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

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Abstract

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—We included 6,809 participants, aged 45–84 years, without clinical cardiovascular disease (2000–2002), from the Multi-Ethnic Study of Atherosclerosis. 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,

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Imo Ebong proposed the study, analysed data and drafted the manuscript. David Goff, Carlos Rodriguez, and Alain Bertoni contributed to study design and proposal development. Haiying Chen analysed 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.

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.

Keywords

Obesity; heart failure; body mass index and waist circumference

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 (CAD), hypertension, diabetes and obstructive sleep apnea (OSA) (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 6,814 men and women of Caucasian, African-American, Hispanic, and Chinese descent, aged 45–84 years and without known clinical CVD at baseline (2000–2002). Participants were recruited from six regions in the US. 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 intrareader 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/m^2) and used as an indicator of generalized obesity. Participants were categorized as having normal weight (BMI <25 kg/m^2), being overweight (BMI: 25–29.9 kg/m^2), obese (BMI: 30–39.9 kg/m^2) or severely obese (BMI ≥40 kg/m^2). 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 interviewer 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 confounders 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) 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 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. 2-sided p-values of <0.05 were considered significant. Statistical analysis was performed using SAS enterprise guide version 4.3.

Results

We excluded 5 participants, for whom information on their HF status was missing, leaving a sample of 6,809. 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 in figures 1 and 2 respectively. 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 (model 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 online (supplemental table 1). 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 incident HF in Hispanic men. An inverse relationship of WC with incident HF was also apparent in model 3 for Hispanic men.

Obesity, incident HF and age-groups

Characteristics of participants according to age-group are presented online (supplemental table 2). 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 presented 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 online in supplemental table 3. 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 – 5.14), −0.60 (−7.24 – 6.05), and −1.50 (−9.37 – 6.37) in overweight participants, and 0.30 (−4.62 – 5.22), −0.95 (−8.88 – 6.97), and 0.73 (−7.81 – 9.26) in obese participants for the youngest, middle and oldest age-groups respectively. For central obesity, the estimates were 0.29 (−3.95 – 4.53), 0.22 (−5.52 – 5.96) and 0.30 (−6.84 – 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 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 with 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 remodelling 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. 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 US. 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, LVH, 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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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; 88:1273–94. [PubMed: 15331317]
2. Loehr LR, Rosamond WD, Poole C, McNeill AM, Chang PP, Folsom AR, 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. [PubMed: 19808311]
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; 2:202–8. [PubMed: 19808341]
4. Van-Lieshout MA, Verwoert GC, Mattace-Raso FU, Zillikens MC, Sijbrands EJ, Deckers JW, et al. Measures of body composition and risk of heart failure in the elderly: the Rotterdam study. J Nutr Health Aging. 2011; 15:393–7. [PubMed: 21528167]
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; 121:237–44. [PubMed: 20048205]
6. Nicklas BJ, Cesari M, Penninx BWJH, Kritchevsky SB, Ding J, Newman A, et al. Abdominal Obesity is an Independent Risk Factor for Chronic Heart Failure in Older People. J Am Geriatr Soc. 2006; 54:413–20. [PubMed: 16551307]
7. Ingelsson E, Sundstrom J, Arnlov J, Zethelius B, Lind L. Insulin Resistance and Risk of Congestive Heart Failure. JAMA. 2005; 294:334–41. [PubMed: 16030278]
8. Kenchaiah S, Evans JC, Levy D, Wilson PWF, Benjamin EJ, Larson MG, et al. Obesity And The Risk of Heart Failure. N Engl J Med. 2002; 347:305–13. [PubMed: 12151467]
9. Avelar E, Cloward TV, Walker JM, Farney RJ, Strong M, Pendleton RC, et al. Left Ventricular Hypertrophy in Severe Obesity. Interactions Among Blood Pressure, Nocturnal Hypoxemia, and Body Mass. Hypertension. 2007; 49:34–9. [PubMed: 17130310]

10. Baskin ML, Ard J, Franklin F, Allison DB. Prevalence of Obesity in the United States. Obesity reviews. 2005; 6:5–7. [PubMed: 15655032]
11. Burke GL, Bertoni AG, Shea S, Tracy R, Watson KE, Blumenthal RS, et al. The Impact of Obesity on Cardiovascular Disease Risk Factors and Sublinical Vascular Disease. Arch Intern Med. 2008; 168:928–35. [PubMed: 18474756]
12. Poirier P, Giles TD, Bray GA, Hong Y, Stern JS, Pi-Sunyer FX, 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. [PubMed: 16380542]
13. Bahrami H, Kronmal R, Bluemke DA, Olson J, Shea S, Liu K, et al. Differences in the Incidence of Congestive Heart Failure by Ethnicity. The Multi-Ehnic Study of Atherosclerosis. Arch Intern Med. 2008; 168:2138–45. [PubMed: 18955644]
14. Voulgari C, Tentolouris N, Dilaveris P, Tousoulis D, Katsilambros N, Stefanadis C. Increased Heart Failure Risk in Normal-Weight People With Metabolic Syndrome Compared With Metabolically Healthy Obese Individuals. J Am Coll Cardiol. 2011; 58:1343–50. [PubMed: 21920263]
15. Baena-Diez JM, Byram AO, Grau M, Gomez-Fernandez C, Vidal-Solsona M, Ledesma-Ulloa G, et al. Obesity Is an Independent Risk factor for Heart Failure: Zona Franca Cohort Study. Clin Cardiol. 2010; 33:760–4. [PubMed: 21184560]
16. Dagenais GR, Yi Q, Mann JFE, Bosch J, Pogue J, Yusuf S. Prognostic impact of body weight and abdominal obesity in women and men with cardiovascular disease. Am Heart J. 2005; 149:54–60. [PubMed: 15660034]
17. Wannamethee SG, Shaper AG, Whincup PH, Lennon L, Sattar N. Obesity and Risk of Incident Heart Failure in Older Men With and Without Pre-existing Coronary Heart Disease. Does Leptin have a role? J Am Coll Cardiol. 2011; 58:1870–7. [PubMed: 22018297]
18. Bahrami H, Bluemke DA, Kronmal R, Bertoni AG, Lloyd-Jones DM, Shahar E, et al. Novel Metabolic Risk Factors for Incident Heart Failure and Their Relationship With Obesity. J Am Coll Cardiol. 2008; 51:1775–83. [PubMed: 18452784]
19. Murad K, Kitzman DW. Frailty and multiple comorbidities in the elderly patient with heart failure: implications for management. Heart Fail Rev. 201110.1007/s10741-011-9258-y
20. Bild DE, Bluemke DA, Burke GL, Detrano R, Roux AVD, Folsom AR, et al. Multi-Ethnic Study of Atherosclerosis: Objectives and Design. Am J Epidemiol. 2002; 156:871–81. [PubMed: 12397006]
21. Bertoni AG, Whitt-Glover MC, Chung H, Le KY, Barr RG, Mahesh M, et al. The Association Between Physical Activity and Subclinical Atherosclerosis. The Multi-Ethnic Study of Atherosclerosis. Am J Epidemiol. 2009; 169:444–54. [PubMed: 19075250]
22. Natori S, Lai S, Finn JP, Gomes AS, Hundley WG, Jerosch-Herold M, et al. Cardiovascular Function in Multi-Ethnic Study of Atherosclerosis: Normal Values by Age, Sex, and Ethnicity. Am J Roentgenol. 2006; 186:s357–65. [PubMed: 16714609]
23. Paramsothy P, Knopp RH, Bertoni AG, Blumenthal RS, Wasserman BA, Tsai MY, et al. Association of Combinations of Lipid Parameters With Carotid Intima-Media Thickness and Coronary Artery Calcium in the MESA (Multi-Ethnic Study of Atherosclerosis). J AM Coll Cardiol. 2010; 56:1034–41. [PubMed: 20846602]
24. Janssen I, Katzmarzyk PT, Ross R. Waist circumference and not body mass index explains obesity-related health risk. BMJ. 2004; 79:379–84.
25. Awua-Larbi S, Wong TY, Cotch MF, Durazo-Arvizu R, Jacobs DR, Klein BEK, et al. Retinal arteriolar caliber and urine albumin excretion: the Multi-Ethnic Study of Atherosclerosis. Nephrol Dial Transplant. 2011; 26:3523–8. [PubMed: 21398363]
26. Lakoski S, Cushman M, Siscovick D, Blumenthal R, Palmas W, Burke G, et al. The relationship between inflammation, obesity and risk for hypertension in the Multi-Ethnic Study of Atherosclerosis (MESA). J Hum Hypertens. 2011; 25:73–9. [PubMed: 20944659]
27. Lean MEJ, Han TS, Morrison CE. Waist circumference as a measure for indicating need for weight management. BMJ. 1995; 311:158–61. [PubMed: 7613427]

28. Mukuddem-Petersen J, Snijder MB, Dam RMV, Dekker JM, Bouter LM, Stehouwer CD, et al. Sagittal abdominal diameter: no advantage compared with other anthropometric measures as a correlate of components of metabolic syndrome in elderly from the Hoorn study. Am J Clin Nutr. 2006; 84:995–1002. [PubMed: 17093149]
29. Jain A, Tandri H, Dalal D, Chahal H, Soliman EZ, Prineas RJ, et al. Diagnostic and prognostic utility of electrocardiography for left ventricular hypertrophy defined by magnetic resonance imaging in relationship to ethnicity: The Multi-Ethnic Study of Atherosclerosis (MESA). Am Heart J. 2010; 159:652–8. [PubMed: 20362725]
30. Chambless LE, Diao G. Estimation of time-dependent area under the ROC curve for long-term risk prediction. Statist Med. 2006; 25:3474–86.
31. Polonsky TS, McClelland RL, Jorgensen NW, Bild DE, Burke GL, Guerci AD, et al. Coronary Artery Calcium Score and Risk Classification for Coronary Heart Disease Prediction. JAMA. 2010; 303:1610–6. [PubMed: 20424251]
32. Spiegelman D, Hertzmark E. Easy SAS calculations for Risk or Prevalence Ratios and Differences. Am J Epidemiol. 2005; 162:199–200. [PubMed: 15987728]
33. Alpert MA. Obesity Cardiomyopathy: Pathophysiology and Evolution of the Clinical Syndrome. Am J Med Sci. 2001; 321:225–36. [PubMed: 11307864]
34. Abell JE, Egan BM, Wilson PWF, Lipsitz S, Woolson RF, Lackland DT. Differences in Cardiovascular Disease Mortality Associated With Body Mass Bewteen Black and White Persons. Am J Public Health. 2008; 98:63–6. [PubMed: 18048799]
35. Bays HE. Adisopathy: Is “Sick Fat” a Cardiovascular Disease? J Am Coll Cardiol. 2011; 57:2461–73. [PubMed: 21679848]
36. Deswal A. Obesity, Leptin and Incident Heart Failure. J Am Coll Cardiol. 2011; 58:1878–80. [PubMed: 22018298]
37. Horwich TB, Fonarow GC. Glucose, Obesity, Metabolic Syndrome, and Diabetes. J Am Coll Cardiol. 2010; 55:283–93. [PubMed: 20117431]
38. Frankel DS, Vasan RS, D’Agostino RB, Benjamin EJ, Levy D, Wang TJ, et al. Resistin, Adiponectin and Risk of Heart Failure. The Framingham Offspring Study. J Am Coll Cardiol. 2009; 53:754–62. [PubMed: 19245965]
39. Schaffer JE. Lipotoxicity: when tissues overeat. Curr Opin Lipidol. 2003; 14:281–7. [PubMed: 12840659]
40. Szczepaniak LS, Dobbins RL, Metzger GJ, Sartoni-D’Ambrosia G, Arbique D, Vongpatanasin W, et al. Myocardial Triglycerides and Systolic Function in Humans: In Vivo Evaluation by Localized Proton Spectroscopy and Cardiac Imaging. Magn Reson Med. 2003; 49:417–23. [PubMed: 12594743]

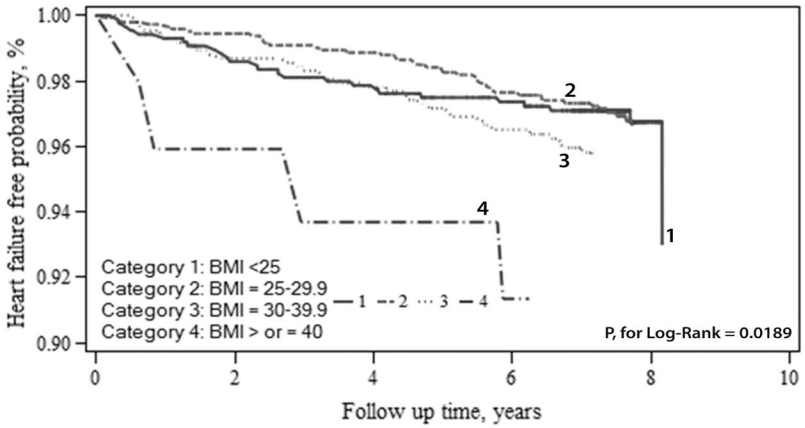

Figure 1a.

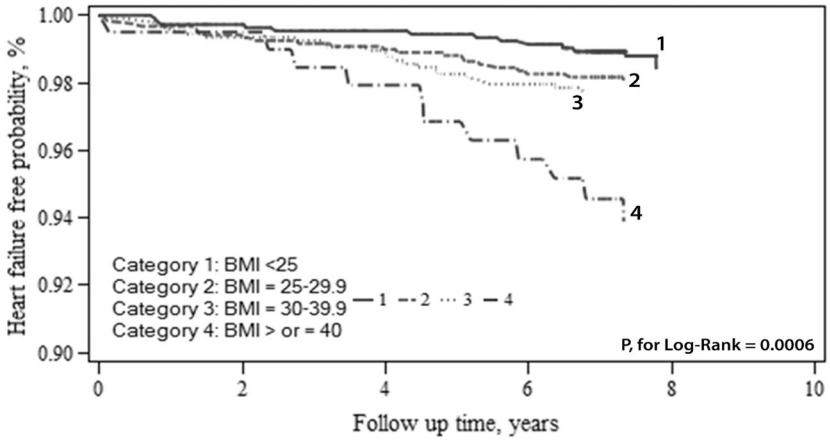

Figure 1b.

Figure 1.

Figure 1a. Heart failure free probability in MESA according to body mass index categories in men. BMI refers to body mass index in kg/m^2.

Figure 1b. Heart failure free probability in MESA according to body mass index categories in women. BMI refers to body mass index in kg/m^2.

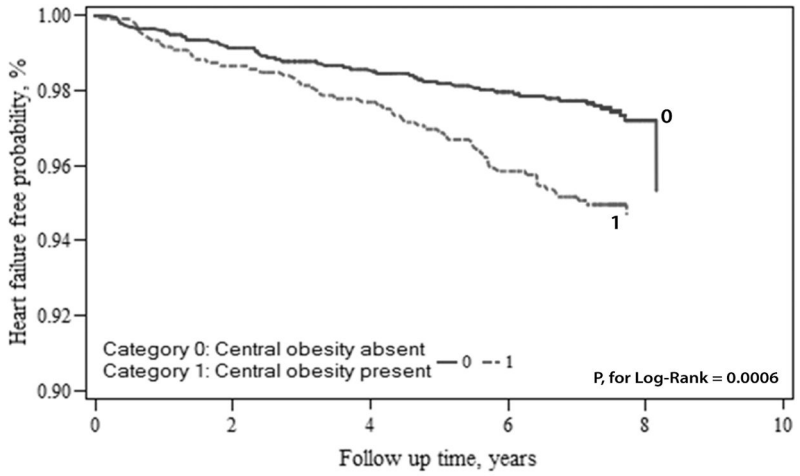

Figure 2a.

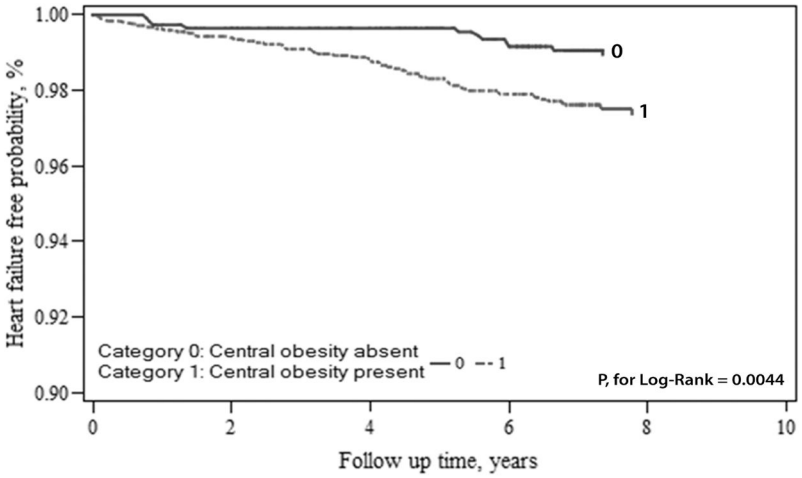

Figure 2b.

Figure 2.

Figure 2a. Heart failure free probability in MESA according to central obesity categories in men. Central obesity is present if waist circumference >102 cm in men.

Figure 2b. Heart failure free probability in MESA according to central obesity categories in women. Central obesity is present if waist circumference >88 cm in women.

Table 1

Characteristics of MESA participants at baseline (2000–2002) according to incident heart failure status

	Incident Heart Failure		
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 (30–300 mg/g), %	23.3	7.7	
- Macroalbuminuria (>300 mg/g), %	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 less than 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.

[a]Values are geometric mean of il-6.

Abbreviations: ECG, electrocardiogram; IQR, interquartile range; SD, standard deviation.

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 n=3210 HR (95% CI)	p-value	Women n=3599 HR (95% CI)	P value
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 4[a]	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 4[a]	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[a]: 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.

[a]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.

Abbreviations: 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.

Table 3

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 ethnicity in MESA

	Ethnicity specific analysis				
	Caucasian n=2619 HR (95% CI)	**Chinese-American[a] n=803 HR (95% CI)**	**African-American n=1892 HR (95% CI)**	**Hispanic n=1495 HR (95% CI)**	**Total, stratified by ethnicity n=6809 HR (95% CI)**
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)**	1.05 (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)

Model 1: Sex specific analysis;

Model 2: Model 1, adjusted for age, educational status, cigarette smoking, intentional 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 4.45 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.

[a] Due to limited number of events, adjusted associations are not presented for Chinese-Americans.

Abbreviations: BMI, body mass index; WC, waist circumference.

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			
	45–64 years n=3829 HR (95% CI)	**65–74 years n=2015 HR (95% CI)**	**75–84 years n=965 HR (95% CI)**	**Total, stratified by age-group n=6809 HR (95% CI)**
BMI				
Men				
Model 1	**1.50 (1.08–2.09)**	**1.46 (1.13–1.89)**	1.25 (0.91–1.72)	**1.43 (1.19–1.70)**
Model 2	1.37 (0.96–1.96)	**1.36 (1.01–1.84)**	1.07 (0.76–1.51)	**1.30 (1.08–1.58)**
Model 3	1.00 (0.69–1.46)	1.00 (0.71–1.43)	0.94 (0.62–1.41)	1.06 (0.85–1.31)
Women				
Model 1	**1.72 (1.23–2.40)**	**1.63 (1.14–2.34)**	1.40 (0.99–1.97)	**1.63 (1.32–2.01)**
Model 2	**1.86 (1.26–2.74)**	**1.63 (1.10–2.42)**	1.30 (0.88–1.94)	**1.64 (1.29–2.08)**
Model 3	1.59 (0.95–2.68)	1.12 (0.71–1.78)	1.08 (0.68–1.70)	1.28 (0.97–1.68)
WC				
Men				
Model 1	**1.63 (1.15–2.29)**	**1.60 (1.22–2.09)**	**1.33 (1.06–1.67)**	**1.47 (1.27–1.69)**
Model 2	**1.45 (1.00–2.09)**	**1.50 (1.10–2.05)**	1.25 (0.96–1.63)	**1.38 (1.17–1.62)**
Model 3	1.06 (0.71–1.57)	1.08 (0.75–1.56)	1.24 (0.89–1.72)	1.17 (0.96–1.44)
Women				
Model 1	**1.88 (1.32–2.68)**	**1.61 (1.11–2.34)**	**1.49 (1.03–2.16)**	**1.70 (1.37–2.11)**
Model 2	**1.91 (1.28–2.85)**	**1.58 (1.06–2.35)**	1.41 (0.96–2.08)	**1.64 (1.30–2.07)**
Model 3	1.62 (0.96–2.74)	1.09 (0.68–1.73)	1.18 (0.74–1.88)	1.27 (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 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.

Abbreviations: BMI, boody mass index; ECG, electrocardiogram; il-6, interleukin-6; LVH, left ventricular hypertrophy; WC, waist circumference.