Original Article



Association of Z–Score of the Log–Transformed A Body Shape Index with Cardiovascular Disease in People Who Are Obese but Metabolically Healthy: The Korea National Health and Nutrition Examination Survey 2007–2010

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Background: We aimed at evaluating the effect of the z-score of the log-transformed A Body Shape Index (LB-SIZ) on cardiovascular disease (CVD) outcomes according to obesity phenotype.

Methods: Data were collected from the Korea National Health and Nutrition Examination Survey conducted from 2007 to 2010. Obesity was defined as a body mass index above 25 kg/m² and metabolic abnormality was defined as the presence of two or more metabolic risk factors of the Adult Treatment Panel III definition. The participants were classified by obesity and metabolic healthy status: metabolically healthy non-obese (MHNO), metabolically healthy obese (MHO), metabolically unhealthy non-obese (MUNO), and metabolically unhealthy obese (MUO). Each group was further classified into three groups based on the tertile of LBSIZ. A multivariate logistic regression analysis with adjustment for age, sex, smoking status, income, education level, physical activities, alcohol, and energy intake was conducted to evaluate the odds ratio (OR) for CVD events.

Results: In the multivariate logistic regression model, MHO participants who are within the third tertile of LBSIZ had a significantly higher OR for CVD events, whereas those who are within the first and second tertile of LBSIZ were not at high risk of developing CVDs compared to MHNO participants who are within the first tertile of LB-SIZ. In addition, a similar increase in the OR was observed in MUNO or MUO participants.

Conclusion: LBSIZ had the lowest risk for CVDs in the first tertile of LBSIZ and a linear relationship with all its tertiles in MHO, MUNO, and MUO participants.

Key words: Obesity, Metabolically benign, Body mass index, Body constitution, Cardiovascular disease

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INTRODUCTION

The World Health Organization (WHO) reported that 13% of the world's adult population were obese (body mass index [BMI] \geq 30 kg/m²) in 2016 and the worldwide prevalence of obesity was nearly tripled between 1975 and 2016.¹ According to the Korea National Health and Nutrition Examination Survey (KNHANES), the prevalence of obesity with a BMI \geq 25 kg/m² in Korean adults increased from 25.8% in 1998 to 31.5% in 2014.² This increase is particularly significant when the association between obesity and poor clinical outcomes, such as type 2 diabetes mellitus (T2DM), cardiovascular diseases (CVDs), stroke, and mortality, is considered.^{1,3-6} However, obese individuals do not always have metabolic dysfunction. This type of obesity is referred to as metabolically healthy obesity phenotype. Although, by definition, individuals with metabolically healthy obesity are metabolically healthy, the

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clinical outcomes of this condition remain controversial. Hamer and Stamatakis⁷ have conducted a 7-year observational study involving 22,203 participants without CVD, and failed to show the association between metabolically healthy obesity and the risk for CVD or all-cause mortality. In addition, several observational studies have shown that metabolically healthy obesity did not increase the risk for coronary atherosclerosis⁸ and heart failure.⁹ On the other hand, several large-scale population-based studies have reported that metabolically healthy obesity is considered as a significant risk factor for CVDs.^{10,11} The differences in these results suggest that metabolically healthy obesity phenotype represents a heterogeneous group. Therefore, the key factors that determine poor clinical outcomes in individuals with metabolically healthy obesity must be investigated.

In the present study, we focused on the drawback of BMI as a key factor for the heterogeneous prognosis. BMI cannot distinguish between muscle and fat, and it cannot accurately predict the percentage of body fat.¹² In addition, several epidemiological studies have reported the limitations of BMI in predicting the risk of heart attack, stroke, and death.¹³⁻¹⁵ To overcome this, Krakauer and Krakauer¹⁶ developed A Body Shape Index (ABSI), a new equations for estimating body shape using waist circumference (WC), weight, and height in the U.S. population. However, there have been few studies to examine the usefulness of ABSI in the other ethnic group. Therefore, we used the z-score of the log-transformed A Body Shape Index (LBSIZ) to control for age, sex, and ethnic differences.¹⁷ This study aimed at assessing the effect of body shape index on CVD outcomes according to obesity phenotype in a representative sample of the Korean population.

METHODS

Study population

Data were collected from the KNHANES conducted from 2007 to 2010. The surveys were cross-sectional and nationally representative with a multistage and stratified sample design. In total, 33,829 individuals were included in the study. Participants with missing data or those under 20 years of age were excluded. The total number of eligible participants was 21,948 (Fig. 1).





Clinical and laboratory measurements

WC was measured at the midpoint between the lowest border of the rib cage and the upper lateral border of the iliac crest at the end of normal expiration. Blood pressure (BP) was measured three times while the patient is in a sitting position after at least 5 minutes of rest. An average of three recorded BP measurements was used. After an 8-hour overnight fasting, triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and glucose levels were measured using ADVIA 1650 (Siemens, Washington, DC, USA) in 2007 and Hitachi Automatic Analyzer 7600 (Hitachi, Tokyo, Japan) from 2008 to 2010. We used the revised HDL-C values between 2007 and 2010 according to the Korea Centers for Disease Control and Prevention (KCDC) guidelines for consistency in each survey.^{18,19}

Measurement of obesity

In the present study, obesity was defined as a BMI above 25 kg/m² based on the Asia-Pacific BMI criteria by the WHO Western Pacific Region.²⁰ Because of the lack of a standard definition for metabolic health and obesity²¹, we used the National Cholesterol Education Program–Adult Treatment Panel III (NCEP–ATP III) criteria for metabolic syndrome, which is the most frequently used definition in recent studies.²¹⁻²⁷ Briefly, metabolic health was defined as ≤ 1 of the following NCEP–ATP III criteria, including impaired fasting glucose level (at least 100 mg/dL), hypertension (a systolic BP above 130 mmHg and/or a diastolic BP above 85 mmHg or the use of antihypertensive drugs), TG level of at least 150 mg/dL, and a low level of HDL-C (40 mg/dL in men and 50 mg/dL in women). Due to the collinearity between BMI and WC, the central obesity criterion was not used. The participants were classified based on these criteria: metabolically healthy non-obese (MHNO),

metabolically healthy obese (MHO), metabolically unhealthy nonobese (MUNO), and metabolically unhealthy obese (MUO).

ABSI is calculated using the following equation¹⁶:

 $ABSI = WC \times weight^{-2/3} \times height^{5/6} = WC / (BMI^{2/3} \times height^{1/2})$

However, because of its statistical limitations in terms of skewness and symmetry, the z-score of the log-transformed ABSI was used. The detailed equation used for the calculation of LBSIZ was described in our previous study.¹⁷

Statistical analysis

Summary statistics are presented as mean and standard deviation or prevalence (%). One-way analysis of variance and the Pearson chisquare test were used to compare each variable according to obesity phenotypes. A multivariate logistic regression analysis with adjustment for age, sex, smoking status, income, education level physical activities, alcohol, and energy intake was carried out to evaluate the odds ratio (OR) and 95% confidence interval (CI) for CVD events according to obesity phenotype and LBSIZ. The graphical relation-

Table 1. Characteristics of the participants according to obesity phenotypes

ships were also evaluated with restricted cubic spline plots with three knots according to obesity phenotypes. Analyses were performed using IBM SPSS version 24.0 (IBM Corp., Armonk, NY, USA) and the statistical program R (R version 3.1.0, 2014; https://www.r-project.org). A *P*-value of 0.05 was considered statistically significant.

Ethical considerations

The study protocol was approved by the Institutional Review Board of the KCDC (2007-02CON-04-P, 2008-04EXP-01-C, 2009-01CON-03-2C, 2010-02CON21-C). Written informed consent was obtained from each study participant prior to the survey.

RESULTS

Baseline characteristics of the participants

The data of 21,948 participants were assessed. The general characteristics of the participants according to obesity phenotypes are summarized in Table 1.

| Variable | MHNO (n=10,134) | MHO (n=2,665) | MUNO (n=4,822) | MUO (n=4,327) | Р |
|---------------------------|------------------|------------------|------------------|-------------------|---------|
| Male sex | 3,766 (37.2) | 1,235 (46.3) | 2,301 (47.7) | 2,093 (48.4) | < 0.001 |
| Age (yr) | 43.7±15.4 | 45.7 ± 14.6 | 57.8±14.7 | 54.4 ± 14.2 | < 0.001 |
| CVD events* | 193 (1.9) | 78 (2.9) | 334 (6.9) | 278 (6.4) | < 0.001 |
| Smoking | 3,801 (37.5) | 1,144 (42.9) | 2,235 (46.4) | 1,967 (45.5) | < 0.001 |
| BMI (kg/m²) | 21.6±2.1 | 27.1±2.0 | 22.6±1.8 | 27.6±2.4 | < 0.001 |
| Waist circumference (cm) | 75.2±7.2 | 89.0 ± 7.1 | 80.8 ± 6.9 | 92.0 ± 7.0 | < 0.001 |
| LBSIZ | -0.2 ± 1.0 | -0.2 ± 1.0 | 0.4 ± 1.0 | 0.1 ± 0.9 | < 0.001 |
| Systolic BP (mmHg) | 109.6±13.9 | 115.3 ± 14.1 | 126.1±18.2 | 127.1±16.6 | < 0.001 |
| Diastolic BP (mmHg) | 71.1±9.2 | 75.2±9.2 | 78.1±10.8 | 80.8 ± 10.4 | < 0.001 |
| FBG level (mg/dL) | 89.8±11.9 | 92.7±13.5 | 106.6 ± 30.8 | 109.0 ± 29.2 | < 0.001 |
| HbA1c (%) | 7.1±1.8 | 7.0 ± 1.3 | 7.4±1.6 | 7.3 ± 1.4 | 0.120 |
| Total cholesterol (mg/dL) | 180.0 ± 32.8 | 193.7 ± 35.7 | 192.7 ± 38.1 | 198.0 ± 37.6 | < 0.001 |
| HDL-C (mg/dL) | 52.7 ± 10.4 | 49.6 ± 9.4 | 42.9±9.2 | 41.7±8.4 | < 0.001 |
| TG (mg/dL) | 87.8±45.2 | 107.3±57.8 | 184.8±131.1 | 201.8 ± 135.5 | < 0.001 |
| Metabolic state | | | | | |
| Central obesity | 1,252 (12.4) | 1,894 (71.1) | 1,403 (29.1) | 3,544 (81.9) | < 0.001 |
| High BP | 1,210 (11.9) | 529 (19.8) | 3,110 (64.5) | 3,037 (70.2) | < 0.001 |
| Hyperglycemia | 710 (7.0) | 268 (10.1) | 2,520 (52.3) | 2,482 (57.4) | < 0.001 |
| Low HDL-C level | 2,607 (25.7) | 755 (28.3) | 3,484 (72.3) | 3,170 (73.3) | < 0.001 |
| High TG level | 521 (5.1) | 247 (9.3) | 2,783 (57.7) | 2,800 (64.7) | < 0.001 |

Values are presented as number (%) or mean ± standard deviation.

*Participants who had either myocardial infarction, coronary heart disease, congestive heart failure, cerebrovascular disease, or peripheral arterial disease.

MHNO, metabolically healthy non-obese; MHO, metabolically healthy obese; MUNO, metabolically unhealthy non-obese; MUO, metabolically unhealthy obese; CVD, cardiovascular disease; BMI, body mass index; LBSIZ, z-score of the log-transformed A Body Shape Index; BP, blood pressure; FBG, fasting blood glucose; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride.

Association between obesity phenotypes and risk of CVD events

A total of 883 CVD events were reported. In the multivariate logistic regression model, participants with MHO were at moderate risk of developing CVD compared with participants with MHNO (OR, 1.485; 95% CI, 1.031–2.139), whereas participants with metabolic abnormalities were at high risk regardless of obesity (MUNO: OR, 1.768; 95% CI, 1.373–2.278; MUO: OR, 2.179; 95% CI, 1.664– 2.855) (Table 2). Although the CVD events were most frequently reported in MUNO group, MUO showed the highest OR for CVD event after adjustment for the confounding factors.

Risk of developing CVDs according to obesity phenotypes and LBSIZ

We divided the LBSIZ into tertiles and examined the relative risk of developing CVDs across the tertiles based on obesity phenotype. The distribution of LBSIZ was described in Table 3 according to obesity phenotype. In the multivariate logistic regression analysis, MHO participants who are within the third tertiles of LB-SIZ had a significantly higher OR for CVDs, whereas those who are within the first and second tertile of LBSIZ were not at risk for

Table 2. Odds ratios for CVD events according to obesity phenotypes

| Variable | Unweighted mo | odel | Weighted model | | |
|----------|---------------------|---------|---------------------|---------|--|
| Valiable | Odds ratio (95% CI) | Р | Odds ratio (95% CI) | Р | |
| MHNO | 1 (Reference) | | 1 (Reference) | | |
| MHO | 1.568 (1.194-2.060) | 0.001 | 1.485 (1.031-2.139) | 0.034 | |
| MUNO | 1.758 (1.456–2.122) | < 0.001 | 1.768 (1.373–2.278) | < 0.001 | |
| MUO | 2.147 (1.770–2.603) | < 0.001 | 2.179 (1.664–2.855) | < 0.001 | |

Adjusted for age, sex, family income level, education level, moderate intensity physical activities (>120 minute per week), alcohol consumption, smoking status, and energy intake.

CVD, cardiovascular disease; CI, confidence interval; MHNO, metabolically healthy nonobese; MHO, metabolically healthy obese; MUNO, metabolically unhealthy non-obese; MUO, metabolically unhealthy obese.

| Table 5. The distribution of LBSIZ by obesity phenotype | Fable 3 . |
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|---|------------------|

CVD compared to MHNO participants who are within the first tertile. In addition, the ORs of the MUNO and MUO participants increased similarly (Fig. 2). Because age and sex ratio were significantly different across the subgroups by obesity phenotypes, further analysis with propensity score matching methods was performed and showed similar results (Table 4). In the restricted cubic spline regression, LBSIZ showed a linear relationship with CVD events according to each obesity phenotype (Fig. 3).

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DISCUSSION

In this study, we investigated the risk for CVD events based on MHO phenotype. MHO participants are at moderate risk for CVD than MHNO participants. Notably, we found that LBSIZ had a positive linear relationship with CVD events in MHO participants. Although, the linear relationship disappeared in MUO participants after weighting, similar pattern was shown in MHNO and MUO participants in the unweighted logistic regression analysis and the restricted cubic spline regression.

These results show that patients with MHO phenotype are not homogenous. This heterogeneity might be due to a limitation in the definition of obesity based on BMI, which is used to define the severity of obesity in the general population based on the guidelines of the WHO.²⁰ However, BMI could not accurately obtain body fat mass because body weight cannot be used to differentiate excess fat from bone or muscle mass.²⁸ In addition, BMI does not consider age-related changes in muscle mass.²⁹ Although body fat increases and muscle mass decreases with age, BMI may not reflect the proportional changes in body fat or muscle mass.^{29,30} Other disadvantages of using BMI are the following: BMI cannot not measure the regional body fat composition, and it does not consider the distribution of fats in terms of sex. In addition, the metabolic

| Percentile | 10th | 20th | 30th | 40th | 50th | 60th | 70th | 80th | 90th |
|------------|-------|-------|-------|-------|-------|------|------|------|------|
| Total | -1.28 | -0.84 | -0.53 | -0.25 | 0 | 0.25 | 0.50 | 0.81 | 1.24 |
| MHNO | -1.43 | -1.02 | -0.70 | -0.44 | -0.19 | 0.06 | 0.32 | 0.60 | 1.01 |
| MHO | -1.47 | -0.99 | -0.71 | -0.46 | -0.21 | 0.04 | 0.28 | 0.57 | 1.00 |
| MUNO | -0.90 | -0.46 | -0.15 | 0.13 | 0.37 | 0.62 | 0.88 | 1.19 | 1.59 |
| MUO | -1.08 | -0.64 | -0.32 | -0.08 | 0.14 | 0.37 | 0.59 | 0.88 | 1.30 |

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.



Figure 2. Odds ratio (OR; 95% confidence interval [CI]) for cardiovascular events in terms of obesity phenotype and tertile of LBSIZ. (A) Unweighted model. (B) Weighted model. Adjusted for age, sex, family income level, education level, moderate intensity physical activities (> 120 minute per week), alcohol consumption, smoking status, and energy intake. LBSIZ, z-score of the log-transformed A Body Shape Index; MHNO, metabolically healthy non-obese; MHO, metabolically healthy obese; MUNO, metabolically unhealthy obese.

 Table 4. Odds ratio (95% CI) for cardiovascular events in terms of obesity phenotype and tertile of LBSIZ after propensity score matching with age and sex

| Variable | Odds ratio (95% CI) | Р | | | |
|---------------------------|---------------------|---------|--|--|--|
| MHNO tertile 1st vs. MHO | | | | | |
| Tertile 1st | 1.551 (0.794–3.030) | 0.198 | | | |
| Tertile 2nd | 1.462 (0.766–2.791) | 0.250 | | | |
| Tertile 3rd | 1.970 (1.103–3.518) | 0.022 | | | |
| MHNO tertile 1st vs. MUNO | | | | | |
| Tertile 1st | 1.228 (0.733–2.058) | 0.435 | | | |
| Tertile 2nd | 1.564 (1.009–2.423) | 0.045 | | | |
| Tertile 3rd | 2.157 (1.456–3.194) | < 0.001 | | | |
| MHN0 tertile 1st vs. MU0 | | | | | |
| Tertile 1st | 1.805 (1.069–3.047) | 0.027 | | | |
| Tertile 2nd | 2.079 (1.317–3.281) | 0.002 | | | |
| Tertile 3rd | 2.173 (1.395–3.382) | 0.001 | | | |

Adjusted for age, sex, family income level, education level, moderate intensity physical activities (>120 minute per week), alcohol consumption, smoking status, and energy intake.

CI, confidence interval; 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.

effects of fat differ according to its location. For instance, visceral fat is associated with T2DM and CVDs³¹, whereas subcutaneous fat has beneficial effects on metabolism.³² Therefore, BMI has limitations in terms of classifying obesity. A person with excessive visceral fat and insufficient muscle mass can have a normal BMI but have a high mortality risk.³³

A number of studies attempted to investigate obesity using other body index parameters, such as WC, because of the limitations of BMI.³⁴ WC is strongly associated with visceral adiposity and metabolic risk and increased morbidity and mortality.^{35,36} However, WC could not distinguish subcutaneous fat from visceral fat deposition.³⁷ In addition, there are insufficient age- and sex-specific data that can define obesity.²⁹

ABSI, which is another obesity index, was recently introduced using WC, weight, and height. This index was closely associated with mortality in the United States.¹⁶ However, it has limitations in terms of its applicability to different genders and countries.^{17,38} Moreover, it may have statistical limitations with regard to skewness and symmetry. LBSIZ has recently been proposed to complement and improve ABSI.¹⁷ Our previous study has demonstrated that LBSIZ is a standard normalized obesity measurement that is independent of weight, height, and BMI, and it can be age and sex independent. Importantly, while LBSIZ was not correlated with BMI in Korean population¹⁷, it had a linear relationship with CVD risks across different obesity phenotype, grouped by BMI and criteria for metabolic syndrome in the present study. This result evidently showed the usefulness of LBSIZ as a complementary mea-



Figure 3. Relationship between continuous LBSIZ and the odds ratio for cardiovascular events according to obesity phenotypes. (A) Total. (B) Subgroup by obesity phenotypes. Adjusted for age, sex, family income level, education level, moderate intensity physical activities (>120 minute per week), alcohol consumption, smoking status, and energy intake. LBSIZ, z-score of the log-transformed A Body Shape Index; MUO, metabolically unhealthy obese; MUNO, metabolically unhealthy nonobese; MHO, metabolically healthy obese; MHNO, metabolically healthy nonobese.

sure to overcome the drawbacks of BMI.

Our findings can provide a convincing explanation for the heterogeneous results of the previous studies with regard to the risk of developing CVDs in MHO individuals.^{8,37,39} Taking these into consideration, the findings show that the limitation of BMI should be considered along with other determining factor, such as total body fat mass, fat distribution or body shape, when predicting cardiovascular risk.

The main strength of the present study is that it was a large-scale observational study with a representative sample. However, there were several limitations in this study as well. First, this is a crosssectional study. To clarify the relationship between each obesity phenotype and CVD events, further prospective studies must be conducted. Second, because the present study involved a population of Korean adults, the results are applicable only in Koreans. Third, we could not assess data on mortality, and fatal CVD events may have been missed.

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In conclusion, we analyzed the association between the CVD outcomes and obesity phenotype by body shape. LBSIZ had a linear relationship in individuals with MHO phenotype. These findings may have implications in terms of CVD risk assessment in MHO group. In addition, the applications of these findings are important to supplement the drawback of BMI in both clinical practice and epidemiologic studies. However, further prospective studies must be conducted to redefine MHO phenotype in view of body shape to validate MHO.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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