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The Impact of Persistent Low Weight Status on the Occurrence of Vertebral Fractures: A Nationwide Population-Based Cohort Study

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ABSTRACT

Background: Although, being underweight is commonly associated with osteoporosis and sarcopenia, its association with vertebral fractures (VFs), is less well researched. We investigated the influence of cumulative, chronic periods of low weight and changes in body weight on VF development.
Methods: We used a nationwide, population-based database with data on people (> 40 years) who attended three health screenings between January 1, 2007, and December 31, 2009 to assess the incidence of new VFs. Cox proportional hazard analyses were used to establish the hazard ratios (HRs) for new VFs based on the degree of body mass index (BMI), the cumulative numbers of underweight participants, and temporal change in weight.
Results: Of the 561,779 individuals in this analysis, 5,354 (1.0%) people were diagnosed three times, 3,672 (0.7%) were diagnosed twice, and 6,929 (1.2%) were diagnosed once. The fully adjusted HR for VFs in underweight individuals was 1.213. Underweight individuals diagnosed only once, twice, or three times had an adjusted HR of 0.904, 1.443, and 1.256, respectively. Although the adjusted HR was higher in adults who were consistently underweight, there was no difference in those who experienced a temporal change in body weight. BMI, age, sex, and household income were significantly associated with VF incidence.
Conclusion: Low weight is a risk factor for VFs in the general population. Given the significant correlation between cumulative periods of low weight and the risk of VFs, it is necessary to treat underweight patients before a VF to prevent its development and other osteoporotic fractures.

Keywords: Claim Database; Vertebral Fracture; Osteoporosis; Underweight

INTRODUCTION

Vertebral fractures (VFs) are one of the most prevalent types of fractures and are becoming increasingly common in an ageing population.[1-4] Over 700,000 VFs occur in the United States each year, with more than 40% of women experiencing at least one VF during their lifetime.[5]

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Disclosure

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Park SM, Park J, Han K, Hong JY. Data curation: Han K, Hong JY. Formal analysis: Han K, Hong JY. Funding acquisition: Park SM. Investigation: Park SM, Park J. Methodology: Han S, Jang HD. Software: Han K, Hong JY. Validation: Kim HJ, Yeom JS. Visualization: Park SM. Writing - original draft: Park SM. Writing - review & editing: Park J, Kim HJ, Yeom JS.

VFs cause a lower quality of life and increased social expenses, particularly in older adults with osteoporosis.[6] As a result, it is critical to identify and improve the risk factors for VFs.

Previous research has identified several risk factors for osteoporosis, such as weight, body mass index (BMI), drinking, smoking, and physical activity.[7-9] In addition to bone mass density (BMD), BMI and body weight are the most important parameters in the World Health Organization (WHO) Fracture Risk Assessment tool.[10,11] According to previous studies, BMI is either a risk or a protective factor of bone fractures.[12-14] It has been found that decreased activity and muscular function in obese people leads to frequent falls, which contributes to an increase in fractures.[14] On the other hand, a lower BMI has been linked to an increased risk of muscle loss, known as sarcopenia and osteoporosis, leading to an increase in the risk of fractures.[12,13] However, only a few studies have investigated the relationship between low body weight and VFs.[15] In addition, there is no study on the incidence of VFs in relation to the status change of low body weight, nor is there a large-scale study in East Asia examining the association between low body weight and VFs. Using data from the population-based, nationwide Korean National Health Insurance Service (KNHIS) database, we previously studied the association between the severity of underweight and all types of fractures,[16] as well as the relationship between changes in underweight status and hip fractures.[17,18]

To the best of our knowledge, no study has used a nationwide population-based database to investigate the impact of being underweight on VFs. The purpose of this study was to investigate how being underweight affects the incidence of VFs, as well as the influence of cumulative, longitudinal periods of low BMI and changes in body weight on VF development.

METHODS

Data source and study design

We used nationwide, population-based KNHIS database. The KNHIS database includes all Korean population health information, such as patient diagnoses (International Classification of Disease, 10th revision [ICD-10]), prescriptions, and procedures. Therefore, this database contains all medical information for the entire Korean population (approximately 50 million people). Furthermore, all Korean adults over the age of 40 years attend general health screening once every two years.[19] In this health screening data, not only are regular health screening records, such as anthropometric measurements, lifestyle questionnaires, and basic laboratory results recorded, but also socioeconomic information, prescription records, hospitalization records, outpatient records, and the date of death of the insured Korean population. Based on this database, we created a longitudinal cohort using health screening data from January 1, 2002, to December 31, 2017, and extracted data on people over the age of 40 years who underwent three serial general health screenings between January 1, 2007, and December 31, 2009. To eliminate the effects of previous fractures, we excluded people who had a history of osteoporotic fractures before the health screening date. A one-year lag period after health screening was also applied to increase the effect of being underweight. Individuals with missing data values were excluded. Ultimately, 561,779 participants were included in this study (**Fig. 1**). In this cohort, we followed up instances of VFs after health screening until the cohort termination date or death. A VF was defined as a fracture for which a claim for hospitalization or outpatient treatment was received by fracture code after the general health-screening date.

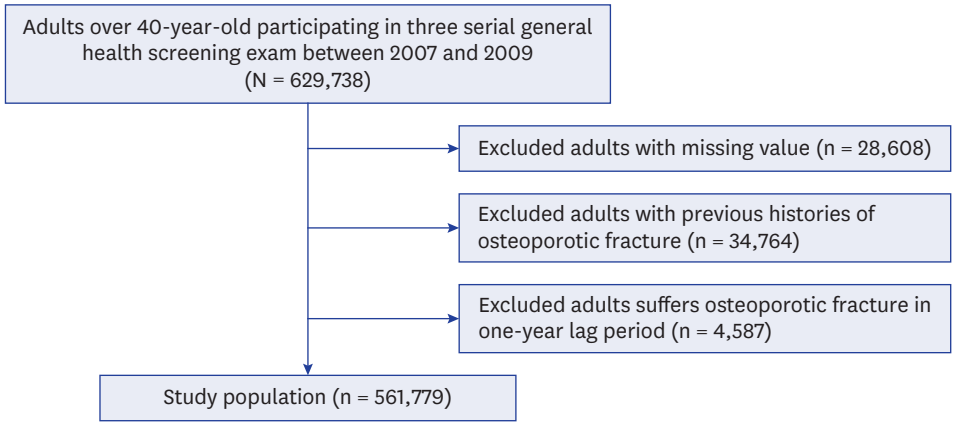

Fig. 1. Flow chart of study population.

Evaluation of underweight and VF

Weight and height were extracted from the results of the general health screening. The BMI was calculated as the ratio of weight (kg) to height (m) squared (kg/m^2). Based on the WHO Asia-Pacific regional guidelines, BMI was classified as underweight (< 18.5 kg/m^2), overweight (≥ 23.0 kg/m^2), obese (≥ 25.0 kg/m^2), and severely obese (≥ 30.0 kg/m^2), respectively.[20,21]

During each health screening, the patients' underweight status would be noted. The number of underweight individuals was defined as the cumulative number of underweight patients diagnosed at each health screening. To estimate the influence of temporal trends in BMI changes on VFs, we compared the diagnosis of an underweight status at the first health screening with that at the third (last) health screening. The study population was divided into four groups according to changes in underweight status: underweight to underweight (U-to-U), underweight to non-underweight (U-to-N), non-underweight to underweight (N-to-U), and non-underweight to non-underweight (N-to-N).

To identify VFs, we used ICD-10 codes (S22.0 Fracture of thoracic vertebra, S22.1 Multiple fracture of thoracic spine, S32.0 Fracture of lumbar vertebra, S32.8 Multiple fractures of lumbar spine, T08 fracture of spine, level unspecified) to find the claims in the database.[22-24] VF was defined as each fracture code with admission, repeated outpatient clinic claims, or emergency clinic visits.

Covariates and measurements

Baseline demographic data in this study were defined as that in the last health screening data. These basic characteristics included socioeconomic data, laboratory results (total cholesterol, glucose, blood pressure), answers to lifestyle questionnaires (regular exercise, smoking, alcohol drinking), anthropometric measurements (height, weight, waist circumference), and medical histories, which included hypertension, diabetes, dyslipidemia, and chronic kidney disease.[25] Regarding medical history, comorbidities were described if a record confirmed this at the health screening or treatment was received in the past medical claim data.

Smoking status was classified as non-smoker, past smoker, or current smoker. Alcohol consumption was classified as non-drinkers, mild drinkers (less than 30 g/day), or heavy drinkers (more than 30 g/day) according to the amount of alcohol consumed per day. Regular

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exercise was defined as the level of physical activity that included at least 20 minutes of vigorous physical activity over three or more days per week or 30 minutes of moderate to intense physical activity five or more days per week. Income status was divided into low as income in the bottom 20% of the insured's annual income, and normal. The ICD-10 codes used in this study are listed in Appendix 1.

Statistical analysis

Baseline characteristics of this study population are presented as mean ± standard deviation or counts and percentages in parentheses according to the cumulative number of underweight patients. The incidence rate (IR) was defined as the IR per 1,000 person-years (PY). The risk of VF development was analyzed using Cox proportional regression analysis to calculate the hazard ratios (HRs) and 95% confidence intervals (95% CIs) between VFs and the number of underweight patients. To reduce the bias of co-variates, we analyzed the HRs for unadjusted and three adjusted models: Model 1 was adjusted for age and sex; Model 2 was adjusted for age, sex, and other environmental factors such as smoking, alcohol consumption, physical activity, and household income; Model 3 was fully adjusted for age, sex, other environmental factors (smoking, alcohol consumption, physical activity, and household income), and comorbidities (diabetes, hypertension, dyslipidemia, and chronic kidney disease). Subgroup analysis was performed based on several factors, including age (< 65 years, ≥ 65 years), sex, smoking, alcohol consumption, physical activity, and household income.

Statistical analysis was performed using the SAS software 9.3 (SAS Institute, Cary, NC, USA). Student's *t*-test for continuous variables and the chi-square test for categorical variables were used, and two-tailed statistical significance was considered at $P < 0.05$.

RESULTS

Baseline characteristics

The baseline characteristics of the adults according to the cumulative number of underweight participants at each health screening examination are summarized in **Table 1**. Of the 561,779 individuals included in this analysis, 545,824 (97.2%) were never diagnosed as underweight. Regarding those underweight, 5,354 (1.0%) people were diagnosed three times, 3,672 (0.7%) people were diagnosed twice, and 6,929 (1.2%) people were diagnosed once of the three screenings. Except for age, the baseline characteristics of individuals in the four groups who were never diagnosed, were diagnosed once, twice, and three times revealed statistically significant variations in all categories evaluated. Individuals in the underweight group were more likely than those in the non-underweight group to be current smokers, have no alcohol consumption, engage in regular physical activity, and have low household income, regardless of the duration the participant was underweight.

The incidence and risk of VFs according to BMI

The IR was 2.04/1000 PY in the underweight group. The unadjusted and adjusted HRs (models 1, 2, and 3) were also significantly higher in the underweight group. The fully adjusted HR (model 3) for VFs according to BMI were 1.213 (1.037–1.417), 0.982 (0.925–1.042), 1.053 (0.994–1.117), and 1.081 (0.929–1.259), respectively (**Table 2**).

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Table 1. Baseline characteristics of this study according to the cumulative number of the presence of underweight

Variables	The cumulative number of the presence of underweight[a] at each health screening				*P* value
	0	1	2	3	
Participants	545,824	6,929	3,672	5,354	
Age, yr	49.69 ± 7.14	49.73 ± 7.77	49.67 ± 7.78	49.58 ± 7.87	0.682
Sex					< 0.001
Men	403,926 (74)	4,270 (61.63)	2,373 (64.62)	3,495 (65.28)	
Women	141,898 (26)	2,659 (38.37)	1,299 (35.38)	1,859 (34.72)	
Height, cm	165.72 ± 8.03	163.99 ± 8.23	164.4 ± 7.9	164.81 ± 7.86	< 0.001
Weight, kg	66.39 ± 10.19	51.26 ± 6.2	49.62 ± 5.22	47.35 ± 4.99	< 0.001
BMI, kg/m^2	24.1 ± 2.73	19.02 ± 1.46	18.32 ± 0.87	17.39 ± 0.77	< 0.001
Smoking					< 0.001
Non	257,094 (47.1)	3,699 (53.38)	1,808 (49.24)	2,683 (50.11)	
Ex	127,920 (23.44)	960 (13.85)	515 (14.03)	580 (10.83)	
Current	160,810 (29.46)	2,270 (32.76)	1,349 (36.74)	2,091 (39.05)	
Alcohol consumption[b]					< 0.001
Non	234,442 (42.95)	3,738 (53.95)	1,916 (52.18)	2,817 (52.61)	
Mild to moderate	264,341 (48.43)	2,826 (40.79)	1,539 (41.91)	2,247 (41.97)	
Heavy	47,041 (8.62)	365 (5.27)	217 (5.91)	290 (5.42)	
Physical activity[c]	122,611 (22.46)	1,010 (14.58)	476 (12.96)	655 (12.23)	< 0.001
Low household income[d]	112,089 (20.54)	1,570 (22.66)	823 (22.41)	1,222 (22.82)	< 0.001
Comorbidities					
Diabetes	51,701 (9.47)	409 (5.9)	205 (5.58)	244 (4.56)	< 0.001
Hypertension	157,011 (28.77)	1,052 (15.18)	490 (13.34)	641 (11.97)	< 0.001
Dyslipidemia	103,324 (18.93)	620 (8.95)	291 (7.92)	352 (6.57)	< 0.001
CKD	42,114 (7.72)	378 (5.46)	202 (5.5)	315 (5.88)	< 0.001

Numeric parameters are expressed as mean ± standard deviation and categorical parameters are expressed as counts and percentages in parentheses.
BMI = body mass index, CKD = chronic kidney disease.
[a]Underweight was defined as body mass index under 18.5 kg/m^2.
[b]Alcohol consumption was divided into 3 categories; Non (no alcohol consumption), Mild (under 30g/day consumption), and heavy (over 30 g/day consumption).
[c]Physical activity is defined as performing over 30 minutes moderate intensity exercise over 5 times per a week or over 20 minutes vigorous intensity exercise over 3 times per a week.
[d]Low household income is defined as total household monthly income belongs to lower 20% group among Korean entire population.

Table 2. The risk of vertebral fracture according to body mass index using Cox regression analysis

Body mass index, kg/m^2	No. of fracture	IR[a]	Unadjusted			Model 1			Model 2			Model 3		
			HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value
< 18.5	167	2.04	1.33	1.137–1.555		1.232	1.054–1.441		1.217	1.040–1.423		1.213	1.037–1.419	
18.5 ≤ and < 23	2,545	1.54	1		0.002	1		0.015	1		0.022	1		0.020
23 ≤ and < 25	1,923	1.47	0.954	0.899–1.012		0.974	0.918–1.034		0.979	0.923–1.039		0.982	0.925–1.042	
25 ≤ and < 30	2,232	1.53	0.995	0.940–1.053		1.043	0.985–1.105		1.048	0.990–1.110		1.053	0.994–1.117	
30 ≤	182	1.56	1.014	0.872–1.178		1.074	0.924–1.248		1.073	0.923–1.247		1.081	0.929–1.259	

IR = incidence rate, HR = hazard ratio, 95% CI = 95% confidence interval.
[a]Incidence rate is defined as incidence rate per 1,000 person-year.
Model 1 was adjusted by age, and sex; Model 2 was adjusted by age, sex, and other environmental factors such as smoke, alcohol consumption, physical activity, household income; Model 3 was fully adjusted by age, sex, other environmental factors (smoke, alcohol consumption, physical activity, household income), and comorbidities (diabetes, hypertension, dyslipidemia, chronic kidney disease).

The incidence and risk of VFs according to the cumulative number of underweight

A total of 7,049 VFs were observed (1.2%). The IR of VFs was 1.53/1000 PY in the once diagnosed underweight group, 2.35/1000 PY in the twice diagnosed underweight group, and 1.98/1000 PY in the three times diagnosed underweight group, with the IR being greater in the underweight group overall. In contrast, there was no statistically significant serial increase in fractures according to the number of underweight diagnoses; nonetheless, it was significantly greater in the groups with two or more underweight diagnoses. In the multivariate-adjusted analysis, this correlation was statistically significant. Underweight individuals who were diagnosed only once, twice, or three times had an adjusted HR (Model 3) of 0.904 (0.731–1.117), 1.443 (1.140–1.827), and 1.256 (1.028–1.482) for VFs, respectively (**Table 3**).

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Table 3. The risk of vertebral fracture according to the cumulative number of the presence of underweight using Cox regression analysis

Cumulative number of underweight	No. of fracture	IR[a]	Unadjusted			Model 1			Model 2			Model 3		
			HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value
0	6,806	1.51	1		< 0.001	1		0.003	1		0.005	1		0.005
1	87	1.53	1.016	0.822–1.255		0.912	0.738–1.126		0.904	0.731–1.117		0.901	0.729–1.114	
2	70	2.35	1.554	1.228–1.967		1.464	1.157–1.853		1.443	1.140–1.827		1.438	1.136–1.821	
3	86	1.98	1.312	1.061–1.623		1.268	1.037–1.509		1.256	1.028–1.482		1.241	1.002–1.480	

IR = incidence rate, HR = hazard ratio, 95% CI = 95% confidence interval.
[a]Incidence rate is defined as incidence rate per 1,000 person-year.
Model 1 was adjusted by age, and sex; Model 2 was adjusted by age, sex, and other environmental factors such as smoke, alcohol consumption, physical activity, household income; Model 3 was fully adjusted by age, sex, other environmental factors (smoke, alcohol consumption, physical activity, household income), and comorbidities (diabetes, hypertension, dyslipidemia, chronic kidney disease).

Table 4. The risk of vertebral fracture according to temporal trends in body mass index changes using Cox regression analysis

Underweight status[a]	No. of fracture	IR[b]	Unadjusted			Model 1			Model 2			Model 3		
			HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value
N to N	6,827	1.51	1		0.001	1		0.060	1		0.098	1		0.108
N to U	61	2.02	1.338	1.040–1.721		1.160	0.901–1.493		1.146	0.890–1.474		1.142	0.887–1.470	
U to N	55	1.72	1.143	0.876–1.490		1.098	0.842–1.432		1.089	0.835–1.420		1.086	0.832–1.416	
U to U	106	2.05	1.359	1.122–1.646		1.263	1.043–1.531		1.242	1.025–1.505		1.239	1.022–1.502	

IR = incidence rate, HR = hazard ratio, 95% CI = 95% confidence interval, N = non-underweight (body mass index ≥ 18.5 kg/m^2), U = underweight (body mass index < 18.5 kg/m^2).
[a]Temporal changes of underweight status (first to 3rd health screening) are divided into four groups: non-underweight to non-underweight, non-underweight to underweight, underweight to non-underweight, and underweight to underweight.
[b]Incidence rate is defined as incidence rate per 1,000 person-year.
Model 1 was adjusted by age, and sex; Model 2 was adjusted by age, sex, and other environmental factors such as smoke, alcohol consumption, physical activity, household income; Model 3 was fully adjusted by age, sex, other environmental factors (smoke, alcohol consumption, physical activity, household income), and comorbidities (diabetes, hypertension, dyslipidemia, chronic kidney disease).

The risk of VF according to temporal trends in BMI changes

The IR was 1.51/1000 PY in the N-to-N group, 2.02/1000 PY in the N-to-U group, 1.72/1000 PY in the U-to-N group, and 2.05/1000 PY in the U-to-U group. After multivariate-adjusted analysis, adults in the U-to-U group had a significantly higher risk of VF (HR, 1.239; 95% CI, 1.022–1.502). Although the adjusted HR was higher in adults who were consistently underweight, there was no difference in those who experienced a temporal change in body weight (**Table 4**).

Subgroup analysis

VFs were more likely to occur in underweight adults who were under the age of 65 (1.203; 95% CI, 1.006–1.440), men (1.289; 95% CI, 1.046–1.588), and low-income (1.364; 95% CI, 1.077–1.727) (**Fig. 2**). In the stratified analysis, none of the covariates had a statistically significant association with the risk of VFs in groups defined by the cumulative number of underweight diagnoses (*P* for interaction > 0.05) (**Fig. 3**).

Ethics statement

The study protocol was approved by the Institutional Review Board of Korea University Ansan Hospital (approval no. K2021-2601-001). The ethics committees of Korea University Ansan Hospital have waived the requirement to obtain informed consent as the register data analysed in this study are in anonymised and deidentified format. This study was performed in accordance with the tenets of the Declaration of Helsinki, and all research methods were carried out in accordance with appropriate regulations and guidelines.

Subgroup	BMI	Incidence rate (per 1000)	Hazard ratio (95% CI)	*P* value	*P* for interaction
Age					
under 65	under 18.5	1.637	1.203 1.006 to 1.44	0.016	0.022
	18.5 to 23	1.315	1 Reference		
	23 to 25	1.281	0.999 0.935 to1.066		
	25 to 30	1.352	1.083 1.016 to 1.154		
	over 30	1.409	1.13 0.96 to 1.33		
over 65	under 18.5	8.975	1.202 0.869 to 1.662	0.051	
	18.5 to 23	6.897	1 Reference		
	23 to 25	5.773	0.862 0.745 to 0.997		
	25 to 30	5.868	0.853 0.738 to 0.986		
	over 30	6.427	0.761 0.494 to 1.172		
Sex					
Male	under 18.5	1.811	1.289 1.046 to 1.588	0.008	0.024
	18.5 to 23	1.263	1 Reference		
	23 to 25	1.118	0.907 0.837 to 0.982		
	25 to 30	1.143	0.953 0.882 to 1.03		
	over 30	1.064	0.985 0.795 to 1.219		
Female	under 18.5	2.436	1.128 0.889 to 1.432	0.134	
	18.5 to 23	2.058	1 Reference		
	23 to 25	2.597	1.042 0.952 to 1.141		
	25 to 30	3.133	1.123 1.026 to 1.228		
	over 30	2.950	1.106 0.890 to 1.374		
Smoke					
No	under 18.5	2.098	1.134 0.934 to 1.377	0.135	0.401
	18.5 to 23	1.648	1 Reference		
	23 to 25	1.620	1.002 0.937 to 1.073		
	25 to 30	1.711	1.072 1.003 to 1.146		
	over 30	1.804	1.104 0.932 to 1.307		
Yes	under 18.5	1.931	1.385 1.06 to 1.81	0.044	
	18.5 to 23	1.263	1 Reference		
	23 to 25	1.088	0.905 0.798 to 1.026		
	25 to 30	1.099	0.975 0.862 to 1.102		
	over 30	0.973	0.971 0.685 to 1.378		
Drink					
No	under 18.5	1.985	1.18 1.002 to 1.389	0.027	0.221
	18.5 to 23	1.547	1 Reference		
	23 to 25	1.493	0.984 0.925 to 1.047		
	25 to 30	1.584	1.065 1.003 to 1.132		
	over 30	1.635	1.092 0.933 to 1.28		
Yes	under 18.5	2.922	1.844 1.045 to 3.255	0.161	
	18.5 to 23	1.381	1 Reference		
	23 to 25	1.173	0.931 0.735 to 1.18		
	25 to 30	1.053	0.89 0.707 to 1.119		
	over 30	0.981	0.909 0.521 to 1.585		
Exercise					
No	under 18.5	1.943	1.171 0.986 to 1.391	0.017	0.227
	18.5 to 23	1.548	1 Reference		
	23 to 25	1.482	0.971 0.908 to 1.039		
	25 to 30	1.583	1.064 0.997 to 1.137		
	over 30	1.697	1.143 0.969 to 1.349		
Yes	under 18.5	2.672	1.48 1.011 to 2.167	0.263	
	18.5 to 23	1.489	1 Reference		
	23 to 25	1.413	1.014 0.891 to 1.155		
	25 to 30	1.357	1.01 0.888 to 1.15		
	over 30	1.051	0.821 0.555 to 1.213		
Low income					
No	under 18.5	1.455	1.107 0.897 to 1.366	0.018	0.001
	18.5 to 23	1.237	1 Reference		
	23 to 25	1.236	1.035 0.961 to 1.114		
	25 to 30	1.301	1.127 1.049 to 1.212		
	over 30	1.286	1.129 0.932 to 1.367		
Yes	under 18.5	3.996	1.364 1.077 to 1.727	0.003	
	18.5 to 23	2.678	1 Reference		
	23 to 25	2.399	0.885 0.799 to 0.98		
	25 to 30	2.413	0.92 0.833 to 1.017		
	over 30	2.431	0.996 0.775 to 1.28		

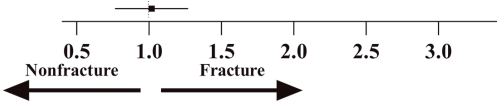

Fig. 2. Incidence and hazard ratios of vertebral fractures according to several subgroups and body mass index.
BMI = body mass index, CI = confidence interval.

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Subgroup	Underweight No.	Incidence rate (per 1000)	Hazard ratio (95% CI)		*P* value	*P* for interaction
Age						
under 65	0	1.319	1	Reference	0.012	0.168
	1	1.305	0.926	0.731 to 1.172		
	2	2.060	1.53	1.181 to 1.982		
	3	1.431	1.063	0.822 to 1.374		
over 65	0	6.222	1	Reference	0.052	
	1	5.551	0.822	0.508 to 1.329		
	2	7.211	1.171	0.662 to 2.072		
	3	12.291	1.663	1.133 to 2.441		
Sex						
Male	0	1.170	1	Reference	0.004	0.567
	1	1.387	1.029	0.774 to 1.369		
	2	2.201	1.637	1.207 to 2.221		
	3	1.710	1.322	0.994 to 1.76		
Female	0	2.487	1	Reference	0.275	
	1	1.766	0.808	0.589 to 1.109		
	2	2.606	1.298	0.894 to 1.883		
	3	2.475	1.079	0.783 to 1.486		
Smoke						
No	0	1.666	1	Reference	0.075	0.184
	1	1.487	0.796	0.613 to 1.033		
	2	2.319	1.3	0.966 to 1.75		
	3	2.104	1.135	0.872 to 1.478		
Yes	0	1.145	1	Reference	0.007	
	1	1.635	1.222	0.851 to 1.756		
	2	2.396	1.79	1.213 to 2.64		
	3	1.785	1.355	0.943 to 1.947		
Drink						
No	0	1.545	1	Reference	0.038	0.140
	1	1.563	0.91	0.734 to 1.129		
	2	2.241	1.37	1.068 to 1.756		
	3	1.921	1.151	0.921 to 1.438		
Yes	0	1.174	1	Reference	0.015	
	1	1.017	0.709	0.227 to 2.209		
	2	4.086	2.633	1.244 to 5.571		
	3	3.049	2.117	1 to 4.483		
Exercise						
No	0	1.543	1	Reference	0.011	0.065
	1	1.569	0.927	0.739 to 1.163		
	2	2.428	1.506	1.174 to 1.932		
	3	1.729	1.067	0.837 to 1.361		
Yes	0	1.409	1	Reference	0.017	
	1	1.331	0.761	0.42 to 1.378		
	2	1.806	1.024	0.487 to 2.153		
	3	3.808	1.997	1.282 to 3.109		
Low income						
No	0	1.259	1	Reference	0.370	0.080
	1	1.183	0.844	0.642 to 1.11		
	2	1.676	1.224	0.892 to 1.678		
	3	1.365	1.035	0.774 to 1.385		
Yes	0	2.502	1	Reference	0.001	
	1	2.745	1.006	0.72 to 1.406		
	2	4.733	1.861	1.305 to 2.654		
	3	4.115	1.455	1.063 to 1.992		

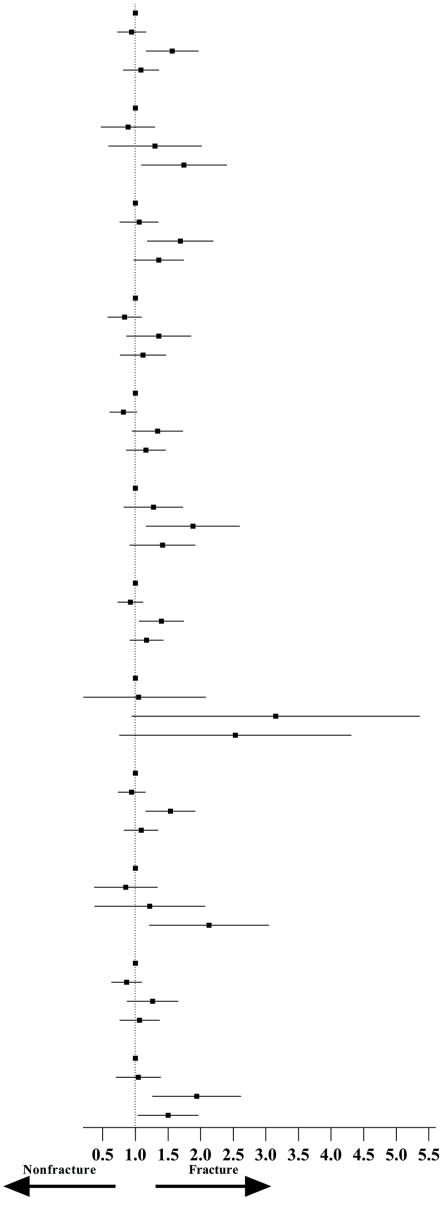

Fig. 3. Incidence and hazard ratios of vertebral fractures according to several subgroups and the cumulative numbers of underweight participants.
CI = confidence interval.

DISCUSSION

To the best of our knowledge, this is the first study to determine the risk of VFs associated with the cumulative burden of low body weight in a large nationwide population-based cohort study. Through various analyses, we confirmed the following: 1) Underweight status increased the risk of VFs. 2) The cumulative burden of being underweight increased the risk of VFs. 3) There was no increase in the risk of VFs if the cumulative burden of being underweight was small or if there was a temporal change in body weight. 4) Among several factors, under 65-year, male sex and low household income were significantly more affected.

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Osteoporosis is a risk factor for fractures, particularly when combined with physical activity, smoking, alcohol consumption, and body weight.[7,8] The relationship between fractures and body weight varies according to the location of the fracture. Weight gain is associated with a considerable reduction in hip fractures.[26] VF research continues to be contentious, with studies indicating that being underweight is both a risk and protective factor for VFs.[13,27] However, there is no conclusive evidence of the association between low weight and VFs.

Although the mechanism by which low weight increases the frequency of VF is unknown, this study revealed that underweight is a risk factor for increased VFs. In humans, being underweight is often related to malnutrition, which is hypothesized to lead to osteoporosis.[28] Malnutrition causes bone loss and, eventually, osteoporosis.[29,30] In addition, low BMI is highly associated with the development of sarcopenia. Previous research has shown that malnourished individuals are more prone to sarcopenia.[31] Physical capacity and muscular function are diminished as a result of sarcopenia, resulting in falls that increase the likelihood of VF.[32,33] In conclusion, lower BMI is thought to be associated with lower BMD levels and decreased muscle strength. However, this study was a population-based study using the ICD-10 diagnostic code, and the actual skeletal muscle index and BMD scores of the patients could not be determined. Although this study cannot clearly elucidate the relationship between low BMI, BMD, and skeletal muscle index, the fact that low BMI is related to VFs was confirmed using the large population-based database.

Low body weight was investigated as a risk factor for VFs after controlling for several variables. In a further analysis, transient underweight status (cumulative number = 1) did not increase the risk of VF (HR, 0.901; 95% CI, 0.729–1.114). There was no increase in risk, even when changing from normal weight to underweight or from underweight to normal weight. In other words, it can be considered that VFs increase only when the body weight is continuously low. This suggests that being underweight does not increase fractures directly; rather, fractures occur as a result of low bone density or muscle loss following underweight.

In the subgroup analysis, the effect of being underweight was greater, especially those who were under 65 years of age, men, and who had low household income. Thus, the importance of being underweight as a risk factor for VFs varies with age, sex, and household income. Although the specific mechanism of VFs in young individuals remains unknown in this study, a possible explanation is that younger underweight individuals have quicker bone loss due to a relatively rapid change in metabolism compared to older individuals. The finding that underweight men had a greater risk of VFs than women after correcting for age is consistent with previous research indicating that men have a greater risk of fractures than women.[5,34] Low household income is also associated with malnutrition, which may have contributed to the low BMI and skeletal muscle index, which may have led to an increase in fractures.

To our knowledge, this is the only study to evaluate the risk of VF in the underweight population using a nationwide database. The major strength of this study is that it used national health insurance data in which all citizens were enrolled. This is a large amount of data, and the database is maintained constantly. Consequently, it produces significant results that are representative of the real world. However, this study had several limitations. First, the T-scores of the BMD results could not be directly verified. Being underweight is thought to have had an effect on the BMD score, but the direct effect was unknown in this study. In addition, grip strength and muscle mass for analyzing sarcopenia could not be further analyzed. This limitation of further data analysis is due to the limitation of KNHIS database,

which consists of only basic demographics, diagnostic, radiographic, and treatment codes. Second, it was difficult to determine the exact number of VFs. Because VFs are frequently asymptomatic or weak, some patients do not visit outpatient clinics or hospitals. Third, this study used a nationwide database from national health insurance services in one nation, so it is difficult to apply it to multiple ethnicities. Finally, because the diagnosis of VFs in this investigation was made using the fracture diagnostic code, we were unable to confirm that all VFs were accurately diagnosed. To identify VFs, an algorithm used in this study identical to that employed in prior studies was applied.[22-24] Validation studies are the best method to confirm the proposed algorithm of diagnostic codes.[24] According to our recent study, the sensitivity was 62.5% and the positive predictive value of operational definition was 59.7%, which was lower than that of hip[35] or wrist fractures,[36] but higher than that of other VFs.[37] To diagnose VFs as accurately as possible, we used a one-year lag time period after being diagnosed as underweight and excluded patients with previous VFs. Because this study used the most conservative algorithm, it is quite likely that the incidence rate of VFs was slightly underestimated, as previously stated.

This study investigated whether being underweight is an important factor that increases the risk of VF in the Korean population using a nationwide population-based cohort. The risk of VFs was particularly high among people who were persistently underweight, and men under the age of 65 and those with low household income had a higher risk of VFs. Therefore, patients with these risk factors require treatment to reduce the risk of VF.

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Appendix 1. Definitions of covariates and measurements

Diagnosis	ICD-10-CM code and medication	Number of diagnosis	Diagnosis test or treatment	Combinationa
Inclusion				
Vertebral fracture	S22.0 Fracture of thoracic vertebra, S22.1 Multiple fracture of thoracic spine, S32.0 Fracture of lumbar vertebra, S32.8 Multiple fractures of lumbar spine, T08 Fracture of spine, level unspecified	Admission ≥ 1 or outpatient department with diagnostic test or treatment ≥ 1	N0471, N0472, Percutaneous vertebroplasty; N0473, N0474, Percutaneous balloon kyphoplasty; N0630, Closed reduction of fracture and/or dislocated spine G430 Thoracic spine G440 Thoracolumbar spine G450 Lumbar spine G460 Lumbosacral spine	
Exclusion				
Other fractures	S02, S12, S222, S223, S224, S228, S229, S323, S324, S325, S327, S328, S42-92, T02, T10, T12, T14, T90, T91, T92, T93	Exclude when these other fractures codes coexist in the vertebral fracture codes		
Comorbidities based on the last health examination				
Comorbidities				
Hypertension	I10-I13, I15; and minimum 1 prescription of anti-hypertensive drug (thiazide, loop diuretics, aldosterone antagonist, alpha-/beta-blocker, calcium-channel blocker, angiotensin-converting enzyme inhibitor, or angiotensin II receptor blocker)	Admission ≥ 1 or outpatient department ≥ 2	Systolic/diastolic blood pressure ≥ 140/90 mmHg	1 + 2 or 3
Diabetes mellitus	E11-E14; and minimum 1 prescription of anti-diabetic drugs (sulfonylureas, metformin, meglitinides, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, α-glucosidase inhibitors, or insulin)	Admission ≥ 1 or outpatient department ≥ 2	Fasting glucose level ≥ 126 mg/dL	1 + 2 or 3
Dyslipidemia	E78	Admission ≥ 1 or outpatient department ≥ 1	Total cholesterol ≥ 240 mg/dL	1 + 2 or 3
CKD	N/A	N/A	eGFR< 60mL/min/1.73m2	3
Definitions of life style behavior based on the last health examination questionnaire				
Alcohol consumption				
Mild to moderate drinker	Alcohol consumption > 0 g to < 30 g per day			
Heavy drinker	Alcohol consumption ≥ 30 g per day			
Physical activity	Performing over 30 minutes moderate intensity exercise over 5 times per a week or over 20 minutes vigorous intensity exercise over 3 times per a week			
Smoking				
Ex-smoker	Ex-smoker at the 1st examination and sustaining non-smoking till the 2nd examination			
Current smoker	Current smoker at the 2nd examination regardless of the smoking status at the 1st examination.			
Information of household income				
Low household income	Income belongs to lower 20% among the entire Korean population and supported by the Medical Aid program			

CKD = chronic kidney disease, N/A = not applicable.
[a]Combination: 1 = ICD-10-CM code and medication; 2 = number of diagnosis; and 3 = diagnosis test or treatment.