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Combining Body Mass Index With Measures of Central Obesity in the Assessment of Mortality in Subjects With Coronary Disease

Role of "Normal Weight Central Obesity"

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Objectives This study sought to assess the mortality risk of patients with coronary artery disease (CAD) based on a combination of body mass index (BMI) and measures of central obesity.

Background In CAD patients, mortality has been reported to vary inversely with BMI ("obesity paradox"). In contrast, central obesity is directly associated with mortality. Because of this bi-directional relationship, we hypothesized that CAD patients with normal BMI but with central obesity would have worse survival compared with subjects with other combinations of BMI and central adiposity.

Methods We included 15,547 participants with CAD who took part in 5 studies from 3 continents. Multivariate stratified Cox-proportional hazard models that adjusted for potential confounders were used to assess mortality risk according to different patterns of adiposity that combined BMI with measures of central obesity.

Results Mean age was 66 years; 55% were men. There were 4,699 deaths over a median follow-up of 4.7 years. Subjects with normal weight but central obesity had the worst long-term survival: a person with BMI of 22 kg/m^2 and waist-to-hip ratio (WHR) of 0.98 had higher mortality than a person with similar BMI but WHR of 0.89 (hazard ratio [HR]: 1.10; 95% confidence interval [CI]: 1.05 to 1.17); than a person with BMI of 26 kg/m^2 and WHR of 0.89 (HR: 1.20; 95% CI: 1.09 to 1.31), than in a person with BMI of 30 kg/m^2 and WHR of 0.89 (HR: 1.61; 95% CI: 1.39 to 1.86), and than a person with BMI of 30 kg/m^2 and WHR of 0.98 (HR: 1.27; 95% CI: 1.18 to 1.39) ($p < 0.0001$ for all).

Conclusions In patients with CAD, normal weight with central obesity was associated with the highest risk of mortality. (J Am Coll Cardiol 2013;61:553–60) © 2013 by the American College of Cardiology Foundation

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Abbreviations and Acronyms

BMI = body mass index
CAD = coronary artery disease
CI = confidence interval
HR = hazard ratio
WC = waist circumference
WHR = waist-to-hip ratio

Over the last decade, attention has been directed to the prognostic value of obesity, as defined by the body mass index (BMI), among subjects with coronary artery disease (CAD). Despite the fact that obesity has been associated with higher prevalence of cardiovascular risk factors and cardiovascular disease (1), several publications have shown BMI to be inversely associated with mortality in patients with CAD (the so-called "obesity paradox") (2). Such findings challenge conventional wisdom, because obesity is known to be associated with diabetes, hypertension, and dyslipidemia (3); and the majority of subjects with CAD are either overweight or obese (4). Because BMI has been shown to be a poor discriminator of body fat and lean mass, especially in CAD patients (5), the entity of "normal weight obesity" (i.e., normal BMI but high body fat content) has been recently described and shown to be associated with cardiovascular risk factors, and also with increased mortality in women (6). In addition, we have recently demonstrated that measures of fat distribution, such as the waist circumference (WC) and waist-to-hip ratio (WHR), are directly associated with mortality in people with CAD (7), in contrast to BMI. However, what remains poorly defined is whether the combination of BMI with measures of central obesity can help better discriminate CAD patients at greater mortality risk, and how patients with normal BMI but who are centrally obese fare in comparison to patients with other body adiposity patterns.

Thus, we hypothesized that patients with CAD with normal BMI but who have central obesity would have worse long-term survival compared with subjects with normal, overweight and obese BMI who do not have central obesity. To this end, we sought to investigate the mortality risk associated with patterns of body adiposity based on a combination of BMI and either WC or WHR in a large, multiethnic sample of patients with CAD.

Methods

Subjects. Through a systematic review of the literature and collaborative effort to assess the prognostic value of central obesity in CAD, we created a large database comprising 15,923 subjects with CAD from 3 different continents, Details regarding the systematic review, inclusion and exclusion criteria, origin of the cohorts included, and approach to obtain individual-level data have been previously published (7). In summary, we identified 6 studies that assessed risk of mortality associated with either WC or WHR in CAD patients from 1980 to 2008. Four of these studies agreed to share individual-level data, and then we further pooled unpublished data from the Mayo Clinic Cardiovascular Rehabilitation database, yielding our final study sample. Because there is no controversy surrounding the increased mortality observed in extremely thin individuals (2), presumably due to higher prevalence of chronic diseases and terminal conditions that affect prognosis, we excluded 373 underweight subjects (BMI <18.5 kg/m^2). We also excluded 3 participants with erroneous anthropometric measurements.

Patterns of adiposity. It was hypothesized that among patients with CAD a combination of normal BMI and central obesity would result in a higher risk of mortality compared with other patterns of adiposity. BMI was calculated by dividing weight (in kilograms) by the square of height (meters). Central obesity was quantified using either WC or WHR. WC was available for subjects from 4 studies (8–11), and WHR was available for subjects in 3 studies (9–11). BMI was available for all subjects.

Statistical modeling. The overarching goal of the analysis was to develop a parsimonious Cox model to quantify the relative hazard of mortality based on comparisons of combinations of body mass and measures of central obesity.

Stratified Cox models were estimated using each study as the stratification factor (i.e., the model allowed for each study to have its own background hazard rate while estimating common hazard ratios [HRs] for variables included in the model). Higher order interactions of WHR or WC with BMI were considered to allow for nonlinear relationships in the risk for various combinations of values for these variables. Likewise, interactions between the measures of adiposity with sex were also tested. Likelihood ratio tests were used to determine if these higher order model terms could be removed. Once the final model was established, HRs were estimated for different profiles of participants (represented as candidate persons with different body adiposity patterns that combine BMI with a measure of central obesity) using the estimated model parameters. For these comparisons, we chose a BMI of 22 kg/m^2 to represent "normal BMI," 26 kg/m^2 to represent "overweight BMI," and 30 kg/m^2 to represent "obese BMI." For WC and WHR, we chose the values that represented the 25th and 75th percentiles of the sample. For WC, these values were 85 and 101 cm, respectively; for WHR, these values were 0.89 and 0.98, respectively. HRs and their estimated SEs were used to conduct Wald (or large sample) tests for statistical significance between the representative patient profiles. These estimates were adjusted for age, sex, history of smoking, and the presence of hypertension, diabetes, and heart failure. These adjustment variables have been shown to predict survival in patients with CAD (12). Inclusion of other putative confounding variables was hindered due to

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unavailability of data across all studies. The proportional hazards assumption for WC, WHR, and BMI was assessed and was satisfied for the final models.

The robustness of the modeling framework was tested by replacing the continuous measures of central obesity and BMI by a set of indicator variables representing different groups of patients based on BMI and WC or WHR. Because this method of testing for association is less powerful (13), these models were used to qualitatively assess the magnitude of associations observed in the more complex Cox models. These results from the analysis using the categorized variables agreed with the estimates obtained using the continuous variable representation.

Modeling was supported through standard descriptive statistics of the sample data. Continuous variables were reported as mean ± SD, and categorical variables were reported as percentages. Statistical analyses were performed using JMP version 9.0.1 (SAS Institute Inc., Cary, North Carolina) and the SAS System version 9.3 (SAS Institute Inc.).

Results

Mean age of the subjects was 65.5 ± 11.5 years, and 60% were men. There were 5,507 deaths over a median follow-up of 2.4 years (interquartile range 0.5 to 7.4 years). The remaining baseline characteristics of the participants are outlined in Table 1.

The interaction term analyses showed that there was a significant interaction between BMI and WC or WHR ($p < 0.001$). Interactions between sex and BMI, sex and WC, and sex and WHR were not statistically significant ($p > 0.05$ for all). The crude death risk based on different combinations of BMI with central obesity can be seen in Figure 1 (WC) and Figure 2 (WHR). Examination of Figures 1 and 2 reveals that subjects who have a normal BMI but are in the highest quintiles of central obesity have higher mortality risk than any other combination of BMI and central obesity. Conversely, subjects who had a BMI in the overweight or obese categories but were in the lowest quintiles of central obesity had the lowest mortality. Similar findings were observed when using WC or WHR as the measure of central obesity.

The final multivariate stratified Cox model is depicted in Table 2. Based on the results from this model, we estimated the HRs for mortality attributed to patients with normal weight central obesity compared with subjects with other patterns of adiposity. Results are illustrated in Figure 3 (using WC) and Figure 4 (using WHR), and show that subjects with normal weight central obesity ("Person 2" in Figs. 3 and 4) have higher mortality than subjects with any other combination of BMI with WC or WHR. Specifically, a person with normal weight central obesity had 10% to 17% higher mortality risk than a person with similar BMI but no central obesity, 20% to 31% higher risk of mortality than an overweight subject without central obesity, 57% to 61% greater mortality than an obese person without central obesity, and 27% to 44% higher risk of dying than an obese subject with similar WC or WHR. Together, the results depicted in Figures 1 to 4 confirm that subjects with CAD who have a BMI in the normal range but are centrally obese have the worst prognosis. Results were similar when a BMI of 23.5 kg/m^2 was chosen instead of 22 kg/m^2 to represent normal BMI in the groups (analyses not shown).

Lastly, we found that although increasing age attenuated the effects of normal weight central obesity on mortality,

Table 1 Baseline Characteristics of Participants

	Whole Group (n = 15,547)	Women (n = 6,286)	Men (n = 9,261)
Age (yrs)	65.6 ± 11.5	69.0 ± 9.6	63.2 ± 12.1
Height (cm)	166.1 ± 9.2	159.5 ± 6.7	171.9 ± 7.0
Weight (kg)	73.6 ± 14.4	68.3 ± 14.4	77.2 ± 13.3
Body mass index (kg/m^2)	26.3 ± 4.4	26.8 ± 5.2	26.0 ± 3.7
Waist circumference (cm) (n = 13,935)	93.4 ± 12.5	91.5 ± 13.5	94.9 ± 11.5
Hip circumference (cm) (n = 12,525)	98.6 ± 10.8	101.1 ± 12.6	96.6 ± 8.6
Waist-to-hip ratio (n = 12,525)	0.93 ± 0.08	0.90 ± 0.08	0.96 ± 0.06
History of hypertension	6,016 (39%)	3,130 (50%)	2,886 (31%)
History of diabetes	2,888 (19%)	1,376 (22%)	1,512 (16%)
History of smoking	9,612 (62%)	3,117 (50%)	6,495 (70%)
History of heart failure	2,126 (14%)	934 (15%)	1,192 (13%)
Serum creatinine (μmol/l) (n = 12,251)*†	94.6 (79.6–108.4)	88.4 (79.6–106.8)	97.2 (84.0–114.0)
Aspirin use (n = 12,312)	9,640 (78%)	4,197 (76%)	5,443 (80%)
Beta blocker use (n = 12,316)	3,811 (31%)	1,665 (30%)	2,146 (32%)
ACEi/ARB use (n = 12,316)	3,481 (28%)	1,235 (22%)	2,246 (33%)
Deaths	5,507 (35%)	2,127 (35.5%)	3,380 (44.1%)

Values are mean ± SD, n (%), or median (interquartile range). *Serum creatinine was reported as median (interquartile range) because of the skewness of its distribution. †To convert serum creatinine to milligrams per deciliter, divide by 88.4.

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker. BMI = body mass index; IQR= interquartile range; WC = waist circumference; WHR = waist-to-hip ratio.

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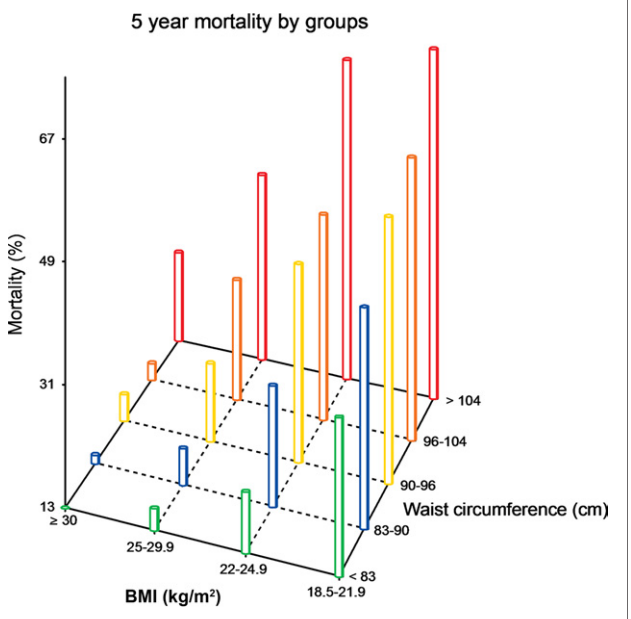

Figure 1 **5-Year Mortality in Patients With Coronary Artery Disease Based on Different Combinations of Body Mass Index With Central Obesity (Waist Circumference)**

Categories of body mass index (BMI) are depicted in the X axis. "Normal BMI" was divided into 2 categories: 18.5 to 21.9 and 22 to 24.9 kg/m^2. BMI of 25 to 29.9 kg/m^2 represents the overweight, and BMI ≥30 kg/m^2 represents the obese. In the Z axis, patients were categorized into quintiles of waist circumference. The Y axis depicts the mortality associated with each combination of BMI with central obesity.

this association remained statistically significant across different age groups (data not shown).

Discussion

In a large cohort of subjects with CAD from 3 different continents and with different manifestations of CAD, we have shown that subjects with normal weight central obesity have the worst long-term survival compared with subjects with other adiposity patterns. Furthermore, we have demonstrated that being overweight or obese by BMI criteria does not lead to higher mortality in the absence of central obesity. Our findings support the concept that clinicians should go beyond BMI when assessing mortality risk in patients with CAD, because combining BMI with measures of central obesity allows us to better discriminate those at the highest and lowest risk of dying.

Central obesity has been shown to be a predictor of mortality in the general population (14,15) and among patients with CAD (8,9,11). In the general population, BMI in the overweight and obese ranges was associated with higher overall mortality (16). In contrast, when BMI was used as a measure of adiposity in CAD patients, higher BMI was associated with lower mortality (2), which has been named "the obesity paradox." The divergent associations of central obesity and BMI with mortality in CAD patients were the basis for the present study. Although we have previously compared and contrasted the independent prognostic value attributed to central obesity and to BMI in patients with CAD (7), the present study further adds to the literature by assessing the additive prognostic information obtained by combining BMI with WC or WHR, and by comparing the prognostic implications of normal weight central obesity relative to other combinations of body adiposity, including subjects with overweight and obesity by BMI but without central obesity.

Although this is the first study to primarily focus on the assessment of mortality in patients with CAD based on combined assessment of BMI and central obesity, secondary analyses from 3 previous studies (8,11,17) also assessed the prognosis associated with body adiposity patterns in CAD patients, yielding preliminary results. However, the methodologies of these studies were significantly different from our study. In a substudy of patients with acute coronary syndromes from the MERLIN–TIMI 36 (Metabolic Efficiency With Ranolazine for Less Ischemia in NSTE-ACS–Thrombolysis In Myocardial Infarction 36) trial (17), only WC was used, and underweight patients were grouped together with normal BMI patients, potentially increasing the mortality of the reference group. In that study, normal weight central obesity showed a trend toward an association with cardiovascular events after adjustment for confounders,

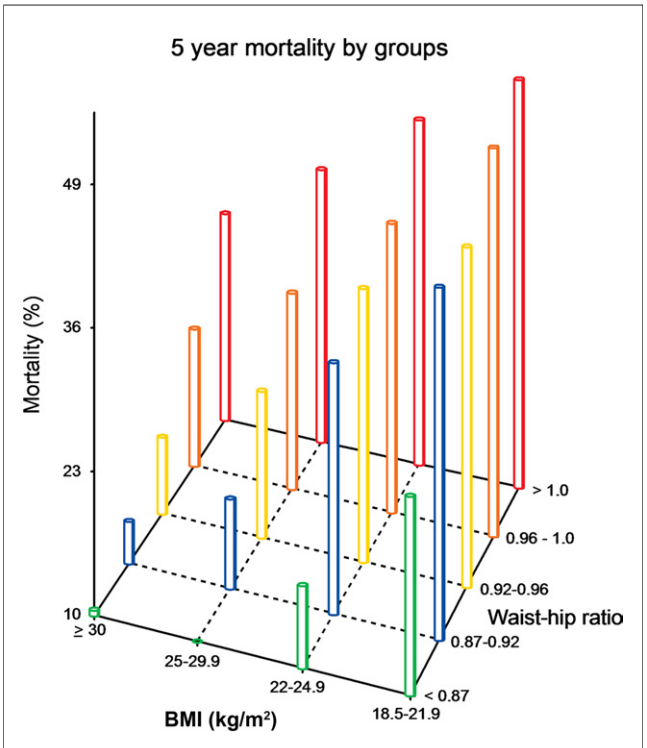

Figure 2 **5-Year Mortality in Patients With Coronary Artery Disease Based on Different Combinations of Body Mass Index With Central Obesity (Waist-to-Hip Ratio)**

In the Z axis, patients were categorized into quintiles of waist-to-hip ratio. Legends for the X and Y axis are the same as in Figure 1.

Table 2 Final Cox Proportional Hazards Models for the WC and WHR Ratio Predictors

	WC Model				WHR Model			
	HR	95% CI	Parameter Estimates	SE	HR	95% CI	Parameter Estimate	SE
Age	1.06	1.06–1.07	0.06	0.002	1.06	1.06–1.07	0.06	0.002
Male	1.18	1.10–1.27	0.17	0.03	1.14	1.06–1.22	0.13	0.04
Smoking	1.10	1.03–1.17	0.09	0.03	1.12	1.04–1.19	0.11	0.03
Hypertension	1.23	1.16–1.31	0.21	0.03	1.24	1.16–1.32	0.21	0.03
Diabetes	1.59	1.47–1.72	0.46	0.04	1.63	1.50–1.76	0.49	0.04
CHF	2.03	1.89–2.18	0.71	0.04	1.94	1.80–2.09	0.66	0.04
BMI	0.97	0.96–0.98	−0.03	0.006	0.97	0.96–0.98	−0.03	0.005
WC	1.01	1.00–1.01	0.007	0.002	—	—	—	—
WHR	—	—	—	—	4.25	2.84–6.36	1.45	0.20
BMI × WC interaction	1.00	1.00–1.00	0.001	0.0002	—	—	—	—
BMI × WHR interaction			—	—	1.09	1.00–1.18	0.08	0.04
BMI × BMI			—	—	1.00	1.00–1.00	0.002	0.0004

Two separate Cox regression models were fit. In the model including WC, all model parameters were statistically significant with $p < 0.001$. The overall model chi-square was 2,636 on 9 degrees of freedom ($p < 0.001$). The model with waist-to-hip (WHR) also was statistically significant (chi-square = 2,538 on 10 degrees of freedom, $p < 0.001$). Each estimated parameter was statistically significant with $p < 0.001$ except for the interaction term of body mass index (BMI) with WHR. This parameter estimate's p value was 0.038. Hazard ratios (HRs) are presented as a 1-unit increase in the variables.
CHF = coronary heart failure; CI = confidence interval; WC = waist circumference; WHR = waist-to-hip ratio.

but it was not statistically significant. In a study of Korean patients with myocardial infarction (11), normal weight central obesity was not significantly associated with increased mortality using WHR as the measure of central obesity. In addition, in a study of post-menopausal women with CAD (8), normal weight central obesity (defined by WC) was associated with increased mortality after adjustment for age only. Furthermore, in the INTERHEART study, a multinational case-control study of risk factors for first myocardial infarction (18), WC and WHR were also found to be predictors of first myocardial infarction even in normal BMI ranges. However, INTERHEART was not designed to assess risk among those with established CAD, and mortality data were not available. In contrast, Lavie et al. (19) showed that CAD patients with low body fat percentage had higher 3-year mortality than those with high body fat percentage, and in a separate study, also showed that CAD patients with normal BMI and high body fat, and

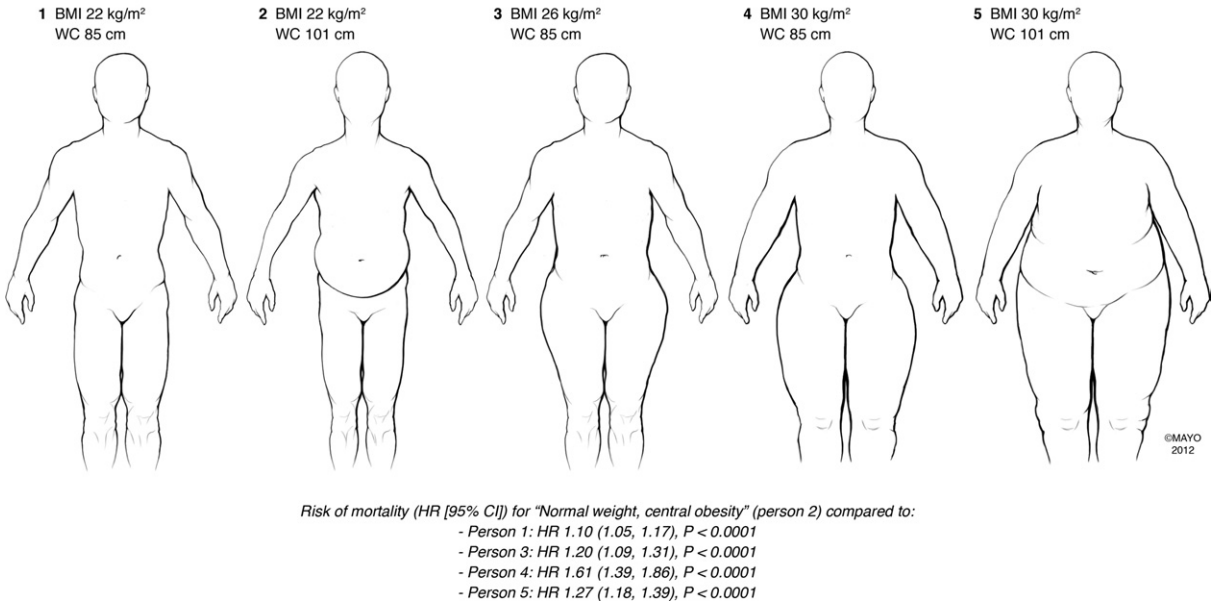

Figure 3 Mortality Risk of Subjects With Normal Weight Central Obesity Compared With Subjects With Other Patterns of Adiposity, Using Waist Circumference as a Measure of Central Obesity

A body mass index (BMI) of 22 kg/m^2 was chosen to represent normal BMI, 26 kg/m^2 was chosen to represent overweight BMI, and 30 kg/m^2 represents obese BMI. Measures of waist circumference (WC) were chosen to represent the 25th (85 cm) and 75th (101 cm) percentiles of the distribution of WC in the sample. CI = confidence interval; HR = hazards ratio.

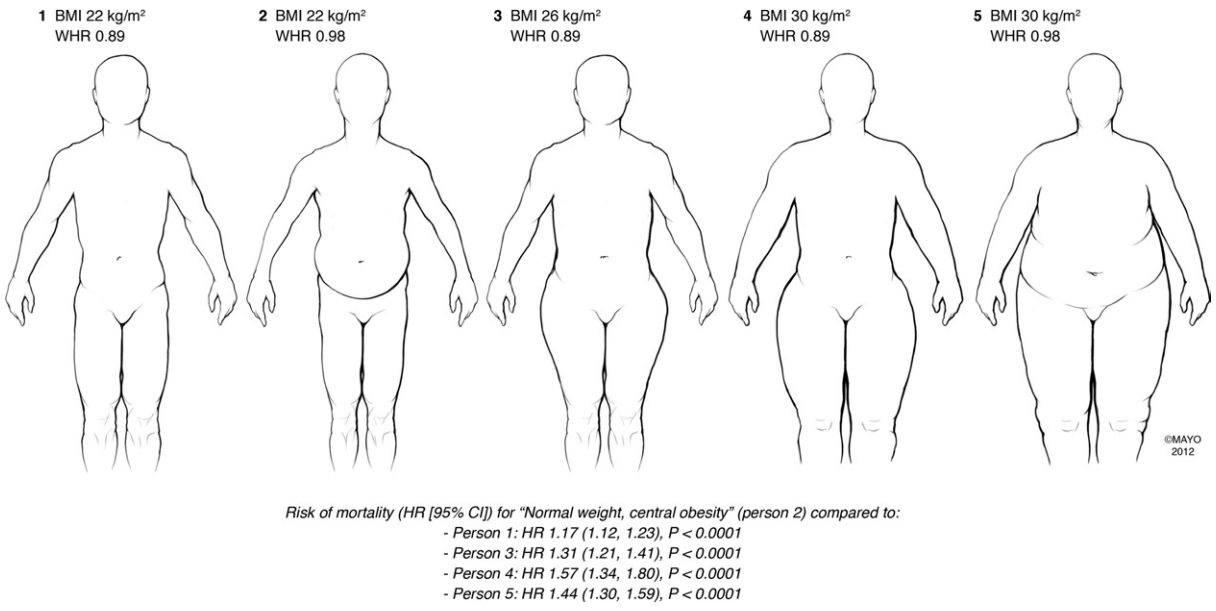

Figure 4 **Mortality Risk of Subjects With Normal Weight Central Obesity Compared With Subjects With Other Patterns of Adiposity, Using Waist-to-Hip Ratio as a Measure of Central Obesity**

A body mass index (BMI) of 22 kg/m^2 was chosen to represent normal BMI, 26 kg/m^2 was chosen to represent overweight BMI, and 30 kg/m^2 represents obese BMI. Measures of waist-to-hip ratio (WHR) were chosen to represent the 25th (0.89) and 75th (0.98) percentiles of the distribution of WHR in the sample. Abbreviations as in Figure 3.

with high BMI and low body fat did not differ with respect to survival (20). These results contrast with our findings, probably because body fat percentage was measured by a simplified method (sum of skinfolds), which assessed subcutaneous fat but not visceral fat, and like BMI, it is also related to total body fat but gives no insight into fat distribution. In addition, contrasting results were also found in a large study of patients with heart failure with reduced ejection fraction (21), where men (but not women) with high WC had lower event-free survival than men with normal WC. However, due to the composite endpoint of the study, we could not directly infer the association of WC with mortality in that cohort.

Given the high prevalence of obesity and its associated comorbidities in the United States, the American Heart Association recently released a Scientific Statement regarding the assessment of adiposity (22). Our novel findings help redefine our practice regarding obesity in patients with CAD, because these results emphasize the need to utilize BMI in combination with measures of central obesity to improve stratification of mortality risk. Furthermore, our results highlight those with normal weight central obesity, whose adiposity-related risk may go unnoticed during clinical assessments due to their normal BMI, as a group that may require greater attention toward risk stratification and modification from the medical community. By restricting the anthropometric assessment to BMI, healthcare providers could miss the opportunity to identify and counsel those with normal weight central obesity, whom our data identify as those at highest risk of death. This is an important point, because physician diagnosis of obesity almost triples the odds of achieving successful weight loss among subjects with CAD (23). Although aerobic exercise has been shown to decrease visceral fat (24), further prospective studies are needed to establish the optimal lifestyle and therapeutic interventions to improve the prognosis of CAD patients with normal weight central obesity.

There are several possible explanations for our findings. First, central obesity is associated with greater amounts of visceral fat, which is implicated in the pathogenesis of hypertension, inflammation, and insulin resistance (25). In contrast, BMI has been demonstrated to have a suboptimal correlation with body fat, particularly in patients with CAD (5), which may indicate that some CAD patients with high BMI but without central obesity may have preserved muscle mass rather than increased adiposity. Additionally, normal weight centrally obese subjects may have sarcopenia, a condition linked to poor functional capacity (26) and worse metabolic profile (27). Patients with low lean mass index and low body fat percentage have been found to have the highest mortality among those with stable CAD (28). This also raises the issue of residual confounding, because normal weight subjects from the current era may have some of the same comorbidities that have been thought to contribute to higher mortality risk in the underweight (29), although this remains a controversial topic. Alternatively, large amounts of subcutaneous fat located in the hips and legs, which are

likely reflected in BMI estimates, have been linked to healthy metabolic profiles that may be manifested in CAD patients with lower mortality (30). The higher mortality risk observed in normal weight, centrally obese patients could also be explained by less aggressive risk reduction because these patients may be less likely to receive recommendations for a healthy diet, exercise, cardiac rehabilitation, or high doses of preventive medications than their overweight or obese counterparts. Lastly, previous studies suggest that subjects who have a normal BMI but low fitness level have the highest mortality risk (31,32), whereas Sui et al. (33) demonstrate that patients with high WC have decreased cardiorespiratory fitness. Thus, it is possible that lower fitness level among patients with normal weight central obesity may account for the increased risk of death observed in our study. A recent study by McAuley et al. (34) again demonstrates the obesity paradox when BMI is used, while also showing that CAD patients with WC in the second tertile have the lowest mortality. However, these associations are no longer statistically significant after adjustment for cardiorespiratory fitness, supporting the concept that low cardiorespiratory fitness may play a role in the obesity paradox.

The main strength of the present study is the large, multiethnic cohort of patients with different manifestations of CAD from 3 different continents, and the novelty of our findings. Furthermore, measurements of BMI, WC, and WHR are simple and universally available, which makes our results highly applicable to clinical practices worldwide. A shortcoming of our study is the lack of disease-specific mortality data, as well as lack of data on fitness level, comprehensive lipid analysis, and body fat percentage. However, recent evidence suggests that the presence of risk factors like dyslipidemia and hypertension does not predict mortality in patients with CAD (35), and therefore, the lack of adjustment for these risk factors is unlikely to alter the results. Also, because our cohort is derived from previously published studies, we cannot exclude the possibility of publication bias influencing the results, or control for issues regarding uniform recording of anthropometric variables. Finally, our data on ethnicity are not comprehensive enough to allow race-specific analyses.

Conclusions

Patients with CAD with normal BMI but who are centrally obese have the highest long-term mortality compared with other patterns of adiposity. In contrast, having an elevated BMI in the setting of CAD is not detrimental to survival in the absence of central obesity. When used alone, BMI is a misleading anthropometric measurement in patients with CAD, and although measures of central obesity predict mortality more reliably than BMI, our findings indicate that combining BMI and measures of central obesity in the assessment of mortality risk in CAD patients is superior to documenting BMI alone, and may redefine current practice.

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