For chronic weight management in adults with a BMI of ≥30 kg/m² (obesity), or ≥27 kg/m² (overweight) in the presence of a weight-related comorbidity, as an adjunct to a reduced calorie diet and increased physical activity.

NOW APPROVED

ONCE-WEEKLY

wegovy™

semaglutide injection 2.4 mg

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Indications and Usage

Wegovy™ (semaglutide) injection 2.4 mg is indicated as an adjunct to a reduced calorie diet and increased physical activity for chronic weight management in adults with an initial body mass index (BMI) of ≥30 kg/m² (obesity) or ≥27 kg/m² (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, type 2 diabetes mellitus, or dyslipidemia).

Limitations of Use

- Wegovy™ contains semaglutide and should not be coadministered with other semaglutide-containing products or with any GLP-1 receptor agonist.
- The safety and effectiveness of Wegovy™ in combination with other products intended for weight loss, including prescription drugs, over-the-counter drugs, and herbal preparations, have not been established.
- Wegovy™ has not been studied in patients with a history of pancreatitis.

Important Safety Information

WARNING: RISK OF THYROID C-CELL TUMORS

- **In rodents, semaglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures. It is unknown whether Wegovy™ causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as human relevance of semaglutide-induced rodent thyroid C-cell tumors has not been determined.**
- **Wegovy™ is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk for MTC with the use of Wegovy™ and inform them of symptoms of thyroid tumors (e.g. a mass in the neck, dysphagia, dyspnea, persistent hoarseness). Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with Wegovy™.**

Contraindications

- Wegovy™ is contraindicated in patients with a personal or family history of MTC or in patients with MEN 2, and in patients with a prior serious hypersensitivity reaction to semaglutide or to any of the excipients in Wegovy™. Serious hypersensitivity reactions, including anaphylaxis and angioedema have been reported with semaglutide.

Warnings and Precautions

- **Risk of Thyroid C-Cell Tumors:** Patients should be further evaluated if serum calcitonin is measured and found to be elevated or thyroid nodules are noted on physical examination or neck imaging.
- **Acute Pancreatitis:** Acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, has been observed in patients treated with GLP-1 receptor agonists, including semaglutide. Acute pancreatitis was observed in patients treated with Wegovy™ in clinical trials. Observe patients carefully for signs and symptoms of acute pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back, and which may or may not be accompanied by vomiting). If acute pancreatitis is suspected, discontinue Wegovy™ promptly, and if acute pancreatitis is confirmed, do not restart.
- **Acute Gallbladder Disease:** In clinical trials, cholelithiasis was reported by 1.6% of Wegovy™ patients and 0.7% of placebo patients. Cholecystitis was reported by 0.6% of Wegovy™ patients and 0.2% of placebo patients. If cholelithiasis is suspected, gallbladder studies and appropriate clinical follow-up are indicated.
- **Hypoglycemia:** Wegovy™ lowers blood glucose and can cause hypoglycemia. In a trial of patients with type 2 diabetes, hypoglycemia was reported in 6.2% of Wegovy™ patients versus 2.5% of placebo patients. Patients with type 2 diabetes taking Wegovy™ with an insulin secretagogue (e.g. sulfonylurea) or insulin may have an increased risk of hypoglycemia, including severe hypoglycemia. Inform patients of the risk of hypoglycemia and educate them on the signs and symptoms. Monitor blood glucose in patients with type 2 diabetes.
- **Acute Kidney Injury:** There have been postmarketing reports of acute kidney injury and worsening of chronic renal failure, which in some cases required hemodialysis, in patients treated with semaglutide. Patients with renal impairment may be at a greater risk of acute kidney injury, but some events have been reported in patients without known underlying renal disease. A majority of the events occurred in patients who experienced nausea, vomiting, or diarrhea, leading to volume depletion. Monitor renal function when initiating or escalating doses of Wegovy™ in patients reporting severe adverse gastrointestinal reactions and in patients with renal impairment reporting any adverse reactions that could lead to volume depletion.
- **Hypersensitivity:** Serious hypersensitivity reactions (e.g., anaphylaxis, angioedema) have been reported with semaglutide. If hypersensitivity reactions occur, discontinue use of Wegovy™, treat promptly per standard of care, and monitor until signs and symptoms resolve. Use caution in a patient with a history of anaphylaxis or angioedema with another GLP-1 receptor agonist.
- **Diabetic Retinopathy Complications in Patients with Type 2 Diabetes:** In a trial of patients with type 2 diabetes, diabetic retinopathy was reported by 4.0% of Wegovy™ patients and 2.7% of placebo patients. Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy. Patients with a history of diabetic retinopathy should be monitored for progression of diabetic retinopathy.
- **Heart Rate Increase:** Mean increases in resting heart rate of 1 to 4 beats per minute (bpm) were observed in Wegovy™ patients compared to placebo in clinical trials. More Wegovy™ patients compared with placebo had maximum changes from baseline of 10 to 19 bpm (41% versus 34%) and 20 bpm or more (26% versus 16%). Monitor heart rate at regular intervals and instruct patients to report palpitations or feelings of a racing heartbeat while at rest. If patients experience a sustained increase in resting heart rate, discontinue Wegovy™.
- **Suicidal Behavior and Ideation:** Suicidal behavior and ideation have been reported in clinical trials with other weight management products. Monitor patients for depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior. Discontinue Wegovy™ in patients who experience suicidal thoughts or behaviors and avoid in patients with a history of suicidal attempts or active suicidal ideation.

Adverse Reactions

- The most common adverse reactions reported in ≥5% of patients treated with Wegovy™ are nausea, diarrhea, vomiting, constipation, abdominal pain, headache, fatigue, dyspepsia, dizziness, abdominal distention, eructation, hypoglycemia in patients with type 2 diabetes, flatulence, gastroenteritis, and gastroesophageal reflux disease.

Drug Interactions

- The addition of Wegovy™ in patients treated with insulin has not been evaluated. When initiating Wegovy™, consider reducing the dose of concomitantly administered insulin secretagogues (such as sulfonylureas) or insulin to reduce the risk of hypoglycemia.
- Wegovy™ causes a delay of gastric emptying and has the potential to impact the absorption of concomitantly administered oral medications. Monitor the effects of oral medications concomitantly administered with Wegovy™.

Use in Specific Populations

- **Pregnancy:** May cause fetal harm. When pregnancy is recognized, discontinue Wegovy™. Discontinue Wegovy™ in patients at least 2 months before a planned pregnancy.

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Original Article
EPIDEMIOLOGY/GENETICS

Obesity

Implication of High-Body-Fat Percentage on Cardiometabolic Risk in Middle-Aged, Healthy, Normal-Weight Adults

Ji Young Kim[1], *Sang-Hwan Han*[2] *and Bong-Min Yang*[3]

Objective: This study investigated the number of Korean adults who had a normal body mass index (BMI) but high body-fat percentage (BF%) and determined their increased risk factors for cardiovascular diseases, including high blood pressure, hyperglycemia, and dyslipidemia.

Design and Methods: This cross-sectional study was based on 12,386 subjects (6,534 men and 5,852 women), with a normal BMI, between 30 and 49 years of age. Subjects were categorized into two groups by BF% (normal BF% group, BF% <25 for men, and BF% <30 for women; high BF(%) group, BF% ≥ 25 for men, and BF% ≥ 30 for women).

Results: The proportion of subjects with a normal BMI and high BF% was 12.7% ($n = 1,572$; 291 [4.5%] men and 1,281 [21.9%] women). Subjects with a high BF% had a significantly higher prevalence of high blood pressure (men only), hyperglycemia, and dyslipidemia. Multiple logistic regression analyses revealed that subjects with a normal BMI and high BF% had a 1.63 (adjusted odds ratio, 95% confidence interval: 1.21–2.19) in men and 1.56 (adjusted odds ratio, 95% confidence interval: 1.36–1.80) in women increased risk of one or more cardiovascular risk factors compared to subjects in the normal BMI and normal BF% group, even after adjusting for abdominal obesity.

Conclusion: High BF% is associated with a high cardiometabolic risks, regardless of abdominal obesity, in normal-weight Korean adults. Thus, follow-up screening of those with a high BF% may be necessary to detect and prevent cardiometabolic diseases, particularly for women with a normal BMI.

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Introduction

Obesity is defined as excess body fat that results in an increased risk of metabolic abnormalities. Obesity increases the risk of diseases, such as cardiovascular disease, type 2 diabetes, and several cancers (1). The World Health Organization (WHO) defines obesity based on body mass index (BMI) and waist circumference (WC) (2). Most countries report obesity-related statistics based on BMI. However, BMI is limited when used as the only obesity index. Obesity based on BMI classifies those who have lower body weight despite excessive fat as normal, such as the elderly, whereas it classifies young men with less fat and more muscle as obese (3). The standard obesity indices related to cardiometabolic risk factors including BMI, body fat percentage (BF%), WC, and waist-to-hip ratio (4,5). WC and waist-to-hip ratio reflect the cardiometabolic risk represented by abdominal obesity (6). However, the results showed that high BF% increases the risk factors for cardiovascular diseases in normal- and low-BMI Asians populations (7). Previous studies have shown that those with a high-body-fat percentage (BF%) despite normal body weight have an increased cardiometabolic risk (8–11).

Subjects in the normal body weight range who have metabolic abnormalities are defined as metabolically obese normal weight (MONW). These individuals are not obese based on BMI, but are hyperinsulinemic, insulin resistant, and predisposed to type 2 diabetes mellitus and premature coronary heart disease (12). Based on the data from the third Korean National Health and Nutrition Examination Survey (KNHANES III), the prevalence of MONW is 8.7% (10.1% men, 7.6% women) (13). Indeed, the BF% measurement was used for the first time in the Fourth Korean National Health and Nutrition Examination Survey (KNHANES IV) conducted during 2007–2009 in South Korea, in which BF% was measured using the dual-energy X-ray absorptiometry (DEXA) method.

In one of the recent reports using the US third National Health and Nutrition Examination Survey (NHANES III) population, subjects with a normal BMI but high BF%, that is, normal weight obesity (NWO), have a higher prevalence of cardiometabolic risks. In women, NWO is strongly associated with an increased risk of cardiovascular mortality (14).

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When comprehensive health examinations are administered in the clinical field, there are many cases in which the results of hematological tests and blood pressure are abnormal even for subjects with a normal body weight. In such cases, the BF% is often high despite the absence of underlying disease. Such a phenomenon is particularly pronounced among women.

However, to the best of our knowledge, there has not been a large epidemiologic study of the prevalence and association of cardiometabolic risks with normal weight obesity in Korean adults. Therefore, this study was conducted to determine the prevalence of high BF% but normal BMI in Middle-Age and Healthy adults and to evaluate their risk factors for cardiovascular diseases.

Methods and Procedures

Study population

This study included 17,206 subjects (10,439 men and 6,767 women) between 30 and 49 years of age. Subjects underwent a comprehensive health examination in a single health promotion center at a university hospital from January to December 2007, and gave consent for the use of the examination results for research purposes. The survey was conducted as part of regular surveillance. Exclusion criteria were (i) BMI <18.5 or ≥ 25 kg/m^2; (ii) subjects who had been diagnosed and given treatment for hypertension, diabetes, or hyperlipidemia (600 men and 190 women); (iii) subjects who had been diagnosed with a chronic disease, such as chronic hepatitis, hyperthyroidism, or hypothyroidism; (iv) pregnant women; (v) subjects who did not respond to one or more of the questions in the questionnaire about alcohol consumption, smoking, and exercise; and (vi) subjects with any blood test result greater than the mean + three times the standard deviation (SD) (fasting plasma glucose [FPG], <141.6 [mg/dl], 119 men and 42 women; total cholesterol [TChol], >288.7 [mg/dl], 78 men and 32 women; triglycerides [TGs], >379.6 [mg/dl], three men and four women). Thus, a total of 12,386 subjects (6,534 men and 5,852 women) were analyzed in this study. The ethical committee of Gil Medical Center (Incheon, Korea) approved this study.

Questionnaire information

Information regarding alcohol consumption, smoking, and exercise was obtained from structured questionnaires. Smoking status was classified into three groups: nonsmoker, ex-smoker, or current smoker. The amount and frequency of alcohol drinking were similarly studied by dividing the subjects into nondrinkers, moderate drinkers (mean alcohol intake, <24 g/day), and heavy drinkers (mean alcohol intake, >24 g/day) (15). We investigated how many times per week the subjects exercised for >30 min at a moderate or higher intensity, and then divided subjects into a nonexercise group, for those who did not exercise at all, an irregular exercise group (one or two times per week), and a regular exercise group ($\geq$3 times/week).

Anthropometric measurements

All anthropometric measurements were performed using the same instrument and technique by trained examiners. Blood pressure was measured with an automatic hematomanometer (ERKA type 113, German) using the right arm, whereas the subjects sat in a stable sitting position after resting for more than 10 min. WC was measured with anthropometric tape after expiration at a point midway between the lowest rib and the iliac crest of the pelvis, whereas the subjects were standing comfortably. BMI was calculated as body weight (kg) divided by square of the height (m^2). Height (cm), body weight (kg), body fat (kg), body muscle (kg), and BF% were simultaneously measured with a bioelectrical impedance analysis (BIA) instrument (InBody3.0; Biospace, Seoul, South Korea). The resistance of arms, trunk, and legs was measured at frequencies of 5, 50, 250, and 500 kHz with an 8-polar tactile-electrode impedance meter: four were in contact with the palm and thumb of both hands and four with the anterior and posterior aspects of the sole of both feet. The correlation coefficient of BF% between the InBody 3.0 and the DEXA was 0.96 in men and 0.93 in women (16). To measure BF% accurately, the subjects were given directions in advance, which included no physical exercise or alcohol consumption for at least 24-h before the examination.

Laboratory measurements

All blood tests were performed in the morning after 12-h fasting. Total cholesterol and TG levels were measured using an enzymatic colorimetric test. High-density lipoprotein cholesterol (HDLC) was measured using the selective-inhibition method, and low-density lipoprotein cholesterol (LDLC) was measured using the homogeneous enzymatic colorimetric test. FPG was measured using the hexokinase method, and the fasting insulin (FI) level was determined using an immunoradiometric assay (Biosource Diagnostic, Aartrijke, Belgium). The homeostatic model assessment (HOMA) was used as an index for insulin resistance (IR) (17), calculated as follows: HOMA-IR = (FI [μIU/ml] $\times$ FPG [mg/dl])/405.

Criteria of obesity and cardiovascular disease risk factors

The BMI-based obesity criterion was defined as a BMI ≥ 25 kg/m^2, according to the WHO standard for Asians (18,19). In 2005, the Ministry of Health and Welfare of Korea also accepted a BMI of ≥ 25 kg/m^2 for obesity (13). Although there is no standardized definition of obesity by body fat, BF%-based obesity was defined as a BF% $\geq$25% for men and $\geq$30% for women with reference to several epidemiologic studies of the BF% (20–23) and health examination criteria in a clinical setting. The subjects were divided into normal BMI and normal body fat groups based on the BMI- and BF%-based obesity criteria (BMI <25 kg/m^2 and BF% <25% [30% for women]) and a normal BMI and high-body-fat group (BMI <25 kg/m^2 and BF% $\geq$25% [30% for women]). The cutoff points of WC for abdominal obesity are $\geq$90 cm for men and $\geq$80 cm for women. This is used to indicate central obesity according to the Asian-specific WC cutoff points of the International Diabetes Federation criteria (24,25). The risk factors for cardiovascular disease were defined as follows (26,27):

(i) High blood pressure: systolic pressure $\geq$130 mmHg/diastolic pressure $\geq$85 mmHg.
(ii) Hyperglycemia: FPG $\geq$100 mg/dl.
(iii) Dyslipidemia: TG $\geq$150 mg/dl, HDLC $\leq$40 mg/dl (50 mg/dl for women), LDLC $\geq$160 mg/dl.

Statistical analysis

The mean levels of the anthropometric variables and blood tests were calculated, such as cardiometabolic risk parameters. The mean

TABLE 1 General characteristics of 12,386 normal BMI individuals

	Men (n = 6,534)			Women (n = 5,852)		
N = 12,386	Normal BF (%) n = 6,243 (95.5)	High BF (%) n = 291 (4.5)	P-value	Normal BF (%) n = 4,571 (78.1)	High BF (%) n = 1,281 (21.9)	P-value
Age						
Mean ± SD[a]	39.0 ± 5.4	39.8 ± 5.3	0.018	37.4 ± 5.0	37.4 ± 5.1	0.779
30–39	3,354 (53.7)	127 (43.6)	0.001	3,022 (66.1)	833 (65.0)	0.469
40–49	2,899 (46.3)	164 (56.4)		1,549 (33.9)	448 (35.0)	
Smoking			<0.001			0.711
Nonsmoker	2,146 (34.4)	120 (41.2)		4,438 (97.1)	1,241 (96.9)	
Ex-smoker	1,506 (24.1)	85 (29.2)		75 (1.6)	24 (1.9)	
Current smoker	2,591 (41.5)	86 (29.6)		58 (1.3)	16 (1.2)	
Alcohol[b]			0.002			0.876
Nondrinker	987 (15.8)	52 (17.9)		3,026 (66.2)	835 (65.2)	
Moderate	3,943 (63.2)	174 (59.8)		1,474 (32.2)	430 (33.6)	
Heavy	1,313 (21.0)	65 (22.3)		71 (1.6)	16 (1.2)	
Exercise[c]			0.052			0.693
Regular	882 (14.1)	21 (7.2)		833 (18.2)	186 (14.5)	
Irregular	2,192 (35.1)	96 (33.0)		795 (17.4)	273 (21.3)	
No	3,169 (50.8)	174 (59.8)		2,943 (64.4)	822 (64.2)	
Abdominal obesity[d]			<0.001			<0.001
No	6,045 (96.8)	155 (53.3)		4,562 (99.8)	1,061 (82.8)	
Yes	198 (3.2)	136 (46.7)		9 (0.2)	220 (17.2)	

Values are expressed as number (percentage) except for notation[a]; χ^2 analyses for age and WC; Mantel–Haenszel χ^2 analyses for smoking, alcohol, and exercise.
Normal BF%, BF% <25% (30%, female); High BF%, BF%≥25% (30%, female); BF%, body fat percentage; SD, standard deviation; WC, waist circumference.
[a]Values are expressed as mean ± standard deviation. P-value by t-tests.
[b]Nondrinker, 0 g/day; moderate, <24 g/day; heavy, ≥24 g/day.
[c]No, 0 time a week; irregular, one to two times a week; regular, at least three times a week.
[d]No, waist circumference <90 cm (80cm, female); yes, waist circumference ≥90 cm (80 cm, female).

differences between the normal BF% group and the high BF% group were assessed using the Levene equal variance test and Student's t-test.

Means were adjusted for age, BMI, and the lifestyle factors, such as alcohol consumption, smoking, and exercise, respectively, and the adjusting mean differences were examined with an analysis of covariance (ANCOVA). The differences in cardiovascular risk and lifestyle factors among groups were determined using the χ^2-test. The odds ratios (ORs) for clustering of one or more cardiovascular risk factors were calculated in each group using a multiple logistic regression analysis after adjusting for age, smoking, alcohol, exercise, and WC. The analysis was further adjusted for BMI. As medications could affect blood test and body composition, we repeated the same analysis after including subjects in treatment for hypertension, type 2 diabetes mellitus, and/or dyslipidemia.

All P-values presented are two-tailed, and P-values of <0.05 were considered to indicate statistical significance. Statistical analyses were performed with SPSS ver. 19.0 for Windows (SPSS, Inc., Chicago, IL).

Results

The 12,386 subjects included 6,534 men (52.8%) and 5,852 women (47.2%). The number of subjects with a high BF% (≥25% for men and ≥30% for women) and normal BMI was 291 (4.5%) in men and 1,281 (21.9%) in women. Male subjects in the high BF% group were older compared to men in the normal BF% groups ($P < 0.05$). No significant difference in the age distribution between the groups was found for the female subjects. The high BF% group showed a lower frequency of regular exercise, and many of these subjects were in the nonexercise group. The frequency of abdominal obesity was significantly higher in both men and women in the high BF% group (Table 1).

WC was significantly greater in high BF% groups ($P < 0.05$). For both male and female subjects, high BF% group had significantly higher values for systolic blood pressure, diastolic blood pressure, TChol, TG, LDLC, FPG, FI, and IR compared to those in the normal BF% group ($P < 0.05$) (Table 2). In addition, we performed an ANCOVA between the high and the low BF% group for the cardiometabolic risk parameters after adjusting for age, BMI, and the lifestyle factors, respectively. For both male and female subjects, high BF% groups had significantly higher values for all cardiometabolic risk parameters compared to those in the normal BF% groups ($P < 0.001$) after adjusting age. Meanwhile, no significant differences were found with FPG and HDLC after adjusting BMI. After adjusting for the lifestyle factors in male subjects, no significant difference was found with in the FPG and blood pressure.

We divided subjects according to the abdominal obesity status. Then, we performed t-test between the high and the low BF% group

TABLE 2 The mean levels of anthropometric parameters and cardiometabolic risk parameters in 12,386 normal BMI individuals

	Men (n = 6,534)			Women (n = 5,852)		
N = 12,386	Normal BF (%) n = 6,243	High BF (%) n = 291	P-value	Normal BF (%) n = 4,571	High BF (%) n = 1,281	P-value
Anthropometric parameters						
Height (cm)	172.6 (5.7)	169.8 (5.6)	<0.001	160.1 (5.1)	158.4 (5.1)	<0.001
Weight (kg)	67.6 (6.3)	69.5 (5.1)	<0.001	54.2 (5.0)	58.0 (4.8)	<0.001
BMI (kg/m^2)	22.7 (1.6)	24.1 (0.7)	<0.001	21.1 (1.5)	23.1 (1.2)	<0.001
Body fat (%)	18.7 (3.3)	26.4 (1.3)	<0.001	25.1 (3.0)	31.9 (1.6)	<0.001
Fat mass (kg)	12.7 (2.8)	18.3 (1.6)	<0.001	13.6 (2.4)	18.5 (1.9)	<0.001
Muscle mass (kg)	51.9 (4.8)	48.4 (3.8)	<0.001	38.2 (3.4)	37.2 (3.2)	<0.001
WC (cm)	84.8 (2.8)	89.4 (1.6)	<0.001	73.8 (2.3)	78.0 (1.8)	<0.001
Cardiometabolic risk parameters						
SBP (mmHg)	116.4 (9.2)	117.9 (9.2)	0.007	104.8 (10.6)	107.2 (10.6)	<0.001
DBP (mmHg)	73.9 (7.4)	75.2 (7.6)	0.003	65.3 (7.5)	67.0 (8.0)	<0.001
TChol (mg/dl)	185.2 (27.8)	197.0 (28.0)	<0.001	175.5 (27.3)	183.8 (27.7)	<0.001
TG (mg/dl)	121.6 (59.6)	148.6 (68.6)	<0.001	79.8 (37.5)	94.8 (46.0)	<0.001
HDLC (mg/dl)	49.8 (10.2)	47.5 (9.2)	<0.001	58.2 (12.0)	56.0 (11.8)	<0.001
LDLC (mg/dl)	108.0 (25.1)	119.7 (24.0)	<0.001	93.9 (22.8)	103.1 (24.2)	<0.001
FPG (mg/dl)	96.5 (7.9)	98.0 (7.4)	0.001	92.3 (7.0)	93.5 (7.5)	<0.001
FI (μIU/ml)	4.6 (2.5)	6.1 (2.8)	<0.001	4.7 (2.3)	5.8 (2.9)	<0.001
HOMA-IR	1.1 (0.6)	1.5 (0.7)	<0.001	1.0 (0.5)	1.3 (0.7)	<0.001

Values are expressed as means (standard deviation). P-value by t-tests.
Normal BF%, BF% <25%(30%, female); high BF%, BF%≥25%(30%, female); BMI, body mass index; BF%, body fat percentage; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; TChol, total cholesterol; TG, triglyceride; HDLC, high-density lipoprotein cholesterol; LDLC, low-density lipoprotein cholesterol; FPG, fasting plasma glucose; FI, fasting insulin; HOMA-IR, homeostasis model assessment of insulin resistance.

for the cardiometabolic risk parameters. For the males without abdominal obesity (n = 6,200), high BF% group had significantly differences for FI, IR, TChol, TG, HDLC, and LDLC (P < 0.001). In male subjects with abdominal obesity (n = 334), high BF% group had significantly higher values for FI and IR (P < 0.05). Meanwhile, significant differences in all the cardiometabolic risk parameters between the BF% groups were found for female subjects without abdominal obesity (n = 5,623, P < 0.001). In females with abdominal obesity (n = 229), high BF% group had significantly higher values only for FI (P < 0.001).

In our study, a correlation analysis of BF%, BMI, and WC of the subjects determined that the Pearson's correlation coefficient between WC and BMI was 0.88 in men and 0.86 in women. Between BF% and WC, it was 0.90 in both men and women, and that between BF% and BMI it was 0.78 in men and 0.79 in women; all correlations was significant (P < 0.05). In addition, BF% controlled for age, WC, and BMI was significantly correlated with lipid profiles, FI, and IR in men (P < 0.05), whereas in women, there was no significant correlation with TChol and TG. Correlations between BF% and cardiometabolic risk parameters were weak in both male and female subjects (data not shown).

The prevalence of high blood pressure, hyperglycemia, dyslipidemia, and clustering of one or more cardiovascular risk factor was higher in the high BF% group (P < 0.001) (Table 3). The adjusted ORs for having cardiovascular disease risk factors in the high BF% group were investigated using a multiple logistic regression analysis and compared to those of the normal BF% group. Age, smoking, drinking, exercise, and abdominal obesity were adjusted for in the multiple logistic regression analysis. The adjusted ORs for at least one cardiovascular risk factor in the high BF% group were 1.63 (95% confidence interval [CI], 1.21–2.19) in men, and 1.56 (95% CI, 1.36–1.80) in women. In addition, the results from multiple logistic regression analyses, with adjustment for BMI, were also consistent. To test the sensitivity of our results, we performed analysis including subjects undergoing treatment for hypertension, diabetes mellitus, and/or hyperlipidemia (adjusted ORs = 1.73, 95% CI, 1.29–2.31 in men and adjusted ORs = 1.50, 95% CI, 1.33–1.70 in women). Including them did not affect the associations. We performed subanalysis of normal-weight to overweight subjects for 18.5 ≤ BMI (kg/m^2) < 23. The adjusted ORs for subjects of BMI <23 kg/m^2 for at least one cardiovascular risk factor in the high BF% group were 4.48 (95% CI, 1.51–13.3) in men, and 1.43 (95% CI, 1.18–1.72) in women (Table 4).

Discussion

This study was conducted to investigate the prevalence of adults with a normal BMI but high BF% and to determine the association between an increase in BF% and the risk of cardiometabolic

TABLE 3 Frequency of cardiovascular risk factors in 12,386 normal BMI individuals

	Men (n = 6,534)			Women (n = 5,852)		
N = 12,386	Normal BF (%) n = 6,243	High BF (%) n = 291	P-value	Normal BF (%) n = 4,571	High BF (%) n = 1,281	P-value
High BP[a]	1,134 (18.2)	67 (23.0)	0.036	207 (4.5)	74 (5.8)	0.065
Hyperglycemia[b]	1,927 (30.9)	122 (41.9)	<0.001	632 (13.8)	250 (19.5)	<0.001
Dyslipidemia[c]	2,084 (33.4)	155 (53.3)	<0.001	1,275 (27.9)	467 (36.5)	0.001
High triglycemia	1,539 (24.7)	119 (40.9)	<0.001	227 (5.0)	142 (11.1)	<0.001
High LDLC	140 (2.2)	14 (4.8)	0.005	22 (0.5)	10 (0.8)	0.199
Low HDLC	1,120 (17.9)	73 (25.1)	0.002	1,288 (28.2)	457 (35.7)	<0.001
Cardiovascular risk factors						
None	2,534 (40.6)	69 (23.7)	<0.001	2,775 (60.7)	631 (49.3)	<0.001
Having one or more	3,709 (59.4)	222 (76.3)	<0.001	1,796 (39.3)	650 (50.7)	<0.001
Having two or more	1,248 (20.0)	106 (36.4)	<0.001	305 (6.7)	130 (10.1)	<0.001
Having three or more	188 (3.0)	16 (5.5)	<0.001	13 (0.3)	11 (0.9)	<0.001

Values are expressed as number (percentage). P-value by χ^2 tests.
Normal BF%, BF% <25%(30%, female); high BF%, BF%≥25%(30%, female); BF%, body fat percentage; BP, blood pressure; HDLC, high-density lipoprotein cholesterol; LDLC, low-density lipoprotein cholesterol.
[a]Systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85 mmHg.
[b]Fasting plasma glucose ≥100 mg/dl.
[c]Triglyceride ≥150 mg/dl and/or HDLC ≤40 mg/dl (50 mg/dl, female) and/or LDLC ≥160 mg/dl.

diseases, including high blood pressure, hyperglycemia, and dyslipidemia among healthy subjects with normal body weight and without diseases. BF%-based obesity was defined as a BF% ≥ 25% for men and BF% ≥ 30% for women. The proportion of subjects with a normal BMI and a high BF% was 291 (4.5%) men and 3,782 (64.6%) women. The adjusted ORs of the high BF% group with clustering of one or more cardiovascular disease risk factors were 1.63 (95% CI, 1.21–2.19) in men and 1.56 (95% CI, 1.36–1.80) in women, indicating that the adjusted ORs were significantly higher in the high BF% group, even after adjusting for abdominal obesity.

TABLE 4 Multiple logistic regression analysis on clustering of one or more cardiovascular risk factors

	Men			Women		
	n (%)	aOR (95% CI)	P-value	n (%)	aOR (95% CI)	P-value
Normal BMI (without hypertension, DM, dyslipidemia)[a]	6,534 (100.0)			5,852 (100.0)		
Normal BF (%)	6,243 (95.5)	1.00 (Reference)		4,571 (78.1)	1.00 (Reference)	
High BF (%)	291 (4.5)	1.63 (1.21–2.19)	<0.001	1,281 (21.9)	1.56 (1.36–1.80)	<0.001
Normal BMI (without hypertension, DM, dyslipidemia)[b]	6,534 (100.0)			5,852 (100.0)		
Normal BF (%)	6,243 (95.5)	1.00 (Reference)		4,571 (78.1)	1.00 (Reference)	
High BF (%)	291 (4.5)	1.56 (1.18–2.07)	0.002	1,281 (21.9)	1.23 (1.07–1.42)	0.004
Normal BMI (with hypertension, DM, dyslipidemia)[c]	7,134 (100.0)			6,042 (100.0)		
Normal BF (%)	6,790 (95.2)	1.00 (Reference)		4,694 (77.7)	1.00 (Reference)	
High BF (%)	344 (4.8)	1.73 (1.29–2.31)	<0.001	1,348 (22.3)	1.50 (1.33–1.70)	<0.001
18.5≤BMI 23 (without hypertension, DM, dyslipidemia)[d]	3,293 (100.0)			4,560 (100.0)		
Normal BF (%)	3,268 (99.2)	1.00 (Reference)		4,018 (88.1)	1.00 (Reference)	
High BF (%)	25 (0.8)	4.48 (1.51–13.28)	0.007	542 (11.9)	1.43 (1.18–1.72)	<0.001

The cardiovascular risk factors include high blood pressure, hyperglycemia, and dyslipidemia. High blood pressure: systolic pressure ≥130 mmHg/diastolic pressure ≥85 mmHg; hyperglycemia: FPG ≥100 mg/dl; dyslipidemia: TG ≥150 mg/dl/HDLC ≤40 mg/dl (50 mg/dl for female)/LDLC ≥160 mg/dl.
Normal BMI, 18.5≤BMI (kg/m^2) <25; normal BF%, BF% <25%(30%, female); high BF%, BF%≥25%(30%, female).
BMI, body mass index; BF%, body fat percentage; aOR, adjusted OR; CI, confidence interval; DM, type 2 diabetes mellitus.
[a,c,d]Age, smoking, alcohol, exercise, and waist circumference were adjusted.
[b]Age, smoking, alcohol, exercise, and body mass index were adjusted.
[a,b,d]Analysis based on normal BMI subject excluding subjects undergoing treatment for type 2 diabetes mellitus, hypertension, and/or dyslipidemia.
[c]Analysis based on normal BMI subject including subjects undergoing treatment for type 2 diabetes mellitus, hypertension, and/or dyslipidemia.

Ruderman et al. (12) suggested the concept of MONW. These individuals are not obese based on BMI but have hyperinsulinemia, IR, and are predisposed to type 2 diabetes mellitus and premature coronary heart disease despite having normal weight. Recently, the new syndrome NWO was defined as a normal BMI with increased body fat (28). Women with NWO have been shown to present differences in lean mass relative to normal-fat, normal-weight women (29), which might influence cardiovascular risk factors (28).

Romero-Corral et al. used 6,171 normal BMI subjects from the US Third National Health and Nutrition Examination Surveys (NHANES III) and found that the prevalence of metabolic syndrome was 15.8% (143/1,017) for BF% >23.15 in men and 17.2% (178/1,045) for BF% >33.3 in women. This study shows that the NWO, normal BMI, and BF%-based obesity group had a higher prevalence of cardiometabolic risk factors. The prevalence of metabolic syndrome in subjects with NWO was four–fold higher compared to the low BF% group. In addition, Romero-Corral et al. (14) reported that NWO women had a significantly greater (2.2-fold increased) risk of total cardiovascular mortality compared to the low BF group.

In the Quebec Family Study and the Heritage Family Study, Tanaka et al. (10) reported that the ORs of having cardiovascular risk factors were approximately 3.15-fold higher in the high BF% group than in the low BF% group among normal-weight males. A study conducted on 40 Italian women showed that the normal weight, high BF% group had higher mean inflammatory blood indices, such as interleukin (IL)-1α, IL-1β, IL-6, IL-8, and TNF-α, than the normal weight, normal BF% group. High BF% may be a predisposing factor for cardiovascular diseases (30).

The analysis in our study showed that subjects with high BF% have short stature (Table 2), a finding consistent with that of Cho et al. (21). The study on Mexican Population showed that short stature subjects have significantly higher amount of body fat compared to tall stature subjects in the same ethnic group matched for BMI, age, and gender (31). In addition, Bosy-Westphal et al. (32) showed that shorter-than-average adults are at a higher risk for obesity and are more susceptible to diabetes and cardiovascular disease, independent of BMI.

Cho et al. (21) studied 5,543 Korean male adults, and found that the risk of having at least two cardiovascular risk factors was approximately 1.77-fold higher in the high BF% group with a normal weight than in the normal BF% group, which was similar to the adjusted OR (1.63) found in our study. However, Cho et al. (21) included subjects older than 50 years of age and receiving treatment for hypertension, type 2 diabetes mellitus, and/or dyslipidemia in their analysis. The results in the Cho et al. were consistent when subjects without treatment for hypertension, type 2 diabetes mellitus, and/or dyslipidemia. In our study, subjects undergoing treatment for cardiometabolic diseases such as hypertension, DM, and/or dyslipidemia were included and additional analyses were conducted. The results did not cause a significant bias to the results (Table 4). In comparison with the total number of study subjects (12,386), those considered here were comparatively few (790; 600 men and 190 women). When additional analyses were conducted after including research subjects with diseases, the results were as follows: for men, OR = 1.73 (95% CI, 1.29–2.31; $P = 0.002$); and for women, OR = 1.50 (95% CI, 1.33–1.70; $P = 0.004$). These results were similar to the results of the initial analysis from which subjects receiving treatment for cardiometabolic diseases were excluded. As they confirm the strength of the association and the direction of the results of this study according to the sensitivity analysis, the results are considered consistent.

The difference in cardiovascular risk factors is caused by a high BF% as well as excessive local body fat distribution (33). In other words, the location of body fat is as much a risk factor as the absolute quantity. Ito et al. (9) reported that excessive body fat distributed in the upper body increased the risk of hyperlipidemia in both men and women with a normal body weight. In one study, female hormone, estrogen reportedly reduced the risk of cardiovascular disease (34). Thus, further studies will be conducted on the gender-based effect and the difference in body fat distribution with adjustment for more risk factors.

Our study has a few limitations. First, it had a cross-sectional design, and hence no causal relationship and the directionality of the associations can be suggested. However, the association between BF% and cardiovascular diseases risk factors was clear. The findings of our study are consistent with those of numerous previous studies. Second, we used BIA to measure BF%. DEXA is more accurate but is not used commonly in clinical setting because it is expensive and inconvenient. However, previous study reported a good correlation between the BF% results obtained from the two methods (35). Third, the results of our study cannot be generalized to the general population because the subjects were adults only between 30 and 49 years who regularly underwent comprehensive health examinations. Finally, the recall bias caused by information on self-reporting alcohol consumption, smoking, and exercise questionnaires. Also, exercise questionnaires were not validated in our study.

Despite these limitations, our study has some advantages. It included a relatively large number of subjects: 12,386 adult men and women. A further strength is that this study was performed in an Asian population, whereas most others have been conducted on Caucasian populations or small studies of Asian populations. In addition, we simultaneously measured anthropometrics, FPG, cholesterol levels, and blood pressure. Also, lifestyle factors, such as alcohol consumption, smoking, and exercise, were adjusted in the multivariate analyses.

The effect of an increase in BMI and in BF% on the risk of cardiometabolic diseases may follow disparate mechanisms. Consequently, when the results of these two anthropometric measurement indices disagree, different approaches must be taken to decrease the risk factors. BF% measurement in subjects with a normal body weight will provide additional information and allow physicians to determine and reduce their cardiometabolic risk. Additionally, not only in the clinical field but also in public health, care and concern for such population groups are necessary, along with preventive strategies. Thus, prolonged tracking and follow-up research including comparative studies of the incidence and mortality rate of cardiovascular diseases according to body fat and BMI-based obesity are necessary.

Conclusions

In conclusion, high BF% was consistently associated with the cardiometabolic risk factors, such as high blood pressure, hyperglycemia,

and hyperlipidemia, regardless of abdominal obesity in middle-aged, healthy, normal-weight adults. O

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