

Central Obesity and Survival in Subjects With Coronary Artery Disease

A Systematic Review of the Literature and Collaborative Analysis With Individual Subject Data

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Objectives	The aim of this study was to examine the association of central (waist circumference [WC] and waist-hip ratio [WHR]) and total obesity (body mass index [BMI]) measures with mortality in coronary artery disease (CAD) patients.
Background	The question of which measure of obesity better predicts survival in patients with CAD is controversial.
Methods	We searched OVID/Medline, EMBASE, CENTRAL, and Web of Science from 1980 to 2008 and asked experts in the field for unpublished data meeting inclusion criteria, in which all subjects had: 1) CAD at baseline; 2) measures of WC or WHR; 3) mortality data; and 4) a minimum follow-up of 6 months.
Results	From 2,188 studies found, 6 met inclusion criteria. We obtained individual subject data from 4, adding unpublished data from a cardiac rehabilitation cohort. A variable called “central obesity” was created on the basis of tertiles of WHR or WC. Cox-proportional hazards were adjusted for age, sex, and confounders. The final sample consisted of 15,923 subjects. There were 5,696 deaths after a median follow-up of 2.3 (interquartile range 0.5 to 7.4) years. Central obesity was associated with mortality (hazard ratio [HR]: 1.70, 95% confidence interval [CI]: 1.58 to 1.83), whereas BMI was inversely associated with mortality (HR: 0.64, 95% CI: 0.59 to 0.69). Central obesity was also associated with higher mortality in the subset of subjects with normal BMI (HR: 1.70, 95% CI: 1.52 to 1.89) and BMI ≥ 30 kg/m ² (HR: 1.93, 95% CI: 1.61 to 2.32).
Conclusions	In subjects with CAD, including those with normal and high BMI, central obesity but not BMI is directly associated with mortality. (J Am Coll Cardiol 2011;57:1877–86) © 2011 by the American College of Cardiology Foundation

Obesity is a worldwide epidemic (1), and its prevalence among children, adolescents, and adults has increased markedly (2). Although the rates of obesity seem to have plateaued in recent years, its prevalence continues to be significantly elevated among U.S. adults (32.2% in men,

35.5% in women in 2007 to 2008) (3). Overweight and obesity are associated with excess cardiovascular and noncardiovascular deaths in the general population (4).

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**Abbreviations
and Acronyms****BMI** = body mass index**CAD** = coronary artery disease**CI** = confidence interval**HF** = heart failure**HR** = hazard ratio**WC** = waist circumference**WHR** = waist-hip ratio

Historically, the relationship between obesity and coronary artery disease (CAD) has been attributed to cardiovascular risk factors associated with obesity. However, longitudinal studies suggest that obesity is an independent predictor of CAD (5,6). Alternatively, studies have also reported an inverse association between body mass index (BMI) and mortality in subjects with CAD. This has been called the “obesity paradox” (7,8) and has been attributed to residual confounding (9).

Measures of central obesity, such as waist circumference (WC) and waist-hip ratio (WHR), might help to better assess body fat distribution in CAD patients. However, data regarding the effect of central obesity on mortality in patients with CAD are scant. Furthermore, the prognostic value of central obesity in subjects with CAD and normal BMI is unknown. Thus, we hypothesized that the “obesity paradox” would not be observed if measures of central obesity were used to assess outcomes in people with CAD, instead of BMI.

To this end, the aims of this project were: 1) to conduct a systematic review of the published data on studies assessing the association between measures of abdominal obesity (WC and WHR) and mortality in people with CAD; 2) to determine the independent and incremental prognostic information of measures of central obesity on mortality in people with CAD and also specifically in those with normal BMI; and 3) to calculate the risk of mortality attributable to measures of central obesity.

Methods

Systematic review: search strategy. We searched the OVID/Medline, EMBASE, CENTRAL, and Web of Science databases from January 1980 to October 2008 for studies that reported the association of either WC or WHR with mortality in patients with established CAD.

Terms used in the search included words related to measures of abdominal obesity (*obesity, hip or trunk or abdominal or waist and girth or circumference or ratio, waist-hip ratio, body composition, body fat distribution, adipose tissue, abdominal fat, intra-abdominal fat, anthropometry, trunk, or visceral or central or abdominal and fat or obesity or adipose*); terms related to mortality (*mortality, survival, death, outcomes*); and presence of CAD (*coronary disease, myocardial infarction, myocardial revascularization, CABG, coronary bypass, coronary catheterization, percutaneous coronary intervention*). The search was limited to Medical Subject Headings fields labeled as comparative studies, evaluation studies, meta-analyses, multicenter studies, randomized controlled trials, cohort studies, and follow-up studies.

Inclusion criteria. Inclusion criteria were prospective cohort studies in which all reported subjects had: 1) CAD at baseline (defined as a previous history of myocardial infarction, percutaneous coronary intervention, and/or coronary artery bypass grafting); 2) measures of either WC or WHR; 3) mortality data on the basis of measures of WC or WHR; and 4) minimum follow-up of 6 months.

Two investigators (T.C. and D.C.S.) independently reviewed all titles and abstracts of the studies identified through the screening search, to determine eligibility. Once potentially relevant abstracts were identified, the same investigators independently read the selected studies in entirety to determine whether they met inclusion criteria, selecting the final studies that met eligibility criteria to enter the analysis. There was 100% agreement between the 2 investigators.

One author (T.C.) contacted the authors of all of the eligible studies by either e-mail or letter requesting subject-level data from their respective studies. We also asked experts in the field for unpublished data that might fulfill inclusion criteria and included unpublished data from the Mayo Clinic Cardiovascular Rehabilitation Program database, for patients meeting the same eligibility criteria described in the preceding text.

The use of the Mayo Clinic Cardiovascular Rehabilitation Database in this study was approved by the Mayo Clinic Institutional Review Board. The studies included in this analysis also received approval from their respective institutional review boards.

Definition of variables of interest. Our predictor variables were WC, WHR, a unified variable for central obesity, and BMI. Body mass index was defined as the weight (in kilograms) divided by the square of height (in meters). Abnormal WC and WHR were defined with clinically acceptable standard cutoffs. High WC was defined by National Cholesterol Education Program Adult Treatment Panel III cutoffs of >88 cm for women and >102 cm for men (10); high WHR was defined on the basis of World Health Organization criteria as ≥ 0.85 for women and ≥ 0.90 for men (11). Furthermore, we also classified subjects on the basis of sex-specific tertiles for BMI, WC, and WHR. Because 1 study had no information on WC and another had no information on WHR, we created a variable called central obesity, which included either WC or WHR, whichever was available. If both were available, we preferentially used WHR because WHR is a specific measure of fat distribution (“apple shape” vs. “pear shape”), which could not be inferred from measuring WC alone.

For the BMI calculation, weight was measured with a standard balance beam scale in all studies. The WC was measured between the iliac crest and the lower ribs at a level that had the minimum circumference in 4 studies and at the level of the navel in 1 study. Hip circumference was measured horizontally over the greatest posterior extension of the buttocks in 3 studies and at the level of the major trochanter in 1 study. The WHR was calculated by dividing

the waist circumference by the hip circumference, both in centimeters.

We created sex-specific BMI quintiles for the entire cohort of subjects and also divided subjects into 5 categories of BMI on the basis of clinically applicable standard cutoffs (low BMI, if BMI ≤ 18.5 kg/m²; normal, if BMI was between 18.5 and 24.9 kg/m²; overweight, if BMI was 25 to 29.9 kg/m²; obesity, if BMI was 30 to 34.9 kg/m²; and obesity grade II was defined as BMI ≥ 35 kg/m²).

Statistical analysis. Continuous variables were presented as mean \pm SD. Heterogeneity was assessed with the chi-square test with the RevMan software (version 4.2, The Nordic Cochrane Centre, The Cochrane Collaboration Copenhagen, Denmark), and a p value < 0.05 was considered significant. We created Cox-proportional hazards models to determine the independent association of tertiles of WC, WHR, central obesity and BMI, and sex-specific quintiles of BMI with mortality after adjusting for potential confounders. Models were also created to determine the association between groups on the basis of clinically applicable cutoffs of WC, WHR, and BMI with mortality. Covariates included in all the models were those that have been shown to predict survival in cohorts of subjects with CAD. We were limited to variables that were available for most individuals across all of the cohorts included in the pooled analysis (age, sex, history of smoking, diabetes, hypertension, and heart failure [HF]). Additionally, models assessing WC, WHR, or central obesity were adjusted for BMI. Models using BMI were adjusted for central obesity. The demographic differences among tertiles of WC, WHR, and BMI were assessed with chi-square analysis for categorical variables and with 1-way analysis of variance for continuous variables.

Subgroup analyses (adjusted for the aforementioned confounders) for men versus women, younger versus older than 65 years of age, smokers versus nonsmokers, and diabetic versus nondiabetic persons were performed to assess the effect of 1-SD increase in WC, WHR, or BMI on mortality. Furthermore, we tested the interaction between the central obesity exposures and each of the following covariates: sex, age, smoking, and presence of diabetes.

We created new tertiles of WC, WHR, and central obesity for subjects with normal BMI and for subjects with BMI ≥ 30 kg/m². We created Cox-proportional hazards models as described in the survival analysis for the whole sample. Furthermore, we assessed whether measuring both WC and WHR provided incremental prognostic information. To this end, individuals were categorized into 4 groups according to the clinical cutoffs for WC and WHR: low WC with low WHR (reference), high WC with low WHR, low WC with high WHR, and high WC with high WHR. We also assessed the correlation among BMI, WC, and WHR with simple linear correlation in different pairs of these measures and tested the concordance between tertiles of WC and tertiles of WHR with kappa statistics. If the results showed that WC and WHR were not strongly

correlated/concordant, we assumed there would not be significant collinearity. This would validate the inclusion of both variables in the model to evaluate the association of both measures of central obesity with mortality independently of each other. To evaluate whether follow-up time had an impact in the overall results, we performed hazard models truncating the follow-up time to (≤ 6 months) while incorporating the same covariates used in the main models. The SPSS software (version 15.0, SPSS, Inc., Chicago, Illinois) was used for statistical analysis.

To determine how many deaths could be attributed to measures of central obesity in people with CAD, we calculated the attributable risk of mortality to central obesity with a previously validated formula (12).

Results

Published data search and data collection. After the published data search, we identified 2,188 potentially relevant abstracts, of which 6 met the inclusion criteria (13–18). Details of the study selection process are outlined in Figure 1.

After the lead authors of the 6 eligible studies were contacted, 4 agreed to share de-identified individual subject data from their respective studies (14–16,18). We pooled unpublished data from the Mayo Clinic Cardiovascular Rehabilitation Cohort and constituted our final dataset for analysis (total of 5 studies included). Further details about each of the studies included are reported in Table 1. Individuals with missing data on height or weight were excluded, leaving 15,923 participants for the final analysis.

Of the 5 included studies, 3 had information on both WC and WHR. One had data on WC but not on WHR, and another study had WHR data but no information on WC. The WC and WHR were available in 14,284 and 12,836 subjects, respectively. We excluded 1 patient with erroneous WHR measurement and 2 patients with erroneous WC measurement. Heterogeneity analysis showed that the effects of each individual study were not heterogeneous with respect to results on the basis of measures of central obesity ($I^2 = 0\%$, $p = 0.41$) or on the basis of BMI ($I^2 = 35\%$, $p = 0.19$). The results of each individual study and in the pooled sample are summarized in Figure 2.

Sample characteristics. Descriptive characteristics of the 15,923 subjects are presented in Table 2. Mean \pm SD age was 65.7 ± 11.5 years, and 59% were men. The percentage of subjects with a history of diabetes, hypertension, and HF was significantly higher in the highest tertile of central obesity (Table 2). From the pooled data of 15,923 subjects, 6,648 comprised the “Normal Weight” group (BMI: 18.5 to 24.9 kg/m²), whereas 2,396 comprised the “Obese” group (BMI ≥ 30 kg/m²). Duration of follow-up was different amongst the studies and ranged from 6 months to 16 years. Median (interquartile range) follow-up period for the pooled data was 2.3 (0.5 to 7.4) years, and there were 5,696 deaths.

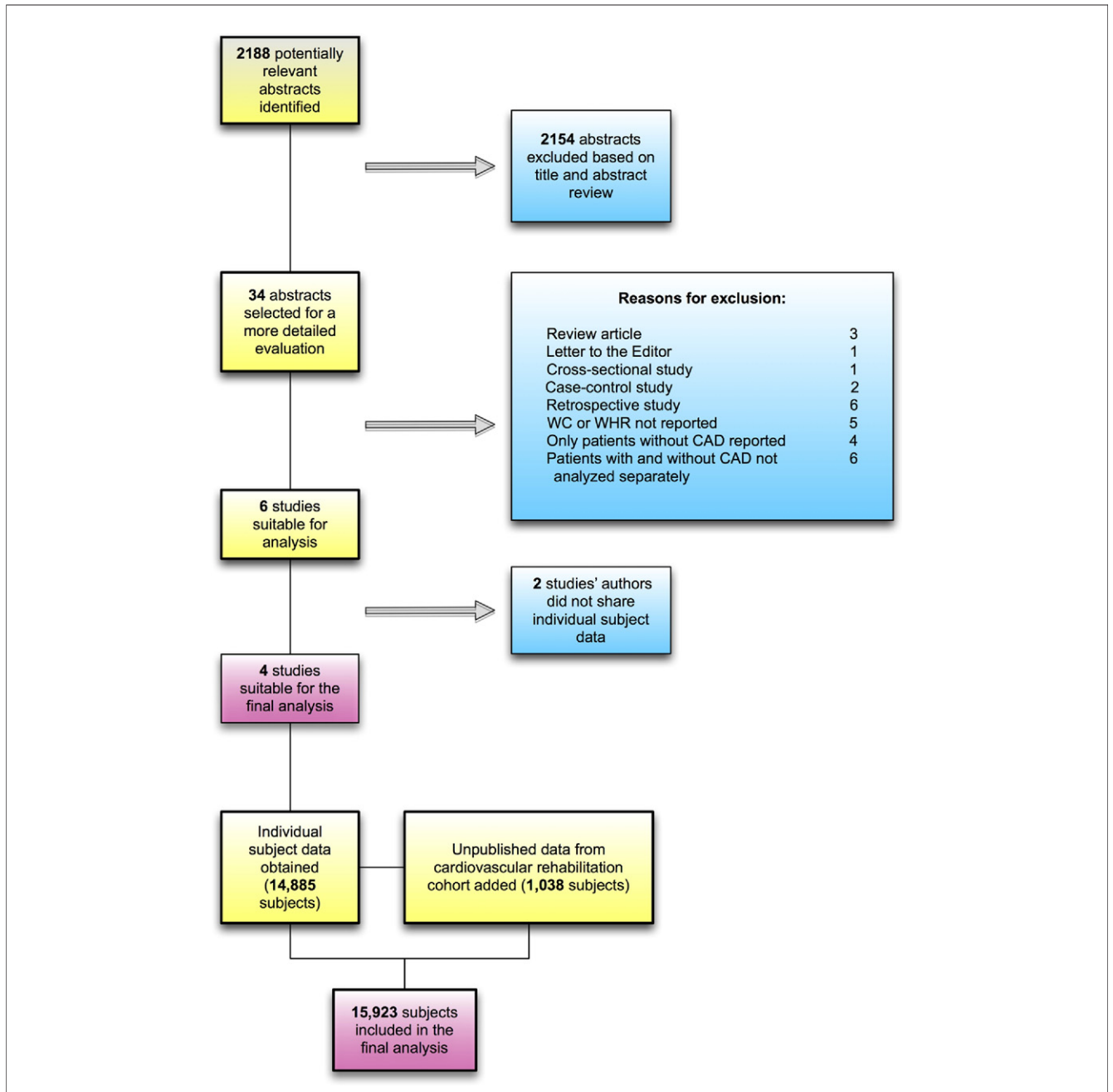


Figure 1. Systematic Review and Article Selection

Flowchart outlining the published data search and exclusion of articles, leading to the final studies included in the analysis.
CAD = coronary artery disease; WC = waist circumference; WHR = waist-hip ratio.

Associations of different measures of obesity with mortality. Cutoff values for tertiles for men in the whole cohort were: WC: second tertile 89 cm, third tertile 99 cm; WHR: second tertile 0.94, third tertile 0.98; BMI (in kg/m²): second tertile 24.1, third tertile 27.1. For women, cutoff values were: WC: second tertile 84 cm, third tertile 96 cm; WHR: second tertile 0.86, third tertile 0.93; BMI (in kg/m²): second tertile 23.7, third tertile 27.9.

A direct and statistically significant association with mortality was noted for the second and third tertiles of measures of central obesity after adjustment for age, sex, smoking, diabetes, hypertension, HF, and BMI (Fig. 3). In the multivariable model using central obesity cutoffs, high WHR (hazard ratio [HR]: 1.69; 95% confidence interval [CI]: 1.55 to 1.84) and high WC (HR: 1.29; 95% CI: 1.20 to 1.39) were significantly associated with

Table 1 Characteristics of the Included Studies

First Author (Ref. #)	Origin	Characteristics of CAD	Enrollment	No. of Subjects (% Women)	Follow-Up (Months), Mean ± SD	Deaths, n	Main Results
Kanaya <i>et al.</i> (14)	United States	MI, CABG, PCI, or angiographic occlusion ≥50% of ≥1 coronary arteries	1993-1994	2,739 (100%)	81.6 ± 4.8	498	Increasing WC was directly related to higher mortality, whereas BMI exhibited a “U-shaped” association with mortality.
Kragelund <i>et al.</i> (15)	Denmark	Acute myocardial infarction	1990-1992	6,676 (33%)	73.8 ± 57.5	4,534	Men in the upper quartile of WHR had increased mortality compared with the lowest quartile, but the association was not significant in women. There was no association of BMI with mortality.
Zeller <i>et al.</i> (16)	France	Acute myocardial infarction	2001-2007	2,229 (27%)	Median 12 months	301	WC and BMI were not independent predictors of death, but subjects with normal BMI and high WC had increased mortality.
Lee <i>et al.</i> (18)	Korea	STEMI	2005-2006	3,734 (26%)	6.6 ± 1.0	175	Increasing WHR was directly associated with higher mortality, whereas increasing BMI was inversely associated with mortality.
Mayo Clinic Cardiovascular Rehabilitation cohort	Rochester, MN	MI, CABG, PCI, or known history of CAD	1993-2007	1,038 (20%)	104 ± 44	188	Unpublished data

BMI = body mass index; CABG = coronary artery bypass grafting; CAD = coronary artery disease; MI = myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; WC = waist circumference; WHR = waist-hip ratio.

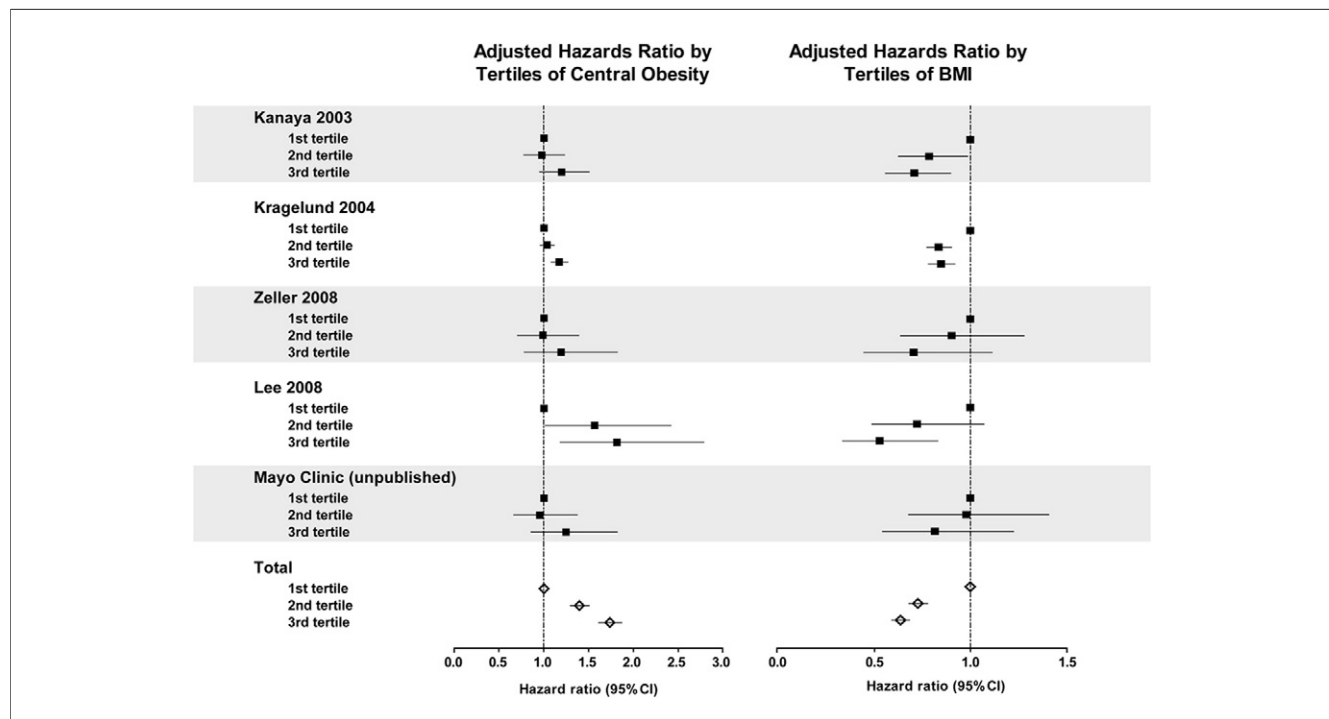


Figure 2 Mortality on the Basis of Tertiles of Central and Total Obesity, Stratified by Study and in the Pooled Sample

The analysis for each individual study was performed with study-specific tertiles, and the “total” row shows the results on the basis of tertiles of the pooled sample with individual subject data. BMI = body mass index; CI = confidence interval.

Table 2 Descriptive Characteristics of the Study Participants

Variable	Combined Data (n = 15,923)			Tertiles of Central Obesity (n = 15,125)				Tertiles of BMI (n = 15,923)				
	n	Values	p Value	First	Second	Third	p Value	n	First	Second	Third	p Value
Age, yrs	15,923	65.7 ± 11.5	<0.001	64.4 ± 11.5	65.7 ± 11.6	66.7 ± 11.3	<0.001	15,923	67.7 ± 12.0	65.7 ± 11.3	63.7 ± 10.9	<0.001
Women	15,923	40.9	0.14	42.5	41.1	40.6	0.14	15,923	40.9	40.9	40.9	0.99
Smoking, past or current	15,822	62.2	<0.001	66.2	63.2	57.0	<0.001	15,822	64.8	60.3	61.4	<0.001
History of diabetes	15,899	18.4	<0.001	13.2	18.3	23.2	<0.001	15,899	15.4	16.2	23.6	<0.001
Hyperlipidemia	15,866	38.6	<0.001	34.0	38.6	43.5	<0.001	15,866	32.0	38.7	45.2	<0.001
Hyperlipidemia	11,949	24.8	0.78	25.3	24.6	24.9	0.78	11,949	21.1	27.7	26.4	<0.001
Creatinine (mg/dl)	12,588	1.15 ± 0.81	0.002	1.12 ± 0.76	1.14 ± 0.74	1.18 ± 0.93	0.002	12,588	1.15 ± 0.93	1.16 ± 0.83	1.14 ± 0.58	0.64
Heart failure	15,492	14.1	<0.001	11.0	14.0	17.6	<0.001	15,492	12.6	13.4	16.3	<0.001
History of stroke/transient ischemic attacks	7,777	4.2	0.51	4.6	3.7	4.3	0.51	7,777	3.6	4.1	4.8	0.11
WC (cm)	14,282	93.0 ± 13.2	<0.001	83.7 ± 9.3	91.9 ± 9.0	101.4 ± 12.5	<0.001	14,282	83.2 ± 8.7	92.1 ± 8.4	104.2 ± 11.1	<0.001
WHR	12,835	0.93 ± 0.08	<0.001	0.86 ± 0.06	0.93 ± 0.04	1.01 ± 0.05	<0.001	12,835	0.91 ± 0.08	0.93 ± 0.08	0.95 ± 0.08	<0.001
BMI (kg/m ²)	15,923	26.1 ± 4.5	<0.001	24.7 ± 4.4	25.9 ± 4.1	27.8 ± 4.6	<0.001	15,923	21.7 ± 1.8	25.6 ± 1.0	31.1 ± 3.7	<0.001

Values are % or mean ± SD.
Abbreviations as in Table 1.

increased mortality. In contrast, increasing tertiles of BMI were inversely associated with mortality (Fig. 3). This association persisted even after using 5 sex-specific BMI groups on the basis of BMI cutoffs. With normal BMI as reference, the adjusted HRs were: BMI <18.5 kg/m²: 1.78 (95% CI: 1.53 to 2.01); BMI 25 to 29.9 kg/m²: 0.84 (95% CI: 0.79 to 0.89); BMI 30 to 34.99 kg/m²: 0.75 (95% CI: 0.69 to 0.82); and BMI ≥35 kg/m²: 0.78 (95% CI: 0.67 to 0.91). Similar results were seen after dividing the groups into 5 quintiles and also without adjusting for central obesity in multivariable models assessing BMI (data not shown).

Results of the subgroup analyses showed that a 1-SD increase of WC and of WHR was associated with higher mortality, whereas a 1-SD increase of BMI was associated with lower mortality across all subgroups (Fig. 4). A significant interaction was only found between sex and tertiles of central obesity (p < 0.001) and smoking and tertiles of central obesity (p = 0.02) for mortality.

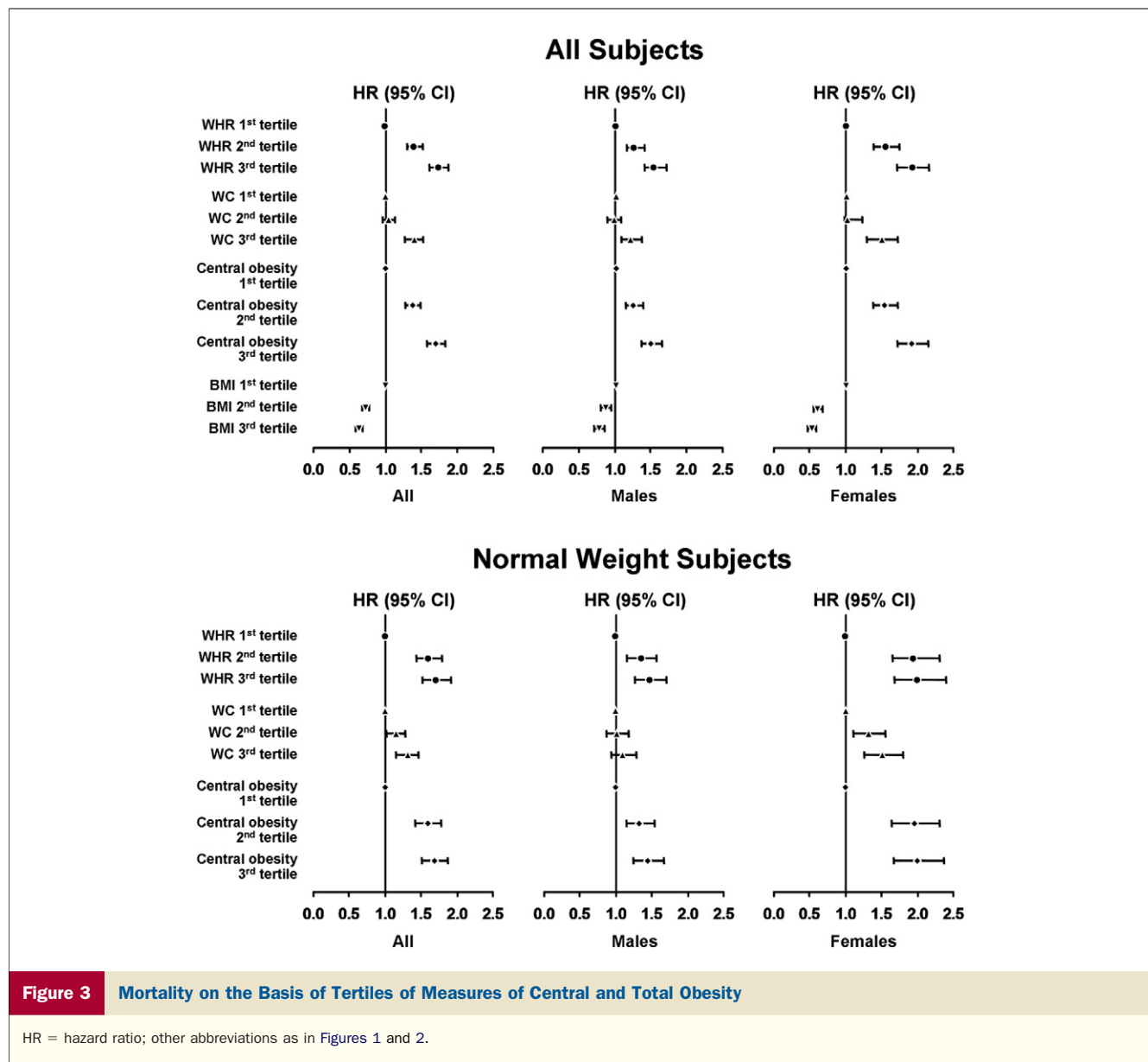
In subjects with normal weight, the cutoff values used for definition of the tertiles in men were: WC: second tertile 84 cm, third tertile 90 cm; WHR: second tertile 0.92, third tertile 0.97; BMI (in kg/m²): second tertile 22.2, third tertile 23.8. In women, cutoffs were: WC: second tertile 78 cm, third tertile 85.5 cm; WHR: second tertile 0.85, third tertile 0.92; BMI (in kg/m²): second tertile 21.6, third tertile 23.4. Increasing tertiles of central obesity, WHR, and WC were also significantly associated with higher mortality (Fig. 3).

In obese individuals with CAD, the cutoff values used to define the tertiles in men were: WC: second tertile 107 cm, third tertile 115 cm; WHR: second tertile 0.98, third tertile 1.03; BMI (in kg/m²): second tertile: 31.1, third tertile 32.8. In women, cutoffs were: WC: second tertile 101 cm, third tertile 110 cm; WHR: second tertile 0.87, third tertile 0.95; BMI (in kg/m²): second tertile 31.9, third tertile 35.2. We again observed that WC, WHR, and central obesity were directly associated with mortality, whereas BMI was inversely associated with mortality in men and women (Fig. 5).

When follow-up time was truncated at ≤6 months, results were similar to the overall findings of the study, suggesting that time of follow-up was not a major effect modifier.

The factorial analysis showed that individuals with a high WC as well as high WHR had the highest mortality risk (Table 3). Similar results were found in normal weight subjects (Table 3).

Attributable risk to central obesity. The combined attributable mortality risk for the second and third tertiles of central obesity in the whole cohort was 30.8% (43.2% in women, 19.4% in men). Among normal weight subjects, the attributable risk for central obesity was 33.1% (51.5% in women, 19.9% in men).



Discussion

This study represents a collaborative effort to assess the prognostic value of central obesity in individuals with CAD by gathering data from 3 continents and over 15,000 subjects, therefore representing the largest analysis on this subject. Our study shows several key findings: 1) increasing central obesity was associated with higher mortality in subjects with CAD, and central obesity shares a significant attributable risk in this population; 2) BMI, a measure of total adiposity, was inversely associated with mortality; 3) increasing central obesity was also associated with higher mortality in obese individuals and in those with normal BMI; 4) the prognostic impact of central obesity on mortality in CAD patients is demonstrable in different subgroups of subjects; and 5) subjects with CAD who had

abnormal WC and WHR had higher mortality than those with an abnormality in only 1 of the parameters.

First, our finding that central obesity is associated with higher mortality in subjects with CAD mirrors the results of meta-analyses of central obesity and incidence of cardiovascular events in healthy subjects (19,20). A potential mechanism underlying this association is that adipose tissue interacts closely with vascular function, inflammatory pathways, sympathetic activation, and renin-angiotensin-aldosterone systems. It also contributes to insulin resistance and hypertension (21). Central obesity correlates closely with excessive visceral fat, which is associated with insulin resistance, hypertriglyceridemia, highly atherogenic small LDL particles, and low HDL levels, features considered pro-atherogenic (22). Furthermore, visceral fat also seems to play a role in inflammation (23), and has been found to be

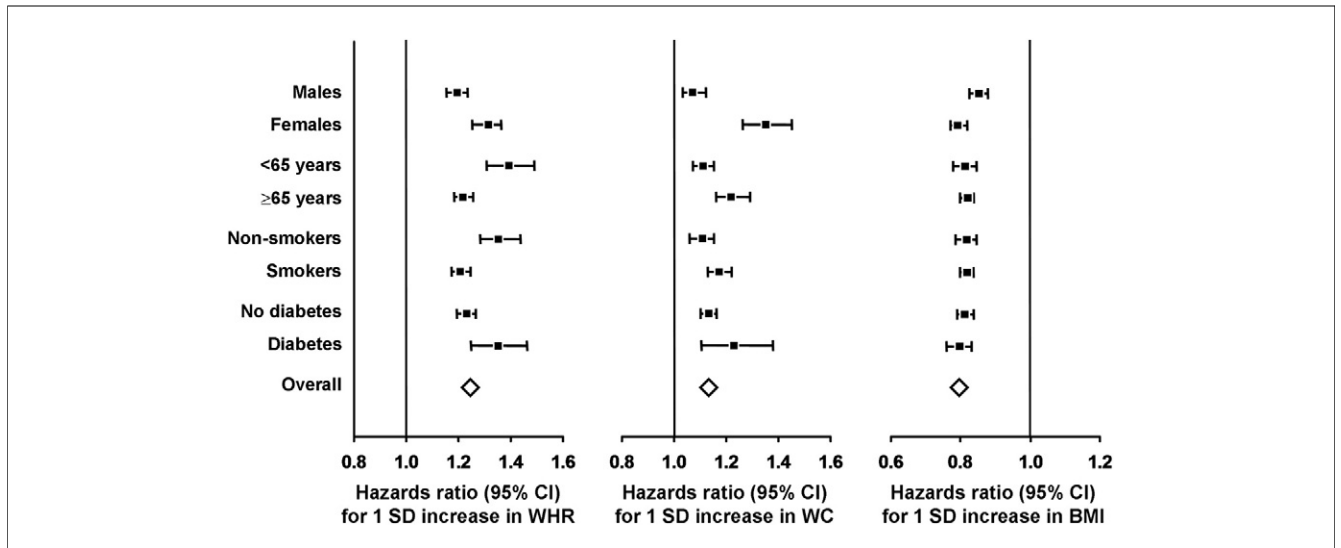


Figure 4 Mortality on the Basis of Measures of Obesity in Different Subgroups

Adjusted hazard ratios for mortality in different subgroups defined a priori according to 1-SD increase in different measures of central and total obesity. Abbreviations as in Figures 1 and 2.

a direct link between obesity and hypertension (24). Therefore, the heightened inflammatory state, coupled with a more atherogenic lipid profile and hypertension might lead to an excess of clinical cardiovascular events in individuals with visceral and central obesity, regardless of their weight.

Second, our study also showed that a measure of total adiposity (BMI) was inversely associated with mortality in CAD patients. Although the relationship between increasing BMI and mortality in the general population has been demonstrated (4,25), this association seems to be more complex in subjects with CAD. We have previously re-

ported that overweight and obese individuals, who represent the majority of people with myocardial infarction, have lower mortality rates as compared with subjects with normal BMI (26). In a meta-analysis of 40 studies, we found that although underweight CAD subjects had increased mortality compared with those with normal BMI, overweight individuals had lower mortality, and obese subjects had no increase in mortality (7). Although the obesity paradox has been attributed to residual confounding, the results of the present analysis suggest that other possible explanations need to be considered, because factors acting as confounders

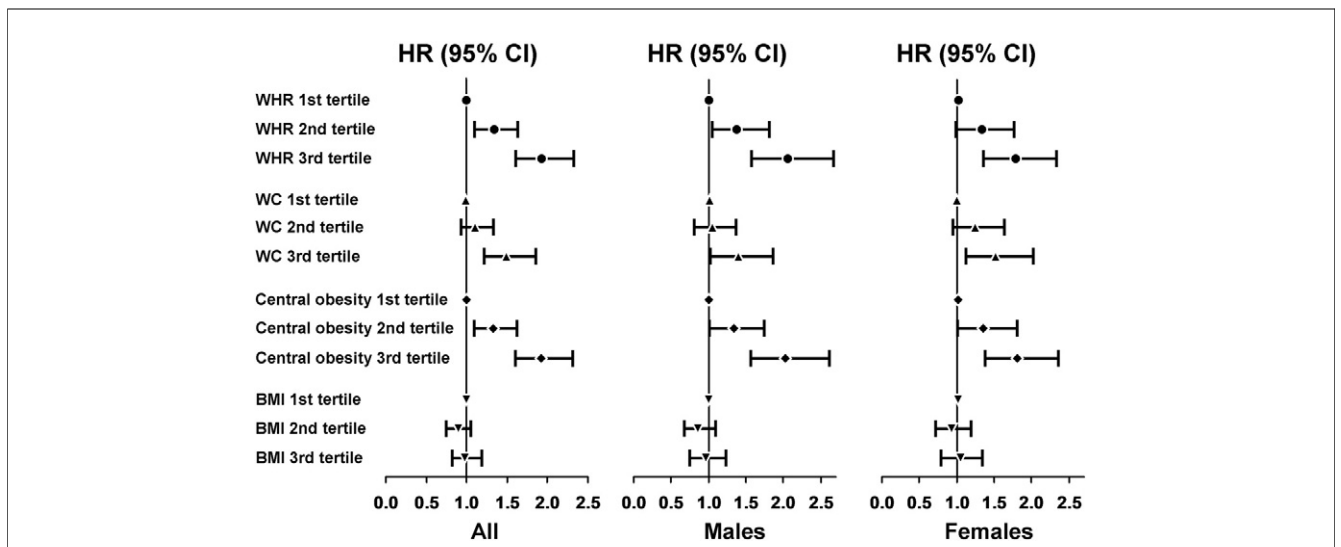


Figure 5 Mortality on the Basis of Tertiles of Measures of Central and Total Obesity in Obese Subjects (BMI ≥ 30 kg/m²)

Abbreviations as in Figures 1 and 2.

Table 3 Adjusted Analysis of the Potential Additive Effects of WC and WHR on Mortality for the Entire Cohort and for Subjects With Normal Weight

Group	Whole Cohort			Normal Weight Subjects Only		
	n	HR (95% CI)	p Value	n	HR (95% CI)	p Value
Low WC + Low WHR	2,056	1.00 (Reference)		1,340	1.00 (Reference)	
Low WC + High WHR	5,838	1.41 (1.28–1.56)	<0.0001	3,401	1.54 (1.36–1.73)	<0.001
High WC + Low WHR	361	1.11 (0.87–2.11)	0.40	6	—*	—*
High WC + High WHR	3,597	1.75 (1.57–1.95)	<0.0001	502	1.75 (1.49–2.07)	<0.001

Adjustment included age, sex, smoking, hypertension, diabetes, heart failure, and body mass index as covariates. *Not calculated, due to small number of subjects. Abbreviations as in Table 1.

between low body weight and mortality would be expected to affect measures of central obesity as well.

A potential explanation for this obesity paradox is that BMI seems to be a poor marker of general adiposity, given its inability to discriminate between fat and lean mass, particularly in individuals with intermediate BMI values (27). In the general population, a BMI >30 kg/m² was shown to have good specificity but poor sensitivity to detect excess body fatness (28). Body mass index values between 25 and 29 kg/m² failed to detect excess fat mass in approximately 50% of people (28), and BMI was also shown to have poor diagnostic accuracy in people with CAD (27). By contrast, the aforementioned concept has been recently challenged by Lavie et al. (29), who demonstrated an inverse relationship not only between BMI and mortality but also between body fat percentage and mortality in CAD patients. These results, along with the results of our analysis suggest that the association between fatness and mortality is complex and might rely more on measures of fat distribution than on the amount of body fat.

The third finding from our study is that central obesity is associated with higher mortality even in individuals with normal BMI. To the best of our knowledge, this is the first study to identify the adverse prognosis associated with central obesity in subjects with CAD and normal weight. These findings might have significant implications for clinical practice, because it is generally accepted that, if BMI is normal, no further measures of obesity are necessary, and no lifestyle modifications to induce weight loss might be recommended. Similarly, WC, WHR, and central obesity remained independent predictors of higher mortality in people with BMI in the obese category, suggesting that measures of central obesity are stronger prognostic markers than BMI in CAD patients, irrespective of BMI. In light of these results, we suggest that WC and/or WHR should be documented in patients with CAD, regardless of their BMI, to improve risk stratification and foster therapeutic recommendations for fat loss.

Our results also indicate that the combination of abnormal WC and WHR, present in over 20% of subjects, is associated with the highest mortality risk in the whole cohort and in subjects with normal BMI. Lastly, in our cohort, central obesity alone explained approximately 30% of all deaths, underscoring the importance of assessing body

fat distribution and implementing weight loss strategies that might increase survival.

The strengths of our study include the use of individual-level data from a large cohort of subjects from 3 different continents and with different manifestations of CAD to directly compare the mortality risk of measures of central (WC and WHR) and total adiposity (BMI) not only in the entire sample but also in the subset of patients with normal and elevated BMI.

The main shortcoming of our study was the lack of uniform data on some variables that might be relevant in survival analyses of CAD patients. However, we believe that we have adequately adjusted our models for the main factors that might lead to cardiovascular events in CAD, as shown in the Framingham risk prediction model for secondary events (30). It is also possible that the impact of central obesity might be different for different ethnic groups, but our data on ethnicity were not complete enough to perform race-specific analyses.

Conclusions

Central obesity is directly associated with higher mortality in individuals with CAD, whereas the opposite is observed with BMI. The effect of central obesity on mortality is observed even in subjects with normal BMI. Our data suggest WC and WHR to be more reliable than BMI in stratifying mortality risk in CAD patients, and WC and/or WHR should be documented in individuals with CAD and normal BMI for better risk stratification and therapeutic considerations.

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Key Words: central obesity ■ coronary artery disease ■ mortality
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