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Metabolically-Healthy Obesity and Coronary Artery Calcification

Yoosoo Chang, MD,*† Bo-Kyoung Kim, MD,* Kyung Eun Yun, MD, PhD,* Juhee Cho, PhD,‡§ Yiyi Zhang, PhD,‡ Sanjay Rampal, MD,‡‖ Di Zhao, MHS,‡ Hyun-Suk Jung, MD,* Yuni Choi, BS,* Jiin Ahn, MSPH,* João A. C. Lima, MD,¶ Hocheol Shin, MD, PhD,# Eliseo Guallar, MD, DrPH,‡ Seungho Ryu, MD, PhD*†

Seoul, South Korea; Baltimore, Maryland; and Kuala Lumpur, Malaysia

Objectives The purpose of this study was to compare the coronary artery calcium (CAC) scores of metabolically-healthy obese (MHO) and metabolically healthy normal-weight individuals in a large sample of apparently healthy men and women.

Background The risk of cardiovascular disease among obese individuals without obesity-related metabolic abnormalities, referred to as MHO, is controversial.

Methods We conducted a cross-sectional study of 14,828 metabolically-healthy adults with no known cardiovascular disease who underwent a health checkup examination that included estimation of CAC scores by cardiac tomography. Being metabolically healthy was defined as not having any metabolic syndrome component and having a homeostasis model assessment of insulin resistance <2.5.

Results MHO individuals had a higher prevalence of coronary calcification than normal weight subjects. In multivariable-adjusted models, the CAC score ratio comparing MHO with normal-weight participants was 2.26 (95% confidence interval: 1.48 to 3.43). In mediation analyses, further adjustment for metabolic risk factors markedly attenuated this association, which was no longer statistically significant (CAC score ratio 1.24; 95% confidence interval: 0.79 to 1.96). These associations did not differ by clinically-relevant subgroups.

Conclusions MHO participants had a higher prevalence of subclinical coronary atherosclerosis than metabolically-healthy normal-weight participants, which supports the idea that MHO is not a harmless condition. This association, however, was mediated by metabolic risk factors at levels below those considered abnormal, which suggests that the label of metabolically healthy for obese subjects may be an artifact of the cutoff levels used in the definition of metabolic health. (J Am Coll Cardiol 2014;63:2679–86) © 2014 by the American College of Cardiology Foundation

Obesity, an established risk factor for cardiovascular disease (CVD), has increased at an alarming rate over the past decades worldwide (1–3). The impact of obesity on the development of CVD is mediated through a number of metabolic abnormalities, such as dyslipidemia, hyperglycemia, and hypertension (4,5); however, the incidence of obesity-related metabolic disturbances varies widely among obese individuals (6,7). Indeed, a subset of obese individuals without obesity-related metabolic abnormalities (7,8), referred to as metabolically-healthy obese (MHO), are relatively insulin sensitive (9). Whether MHO is associated with excess risk of CVD is controversial. MHO individuals had similar risk for cardiovascular events as metabolically-healthy normal-weight subjects in some studies (5,10,11) but had increased risk in others (4,12). Importantly, a substantial fraction of MHO individuals develop adverse metabolic changes associated with obesity over time (13,14).

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From the *Center for Cohort Studies, Total Healthcare Center, Kangbuk Samsung Hospital, Sungkyunkwan University, School of Medicine, Seoul, South Korea; †Department of Occupational and Environmental Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University, School of Medicine, Seoul, South Korea; ‡Departments of Epidemiology and Medicine and Welch Center for Prevention, Epidemiology, and Clinical Research, Johns Hopkins University Bloomberg School of Public Health, Baltimore, Maryland; §Department of Health Sciences and Technology, Samsung Advanced Institute for Health Sciences and Technology, Sungkyunkwan University, Seoul, South Korea; ‖Department of Social and Preventive Medicine, Julius Centre University of Malaya, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia; ¶Division of Cardiology, Johns Hopkins University School of Medicine, Baltimore, Maryland; and the #Department of Family Medicine, Kangbuk Samsung Hospital and Sungkyunkwan University School of Medicine, Seoul, South Korea. The authors have reported that they have no relationships relevant to the contents of this paper to disclose. Drs. Chang and Kim contributed equally to this work. Stephen Nicholls, MBBS, PhD, served as Guest Editor for this paper.

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Abbreviations and Acronyms

BMI = body mass index
CAC = coronary artery calcium
CI = confidence interval
CT = computed tomography
CVD = cardiovascular disease
HDL-C = high-density lipoprotein-cholesterol
HOMA-IR = homeostasis model assessment of insulin resistance
hsCRP = high-sensitivity C-reactive protein
LDL-C = low-density lipoprotein cholesterol
MHO = metabolically-healthy obese/obesity

Coronary artery calcium (CAC) scoring with computed tomography (CT) is a useful method to identify subclinical atherosclerosis (15). CAC scores reflect the long-term impact of elevated CVD risk factors and independently predict future risk of CVD events (16). The only study that has examined the association between MHO and CAC scores found no association (17), but that study included participants with hypertension or diabetes mellitus in the metabolically-healthy group and overweight participants in the comparison group, thus it did not provide a clear comparison of MHO with metabolically-healthy normal-weight individuals. Therefore, we compared the CAC scores of MHO and metabolically-healthy normal-weight individuals in a large sample of apparently-healthy Korean men and women who participated in a health screening examination program.

Methods

Study population. The Kangbuk Samsung Health Study is a cohort study of South Korean men and women 18 years of age or older who underwent a comprehensive annual or biennial health examination at the clinics of the Kangbuk Samsung Hospital Total Healthcare Center in Seoul and Suwon, South Korea. The study population consisted of the subset of Kangbuk Samsung Health Study participants who underwent a cardiac CT to measure CAC scores as part of a comprehensive health examination from 2010 to 2012 (N = 45,809). CAC scoring has become a common CVD screening test in Korea (18). More than 80% of participants were employees of various companies and local governmental organizations and their spouses. In South Korea, the Industrial Safety and Health Law requires annual or biennial health screening examinations of all employees, offered free of charge. The remaining participants were people voluntarily taking screening examinations.

For this analysis, we excluded participants with a history of CVD or cancer (n = 1,258) and participants with missing data for anthropometric measures or other covariates, including smoking status, alcohol consumption, and physical activity (n = 3,547), which left a total of 41,205 participants eligible for the study. We then excluded participants who had any of the following metabolic abnormalities (7,19): 1) fasting blood glucose ≥100 mg/dl or current use of blood glucose–lowering agents (20); 2) blood pressure ≥130/85 mm Hg or current use of blood pressure–lowering agents (20); 3) triglyceride levels ≥150 mg/dl or current use of lipid-lowering agents (20); 4) high-density lipoprotein cholesterol (HDL-C) <40 mg/dl in men or <50 mg/dl in women (20); or 5) homeostasis model assessment of insulin resistance (HOMA-IR) ≥2.5 (21). The total number of metabolically-healthy subjects included in the study was 14,828 (Fig. 1).

This study was approved by the Institutional Review Board of the Kangbuk Samsung Hospital, which exempted the requirement for informed consent because we only accessed deidentified data routinely collected as part of health screening examinations.

Measurements. Data on medical history, medication use, family history, physical activity, alcohol intake, smoking habits, and education level were collected through a self-administered questionnaire, whereas anthropometry, blood pressure, and serum biochemical parameters were measured by trained staff during the health examinations (22,23). Smoking status was categorized as never, former, or current smoker. Alcohol consumption was categorized as none, moderate (≤20 g/day), or high (>20 g/day). The weekly frequency of moderate- or vigorous-intensity physical activity was also assessed. Education level was categorized as less than college graduate or college graduate or more.

Height, weight, and body composition were measured by trained nurses with the participants wearing a lightweight hospital gown and no shoes. The percentage of body fat was estimated with a multifrequency bioimpedance analyzer with 8-point tactile electrodes (InBody 720, Biospace Co., Seoul, Korea), which was validated with regard to reproducibility and accuracy for body composition (24). Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. BMI was classified according to Asian-specific criteria (25): underweight, BMI <18.5 kg/m^2; normal weight, BMI of 18.5 to 23 kg/m^2; overweight, BMI of 23 to 25 kg/m^2; and obese, BMI ≥25 kg/m^2. Waist circumference was measured by trained personnel to the nearest 0.1 cm at the midpoint between the bottom of the rib cage and the top of the iliac crest with the subjects standing, their weight equally distributed on both feet, their arms at their sides, and head facing straight forward. Waist circumference was not measured in the Suwon clinic until 2012, so data on waist circumference were restricted to 4,674 participants.

Blood samples were taken from the antecubital vein after at least a 10-h fast. Serum total cholesterol, triglycerides, and uric acid were determined with an enzymatic colorimetric assay. Low-density lipoprotein cholesterol (LDL-C) and HDL-C were measured directly with a homogeneous enzymatic colorimetric assay. Serum high-sensitivity C-reactive protein (hsCRP) was determined with a particle-enhanced immunoturbidimetric assay on a Modular Analytics P800 apparatus (Roche Diagnostics, Tokyo, Japan). Serum insulin was measured with an electrochemiluminescence immunoassay on a Modular Analytics E170 apparatus (Roche

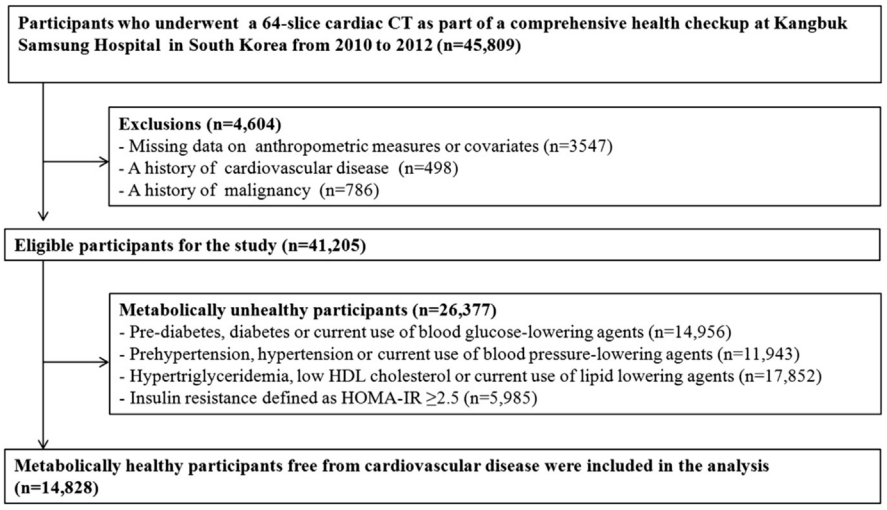

Figure 1 Flow Diagram

Flow diagram for the selection of study subjects. CT = computed tomography; HDL = high-density lipoprotein; HOMA-IR = homeostasis model assessment of insulin resistance.

Diagnostics). Serum glucose was measured by the hexokinase method on a Cobas Integra 800 apparatus (Roche Diagnostics). Insulin resistance was assessed with the HOMA-IR according to the following equation: fasting blood insulin (μU/ml) × fasting serum glucose (mmol/l)/22.5. The Laboratory Medicine Department at the Kangbuk Samsung Hospital in Seoul, Korea has been accredited by the Korean Society of Laboratory Medicine and the Korean Association of Quality Assurance for Clinical Laboratories. The laboratory participates in the College of American Pathologists' Survey/Proficiency Testing program.

Measurement of CAC by multidetector CT. CT scans were performed with a LightSpeed VCT XTe-64-slice multidetector CT scanner (GE Healthcare, Tokyo, Japan) in both the Seoul and Suwon centers using the same standard scanning protocol: 2.5-mm thickness, 400-ms rotation time, 120-kV tube voltage, and 124-mAs (310 mA·0.4 s) tube current under electrocardiogram-gated dose modulation. CAC scores were calculated as described previously by Agatston et al. (26). The interobserver and intraobserver reliability for CAC scores were both excellent (intraclass correlation coefficient: 0.99) (23). CAC scores were categorized as 0, 1 to 80, and >80 (27,28).

Statistical analyses. Descriptive statistics were used to summarize the characteristics of participants by BMI categories. To test for linear trends, we included the median value of each BMI category as a continuous variable in the regression models. We assumed that CAC scores followed a log-normal distribution with left-censored values at 0 Agatston units (nondetectable CAC scores). To evaluate the association between BMI categories and CAC, we used a Tobit regression model for natural log(CAC score + 1) with Huber-White estimation of standard errors (29,30). Tobit models were used to estimate ratios and 95% confidence intervals (CIs) of CAC score + 1 comparing BMI categories with the normal BMI category. As secondary analyses, we also estimated prevalence ratios and 95% CIs for CAC scores of 1 to 80 and >80 for BMI categories compared with normal BMI using participants with a CAC score of 0 as the reference group in multinomial logistic regression models.

Models were adjusted initially for age and sex and then further adjusted for potential confounding factors, including education level, smoking status, alcohol intake, and exercise. We also fitted additional models adjusted for potential intermediate variables, including systolic blood pressure, fasting serum glucose, triglycerides, HDL-C, HOMA-IR, and LDL-C, to evaluate potential mediators of the association between obesity and CAC score. Subgroup analyses to identify interactions between BMI categories and clinically-relevant factors were tested by likelihood ratio tests that compared models with and without multiplicative interaction terms. Statistical analyses were performed with Stata version 11.2 (StataCorp LP, College Station, Texas). All reported p values are 2-tailed, and comparisons with $p < 0.05$ were considered statistically significant.

Results

The mean ± SD age and BMI of the 14,828 metabolically healthy participants were 39.3 ± 6.6 years and 23.0 ± 2.7 kg/m^2 (BMI range: 14.5 to 39.9 kg/m^2), respectively. Age, fasting glucose, systolic and diastolic blood pressure, total cholesterol, triglycerides, LDL-C, uric acid, insulin, HOMA-IR, hsCRP, exercise, and current alcohol use were

Table 1 Baseline Characteristics of Metabolically-Healthy Participants by BMI Category

		BMI Categories, kg/m^2				
	Overall	Underweight (<18.5)	Normal Weight (18.5–22.9)	Overweight (23.0–24.9)	Obese (≥25.0)	p Value for Trend
Number of participants	14,828	581	6,996	3,997	3,254	
Age, yrs	39.3 ± 6.6	37.7 ± 6.6	39.1 ± 6.7	39.7 ± 6.7	39.3 ± 6.5	<0.001
Men	74.2	34.9	63.5	86.2	89.6	<0.001
% Body fat	22.9 ± 5.9	18.6 ± 5.7	21.4 ± 5.8	23.1 ± 5.1	26.7 ± 5.3	<0.001
Current smoker	22.3	16.2	19.6	24.0	27.2	<0.001
Alcohol intake*	17.3	5.3	13.2	20.2	24.5	<0.001
Regular exercise†	14.4	8.4	13.2	15.6	16.4	<0.001
Education level‡	87.5	86.2	86.2	88.3	89.3	<0.001
Systolic BP, mm Hg	109.5 ± 9.8	102.8 ± 10.3	107.5 ± 9.9	111.0 ± 9.1	113.3 ± 8.5	<0.001
Diastolic BP, mm Hg	69.3 ± 7.5	65.5 ± 7.5	67.9 ± 7.6	70.4 ± 7.2	71.9 ± 6.9	<0.001
Waist circumference, cm§	80.7 ± 8.0	67.2 ± 4.0	76.5 ± 5.2	83.9 ± 4.1	90.6 ± 5.5	<0.001
Glucose, mg/dl	90.3 ± 5.8	88.3 ± 6.2	89.9 ± 5.9	90.8 ± 5.7	91.1 ± 5.4	<0.001
Uric acid, mg/dl	5.43 ± 1.32	4.45 ± 1.09	5.11 ± 1.26	5.68 ± 1.24	6.00 ± 1.27	<0.001
Total cholesterol, mg/dl	195.7 ± 32.1	183.4 ± 30.6	191.9 ± 31.8	198.5 ± 31.5	202.6 ± 32.2	<0.001
LDL-C, mg/dl	121.5 ± 30.2	102.3 ± 26.0	115.8 ± 29.2	126.2 ± 29.1	131.5 ± 29.9	<0.001
HDL-C, mg/dl	59.7 ± 12.5	69.6 ± 13.6	62.7 ± 12.7	57.3 ± 11.0	54.5 ± 10.3	<0.001
Triglycerides, mg/dl	84 (64–109)	64 (52–81)	77 (59–99)	90 (70–113)	99 (77–122)	<0.001
ALT, U/l	18 (13–25)	13 (10–17)	16 (12–21)	19 (15–27)	24 (18–34)	<0.001
GGT, U/l	21 (15–31)	15 (12–20)	18 (13–25)	23 (17–34)	29 (20–43)	<0.001
hsCRP, mg/l	0.4 (0.3–0.8)	0.3 (0.2–0.4)	0.3 (0.2–0.6)	0.4 (0.3–0.8)	0.6 (0.4–1.2)	<0.001
HOMA-IR	0.88 (0.59–1.25)	0.64 (0.43–0.89)	0.78 (0.53–1.09)	0.91 (0.62–1.27)	1.14 (0.81–1.56)	<0.001
CAC score >0	6.8	4.0	5.4	7.5	9.2	<0.001

Values are mean ± SD, %, or median (interquartile range), unless otherwise indicated. *Alcohol intake ≥20 g of ethanol per day. †Exercised ≥3 times per week. ‡College graduate or more. §Among 4,674 subjects with available waist circumference data (3,438 men, 1,236 women).

ALT = alanine aminotransferase; BMI = body mass index; BP = blood pressure; CAC = coronary artery calcification; GGT, gamma-glutamyltransferase; HDL-C = high-density lipoprotein cholesterol; HOMA-IR = homeostasis model assessment of insulin resistance; hsCRP = high-sensitivity C-reactive protein; LDL-C = low-density lipoprotein cholesterol.

positively associated with BMI, whereas HDL-C and current smoking were inversely associated with BMI (Table 1). Of the 14,828 subjects, 859 (5.8%) had a CAC score of 1 to 80 and 144 (1.0%) had a CAC score >80.

In multivariable-adjusted models that accounted for potential confounders, the CAC score ratio comparing MHO with normal-weight participants was 2.26 (95% CI: 1.48 to 3.43) (Table 2). Similarly, the prevalence ratios comparing MHO with normal-weight participants were 1.39 (95% CI: 1.15 to 1.67) for CAC score 1 to 80 and 1.67 (95% CI: 1.09 to 2.56 for CAC score >80 (Table 3). Overweight participants had a modest and not statistically significant increase in the prevalence of coronary calcification. The CAC score ratio comparing overweight and normal-weight participants was 1.21 (95% CI: 0.80 to 1.84), whereas the prevalence ratios comparing overweight and normal-weight participants were 1.09 (95% CI: 0.91 to 1.31) for a CAC score of 1 to 80 and 1.09 (95% CI: 0.70 to 1.68) for a CAC score >80. Further adjustment for hsCRP levels did not affect the results (data not shown).

To explore whether the increased prevalence in coronary calcification observed in MHO participants was mediated by metabolic components associated with obesity, we performed additional analyses adjusted for metabolic risk factors. Adjustment for fasting blood glucose, systolic blood pressure, triglyceride levels, HDL-C, and HOMA-IR slightly reduced the associations, but they remained statistically significant (Table 4, model 1). However, after

Table 2 CAC Score Ratios* by BMI Categories in 14,828 Metabolically-Healthy Participants

	BMI Categories, kg/m^2			
	Underweight (<18.5)	Normal Weight (18.5–22.9)	Overweight (23.0–24.9)	Obese (≥25.0)
Number of participants	581	6,996	3,997	3,254
Age- and sex-adjusted	1.66 (0.55–5.04)	Reference	1.29 (0.86–1.93)	2.52 (1.68–3.78)
Multivariate-adjusted	1.56 (0.50–4.89)	Reference	1.21 (0.80–1.84)	2.26 (1.48–3.43)

Values are n or CAC score ratio (95% confidence interval). *Estimated from robust Tobit regression models used with natural log(CAC + 1) as the outcome. Multivariable model adjusted for age, sex, smoking status, alcohol intake, regular exercise, and education level.

Abbreviations as in Table 1.

Table 3 Prevalence Ratios* for CAC by BMI Categories in 14,828 Metabolically-Healthy Participants

	BMI Categories, kg/m^2			
	Underweight (<18.5)	Normal Weight (18.5–22.9)	Overweight (23.0–24.9)	Obese (≥25.0)
Number of participants	581	6,996	3,997	3,254
CAC score 1 to 80				
Prevalent cases	19	329	259	252
Age- and sex-adjusted PR*	1.05 (0.64–1.73)	Reference	1.11 (0.94–1.33)	1.42 (1.19–1.70)
Multivariate-adjusted PR*	1.03 (0.62–1.72)	Reference	1.09 (0.91–1.31)	1.39 (1.15–1.67)
CAC score >80				
Prevalent cases	4	50	42	48
Age- and sex-adjusted PR*	1.48 (0.49–4.44)	Reference	1.15 (0.75–1.76)	1.91 (1.27–2.89)
Multivariate-adjusted PR*	1.53 (0.50–4.73)	Reference	1.09 (0.70–1.68)	1.67 (1.09–2.56)

Values are n or PR (95% confidence interval). *Estimated from multinomial logistic regression models that used CAC scores as outcomes categorized as 0, 1 to 80, and >80. Multivariable model adjusted for age, sex, smoking status, alcohol intake, regular exercise, and education level.
Abbreviations as in Table 1.

adjustment for LDL-C, the association between MHO and CAC was markedly attenuated and no longer statistically significant (Table 4, model 2). Similar findings were evident in multinomial regression models with categorized CAC scores as outcomes (data not shown).

The associations between the BMI categories and CAC scores were similar across participant subgroups (Table 5), with no significant interactions by age (<40 years of age vs. ≥40 years of age), sex (women vs. men), smoking (current smoker vs. noncurrent smoker), alcohol intake (<20 g/day vs. ≥20 g/day), regular exercise (<3 times/week vs. ≥3 times/week), hsCRP levels (<1.0 mg/l vs. ≥1.0 mg/l), and Framingham risk score (<10% vs. ≥10%). Even among participants with Framingham risk score <10%, MHO participants compared with normal-weight participants had a significantly increased CAC score ratio of 2.20 (95% CI: 1.43 to 3.40).

Discussion

In this large study of metabolically-healthy Korean men and women participating in health screening examinations, we identified 2 major findings. First, MHO participants had a higher prevalence of subclinical coronary atherosclerosis than metabolically-healthy normal-weight participants. This association was observed in all subgroups that were evaluated and indicated that MHO is not a harmless condition. Second, the association was largely attenuated and no longer statistically significant after adjustment for metabolic risk factors and LDL-C, even though all participants had healthy levels of metabolic risk factors. This indicates that the association between MHO and subclinical atherosclerosis is mediated by metabolic risk factors below levels considered abnormal, and consequently, the label of metabolically healthy for obese participants is an artifact of the cutoff levels used and the choice of factors included in the definition of metabolic health.

To the best of our knowledge, this is the first study to demonstrate that the MHO phenotype was associated with subclinical coronary atherosclerosis as measured by CAC scores. A previous study of the association between MHO and CAC scores defined metabolically-healthy participants as those with fewer than 2 metabolic components but included participants with hypertension or diabetes mellitus in the metabolically-healthy group (17). Moreover, that study included overweight participants in the reference group. Although that study found no association between MHO and CAC scores, the definition of the comparison groups makes these findings difficult to interpret. In our study, the large sample size allowed us to select a group of participants without any metabolic abnormality, as evidenced by a low prevalence of CAC scores >0 (6.8%).

Table 4 Mediation Analysis of the Association Between BMI Categories and CAC in 14,828 Metabolically-Healthy Participants

	BMI Categories, kg/m^2			
	Underweight (<18.5)	Normal Weight (18.5–22.9)	Overweight (23.0–24.9)	Obese (≥25.0)
Model 1: CAC score ratio*	1.92 (0.60–6.13)	Reference	1.10 (0.72–1.67)	1.84 (1.17–2.91)
Model 2: CAC score ratio*	3.01 (0.95–9.55)	Reference	0.87 (0.57–1.32)	1.24 (0.79–1.96)

Values are CAC score ratio (95% confidence interval). Model 1 adjusted for age, sex, smoking status, alcohol intake, regular exercise, education level, glucose, systolic blood pressure, triglycerides, high-density lipoprotein cholesterol, and homeostasis model assessment of insulin resistance. Model 2 further adjusted for low-density lipoprotein cholesterol. *Estimated from robust Tobit regression models used with natural log(CAC + 1) as the outcome.
Abbreviations as in Table 1.

Table 5 CAC Score Ratios* by BMI Categories in Clinically-Relevant Subgroups of Metabolically-Healthy Participants

Subgroup	BMI Categories (kg/m^2)				p Value for Interaction
	Underweight (<18.5)	Normal Weight (18.5–22.9)	Overweight (23.0–24.9)	Obese (≥25.0)	
Age, yrs					0.57
<40 (n = 7,779)	3.78 (0.61–23.5)	Reference	1.55 (0.63–3.85)	2.82 (1.16–6.86)	
≥40 (n = 7,049)	0.92 (0.22–3.78)	Reference	1.14 (0.69–1.87)	2.18 (1.30–3.67)	
Sex					0.41
Female (n = 3,822)	4.27 (0.57–32.0)	Reference	2.52 (0.59–10.8)	1.67 (0.28–10.0)	
Male (n = 11,006)	0.83 (0.20–3.41)	Reference	1.12 (0.73–1.73)	2.23 (1.45–3.44)	
Smoking					0.52
Nonsmoker or ex-smoker (n = 11,520)	1.43 (0.34–5.94)	Reference	1.10 (0.66–1.83)	2.57 (1.54–4.28)	
Current smoker (n = 3,308)	1.67 (0.24–11.4)	Reference	1.48 (0.72–3.06)	1.68 (0.81–3.50)	
Alcohol intake					0.86
<20 g/day (n = 12,266)	1.50 (0.45–5.03)	Reference	1.11 (0.69–1.78)	2.27 (1.41–3.66)	
≥20 g/day (n = 2,562)	2.05 (0.06–68.3)	Reference	1.75 (0.73–4.23)	2.60 (1.10–6.14)	
Exercise					0.13
<3 times/week (n = 12,700)	1.34 (0.39–4.62)	Reference	1.00 (0.63–1.58)	1.90 (1.19–3.03)	
≥3 times/week (n = 2,128)	4.88 (0.24–98.2)	Reference	3.75 (1.40–10.0)	5.96 (2.23–15.9)	
High-sensitivity C-reactive protein					0.24
<1.0 mg/l (n = 11,799)	0.95 (0.26–3.47)	Reference	1.14 (0.72–1.83)	2.11 (1.29–3.47)	
≥1.0 mg/l (n = 3,029)	16.4 (1.23–218.6)	Reference	1.65 (0.66–4.12)	3.00 (1.29–6.97)	
Framingham risk score					0.56
<10% (n = 14,718)	1.56 (0.48–5.05)	Reference	1.22 (0.79–1.86)	2.20 (1.43–3.40)	
≥10% (n = 109)	0.77 (0.44–1.32)	Reference	1.07 (0.76–1.50)	4.97 (3.41–7.25)	

Values are CAC score ratio (95% confidence interval). Models were adjusted for age, sex, smoking status, alcohol intake, regular exercise, and education level. *Estimated from robust Tobit regression models used with natural log(CAC + 1) as the outcome.

Abbreviations as in Table 1.

Furthermore, in our study, the association between MHO and CAC scores persisted even among participants with hsCRP levels <1.0 mg/l and among those with Framingham risk scores <10%.

Although MHO individuals were protected from CVD in some studies (5,10), recent longitudinal studies with greater statistical power have suggested that MHO individuals have a higher risk of CVD events and death than metabolically-healthy normal-weight individuals (4,12,19). Previous studies of MHO and CVD risk, however, assessed only baseline metabolic status in classifying MHO phenotype and did not integrate metabolic changes in MHO individuals over time. This may be important, because the transition to a metabolically-unhealthy status may affect CVD risk. Indeed, several studies have shown that the MHO phenotype may be unstable and progress toward overt metabolic abnormalities (13,14).

A challenge in evaluating the health implications of the MHO phenotype is the lack of a universal definition. In our study, we defined the metabolically-healthy phenotype as the absence of any components of the metabolic syndrome or insulin resistance (7). As a consequence, the prevalence of the MHO phenotype in our study population was much lower than in previous studies, which classified up to 30% of metabolically-healthy participants among the obese (31,32). By using a very strict definition of MHO in a relatively young population, we were able to provide a very specific test of the association between MHO and the prevalence of subclinical coronary atherosclerosis (18). Even in this apparently healthy population, however, the values of metabolic parameters increased across BMI categories, and the MHO phenotype was associated with increased CAC scores. Furthermore, adjustment for residual metabolic abnormalities and by LDL-C substantially attenuated the association, which suggests both that these residual abnormalities partly mediate the association between MHO and CAC and that, even among MHO subjects, obesity may induce metabolic changes that result in coronary atherosclerosis. This finding provides a cautionary reminder that the cutoffs for identifying metabolic abnormalities are arbitrary and that the association between cardiometabolic risk factors and CVD risk is continuous, without clear thresholds (33,34). Also, even though LDL-C is a major risk factor for CVD, many of the prior studies that addressed the MHO phenotype did not include LDL-C as a criterion for metabolic health status (7). Thus, the label of "metabolically healthy" for obese participants can be an artifact of the choice of factors included and the cutoffs used in the definition of metabolic health.

In addition to a residual association with traditional metabolic factors, other mechanisms could explain the association between MHO and CAC scores. Adipose tissue is an active endocrine organ that produces and releases adipokines with a number of proinflammatory and other effects (35). Several adipokines may have direct effects on endothelial function, vascular homeostasis, and atherogenesis

independent of their effects on glucose and fat metabolism (36,37) and may be associated with atherosclerosis or CVD independent of conventional risk factors (30,38,39). Circulating levels of interleukin-6 and tumor necrosis factor-alpha, secreted by adipose tissue, may also be involved in atherogenesis (40,41). Finally, obese subjects may also have impaired fibrinolysis and increased hypercoagulability (42). Further mechanistic studies, however, are needed to understand why the MHO phenotype is associated with increased prevalence of CAC scores.

Study limitations. First, the cross-sectional design precludes the determination of causality; however, we studied asymptomatic, healthy, relatively young individuals free of clinically-manifest CVD, thereby minimizing the possibility of reverse causation. Second, the definition of insulin resistance used in this study was based on HOMA-IR levels, not on invasive and time-consuming euglycemic insulin clamp analyses. HOMA-IR and euglycemic insulin clamp data are strongly correlated (43), but we cannot discard the possibility that some participants in our study were insulin resistant. Third, we used BMI as a measure of obesity, but BMI does not distinguish fat tissue from lean tissue. If the MHO group had a higher proportion of lean mass than normal-weight participants, the association between MHO and the presence of CAC in our study could be attenuated. Waist circumference measurements, however, were available only in a fraction of study participants, which limited our ability to examine the role of fat distribution on CAC scores. Finally, our study was conducted in asymptomatic, relatively young Korean men and women, and our findings cannot be extrapolated to other populations. Strengths of our study include the large sample size; the use of carefully standardized clinical, imaging, and laboratory procedures; and the availability of carefully phenotyped participants with no metabolic abnormalities.

Conclusions

The MHO phenotype was associated with an increased prevalence of subclinical atherosclerosis in a relatively young, healthy Korean population. These findings provide strong support to the hypothesis that MHO is not a harmless condition. Furthermore, the association between MHO and CAC scores was mediated in large part by residual levels of cardiometabolic risk factors, which suggests that the concept of MHO may be an artifact of the cutoffs used to define metabolic abnormalities and of the parameters included in the definition of MHO. As a consequence, physicians should adequately address the increased risk of CVD in MHO individuals in addition to counseling them about healthy weight and lifestyle.

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Reprint requests and correspondence: Dr. Seungho Ryu, Kangbuk Samsung Hospital, Samsung Main Building B2, 250, Taepyung-ro 2ga, Jung-gu, Seoul 100-742, South Korea. E-mail: sh703.yoo@gmail.com.

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