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Effect of body shape on the development of cardiovascular disease in individuals with metabolically healthy obesity

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Abstract

Studies about the effects of metabolically healthy obesity on cardiovascular disease (CVD) have yielded conflicting results. These heterogeneous results could be due to the limited usefulness of BMI in measuring general adiposity, as body mass index (BMI) does not accurately reflect body composition. This study aimed to evaluate the effect of body shape on CVD outcomes across different obesity phenotypes, and to provide an explanation for the heterogeneous effects of metabolically healthy obese (MHO) phenotype on CVD.

We analyzed data from the Korean Genome and Epidemiology Study, a population-based cohort study conducted between 2001 and 2012. We divided the participants into 4 groups: metabolically healthy non-obese (MHNO), MHO, metabolically unhealthy non-obese (MUNO), and metabolically unhealthy obese (MUO). To assess body shape, we calculated the *z*-score of the log-transformed a body shape index (LBSIZ). We computed Pearson correlation coefficients to examine the association of LBSIZ with muscle mass index, percentage of total fat mass (%Total FM), and percentage of abdominal fat mass (%Abdominal FM). We also used Cox proportional hazards regression to evaluate the effect of LBSIZ on CVD events according to the obesity phenotypes.

A total of 9460 participants were assessed in this study. The incidence of CVD was 8.53 cases per 1000 person-year. LBSIZ showed strong positive correlation with %Total FM and %Abdominal FM, but negative correlation with muscle mass index. In Cox regression, MHO individuals did not show increased risk of CVD compared with MHNO individuals (hazard ratio [HR], 1.29; 95% confidence interval [CI], 0.96–1.73). However, MHO individuals in the 3rd (HR, 2.40; 95% CI, 1.28–4.51) and 4th (HR, 3.67; 95% CI, 1.99–6.74) quarters of LBSIZ showed significantly higher risk of CVD compared with MHNO individuals in the 1st quarter of LBSIZ. Moreover, LBSIZ showed a linear relationship with CVD among MHO individuals.

While the MHO individuals showed similar CVD risk to the MHNO individuals, CVD risk increases with LBSIZ among the MHO individuals. LBSIZ appears to be a useful measure for CVD risk assessment in clinical practice and epidemiologic studies, especially for MHO patients.

Abbreviations: %Abdominal FM = percentage of abdominal fat mass, %Total FM = percentage of total fat mass, ABSI = a body shape index, BMI = body mass index, BP = blood pressure, CI = confidence interval, CVD = cardiovascular diseases, HbA1c = hemoglobin A1c, HDL-C = high dense lipoprotein cholesterol, LBSIZ = z-score of the log-transformed a body shape index, LDL-C = low dense lipoprotein cholesterol, MHNO = metabolically healthy non-obese, MHO = metabolically healthy obese, MUNO = metabolically unhealthy non-obese, MUO = metabolically unhealthy obese, SD = standard deviation, T2DM = Type 2 diabetes, WC = waist circumference.

Keywords: body shape, cardiovascular disease, metabolically healthy obesity

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The data that support the findings of this study are available from a third party, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are available from the authors upon reasonable request and with permission of the third party.

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1. Introduction

Obesity, which is one of the major risk factors contributing to cardiometabolic diseases such as type 2 diabetes (T2DM), cardiovascular disease (CVD), and some cancers, has become a major problem in global health.[1,2] The World Health Organization reported that >650 million adults had obesity, and this prevalence of obesity nearly tripled between 1975 and 2016.[3] This increasing prevalence of obesity is an important factor when considering the known association between obesity and T2DM, CVD, stroke, cancer, and the socioeconomic burden of obesity.[4,5]

However, not all people with obesity have metabolic problems. The metabolic syndrome can arise even in normal-weight individuals.[6,7] On the contrary, a subgroup of overweight or obese individuals has no cardio-metabolic dysfunction.[8] They are known to have a metabolically healthy obesity (MHO) phenotype. This phenotype is the result of the complex interaction between genetic, environmental, dietary, and lifestyle factors.[9,10] However, there are no universally accepted criteria on this novel concept of MHO phenotype. Therefore, the prevalence of the MHO phenotype is reported to be diverse, ranging from 6% to 75%.[11–13] In addition, long-term epidemiologic studies of the effect of MHO on CVD have yielded conflicting results.[14–18] Drawbacks of body mass index (BMI) may be responsible for the heterogeneous CVD risks within MHO individuals. Although BMI is the most widely used measure to define obesity, it does not identify fat distribution and cannot distinguish muscle from fat.[11] Therefore, we focused on the body shape to overcome the limitations of BMI to define obesity. A previous study showed that an index for body shape using waist circumference (WC), weight, and height had a positive linear relationship with CVD events in MHO participants in Korea.[19] However, this previous study was a cross-sectional investigation, and could not assess the causal relationship between body shape and CVD in MHO.

The aim of this study was to assess the effect of body shape on CVD outcomes across different obesity phenotypes from the Korean population-based longitudinal study, and to provide an explanation for the heterogeneous effects of MHO on CVD.

2. Methods

2.1. Study populations

The Korean Genome and Epidemiology Study (KOGES) is a prospective longitudinal study started in 2001. The participants, aged ≥40 years at baseline, were recruited from 2 cohorts from Ansung and Ansan.[20] Ansung is a rural community with approximately 190,000 residents in the Republic of Korea. A total of 5018 participants were recruited from the Ansung area and underwent a baseline health examination at the Ajou University Medical Center. Ansan is an urban community with approximately 693,000 residents. A total of 5020 participants were recruited from Ansan and underwent a baseline health examination at the Korea University Ansan Hospital. Follow-up examinations were conducted biennially.[20] The 2 cohort studies shared the core questionnaire, physical examinations, and laboratory tests during the baseline and follow-up phases. Trained interviewers conducted the survey using a structured questionnaire regarding socio-demographic status; lifestyle including smoking, drinking, and physical activity; personal medical history; and dietary information. Anthropometric measurements and laboratory tests were also conducted, including height, weight, WC, and blood pressure (BP). Biochemical analyses included blood sugar and lipid profiles. Detailed information about KOGES has been provided in previous studies.[21,22] We used the 10-year follow-up data from 2001 to 2012. Among 10,030 participant in KoGES, 9460 were assessed in our study, excluding those with a history of CVD, those with cancer at baseline, and those who had received steroids or anticoagulants (Fig. 1).

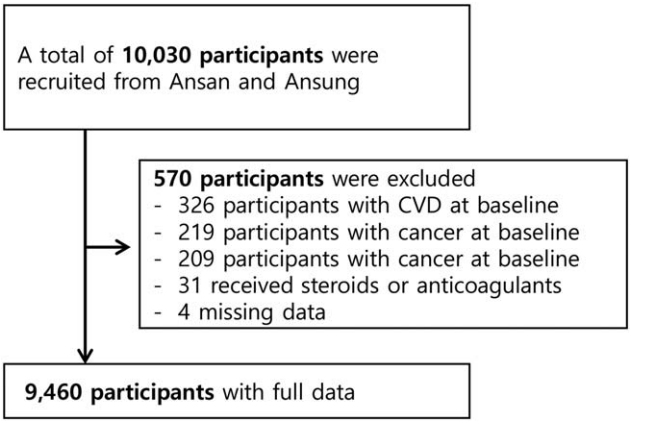

Figure 1. Flow chart of the final cohort selection.

2.2. Measurements

Demographic information and life style data including physical activity, alcohol consumption, and smoking status, as well as personal medical histories were investigated using biennial questionnaires. The details of the questionnaire are as follow:

Physical activity: Average duration of high intensity physical activity per day.
Alcohol consumption: Did you ever drink alcohol? Do you currently drink alcohol?
Smoking status: Have you smoked >5 packs of cigarettes (100 cigarettes) in your entire life? Do you currently smoke cigarettes?
Personal medical history: Have you ever been told by a health professional that you had one of the following diseases? (Hypertension, diabetes mellitus, any type of cancer, angina/myocardial infarction, coronary heart disease, congestive heart failure, peripheral arterial disease, or cerebrovascular disease).

We defined as physically active the participants undertaking at least 30 minutes per day of high-intensity physical activity. Participants were classified into never smokers, former smokers, and current smokers according to smoking status; and never drinkers, former drinkers, and current drinkers according to alcohol consumption. A CVD event was defined as at least one of the following: coronary heart disease, myocardial infarction, congestive heart failure, peripheral arterial disease, and cerebrovascular disease. Trained technicians measured weight, height, WC, and BP using standardized measurement techniques. WC was measured at the narrowest point between the rib cage and iliac crest in an upright position at the end of normal expiration. After at least 5 minutes of rest, trained technicians measured BP in the sitting position. Muscle mass, percentage of total fat mass (% Total FM), and percentage of abdominal fat mass (%Abdominal FM) were measured by bioelectrical impedance analysis using the

body composition analyzer ZEUS 9.9 (Jawon Medical Co., Ltd., Kungsang Bukdo, Republic of Korea). The muscle mass index was defined as muscle mass (kg) divided by the squared height (m^2), and the fat mass index as the fat mass (kg) divided by squared height (m^2). Blood samples were obtained after overnight fasting for at least 8 hours. The ADVIA 1650 chemistry analyzer (Bayer HealthCare Ltd., Tarrytown, NY) was used for biochemical assays such as plasma glucose, total cholesterol, triglycerides, and high-density lipoprotein cholesterol (HDL-C). The Friedewald equation was used to calculate the low-density lipoprotein cholesterol (LDL-C) level.

2.3. Definitions of metabolic health and body shape index

BMI was calculated as kg/m^2 at enrollment. Obesity was defined using the Asia-Pacific BMI criteria[23]: normal weight (BMI ≥18 and <23 kg/m^2) and overweight (BMI ≥23 and <25 kg/m^2) individuals were classified as non-obese, and those with BMI ≥25 kg/m^2 as obese. To define a metabolically healthy status, we used the metabolic syndrome diagnostic criteria based on the Adult Treatment Panel-III (ATP-III). Metabolic abnormality was defined as ≥2 of the following conditions: impaired fasting glucose level (fasting plasma glucose level ≥100 mg/dL or on treatment for DM), high BP (a systolic BP ≥130 mmHg and/or a diastolic BP ≥85 mmHg, or on antihypertensive treatment), high triglycerides (triglycerides ≥150 mg/dL), and low HDL-C (HDL-C < 40 mg/dL in men and <50 mg/dL in women). The criterion for central obesity was not used to avoid its collinearity with BMI. The participants were divided into the following 4 obesity phenotypes according to the criteria for obesity and metabolic abnormality: metabolically healthy non-obese (MHNO); metabolically healthy obese (MHO); metabolically unhealthy non-obese (MUNO); and metabolically unhealthy obese (MUO). The MHNO group was used as the reference in the analysis.

2.4. Calculation of the z-score of the log-transformed a body shape index

We used the *z*-score of the log-transformed a body shape index (LBSIZ), a modified a body shape index (ABSI), to assess the body shape. The recently introduced ABSI is calculated with a formula based on WC, height, and weight, but has limited usefulness because it does not reflect sex or ethnic differences, and does not specify the cut-off points for identifying individuals at higher risk for obesity-related diseases.[24,25]

We calculated the LBSIZ in 2 steps. In the first step, we used the log–log regression of WC on both weight and height using the equation [$\ln(WC) = a_0 + a_1 \ln(\text{weight}) + a_2 \ln(\text{height}) + \delta$], where the scaling exponents (a_0, a_1, and a_2) were estimated to calculate the log-transformed ABSI: the log-transformed ABSI = log [WC/(exp (a_0) × weight^{a1} × height^{a2}]. In the second step, we calculated LBSIZ using the mean of the log-transformed ABSI and its standard deviation (SD): LBSIZ = (the log-transformed ABSI-mean [the log-transformed ABSI])/SD [the log-transformed ABSI]).[25,26] The respective calculations using representative samples both from Korea and the United States were made in previous studies, utilizing therein provided supplementary Excel templates.[25,26]

2.5. Statistical analysis

Summary values were expressed as mean and SD or prevalence (%) according to CVD events. We performed multiple imputations of the missing data. To compare each variable by CVD events, one-way analysis of variance was used for continuous variables and the Pearson chi-squared test for categorical variables. We computed the Pearson correlation coefficient to examine the correlation of LBSIZ with muscle mass index, %Total FM, and %Abdominal FM. We used Cox proportional hazards regression to evaluate the hazard ratio (HR) for CVD events of each obesity phenotype. In the secondary analysis, we divided the LBSIZ into quartiles (1st quartile: ≤–0.74; 2nd quartile: >–0.74 and ≤–0.07; 3rd quartile: >–0.07 and ≤0.68; 4th quartile: >0.68) and examined the HR for CVD events of each LBSIZ quarter according to the obesity phenotypes. Restricted cubic spline plots with 4 knots were used to evaluate the graphical relationships between LBSIZ and CVD events according to obesity phenotypes. All statistical analyses were carried out using the SPSS software (version 21.0, IBM, Armonk, NY) and the R statistical environment (R version 3.5.2, 2018, www.r-project.org). Two-sided *P* value <.05 was considered statistically significant for all analyses.

2.6. Ethics statement

The study protocol was approved by the institutional review board of the Gwangju Institute of Science and Technology (IRB No. 20200414-EX-01-02). All participants volunteered and provided written informed consent prior to their enrolment. All participants' records were anonymized before being accessed by the authors.

3. Results

3.1. Baseline characteristics

A total of 9460 participants (mean age, 52.1 years; 4528 men and 4932 women) were assessed in this cohort study. Among them, 597 (6.3%) had a new CVD event during the 10 years of follow-up. The incidence of CVD was 8.53 cases per 1000 person-year. The 4 groups' anthropometric, clinical, and biochemical characteristics are shown in Table 1. Compared with MHNO individuals, MHO individuals were more often women and had higher BMI (26.6 kg/m^2 vs 22.5 kg/m^2, $P < .01$) and lower LBSIZ (–0.27 vs –0.20, $P = .03$). Participants in both metabolically unhealthy groups (MUNO and MUO) were likely to be older, had higher LBSIZ, and higher prevalence of prehypertension, prediabetes, abnormality in lipid profiles, including triglycerides and HDL-C, and CVD showing worse metabolic parameters than those in the healthy groups (MHNO and MHO). Within the metabolically unhealthy group, the prevalence of CVD was higher among participants with prehypertension (8.2% vs 11.7%, $P < .01$) or prediabetes (6.8% vs 10.6%, $P < .01$) than that among those without. There was no difference in the prevalence of CVD according to abnormalities in triglycerides or HDL-C in the metabolically unhealthy group.

3.2. Correlation of LBSIZ with body composition

LBSIZ, WC, and BMI showed a strong positive correlation with %Total FM and %Abdominal FM (Table 2). However, while both WC and BMI showed a positive correlation with muscle mass index, LBSIZ showed a negative correlation with muscle mass index. Results from its subgroup analysis according to sex and obesity phenotype were summarized in Table 2.

Table 1

Characteristics of subjects according to obesity and metabolic health status.

Variables	Metabolically healthy		Metabolically unhealthy		*P*-value
	Without obesity (MHNO) (N = 3395)	Obesity (MHO) (N = 1463)	Without obesity (MUNO) (N = 2016)	Obesity (MUO) (N = 2528)	
Age, yr	50.6 ± 8.8	49.9 ± 8.0	54.7 ± 9.1	53.1 ± 8.6	<.001
Men, N	1721 (50.7%)	633 (43.3%)	1018 (50.5%)	1127 (44.4%)	<.001
Smoking, N					<.001
Never smoker	1883 (56.1%)	927 (64.2%)	1104 (55.4%)	1523 (61.0%)	
Former smoker	477 (14.2%)	226 (15.6%)	327 (16.4%)	389 (15.6%)	
Current smoker	994 (29.6%)	292 (20.2%)	560 (28.1%)	583 (23.4%)	
Alcohol, N					<.001
Never drinker	1466 (43.5%)	623 (42.9%)	932 (46.7%)	1265 (50.4%)	
Former drinker	194 (5.8%)	83 (5.7%)	140 (7.0%)	168 (6.7%)	
Current drinker	1709 (50.7%)	747 (51.4%)	924 (46.3%)	1075 (42.9%)	
Physical activity (≥30 min per day), N	1271 (38.7%)	570 (40.0%)	695 (35.4%)	842 (34.2%)	<.001
BMI	22.2 ± 1.9	27.1 ± 1.9	22.9 ± 1.6	27.6 ± 2.2	<.001
Waist circumference	76.5 ± 6.7	86.5 ± 6.9	80.7 ± 6.6	90.1 ± 6.8	<.001
LBISZ	−0.20 ± 1.04	−0.27 ± 0.91	0.30 ± 1.00	0.13 ± 0.90	<.001
Muscle mass index	16.0 ± 1.5	17.7 ± 1.5	16.2 ± 1.4	17.9 ± 1.6	<.001
%Total FM	23.4 ± 6.4	30.4 ± 6.4	25.1 ± 5.9	30.9 ± 6.3	<.001
%Abdominal FM	0.87 ± 0.03	0.93 ± 0.04	0.89 ± 0.03	0.94 ± 0.04	<.001
Systolic BP, mmHg	113.8 ± 15.4	116.0 ± 14.7	127.7 ± 19.1	129.9 ± 18.2	<.001
Diastolic BP, mmHg	75.3 ± 9.8	77.9 ± 9.8	83.4 ± 11.4	85.7 ± 11.2	<.001
Hypertension	381 (11.2%)	226 (15.4%)	950 (47.1%)	1422 (56.0%)	<.001
Fasting glucose, mg/dL	82.1 ± 12.1	83.7 ± 10.5	91.6 ± 29.9	93.2 ± 26.0	<.001
HbA1c, %	5.5 ± 0.5	5.6 ± 0.5	6.0 ± 1.3	6.1 ± 1.1	<.001
Diabetes mellitus	65 (1.9%)	27 (1.8%)	423 (21.0%)	615 (24.2%)	<.001
Total cholesterol, mg/dL	183.5 ± 33.3	193.9 ± 34.9	190.8 ± 37.9	199.3 ± 35.9	<.001
HDL-C, mg/dL	49.6 ± 10.1	47.5 ± 9.4	40.8 ± 8.6	39.5 ± 7.4	<.001
Triglycerides, mg/dL	110.2 ± 44.5	121.8 ± 52.7	206.2 ± 116.8	220.2 ± 128.8	<.001
LDL-C, mg/dL	112.0 ± 30.3	122.2 ± 31.0	111.3 ± 34.3	118.9 ± 32.5	.097
Metabolic state, N					
High BP	547 (16.1%)	282 (19.3%)	1251 (62.1%)	1769 (69.7%)	<.001
Hyperglycemia	111 (3.3%)	52 (3.6%)	577 (28.6%)	809 (31.9%)	<.001
Low HDL-C	1011 (29.8%)	540 (36.9%)	1513 (75.0%)	2047 (80.7%)	<.001
High triglycerides	283 (8.3%)	187 (12.8%)	1485 (73.7%)	1946 (76.7%)	<.001
CVD events, N	142 (4.7%)	71 (5.4%)	163 (9.0%)	217 (9.5%)	<.001

Data were presented as the means (±standard deviation) or numbers (%).

BMI = body mass index, BP = blood pressure, CVD = cardiovascular diseases, HbA1c = hemoglobin A1c, HDL-C = high dense lipoprotein cholesterol, LBSIZ = z-score of the log-transformed a body shape index, LDL-C = low dense lipoprotein cholesterol, MHNO = metabolically healthy non-obese, MHO = metabolically healthy obese, MUNO = metabolically unhealthy non-obese, MUO = metabolically unhealthy obese, N = number.

3.3. Risk for CVD events of each obesity phenotype

During the 10-year follow-up period, 597 CVD events occurred among the participants. Table 3 shows the HRs of CVD according to the obesity phenotypes. In the multivariate Cox regression model adjusted for age, sex, and other covariates including smoking status, alcohol consumption, physical activity, LDL cholesterol, and medication for dyslipidemia, the MHO group did not have an increased risk for CVD compared with the MHNO group (HR, 1.29; 95% confidence interval [CI], 0.96–1.73). The metabolically unhealthy participants showed significantly higher risk of CVD (MUNO: HR, 1.46; 95% CI, 1.15–1.85 and MUO: HR, 1.82; 95% CI, 1.45–2.27, Table 3). Similar results were shown in the analysis of the 5 datasets with imputation for missing data (Supplementary Table 1, http://links.lww.com/MD/E872).

3.4. Association of LBSIZ and CVD events according to the obesity phenotypes

Figure 2 shows the Kaplan–Meier survival curves of MHO participants. The secondary analysis showed a significantly higher incidence of CVD events in MHO participants with the higher LBSIZ values ($P < .01$; Fig. 2). In the multivariate analysis, the MHO participants in the 3rd and 4th quarters of LBSIZ showed a significantly higher HR compared with the MHNO participants in the 1st quarter of LBSIZ. It is notable, however, that the MHO participants in the 1st and 2nd quarters of LBSIZ did not show significantly higher HRs compared with the MHNO participants in the 1st quarter of LBSIZ (Table 4). A similar steady increase of the HR was also shown with LBSIZ within the MUO group, and the results remain the same in the further analysis of 5 datasets with imputation for missing data (Supplementary Table 2, http://links.lww.com/MD/E873). The restricted cubic spline regression plot showed that the risk of CVD events increased linearly with LBISZ, regardless of metabolic abnormality and obesity (Fig. 3).

4. Discussion

In this long-term follow-up cohort study of 9460 individuals, we assessed the risk of CVD according to the metabolic phenotypes and body shape. We found that the unhealthy metabolic groups

Table 2

Correlation of LBSIZ with body composition.

	Correlation coefficients		
	Muscle mass index	%Total FM	%Abdominal FM
LBSIZ			
Total	–0.07**	0.09**	0.18**
Men	–0.14**	0.24**	0.25**
Women	–0.04*	0.04*	0.14**
Obesity phenotype			
MHNO	–0.12**	0.08**	0.22**
MHO	–0.01	0.05	0.21**
MUNO	–0.12**	0.12**	0.22**
MUO	–0.11**	0.06**	0.12**
Waist circumference			
Total	0.58**	0.36**	0.68**
Men	0.67**	0.72**	0.74**
Women	0.59**	0.62**	0.68**
Obesity phenotype			
MHNO	0.46**	0.09**	0.48**
MHO	0.39**	0.04	0.46**
MUNO	0.40**	0.09**	0.39**
MUO	0.33**	0.14**	0.46**
BMI			
Total	0.62**	0.61**	0.79**
Men	0.86**	0.74**	0.78**
Women	0.82**	0.80**	0.80**
Obesity phenotype			
MHNO	0.52**	0.45**	0.54**
MHO	0.26**	0.46**	0.68**
MUNO	0.51**	0.34**	0.47**
MUO	0.33**	0.48**	0.70**

%Abdominal FM = percentage of abdominal fat mass, %Total FM = percentage of total fat mass, LBSIZ = z-score of the log-transformed a body shape index, MHNO = metabolically healthy non-obese, MHO = metabolically healthy obese, MUNO = metabolically unhealthy non-obese, MUO = metabolically unhealthy obese.

* $P < .05$.

** $P < .001$.

Table 3

Hazard ratios for CVD events according to obesity phenotype.

Groups	HR (95% CI)
MHNO	Reference
MHO	1.29 (0.96–1.73)
MUNO	1.46 (1.15–1.85)
MUO	1.82 (1.45–2.27)

Adjusted for age, sex, alcohol consumption, smoking status, physical activity, low-density lipoprotein cholesterol, and medication for dyslipidemia.

CI = confidential interval, HR = hazard ratios, MHNO = metabolically healthy non-obese, MHO = metabolically healthy obese, MUNO = metabolically unhealthy non-obese, MUO = metabolically unhealthy obese.

(MUO and MUNO individuals) had a significantly higher risk of CVD than the MHNO group.

Meanwhile, CVD risk in the MHO group was not significantly higher than that in the MHNO group. When we further analyzed the CVD risk using a body shape measure of LBSIZ, the MHO participants in the higher quarters of LBSIZ showed worse prognosis than the MHNO participants in the first quarter of LBSIZ. The MHO participants in the lower quarters of LBSIZ, however, showed similar risks, despite the presence of BMI-defined obesity.

A number of studies reported that MHO individuals showed inconsistent CVD outcomes.[16,19] An observational study by Hamer and Stamatakis,[14] who analyzed the clinical outcomes after a follow-up longer than 7 years of 22,203 subjects without CVD, reported that MHO did not increase the risk of all-cause or cardiovascular mortality. A population-based longitudinal cohort study (Multi-Ethnic Study of Atherosclerosis [MESA]) in the United States reported that MHO was not significantly associated with CVD development.[15] However, in another

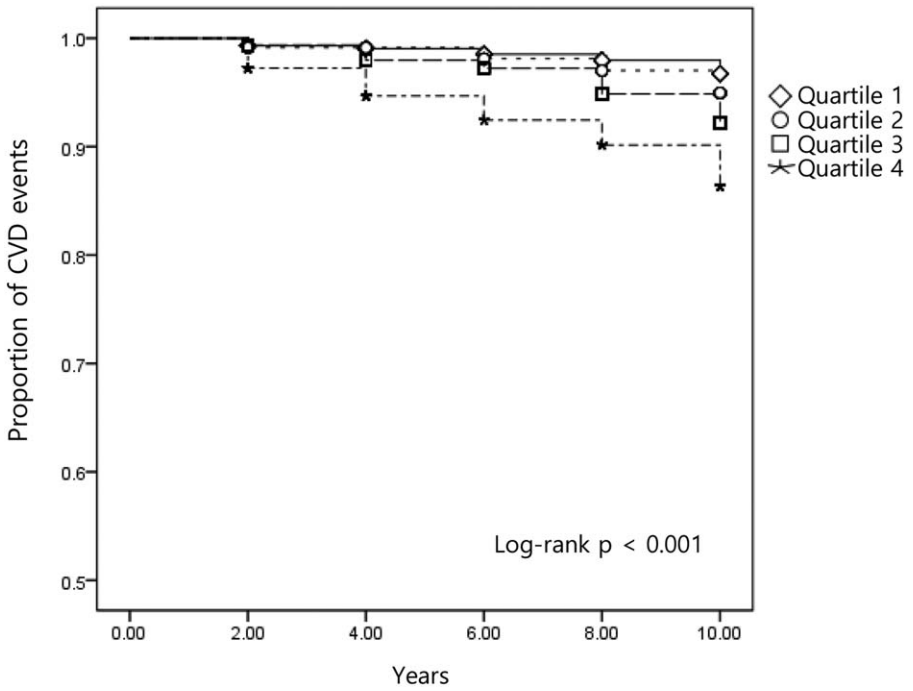

Figure 2. Kaplan–Meier curves of cardiovascular disease events in MHO participants according to LBSIZ quartiles. LBSIZ = z-score of the log-transformed a body shape index; MHO = metabolically healthy obese.

Table 4

Hazard ratio (95% confidence interval) for cardiovascular events by obesity phenotype and quartile of LBSIZ.

Groups	MHNO HR (95% CI)	MHO HR (95% CI)	MUNO HR (95% CI)	MUO HR (95% CI)
Quartile 1	Reference	1.50 (0.72–3.09)	3.11 (1.66–5.83)	1.95 (0.99–3.84)
Quartile 2	1.54 (0.86–2.76)	1.95 (0.98–3.90)	2.20 (1.17–4.13)	2.73 (1.56–4.77)
Quartile 3	2.92 (1.72–4.96)	2.40 (1.28–4.51)	3.61 (2.12–6.17)	3.30 (1.95–5.58)
Quartile 4	1.89 (1.07–3.35)	3.67 (1.99–6.74)	2.41 (1.41–4.11)	4.46 (2.68–7.41)

Adjusted for age, sex, alcohol consumption, smoking status, physical activity, low-density lipoprotein cholesterol, and medication for dyslipidemia.
CI = confidential interval, HR = hazard ratios, LBSIZ = z-score of the log-transformed A Body Shape Index, MHNO = metabolically healthy non-obese, MHO = metabolically healthy obese, MUNO = metabolically unhealthy non-obese, MUO = metabolically unhealthy obese.

population-based longitudinal cohort study (HUNT study, Norway), MHO individuals developed metabolic risk factors during follow-up[27] and had increased risk for heart failure (HF)[16] and atrial fibrillation.[17] An electronic health record-based study involving 3.5 million people reported that MHO individuals had a higher risk of coronary artery disease, CVD, and HF.[18] A recent meta-analysis of 19 studies reported that individuals with MHO were at a high risk of CVD. However, 9 out of the 19 studies included in meta-analysis did not produce statistically significant results.[28]

Our study showed no significantly higher CVD risk for the MHO group compared with the MHNO group. However, further analysis with LBSIZ provided a consistent result with the previous cross-sectional study[19] that CVD risk increases with LBSIZ among the MHO group. These results clearly show the limited usefulness of BMI in measuring general adiposity as BMI does not accurately reflect abdominal fat mass and body composition.[29] It is also crucial to note the separate role of muscle mass because numerous epidemiological studies have found that sarcopenia, a state of decreased muscle mass, is associated with insulin resistance,[30] T2DM,[31] increased risk of CVD-related mortality, and all-cause mortality.[32–34] Given that sarcopenia and obesity are both factors associated with metabolic disorders, morbidity, and mortality,[35] it was previously suggested that the presence of sarcopenic obesity exacerbated the risk of CVD.[36,37] A number of studies reported sarcopenic obesity to be associated with hyperglycemia, hypertension, dyslipidemia, insulin resistance, and all-cause mortality.[38–40] Such studies illustrate the need of taking into account muscle mass measurements when defining normal weight and obesity. Since the BMI is positively correlated with both muscle mass and fat mass, without distinguishing between them,[25,41–43] it has clear limitations as an identifier of sarcopenic obesity. For example, a person with excessive visceral fat and insufficient muscle mass can have a normal BMI yet harbor a higher mortality risk.[44] Interestingly, recent studies found an association of ABSI and LBSIZ with sarcopenic obesity.[25,26,41,42,43] Our study also showed similar associations, namely that LBSIZ had a positive association with fat mass, and a negative association with muscle mass. Considering the fact that a high LBSIZ value means that an individual has a high proportion of abdominal fat and relatively little muscle mass, this result implies that LBSIZ, by overcoming the limitations of BMI, is a useful parameter to identify individuals at high risk of CVD in the MHO group.

Although both MUO and MUNO individuals are unhealthy, MUO group showed higher risk of CVD than MUNO group. However, this difference was not statistically significant. This "insignificance" can be explained by LBSIZ grouping. Further analysis with LBSIZ showed that CVD risk increased with LBSIZ among the patients in the MUO group, which has a pattern similar to that with patients in the MHO group. Surprisingly, although average CVD risk of MUO is higher than the average CVD risk of MUNO, MUO with the first quartile of LBSIZ did not show significantly higher CVD risk than MHNO group with the first quartile of LBSIZ. This suggests that we must analyze the

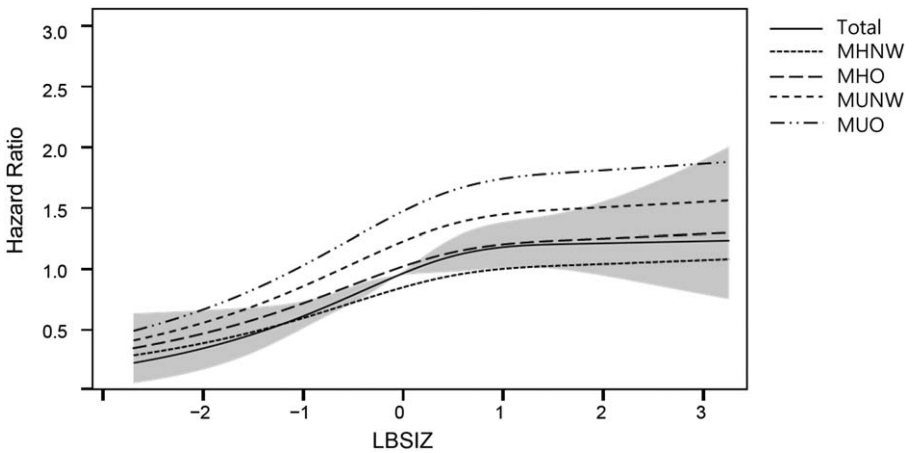

Figure 3. Relationship between LBSIZ and the hazard ratio for cardiovascular events according to obesity phenotypes. Restricted cubic spline plot with 4 knots using Cox proportional hazards regression analysis adjusted for age, sex, alcohol consumption, smoking status, physical activity, low-density lipoprotein cholesterol level, and medication for dyslipidemia. LBSIZ = z-score of the log-transformed a body shape index.

body shape of Korean adults with obesity to determine whether they have metabolic abnormalities.

Our study is the first longitudinal study to investigate the association between LBISZ and CVD events according to obesity phenotypes with a large sample. Our findings might provide one explanation for the heterogeneous results produced by previous studies with respect to the risk of developing CVD in MHO. However, this study has limitations. First, this study might have selection bias because the cohort only included Koreans aged ≥40 years at baseline. Second, there could be selective survival bias because fatal CVD events may have been missed as we did not assess the mortality data. In addition, the competing risk, including non-cardiovascular death, was not considered in this study. Third, the study had a measurement bias on the assessment of body composition because bioelectrical impedance analysis is not the gold standard for measurement. Owing to the lack of abdominal CT or dual-energy x-ray absorptiometry data, we could not accurately analyze fat mass or body fat composition. Further studies are warranted on whether LBSIZ reflects real visceral fat mass or appendicular muscle mass.

In conclusion, while the MHO group showed similar CVD risk to the MHNO group, CVD risk increases with LBSIZ among the MHO group. LBSIZ appears to be a useful measure for CVD risk assessment in clinical practice and epidemiologic studies, especially for MHO patients.

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Author contributions

Shinje Moon and Jun Goo Kang conceived of and designed the study; all authors participated in the acquisition, analysis, or interpretation of data; Jung Hwan Park, Chang-Myung Oh, and Shinje Moon drafted the manuscript; Shinje Moon, Wankyo Chung and Jun Goo Kang reviewed and edited the manuscript; Shinje Moon, Chang-Myung Oh, and Jung Hwan Park had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis; Shinje Moon, Wankyo Chung and Jun Goo Kang performed the formal analysis; Shinje Moon and Chang-Myung Oh obtained funding; Hye Soo Chung and Jae Myung Yu provided study supervision.

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