Impact of Discrepancies in General and Abdominal Obesity on Major Adverse Cardiac Events

Daein Choi, MD,* Seulggie Choi, MD,* Joung Sik Son, MD, MSc; Sang Woo Oh, MD, PhD; Sang Min Park, MD, PhD, MPH

Background—Body mass index and waist circumference (WC) are commonly used metrics that reflect general obesity and abdominal obesity. However, the impact of general and abdominal obesity discrepancies on the risk for major adverse cardiac events (MACE) is less explored.

Methods and Results—The study population was derived from the Korean National Health Insurance Service-Health Screening Cohort. Among 315,982 participants aged 40 years or older who underwent health examinations between 2008 and 2009, body mass index and WC were used to determine the obesity status. The participants were followed from January 1, 2010 for MACE until December 31, 2015. Cox proportional hazards models were used to evaluate the association of obesity and the risk of MACE. Compared with men who were not obese, those with abdominal obesity without general obesity (adjusted hazard ratio (aHR) 1.29, 95% CI 1.16–1.43), and general and abdominal obesity (aHR 1.20, 95% CI 1.12–1.29) had elevated risk of MACE, while those with general obesity without abdominal obesity (aHR 1.06, 95% CI 0.98–1.16) did not. Similarly, women with abdominal obesity without general obesity (aHR 1.13, 95% CI 1.03–1.24) and those with general and abdominal obesity (aHR 1.15, 95% CI 1.06–1.25) had increased risk of MACE, while those with general obesity without abdominal obesity (aHR 1.07, 95% CI 0.88–1.30) did not.

Conclusions—Abdominal obesity without general obesity was associated with an elevated risk of major cardiovascular outcomes while general obesity without abdominal obesity did not. Concurrent determination of body mass index and WC may be beneficial for the accurate determination of future cardiovascular risk. (J Am Heart Assoc. 2019;8:e013471. DOI: 10.1161/JAHA.119.013471.)

Key Words: cardiovascular disease risk factors • cardiovascular events • obesity

Cardiovascular disease (CVD) is recognized as the leading cause of death worldwide, with 32% of all deaths or a total of 17 million deaths attributable to CVD in 2013.1,2 Various previous studies that attempted to identify and control the risk factors associated with CVD have revealed that obesity is one of the risk factors for CVD.3–5 Obesity also has been recognized as an increasing public problem in developed countries because of the continuously increasing epidemic proportion of obesity.6–7 and numerous studies have reported the association of obesity with multiple chronic diseases such as coronary heart disease, including type 2 diabetes mellitus, hypertension, and stroke.8–10 While body mass index (BMI) is one of the most commonly used methods of measuring obesity, it has been criticized as being a measure of general obesity and may not accurately depict the degree of regional adiposity. Abdominal visceral adiposity has been previously suggested to be a more important measure of obesity.11–13 Waist circumference (WC), which is a more direct measure of abdominal obesity, has been previously shown to predict obesity-related outcomes including various CVDs.13–15 Although multiple studies have determined the separate effects of general obesity measured by BMI and abdominal obesity measured by WC on CVD,4,16–18 whether the discrepancy between general and abdominal obesity alters the risk of major CVD is less explored, especially among the Asian population. Since Asians tend to have different body composition and lower cutoff points for WC compared with other ethnicities,19,20 the effect of general obesity and abdominal obesity on the major adverse cardiovascular events (MACE) might also differ.
Clinical Perspective

What Is New?

• This study investigated the risk of major adverse cardiovascular events according to the general and abdominal obesity status for Korean adults aged 40 years or older.
• Participants with abdominal obesity (measured by waist circumference) without general obesity (measured by body mass index) and abdominal obesity with general obesity had increased risk of major adverse cardiovascular events compared with nonobese participants, while participants with general obesity without abdominal obesity did not.

What Are the Clinical Implications?

• These results suggest that concurrent determination of body mass index and waist circumference would be beneficial to assess future cardiovascular risk.

Therefore, in this population-based longitudinal study using the Korean National Health Insurance Service (NHIS) database, we investigated the impact of general and abdominal obesity discrepancies on the risk for MACE.

Methods

The data will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Study Population

The study population was derived from the National Health Insurance Service—Health Screening Cohort (NHIS-HEALS). Nearly all Korean citizens are ensured under the NHIS, which provides universal health insurance covering most forms of health services. Moreover, all citizens aged 40 years or older are required to undergo a health screening examination every 2 years. Within the health screening examination, participants are evaluated for health behaviors via a self-reported questionnaire as well as health status via anthropometric measurements such as weight and WC as well as blood tests. Using the health insurance claims information, the NHIS provides a part of the data for research purposes called the NHIS-HEALS. The NHIS-HEALS database contains information on sociodemographic factors, all forms of hospital use including inpatient and outpatient visits, pharmaceutical drug prescriptions, and results from health screening examinations. The NHIS database has previously been used in multiple epidemiological studies and its validity is described in detail elsewhere.

Among 361,043 participants who underwent health examinations in 2008 and 2009, we excluded 660 participants with missing values for BMI or WC. Then, 16,164 participants with missing values for covariates were further excluded. Finally, 1056 and 27,181 participants who died or had MACE before the index date of January 1, 2010 were excluded, respectively. The final study population consisted of 315,982 participants with information on BMI and WC during 2008 and 2009. All participants were followed up starting from January 1, 2010 until diagnosis of MACE, death, or December 31, 2015, whichever came first.

Key Variables

All participants who underwent health screening examinations were evaluated for obesity by weight, height, and WC measurements. WC was measured by trained professionals using a standardized protocol and all participants underwent WC measurement using the same protocol. BMI was calculated by dividing the weight in kilograms by height in meters squared. General obesity was defined as BMI of 25.0 kg/m² or more according to the World Health Organization Western Pacific Region guidelines. Abdominal obesity was defined as WC of 90 cm or more for men and 80 cm or more for women according to the International Diabetes Federation for Asian populations. All participants were then divided into normal (not generally nor abdominally obese), general obesity without abdominal obesity, abdominal obesity without general obesity, and general and abdominal obesity.

The primary outcome was MACE, which was defined as myocardial infarct (MI), stroke, and related deaths. Physicians are required to fill in the main diagnosis for all patients upon admission and upon death, and the attending physician is required to diagnose the main cause of death. Using the diagnosis and death codes, we defined MI and stroke events as being hospitalized for 2 or more days or death under the International Classification of Diseases, Tenth Revision (ICD-10) codes pertaining to each disease outcome. ICD-10 codes for MI (I21) and stroke (I60–I64) are in line with those used by the American Heart Association. Furthermore, cardiovascular death was defined as having CVD (ICD-10 codes I20–I25 or I60–I69) as the main cause of death.

Statistical Analysis

Participants were evaluated for adjusted hazard ratios (aHRs) and 95% CIs for MACE, MI, and stroke risk according to obesity status using multivariate Cox proportional hazards regression. The considered covariates included age (continuous, years), household income (categorical, first, second, third, and fourth quartiles), smoking (categorical, never, past, and current smokers), physical activity (categorical, 0, 1–2, 3–
4, 5–6, and 7 times per week), alcohol consumption (categorical, 0, 0–1, 1–2, 3–4, and 5 or more times per week), and Charlson comorbidity index (continuous). Physical activity was assessed by a self-reported questionnaire during the health examination. Household income was derived from the insurance premium and the algorithm for calculating Charlson comorbidity index was adapted from a previous study.29

The distribution of covariates in each obesity group was calculated. Chi-squared test for categorical variables and analysis of variance for continuous variables were used to compare the differences in distribution of covariates among obesity groups. Compared with normal participants, those with general obesity without abdominal obesity, abdominal obesity without general obesity, and general obesity and abdominal obesity were assessed for MACE, MI, and stroke risk. In order to determine the differences in risk among these groups according to the discrepancies between general and abdominal obesity, the risk for MACE, MI, and stroke were evaluated for abdominal obesity without abdominal obesity participants compared with general obesity without abdominal obesity participants. Also, sensitivity analyses with an adjusted cutoff value of WC were conducted. Abdominal obesity was defined as WC of 85 cm or more for men and 90 cm or more for women according to the previous Japanese study.30 Finally, Kaplan–Meier curves for the MACE according to the obesity status were constructed. Statistical significance was defined as a 2-sided $P$ value of <0.05. All data collection and statistical analyses were conducted using SAS 9.4 (SAS Institute Inc).

**Ethical Considerations**

This study was approved by the Seoul National University Hospital Institutional Review Board (IRB number: 1703-039-836). The requirement for informed consent was waived since the NHIS database is anonymized according to strict confidentiality guidelines before distribution.

**Results**

Table 1 depicts the descriptive characteristics of the study population. The number of participants who were normal, general obesity without abdominal obesity, abdominal obesity without general obesity, and general and abdominal obesity was 174 237, 35 081, 33 902, and 72 763 participants, respectively. The mean (standard deviation) ages for normal, general obesity without abdominal obesity, abdominal obesity without general obesity, and general and abdominal obesity participants were 57.2 (8.6), 55.5 (7.2), 61.4 (9.3), and 59.0 (8.6) years, respectively. Compared with participants who were not obese, those who were generally and abdominally obese tended to be older, female, smoke less, have low physical activity, consume less alcohol, and have more comorbidities. Compared with general obesity without abdominal obesity participants, abdominal obesity without general obesity participants tended to be older, female, smoke less, have low physical activity, consume less alcohol, and have more comorbidities.

The risks for MACE, MI, and stroke according to obesity status are shown in Table 2. Among men, the aHR (95% CI) for MACE among general obesity without abdominal obesity, abdominal obesity without general obesity, and general and abdominal obesity participants were 1.06 (0.98–1.16), 1.29 (1.16–1.43), and 1.20 (1.12–1.29), respectively. Similarly, the respective aHR (95% CI) for MACE were 1.07 (0.88–1.30), 1.13 (1.03–1.24), and 1.15 (1.06–1.25) among generally obese without being abdominally obese, abdominally obese without being generally, and generally and abdominally obese women compared with nonobese women.

Table 3 shows the risk for MACE, MI, and stroke for abdominal obesity without general obesity participants compared with general obesity without abdominal obesity participants. Compared with general obesity without abdominal obesity participants, abdominal obesity without general obesity participants have a higher risk for MACE for men (aHR 1.25, 95% CI 1.10–1.43) but not for women (aHR 1.08, 95% CI 0.88–1.32).

The results of sensitivity analyses with adjusted WC cutoff value are depicted in Tables S1 and S2. Table S1 shows the risk of MACE, MI, and stroke according to obesity status. Even with this new definition of abdominal obesity, the participants with abdominal obesity without general obesity and general and abdominal obesity tended to have increased risk of MACE, while participants with general obesity without abdominal obesity did not. Table S2 depicts the risk for MACE, MI, and stroke for abdominal obesity without general obesity participants compared with general obesity without abdominal obesity participants. There was a tendency toward increased risk of MACE among participants with abdominal obesity without general obesity compared with those with general obesity without abdominal obesity. The Kaplan–Meier curves for MACE according to the obesity status are shown in Figure S1. Participants with abdominal obesity without general obesity and general and abdominal obesity had increased risk of MACE compared with the nonobese group. Participants with general obesity without abdominal obesity had decreased risk of MACE compared with the nonobese group among men.

**Discussion**

In this nationwide population-based study of more than 300 000 Korean men and women, we have shown that being abdominally obese without being general obese was associated with higher risk of MACE, while general obesity without abdominal obesity was not associated with MACE. While
some previous studies have noted both BMI and WC as important risk factors for CVD,\textsuperscript{11,31} this is the first study to determine the risk of MACE among people with discrepancies between general and abdominal obesity among the Asian population.

While BMI and WC, the most commonly used surrogate markers of general and abdominal obesity, respectively, have been depicted as the major risk factors for CVD, the risks for those with high BMI only or high WC only are relatively unexplored. Our results demonstrate that being abdominally obese but not generally obese has a higher association with major cardiovascular outcomes, compared with being generally obese but not abdominally obese. This may be because of the fact that being abdominally obese without generally obese is associated with higher fat mass more so than being generally obese without abdominally obese, which is a group with leaner body composition with high muscle mass and lower fat mass. Previous studies have noted that high muscle mass

### Table 1. Descriptive Characteristics of the Study Population

| WC <90 (Men) or 80 (Women) cm | WC ≥90 (Men) or 80 (Women) cm |
|-------------------------------|-------------------------------|
| **BMI <25.0 kg/m\^2** | **BMI ≥25.0 kg/m\^2** | **BMI <25.0 kg/m\^2** | **BMI ≥25.0 kg/m\^2** |
| Normal | General Obesity Without Abdominal Obesity | Abdominal Obesity Without General Obesity | General and Abdominal Obesity |
| Number of people | 174 237 | 35 081 | 33 902 | 72 763 |
| Age, y, mean (SD) | 57.2 (8.6) | 55.5 (7.2) | 61.4 (9.3) | 59.0 (8.6) |
| Sex, N (%) | | | | |
| Men | 101 683 (58.4) | 27 693 (78.9) | 8147 (24.0) | 32 987 (45.3) |
| Women | 72 554 (41.6) | 7388 (21.1) | 25 755 (76.0) | 39 776 (54.7) |
| Household income, N (%) | | | | |
| First quartile (highest) | 64 338 (36.9) | 14 419 (41.1) | 11 099 (32.7) | 24 513 (33.7) |
| Second quartile | 50 291 (28.9) | 10 371 (29.6) | 10 138 (29.9) | 22 360 (30.7) |
| Third quartile | 36 930 (21.2) | 6474 (18.5) | 7326 (21.6) | 15 434 (21.2) |
| Fourth quartile (lowest) | 22 678 (13.0) | 3817 (10.9) | 5339 (15.8) | 10 456 (14.4) |
| Smoking, N (%) | | | | |
| Never smoker | 112 463 (64.6) | 18 953 (54.0) | 28 569 (84.3) | 52 825 (72.6) |
| Past smoker | 26 498 (15.2) | 8378 (23.9) | 2326 (6.9) | 9899 (13.6) |
| Current smoker | 35 276 (20.3) | 7750 (22.1) | 3007 (8.9) | 10 039 (13.8) |
| Physical activity, times per wk, N (%) | | | | |
| 0 | 89 059 (51.1) | 15 528 (44.3) | 20 101 (59.3) | 39 851 (54.8) |
| 1–2 | 43 515 (25.0) | 10 084 (28.7) | 6635 (19.6) | 16 614 (22.8) |
| 3–4 | 24 301 (14.0) | 5744 (16.4) | 3842 (11.3) | 9094 (12.5) |
| 5–6 | 9304 (5.3) | 2086 (6.0) | 1479 (4.4) | 3527 (4.9) |
| 7 | 8058 (4.6) | 1639 (4.7) | 1845 (5.4) | 3677 (5.1) |
| Alcohol consumption, times per wk, N (%) | | | | |
| 0 | 99 695 (57.2) | 15 742 (44.9) | 25 408 (75.0) | 45 772 (62.9) |
| 0–1 | 28 676 (16.5) | 7112 (20.3) | 3604 (10.6) | 10 000 (13.7) |
| 1–2 | 22 958 (13.2) | 6505 (18.5) | 2329 (6.9) | 8586 (11.8) |
| 3–4 | 14 575 (8.4) | 4110 (11.7) | 1528 (4.5) | 5656 (21.9) |
| 5 or more | 8333 (4.8) | 1612 (4.6) | 1033 (3.1) | 2749 (3.8) |
| Charlson comorbidity index, N (%) | | | | |
| ≤1 | 102 847 (59.0) | 21 574 (61.5) | 15 576 (45.9) | 35 581 (48.9) |
| 2–3 | 55 336 (31.8) | 10 714 (30.5) | 13 330 (39.3) | 27 233 (37.4) |
| ≥4 | 16 054 (9.2) | 2793 (8.0) | 4996 (14.7) | 9949 (13.7) |

\( P \) value calculated by \( \chi^2 \) test for categorical variables and analysis of variance for continuous variables. BMI indicates body mass index; N, number of people; WC, waist circumference.
mass and low fat mass was associated with significantly lower insulin resistance and metabolic syndrome, which is directly related to cardiovascular outcomes. Conversely, participants with normal BMI and high WC are thought to have higher visceral fat composition compared with subcutaneous fat, and multiple previous studies noted that visceral fat accumulation is associated with cardiovascular outcomes, while subcutaneous fat accumulation is not. Numerous previous studies have consistently described that obesity and metabolic syndrome are major risk factors of CVDs. However, there has been a suggestion that BMI does not accurately reflect body fat distribution, and surrogate markers of regional obesity such as WC, waist–hip ratio, or skinfold thickness might be more important predictors of either coronary heart disease or stroke. Winter and colleagues reported that markers of abdominal adiposity, including WC and related ratios, better predict stroke and cerebrovascular events than BMI on their case–control study. Similarly, Lakka and colleagues noted abdominal obesity as an independent risk factor for coronary heart disease in middle-aged men and even more important than overall obesity, based on BMI. Other studies have suggested both BMI and WC as independent risk factors of CVD. Taylor and colleagues analyzed more than 7000 adults from 4

Table 2. Hazard Ratios for Major Adverse Cardiovascular Events, Myocardial Infarction, and Stroke According to General and Abdominal Obesity

|                      | WC <90 (Men) or 80 (Women) cm | WC ≥90 (Men) or 80 (Women) cm |
|----------------------|-------------------------------|-----------------------------|
|                      | BMI <25.0 kg/m² | BMI ≥25.0 kg/m² | BMI <25.0 kg/m² | BMI ≥25.0 kg/m² |
| Normal               | General Obesity Without Abdominal Obesity | Abdominal Obesity Without General Obesity | General and Abdominal Obesity |

### Men

#### Major adverse cardiovascular events

|                      | Person-y | aHR (95% CI) |
|----------------------|----------|--------------|
| Events               | 2973     | 0.66         |
| Person-y             | 588 027  | 1.06 (0.98–1.16) |
| aHR (95% CI)         | 1.29 (1.16–1.43) |
|                      | 1.20 (1.12–1.29) |

#### Myocardial infarction

|                      | Person-y | aHR (95% CI) |
|----------------------|----------|--------------|
| Events               | 842      | 0.66         |
| Person-y             | 588 027  | 1.06 (0.98–1.16) |
| aHR (95% CI)         | 1.29 (1.16–1.43) |
|                      | 1.20 (1.12–1.29) |

#### Stroke

|                      | Person-y | aHR (95% CI) |
|----------------------|----------|--------------|
| Events               | 2323     | 0.66         |
| Person-y             | 588 027  | 1.06 (0.98–1.16) |
| aHR (95% CI)         | 1.29 (1.16–1.43) |
|                      | 1.20 (1.12–1.29) |

### Women

#### Major adverse cardiovascular events

|                      | Person-y | aHR (95% CI) |
|----------------------|----------|--------------|
| Events               | 1157     | 0.66         |
| Person-y             | 428 344  | 1.07 (0.88–1.30) |
| aHR (95% CI)         | 1.13 (1.03–1.24) |
|                      | 1.15 (1.06–1.25) |

#### Myocardial infarction

|                      | Person-y | aHR (95% CI) |
|----------------------|----------|--------------|
| Events               | 182      | 0.66         |
| Person-y             | 428 344  | 0.92 (0.54–1.59) |
| aHR (95% CI)         | 1.04 (0.83–1.31) |
|                      | 1.28 (1.05–1.57) |

#### Stroke

|                      | Person-y | aHR (95% CI) |
|----------------------|----------|--------------|
| Events               | 1038     | 0.66         |
| Person-y             | 428 344  | 1.11 (0.90–1.35) |
| aHR (95% CI)         | 1.13 (1.02–1.24) |
|                      | 1.12 (1.02–1.22) |

Hazard ratio calculated by Cox proportional hazards regression analysis after adjustments for age, household income, smoking, physical activity, alcohol consumption, and Charlson comorbidity index. aHR indicates adjusted hazard ratio; BMI, body mass index; WC, waist circumference.
Obesity and Major Adverse Cardiac Events

Choi et al

Authors noted that BMI, WC, and waist adiposity, including WC. Most recently, a study of collaborative analysis on 58 prospective studies also evaluated the combined effects of BMI and WC on CVD among 221 934 people. The study reported the HR for CVD to be 1.29 per 4.56 kg/m² higher BMI and 1.32 per 12.6 cm higher WC. The authors noted that BMI, WC, and waist–hip ratio each have a similar strength of association with CVD.

The major mechanisms linking obesity with CVD are relatively well elaborated in multiple previous studies. Obesity is known to increase the risk of multiple classic cardiovascular risk factors, such as dyslipidemia, glucose intolerance, and hypertension. Higher sympathetic nervous system activity and angiotensin-aldosterone activity in obesity are suggested to cause increasing circulating blood volume and peripheral resistance, thus leading to higher blood pressure. Adipose tissue also releases several cytokines and bioactive mediators, such as leptin, adiponectin, interleukin-6, and tumor necrosis factor-α, which influences insulin resistance and thus causes hypercholesterolemia and glucose intolerance. In addition to total body fat, abdominal visceral adiposity is associated with impaired suppression of adipocyte lipolysis and elevated nonesterified fatty acid levels, potentially leading to vascular endothelial dysfunction. Visceral adiposity is also associated with elevating C-reactive protein levels and increased macrophage-related atherogenic cytokines, causing low-grade systemic inflammation, which contributes to CVD. The attenuated risk of general obesity without abdominal obesity participants for MACE in this study is possibly because of the combined effect of low fat mass and high muscle mass.

One notable finding in the survival curves was that men with general obesity without abdominal obesity appeared to have improved survival for MACE compared with nonobese men, which is in contrast to the result from Table 2. This discrepancy might be because of possible confounders that were not considered in the Kaplan–Meier curves. The descriptive characteristics of Table 1 support this explanation since the nonobese participants tended to be older and have more comorbidities than participants of general obesity without abdominal obesity.

There are several limitations to be considered in this study. First, BMI and WC were not followed up after the index date and the effect of possible weight changes afterward was not accounted for. Second, the exact measures of body composition were not available. The attenuated risk of MACE among the general obesity without abdominal obesity group in this study is assumed to be because of the effect of high muscle, and low fat mass, particularly visceral fat. Additionally, adjustment of other measures on defining abdominal obesity, such as waist-to-height ratio, could be beneficial, which was not available in this study because of lack of data on height. Therefore, future studies using other measures of abdominal obesity such as waist-to-height ratio with reliable measurement of body composition of muscle, total fat, and visceral fat mass are needed to validate our findings. Third, the study population was restricted to men and women older than 40 years of age. Also, although we attempted to account for physical activity according to the self-reported questionnaire, this measure may be insufficient to determine the physical activity accurately. Therefore, future studies with a younger study population and using a more detailed measure of physical activity are also merited.

Finally, the increased risk for MACE in abdominal obesity was weaker among women compared with men. The statistical difference between abdominal obesity without general obesity
compared with general obesity was also not significant among women. One possible explanation for the result is because of the relatively low specificity of classical WC cutoff (80 cm) among women. The previous study among Korean men and women has suggested the obesity-related disorder was significant for women who had WC higher than 86.1 cm,52 and the other Japanese study suggested WC cutoff of 85 cm in men and 90 cm in women as a measure of central obesity reflecting the visceral fat area.30 The descriptive characteristics of the study population according to sex in Table 1 also support this suggestion, since more men tended to be generally obese without being abdominally obese, while more women tended to be abdominally obese according to classical BMI and WC cutoff. We attempted to account for the body composition discrepancy among men and women, and the result from supplemental analysis (Table S2) revealed women with abdominal obesity only without general obesity had a tendency toward increased risk of MACE (aHR 1.25, 95% CI 0.98–1.58), compared with those with general obesity without abdominal obesity. Although it seems that the WC cutoff value, which better reflects visceral fat, gives more consistent results among men and women, visceral obesity does not explain the entire discrepancy among men and women. Possible mechanisms other than visceral obesity might exist regarding this difference, such as the biological and hormonal difference between sexes, which could be associated with adipocyte metabolism and cardiovascular outcome.53 Therefore, future studies among the female population regarding WC-related health outcomes as well as studies on mechanisms regarding discrepancy among sex are needed to validate and confirm our findings.

Despite these limitations, our study has a number of strengths. The effect of general obesity and abdominal obesity on CVD has been less explored in Asian ethnicities. A large study population with adjustment of a wide range of covariates also enhances the generalizability and reliability of the results. Finally, to our knowledge, this is the first study to compare the risk of MACE among people with the discrepancies between general and abdominal obesity.

In conclusion, abdominal obesity without being generally obese, as well as general and abdominal obesity were associated with increased risk of MACE, while general obesity without abdominal obesity was not. Our results suggest that the concurrent determination of BMI and WC may be beneficial in more accurately determining the body composition in terms of muscle and fat mass. Consideration of both general and abdominal obesity may be associated with a more accurate determination of future cardiovascular risk.

**Author Contributions**

D. Choi, S. Choi, and S. Park contributed to the conception and design, analysis and interpretation of data, critical revision for important intellectual content, and final approval of the article. D. Choi and S. Choi contributed to the drafting of the article. S. Choi conducted collection and assembly of the data. All authors approved the final copy of the article. Park is the corresponding author and had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Sources of Funding**

This study was supported by the Basic Science Research Program through the National Research Foundation of Korea funded by the Ministry of Education (grant number: 2017R1D1A1B03033721), the Seoul National University Research Fund (grant number: 04-2018-0370), and the Korea Association of Health Promotion (grant number: 2019-04). S. Choi received a grant from the Brain Korea 21-Plus Education Program from the National Research Foundation of Korea. **Role of the Sponsors:** None of the funders had any role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

**Disclosures**

None.

**References**

1. Roth GA, Huffman MD, Moran AE, Feigin V, Mensah GA, Naghavi M, Murray CJ. Global and regional patterns in cardiovascular mortality from 1990 to 2013. Circulation. 2015;132:1667–1678.

2. Mortality GBD, Causes of Death C. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2015;385:117–171.

3. Willett WC, Manson JE, Stampfer MJ, Colditz GA, Rosner B, Speizer FE, Hennekens CH. Weight, weight change, and coronary heart disease in women. Risk within the ‘normal’ weight range. JAMA. 1995;273:461–465.

4. Emerging Risk Factors C, Wormser D, Kaptoge S, Di Angelantonio E, Wood AM, Pennells L, Thompson A, Sarwar N, Kizer JR, Lawlor DA, Nordestgaard BG, Ridker P, Salomaa V, Stevens J, Woodward M, Sattar N, Collins R, Thompson SG, Whitlock G, Danesh J. Separate and combined associations of body-mass index and abdominal adiposity with cardiovascular disease: collaborative analysis of 58 prospective studies. Lancet. 2011;377:1085–1095.

5. Prospective Studies C, Whitlock G, Lewington S, Sherliker P, Clarke R, Emberson J, Halsey J, Gilding N, Collins R, Peto R. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. Lancet. 2009;373:1093–1096.

6. Panikhi NK, Pencina MJ, Wang TJ, Lanier KJ, Fox CS, D’Agostino RB, Vasan RS. Increasing trends in incidence of overweight and obesity over 5 decades. Am J Med. 2007;120:242–250.

7. Abelsohn P, Kennedy D. The obesity epidemic. Science. 2004;304:1413.

8. Haslam DW, James WP. Obesity. Lancet. 2005;366:1197–1209.

9. Akil L, Ahmad HA. Relationships between obesity and cardiovascular diseases in four southern states and Colorado. J Health Care Poor Underserved. 2011;22:61–72.

10. Lavie CJ, Milani RV, Ventura HO. Obesity and cardiovascular disease: risk factor, paradox, and impact of weight loss. J Am Coll Cardiol. 2009;53:1925–1932.

11. Donahue RP, Abbott RD, Bloom E, Reed DM, Yano K. Central obesity and coronary heart disease in men. Lancet. 1987;1:821–824.
Obesity and Major Adverse Cardiac Events

12. Rimm EB, Stampfer MJ, Giovannucci E, Ascherio A, Spiegelman D, Colditz GA, Willett WC. Body size and fat distribution as predictors of coronary heart disease among middle-aged and older US men. Am J Epidemiol. 1995;141:1117–1127.

13. Lakka HM, Lakka TA, Tuomilehto J, Salonen JT. Abdominal obesity is associated with increased risk of acute coronary events in men. Eur Heart J. 2002;23:706–713.

14. Jansen I, Katzmarzyk PT, Ross R. Waist circumference and not body mass index explains obesity-related health risk. Am J Clin Nutr. 2004;79:379–384.

15. Litwin SE. Which measures of obesity best predict cardiovascular risk? J Am Coll Cardiol. 2008;52:616–619.

16. Carmienke S, Freitag MH, Pischon T, Schlattmann P, Fankhaenel T, Goebel H, Gensichen J. General and abdominal obesity parameters and their combination in relation to mortality: a systematic review and meta-regression analysis. Eur J Clin Nutr. 2013;67:573–585.

17. Rexrode KM, Carey VJ, Hennekens CH, Walters EE, Colditz GA, Stampfer MJ, Willett WC, Manson JE. Abdominal adiposity and coronary heart disease in women. JAMA. 1998;280:1843–1848.

18. Taylor AE, Ebrahim S, Ben-Shlomo Y, Martin RM, Whincup PH, Yarnell JW. Waist circumference, BMI, smoking, and mortality in middle-aged and men. Obes Res. 2003;11:895–903.

19. Nishida C, Ko GT, Kumanyika S. Body fat distribution and noncommunicable disease. Eur J Clin Nutr. 2013;67:585–590.

20. Son JS, Choi S, Kim K, Kim SM, Choi D, Lee G, Jeong SM, Park SY, Kim YY, Yun JM, Choi K, Kim SM, Choi D, Lee G, Jeong SM, Park SY, Kim YY, Yun JM. Association of muscle mass and fat mass with insulin resistance and cardiometabolic risk: the Jackson Heart Study. J Clin Endocrinol Metab. 2010;95:5419–5426.

21. Cheol Seong S, Kim YY, Khang YH, Heon Park J, Kang HJ, Lee H, Do CH, Song JS, Hyon Bang J, Ha S, Lee EJ, Ae Shin S. Data resource profile: the national health information database of the National Health Insurance Service in South Korea. Int J Epidemiol. 2017;46:799–800.

22. Seong SC, Kim YV, Park SK, Yoon KY, Hong CH, Park JC, Park JH, Kang HJ, Do CH, Song JS, Lee EJ, Ha S, Shin SA, Jeong SL. Cohort profile: the National Health Insurance Service-National Health Screening Cohort (NHIS-HEALS) in Korea. BMJ Open. 2017;7:e016640.

23. Son JS, Choi S, Kim K, Kim SM, Choi D, Lee G, Jeong SM, Park SY, Kim YY, Yun JM. Waist circumference criteria for the diagnosis of abdominal obesity are not applicable uniformly to all populations and ethnic groups. Nutrition. 2005;21:969–976.

24. Alberti KG, Zimmet P, Shaw J. Metabolic syndrome—a new worldwide definition. A consensus statement from the International Diabetes Federation. Diabet Med. 2006;23:469–480.

25. de Jong M, van der Worp HB, van der Graaf Y, Visseren FLJ, Westerink J, Pioglitazone and the secondary prevention of cardiovascular disease. A meta-analysis of randomized-controlled trials. Cardiovasc Diabetol. 2017;16:134.

26. Kim K, Park SM, Lee K. Weight gain after smoking cessation does not modify its protective effect on myocardial infarction and stroke: evidence from a cohort study of men. Eur Heart J. 2018;39:1523–1531.

27. Writing Group, Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, Das SR, De Ferrari DS, Despres JP, Fullerton HD, Howard VJ, Huffman MD, Isasi CR, Jimenez MC, Judd SE, Kissela BM, Lichtman JH, Ljungman B, Lincoff AM, Matsushita K, Meng CK, Mozaffarian D, Mussolino ME, Narisawa T, Neumar RW, Nichol G, Palaniappan L, Pandey DK, Reeves MJ, Rodriguez CJ, Rosamond W, Sorlie PD, Stein J, Towbin J, Tofler GH, Turk J, Towfighi A, Turan TN, Virani SS, Woo D, Yeh RW, Turner MB; American Heart Association Task Force on Blood Pressure Control in General Practice; European Society of Cardiology; International Society and Federation of Cardiology. 2017 AHA/ACC/ASH guideline for the prevention of cardiovascular disease in women: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2018;71:e104–e147.

28. Doghramji K, Szklo M. Association guidelines with subsequent cardiovascular disease events. Am J Epidemiol. 2015;181:1217–1226.

29. Kim K, Park SM. Association of muscle mass and fat mass with insulin resistance and the prevalence of metabolic syndrome in Korean adults: a cross-sectional study. Sci Rep. 2018;8:2703.
SUPPLEMENTAL MATERIAL
Table S1. Sensitivity analysis on the association of obesity with major adverse cardiovascular events with abdominal obesity defined as 85 or 90 cm or more for men and women, respectively.

|                      | WC<85 (men) or 90 (women) cm | WC≥85 (men) or 90 (women) cm |   |   |
|----------------------|-----------------------------|-------------------------------|---|---|
|                      | BMI<25.0 kg/m²               | BMI≥25.0 kg/m²                |   |   |
|                      | Normal                       | General obesity without abdominal obesity | Abdominal obesity without general obesity | General and abdominal obesity |
| Major adverse cardiovascular events |                      |                               |   |   |
| Events               | 2,127                        | 201                           | 1,231 | 1,563 |
| Person-years         | 444,796                      | 50,267                        | 189,360 | 303,753 |
| aHR (95% CI)         | 1.00 (reference)             | 1.14 (0.98-1.32)              | 1.22 (1.14-1.31) | 1.21 (1.13-1.29) |
| Myocardial infarction |                      |                               |   |   |
| Events               | 583                          | 61                            | 360  | 497  |
| Person-years         | 444,796                      | 50,267                        | 189,360 | 303,753 |
| aHR (95% CI)         | 1.00 (reference)             | 1.18 (0.90-1.53)              | 1.36 (1.19-1.55) | 1.38 (1.22-1.56) |
| Stroke               | 1,681                        | 148                           | 948  | 1,163 |
| Person-years         | 444,796                      | 50,267                        | 189,360 | 303,753 |
| aHR (95% CI)         | 1.00 (reference)             | 1.10 (0.93-1.31)              | 1.17 (1.08-1.27) | 1.15 (1.07-1.24) |
| Major adverse cardiovascular events |                      |                               |   |   |
| Events               | 1,831                        | 704                           | 79   | 451  |
| Person-years         | 569,666                      | 200,508                       | 8,888 | 76,509 |
| aHR (95% CI)         | 1.00 (reference)             | 1.04 (0.96-1.14)              | 1.21 (0.97-1.52) | 1.20 (1.08-1.33) |
| Myocardial infarction |                      |                               |   |   |
| Events               | 290                          | 121                           | 13   | 85   |
| Person-years         | 569,666                      | 200,508                       | 8,888 | 76,509 |
| aHR (95% CI)         | 1.00 (reference)             | 1.16 (0.94-1.44)              | 1.06 (0.61-1.85) | 1.34 (1.05-1.71) |
| Stroke               | 1,640                        | 620                           | 69   | 391  |
| Person-years         | 569,666                      | 200,508                       | 8,888 | 76,509 |
| aHR (95% CI)         | 1.00 (reference)             | 1.02 (0.93-1.12)              | 1.19 (0.94-1.52) | 1.16 (1.04-1.30) |

Hazard ratio calculated by Cox proportional hazards regression analysis after adjustments for age, household income, smoking, physical activity, alcohol consumption, and Charlson comorbidity index.

WC, waist circumference; BMI, body mass index; aHR, adjusted hazard ratio; CI, confidence interval.
Table S2. Sensitivity analysis on the association of general or abdominal obesity only with major adverse cardiovascular events with abdominal obesity defined as 85 or 90 cm or more for men and women, respectively.

|                | General obesity without abdominal obesity | Abdominal obesity without general obesity |
|----------------|-------------------------------------------|------------------------------------------|
| **Men**        |                                           |                                          |
| Major adverse cardiovascular events |                                           |                                          |
| Events         | 201                                       | 1,231                                    |
| Person-years   | 50,267                                    | 189,360                                  |
| aHR (95% CI)   | 1.00 (reference)                          | 1.07 (0.92-1.24)                        |
| Myocardial infarction |                                           |                                          |
| Events         | 61                                        | 360                                      |
| Person-years   | 50,267                                    | 189,360                                  |
| aHR (95% CI)   | 1.00 (reference)                          | 1.15 (0.87-1.52)                        |
| Stroke         |                                           |                                          |
| Events         | 148                                       | 948                                      |
| Person-years   | 50,267                                    | 189,360                                  |
| aHR (95% CI)   | 1.00 (reference)                          | 1.05 (0.88-1.25)                        |
| **Women**      |                                           |                                          |
| Major adverse cardiovascular events |                                           |                                          |
| Events         | 704                                       | 79                                       |
| Person-years   | 200,508                                   | 8,888                                    |
| aHR (95% CI)   | 1.00 (reference)                          | 1.24 (0.98-1.58)                        |
| Myocardial infarction |                                           |                                          |
| Events         | 121                                       | 13                                       |
| Person-years   | 200,508                                   | 8,888                                    |
| aHR (95% CI)   | 1.00 (reference)                          | 0.94 (0.52-1.69)                        |
| Stroke         |                                           |                                          |
| Events         | 620                                       | 69                                       |
| Person-years   | 200,508                                   | 8,888                                    |
| aHR (95% CI)   | 1.00 (reference)                          | 1.25 (0.97-1.62)                        |

Hazard ratio calculated by Cox proportional hazards regression analysis after adjustments for age, household income, smoking, physical activity, alcohol consumption, and Charlson comorbidity index.

WC, waist circumference; BMI, body mass index; aHR, adjusted hazard ratio; CI, confidence interval.
Figure S1. The Kaplan-Meier curves for MACE according to the obesity status.

a. The Kaplan-Meier curves for MACE according to the obesity status among men

b. The Kaplan-Meier curves for MACE according to the obesity status among women

c. The Kaplan-Meier curves for AMI according to the obesity status among men
d. The Kaplan-Meier curves for AMI according to the obesity status among women

e. The Kaplan-Meier curves for stroke according to the obesity status among men

f. The Kaplan-Meier curves for stroke according to the obesity status among women

MACE, major adverse cardiovascular events; AMI, acute myocardial infarction