

## Article

# Metabolically Healthy Obesity Versus Metabolic Obesity on Long-Term Major Adverse Cardiovascular Events and Mortality in Women with Suspected Ischemic Heart Disease

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## Abstract

**Background:** Obesity and metabolic syndrome (MS) often co-exist; however, these conditions can exist independently as metabolically healthy obesity (MHO) and as metabolic obesity (MO). **Methods:** We investigated the association between metabolic status and body weight and risk of obstructive angiographic coronary artery disease (CAD), long-term major adverse cardiovascular events (MACEs), and all-cause mortality in women with signs/symptoms of ischemic heart disease (IHD) enrolled in the original cohort of the Women's Ischemia Syndrome Evaluation (WISE) study (1997–2001) followed for mortality for a median of 8.6 years (range: 0–11.3 years). Normal weight (NW) was defined as a body mass index (BMI) < 25 kg/m<sup>2</sup>, overweight (OW) was defined as a BMI of 25–29 kg/m<sup>2</sup>, obesity (O) was defined as ≥30 kg/m<sup>2</sup>. MS was defined according to the NCEP ATP III Harmonized definition, metabolically healthy (MHO) was defined as obesity in the absence of MS, and MO was defined as MS in NW individuals. **Results:** 503 women were evaluated including 20.7% MH-NW, 14.7% MH-OW, 8.5% MHO, 6.2% MO, 21.9% MS-OW, 28.0% MS-O. Compared to MH-NW (reference), MHO was associated with a lower risk of MACEs (aHR 0.50; 95% CI 0.29, 0.85,  $p = 0.011$ ) and mortality (aHR 0.50; 95% CI 0.27, 0.95,  $p = 0.035$ ). MO was associated with higher odds of obstructive CAD (aOR 2.10; 95% CI 1.33, 3.33,  $p = 0.002$ ) and a higher risk of MACEs (aHR 1.67, 95% CI 1.07, 2.59,  $p = 0.023$ ). **Conclusions:** In women with suspected IHD, compared with MH-NW, MHO was associated with a lower risk of MACEs and mortality, whereas MO had higher odds of obstructive CAD and a greater MACE risk. These findings challenge simplistic BMI-based risk paradigms and emphasize the benefits of using metabolic status assessment over weight alone.

**Keywords:** ischemic heart disease; metabolically healthy obesity; MHO; metabolic obesity (MO); metabolic syndrome; body weight; obesity; women



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## 1. Introduction

The prevalence of obesity in the United States has risen steadily and is projected to reach 48.9% of the population by 2030 [1–4]. Parallel increases have occurred in related conditions such as metabolic syndrome (MS) [5]. MS is defined by a cluster of metabolic abnormalities including hyperglycemia, hypertension, hypertriglyceridemia, low high-density lipoprotein (HDL) cholesterol and increased waist circumference. Although MS and obesity often co-exist, they can occur independently [6]. Metabolically healthy obesity (MHO) refers to obese individuals without MS and is reported for up to 32% of obese individuals [7]. Metabolic obesity weight (MO) describes individuals with MS and normal body weight.

Both obesity and MS are established, independent predictors of cardiovascular disease (CVD) and mortality [8–15]. Evidence on long-term outcomes shows that compared with metabolically healthy normal-weight (MH-NW) individuals, MHO is associated with a higher risk of major adverse cardiovascular events (MACEs) and mortality, but the risk is greatest in MO individuals [16,17]. Other studies suggest that isolated obesity in MH individuals (MHO) may not increase MACE or mortality risk [18,19], particularly in women, as demonstrated in sex-stratified analyses [16,20,21].

We leveraged the Women's Ischemia Syndrome Evaluation (WISE) study to examine the associations between metabolic status and body weight measured by body mass index (BMI) with respect to the risk of obstructive angiographic coronary artery disease (CAD), long-term MACEs, and all-cause mortality in women presenting with signs and symptoms of ischemic heart disease (IHD).

## 2. Methods

### 2.1. Study Population

The study population consisted of women enrolled in the multicenter National Heart, Lung, and Blood Institute (NHLBI) Women's Ischemia Syndrome Evaluation (WISE) study (1997–2001). As previously described, women with signs/symptoms of IHD who were clinically referred for invasive coronary angiography were enrolled at four sites (University of Alabama at Birmingham, Birmingham, AL; University of Florida, Gainesville, FL; University of Pittsburgh, Pittsburgh, PA; and Allegheny General Hospital, Pittsburgh, PA, USA) [22]. Each woman provided informed consent approved by the institutional review board.

At the time of enrollment, each woman had undergone a baseline evaluation that included collection of demographic information, CAD risk factors, medical and reproductive history; and a physical examination with blood pressure and anthropometric measurements including body mass index (BMI), fasting blood samples, and angiography assessment of coronary arteries, as previously described [22].

### 2.2. Classification of Metabolic Status and Body Weight

The NCEP ATP III Harmonized definition was used to classify study participants as having MS based on the presence of  $\geq 3$  of the following factors: (1) waist circumference  $> 88$  cm, (2) fasting triglyceride levels  $\geq 150$  mg/dL (measured by enzymatic assay at the WISE core lipid laboratory), (3) HDL cholesterol (HDL-C)  $< 50$  mg/dL, (4) hypertension (systolic blood pressure  $\geq 130$  mm Hg, diastolic blood pressure  $\geq 85$  mm Hg or use of antihypertensive medication), and (5) fasting glucose  $\geq 100$  mg/dL [23–25]. Metabolically healthy (MH) was defined as the absence of  $\geq 3$  MS components. BMI was calculated as body weight in kilograms divided by height in meters squared ( $\text{kg}/\text{m}^2$ ). Normal weight was defined as BMI  $< 25$   $\text{kg}/\text{m}^2$ , overweight was defined as BMI 25 to 29  $\text{kg}/\text{m}^2$ , obesity was defined as BMI  $\geq 30$   $\text{kg}/\text{m}^2$ , and underweight was defined as

$\text{BMI} \leq 18.5 \text{ kg/m}^2$  [26]. MHO was defined as obesity in the absence of MS, and MO was defined as MS in NW individuals.

### 2.3. Angiographic Assessment of Coronary Artery Disease

Each participant underwent invasive coronary angiography completed upon enrollment in the study. WISE angiographic core laboratory (Rhode Island Hospital, Providence, RI) investigators blinded to all other subject data performed quantitative analysis of coronary angiograms [22]. Obstructive CAD was defined as the presence of  $\geq 1$  stenoses  $\geq 50\%$  in diameter, minimal CAD was defined as maximum stenosis diameter of 20–49%, and no CAD was defined as  $<20\%$  stenosis in all coronary arteries. The WISE CAD severity score was calculated based on angiographic severity of stenoses, presence of partial or complete collateral flow, and location of stenoses with values ranging from 5.0 to 88.5 [27].

### 2.4. Follow-Up and Cardiovascular Events

Follow-ups for cardiovascular events were conducted via annual telephone interviews by experienced site staff and/or over mail. The primary outcomes of interest were all-cause mortality and MACE, defined as a composite of nonfatal myocardial infarction, stroke, or congestive heart failure and all-cause mortality adjudicated by review of medical records. The National Death Index (NDI) was used to verify death through 10-year follow-up.

### 2.5. Statistical Analysis

The analytical sample included 503 (53.3%) of the 944 women enrolled who had complete data for MS, body weight, and follow-up events and did not have treated diabetes mellitus ( $N = 199$ ). The cohort was divided into 6 groups by metabolic status and body weight—MH-NW (reference-control), MH-OW, MHO, MO, MS-OW and MS-O—based on the definitions outlined.

Differences in baseline demographics and clinical characteristics by metabolic status and body weight were assessed by chi-square tests for categorical variables and ANOVA or Kruskal–Wallis tests for continuous variables. Logistic regression was used to obtain adjusted odds ratios of having obstructive angiographic CAD in relation to metabolic status and body weight, with MH-NW as the reference group. Covariates in the adjusted model included age, race, smoking status, and history of heart failure.

Kaplan–Meier (KM) methods estimated cumulative incidence of MACE and all-cause mortality, and log-rank tests compared KM curves. Participants who had not experienced events were censored at 10 years or the last date of follow-up before 10 years. Cox proportional hazards regression estimated unadjusted and adjusted hazard ratios (HRs) for 10-year relative risk of MACEs and all-cause mortality in relation to metabolic status and weight groups (MH-OW, MHO, MO, MS-OW and MS-O), with MH-NW as the reference group. Stepwise selection was used as an exploratory variable selection approach to identify a parsimonious set of independent predictors from a large pool of candidate variables for inclusion in the multivariable models. All variables in Table 1 were considered except those with  $>5\%$  missing data. Furthermore, among highly correlated variables, the one with the lowest univariable  $p$ -value was selected. Predictors with  $p < 0.10$  were included in the multivariable model. As a result of the stepwise selection described, CAD severity score, history of congestive heart failure, and smoking status were included in both models. In addition, age was added to the mortality model. Race, Duke Activity Status Index (DASI)-derived metabolic equivalents (METs), and postmenopausal status were added to the MACE model. The proportional hazards assumption was assessed using the Kolmogorov–Smirnov supremum-type test.

**Table 1.** Baseline characteristics stratified by metabolic status and body-weight groups.

| Characteristics upon Study Entry | MH-NW<br>(N = 104) | MH-OW<br>(N = 74) | MHO<br>(N = 43) | MO<br>(MS-NW)<br>(N = 31) | MS-OW<br>(N = 110) | MS-O<br>(N = 141) | p-Value<br>for Trend |
|----------------------------------|--------------------|-------------------|-----------------|---------------------------|--------------------|-------------------|----------------------|
| Age, mean (SD), yrs              | 60.1 (12.3)        | 55.7 (10.4)       | 54.5 (9.2)      | 61.9 (13.8)               | 59.4 (11.6)        | 56.8 (11.5)       | 0.005                |
| Nonwhite race, No. (%)           | 8 (7.7%)           | 10 (13.5%)        | 14 (32.6%)      | 4 (12.9%)                 | 19 (17.3%)         | 27 (19.1%)        | 0.008                |
| History of hypertension, No. (%) | 40 (38.5%)         | 21 (28.4%)        | 20 (46.5%)      | 14 (45.2%)                | 70 (64.2%)         | 89 (63.6%)        | <0.001               |
| History of dyslipidemia, No. (%) | 49 (48.0%)         | 24 (33.3%)        | 19 (46.3%)      | 18 (58.1%)                | 57 (57.6%)         | 69 (53.1%)        | 0.036                |
| Smoker, No. (%)                  | 21 (20.2%)         | 14 (18.9%)        | 5 (11.6%)       | 14 (45.2%)                | 34 (31.2%)         | 23 (16.3%)        | 0.001                |
| Postmenopausal, No. (%)          | 86 (82.7%)         | 47 (63.5%)        | 29 (67.4%)      | 24 (77.4%)                | 88 (80.0%)         | 102 (72.3%)       | 0.038                |
| History of HRT, No. (%)          | 64 (62.1%)         | 36 (48.6%)        | 26 (60.5%)      | 17 (54.8%)                | 63 (58.3%)         | 63 (45.0%)        | 0.084                |
| CAD severity score, mean (SD)    | 11.7 (10.7)        | 11.4 (12.4)       | 11.0 (14.1)     | 16.8 (14.8)               | 16.1 (15.0)        | 13.4 (14.3)       | <0.001               |
| DASI, mean (SD)                  | 24.6 (15.4)        | 22.9 (14.1)       | 22.8 (15.1)     | 20.7 (16.1)               | 20.6 (15.7)        | 18.2 (13.3)       | 0.017                |
| WC, mean (SD), cm                | 73.8 (8.9)         | 85.9 (10.4)       | 96.1 (11.8)     | 84.3 (10.5)               | 94.1 (8.5)         | 107.9 (16.5)      | <0.001               |
| Waist–hip ratio, mean (SD)       | 0.8 (0.1)          | 0.8 (0.1)         | 0.8 (0.1)       | 0.9 (0.1)                 | 0.9 (0.1)          | 0.9 (0.1)         | <0.001               |
| Waist–height ratio, mean (SD)    | 0.5 (0.1)          | 0.5 (0.1)         | 0.6 (0.1)       | 0.5 (0.1)                 | 0.6 (0.1)          | 0.7 (0.1)         | <0.001               |
| SBP, mean (SD), mmHg             | 128.8 (23.7)       | 129.0 (18.3)      | 137.7 (20.7)    | 128.1 (24.5)              | 139.2 (19.3)       | 139.4 (20.3)      | <0.001               |
| DBP, mean (SD), mmHg             | 73.1 (11.6)        | 77.0 (11.8)       | 79.0 (11.1)     | 72.7 (14.7)               | 77.6 (11.7)        | 79.3 (12.5)       | 0.002                |
| Lipids, mean (SD), mg/dL         |                    |                   |                 |                           |                    |                   |                      |
| Total cholesterol                | 209.3 (49.1)       | 200.8 (38.1)      | 206.0 (31.8)    | 220.9 (56.9)              | 219.0 (54.7)       | 216.0 (46.2)      | 0.139                |
| HDL-C                            | 62.5 (16.3)        | 58.1 (15.0)       | 62.8 (12.8)     | 44.2 (12.9)               | 46.2 (12.9)        | 46.5 (11.1)       | <0.001               |
| LDL-C                            | 120.3 (42.7)       | 122.6 (34.4)      | 119.0 (32.2)    | 141.7 (50.7)              | 128.1 (43.4)       | 132.3 (47.7)      | 0.125                |
| Triglycerides                    | 132.6 (87.0)       | 107.1 (39.5)      | 118.9 (60.8)    | 185.1 (92.4)              | 212.2 (146.2)      | 206.7 (136.4)     | <0.001               |
| FBG, mean (SD), mg/dL            | 86.8 (23.6)        | 84.3 (22.8)       | 91.0 (11.8)     | 116.5 (43.7)              | 104.2 (28.4)       | 115.3 (40.4)      | <0.001               |
| Insulin, mean (SD), µU/mL        | 4.7 (3.9)          | 4.9 (7.7)         | 5.7 (5.4)       | 6.2 (6.0)                 | 8.5 (10.2)         | 12.2 (11.4)       | <0.001               |
| Inflammatory markers             |                    |                   |                 |                           |                    |                   |                      |
| hs-CRP, mean (SD), mg/dL         | 0.5 (0.7)          | 0.7 (1.4)         | 0.7 (0.6)       | 1.1 (1.9)                 | 1.4 (2.9)          | 0.9 (1.1)         | <0.001               |
| Interleukin-6, mean (SD), pg/dL  | 2.9 (2.7)          | 4.5 (3.8)         | 3.5 (3.2)       | 7.8 (8.5)                 | 5.3 (5.9)          | 4.5 (3.2)         | <0.001               |

CAD, coronary artery disease; DASI, Duke Activity Status Index; DBP, diastolic blood pressure; FBG, fasting blood glucose; HDL-C, high density lipoprotein cholesterol; HRT, hormone replacement therapy; hs-CRP, high sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; WC, waist circumference; MH-NW, metabolically healthy and normal weight; MH-OW, metabolically healthy and overweight; MHO, metabolically healthy obesity (obesity without metabolic syndrome); MO, metabolic obesity defined as metabolic syndrome and normal weight (MS-NW); MS-OW, metabolic syndrome and overweight; MS-O, metabolic syndrome and obesity.

We did not form a separate analysis group for “underweight” subjects, because only 13 subjects (2.6% of study cohort) met this definition. Statistical analyses were performed using SAS software (SAS, version 9.4, Carey, NC, USA) and R statistical software (version 4.2.2; R Foundation, Vienna, Austria) with two-sided tests and a significance level of 0.05.

### 3. Results

#### 3.1. Baseline Characteristics Stratified by Metabolic Status and Body Weight

Among the 503 women included in the analysis, the distribution was 20.7% MH-NW, 14.7% MH-OW, 8.5% MHO, 6.2% MO, 21.9% MS-OW, and 28.0% MS-O. Women with MH-NW had the lowest rates of being ever-smokers, the highest rates of being in a postmenopausal state, the lowest waist circumference, the highest mean DASI, the lowest insulin levels, and the lowest inflammatory marker levels (hs-CRP and IL-6) compared to the other groups (Table 1). MH-OW women had the lowest rates of hypertension, dyslipidemia, and being postmenopausal and the lowest levels of triglycerides and fasting blood glucose compared with the other groups. Women with MHO were the youngest on average and had the lowest CAD severity scores and highest HDL-C levels compared to other groups. MO women were the oldest on average, had the highest rates of dyslipidemia and being smokers, had the lowest systolic and diastolic blood pressure, and had the highest fasting blood glucose and IL-6 levels compared to the other groups. Women with MS-O and MS-OW had the highest rates of hypertension, the lowest DASI, and the highest systolic blood pressure, triglyceride, and insulin levels compared to the other groups.

### 3.2. Angiographic CAD Stratified by Metabolic Status and Body Weight

Angiographically, 163 (32.5%) had obstructive CAD. MHO women had the lowest prevalence of obstructive CAD, whereas MO women had the highest prevalence of obstructive CAD, compared to the other groups (Table 2). Compared to the MH-NW group (reference), MO women had 2.1-fold higher odds of having obstructive CAD, and women with MS-OW had 2.38-fold higher odds in adjusted models.

**Table 2.** Prevalence of obstructive coronary artery disease and likelihood by metabolic status and body-weight status.

| Variables                       | <i>n</i> | Prevalence<br>of CAD | Unadjusted<br>OR (95% CI) | Adjusted<br>OR † (95% CI) | <i>p</i> -Value |
|---------------------------------|----------|----------------------|---------------------------|---------------------------|-----------------|
| <b>Metabolic and BMI Groups</b> |          |                      |                           |                           |                 |
| MH-NW                           | 104      | 26.9%                | Reference                 | Reference                 | -               |
| MH-OW                           | 73       | 28.8%                | 0.95 (0.57, 1.58)         | 1.13 (0.66, 1.94)         | 0.6             |
| MHO                             | 42       | 11.9%                | 0.49 (0.28, 0.86)         | 0.62 (0.34, 1.12)         | 0.1             |
| MO (MS-NW)                      | 31       | 48.4%                | 2.41 (1.55, 3.76)         | 2.10 (1.33, 3.33)         | 0.002           |
| MS-OW                           | 110      | 44.5%                | 2.30 (1.33, 3.98)         | 2.38 (1.34, 4.24)         | 0.003           |
| MS-O                            | 141      | 31.9%                | 1.19 (0.70, 2.02)         | 1.31 (0.75, 2.29)         | 0.3             |

MH-NW, metabolically healthy and normal weight; MH-OW, metabolically healthy and overweight; MHO, metabolically healthy obesity (obesity without metabolic syndrome); MO, metabolic obesity defined as metabolic syndrome and normal weight (MS-NW); MS-OW, metabolic syndrome and overweight; MS-O, metabolic syndrome and obesity. † Indicates models adjusted for age, race, smoking status, and history of heart failure.

### 3.3. Cardiovascular Events and All-Cause Mortality Stratified by Metabolic Status and Body Weight

Overall, in the cohort, 119 (23.7%) patients had a MACE during a median follow-up time of 5.9 years (range: 0 to 9.3 years); and 80 (16.0%) died during a median follow-up of 8.6 years (range: 0 to 11.3 years). Kaplan–Meier analysis showed a significant difference in MACEs and all-cause mortality between the groups according to metabolic status and body weight (Figure 1). Women with MO had the lowest MACE-free survival and overall survival (Figure 1). Compared to MH-NW (reference), MHO was associated with a lower risk of MACEs (HR 0.50; 95% CI 0.29–0.85) and all-cause mortality (HR 0.50; 95% CI 0.27–0.95) in adjusted models (Figure 2). MO women were at an increased risk of MACEs (HR 1.67; 95% CI 1.07–2.59), relative to the reference MH-NW group. Table S1 shows the HRs of the variables included in the multivariable Cox regression model for the 10-year relative risks for MACEs and all-cause mortality in relation to body weight and metabolic health. The results were unchanged when “underweight” subjects were excluded from the normal-weight group.

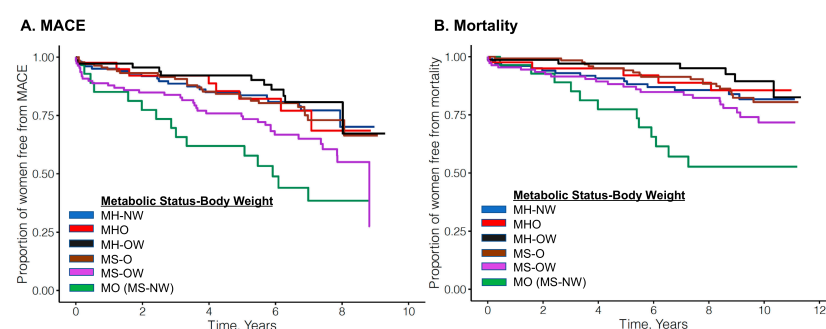


**Figure 1.** Major adverse cardiovascular event (MACE)-free survival (A) and survival (B) during long-term follow-up stratified by metabolic status and body weight. MH-NW, metabolically healthy

and normal weight; MH-OW, metabolically healthy and overweight; MHO, metabolically healthy obesity (obesity without metabolic syndrome); MO, metabolic obesity defined as metabolic syndrome and normal weight (MS-NW); MS-OW, metabolic syndrome and overweight; MS-O, metabolic syndrome and obesity.

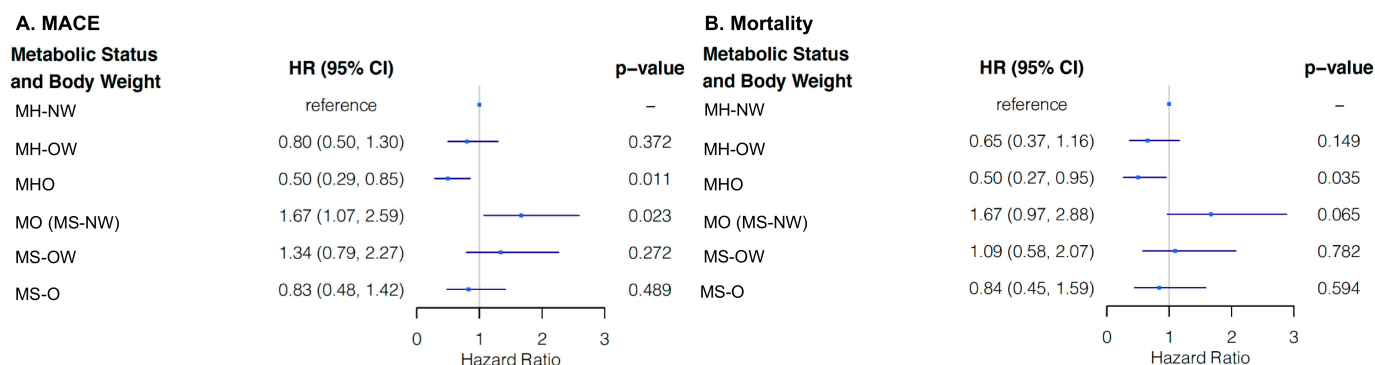


**Figure 2.** Adjusted risk of major adverse cardiovascular events (A) and all-cause mortality (B) stratified by metabolic status and body weight. MH-NW, metabolically healthy and normal weight; MH-OW, metabolically healthy and overweight; MHO, metabolically healthy obesity (obesity without metabolic syndrome); MO, metabolic obesity defined as metabolic syndrome and normal weight (MS-NW); MS-OW, metabolic syndrome and overweight; MS-O, metabolic syndrome and obesity. Reference: group MH-NW. MACE model adjusted for race, coronary artery disease (CAD) severity score, history of heart failure, smoking status, Duke Activity Status Index (DASI)-derived metabolic equivalents (METs), and postmenopausal status. Mortality model adjusted for age, CAD severity score, history of heart failure, and smoking status.

#### 4. Discussion

Among women with suspected IHD, MHO was associated with a lower risk of MACEs and all-cause mortality, whereas MO women had higher odds of obstructive CAD and a higher risk of experiencing an MACE compared with the reference group (MH-NW).

The prevalence of MHO in our study was 8.5%, which is consistent with previous reports [28,29]. Obesity accelerates atherosclerosis through inflammation, insulin resistance, adverse lipid profiles and endothelial dysfunction and is strongly linked to a higher risk of CAD and IHD [15,30–32]. However, the “obesity paradox,” consisting of a lower risk of MACEs and mortality in obese patients with established CAD, has been described in multiple cohorts [33–35]. Our findings are consistent with a prior study of patients with acute coronary syndrome showing a lower risk of MACEs in women with MHO compared to MH-NW women [20]. The higher prevalence of hormone replacement therapy in the MHO group may have contributed to these findings, which warrants further investigation [36]. We also observed a lower risk of MACEs and all-cause mortality in MH-OW women. Overall, our results suggest that overweight and obesity in the absence of cardiometabolic abnormalities may represent a lower-risk overweight and obese phenotype that could partly explain the “obesity paradox” and warrants future investigation.

The markedly higher risk of CAD and MACEs associated with MS is well established [14,37]. Growing evidence indicates that the excess risk associated with MS persists even in individuals with a normal weight determined by BMI assessment, i.e., the MO phenotype [16,17,38]. For example, in the Women’s Health Study, women free of CVD but with MO had a 2-fold-higher risk of experiencing CV events at 10 years. Our results extend these observations to women with suspected IHD [38]. Our findings are further supported by two meta-analyses showing a 2-fold-higher risk of CV events in MO women [16,17]. Independent of BMI, the insulin resistance, atherogenic dyslipidemia, hypertension, visceral adiposity, and the proinflammatory/prothrombotic milieu that characterizes MS

promotes endothelial dysfunction, aortic stiffness, and subclinical atherosclerosis and CAD. In our cohort, women with MO had the lowest systolic and diastolic blood pressure but the highest fasting blood glucose, suggesting insulin resistance may be an important driver of the higher risk of CAD and MACEs we observed in this group. This hypothesis is consistent with prior studies linking insulin resistance (higher fasting insulin) to a greater risk of CAD and IHD [39]. We also found that menopausal status predicted MACEs in our cohort; therefore, the predominance of postmenopausal women in the MO group may have contributed to our results supported by the increased incidence of CAD and IHD associated with menopause [36]. In contrast to other studies [16,17], we observed that MACE and mortality risks in MS-OW and MS obese women were similar to those for MH-NW women. These findings are not fully understood and warrant validation in other cohorts of women with IHD, as overweight and obesity with co-morbid MS have been associated with atherosclerotic plaque progression. Our findings suggest that diagnosis of MO which requires cardiometabolic assessment beyond BMI-measured body weight, including waist circumference, fasting glucose/insulin, lipids, and blood pressure, should be obtained and guide aggressive preventive strategies.

BMI-based body weight alone has limitations, as it does not capture body composition, body fat distribution, nutritional status, cardiorespiratory fitness, or other determinants of long-term cardiovascular outcomes [40]. Abdominal obesity, reflecting excess visceral adiposity, is more strongly associated with metabolic abnormalities and MS than isolated BMI-defined obesity and has been linked to increased cardiovascular risk in MHO individuals [41–44]. We therefore hypothesize that the differences in body composition among MHO women in our study may have contributed to their more favorable outcomes [42]. Cardiorespiratory fitness, which improves cardiovascular outcomes irrespective of BMI, may also have played a role in the lower risk observed in MHO women [45–48]. MO individuals in our cohort had the highest fasting glucose and IL-6 and the second-highest hs-CRP levels, supporting a state of insulin resistance and heightened inflammation. Insulin resistance, reflected by elevated fasting glucose levels, promotes metabolic dysregulation, increases in reactive oxygen species, endothelial dysfunction, myocardial injury and inflammatory activation [49–51]. We hypothesize that insulin resistance and inflammation contributed to the higher odds of obstructive CAD and risk of MACEs in the MO women. Collectively, our findings underscore the complex interplay between obesity, MS, and cardiovascular risk and highlight the need for further investigation [52].

*Limitations:* This study uses longitudinal data from a well-characterized cohort of women with signs and symptoms of IHD undergoing coronary angiography. Several limitations merit consideration. First, we relied on BMI as a measure of body weight and did not have measures of visceral fat or more detailed body composition. Second, body weight and metabolic status were assessed only at baseline; changes over time were not captured and may have influenced long-term MACEs and mortality. Third, differences in angiographic findings and medical therapy could have affected our results. Fourth, we used stepwise variable selection to construct multivariable models. While this approach can simplify modeling, it may increase the risk of overfitting and the exclusion of weak but clinically relevant confounders. Thus, although we identified independent associations within our cohort, residual confounding remains possible, and our models require validation in independent populations. Fifth, this is an observational study and cannot establish causality. Finally, our population was limited to women presenting with signs and symptoms of IHD; therefore, these findings may not be generalizable to asymptomatic or lower-risk women. In light of these limitations, our findings should be considered hypothesis-generating and require confirmation in other cohorts.

## 5. Conclusions

In women with suspected IHD, compared with MH-NW, MHO was associated with a lower risk of MACEs and mortality, whereas MO was associated with a higher risk of MACEs. These findings challenge simplistic BMI-based risk paradigms and emphasize the importance of metabolic health assessment over weight alone. Further research is needed to better understand sex-specific differences in the relationship between body weight and metabolic health as well as the mechanisms that drive outcomes in MHO and MO.

**Supplementary Materials:** The following supporting information can be downloaded at <https://www.mdpi.com/article/10.3390/hearts7020018/s1>. Table S1: Multivariable Cox proportional regression model for relative risks of MACE and all-cause mortality in relation to body weight and metabolic status.

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## Abbreviations

|       |                                         |
|-------|-----------------------------------------|
| CVD   | cardiovascular disease                  |
| IHD   | ischemic heart disease                  |
| MACE  | major adverse cardiovascular events     |
| MH-NW | Metabolically healthy and normal weight |
| MH-OW | Metabolically healthy and overweight    |

|       |                                   |
|-------|-----------------------------------|
| MHO   | Metabolically healthy obesity     |
| MO    | metabolic obesity                 |
| MS    | metabolic syndrome                |
| MS-OW | metabolic syndrome and overweight |
| MS-O  | metabolic syndrome and obesity    |

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