods, those within the second, third and fourth quartile of weight variability had increased risk of fractures (aHR 1.23, 95% CI 1.01-1.49; aHR 1.15, 95% CI 0.94-1.39; aHR 1.31, 95% CI 1.07-1.60, respectively) compared to those within the first quartile of weight variability. The risk of fractures increased upon greater degrees of weight variability (*p* for trend=0.029).

Table 15. Hazard ratios for the BMI variability on risk of total fracture according to different 'weight fluctuation' groups

Weight change		BMI variability (ASV)				*p* for trend
		First quartile	Second quartile	Third quartile	Fourth quartile	
Total	Weight +/+, events	247	358	387	300	
	Person-years	48,622	63,041	54,308	36,548	
	aHR (95% CI)	1.00 (ref)	1.06 (0.90-1.24)	1.17 (1.00-1.37)	1.19 (1.00-1.41)	0.019
	Weight +/- or -/+, events	1,235	1,140	1,335	1,882	
	Person-years	225,864	197,773	211,727	243,802	
	aHR (95% CI)	1.00 (ref)	1.04 (0.96-1.13)	1.06 (0.98-1.14)	1.12 (1.04-1.20)	0.003
	Weight -/-, events	253	395	386	339	
	Person-years	52,409	64,782	58,575	41,694	
	aHR (95% CI)	1.00 (ref)	1.24 (1.06-1.45)	1.24 (1.06-1.46)	1.36 (1.15-1.61)	0.001
Men	Weight +/+, events	91	109	111	83	
	Person-years	29,265	37,742	28,837	19,079	
	aHR (95% CI)	1.00 (ref)	0.91 (0.69-1.20)	1.07 (0.81-1.41)	1.08 (0.80-1.46)	0.406
	Weight +/- or -/+, events	378	363	381	485	
	Person-years	131,923	117,849	118,951	122,341	
	aHR (95% CI)	1.00 (ref)	1.07 (0.92-1.23)	1.04 (0.90-1.20)	1.20 (1.05-1.37)	0.015

	Weight -/-, events	82	127	125	82	
	Person-years	31,397	39,127	31,871	19,914	
	aHR (95% CI)	1.00 (ref)	1.27 (0.96-1.68)	1.48 (1.11-1.95)	1.47 (1.08-2.02)	0.006
Women	Weight +/+, events	156	249	276	217	
	Person-years	19,358	25,299	25,471	17,470	
	aHR (95% CI)	1.00 (ref)	1.15 (0.94-1.40)	1.23 (1.01-1.49)	1.26 (1.02-1.55)	0.026
	Weight +/- or -/+, events	857	777	954	1397	
	Person-years	93,941	79,924	92,776	121,461	
	aHR (95% CI)	1.00 (ref)	1.03 (0.94-1.14)	1.06 (0.97-1.16)	1.09 (1.00-1.18)	0.049
	Weight -/-, events	171	268	261	257	
	Person-years	21,011	25,655	26,704	21,780	
	aHR (95% CI)	1.00 (ref)	1.23 (1.01-1.49)	1.15 (0.94-1.39)	1.31 (1.07-1.60)	0.029

Hazard ratio calculated by Cox proportional hazards regression.
Fully-adjusted model includes adjustments for age, sex, initial BMI, change in BMI, household income, smoking, alcohol consumption, physical activity, Charlson comorbidity index, and diagnosis with osteoporosis
Acronyms: BMI, body mass index; ASV, Average successive variability; aHR, adjusted hazard ratio
Weight +/+ continuous weight gain
Weight -/- continuous weight gain
Weight +/- or -/+ others including no change

Table 16. Hazard ratios for the BMI variability on risk of hip fracture according to different 'weight fluctuation' groups

Weight change		BMI variability (ASV)				p for trend
		First quartile	Second quartile	Third quartile	Fourth quartile	
Total	Weight +/+, events	35	33	37	36	
	Person-years	48,622	63,041	54,308	36,548	
	aHR (95% CI)	1.00 (ref)	0.66 (0.41-1.07)	0.75 (0.47-1.20)	0.85 (0.53-1.36)	0.686
	Weight +/- or -/+, events	151	148	206	277	
	Person-years	225,864	197,773	211,727	243,802	
	aHR (95% CI)	1.00 (ref)	1.10 (0.88-1.38)	1.28 (1.04-1.58)	1.25 (1.03-1.53)	0.016
	Weight -/-, events	36	60	73	71	
	Person-years	52,409	64,782	58,575	41,694	
	aHR (95% CI)	1.00 (ref)	1.28 (0.84-1.93)	1.59 (1.06-2.38)	1.88 (1.25-2.85)	0.001
Men	Weight +/+, events	17	12	16	14	
	Person-years	29,265	37,742	28,837	19,079	
	aHR (95% CI)	1.00 (ref)	0.52 (0.25-1.09)	0.73 (0.37-1.45)	0.75 (0.36-1.54)	0.618
	Weight +/- or -/+, events	81	71	79	107	
	Person-years	131,923	117,849	118,951	122,341	
	aHR (95% CI)	1.00 (ref)	0.98 (0.72-1.35)	0.97 (0.71-1.33)	1.14 (0.85-1.53)	0.380

	Weight -/-, events	23	24	37	31	
	Person-years	31,397	39,127	31,871	19,914	
	aHR (95% CI)	1.00 (ref)	0.86 (0.48-1.52)	1.57 (0.93-2.66)	1.98 (1.13-3.45)	0.003
Women	Weight +/+, events	18	21	21	22	
	Person-years	19,358	25,299	25,471	17,470	
	aHR (95% CI)	1.00 (ref)	0.82 (0.44-1.54)	0.79 (0.42-1.49)	0.94 (0.50-1.77)	0.872
	Weight +/- or -/+, events	70	77	127	170	
	Person-years	93,941	79,924	92,776	121,461	
	aHR (95% CI)	1.00 (ref)	1.24 (0.90-1.71)	1.60 (1.19-2.14)	1.37 (1.03-1.81)	0.022
	Weight -/-, events	13	36	36	40	
	Person-years	2,111	25,655	26,704	21,780	
	aHR (95% CI)	1.00 (ref)	2.01 (1.06-3.79)	1.79 (0.95-3.39)	2.03 (1.07-3.85)	0.089

Hazard ratio calculated by Cox proportional hazards regression.
Fully-adjusted model includes adjustments for age, sex, initial BMI, change in BMI, household income, smoking, alcohol consumption, physical activity, Charlson comorbidity index, and diagnosis with osteoporosis
Acronyms: BMI, body mass index; ASV, Average successive variability; aHR, adjusted hazard ratio
Weight +/+, continuous weight gain
Weight -/-, continuous weight gain
Weight +/- or -/+, others including no change

Table 17. Hazard ratios for the BMI variability on risk of spinal fracture according to different 'weight fluctuation' groups

Weight change		BMI variability (ASV) First quartile	Second quartile	Third quartile	Fourth quartile	p for trend
Total	Weight +/+, events	149	206	250	183	
	Person-years	48,622	63,041	54,308	36,548	
	aHR (95% CI)	1.00 (ref)	1.00 (0.81-1.24)	1.22 (1.00-1.50)	1.14 (0.92-1.42)	0.067
	Weight +/- or -/+, events	683	643	757	1131	
	Person-years	226,864	197,773	211,727	243,802	
	aHR (95% CI)	1.00 (ref)	1.06 (0.95-1.18)	1.06 (0.96-1.18)	1.16 (1.05-1.27)	0.004
	Weight -/-, events	141	211	211	200	
	Person-years	52,409	64,782	58,575	41,694	
	aHR (95% CI)	1.00 (ref)	1.18 (0.95-1.46)	1.20 (0.97-1.49)	1.37 (1.10-1.72)	0.008
Men	Weight +/+, events	55	62	78	54	
	Person-years	29,265	37,742	28,837	19,079	
	aHR (95% CI)	1.00 (ref)	0.85 (0.59-1.23)	1.21 (0.86-1.72)	1.11 (0.76-1.62)	0.229
	Weight +/- or -/+, events	217	214	226	293	
	Person-years	131,923	117,849	118,951	122,341	
	aHR (95% CI)	1.00 (ref)	1.10 (0.91-1.33)	1.06 (0.88-1.28)	1.23 (1.03-1.46)	0.039

	Weight -/-, events	51	68	68	46	
	Person-years	31,397	39,127	31,871	19,914	
	aHR (95% CI)	1.00 (ref)	1.09 (0.76-1.57)	1.28 (0.89-1.84)	1.30 (0.86-1.96)	0.134
Women	Weight +/+, events	94	144	172	129	
	Person-years	19,358	25,299	25,471	17,470	
	aHR (95% CI)	1.00 (ref)	1.10 (0.84-1.42)	1.23 (0.96-1.58)	1.16 (0.88-1.51)	0.195
	Weight +/- or -/+, events	466	429	531	838	
	Person-years	93,941	79,924	92,776	121,461	
	Model 2aHR (95% CI)	1.00 (ref)	1.04 (0.91-1.19)	1.06 (0.93-1.20)	1.13 (1.01-1.27)	0.029
	Weight -/-, events	90	143	143	154	
	Person-years	21,011	25,655	26,704	21,780	
	Model 2aHR (95% CI)	1.00 (ref)	1.23 (0.94-1.60)	1.17 (0.89-1.52)	1.41 (1.08-1.84)	0.026

Hazard ratio calculated by Cox proportional hazards regression.
Fully-adjusted model includes adjustments for age, sex, initial BMI, change in BMI, household income, smoking, alcohol consumption, physical activity, Charlson comorbidity index, and diagnosis with osteoporosis
Acronyms: BMI, body mass index; ASV, Average successive variability; aHR, adjusted hazard ratio
Weight +/+, continuous weight gain
Weight -/-, continuous weight gain
Weight +/- or -/+, others including no change

Table 18. Hazard ratios for the BMI variability on risk of Other fracture according to different 'weight fluctuation' groups

Weight change		BMI variability (ASV)				*p* for trend
		First quartile	Second quartile	Third quartile	Fourth quartile	
Total	Weight +/+, events	76	135	121	102	
	Person-years	48,622	63,041	54,308	36,548	
	aHR (95% CI)	1.00 (ref)	1.33 (1.00-1.76)	1.25 (0.93-1.66)	1.49 (1.10-2.01)	0.026
	Weight +/- or -/+, events	457	415	441	597	
	Person-years	225,864	197,773	211,727	243,802	
	aHR (95% CI)	1.00 (ref)	1.05 (0.92-1.19)	0.98 (0.86-1.12)	1.04 (0.92-1.18)	0.752
	Weight -/-, events	85	151	128	86	
	Person-years	52,409	64,782	58,575	41,694	
	aHR (95% CI)	1.00 (ref)	1.44 (1.11-1.88)	1.24 (0.94-1.63)	1.06 (0.78-1.44)	0.958
Men	Weight +/+, events	20	36	23	16	
	Person-years	29,265	37,742	28,837	19,079	
	aHR (95% CI)	1.00 (ref)	1.39 (0.81-2.41)	1.12 (0.62-2.05)	1.19 (0.62-2.32)	0.801
	Weight +/- or -/+, events	100	94	87	103	
	Person-years	131,923	117,849	118,951	122,341	
	aHR (95% CI)	1.00 (ref)	1.05 (0.79-1.39)	0.95 (0.71-1.27)	1.08 (0.82-1.42)	0.763

	Weight -/-, events	10	39	25	10	
	Person-years	31,397	39,127	31,871	19,914	
	aHR (95% CI)	1.00 (ref)	3.13 (1.56-6.28)	2.39 (1.14-5.00)	1.48 (0.61-3.63)	0.542
Women	Weight +/+, events	56	99	98	86	
	Person-years	19,357	25,299	25,471	17,470	
	aHR (95% CI)	1.00 (ref)	1.30 (0.93-1.80)	1.28 (0.92-1.79)	1.57 (1.12-2.21)	0.016
	Weight +/- or -/+, events	357	321	354	494	
	Person-years	93,941	79,924	92,776	121,461	
	aHR (95% CI)	1.00 (ref)	1.05 (0.90-1.22)	0.99 (0.85-1.14)	1.03 (0.90-1.18)	0.834
	Weight -/-, events	75	112	103	76	
	Person-years	21,011	25,655	26,704	21,780	
	aHR (95% CI)	1.00 (ref)	1.21 (0.90-1.62)	1.09 (0.81-1.47)	0.99 (0.71-1.37)	0.745

Hazard ratio calculated by Cox proportional hazards regression.
Fully-adjusted model includes adjustments for age, sex, initial BMI, change in BMI, household income, smoking, alcohol consumption, physical activity, Charlson comorbidity index, and diagnosis with osteoporosis
Acronyms: BMI, body mass index; ASV, Average successive variability; aHR, adjusted hazard ratio
Weight +/+, continuous weight gain
Weight -/-, continuous weight gain
Weight +/- or -/+, others including no change

3) Stratified analysis

Tables below shows the results from stratified analyses of the effect of weight variability on total fractures according to age (Table 19), sex (Table 20), direction of weight change (Table 21), and baseline BMI (Table 22). When the participants were divided into <65 year-old and ≥65year-old during the first health examination, those with the greatest weight variability had elevated risk of fracture for < 65 year-old (aHR 1.20, 95% CI 1.10-1.32) and ≥ 65year-old (aHR 1.14, 95% CI 1.05-1.25) participants. The risk of fractures increased upon greater degrees of weight variability for both <65 year-old (*p* for trend <0.001) and ≥65year-old (*p* for trend=0.007) participants. The association between weight variability and fracture seems to be varied according to age (*p* for interaction <0.001). For men, those with the greatest weight variability had elevated risk of fracture for <65 year-old (aHR 1.22, 95% CI 1.04-1.43) and the risk of fractures increased upon greater degrees of weight variability (*p* for trend=0.008), but ≥65year-old participants tend to have a trend of increased risk of fracture with weight variability but there was no significance (*p* for trend=0.123). For women, those with the greatest weight variability had elevated risk of fracture for <65 year-old (aHR 1.20, 95% CI 1.08-1.34) and ≥65year-old (aHR 1.14, 95% CI 1.03-1.26) participants. The risk of fractures increased upon greater degrees of weight variability for both <65 year-old (*p* for trend <0.001) and ≥65 year-old (*p* for trend=0.030) participants. The association between weight variability and fracture seems to be varied according to age (*p* for interaction=0.001).

The risk of fractures was increased among those with the greatest weight variability compared to those with the lowest weight variability for both men (aHR 1.18, 95% CI 1.05-1.32) and women (aHR 1.13, 95% CI 1.05-1.21). The association between weight variability and fracture was varied according to gender (*p* for interaction=0.003).

Table 19. Stratified analysis of the association between BMI variability and risk of total fracture according to a subgroup of age

Age		BMI variability (ASV)				*p* for trend	*p* for interaction
		First quartile	Second quartile	Third quartile	Fourth quartile		
Total	< 65 year-old, events	744	835	1046	1352		0.001
	Person-years	56,484	58,835	64,355	74,980		
	aHR (95% CI)	1 (ref)	1.08 (0.98-1.19)	1.18 (1.07-1.29)	1.20 (1.10-1.32)	<0.001	
	≥ 65year-old, events	991	1,058	1,062	1,169		
	Person-years	258,106	253,815	246,125	230,518		
	aHR (95% CI)	1 (ref)	1.09 (1.00-1.19)	1.06 (0.97-1.15)	1.14 (1.05-1.25)	0.007	
Men	< 65 year-old, events	252	263	301	362		0.012
	Person-years	32,879	34,195	35,130	36,262		
	aHR (95% CI)	1.00 (ref)	1.00 (0.84-1.19)	1.08 (0.92-1.28)	1.22 (1.04-1.43)	0.008	
	≥ 65year-old, events	299	336	316	88		
	Person-years	155,706	156,433	140,4402	120,854		
	aHR (95% CI)	1.00 (ref)	1,11 (0.95-1.29)	1.12 (0.96-1.31)	1.14 (0.97-1.34)	0.123	

Women	< 65 year-old, events	494	572	745	990		0.001
	Person-years	23,605	24,640	29,225	38,718		
	aHR (95% CI)	1.00 (ref)	1.11 (0.99-1.26)	1.21 (1.08-1.36)	1.20 (1.08-1.34)	0.001	
	≥ 65year-old, events	692	722	746	881		
	Person-years	102,400	97,382	105,685	109,664		
	aHR (95% CI)	1.00 (ref)	1.09 (0.98-1,21)	1,03 (0.93-1.14)	1.14 (1.03-1.26)	0.030	

Hazard ratio calculated by Cox proportional hazards regression.
Fully-adjusted model includes adjustments for sex, initial BMI, change in BMI, household income, smoking, alcohol consumption, physical activity, Charlson comorbidity index, and diagnosis of osteoporosis
Acronyms: BMI, body mass index; ASV, Average successive variability; aHR, adjusted hazard ratio

Table 20. Stratified analysis of the association between BMI variability and risk of total fracture according to a subgroup of sex

			BMI variability (ASV)				p for trend	p for interaction
			First quartile	Second quartile	Third quartile	Fourth quartile		
Sex	Male	events	551	599	617	650		0.003
		Person-years	192,585	194,719	179,660	161,333		
		aHR (95% CI)	1.00 (ref)	1.06 (0.94-1.19)	1.10 (0.98-1.23)	1.18 (1.05-1.32)	0.004	
	Female	events	1,184	1,294	1,491	1,871		
		Person-years	134,309	130,878	144,950	160,711		
		aHR (95% CI)	1.00 (ref)	1.08 (1.00-1.17)	1.09 (1.01-1.17)	1.13 (1.05-1.21)	0.002	

Hazard ratio calculated by Cox proportional hazards regression.
Fully-adjusted model includes adjustments for age, initial BMI, change in BMI, household income, smoking, alcohol consumption, physical activity, Charlson comorbidity index, and diagnosis with osteoporosis
Acronyms: BMI, body mass index; ASV, Average successive variability; aHR, adjusted hazard ratio

Participants with the greatest weight variability had elevated risk of fracture for both those who gained weight (aHR 1.12, 95% CI 1.02–1.23) and who lost weight, within the second, third, and fourth quartile of weight variability had increased risk of fractures (aHR 1.13, 95% CI 1.03–1.24; aHR 1.13, 95% CI 1.03–1.24; aHR 1.20, 95% CI 1.09–1.31, respectively) compared to those within the first quartile of weight variability. The risk of fractures increased upon greater degrees of weight variability for both those who gained weight (*p* for trend=0.002) and who lost weight (*p* for trend <0.001). The association between weight variability and fracture seems to be varied according to direction of weight change (*p* for interaction <0.001).

For men, the participants with the greatest weight variability had elevated risk of fracture for both those who gained weight (aHR 1.26, 95% CI 1.05–1.50) and those who lost weight (aHR 1.24, 95% CI 1.05–1.46). The risk of fractures increased upon greater degrees of weight variability for both those who gained weight (*p* for trend=0.032) and who lost weight (*p* for trend=0.006). The association between weight variability and fracture seems to be varied according to direction of weight change (*p* for interaction=0.001).

For women, the participants with the greatest weight variability had elevated risk of fracture for both those who gained weight (aHR 1.11, 95% CI 1.00–1.22). This association seems to be more obvious in those who lost weight; those within the second, third, and fourth quartile of weight variability had increased risk of fractures (aHR 1.17, 95% CI 1.04–1.31; aHR 1.12, 95% CI 1.00–1.25; aHR 1.19, 95% CI 1.07–1.32, respectively) compared to those within the first quartile of weight variability. The risk of fractures increased upon greater degrees of weight variability for both those who gained weight (p for trend=0.023) and who lost weight (p for trend =0.010). The association between weight variability and fracture seems to be varied according to direction of weight change (p for interaction=0.002).

Table 21. Stratified analysis of the association between BMI variability and risk of total fracture according to a subgroup of direction of weight change

	Direction of Weight change	BMI variability (ASV)				*p* for trend	*p* for interaction
		First quartile	Second quartile	Third quartile	Fourth quartile		
Total	Weight gain, events	958	937	1,081	1,253		<0.001
	Person-years	178,144	166,255	164,308	158,171		
	aHR (95% CI)	1.00 (ref)	1.02 (0.93-1.12)	1.07 (0.98-1.17)	1.12 (1.02-1.23)	0.002	
	Weight loss, events	777	956	1,027	1,268		
	Person-years	148,751	159,343	160,302	163,873		
	aHR (95% CI)	1.00 (ref)	1.13 (1.03-1.24)	1.13 (1.03-1.24)	1.20 (1.09-1.31)	<0.001	
Men	Weight gain, events	293	303	302	333		0.001
	Person-years	104,556	99,836	90,848	81,854		
	aHR (95% CI)	1.00 (ref)	1.09 (0.93-1.28)	1.10 (0.93-1.30)	1.26 (1.05-1.50)	0.032	
	Weight loss, events	258	296	315	317		
	Person-years	88,030	94,883	88,812	79,479		
	aHR (95% CI)	1.00 (ref)	1.06 (0.90-1.26)	1.16 (0.99-1.37)	1.24 (1.05-1.46)	0.006	

Women	Weight gain, events	665	634	779	920		0.002
	Person-years	73,589	66,418	73,460	76,317		
	aHR (95% CI)	1.00 (ref)	1.00 (0.90-1.12)	1.07 (0.97-1.19)	1.11 (1.00-1.22)	0.023	
	Weight loss, events	519	660	712	951		
	Person-years	60,721	64,460	71,490	84,393		
	aHR (95% CI)	1.00 (ref)	1.17 (1.04-1.31)	1.12 (1.00-1.25)	1.19 (1.07-1.32)	0.010	

Hazard ratio calculated by Cox proportional hazards regression.
Fully-adjusted model includes adjustments for age, sex, initial BMI, household income, smoking, alcohol consumption, physical activity, Charlson comorbidity index, and diagnosis with osteoporosis
Acronyms: BMI, body mass index; ASV, Average successive variability; aHR, adjusted hazard ratio

When the participants were divided into normal weight, overweight and obese individuals during the first health examination, those with the greatest weight variability had elevated risk of fractures in normal weight (aHR 1.21, 95% CI 1.10–1.34), overweight (aHR 1.17, 95% CI 1.04–1.32) with significance but obese individuals (aHR 1.06, 95% CI 0.96–1.18). The risk of fractures increased upon greater degrees of weight variability for the normal-weighted (p for trend <0.001) and the overweighted (p for trend=0.007) participants but obese participants (p for trend=0.324). For men, those with the greatest weight variability had elevated risk of fractures in normal weight (aHR 1.30, 95% CI 1.10–1.54) with significance but overweight (aHR 1.16, 95% CI 0.93–1.45) and obese individuals (aHR 1.10, 95% CI 0.88–1.37). The risk of fractures increased upon greater degrees of weight variability for the normal-weighted (p for trend=0.002) but the overweighted (p for trend=0.132) participants obese participants (p for trend=0.530). For women, those with the greatest weight variability had elevated risk of fractures in normal weight (aHR 1.17, 95% CI 1.14–1.33), overweight (aHR 1.18, 95% CI 1.02–1.36) with significance but obese individuals (aHR 1.05, 95% CI 0.93–1.19). The risk of fractures increased upon greater degrees of weight variability for the normal-weighted (p for trend=0.020) and the overweighted (p for trend=0.026) participants but obese participants (p for trend=0.434).

Table 22. Stratified analysis of the association between BMI variability and risk of total fracture according to a subgroup of initial BMI

Initial body mass index		BMI variability (ASV)				*p* for trend
		First quartile	Second quartile	Third quartile	Fourth quartile	
Total	<23.0kg/㎡, events	715	775	804	923	
	Person-years	126,079	120,977	115,328	101,749	
	aHR (95% CI)	1.00 (ref)	1.07 (0.97-1.19)	1.08 (0.98-1.20)	1.21 (1.10-1.34)	<0.001
	23.0-24.9 kg/㎡, events	476	518	583	632	
	Person-years	98,172	95,041	91,616	83,106	
	aHR (95% CI)	1.00 (ref)	1.08 (0.96-1.23)	1.15 (1.02-1.30)	1.17 (1.04-1.32)	0.007
	≥25.0kg/㎡, events	544	600	721	966	
	Person-years	102,643	109,579	117,666	137,190	
	aHR (95% CI)	1.00 (ref)	1.06 (0.94-1.19)	1.06 (0.95-1.18)	1.06 (0.96-1.18)	0.324
Men	<23.0kg/㎡, events	257	279	293	299	
	Person-years	71,283	68,808	62,511	53,345	
	aHR (95% CI)	1.00 (ref)	1.10 (0.93-1.30)	1.16 (0.98-1.38)	1.30 (1.10-1.54)	0.002
	23.0-24.9 kg/㎡, events	150	147	159	158	
	Person-years	60,055	58,461	51,894	42,810	
	aHR (95% CI)	1.00 (ref)	0.98 (0.78-1.23)	1.09 (0.87-1.36)	1.16 (0.93-1.45)	0.132

	≥25.0kg/㎡, events	144	173	165	193	
	Person-years	61,247	67,450	65,255	65,179	
	aHR (95% CI)	1.00 (ref)	1.09 (0.87-1.36)	1.02 (0.82-1.28)	1.10 (0.88-1.37)	0.530
Women	<23.0kg/㎡, events	458	496	511	624	
	Person-years	54,796	52,170	52,817	48,404	
	aHR (95% CI)	1.00 (ref)	1.06 (0.94-1.21)	1.04 (0.92-1.18)	1.17 (1.04-1.33)	0.020
	23.0-24.9 kg/㎡, events	326	371	424	474	
	Person-years	38,118	36,580	39,722	40,296	
	aHR (95% CI)	1.00 (ref)	1.13 (0.98-1.32)	1.17 (1.01-1.35)	1.18 (1.02-1.36)	0.026
	≥25.0kg/㎡, events	400	427	556	773	
	Person-years	41,396	42,129	52,411	72,011	
	aHR (95% CI)	1.00 (ref)	1.05 (0.92-1.20)	1.07 (0.94-1.21)	1.05 (0.93-1.19)	0.434

Hazard ratio calculated by Cox proportional hazards regression.
Fully-adjusted model includes adjustments for age, sex, change in BMI, household income, smoking, alcohol consumption, physical activity, Charlson comorbidity index, and osteoporosis medication
Acronyms: BMI, body mass index; ASV, Average successive variability; aHR, adjusted hazard ratio

Part II. Definition of fracture – An admission or at least three clinic visits in one year

While patients with hip fractures are always admitted to the hospital, spinal and upper extremity fractures rarely require admission. Therefore, fracture rates for spine and upper extremity fractures could be underestimated. Thus, we additionally studied the association between BMI variability and the risk of fracture with another fracture definition, admission or at least three clinic visits in one year.

The impact of weight variability on fractures at three specific sites (hip, spinal, and upper extremity) and sum of the fractures called "total fractures" is shown in Table 23 for total population (Table 24 for men and Table 25 for women). Compared to those within the first quartile (lowest) of weight variability, those within the second, third and fourth quartile (highest) of weight variability had increased risk of total fractures (aHR 1.08, 95% CI 1.03-1.14; aHR 1.07, 95% CI 1.02-1.13; aHR 1.09, 95% CI 1.04-1.15, respectively). Furthermore, the risk of total fractures increased upon greater degrees of weight variability (*p* for trend <0.001). Compared to those within the first quartile of weight variability, those within the second, third, and fourth quartile of weight variability had increased risk of hip fractures (aHR 1.06, 95% CI 0.89-1.26; aHR 1.22, 95% CI 1.03-1.44; aHR 1.22 95% CI 1.04-1.43, respectively). The risk of hip fractures increased upon greater degrees of weight variability (*p* for trend=0.002). Compared to those within the first quartile of weight variability, those within the second, third, and fourth quartile of weight variability had increased risk of spinal fractures (aHR 1.10, 95% CI 1.02-1.19; aHR 1.09, 95% CI

1.01–1.17; aHR 1.15 95% CI 1.07–1.23, respectively). The risk of spinal fractures increased upon greater degrees of weight variability (*p* for trend <0.001). Compared to those within the first quartile of weight variability, those within the second, third, fourth quartile of weight variability had increased risk of other fractures (aHR 1.09, 95% CI 1.01–1.17; aHR 1.04, 95% 0.97–1.12; aHR 1.03, 95% CI 0.95–1.10, respectively), but without significance.

Table 23. Hazard ratios for the BMI variability on risk of fracture

	BMI variability (ASV)				p for trend
	First quartile	Second quartile	Third quartile	Fourth quartile	
Total fracture					
Events	2,711	2,951	3,176	3,658	
Person-years	314,590	312,651	310,480	305,498	
aHR (95% CI)	1.00 (ref)	1.08 (1.03-1.14)	1.07 (1.02-1.13)	1.09 (1.04-1.15)	<0.001
Hip fracture					
Events	245	267	346	420	
Person-years	325,981	324,570	323,348	320,467	
aHR (95% CI)	1.00 (ref)	1.06 (0.89-1.26)	1.22 (1.03-1.44)	1.22 (1.04-1.43)	<0.002
Spinal fracture					
Events	1,304	1,460	1,602	1,972	
Person-years	320,675	318,920	317,202	312,838	
aHR (95% CI)	1.00 (ref)	1.10 (1.02-1.19)	1.09 (1.01-1.17)	1.15 (1.07-1.23)	<0.001
Other fracture					
Events	1,350	1,455	1,501	1,612	
Person-years	320,819	319,211	317,871	314,585	
aHR (95% CI)	1.00 (ref)	1.09 (1.01-1.17)	1.04 (0.97-1.12)	1.03 (0.95-1.10)	0.417

Hazard ratio calculated by Cox proportional hazards regression.
Fully-adjusted model includes adjustments for age, sex, initial BMI, change in BMI, household income, smoking, alcohol consumption, physical activity, Charlson comorbidity index, and diagnosis with osteoporosis
Acronyms: BMI, body mass index; ASV, Average successive variability; aHR, adjusted hazard ratio

Table 24. Hazard ratios for the BMI variability on risk of fracture for men

	BMI variability (ASV)				p for trend
	First quartile	Second quartile	Third quartile	Fourth quartile	
Total fracture					
Events	842	935	925	942	
Person-years	188,585	190,629	175,570	157,116	
aHR (95% CI)	1.00 (ref)	1.06 (0.94-1.19)	1.09 (0.98-1.23)	1.17 (1.04-1.31)	0.002
Hip fracture					
Events	130	122	147	165	
Person-years	192,118	194,255	179,144	160,759	
aHR (95% CI)	1.00 (ref)	0.91 (0.71-1.16)	1.06 (0.84-1.34)	1.13 (0.90-1.43)	0.093
Spinal fracture					
Events	450	490	509	513	
Person-years	190,380	192,484	177,337	158,997	
aHR (95% CI)	1.00 (ref)	1.06 (0.93-1.20)	1.10 (0.96-1.24)	1.10 (0.97-1.25)	0.054
Other fracture					
Events	313	380	321	318	
Person-years	191,050	193,038	178,195	159,771	
aHR (95% CI)	1.00 (ref)	1.19 (1.03-1.39)	1.07 (0.91-1.24)	1.14 (0.97-1.33)	0.203

Hazard ratio calculated by Cox proportional hazards regression.
Fully-adjusted model includes adjustments for age, sex, initial BMI, change in BMI, household income, smoking, alcohol consumption, physical activity, Charlson comorbidity index, and diagnosis with osteoporosis
Acronyms: BMI, body mass index; ASV, Average successive variability; aHR, adjusted hazard ratio

Table 25. Hazard ratios for the BMI variability on risk of fracture for women

	BMI variability (ASV)				*P* for trend
	First quartile	Second quartile	Third quartile	Fourth quartile	
Total fracture					
Events	1,869	2,016	2,251	2,716	
Person-years	133,863	130,316	144,204	159,709	
aHR (95% CI)	1.00 (ref)	1.09 (1.01-1.18)	1.09 (1.01-1.18)	1.12 (1.04-1.21)	0.019
Hip fracture					
Events	115	145	199	255	
Person-years	135,228	131,862	146,647	161,371	
aHR (95% CI)	1.00 (ref)	1.22 (0.95-1.56)	1.38 (1.10-1.74)	1.31 (1.05-1.64)	0.014
Spinal fracture					
Events	854	970	1093	1459	
Person-years	130294	126435	139865	153841	
aHR (95% CI)	1.00 (ref)	1.12 (1.02-1.23)	1.09 (1.00-1.19)	1.17 (1.07-1.27)	0.001
Other fracture					
Events	1,037	1,075	1,180	1,294	
Person-years	129,769	126,173	139,675	154,815	
aHR (95% CI)	1.00 (ref)	1.06 (0.97-1.15)	1.04 (0.95-1.13)	1.00 (0.92-1.09)	0.789

Hazard ratio calculated by Cox proportional hazards regression.
Fully-adjusted model includes adjustments for age, sex, initial BMI, change in BMI, household income, smoking, alcohol consumption, physical activity, Charlson comorbidity index, and diagnosis with osteoporosis
Acronyms: BMI, body mass index; ASV, Average successive variability; aHR, adjusted hazard ratio

Table 26 shows the result from a stratified analysis of the effect of weight variability on total fractures according to presence of osteoporosis. Among individuals who had osteoporosis, those within the second, third and fourth quartile of weight variability had increased risk of fractures (aHR 1.14, 95% CI 1.03-1.25; aHR 1.11, 95% CI 1.01-1.22; aHR 1.14, 95% CI 1.04-1.25, respectively) compared to those within the first quartile of weight variability. The risk of fractures increased upon greater degrees of weight variability (*p* for trend =0.015). Among individuals without osteoporosis, those within the second, third, and fourth quartile of weight variability had increased risk of fractures (aHR 1.06, 95% CI 1.00-1.13; aHR 1.06, 95% CI 1.00-1.13; aHR 1.10, 95% CI 1.03-1.16, respectively) compared to those within the first quartile of weight variability. The risk of fractures increased upon greater degrees of weight variability (*p* for trend=0.006). The relationship between BMI variability and fracture was varied across the presence of osteoporosis (*p* for interaction=0.003).

Table 26. Hazard ratios for BMI variability on risk of total fracture among those who had osteoporosis

Diagnosed with osteoporosis		BMI variability (ASV)				p for trend	p for interaction
		First quartile	Second quartile	Third quartile	Fourth quartile		
Total	Yes, events	804	916	1018	1,271		
	Person-years	47,216	46,587	50,982	58,105		
	aHR (95% CI)	1.00 (ref)	1.14 (1.03-1.25)	1.11 (1.01-1.22)	1.14 (1.04-1.25)	0.015	
	No, events	1,907	2,035	2,158	2,387		
	Person-years	267,374	266,064	259,489	247,393		
	aHR (95% CI)	1.00 (ref)	1.06 (1.00-1.13)	1.06 (1.00-1.13)	1.10 (1.03-1.16)	0.006	0.003
Men	Yes, events	45	62	65	68		
	Person-years	4,325	4,983	4,876	5,084		
	aHR (95% CI)	1.00 (ref)	1.23 (0.84-1.80)	1.21 (0.83-1.78)	1.13 (0.77-1.66)	0.625	
	No, events	797	873	860	874		
	Person-years	184,260	185,646	170,694	152,032		
	aHR (95% CI)	1.00 (ref)	1.08 (0.98-1.19)	1.10 (0.99-1.21)	1.17 (1.06-1.29)	0.002	

Women	Yes, events	759	854	953	1,203	
	Person-years	42,891	41,604	46,107	53,020	
	aHR (95% CI)	1.00 (ref)	1.13 (1.02-1.25)	1.10 (1.00-1.21)	1.14 (1.04-1.25)	0.019
	No, events	1,110	1,162	1,298	1,513	
	Person-years	83,114	804,169	88,804	95,362	
	aHR (95% CI)	1.00 (ref)	1.05 (0.97-1.14)	1.04 (0.96-1.13)	1.06 (0.98-1.14)	0.233

Hazard ratio calculated by Cox proportional hazards regression.
Fully-adjusted model includes adjustments for age, sex, initial BMI, change in BMI, household income, smoking, alcohol consumption, physical activity, Charlson comorbidity index
Acronyms: BMI, body mass index; ASV, Average successive variability; aHR, adjusted hazard ratio

Participants with the greatest weight variability had elevated risk of fracture for both those who gained weight (aHR 1.11, 95% CI 1.04–1.19) and the risk of fractures increased upon greater degrees of weight variability (*p* for trend=0.002). However, this significant association seems to be disappeared in those who lost weight; those within the second, third, and fourth quartile of weight variability had increased risk of fractures (aHR 1.13, 95% CI 1.03–1.24; aHR 1.13, 95% CI 1.03–1.24; aHR 1.20, 95% CI 1.09–1.31, respectively, *p* for trend=0.280) compared to those within the first quartile of weight variability. The trend of association between direction of weight change and risk of total fracture remained consistent in both men and women (Table 27).

Table 27. Stratified analysis of the association between BMI variability and risk of total fracture according to a subgroup of direction of weight change

Direction of Weight change		BMI variability (ASV)				*p* for trend
		First quartile	Second quartile	Third quartile	Fourth quartile	
Total	Weight gain, events	1,443	1,444	1,610	1,792	
	Person-years	171,492	159,883	157,066	150,060	
	aHR (95% CI)	1.00 (ref)	1.05 (0.98-1.13)	1.09 (1.01-1.17)	1.11 (1.04-1.19)	0.002
	Weight loss, events	1,268	1,507	1,566	1,866	
	Person-years	143,097	152,768	153,414	155,438	
	aHR (95% CI)	1.00 (ref)	1.11 (1.03-1.20)	1.06 (0.99-1.14)	1.11 (1.03-1.19)	0.280
Men	Weight gain, events	438	455	441	472	
	Person-years	102,372	97,826	88,793	79,714	
	aHR (95% CI)	1.00 (ref)	1.07 (0.94-1.22)	1.07 (0.93-1.22)	1.16 (1.02-1.33)	0.033
	Weight loss, events	404	480	484	470	
	Person-years	86,212	92,802	86,777	77,402	
	aHR (95% CI)	1.00 (ref)	1.09 (0.95-1.24)	1.10 (0.97-1.26)	1.11 (0.97-1.26)	0.156

Women	Weight gain, events	1,005	989	1,169	1,320	
	Person-years	69,120	62,056	68,273	70,345	
	aHR (95% CI)	1.00 (ref)	1.05 (0.97-1.15)	1.10 (1.01-1.20)	1.10 (1.01-1.19)	0.019
	Weight loss, events	864	1,027	1,082	1,396	
	Person-years	56,885	59,966	66,637	78,036	
	aHR (95% CI)	1.00 (ref)	1.11 (1.01-1.21)	1.02 (0.93-1.12)	1.05 (0.97-1.15)	0.663

Hazard ratio calculated by Cox proportional hazards regression.
Fully-adjusted model includes adjustments for age, sex, initial BMI, household income, smoking, alcohol consumption, physical activity, Charlson comorbidity index, and diagnosis with osteoporosis
Acronyms: BMI, body mass index; ASV, Average successive variability; aHR, adjusted hazard ratio

Ⅴ. Discussion

In this nationwide cohort consisting of more than 166,000 Korean men and women, we have shown that BMI variability is associated with increased risk of fracture. Most observational studies report the association between weight fluctuation and increased morbidity including increased risk of diabetes mellitus (32, 33) as well as cardiovascular and all-cause mortality (26, 34, 35). However, there is sparse data on the effects of weight fluctuation on bone mineral density, and further fracture risk. To our knowledge, this is the first study to show that those with high weight variability had increased risk of fracture within an Asian population of elderly participants aged more than 50 years old.

1. Key variables (weight variability & fracture)

1) Weight variability estimation

It is difficult to define weight fluctuation and a wide range of weight fluctuation measures were used in previous studies. A couple of most well-used measurement methods are average successive variability (ASV) and root mean square error (RMSE) of variation. Many previous studies examined weight variability using RMSE (32, 36-40). Several current studies examined weight variability using ASV indices in relation to incident diseases (24, 26, 33).

Average successive variability (ASV)

The body weight variability was assessed by calculation the ASV indices. In recent well-designed large cohort studies, ASV is popular to estimate body weight variability (26, 41-43). In addition, it is regarded as an appropriate tool to assess many biological variabilities for example, blood pressure, heart rate, and cholesterol variability (44-46). In our study, the ASV of body weight was calculated using body weight using the following formula, Figure 6. It is largely independent of trend effects, but susceptible to differences in mean follow-up levels (47).

Figure 6. Example of average successive variability (ASV)

[Example : BMI Measurement] | 1^{st} BMI | 22 kg/m2 | 2^{nd} BMI | 25 kg/m2 | 3^{rd} BMI | 20 kg/m2

BMI change $= 3^{rd}\text{ BMI} - 1^{st}\text{ BMI} = 20 - 22 = -2\text{ kg/m}^2$

BMI variability
$$= \frac{|3^{rd}\text{ BMI} - 2^{nd}\text{ BMI}| + |2^{nd}\text{ BMI} - 1^{st}\text{ BMI}|}{2}$$
$$= \frac{|20-25|+|25-22|}{2} = 4\text{ kg/m}^2$$

Root mean square error (RMSE) of variation

In many previous literature reviews, there is a well-used alternative method to estimate weight variability, called root mean square error (RMSE) (32, 37-40, 48-51). The RMSE around the slope of weight change over time for each individual (Figure 7), weight variability is divided into the slope (that is the regression coefficient which represents the trend index) and the RMSE (that is the standard error around the linear slope which represents the weight fluctuation index) of variation around the slope of weight change over time for each individual (52, 53). However, the RMSE might misclassify subjects and overestimate weight cyclers. The RMSE method assumes that the overall weight gain trend is linear, which is not often the case. Figure 8 gives three typical examples of weight variability. In the first example, the RMSE gives an incorrect estimation of weight fluctuation. Although the subject does not have a weight cycle, the RMSE value is higher than the second and third examples that both have weight fluctuation (54).

Figure 7. Example of root mean square error (RMSE) of variation

[Example : BMI Measurement]

1st BMI	22 kg/m2	2nd BMI	25 kg/m2	3rd BMI	20 kg/m2

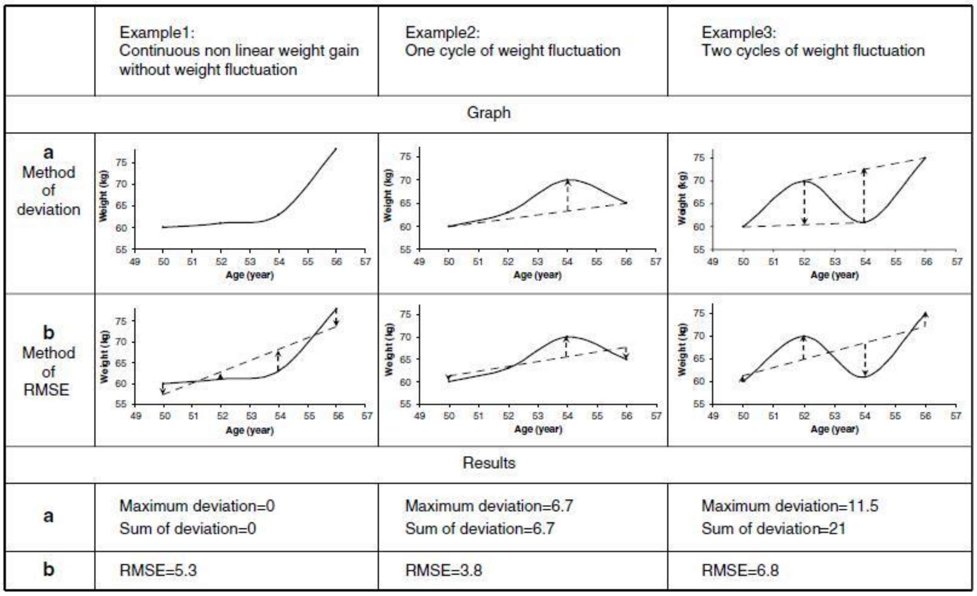
BMI mean $= (1^{st}\ \text{BMI} + 2^{nd}\ \text{BMI} + 3^{rd}\ \text{BMI}) / 3 = (22 + 25 + 20) / 3$

BMI RMSE

$$= \sqrt{\frac{(\text{BMI Mean} - 1^{st}\ \text{BMI})^2 + (\text{BMI Mean} - 2^{nd}\ \text{BMI})^2 + (\text{BMI Mean} - 3^{rd}\ \text{BMI})^2}{3}}$$

$$= \sqrt{\frac{(22.3 - 22)^2 + (22.3 - 25)^2 + (22.3 - 20)^2}{3}} = 2{,}18$$

Figure 8. Overestimation issue for root mean square error (RMSE) of variation



(A-C Vergnaud et al. International Journal of Obesity (2008) 32, 315-321)

In our knowledge, there is no study about direct comparison between ASV and RMSE methods in measuring weight fluctuation, but the results and trends according to previous domestic and international studies are consistent.

2) Fracture definition

Table 28 shows a brief summary with definition of fracture from domestic epidemiological studies. According to previous studies with fracture, mostly epidemiological studies in Korea, the fracture definition commonly consists the admission or outpatient visit. The procedure or treatment codes were mostly included, especially for hip fracture.

However, in longitudinal cohort studies from other countries, they defined the fracture from the admission/discharge record with x-ray verification if possible (Table 29). According to overall previous studies, we additionally studied the association between BMI variability and the risk of fracture with another fracture definition, admission or at least three clinic visits in one year. While patients with hip fractures are always admitted to the hospital, Spinal and upper extremity fractures rarely require admission. Therefore, fracture rates for spine and upper extremity fractures could be underestimated. Thus, we examined if the association between BMI variability and the risk of admission due to fracture remained with the different definition of fracture- admission or at least three clinic visits in one year. Finally, it remained consistent findings; the risk of fracture increased with weight variability, in both fracture definitions; 'admission' and 'admission or at least three clinic visits in one year' due to fracture.

Table 28. Domestic studies with definition of fracture (mostly epidemiological studies)

Previous studies in Korea	Definition of fracture	Fracture incidence	Data base
Lee, et al. Osteoporos Int (2012)	more than three outpatient visits or one admission for vertebral fracture with ICD-10 codes (recounted if 6month or more)	2005: 974/100,000 2006: 995/100,000 2007: 998/100,000 2008: 969/100,000	Health Insurance Review and Assessment Service (HIRA)
Park, et al. J Bone Miner Metab (2011)	more than three outpatient visits or one admission for vertebral fracture with ICD-10 codes (hip : including procedure; reduction, pinning, etc.)	Overall/Hip/Spine/Distal radius/Humerus (/100,000) 2005: 1661/148/974/475/80 2006: 1646/151/995/436/80 2007: 1623/149/998/408/81 2008: 1614/157/969/422/81	HIRA
Kim, et al. J Bone Metab (2017)	one hospitalization two physician visits (within 6-month) for hip, vertebral, radial fracture, and humerus with ICD-10 codes (hip : including procedure; reduction, pinning, etc.)	Age-adjusted 2008: 1,127/100,000 2011: 1,295/100,000	NHIS
Kwon, et al. J Korean Med Sci (2016)	more than three outpatient visits or one admission for radial fracture with ICD-10 codes + treatment codes (including procedure; reduction, pinning, etc.)	2008-2012: 427.9/100,000	NHIS

Table 29. International studies with definition of fracture (mostly cohort studies)

Previous studies	Definition of fracture	Data base
Dai et al. Osteoporos Int (2015)	inpatient discharge information from all public and private hospitals in Singapore (surgical or medical records)	National hospital discharge database + Singapore Registry of Births and Deaths
Compston et al. Journal of Bone and Mineral Research (2014)	self-reported and information on X-ray verification	self-questionnaire
Grønskag et al. Osteoporos Int (2012)	incident hip fracture with either the medical record or the X-ray report.	Hospital medical record
Beck et al. Journal of Bone and Mineral Research (2009)	annual self-report (but, hip fractures with review of medical records)	Self-questionnaire

2. Stratified analysis and Sensitivity analysis

The risk of fracture with weight variability was varied across the presence of osteoporosis. Presence of osteoporosis is a potential confounder and its impact on fracture would be more powerful than weight variability. Thus, the power of association between weight variability and fracture among those who had osteoporosis might be attenuated. As a result, individuals without osteoporosis seemed to be with more significant increased risk of fracture upon greater weight variability compared to those with osteoporosis (p for interaction=0.003). It remained consistent among men, but women; those who had osteoporosis had increased fracture risk with weight variability (p for trend=0.005) but those without osteoporosis showed null association (p for trend=0.058). Potential confounders such as menopause status or hormone replacement therapy for women might affect to fracture risk, which could strengthen the power of association between weight variability and fracture.

The risk of fracture with weight variability varied across the age. It was apparent that age is a powerful and non-modifiable confounder to tell the relationship between weight variability and fracture (p for interaction=0.001). It remained consistent among both men and women. Thus, the power of association between weight variability and fracture among elderly population ≥ 65year-old might be attenuated. This is supported in a previous study, which demonstrated that age is the most informative predictor variable regarding low bone mineral density in postmenopausal white women as well as weight (55).

The risk of fracture with weight variability varied across the direction of weight change (*p* for interaction <0.001). The impact of weight variability on fracture might be attenuated among those who gained weight compared to those who lost weight (*p* for interaction=0.002, *p* for interaction <0.001, respectively). We postulated that weight gain could be a stronger confounder than weight loss in relationship between weight variability and fracture, but this tendency was inconsistent by gender. Thus, further studies are required to clarify this result.

Obese individuals during the first health examination period did not show the significant association between weight variability and fracture (*p* for trend = 0.324). This is in alignment with the results from a previous study which suggested that a history of weight cycling has an adverse effect on total femur and total-body bone mineral density in overweight sedentary premenopausal women (23). According to this meta-analysis, high BMI remained a risk factor for upper arm fracture but was also a risk factor for all osteoporotic fractures when adjusted for BMD (16). Since obesity is itself an important risk factor for fracture, the power of significance in association between weight variability and fracture seemed to be attenuated in obese individuals.

3. Mechanism

Several theories through some observational studies and animal studies have demonstrated the possible mechanism behind the association between weight variability and fracture. First, weight variability, defined as a repeated cycle of weight loss followed by regain, could relate to long-term changes in body composition. The importance of body composition on bone health has been issued. The association between lean mass, fat mass, and bone mineral density has been described according to this meta-analysis, which concluded that lean mass exerts a greater effect on bone mineral density and fat mass in both gender (56). Among Korean population, lean body mass showed an independent association with increased bone mass and bone mineral density, regardless of gender, age in men, and menopausal status in women (57). Lean body mass is not typically regained as much as fat is with weight regain (58, 59). Especially for older population, it is hard to conserve lean mass with weight loss (60-62). This could result in unhealthy fat accumulation, possibly predisposing to an increase in loss of bone mass and strength (63, 64). Asymmetry in change of body composition between weight loss and regain, older adults who are prone to losing weight or failing to regain the weight may be at higher risk for excessive loss of lean mass. It results that older adults who experience weight fluctuation are more likely to experience poor health status (60, 61, 65). According to this animal experiment, it reported a greater increase in total body mass and fat mass after weight cycling despite identical energy intake compared with continuous hypercaloric feeding. This phenotype was associated with altered expression of clock genes in adipose tissue, which may be involved in the metabolic adaptation to weight cycling (66). Both percentage of body fat and trunk fat have negative associations with BMD (63, 67-69). Increasing fat mass may be accompanied by a reduction in bone formation owing to the switching of stem cell differentiation in bone marrow to favor adipocytes over osteoblasts (70). Increased fat mass may trigger bone-strength deficit as previous study showed that the relative bone strength index was inversely associated with fat mass (71).

Secondly, weight cycling itself might lead to low BMD. A study for Finnish premenopausal women aged 29–46 years showed that weight cycling might be associated with lower bone mineral density in the spine and distal radius but not with bone mineral density in the femoral neck and trochanter (72). It has been suggested that since weight loss is often 'unphysiologically' fast, bone loss occurring during weight loss is not fully reversed during the weight gain, which often occurs more slowly (72). It could also be that continuous weight loss episodes including bone loss produce permanent microarchitectural damage in the bones, resulting in a lower fracture threshold (72).

Thirdly, weight cycling may contribute to the systemic chronic inflammation and increased insulin resistance, which could further affect to bone damage. Weight cycling changes adipose tissue to a more hypoxic environment; hypoxic adipose tissue secretes leptin, a stimulus for macrophage activation and accumulation within adipose tissue (73). Leptin secreted by white adipose tissue regulates bone mass and decreases bone mass through central nervous system while also having an anabolic effect on bone by driving stem cell differentiation to the osteoblastic cell lineage (74, 75). A recent animal study also showed that weight cycling impaired glucose intolerance and insulin sensitivity by decreasing insulin and glucose transport molecules and increasing some inflammatory cytokines (76). It has been shown that insulin resistance seems to be inversely related to bone mass and strength (77, 78). It has been studied that for the same BMI, Asians had higher body fat and abdominal obesity components compared with those of the Caucasian population and this may be deleterious for bone health (79).

4. Strength and Limitation

There are several limitations in our study. First, the data for body composition was unavailable, so that proportion of lean mass and fat mass could not be determined. Although BMI is a widely-used measure of adiposity, the exact changes in fat mass according to weight variability could not be measured. Future studies investigating the effect of fat mass and lean mass variability on mortality are needed. Second, the impact of weight variability on fracture was not adjusted for BMD, a major determinant of fracture risk, due to lack of information. Third, for each individual, weight at the time of fracture could be one of potential covariates, but it was not considered in our study. As weight fluctuation was not determined after the third health examination, possible weight changes after the index date were not accounted for. Fourth, we did not distinguish whether the weight variability was intentional or unintentional, which can have different effects on prognosis. Finally, there was lack of information on some confounders which could affect to bone health such as the medication (glucocorticoid, thyroid medication, proton pump inhibitors etc.) use, hormone replacement therapy (HRT) use, and menopause status due to lack of data from the NHIS.

More studies evaluating the impact of weight variability on fractures from both outpatient and inpatient are required to complement our findings. Despite these limitations, our study adds to previous studies investigating the association between weight variability and fracture due to a number of strengths. First, to our knowledge, this is the first nationwide cohort study exploring the association between weight variability and fracture among Asian population. Few western studies examined the relationship of body weight variability and fracture based on a large cohort. We used a nationally representative cohort consisting of over 170,000 Korean men and women, an ethnicity few previous studies have investigated upon. Second, we used the indices of body weight variability, calculating both ASV and RMSE, and assured that the results were consistent (Table 30-35). Third, the advantage of fracture study using NHIS data is that the high-energy trauma that led to the fracture is spontaneously excluded because traffic accidents and industrial accidents are covered by different insurance systems. This study also used directly measured anthropometric data rather than self-reported recall data (80, 81). Finally, there is a differential finding; high weight variability may lead to increased risk of fracture in both men and women regardless of direction of weight change and trend of weight fluctuation. Particularly, subgroup analyses and sensitivity analyses indicate maintaining stable weight might be beneficial.

Table 30. Descriptive characteristics of the study population

		BMI variability (RMSE)			
		First quartile	Second quartile	Third quartile	Fourth quartile
Number of participants (%)		41,733 (25.00)	41,733 (25.00)	41,745 (25.01)	41,721 (24.99)
Age years, mean (SD)		58.90 (7.47)	59.34 (7.59)	59.73 (7.76)	60.68 (8.20)
Sex, N (%)					
	Men	25,916 (62.10)	23,991 (57.49)	23,318 (55.86)	21,155 (50.71)
	Women	15,817 (37.90)	17,742 (42.51)	18,427 (44.14)	20,566 (49.29)
BMI Variability (ASV), kg/㎡,mean(SD)		0.31 (1.15)	0.62 (0.18)	0.94 (0.26)	1.71 (1.09)
Initial BMI, kg/㎡,mean(SD)		23.74 (2.64)	23.92 (2.71)	24.12 (2.80)	24.54 (3.29)
Change in BMI, kg/㎡,mean(SD)		-0.00 (0.38)	-0.01 (0.74)	-0.02 (1.16)	-0.16 (2.61)
Household income, N (%)					
	First quartile	16,518 (39.58)	15,332 (36.74)	14,693 (35.07)	12,809 (30.70)
	Second quartile	11,784 (28.24)	12,142 (25.10)	12,169 (29.15)	12,286 (29.45)
	Third quartile	8,167 (19.57)	8,570 (20.54)	8,956 (21.45)	9,754 (23.38)
	Fourth quartile	5,264 (12.61)	5,689 (13.63)	5,981 (14.33)	6,872 (16.47)
Smoking, N (%)					
	Never smoker	29,969 (71.81)	30,748 (73.70)	30,981 (74.21)	31,875 (76.40)
	Past smoker	4,111 (9.85)	3,761 (9.01)	3,771 (9.03)	3,364 (8.06)
	Current smoker	7,653 (18.34)	7,214 (17.29)	6,993 (16.75)	6,482 (15.54)

Alcohol consumption, times per week, N (%)					
	None	24,287 (58.20)	25,502 (61.11)	26,175 (62.70)	27,806 (66.65)
	<1	6,146 (14.73)	5,683 (13.62)	5,428 (13.00)	4,865 (11.66)
	1-2	7,154 (17.14)	6,509 (15.60)	6,240 (14.95)	5,348 (12.82)
	3-4	2,629 (6.30)	2,542 (6.09)	2,357 (5.65)	2,167 (5.19)
	≥5	1,517 (3.64)	1,497 (3.59)	1,545 (3.70)	1,535 (3.68)
Physical activity, times per week, N (%)					
	None	18,910 (45.31)	19,681 (47.16)	20,537 (49.20)	22,084 (52.93)
	1-2	12,194 (29.22)	11,662 (27.94)	10,975 (26.29)	9,840 (23.59)
	3-4	5,958 (14.28)	5,647 (13.53)	5,353 (12.82)	4,800 (11.50)
	5-6	1,485 (3.56)	1,520 (3.64)	1,445 (3.46)	1,511 (3.62)
	7	3,186 (7.63)	3,223 (7.72)	3,435 (8.23)	3,486 (8.36)
CCI (%)					
	<4	38,367 (91.93)	38,048 (91.17)	37,669 (90.24)	36,511 (87.51)
	≥4	3,366 (8.07)	3,685 (8.83)	4,076 (9.76)	5,210 (12.49)
Diagnosis with osteoporosis (%)					
	Yes	6,164 (14.77)	6,736 (16.14)	7,317 (17.53)	8,099 (19.41)
	No	35,569 (85.23)	34,997 (83.86)	34,428 (82.47)	33,622 (80.59)

Men					
Number of participants (%)		25,916 (27.46)	23,991 (25.42)	23,318 (24.71)	21,155 (22.41)
Age years, mean (SD)		58.66 (7.44)	59.14 (7.60)	59.41 (7.73)	60.29 (8.18)
BMI Variability (ASV), kg/㎡,mean(SD)		0.31 (0.16)	0.62 (0.18)	0.93 (0.26)	1.68 (1.15)
Initial BMI, kg/㎡,mean(SD)		23.80 (2.60)	23.91 (2.64)	24.07 (2.70)	24.31 (3.25)
Change in BMI, kg/㎡,mean(SD)		-0.00 (0.39)	-0.01 (0.75)	-0.03 (1.16)	-0.10 (2.68)
Household income, N (%)					
	First quartile	11,390 (43.95)	9,797 (40.84)	9,137 (39.18)	7,275 (34.39)
	Second quartile	7,293 (28.14)	6,932 (28.89)	6,838 (29.32)	6,353 (30.03)
	Third quartile	4,466 (17.23)	4,453 (18.56)	4,518 (19.38)	4,515 (21.34)
	Fourth quartile	2,767 (10.68)	2,809 (11.71)	2,825 (12.12)	3,012 (14.24)
Smoking, N (%)					
	Never smoker	14423 (55.65)	13338 (55.60)	12915 (55.39)	11712 (55.36)
	Past smoker	4032 (15.56)	3680 (25.17)	3657 (15.68)	3.45 (15.37)
	Current smoker	7461 (28.79)	6973 (29.07)	6746 (28.93)	6191 (29.26)
Alcohol consumption, times per week, N (%)					
	None	10,454 (40.34)	10,034 (41.82)	10,030 (43.01)	9,726 (45.97)
	<1	4,905 (18.93)	4,246 (17.70)	4,040 (17.33)	3,352 (15.82)
	1-2	6,568 (25.34)	5,864 (24.44)	5,559 (23.84)	4,603 (21.76)
	3-4	2,532 (9.77)	2,439 (10.17)	2,249 (9.64)	2,049 (9.69)
	≥5	1,457 (5.62)	1,408 (5.87)	1,440 (6.18)	1,425 (6.74)

Physical activity, times per week, N (%)					
	None	10,305 (39.76)	9,952 (41.48)	9,996 (42.87)	9,739 (46.04)
	1-2	8,810 (33.99)	7,813 (32.57)	7,243 (31.06)	5,960 (28.17)
	3-4	3,922 (15.13)	3,493 (14.56)	3,315 (14.22)	2,788 (13.18)
	5-6	899 (3.47)	880 (3.67)	854 (3.66)	837 (3.96)
	7	1,980 (7.64)	1,853 (7.72)	1,910 (8.19)	1,831 (8.66)
CCI (%)					
	<4	24,027 (92.71)	22,022 (91.79)	21,281 (91.26)	18,733 (88.55)
	≥ 4	1,889 (7.29)	1,969 (8.21)	2,037 (8.74)	2,422 (11.45)
Diagnosis with osteoporosis (%)					
	Yes	6,164 (14.77)	6,736 (16.14)	7,317 (17.53)	8,099 (19.41)
	No	35,569 (85.23)	34,997 (83.86)	34,428 (82.47)	33,622 (80.59)

Women					
Number of participants (%)		15,817 (21.80)	17,742 (24.45)	18,427 (25.40)	20,566 (28.35)
Age years, mean (SD)		59.29 (7.49)	59.60 (7.57)	60.13 (7.77)	61.08 (8.21)
BMI Variability (ASV), kg/㎡,mean(SD)		0.30 (0.15)	0.62 (0.18)	0.94 (0.26)	1.74 (1.03)
Initial BMI, kg/㎡,mean(SD)		23.63 (2.71)	23.94 (2.81)	24.17 (2.92)	24.77 (3.32)
Change in BMI, kg/㎡,mean(SD)		0.00 (0.37)	-0.01 (0.73)	-0.02 (1.15)	-0.23 (2.54)
Household income, N (%)					
	First quartile	5,128 (32.42)	5,535 (31.20)	5,502 (29.86)	5,534 (26.91)
	Second quartile	4,491 (28.39)	5,210 (29.37)	5,331 (28.93)	5,933 (28.85)
	Third quartile	3,701 (23.40)	4,117 (23.20)	4,438 (24.08)	5,239 (25.47)
	Fourth quartile	2,497 (15.79)	2,880 (16.23)	3,156 (17.13)	3,860 (18.77)
Smoking, N (%)					
	Never smoker	15,546 (98.29)	17,420 (98.19)	18,066 (98.04)	20,163 (98.04)
	Past smoker	79 (0.50)	81 (0.46)	114 (0.62)	112 (0.54)
	Current smoker	192 (1.21)	241 (1.36)	247 (1.34)	0.40 (1.41)
Alcohol consumption, times per week, N (%)					
	None	13,833 (87.46)	15,468 (87.18)	16,145 (87.62)	18,080 (87.91)
	<1	1,241 (7.85)	1,437 (8.10)	1,388 (7.53)	1,513 (7.36)
	1-2	586 (3.70)	645 (3.64)	681 (3.70)	745 (3.62)
	3-4	97 (0.61)	103 (0.58)	108 (0.59)	118 (0.57)
	≥5	60 (0.38)	89 (0.50)	105 (0.57)	110 (0.53)

Physical activity, times per week, N (%)					
	None	8,605 (54.40)	9,729 (54.84)	10,541 (57.20)	12,345 (60.03)
	1-2	3,384 (21.39)	3,849 (21.69)	3,732 (20.25)	3,880 (18.87)
	3-4	2,036 (12.87)	2,154 (12.14)	2,038 (11.06)	2,012 (9.78)
	5-6	586 (3.70)	640 (3.61)	591 (3.21)	674 (3.28)
	7	1,206 (7.62)	1,370 (7.72)	1,525 (8.28)	1,655 (8.05)
CCI (%)					
	<4	14,349 (90.66)	16,026 (90.33)	16,388 (88.93)	17,778 (86.44)
	≥4	1,477 (9.34)	1,716 (9.67)	2,039 (11.07)	2,788 (13.56)
Diagnosis with osteoporosis (%)					
	Yes	6,164 (14.77)	6,736 (16.14)	7,317 (17.53)	8,099 (19.41)
	No	35,569 (85.23)	34,997 (83.86)	34,428 (82.47)	33,622 (80.59)

Acronyms: BMI, body mass index; RMSE, Root mean square error; SD, standard deviation; N, number of people; CCI, Charlson Comorbidity Index

Table 31. Hazard ratios for the BMI variability on risk of fracture

	BMI variability (RMSE)				P for trend
	First quartile	Second quartile	Third quartile	Fourth quartile	
Total fracture					
Events	1,676	1,946	2,111	2,524	
Person-years	314,701	312,525	310,911	305,082	
aHR (95% CI)	1.00 (ref)	1.08 (1.01-1.15)	1.10 (1.03-1.17)	1.15 (1.08-1.23)	<0.001
Hip fracture					
Events	269	332	373	479	
Person-years	325,587	324,964	323,831	319,985	
aHR (95% CI)	1.00 (ref)	1.15 (0.98-1.35)	1.20 (1.02-1.40)	1.28 (1.10-1.49)	0.002
Spinal fracture					
Events	1,670	1,915	2,059	2,536	
Person-years	320,500	319,258	317,444	312,432	
aHR (95% CI)	1.00 (ref)	1.06 (0.99-1.13)	1.07 (1.00-1.14)	1.14 (1.07-1.22)	<0.001
Other fracture					
Events	1,467	1,717	1,686	1,834	
Person-years	320,701	319,323	318,308	314,155	
aHR (95% CI)	1.00 (ref)	1.10 (1.02-1.18)	1.05 (0.98-1.12)	1.07 (0.99-1.14)	0.246

Hazard ratio calculated by Cox proportional hazards regression.
Fully-adjusted model includes adjustments for age, sex, initial BMI, change in BMI, household income, smoking, alcohol consumption, physical activity, Charlson comorbidity index, and diagnosis with osteoporosis
Acronyms: BMI, body mass index; RMSE, root mean square error; aHR, adjusted hazard ratio

Table 32. Hazard ratios for the BMI variability on risk of fracture for men

	BMI variability (RMSE)				*P* for trend
	First quartile	Second quartile	Third quartile	Fourth quartile	
Total fracture					
Events	578	575	620	644	
Person-years	197,465	181,924	175,713	156,797	
aHR (95% CI)	1.00 (ref)	1.02 (0.91-1.14)	1.11 (0.99-1.25)	1.16 (1.03-1.30)	0.004
Hip fracture					
Events	162	143	174	184	
Person-years	201,085	185,374	179,359	160,458	
aHR (95% CI)	1.00 (ref)	0.89 (0.71-1.11)	1.07 (0.87-1.33)	1.06 (0.86-1.32)	0.291
Spinal fracture					
Events	663	650	684	721	
Person-years	199,318	183,710	177,518	158,653	
aHR (95% CI)	1.00 (ref)	1.00 (0.90-1.12)	1.06 (0.95-1.18)	1.11 (1.00-1.24)	0.028
Other fracture					
Events	407	400	426	390	
Person-years	199,985	184,307	178,268	159,493	
aHR (95% CI)	1.00 (ref)	1.05 (0.91-1.20)	1.15 (1.00-1.31)	1.14 (0.99-1.31)	0.032

Hazard ratio calculated by Cox proportional hazards regression.
Fully-adjusted model includes adjustments for age, sex, initial BMI, change in BMI, household income, smoking, alcohol consumption, physical activity, Charlson comorbidity index, and diagnosis with osteoporosis
Acronyms: BMI, body mass index; RMSE, root mean square error; aHR, adjusted hazard ratio

Table 33. Hazard ratios for the BMI variability on risk of fracture for women

	BMI variability (RMSE)				*P* for trend
	First quartile	Second quartile	Third quartile	Fourth quartile	
Total fracture					
Events	1,098	1,371	1,491	1,880	
Person-years	117,236	130,601	135,198	148,285	
aHR (95% CI)	1.00 (ref)	1.10 (1.01-1.19)	1.09 (1.01-1.18)	1.15 (1.07-1.24)	0.001
Hip fracture					
Events	107	189	199	295	
Person-years	124,502	139,590	144,472	159,527	
aHR (95% CI)	1.00 (ref)	1.51 (1.19-1.91)	1.39 (1.10-1.76)	1.55 (1.24-1.94)	0.002
Spinal fracture					
Events	1007	1265	1375	1815	
Person-years	121,182	135,549	139,926	153,779	
aHR (95% CI)	1.00 (ref)	1.09 (1.00-1.18)	1.08 (0.99-1.17)	1.16 (1.07-1.25)	0.001
Other fracture					
Events	1060	1317	1260	1444	
Person-years	120,716	135,016	140,040	154,662	
aHR (95% CI)	1.00 (ref)	1.11 (1.02-1.20)	1.02 (0.94-1.10)	1.04 (0.96-1.13)	0.904

Hazard ratio calculated by Cox proportional hazards regression.
Fully-adjusted model includes adjustments for age, sex, initial BMI, change in BMI, household income, smoking, alcohol consumption, physical activity, Charlson comorbidity index, and diagnosis with osteoporosis
Acronyms: BMI, body mass index; RMSE, root mean square error; aHR, adjusted hazard ratio

Table 34. Hazard ratios for BMI variability on total risk of fracture among those who had osteoporosis

		BMI variability (RMSE)				*p* for trend	*p* for interaction
		First quartile	Second quartile	Third quartile	Fourth quartile		
Diagnosed with osteoporosis	Yes	515	634	715	918		0.001
	Person-years	44,859	48,551	52,645	56,834		
	aHR (95% CI)	1.00 (ref)	1.11 (0.99-1.25)	1.10 (0.98-1.23)	1.18 (1.06-1.32)	0.005	
	No	1,161	1,312	1,396	1,606		
	Person-years	269,842	263,974	258,266	248,248		
	aHR (95% CI)	1.00 (ref)	1.06 (0.98-1.15)	1.09 (1.01-1.18)	1.14 (1.05-1.23)	0.001	
Men	Yes	39	43	38	57		
	Person-years	4,682	4,604	5,077	4,905		
	aHR (95% CI)	1.00 (ref)	1.07 (0.70-1.66)	0.86 (0.55-1.35)	1.17 (0.77-1.77)	0.638	
	No	539	532	582	587		
	Person-years	192,783	177,320	170,637	151,891		
	aHR (95% CI)	1.00 (ref)	1.02 (0.90-1.15)	1.13 (1.01-1.27)	1.16 (1.03-1.30)	0.004	
Women	Yes	476	591	677	861		
	Person-years	40,177	43,947	47,569	51,929		
	aHR (95% CI)	1.00 (ref)	1.12 (0.99-1.26)	1.12 (0.99-1.26)	1.19 (1.06-1.33)	0.005	0.049
	No	622	780	814	1,019		
	Person-years	77,059	86,654	87,629	96,356		
	aHR (95% CI)	1.00 (ref)	1.09 (0.98-1.21)	1.07 (0.96-1.19)	1.12 (1.01-1.24)	0.048	

Hazard ratio calculated by Cox proportional hazards regression.
Fully-adjusted model includes adjustments for age, sex, initial BMI, change in BMI, household income, smoking, alcohol consumption, physical activity, Charlson comorbidity index, and diagnosis with osteoporosis
Acronyms: BMI, body mass index; RMSE, root mean square error; aHR, adjusted hazard ratio

Table 35. Stratified analysis of the association between BMI variability and risk of total fracture according to a subgroup of direction of weight change

		BMI variability (RMSE)				p for trend	p for interaction
		First quartile	Second quartile	Third quartile	Fourth quartile		
Direction of Weight change	Weight gain, events	941	1,003	1,025	1,260		<0.001
	Person-years	175,753	160,781	156,623	145,343		
	aHR (95% CI)	1.00 (ref)	1.07 (0.98-1.17)	1.05 (0.95-1.15)	1.20 (1.08-1.34)	0.001	
	Weight loss, events	735	943	1,086	1,264		
	Person-years	138,948	151,744	154,288	159,739		
	aHR (95% CI)	1.00 (ref)	1.10 (1.00-1.21)	1.17 (1.06-1.28)	1.15 (1.04-1.26)	0.003	
Men	Weight gain, events	325	284	297	325		
	Person-years	109,128	94,038	88,310	77,230		
	aHR (95% CI)	1.00 (ref)	0.97 (0.82-1.14)	1.06 (0.89-1.25)	1.20 (0.98-1.47)	0.170	
	Weight loss, events	253	291	323	319		
	Person-years	88,337	87,887	87,403	79,567		
	aHR (95% CI)	1.00 (ref)	1.10 (0.93-1.30)	1.22 (1.03-1.44)	1.23 (1.04-1.46)	0.007	
Women	Weight gain, events	616	719	728	935		
	Person-years	66,625	66,743	68,313	68,113		
	aHR (95% CI)	1.00 (ref)	1.11 (1.00-1.24)	1.04 (0.94-1.16)	1.20 (1.09-1.33)	0.002	
	Weight loss, events	482	652	763	945		
	Person-years	50,611	63,858	66,884	80,172		
	aHR (95% CI)	1.00 (ref)	1.09 (0.97-1.22)	1.14 (1.02-1.28)	1.11 (0.99-1.24)	0.078	

Hazard ratio calculated by Cox proportional hazards regression.
Fully-adjusted model includes adjustments for age, sex, initial BMI, household income, smoking, alcohol consumption, physical activity, Charlson comorbidity index, and diagnosis with osteoporosis
Acronyms: BMI, body mass index; RMSE, root mean square error; aHR, adjusted hazard ratio

Ⅵ. Conclusion

In conclusion, high weight variability may lead to increased risk of subsequent fractures. Weight maintenance, instead of weight fluctuation, may be beneficial in lower the risk of fracture among elderly adults in Korea. The association between weight variability and fracture varied according to age, presence of osteoporosis, and direction of weight change. Its association was preserved among the normal weight and overweight individuals but not among obese individuals. Clinicians should encourage severe weight cyclers to reduce weight variability and stabilize their weight to benefit from reduced risk of fracture.

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국 문 요 약

연구 배경: 한국에서는 고관절, 척추 및 상지 골절의 발생률이 증가하고 골절과 관련된 사망률이 다른 국가에 비해 높은 것으로 보고된다. 본 연구에서는 한국 성인을 대상으로 한 대규모 코호트 연구로써, 체질량 지수 (BMI) 의 변동성과 골절 위험의 연관성을 보았다.

연구 방법: 국민건강보험공단 건강검진 코호트에서 50세 이상의 남녀 166,932 명으로 구성된 인구 기반 코호트 내에서, 2002-2007 년 동안 세 번의 후속 검사에서 얻은 체중 변동은 사분위수로 분류되었다. BMI 변동성에 따른 2008-2015 년 고관절, 요추 및 상지 골절의 입원 위험은 Cox 비례 위험 회귀 분석을 사용하여 위험 비율 (HR) 과 95% 신뢰구간 (CI)을 계산하여 결정되었다.

연구 결과: 체중 변동성의 첫 번째 사분위수 (가장낮은) 내에 있는 것과 비교하여 체중 변동성의 두 번째, 세 번째 및 네 번째 사분위수 (가장높은) 에 있는 것과 비교할 때 골절위험이 증가하였다 (aHR 1.07, 95% CI 1.01-1.15; aHR 1.10, 95% CI 1.03-1.17; aHR 1.16, 95% CI 1.09-1.23; *p* for trend <0.001). 이는 성별에 관계없이 남/여 모두에서 경향성이 유지되었다 (남: aHR 1.07, 95% CI 0.95-1.20; aHR 1.12, 95% CI 1.00-1.25; aHR 1.22, 95% CI 1.09-1.37; *p* for trend=0.001 / 여: aHR 1.08, 95% CI 1.00-1.17; aHR 1.09, 95% CI 1.01-1.18; aHR 1.14, 95% CI 1.06-1.22; *p* for trend=0.001). 골다공증을 진단받은 군에서 체중 변동성의 첫 번째 사분위수 (가장낮은) 내에 있는 것과 비교하여 체중 변동성의 두 번째, 세 번째 및 네 번째 사분위수 (가장높은) 에 있는 것과 비교할 때 골절위험이 증가하였다 (aHR 1.12, 95% CI 0.99-1.25;

aHR 1.11, 95% CI 0.99-1.24; aHR 1.19, 95% CI 1.07-1.32; *p* for trend=0.003). 골다공증을 진단받지 않은 군에서도 동일한 경향성을 보였으며 (aHR 1.05, 95% CI 0.97-1.14; aHR 1.09, 95% CI 1.01-1.18; aHR 1.14, 95% CI 1.06-1.23; *p* for trend=0.001), BMI 변동성과 골절 사이의 관계는 골다공증 유무에 따라 달라지는 것으로 나타났다 (*p* for interaction=0.003). 체중이 증가하는 방향이든 감소하는 방향이든 체중변동성에 따른 골절의 위험은 증가하는 것으로 나타났으며 (aHR 1.02, 95% CI 0.93-1.12; aHR 1.07, 95% CI 0.98-1.17; aHR 1.12, 95% CI 1.02-1.23; *p* for trend=0.002 / aHR 1.13, 95% CI 1.03-1.24; aHR 1.13, 95% CI 1.03-1.24; aHR 1.20, 95% CI 1.09-1.31; *p* for trend <0.001), BMI 변동성과 골절사이의 관계를 체중 변화의 방향에 따라 달라지는 것으로 나타났다 (*p* for interaction <0.001).

연구 결론: 체중 변동성은 고관절, 요추, 상지에서의 골절위험을 증가시키는 것으로 나타났다. 따라서 체중을 유지하는 것이 50세 이상의 한국 성인에서 골절 위험을 낮추는데 도움이 될 수 있다.

주요어: 체중 변화; 골절; 뼈; 골다공증

학 번: 2017-35314