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Risk of Osteoporotic Fractures Among Obese Women Based on Body Mass Index and Waist Circumference: A Nationwide Cohort in South Korea

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ABSTRACT

We evaluated the association between obesity status by body mass index (BMI) or waist circumference (WC) and osteoporotic fracture risk. We collected data of 143,673 women with a mean age of 58.5 years without history of osteoporotic fracture from the Korean National Health Insurance Service Cohort. Participants were divided into four groups according to obesity by BMI and WC, normal BMI/WC (BMI 18.5–24.9 kg/m^2 and WC < 85 cm, reference), obese BMI/normal WC (BMI ≥ 25 kg/m^2 and WC < 85 cm), normal BMI/obese WC (BMI < 25 kg/m^2 and WC ≥ 85 cm), and obese BMI/WC (BMI ≥ 25 kg/m^2 and WC < 85cm). Cox proportional hazards regression analyses were performed to obtain hazard ratios (HRs) with 95% confidence intervals (CIs) for the subsequent median 6.0 years, which were adjusted for age, socioeconomic status, lifestyle, morbidity index, and osteoporosis medication. Compared with the normal group, normal BMI/obese WC was associated with a higher osteoporotic fracture risk after multivariable adjustment (HRs [95% CI], 1.13 [1.05–1.21]), and obese BMI/normal WC was associated with a lower osteoporotic fracture risk (0.89 [0.84–0.94]). Obese BMI/normal WC was associated with a lower risk for hip fractures (0.75 [0.57–0.99]). Obese BMI/normal WC was associated with decreased risk of osteoporotic fracture, whereas normal BMI/obese WC was associated with increased risk of osteoporotic fracture compared with the normal group among East Asian women in their late 40s or more.

Keywords: Osteoporotic fractures; Hip fractures; Obesity; Abdominal obesity

INTRODUCTION

Obesity and osteoporosis are major causes of morbidity and mortality [1,2]. Traditionally, obesity has been defined based on a high body mass index (BMI) and has been shown to be protective against osteoporotic fractures. The underlying protective effect of obesity has been explained by a mechanical load followed by a higher bone mineral density and fat padding effect around the hip caused by aromatase activity affecting free sex-hormones [3-6].

However, the protective effect of obesity on osteoporotic fractures has recently been increasingly challenged. A meta-analysis of 6 studies reported no association between BMI

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Conflict of Interest

The authors declare that they have no competing interests.

Author Contributions

Conceptualization: Lee G, Park SM; Data curation: Choi S; Formal analysis: Lee G; Funding acquisition: Choi S, Park SM; Investigation: Lee G, Cho Y; Methodology: Lee G, Choi S, Cho Y, Park SM; Project administration: Lee G; Resources: Park SM; Software: Lee G, Park SM; Supervision: Park SM; Validation: Choi S; Visualization: Lee G; Writing – original draft: Lee G; Writing - review & editing: Lee G, Choi S, Cho Y, Park SM.

and the risk of vertebral fracture [7]. The Nurses' Health Study recently reported that high BMI was related to reduced vertebral fractures, whereas high waist circumference (WC) was related to an increased risk of vertebral fractures [8]. Other studies have also reported that obesity, defined as high WC or waist-to-hip ratio (WHR), is associated with an increased risk of hip fractures [9,10].

These conflicting results on the effect of obesity on osteoporotic fractures, depending on how obesity is defined, suggest that body composition could be an important predictor of osteoporotic fractures. Normal BMI but obese WC is relatively high fat; conversely, obese BMI but normal WC is relatively high muscle. In particular, normal weight obesity, defined as excessive body fat with normal BMI, was known to be associated with cardiovascular mortality [11]; however, the effect on the osteoporotic fractures is unclear.

There is a paucity of studies investigating the combination of BMI and WC, which can distinguish the misclassification of obesity status caused by different criteria such as BMI or WC. Therefore, we aimed to evaluate the association between obesity status, determined using BMI and WC, and the risk of osteoporotic fractures among women in their late 40s or more with median 6.0 years follow-up period to determine whether there is a discrepancy in the risk on the basis of whether obesity is defined according to BMI or WC.

MATERIAL AND METHODS

Data source and study design

We retrospectively analyzed a large Korean cohort from the National Health Insurance Service-National Health Screening Cohort (NHIS-HEALS) database, which is recorded between January 1, 2002 and December 31, 2015 (NHIS-2018-2-163). The Korean National Health screening is conducted biannually based on whether individuals' birth year is even or odd. The NHIS-HEALS database includes clinical data, date of hospital visits, admissions, diagnoses, and death information. The NHIS database has been used for population-based epidemiological studies, and its validity has been recognized elsewhere [12].

Study population

NHIS-HEALS database is recorded between 2002 and 2015. Because WC measurements were started in 2008, the authors used data from 2008. **Supplementary Fig. 1** shows the flow of the study population. Of 228,881 women who had undergone national health examination from 2008 to 2009, we excluded 1,196 subjects who died and 18,537 participants diagnosed with fractures defined as having one day or more hospitalization or 2 times or more physician visits within 6 months based on osteoporotic fracture diagnoses coded according to the International Classification of Disease 10th revision (ICD-10) before the index date (January 1, 2010). Because the history of prior fracture was significantly associated with an increased risk of new fractures [13], we excluded subjects who had any previous osteoporotic fracture. We also excluded 57,884 women without information on BMI or WC and 4,396 women with missing covariates. Lastly, 3,195 subjects who were underweight (BMI < 18.5 kg/m^2) were excluded, and 143,673 women were included in the analysis.

All participants were followed up starting from the index date of January 1, 2010, until the date of the hospitalization for more than 2 days due to an osteoporotic fracture among vertebral, hip, humerus, and distal radius fractures, death, or December 31, 2015, whichever came first.

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Exposures and covariates

Height, weight, and WC were measured by nurses trained on the NHIS examination. BMI was calculated by weight/height^2 (kg/m^2). Based on the Asian criteria of BMI and WC [14], the cohort was divided into 4 groups: normal (BMI 18.5–24.9 kg/m^2 + WC < 85 cm), obese BMI/normal WC (BMI ≥ 25 kg/m^2 + WC < 85 cm), normal BMI/obese WC (BMI 18.5–24.9 kg/m^2 + WC ≥ 85 cm), and obesity by both BMI and WC (BMI ≥ 25 kg/m^2 + WC ≥ 85 cm). The covariates included age, socioeconomic status, regular exercise, smoking status (never, previous, and current), alcohol habit (none, < 3, ≥ 3 times/week), bisphosphonate medication, and the Charlson Comorbidity Index (CCI) [15] which is the most commonly used comorbidity index for predicting mortality. All covariates were collected before the index date.

Main outcomes

Fractures were identified by ICD-10 codes: vertebral (S22.0 [fracture of the thoracic spine], S22.1 [multiple fractures of the thoracic spine], S32.0 [fracture of the lumbar spine], M48.4 [fatigue fracture of the vertebra] and M48.5 [collapsed vertebra, NEC]); hip (S72.0 [fracture of the femoral neck] and S72.1 [pertrochanteric fracture]); wrist (distal radius) (S52.5 [fracture of the distal radius] and S52.6 [combined fracture of the distal radius/ulna]); and humerus (S42.2 [fracture of the proximal humerus] and S42.3 [fracture of shaft of the humerus]) [16-19].

The primary outcome of this study was defined as being hospitalized for one day or more or physician visits 2 times or more within 6 months of osteoporotic fractures, whichever fracture occurred earliest. In turn, when multiple fractures occurred during the observation period, only the first fracture was considered the outcome [18,19]. The secondary outcome was osteoporotic fractures requiring hospitalization for 2 days or more, as a marker for severe fractures, whichever occurred earliest.

Statistical analysis

Continuous variables are expressed as mean (± standard deviation), and categorical variables are expressed as percentages, and they were compared between groups using the Pearson's χ^2 test. Hazard ratios (HRs) and 95% confidence intervals (CIs) for each outcome, according to the 4 groups were analyzed using the Cox proportional hazards regression analyses. The multivariable-adjusted analysis was adjusted for age, socioeconomic status, regular exercise, smoking status, drinking habit, and CCI. Because not only BMI or WC but also osteoporotic fractures are closely related to age, subgroup analyses according to different age-bands were performed: < 50, 51–60, 61–70, ≥ 71 years. The combination of BMI and WC was additionally categorized as nine groups by tertiles of BMI and WC because BMI and WC increase with age, although the reference value of obesity in BMI and WC was fixed at 25.0 kg/m^2 and 85 cm, respectively. Statistical significance was set as a two-sided p value < 0.05. Data mining and analyses were conducted using SAS Enterprise Guide 7.1 (SAS Institute, Cary, NC, USA).

Ethics

This study was conducted according to the guidelines in the Declaration of Helsinki, and all procedures involving human subjects/patients were waived by the Institutional Review Board of the Seoul National University (IRB number: 1703-039-863). All participants were informed regarding the objective of the survey, and they provided consent. The NHIS database was anonymized according to strict confidentiality guidelines.

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RESULTS

The age range of the study population of 143,673 women was 47–86 years in the index year. The median follow-up duration of the study population was 6.0 years (interquartile range, 5.995–5.995 [the same]), resulting in 818,648 person-years. During the period, 11,742 subjects' osteoporotic fractures required treatment. The crude incidence was 14.3 per 1,000 person-years. **Table 1** summarizes the baseline characteristics of the study participants. Women with normal BMI/obese WC were more likely to be older, have comorbidity, and exercise less. **Table 2** shows the association of obesity status, measured using BMI and WC, with the risk of osteoporotic fractures requiring hospitalization or physician visits (primary outcome), adjusted for 2 steps as age-adjusted and multivariable-adjusted for age, income, smoking status, drinking habit, regular exercise, bisphosphonate medication, and CCI. The risk of fracture differed based on how obesity was defined using BMI or WC. The risk of osteoporotic fractures was the highest in women with normal BMI/obese WC and the lowest in women with obese BMI/normal WC. The risk of osteoporotic fracture was marginally protective in women with obesity by both BMI and WC.

Table 1. General characteristics of the study population (n = 143,673 women)

Obesity status	Normal	Obese BMI/normal WC	Normal BMI/obese WC	Obesity by both BMI and WC
	< 85 cm/18.5–24.9 kg/m^2	< 85 cm/≥ 25 kg/m^2	≥ 85 cm/18.5–24.9 kg/m^2	≥ 85 cm/≥ 25 kg/m^2
No. (%)	87,869 (61.2)	21,400 (14.9)	7,412 (5.2)	26,992 (18.8)
Osteoporotic fracture events	6,703	1,499	962	2,578
Age (yr)	57.3 ± 8.5	57.9 ± 8.1	64.0 ± 9.4	61.5 ± 8.8
≤ 50 (%)	25.8	21.1	8.5	11.5
51–60 (%)	44.5	46.1	31.0	38.1
61–70 (%)	19.2	23.4	31.9	31.6
≥ 71 (%)	10.5	9.4	28.7	19.0
BMI (kg/m^2)	22.3 ± 1.6	26.4 ± 1.4	23.6 ± 1.1	28.0 ± 2.3
WC (cm)	74.7 ± 5.2	80.0 ± 3.4	87.7 ± 3.0	90.6 ± 5.0
Income (%)				
Highest	32.3	28.1	30.9	27.9
Upper middle	28.2	30.5	29.9	31.6
Lower middle	23.3	24.4	22.2	23.6
Lowest	16.3	16.9	17.0	16.9
Smoking (%)				
Never	97.9	98.1	97.5	97.7
Ever	2.1	1.9	2.5	2.3
Alcohol (%)				
Never	84.3	84.0	87.8	86.3
< 3/week	13.8	13.9	10.3	11.7
≥ 3/week	1.9	2.1	1.9	2.1
Exercise (%)				
None	53.0	54.1	62.1	61.4
< 3/week	31.2	29.0	24.7	24.4
≥ 3/week	15.6	16.8	13.3	14.3
CCI (%)				
0	21.3	18.7	12.8	12.9
1–2	53.5	52.9	49.1	48.4
≥ 3	25.3	28.4	38.1	38.7
Bisphosphonate medication				
On medication (%)	15.0	14.1	26.6	19.2

Values are presented as mean ± standard deviation not otherwise specified.
BMI, body mass index; WC, waist circumference; CCI, Charlson Comorbidity Index.

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Table 2. The association of obesity status with the risk of osteoporotic fractures (primary outcome*)

Obesity status	Normal	Obese BMI/normal WC	Normal BMI/obese WC	Obesity by both BMI and WC
	< 85 cm/18.5–24.9 kg/m²	< 85 cm/≥ 25 kg/m²	≥ 85 cm/18.5–24.9 kg/m²	≥ 85 cm/≥ 25 kg/m²
No. of subjects	87,869	21,400	7,412	26,992
The first events				
Person-year	502,604	123,027	40,730	152,286
Events, n (incidence per 1,000†)	6,703 (13.3)	1,499 (12.2)	962 (23.6)	2,578 (16.9)
Age-adjusted, HR (95% CI)	Reference	0.89 (0.84–0.94)	1.15 (1.07–1.23)	0.97 (0.92–1.01)
Multivariable, HR (95% CI)‡	Reference	0.89 (0.84–0.94)	1.13 (1.05–1.21)	0.96 (0.92–1.00)

HR, hazard ratio; CI, confidence interval; BMI, body mass index; WC, waist circumference.
*The primary outcome of this study was defined as having hospitalization for one day or more or physician visits for two times or more within six months under osteoporotic fractures, whichever came the earliest. Osteoporotic fractures include vertebral (S22.0, S22.1, S32.0, M48.4, and M48.5), hip (S72.0 and S72.1), radius (S52.5 and S52.6), and humerus (S42.2 and S42.3) fractures.
†Crude incidence per 1,000 person-years.
‡Adjusted for age, income, smoking status, alcohol habit, regular exercise, bisphosphonate medication, and Charlson Comorbidity Index.

Table 3 depicts the association of obesity status with osteoporotic fractures according to age band. Among women aged over 60 years, normal BMI/obese WC was significantly associated with osteoporotic fractures. The results of an additional analysis using a combination of BMI tertile and WC tertile (total nine subgroups) are shown in **Supplementary Table 1**, results of which were similar to the main results as well as subgroup analysis according to age. **Table 4** demonstrates the association of obesity status with sub-types of fractures, including vertebral, hip, and other fractures, requiring hospitalization or physician visits (primary outcomes) and hospitalization (secondary outcomes), respectively. Normal BMI/obese WC was associated with a higher risk of vertebral and hip fractures in both definitions of outcomes. Hip fractures requiring hospitalization were significantly low in obese BMI/normal WC compared with the normal group. The humerus and distal radius fractures by the primary outcome were significantly low in women with high BMI, including obese BMI/normal WC and obesity by both BMI and WC, compared with the normal group.

Table 3. Stratified analysis according to age-band for the association of obesity status with the risk of osteoporotic fractures (primary outcome*)

Obesity status	Normal	Obese BMI/normal WC	Normal BMI/obese WC	Obesity by both BMI and WC
	< 85 cm/18.5–24.9 kg/m²	< 85 cm/≥ 25 kg/m²	≥ 85 cm/18.5–24.9 kg/m²	≥ 85 cm/≥ 25 kg/m²
≤ 50 years				
No. of subjects	22,684	4,512	630	3,092
No. of events	688	130	25	96
Multivariable HR (95% CI)†	Reference	0.93 (0.77–1.13)	1.27 (0.86–1.90)	0.97 (0.78–1.21)
51–60 years				
No. of subjects	39,128	9,875	2,294	10,270
No. of events	2,377	528	164	648
Multivariable HR (95% CI)†	Reference	0.85 (0.77–0.94)	1.09 (0.93–1.28)	0.96 (0.88–1.05)
61–70 years				
No. of subjects	16,861	5,000	2,363	8,516
No. of events	1,894	526	316	965
Multivariable HR (95% CI)†	Reference	0.93 (0.85–1.03)	1.13 (1.00–1.27)	0.98 (0.91–1.06)
≥ 71 years				
No. of subjects	9,196	2,013	2,125	5,114
No. of events	1,744	315	457	869
Multivariable HR (95% CI)†	Reference	0.83 (0.74–0.94)	1.12 (1.01–1.25)	0.89 (0.82–0.96)

HR, hazard ratio; CI, confidence interval; BMI, body mass index; WC, waist circumference.
*The primary outcome of this study was defined as having hospitalization for one day or more or physician visits for two times or more within six months under osteoporotic fractures, whichever came the earliest. Osteoporotic fractures include vertebral (S22.0, S22.1, S32.0, M48.4, and M48.5), hip (S72.0 and S72.1), radius (S52.5 and S52.6), and humerus (S42.2 and S42.3) fractures.
†Adjusted for age, income, smoking status, alcohol habit, regular exercise, bisphosphonate medication, and Charlson Comorbidity Index.

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Table 4. Subgroup analysis according to the type of osteoporotic fractures according to primary and secondary outcomes*

Obesity status	Normal	Obese BMI/normal WC	Normal BMI/obese WC	Obesity by both BMI and WC
	< 85 cm/18.5–24.9 kg/m²	< 85 cm/≥ 25 kg/m²	≥ 85 cm/18.5–24.9 kg/m²	≥ 85 cm/≥ 25 kg/m²
No. of subtotal subjects	87,869	21,400	7,412	26,992
Vertebral fractures				
No. of events (primary outcome)	2,516	606	465	1,278
Multivariable HR (95% CI)†	Reference	0.97 (0.89–1.06)	1.22 (1.11–1.35)	1.15 (1.07–1.23)
No. of events (secondary outcome)	1,904	459	359	998
Multivariable HR (95% CI)†	Reference	0.98 (0.88–1.08)	1.22 (1.11–1.35)	1.15 (1.07–1.23)
Hip fractures				
No. of events (primary outcome)	353	67	94	176
Multivariable HR (95% CI)†	Reference	0.79 (0.61–1.02)	1.39 (1.11–1.76)	0.98 (0.82–1.18)
No. of events (secondary outcome)	339	61	92	171
Multivariable HR (95% CI)†	Reference	0.75 (0.57–0.99)	1.40 (1.11–1.77)	0.99 (0.83–1.20)
Humerus & radius fractures				
No. of events (primary outcome)	3,834	826	403	1,124
Multivariable HR (95% CI)†	Reference	0.87 (0.80–0.93)	1.05 (0.94–1.16)	0.85 (0.79–0.91)
No. of events (secondary outcome)	1,697	403	202	551
Multivariable HR (95% CI)†	Reference	0.95 (0.85–1.06)	1.14 (0.98–1.32)	0.92 (0.83–1.01)

HR, hazard ratio; CI, confidence interval; BMI, Body mass index (kg/m²); WC, waist circumference (cm)
*The primary outcome of this study was defined as having hospitalization for one day or more or physician visits for two times or more within six months under osteoporotic fractures, whichever came the earliest. The secondary outcome was osteoporotic fractures requiring hospitalization for two days or more, as a marker for severe fractures, whichever came the earliest fracture. ICD-10 codes were used to identify and classify fractures: vertebral (S22.0, S22.1, S32.0, M48.4, and M48.5), hip (S72.0 and S72.1), wrist (S52.5 and S52.6), and humerus (S42.2 and S42.3).
†Adjusted for age, income, smoking status, alcohol habit, regular exercise, bisphosphonate medication, and Charlson Comorbidity Index.

DISCUSSION

In this large nationwide cohort study of 143,673 women in their late 40s or more, the discrepancy in obesity status, measured using BMI and WC, was associated with different risks of osteoporotic fractures that required inpatient treatment. Compared with normal BMI and WC, normal BMI/obese WC was associated with osteoporotic fractures; however, obese BMI/normal WC was related to a reduced risk of osteoporotic fractures. This protective effect of obese BMI/normal WC on the osteoporotic fractures was more prominent in older women. To our knowledge, this is the first study to use a combination of BMI and WC to determine obesity status. The combined use of BMI and WC reduced the likelihood of misclassification of obesity status, which is common when the two measurements are used in isolation.

The results of this study are similar to those of recent studies, although none of the studies considered BMI and WC at the same time. The Nurses' Health Study considered both BMI and WC as obesity surrogate markers, although not in combination. When 54,934 female nurses aged between 30 and 55 years were followed for 12 years, women with WC < 71.0 cm were at a higher risk of self-reported vertebral fractures compared to women with WC > 108.0 cm; even after adjusting for covariates such as BMI [8]. A prospective cohort with 19,918 women aged > 60 years followed for a median of 8.1 years reported that higher WC and higher WHR were related to a higher risk of hip fractures after adjusting for BMI [9]. The Nurses' Health Study and the Health Professionals Follow-up Study reported that abdominal obesity was associated with an increased risk of hip fracture after controlling for BMI in women [10]. We also found that isolated abdominal obesity and combined abdominal and general obesity were related to an increased risk of osteoporotic fractures.

The association between BMI and osteoporotic fractures is controversial. Early studies suggested that higher BMI was protective against osteoporotic fractures and osteoporosis [3-5]. A meta-analysis of 6 studies reported no association between BMI and the risk of vertebral

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fracture in women [7]. The Nurses' Health Study recently reported that women with BMI > 32.0 kg/m^2 had a lower risk of self-reported vertebral fractures than women with a BMI of 21.0–24.9 kg/m^2 [8]. In this study, we found that isolated general obesity is associated with a reduced risk of osteoporotic fractures, whereas combined general and abdominal obesity reduces the risk of osteoporotic fractures.

The conflicting results on the impact of obesity on osteoporotic fractures, depending on the definition used for obesity, suggests that body composition or fat distribution is an important predictor of osteoporotic fractures. Technically, BMI is limited in the assessment of obesity because it cannot distinguish between lean muscle and fat. In this current study, we confirmed that combined BMI and WC alter the risk of osteoporotic fractures. Isolated abdominal obesity increased the risk of osteoporotic fracture risks. Women with isolated abdominal obesity have a relatively higher body fat content than similar weight women without abdominal obesity, which may be missed if obesity status is determined using BMI alone. A study that used percent body fat as a marker of obesity reported that the risk of hip fracture decreased linearly with a higher percent body fat among women [20]. We, therefore, propose that the mechanical load hypothesis on osteoporotic fractures remains relevant among individuals without abdominal obesity.

The complex association between obesity and bone can be explained by two aspects including fat and muscle. Increased adiposity secretes cytokines and adipokines, which are related to bone loss [21] and increased bone-marrow fat, which could increase the risk of fractures [22]. A biopsy study by Cohen et al. demonstrated that premenopausal women with more central adiposity had low bone quality and stiffness and markedly lower bone formation [23]. Additionally, abdominal obesity decreases osteoblast activity by altering the Wnt/β-catenin pathway [24]. A systematic review of 30 prospective cohort studies on muscle strength and incidence of falls reported that lower muscle strength increases the risk of falls [25]. Another study also reported that decreased thigh muscle owing to fatty infiltration of muscle, myosteatosis, increases the risk of hip fractures [26]. Muscle-derived growth factors, namely myokines such as insulin-like growth factor-1 (IGF-1) and basic fibroblast growth factor-2 (FGF-2) secreted from muscles, are known to regulate bone formation [27].

The results of this study should be interpreted considering the following limitations. First, because of the retrospective nature of the study, potential covariates regarded as related to osteoporotic fractures, including calcium intake, rheumatoid arthritis, and corticosteroid use, were not completely evaluated [28,29]. To minimize the effect of confounders, we used the CCI, which is the most commonly used comorbidity index, although a less relevant measure in younger individuals. Additionally, the severity of existing osteoporosis and treatment was not considered, which was regarded as the risk factor for osteoporotic fractures, due to a lack of information on DEXA or bone mineral density in this cohort. To minimize this limitation, we used the medication information of osteoporosis, although the underestimation of osteoporosis still exists. Third, the change in height was not considered, although height loss is associated with prior fracture, which again increases the risk of new fractures [13]. To eliminate this bias, subjects who had any osteoporotic fracture events before the index year were excluded.

Despite these limitations, the 865,888 person-years of follow-up and using hard outcomes, such as fractures and not osteoporosis, and a nationally representative database were strengths associated with the current study.

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CONCLUSION

In conclusion, obese BMI/normal WC was associated with decreased risk of osteoporotic fracture, whereas normal BMI/obese WC was associated with increased risk of osteoporotic fracture compared with the normal group among East Asian women in their late 40s or more. Our findings suggest that fat distribution, particularly central adiposity, rather than simple weight is an important predictor of future osteoporotic fractures requiring hospitalization among East Asian women.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

Subgroup analysis according to age of the association of combination of BMI and WC with osteoporotic fractures*

Click here to view

Supplementary Fig. 1

Study population.

Click here to view

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