The Relationship Between Measures of Obesity and Incident Heart Failure: The Multi-Ethnic Study of Atherosclerosis

Imo A. Ebong1, David C. Goff, Jr2, Carlos J. Rodriguez3,4, Haiying Chen5, David A. Bluemke6, Moyses Szklo7 and Alain G. Bertoni3,4

Objective: To evaluate the strength of association of body mass index (BMI) and waist circumference (WC) with incident heart failure (HF), exploring our associations by ethnicity and age.

Design and Methods: 6,809 participants, aged 45-84 years old, without clinical cardiovascular disease (2000-2002), from the Multi-Ethnic Study of Atherosclerosis were included. Cox-Proportional hazards models were used to examine associations of BMI and WC with incident HF. The predictive abilities of BMI and WC were compared using receiver operating characteristic curves.

Results: Over a median follow-up of 7.6 years, there were 176 cases. BMI and WC were associated with incident HF in men (1.33 [1.10-1.61] and 1.38 [1.18-1.62], respectively) and women (1.70 [1.33-2.17] and 1.64 [1.29-2.08], respectively). These associations became non-significant after adjusting for obesity-related conditions (hypertension, dysglycemia, hypercholesterolemia, left ventricular hypertrophy, kidney disease, and inflammation). The associations of BMI and WC did not vary significantly by ethnicity or age-group, but were inverse in Hispanic men. The area under the curve for BMI and WC was 0.749 and 0.750, respectively, in men and 0.782 and 0.777, respectively, in women.

Conclusions: The association between obesity and incident HF is largely mediated by obesity-related conditions. BMI and WC have similar predictive abilities for incident HF.

Introduction

Heart failure (HF) is a significant cause of morbidity and mortality, and has been associated with obesity in previous studies (1-8). The relationship between obesity and HF could result from direct adverse effects of obesity on cardiac structure and function or could occur because obese individuals have a high prevalence of comorbidities such as coronary artery disease, hypertension, diabetes, and obstructive sleep apnea (9). The prevalences of obesity (10-12) and of HF (13-15) are both rising. The increase in obesity likely contributes to the increase in the incidence of HF (3).

Although generalized obesity and central obesity (indicated by body mass index [BMI] and waist circumference [WC], respectively) have been identified as risk factors for incident HF (2-4), some studies have found that central obesity predicted incident HF better than generalized obesity (6,16), while others have found that central obesity and generalized obesity predicted incident HF to a similar extent (2-5,17). Central obesity is a stronger predictor of cardiovascular disease (CVD) risk factors (3), and may play a more important role than generalized obesity in the etiology of HF. We hypothesized that obesity will be associated with incident HF, after controlling for established risk factors at baseline, and the association will be stronger for measures of central obesity than generalized obesity.

There are variations in the incidence (13) and mechanisms of HF (18) in different ethnic groups, and the burden of obesity may be greater in some ethnicities (1). The effect of ethnicity on the association between obesity and incident HF is therefore an important area of research (1), but previous studies have been limited to predominantly white (3,5,15,17) and bi-racial populations (2,6). We explored the presence of heterogeneity by ethnicity in the relationship between obesity and incident HF, using data from the Multi-Ethnic Study of Atherosclerosis (MESA).

HF disproportionately affects older individuals (6). Although fat mass increases with age (3), studies in non-US populations have shown that the strength of association between obesity and incident...
HF (when measured by hazard ratios), weakens with age (3,4). There is a strong relationship between obesity and CVD risk factors (11), and we speculate that the increase in the incidence of HF in the elderly (19) may not be directly attributable to obesity, but may result from the increased prevalence of CVD risk factors in older age. Hence, we also explored the effects of age on the relationships between obesity and incident HF.

Methods and Procedures

Study population

MESA is a population-based study of 6814 men and women of Caucasian, African-American, Hispanic, and Chinese descent, aged 45-84 years old and without known clinical CVD at baseline (2000-2002). Participants were recruited from six regions in the USA. Details of MESA’s design and objectives have been published (20). The protocol was approved by the Institutional Review Board of participating sites and informed consent was obtained from participants. This cohort study is based on baseline data and incidence of HF during follow-up. Participants without baseline measurements of obesity, and those for whom no follow-up was completed were excluded.

Baseline measurements

Standardized questionnaires were used to collect information on educational status, cigarette smoking, physician diagnosis of hypertension and diabetes, and medications. The MESA Typical Week Physical Activity Survey was used to record the time and frequency spent on intentional exercise such as walking for exercise, sports/dancing, and conditioning activities (21). The total minutes per week spent on each activity was multiplied by its metabolic equivalent (MET) level and summed (MET-minutes/week). Hypertension was defined as systolic blood pressure ≥ 140 mm Hg and/or diastolic blood pressure ≥90 mm Hg and/or use of antihypertensive medications. Glycemic status was classified as normal (fasting blood glucose [FBG] <100 mg/dl, and not on treatment for diabetes), having impaired fasting glucose (FBG = 100-125 mg/dl, and not on treatment for diabetes), or diabetes (FBG ≥ 126 mg/dl or on treatment for diabetes). Resting 12-lead electrocardiograms (ECGs) obtained from fasting participants were centrally read and coded for the presence of left ventricular hypertrophy (LVH) using the Minnesota coding system. Cardiac magnetic resonance imaging (MRI) was obtained in a subset of participants (N = 5504). The MESA cardiac MRI protocol, image analysis, inter- and intrarreader reproducibility have been reported (22).

Serum glucose and plasma total cholesterol were measured by the glucose oxidase and cholesterol oxidase method, respectively (23). Hypercholesterolemia was present if plasma total cholesterol was ≥ 240 mg/dl (24). Spot urine albumin and creatinine were measured using the nephelometry and Jaffe reaction, respectively (25). Urinary albumin creatinine ratios were calculated and participants were classified as normal (<30 mg/g), having macroalbuminuria (>300 mg/g) or microalbuminuria (30-300 mg/g). Interleukin-6 was measured using an ultrasensitive enzyme-linked immunosorbent assay with a coefficient of variation of 6.3% (26).

Measures of obesity

Height was measured to the nearest 0.1 cm with a stadiometer. Weight was measured to the nearest 0.5 kg with a balance scale. BMI was calculated as weight divided by the square of height (kg/m²) and used as an indicator of generalized obesity. Participants were categorized as having normal weight (BMI <25 kg/m²), being overweight (BMI: 25-29.9 kg/m²), obese (BMI: 30-39.9 kg/m²), or severely obese (BMI ≥40 kg/m²). WC was measured to the nearest 0.1 cm with a measuring tape at the level of the umbilicus and used as an indicator of central obesity. Participants were classified as having central obesity if WC was >102 cm in men or >88 cm in women (27).

Follow-up and incident heart failure definition

The median follow-up period was 7.6 years (interquartile range, 0.44 years) with a total of 47,682 person-years of observation. Each participant or their next of kin was contacted by a telephone interview at 6-9 month intervals to inquire about interim hospitalizations, outpatient diagnoses and deaths due to cardiovascular causes (18). Records were obtained on approximately 99% of hospitalized cardiovascular encounters and some information on 97% of outpatient diagnostic encounters. Hospital records were abstracted and reviewed by paired physicians for independent endpoint classification and assignment of incidence dates (18). In cases of disagreements, the reviewing pair adjudicated differences, but if disagreements persisted, the full morbidity and mortality classification committee made the final decision.

The endpoint for our study was symptomatic HF. Multiple HF events in the same participant were considered once and time to the first occurrence was used. Endpoint criteria for HF in MESA included (a) physician-diagnosed HF and medical therapy for HF; and (b) pulmonary edema/congestion on chest radiography; and/or (c) dilated ventricle or poor left ventricular function on echocardiography or ventriculography, or evidence of left ventricular diastolic dysfunction (13,18). Participants not meeting any criteria, including those with a physician diagnosis only, without any other evidence were classified as not having HF.

Statistical analysis

Data are presented using means ± standard deviations or median (interquartile range) for continuous variables and percentages for discrete variables. Due to skewness, logarithmic transformation was performed for interleukin-6. Intentional exercise was non-normally distributed and was divided into quartiles. Comparisons between HF groups were tested using Chi-square test (discrete variables), 2-sample T-test (normally distributed continuous variables), and Mann–Whitney test (non-normally distributed continuous variables). Kaplan–Meier plots for incident HF are displayed according to BMI and central obesity categories, and compared using the Log-Rank test in both sexes. Participants were censored if they were lost to follow-up or failed to experience HF at the end of follow-up.

We estimated the correlation between BMI and WC using Pearson-Correlation coefficients. WC is highly correlated with BMI (2), so we assessed the associations of BMI and WC with incident HF using separate Cox-Proportional hazards (CPH) models. We used sex-specific models because of known differences in body composition between men and women (28). In model 1, we constructed sex-specific models. In Model 2, we adjusted for center and known founders of the association between obesity and incident HF, such as age, ethnicity, educational status (indicator of socioeconomic status), cigarette smoking, and intentional exercise (1,3). In Model 3,
we additionally adjusted for previously identified potential mediators of the association between obesity and incident HF, including hypertension, hypercholesterolemia, dysglycemia, LVH by ECG, albuminuria (indicator of kidney function), and inflammation (indicated by interleukin-6) (1,3). In MESA, interleukin-6 was the inflammatory marker with the strongest prediction for incident HF (18). ECG has limited sensitivity for diagnosing LVH (29). Therefore, in a sensitivity analysis (model 4), we substituted LVH by ECG with the corresponding MRI equivalent. In a subpopulation of 822 men and women without LVH risk factors in MESA, the 95th percentile cutoff of observed left ventricular mass (LVM)/predicted LVM of 1.31 was accepted as corresponding to LVH (29).

Hazard ratios were calculated per standard deviation greater value of BMI and WC. To compare the predictive abilities of BMI and WC for incident HF, we treated our HF endpoint as binary and uncensored and created receiver operating characteristic (ROC) curves for estimation of the area under the curve (AUC). We used the same datasets for the models being compared (model 2) and derived our AUC values based on C-statistics (30,31), estimated from gender-specific multivariable models. We assessed the goodness of fit for each model using Hosmer-Lemeshow tests. In sensitivity analyses, we conducted gender-specific time-dependent ROC curves for BMI and WC that accommodates censored data (30).

We grouped participants according to ethnicity and tested for interactions of BMI and WC with ethnicity. We generated CPH models and sequentially adjusted for confounders and known causal intermediaries. The risk of HF increases with age, so we grouped participants by age-groups (45-64, 65-74, and 75-84 years old) to satisfy the CPH model’s assumption that the baseline hazard for HF would be the same if the entire population had the same exposure (3). We tested for interactions of BMI and WC with age and generated CPH models using the same model building process. We examined adjusted absolute differences in HF incidence according to categories of weight and age-group using log-binomial regression models (32). We also

### TABLE 1 Characteristics of MESA participants at baseline (2000-2002) according to incident heart failure status

| Characteristics                      | Cases (n = 176) | Non-cases (n = 6633) | P value |
|--------------------------------------|----------------|---------------------|---------|
| Age, years                           | 69.1 ± 8.6     | 62.0 ± 10.2         | <0.0001 |
| Male sex, %                          | 60.8           | 46.8                | 0.0002  |
| Ethnicity                            |                |                     | 0.029   |
| White, %                             | 39.2           | 38.4                |         |
| Chinese-American, %                  | 5.1            | 12.0                |         |
| African-American, %                  | 33.5           | 27.6                |         |
| Hispanic, %                          | 22.2           | 22.0                |         |
| > High school education, %           | 56.8           | 63.7                | 0.06    |
| Cigarette smoking                    |                |                     | 0.01    |
| Never, %                             | 39.4           | 50.6                |         |
| Former, %                            | 44.0           | 36.4                |         |
| Current, %                           | 16.6           | 13.0                |         |
| Total intentional exercise, median (IQR), met-minutes/week | 630.0 (1470) | 832.5 (1935) | 0.01 |
| ECG left ventricular hypertrophy, %  | 6.3            | 0.9                 | <0.0001 |
| Hypertension, %                      | 75.6           | 44.1                | <0.0001 |
| Glycemic status                      |                |                     | <0.0001 |
| Diabetes, %                          | 31.8           | 12.1                |         |
| Impaired fasting blood glucose, %    | 15.9           | 13.8                |         |
| Normal, %                            | 52.3           | 74.1                |         |
| Total cholesterol, mg/dl             | 189.6 ± 35.1   | 194.3 ± 35.7        | 0.09    |
| Urine albumin creatinine ratio       |                |                     | <0.0001 |
| Normal (<30 mg/g), %                 | 69.8           | 91.0                |         |
| Microalbuminuria                     | 23.3           | 7.7                 |         |
| (30-300 mg/g), %                     | 15.9           | 22.0                |         |
| Macroalbuminuria                     | 7.0            | 1.3                 |         |
| Interleukin-6, pg/ml^a               | 1.70 ± 1.86    | 1.23 ± 1.95         | <0.0001 |
| Body mass index, kg/m^2              | 30.0 ± 6.2     | 28.3 ± 5.5          | <0.0001 |
| Waist circumference, cm              | 105.3 ± 17.1   | 98.0 ± 14.3         | <0.0001 |

Values are expressed as means ± SD unless otherwise indicated. Variables may contain missing data and the total sum for each variable may not equal sample size, the percentage of missing values is <3% for all variables. P values were determined using Chi-square test for categorical variables, independent 2-sample T-test for normally distributed continuous variables and Mann-Whitney test for non-normally distributed continuous variables. ECG, electrocardiogram; IQR, interquartile range; SD, standard deviation. *Values are geometric mean of il-6.

Significant estimates are indicated in bold.

FIGURE 1 (a) Heart failure free probability in MESA according to body mass index categories in men. BMI refers to body mass index (BMI) in kg/m^2. (b) Heart failure free probability in MESA according to BMI categories in women. BMI refers to BMI in kg/m^2.
evaluated unadjusted and adjusted associations of BMI and WC with causal-intermediaries of HF using logistic regression models.

To maximize statistical power, only participants with missing data on a variable needed for a particular model were excluded from analyses (18). We checked for proportionality of hazards by visually examining the log–log plots. Two-sided P-values of <0.05 were considered significant. Statistical analysis was performed using SAS enterprise guide version 4.3.

Results

We excluded five participants, for whom information on their HF status was missing, leaving a sample of 6809. We observed 176 incident HF cases. The HF incidence over a median follow-up of 7.6 years was 3.69/1000 person-years. Baseline characteristics of participants are presented according to HF occurrence during follow-up (Table 1). HF cases were more commonly male, older, African-American, past or current cigarette smokers, less physically active, and had a lower educational level than non-cases. Hypertension, LVH, glucose and kidney abnormalities were more prevalent, but mean cholesterol levels were lower in HF cases at baseline. HF cases had higher BMI, WC and interleukin-6 levels than non-cases. Kaplan–Meier plots of incident HF are presented for BMI and central obesity categories according to sex (Figures 1 and 2). There were significant differences in the incidence of HF across categories of BMI and WC in both sexes.

The correlation between BMI and WC was 0.892 in men and 0.865 in women. Hazard ratios of incident HF are presented for BMI and WC (Table 2). After adjusting for confounders, BMI and WC were associated with incident HF (model 2), but these associations became non-significant after adjusting for causal-intermediaries of HF (models 3 and 4). The attenuation of these associations was most evident when LVM (measured by MRI) was included in models for WC in women, for whom the association disappeared (model 4).

Based on model 2, the estimated AUC (from C-statistics) for BMI and WC for incident HF prediction was 0.749 and 0.750, respectively in men, and 0.782 and 0.777, respectively in women. Hosmer and Lemeshow tests supported good model fits for BMI and WC in both sexes. In our time-dependent analyses, our findings did not differ much because the estimated AUC at 7.6 years for BMI and WC for incident HF prediction was 0.75 and 0.75, respectively in men, and 0.74 and 0.75, respectively in females.

Obesity, incident HF, and ethnicity. Characteristics of participants according to ethnicity are available in online Supporting Information (Table S1). BMI and WC were lowest in Chinese-Americans and highest in African-Americans. Hypertension was most common in African-Americans while Hispanics had the highest cholesterol levels. African-Americans and Hispanics had the highest prevalence of diabetes. Ethnicity specific and stratified associations are shown in Table 3. Although there were no significant interactions between ethnicity and BMI or WC (P >0.05), we observed inverse associations of BMI with

![FIGURE 2](image_url) (a) Heart failure (HF) free probability in MESA according to central obesity categories in men. Central obesity is present if waist circumference (WC) >102 cm in men. (b) HF free probability in MESA according to central obesity categories in women. Central obesity is present if WC >88 cm in women.

**TABLE 2** Sex-specific and multivariable adjusted hazard ratios of incident heart failure per standard deviation greater value of body mass index and waist circumference in MESA

| Measure of obesity | Men | Women |
|-------------------|-----|-------|
|                    | n = 3210 | P-value | HR (95% CI) | P-value | HR (95% CI) |
| Body mass index |     |       |       |       |       |
| Model 1           | 1.31 (1.10-1.56) | 0.0021 | 1.45 (1.19-1.78) | 0.0003 |
| Model 2           | 1.33 (1.10-1.61) | 0.0033 | 1.70 (1.33-2.17) | <0.0001 |
| Model 3           | 1.09 (0.88-1.35) | 0.4402 | 1.34 (1.01-1.77) | 0.041 |
| Model 4a          | 1.12 (0.84-1.48) | 0.4353 | 1.17 (0.78-1.75) | 0.46 |
| Waist circumference |     |       |       |       |       |
| Model 1           | 1.50 (1.29-1.75) | <0.0001 | 1.63 (1.32-2.01) | <0.0001 |
| Model 2           | 1.38 (1.18-1.62) | <0.0001 | 1.64 (1.29-2.08) | <0.0001 |
| Model 3           | 1.19 (0.98-1.46) | 0.0832 | 1.29 (0.98-1.70) | 0.07 |
| Model 4a          | 1.24 (0.93-1.64) | 0.1413 | 1.00 (0.68-1.47) | 0.99 |

Model 1: sex specific analysis. Model 2: Model 1, adjusted for age, ethnicity, educational status, cigarette smoking, intentional exercise and center. Model 3: Model 2, additionally adjusted for hypertension, hypercholesterolemia, dysglycemia, LVH by ECG, albuminuria and il-6; Model 4*: Model 3, with LVM by MRI substituted for LVH by ECG.

Standard deviations for models 1-3 are 4.45 and 6.22 for BMI in men and women, respectively, and 12.24 and 16.03 for WC in men and women, respectively. Models 1-3 included all study participants, N = 6809. BMI, body mass index; ECG, electrocardiogram; il-6, interleukin-6; LVH, left ventricular hypertrophy; LVM, left ventricular mass, MRI, magnetic resonance imaging; WC, waist circumference.

*Standard deviations for model 4 are 4.10 and 5.59 for BMI in men and women, respectively, and 11.32 and 14.72 for WC in men and women, respectively. Model 4 included participants who had MRI at baseline, N = 5004. Significant estimates are indicated in bold.
Obesity, incident HF, and age-groups. Characteristics of participants according to age-group are presented in online Supporting Information (Table S2). The youngest age-group had the highest BMI while the middle age-group had the highest WC. Cholesterol levels decreased, while interleukin-6 levels increased with age. The prevalence of hypertension, diabetes, LVH, and kidney abnormalities increased with age. Age-group specific and stratified associations are given in Table 4. There were no significant interactions between age-group and BMI or WC (P >0.05). The hazard ratios of BMI and WC with incident HF generally decreased with age in women. In men, the hazard ratios of BMI and WC with incident HF appeared similar in the youngest and middle age-group.

Odds ratios of the associations of BMI and WC with causal-intermediaries of HF are available in online Supporting Information (Table S3). In both sexes, BMI and WC were significantly associated with hypertension, diabetes, and albuminuria at baseline. We had inadequate power to examine adjusted absolute differences for HF incidence in detail, and when compared to normal-weight participants, our estimates were 0.11 (−4.92 to 5.14), −0.60 (−7.24 to 6.05), and −1.50 (−9.37 to 6.37) in overweight participants, and 0.30 (−4.62 to 5.22), −0.95 (−8.88 to 6.97), and 0.73 (−7.81 to 9.26) in obese participants for the youngest, middle and oldest age-groups, respectively. For central obesity, the estimates were 0.29 (−3.95 to 4.53), 0.22 (−5.52 to 5.96), and 0.30 (−6.84 to 7.44) for the youngest, middle, and oldest age-groups, respectively.

Discussion

In this multi-ethnic cohort, obesity is associated with incident HF as shown in previous epidemiological studies (1-8). However, the relationship between obesity and incident HF is largely mediated by obesity-related conditions such as hypertension, hypercholesterolemia, dysglycemia, LVH, kidney disease, and inflammation. Adjusting for factors along the causal pathway results in attenuation of the associations between obesity and incident HF (2,8), as shown in our sequential approach to adjustment.

BMI and WC have similar predictive ability for incident HF. We agree with studies that found that central obesity and generalized

| Ethnicity specific analysis | Caucasian | Chinese-American | African-American | Hispanic | Total, stratified by ethnicity |
|----------------------------|-----------|------------------|------------------|----------|-----------------------------|
| **BMI**                    |           |                  |                  |          |                             |
| **Men**                    |           |                  |                  |          |                             |
| Model 1                    | 1.41 (1.08-1.85) | 1.79 (0.71-4.54) | 1.25 (0.91-1.72) | 0.89 (0.59-1.32) | 1.23 (1.02-1.48) |
| Model 2                    | 1.60 (1.20-2.13) | xxxxx a           | 1.40 (1.01-1.95) | 0.84 (0.56-1.26) | 1.33 (1.10-1.60) |
| Model 3                    | 1.41 (1.03-1.94) | xxxxx a           | 1.21 (0.82-1.78) | 0.50 (0.31-0.82) | 1.09 (0.88-1.35) |
| **Women**                  |           |                  |                  |          |                             |
| Model 1                    | 1.42 (1.02-1.96) | 1.34 (0.62-2.90) | 1.26 (0.88-1.80) | 1.76 (1.15-2.72) | 1.43 (1.16-1.78) |
| Model 2                    | 1.73 (1.18-2.53) | xxxxx a           | 1.52 (1.02-2.27) | 1.88 (1.18-2.98) | 1.71 (1.34-2.18) |
| Model 3                    | 1.35 (0.87-2.09) | xxxxx a           | 1.24 (0.78-1.97) | 1.47 (0.82-2.64) | 1.35 (1.02-1.78) |
| **WC**                     |           |                  |                  |          |                             |
| **Men**                    |           |                  |                  |          |                             |
| Model 1                    | 1.54 (1.27-1.86) | 1.69 (0.65-4.43) | 1.37 (0.99-1.88) | 1.16 (0.81-1.66) | 1.44 (1.22-1.70) |
| Model 2                    | 1.50 (1.23-1.84) | xxxxx a           | 1.44 (1.03-2.00) | 1.06 (0.72-1.52) | 1.38 (1.18-1.62) |
| Model 3                    | 1.49 (1.18-1.89) | xxxxx a           | 1.18 (0.80-1.74) | 0.69 (0.44-1.07) | 1.20 (0.98-1.46) |
| **Women**                  |           |                  |                  |          |                             |
| Model 1                    | 1.71 (1.21-2.40) | 1.70 (0.82-3.50) | 1.45 (1.02-2.06) | 1.66 (1.04-2.67) | 1.62 (1.30-2.01) |
| Model 2                    | 1.75 (1.20-2.55) | xxxxx a           | 1.57 (1.07-2.31) | 1.57 (0.96-2.56) | 1.64 (1.29-2.08) |
| Model 3                    | 1.36 (0.88-2.09) | xxxxx a           | 1.36 (0.85-2.16) | 1.12 (0.62-2.02) | 1.29 (0.98-1.70) |

Significant estimates are indicated in bold.

Model 1: sex specific analysis. Model 2: Model 1, adjusted for age, educational status, cigarette smoking, intemotional exercise and center. Model 3: Model 2, additionally adjusted for hypertension, hypercholesterolemia, dysglycemia, left ventricular hypertrophy by electrocardiogram, albuminuria and interleukin-6. Standard deviations are 4.08, 4.45 and 6.22 for BMI in men and women, respectively, and 12.24 and 16.03 for WC in men and women, respectively. Standard deviations for BMI in men are 4.08, 3.15, 4.71 and 4.30 for Caucasians, Chinese-Americans, African-Americans, and Hispanics, respectively, and in women are 5.82, 3.45, 6.44 and 5.69 for Caucasians, Chinese-Americans, African-Americans, and Hispanics, respectively. Standard deviations for WC in men are 11.38, 9.11, 12.73, and 11.28 for Caucasians, Chinese-Americans, African-Americans, and Hispanics, respectively, and in women are 16.22, 10.57, 16.14, and 14.59 for Caucasians, Chinese-Americans, African-Americans, and Hispanics, respectively.

BMI, body mass index; WC, waist circumference.

*aDue to limited number of events, adjusted associations are not presented for Chinese-Americans.

Significant estimates are indicated in bold.
Obesity and Incident Heart Failure

Obesity and Incident Heart Failure

Obesity predict incident HF to a similar extent (2-5,17) and either measure may be useful for predicting HF risks in the clinical setting. Although central obesity is a potent predictor of CVD risk factors (3), and has been strongly associated with metabolic derangements (2), other mechanisms in generalized obesity may contribute to the development of HF in obese individuals (2). A substantial relationship has been demonstrated between obesity and traditional risk factors in MESA (11), and we observed significant associations of BMI and WC with causal-intermediaries of HF such as hypertension, diabetes and albuminuria. However, this analysis was cross-sectional, and our odds ratios which were calculated per standard deviation increase in BMI and WC may not be directly comparable.

Bahrami et al. previously assessed the associations of obesity (and BMI) with incident HF in MESA (18). They found that obesity (and BMI) was associated with incident HF after adjusting for established risk factors, but the addition of inflammatory markers (interleukin-6 or C-reactive peptide) resulted in nullification of the associations (18). Their analyses measured LVH by ECG (18). We utilized a gender-specific approach and additionally accounted for ethnicity, socioeconomic status, kidney function, and intentional exercise, yet we noted persisting associations between BMI and incident HF for women in ECG-based models that included interleukin-6. Because the extent of cardiac remodeling increases with the duration of obesity (1,33), this difference in our findings may be attributable to greater statistical power from a higher number of HF events, and a longer follow-up duration in our study.

There are racial differences in the severity and prevalence of comorbid conditions (13,34), and we observed a higher burden of hypertension and diabetes in African-Americans. In MESA, Bahrami et al. have reported that the risk of incident HF in African-Americans is related to socioeconomic status, and a higher prevalence of hypertension and diabetes (13), so we expected differences in the associations of obesity and incident HF by ethnicity. Loehr et al.’s findings in the ARIC study did not support significant differences by race, although BMI and WC tended to be more strongly associated with incident HF in whites when compared to blacks (2).

We did not observe statistically significant differences among multiple ethnic groups, but the hazard ratios relating incident HF to BMI and WC appeared to be greater in Caucasians when compared to African-Americans, except for WC in women, for which we observed similar associations in Caucasians and African-Americans after accounting for obesity-related conditions. In Hispanic men, we observed paradoxical associations for BMI, because a higher BMI appeared to be associated with a decreased risk of incident HF.

### TABLE 4 Sex-specific and multivariable adjusted hazard ratios of incident heart failure per standard deviation greater value of body mass index and waist circumference according to age-group in MESA

| Age-group specific analysis | Total, stratified by age-group |
|----------------------------|-------------------------------|
| 45-64 years n = 3829       |                               |
| BMI                        |                               |
| Men                        |                               |
| Model 1                    | 1.50 (1.08-2.09)              |
| Model 2                    | 1.37 (0.96-1.96)              |
| Model 3                    | 1.00 (0.69-1.46)              |
| Women                      |                               |
| Model 1                    | 1.72 (1.23-2.40)              |
| Model 2                    | 1.86 (1.26-2.74)              |
| Model 3                    | 1.59 (0.95-2.68)              |
| WC                         |                               |
| Men                        |                               |
| Model 1                    | 1.63 (1.15-2.29)              |
| Model 2                    | 1.45 (1.00-2.09)              |
| Model 3                    | 1.06 (0.71-1.57)              |
| Women                      |                               |
| Model 1                    | 1.88 (1.32-2.68)              |
| Model 2                    | 1.91 (1.28-2.85)              |
| Model 3                    | 1.62 (0.96-2.74)              |
| Total, stratified by age-group n = 6809 HR (95% CI) | 1.43 (1.19-1.70) |
| Model 1                    | 1.30 (1.08-1.58)              |
| Model 2                    | 1.06 (0.85-1.31)              |
| Model 3                    | 1.64 (1.29-2.08)              |
| Model 3                    | 1.28 (0.97-1.68)              |

Model 1: sex specific analysis; Model 2: Model 1, adjusted for ethnicity, educational status, cigarette smoking, intentional exercise and center; Model 3: Model 2, additionally adjusted for hypertension, hypercholesterolemia, dysglycemia, LVH by ECG, albuminuria and IL-6. Standard deviations for BMI in men are 4.45 and 6.22 for BMI in men and women, respectively and 12.24 and 16.03 for WC in men and women, respectively. Standard deviations for BMI in men are 4.55, 4.36, and 4.07 for age-groups 45-64, 65-74, and 75-84, respectively, and in women are 6.57, 5.96, and 4.98 for age-groups 45-64, 65-74, and 75-84, respectively. Standard deviations for WC in men are 12.46, 11.97, and 11.94 for age-groups 45-64, 65-74, and 75-84, respectively and in women are 16.74, 15.57, and 13.77 for age-groups 45-64, 65-74, and 75-84, respectively. BMI, body mass index; ECG, electrocardiogram; IL-6, interleukin-6; LVH, left ventricular hypertrophy; WC, waist circumference. Significant estimates are indicated in bold.
Various obesity paradoxes have been described, when increased body fat does not increase morbidity or mortality (35), but the mechanisms underlying this association in Hispanic men is unclear, particularly because we did not observe a similar result in Hispanic women.

Previous studies reported that the associations between obesity and incident HF (when measured by hazard ratios) were weaker at older ages (3,4) and we observed a similar pattern in women. In men, the associations of BMI and WC appeared similar in the youngest and middle age-groups. The weakest associations for BMI were observed in the oldest age-group, and because the prevalence of comorbidities was highest in this group, we surmised that comorbidities may play a greater role than generalized obesity in the pathogenesis of HF in this age-group. Interestingly, this pattern was not consistent for central obesity (WC) particularly in men, because when we accounted for obesity-related conditions, the strongest association was observed in this age-group. Despite these patterns, we failed to demonstrate significant interactions among age-groups, after accounting for age-related differences in the baseline risk of incident HF. Due to inadequate power, we cannot make definite conclusions but there may be a tendency for adjusted absolute differences to remain stable or decrease with age due to increases in the baseline risk of HF at older ages in normal-weight participants. This issue should be further explored in adequately powered studies.

Although the relationship between obesity and incident HF is related to hemodynamic and anatomic cardiac changes, and comorbidities resulting from excess body fat, current evidence suggests that obesity-related inflammation, metabolic, and hormonal changes (including adipokines) are contributory to the pathogenesis of obesity-related HF (14,36,37). Other mechanisms that have been postulated include neurohormonal activation, increased oxidative stress, infiltration of myocytes with free fatty acids (FFA), and B-type natriuretic peptide depletion (38). Because the relationship between obesity and incident HF was largely due to causal-intermediaries in our analysis, the concept of direct effects in “obesity cardiomyopathy” requires further scrutiny. Nevertheless, lipotoxicity of the myocardium by excessive FFA (12,39) and high levels of triglycerides (39) has been supported by the demonstration of cardiac steatosis, apoptosis (8,40) and decreased left ventricular systolic function in animal models (40).

MESA involved a large number of participants with diverse age, ethnic, and gender representation from six geographic regions in the USA. HF ascertainment and data collection procedures were highly standardized and our prospective study design enabled us to measure HF incidence. Our sequential approach to adjustment allowed us to illustrate the role of obesity-related conditions in the association between obesity and incident HF. This is the first study to explore ethnic and age-group differences in the relationships between obesity and incident HF in a US population.

We observed relatively few events in subgroups and had limited power for exploratory analyses. Consequently, caution must be applied to interpretations related to subgroup analyses. We used baseline measures of obesity but participants may have undergone changes in adiposity during follow-up. Due to power and sample size restrictions, we retained the full cohort and relied on ECG measures of LVH for exploratory analyses.

Conclusion

The association between obesity and incident HF is largely mediated by obesity-related conditions such as hypertension, hypercholesterolemia, dysglycemia, LHV, kidney disease, and inflammation. WC is not superior to BMI in predicting HF incidence and either measure will be useful in HF prevention strategies. Therefore, HF prevention in obese individuals should be directed against obesity but must also involve treatment of obesity-related conditions (14). The effects of age and ethnicity on the relationship between obesity and incident HF should be further explored.

Acknowledgments

The authors thank the other investigators, the staff, and the participants of the MESA study for their valuable contributions. A full list of participating MESA investigators and institutions can be found at http://www.mesa-nhlbi.org. The MESA study was supported by contracts N01-HC-95159 through N01-HC-95169 from the National Heart, Lung and Blood Institute (NHLBI). The T32 training grant was supported by grant 5 T32 HL087730-03 from the NHLBI. Imo Ebong proposed the study, analyzed data and drafted the manuscript, David Goff, Carlos Rodriguez, and Alain Bertoni contributed to study design and proposal development. Haifying Chen analyzed data and supervised data analysis. Moyses Szklo and David Bluemke contributed to manuscript writing and reviewed the draft for intellectual content. All authors contributed to data interpretation, revision of the manuscript draft, and approved the final version of the manuscript.

References
1. Kenchaiah S, Gaziano JM, Vasan RS. Impact of obesity on the risk of heart failure and survival after the onset of heart failure. Med Clin N Am 2004;88:1273-1294.
2. Loehr LR, Rosamond WD, Poole C, et al. Association of multiple anthropometrics of overweight and obesity with incident heart failure: the atherosclerosis risk in communities study. Circ Heart Fail 2009;2:18-24.
3. Levitan EB, Yang AZ, Wolk A, Mittleman MA. Adiposity and incidence of heart failure hospitalization and mortality: a population-based prospective study. Circ Heart Fail 2009;2:202-208.
4. Van-Lieshout MA, Verwoert GC, Mattace-Raso FU, et al. Measures of body composition and risk of heart failure in the elderly: the Rotterdam study. J Nutr Health Aging 2011;15:393-397.
5. Hu G, Jousilahti P, Antikainen R, Katzmarzyk PT, Tuomilehto J. Joint effects of physical activity, body mass index, waist circumference, and waist-hip ratio on the risk of heart failure. Circulation 2010;121:237-244.
6. Nicklas BJ, Cesari M, Penninx BWJH, et al. Abdominal obesity is an independent risk factor for chronic heart failure in older people. J Am Geriatr Soc 2006;54:413-420.
7. Ingelsson E, Sundstrom J, Arnljot J, Zethelius B, Lind L. Insulin resistance and risk of congestive heart failure. JAMA 2005;294:334-341.
8. Kenchaiah S, Evans JC, Levy D, et al. Obesity and the risk of heart failure. N Engl J Med 2002;347:305-313.
9. Avelar E, Choward TV, Walker JM, et al. Left ventricular hypertrophy in severe obesity. interactions among blood pressure, nocturnal hypoxemia, and body mass. Hypertension 2007;49:34-39.
10. Baskin ML, Ard J, Franklin F, Allison DB. Prevalence of obesity in the United States. Obesity rev 2005;6:5-7.
11. Burke GL, Bertoni AG, Shea S, et al. The impact of obesity on cardiovascular disease risk factors and subclinical vascular disease. Arch Intern Med 2008;168:928-935.
12. Poirier P, Giles TD, Bray GA, et al. Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss: an update of the 1997 American Heart Association Scientific Statement on obesity and heart disease from the obesity committee of the council on nutrition, physical activity, and metabolism. Circulation 2006;113:898-918.
