Association of Multiple Anthropometrics of Overweight and Obesity With Incident Heart Failure
The Atherosclerosis Risk in Communities Study
Laura R. Loehr, MD, PhD; Wayne D. Rosamond, PhD; Charles Poole, ScD; Ann Marie McNeill, PhD; Patricia P. Chang, MD, MHS; Aaron R. Folsom, MD, MPH; Lloyd E. Chambless, PhD; Gerardo Heiss, MD, PhD

Background—The association of central adiposity with incident heart failure (HF) has yet to be studied in a large population-based study.

Methods and Results—The Atherosclerosis Risk in Communities study is an ongoing biracial population-based cohort of those aged 45 to 64 years from 4 US communities with 16 years’ median follow-up for incident, hospitalized, or fatal HF. Waist-hip ratio, waist circumference, and body mass index (BMI) were measured at baseline (1987–1989). After exclusions, the sample size was 14 641. BMI was categorized as <25, 25 to 29.9, and ≥30 kg/m². Waist circumference and waist-hip ratio were divided into gender-specific tertiles. A first occurrence of International Classification of Diseases, 9th Revision, Clinical Modification, codes of HF, either hospital discharge (428.0 to 428.9; n=1451) or on a death certificate (428.0 to 428.9 or I50.0 to I50.9; n=77) was considered an HF event. Cox models were adjusted for alcohol use, smoking, age, center, and educational level. The adjusted hazard ratios for the highest category (obese) compared with the lowest were well above 1.0 for all 3 anthropometric measures (hazard ratio for 3rd versus 1st tertile of waist-hip ratio: 2.27 [1.71, 3.02] for white women; 3.24 [2.25, 4.65] for black women; 2.46 [1.95, 3.09] for white men; and 2.63 [1.90, 3.65] for black men). Hazard ratios for overweight were lower in magnitude, suggesting a graded response between body size and HF.

Conclusions—Obesity and overweight, as measured by 3 different anthropometrics, were associated with incident HF in the Atherosclerosis Risk in Communities cohort. The current study does not support the superiority of waist-hip ratio and waist circumference over BMI for the prediction of incident HF. (Circ Heart Fail. 2009;2:18-24.)

Key Words: epidemiology ■ heart failure ■ obesity

Obesity, as measured by body mass index (BMI), has been identified as a risk factor for heart failure (HF) from the Framingham Heart Study1 and other studies.2,3 The increasing prevalence of both obesity and HF in the United States make this association an important topic for prevention.4 Replication of the association of obesity with HF in nonwhite racial groups has been mentioned as an important area for future research.5

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Furthermore, research on the association of measures of central adiposity with HF has been mentioned as a priority research area.6 Because diabetes and insulin resistance are risk factors for HF,7,8 one would expect that a measure of central adiposity, a correlate of impaired insulin sensitivity, would have a stronger association with incident HF than a measure of generalized adiposity. Waist circumference is highly correlated with BMI and is therefore considered a measure of both central and generalized adiposity, whereas waist-hip ratio (WHR) is a measure of central adiposity only.9 Existing studies imply that waist circumference and WHR are also associated with incident HF8,10,11; however, results vary depending on the population under study.

The Atherosclerosis Risk in Communities (ARIC) study is a biracial longitudinal cohort study of cardiovascular disease and its risk factors in those aged 45 to 64 years. It has anthropometric measures of BMI, WHR, and waist circumference from the baseline visit along with 16 years’ median follow-up for incident HF. In this study, we evaluated the race- and gender-specific associations of overweight and obesity with incident HF. Furthermore, we determined whether a measure of central adiposity (WHR) or a measure of generalized and central adiposity (waist circumference) would be more closely associated with incident HF than BMI.
Methods

Study Population
The ARIC cohort (n=15 792) was recruited between 1987 and 1989 using probability sampling of those aged 45 to 64 years from the following 4 US communities: Forsyth County, NC; Jackson, Miss; suburbs of Minneapolis, Minn; and Washington County, Md. The distribution of blacks and whites from each field center was representative of the area (mostly white in Minneapolis and Washington County, 15% black in Forsyth County), except in Jackson, where only blacks were sampled. Response rates at baseline were 46% in Jackson and between 65% and 67% for the other communities. Three subsequent visits were conducted at approximately 3-year intervals (last visit in 1996 to 1998). The design and rationale of the ARIC study12 and a comparison of responders and nonresponders13 have been previously published. The institutional review boards from each site approved the ARIC study. All participants provided written informed consent.

Racial groups not classified as white or black (n=48) and blacks not from Jackson or Forsyth County (n=120) were excluded in this study because of their limited numbers. Those with missing anthropometry (n=33), prevalent HF at baseline (n=751), or missing criteria used to define prevalent HF (n=289) were excluded. Criteria to define prevalent HF were as follows: (1) those answering “yes” to the question, “Were any of the medications you took during the last 2 weeks for HF?” (n=83); or (2) those with stage 3 HF by applying Gothenburg criteria (n=699).14 Gothenburg criteria were defined by self-reported medical history, medication lists, and electrocardiography.15 After these exclusions, the total sample size was 14 641.

Anthropometric Measures
Anthropometric indices were measured after an overnight fast with participants in standard scrub attire. Technicians measured height with participants barefoot using a wall mounted ruler. An anthropometric measuring tape was applied horizontally to measure hip and abdominal girth; participants stood upright with weight evenly distributed between both feet and breathing quietly. Abdominal girth was measured at the level of the umbilicus and hip girth at the level of maximal protrusion of the gluteal muscles. Weight was measured using a scale (Detecto model 437) that was zeroed daily and calibrated quarterly. BMI was calculated as weight divided by height squared (kg/m²), whereas WHR was the waist girth divided by the hip girth. Inter technician reliability coefficients for waist and hip girth were >0.91.16

Ascertainment of HF Events
The following methods were used for ascertainment of HF events: (1) participants were interviewed annually by phone about interim hospitalizations (93% to 96% response); (2) local hospitals provided lists of hospital discharges with cardiovascular diagnoses and these were reviewed to identify cohort hospitalizations; and (3) health department death certificate files were continuously surveyed. All discharge diagnosis codes for cohort hospitalizations and underlying or contributory causes of death from death certificates were reviewed to identify cohort hospitalizations; and (3) health department death certificate files were continuously surveyed. All discharge diagnosis codes for cohort hospitalizations and underlying or contributory causes of death from death certificates were reviewed.

Incident HF Event Criteria
Incident HF was defined as the first occurrence of either (1) a hospitalization that included an International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) discharge diagnosis code for HF beginning with “428” (ie, 428.0 to 428.9) in any position (n=1451) or (2) a death certificate ICD-9 code beginning with “428” (HF) or ICD-10 code “I50” (HF or I50.0 to I50.9) in any position (n=77). Follow-up time for incident HF events was defined as the time from their baseline examination until the incident event. The date of censoring for those without HF was the first occurrence of either date of last contact or death, or December 31, 2004. Secondary analyses inclusive of a broader range of HF ICD-9 codes resulted in only 139 additional events. These codes were as follows: rheumatic HF (398.91), hypertensive heart disease

Baseline Covariate Definitions
All covariates were collected from the baseline visit. Race was self-reported; educational level, alcohol use, and smoking status were obtained with interviewer-administered questionnaires. History of myocardial infarction (MI) included self-report of physician-diagnosed MI or silent MI identified by electrocardiography. Past coronary heart disease (CHD) included a history of MI, coronary revascularization, or coronary artery bypass surgery.

Hypertension was defined by either a diastolic blood pressure ≥90 mm Hg or a systolic blood pressure ≥140 mm Hg measured with random-zero mercury manometers, or recent antihypertensive medication use. Left ventricular hypertrophy was identified by electrocardiography using Cornell criteria.17 Diabetes mellitus was defined as self-reported physician-diagnosed diabetes, recent diabe-
Waist circumference, cm

<table>
<thead>
<tr>
<th></th>
<th>Total Persons-Years, n (%)</th>
<th>HF Events</th>
<th>Age-Adjusted* HF IR (95% CI) per 1000 Person-Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st tertile, &lt;87</td>
<td>78.9</td>
<td>33 743 (39)</td>
<td>84</td>
</tr>
<tr>
<td>2nd tertile, 87–&lt;100</td>
<td>92.6</td>
<td>29 767 (34)</td>
<td>101</td>
</tr>
<tr>
<td>3rd tertile, ≥100</td>
<td>111.2</td>
<td>23 899 (27)</td>
<td>209</td>
</tr>
</tbody>
</table>

WHR

<table>
<thead>
<tr>
<th></th>
<th>Total Persons-Years, n (%)</th>
<th>HF Events</th>
<th>Age-Adjusted* HF IR (95% CI) per 1000 Person-Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st tertile, &lt;0.86</td>
<td>0.80</td>
<td>32 321 (37)</td>
<td>69</td>
</tr>
<tr>
<td>2nd tertile, 0.86–&lt;0.93</td>
<td>0.89</td>
<td>27 416 (31)</td>
<td>109</td>
</tr>
<tr>
<td>3rd tertile, ≥0.93</td>
<td>0.98</td>
<td>27 671 (32)</td>
<td>216</td>
</tr>
</tbody>
</table>

The predictive ability of each anthropometric variable for incident HF was compared using time-dependent receiver operating characteristic curves for estimation of area under the curve at 10 years (AUC[10]), as described by Chambless and Diao.20 We determined the AUC(10) for each anthropometric measure (categorized) based on predicted probabilities estimated from gender-stratified multivariable Cox proportional hazards models. Predicted probabilities at 10 years were divided into deciles and each compared with the lowest group. Goodness of fit was assessed using Hosmer-Lemeshow tests. Furthermore, we adjusted for optimism due to use of the same dataset for determination of AUC(10) for both models being compared.21

To assess for additive effect measure modification by race, interaction contrast ratios22 with 95% CIs were calculated. A probabilistic sensitivity analysis was performed to assess the impact of systematic error from nondifferential outcome misclassification. A method developed by Lash and Fink23 was used to incorporate uncertainty from outcome misclassification into traditional regression using Monte Carlo uncertainty analysis. All statistical analyses were performed using SAS software version 9.1 (SAS Inc, Cary, NC).

The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.
### Results

Those who developed HF were older at baseline, more likely to be black, male, and less well educated (Table 1). As would be expected, there was a higher percentage of CHD and cardiovascular risk factors among HF events. Waist circumference and WHR cut points for men were higher than they were for women (Table 2). The mean value for each anthropometric by anthropometric category was surprisingly similar by gender and across race. For better comparability across race, for completeness, we present race- and gender-stratified estimates of the association of HF and adiposity. Although we did not find such support for differences in additive or multiplicative effect measure modification by race, for completeness, we present race- and gender-stratified estimates of the association of HF and adiposity.

Multivariable models of each anthropometric measure in continuous form showed positive associations for all race and gender groups (Table 3). Calculation of interaction contrast ratios and thus suggesting a graded response between body size and HF for all 3 anthropometric measures tended to be intermediate, above 2.0. Hazard ratios for the middle category (overweight) race, the adjusted HRs for HF with obesity were all well above 2-fold higher for all measures.

<table>
<thead>
<tr>
<th>Measure</th>
<th>White Men, HR (95% CI)</th>
<th>Black Men, HR (95% CI)</th>
<th>All Men, HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2nd tertile vs 1st tertile</td>
<td>1.19 (0.89, 1.60)</td>
<td>1.32 (0.87, 2.02)</td>
<td>1.24 (0.98, 1.58)</td>
</tr>
<tr>
<td>3rd tertile vs 1st tertile</td>
<td>2.75 (2.11, 3.58)</td>
<td>2.61 (1.77, 3.83)</td>
<td>2.68 (2.16, 3.33)</td>
</tr>
<tr>
<td>Continuous, 1-SD change†</td>
<td>1.61 (1.46, 1.77)</td>
<td>1.47 (1.33, 1.63)</td>
<td>1.54 (1.44, 1.66)</td>
</tr>
</tbody>
</table>

### Table 3. Multivariable Adjusted* HRs for Incident HF by BMI, Waist Circumference, and WHR, Stratified by Race and Gender

<table>
<thead>
<tr>
<th>Measure</th>
<th>White Women, HR (95% CI)</th>
<th>Black Women, HR (95% CI)</th>
<th>All Women, HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overweight vs normal</td>
<td>1.42 (1.10, 1.85)</td>
<td>1.02 (0.69, 1.49)</td>
<td>1.31 (1.05, 1.62)</td>
</tr>
<tr>
<td>Obese vs normal</td>
<td>2.93 (2.28, 3.75)</td>
<td>1.89 (1.33, 2.70)</td>
<td>2.56 (2.09, 3.14)</td>
</tr>
<tr>
<td>Continuous, 1-SD change†</td>
<td>1.64 (1.49, 1.82)</td>
<td>1.36 (1.24, 1.50)</td>
<td>1.49 (1.39, 1.59)</td>
</tr>
</tbody>
</table>

*All models adjusted for age, alcohol use, educational level, smoking status, and center. Models not stratified by race were also adjusted for race using a combined race and center variable. Models exclude 243 (1.7%) participants with missing covariates.

†1-SD change for BMI: women, 6 kg/m²; men, 4.2 kg/m²; 1-SD change for waist circumference: woman, 15.4 cm; men, 10.9 cm; 1-SD change for WHR: women, 0.08; men, 0.05.

### Summary

- **Waist circumference and WHR cut points for men were higher than they were for women (Table 2).**
- **The mean value for each anthropometric by anthropometric category was surprisingly similar by gender and across race.**
- **Calculation of interaction contrast ratios and thus suggesting a graded response between body size and HF for all 3 anthropometric measures tended to be intermediate, above 2.0.**
- **Hazard ratios for the middle category (overweight) race, the adjusted HRs for HF with obesity were all well above 2-fold higher for all measures.**

Estimation of AUC(10) from predicted probabilities from multivariable models for each anthropometric were as follows: BMI (0.73 for men, 0.79 for women); WHR (0.74 for men, 0.79 for women); waist circumference (0.73 for men, 0.79 for women); and BMI stratified by high and low WHR. Age-adjusted HF incidence rates for categories of BMI, stratified by high and low WHR show an increasing trend across these categories, with a particularly high HF incident rate (10.5 per 1000 person-years) in those with both a high BMI and WHR (Figure 2).

The sensitivity analysis assessed the effect of outcome misclassification on the multivariable association between.
obesity (BMI ≥ 30) and HF. Misclassification was assumed nondifferential, meaning it did not depend on values of other variables (namely, BMI) or on errors in measuring them. The selected distributions of the sensitivity parameters for misclassification of HF were initially based on findings from the literature; subsequently, the specified distributions required modification to allow for selection of plausible combinations of the sensitivity parameters (sensitivity: minimum, 0.6; mode 1, 0.7; mode 2, 0.85; maximum, 1; specificity: minimum, 0.94; mode 1, 0.96; maximum, 1). The sensitivity analysis results show the median odds ratio was higher and the 2.5th and 97.5th percentiles much farther apart (odds ratio, 4.54; 95% uncertainty interval, 2.93 to 14.83) than the results of the conventional analysis (odds ratio, 2.89; 95% CI, 2.47 to 3.42), which assumes with complete certainty that outcome classification is perfect. As expected, this suggests that the effect of outcome misclassification on our findings, given the chosen distributions of sensitivity and specificity, was to bias them toward the null, and that the assumption of perfect outcome classification in the conventional analysis understates the actual uncertainty about the true value of the odds ratio. In secondary analyses using the expanded definition of HF (inclusive of a broader range of ICD codes), there were no appreciable differences in any of our findings (results not shown).

Discussion

Generalized obesity and central adiposity, as measured by 3 different anthropometric measures, were associated with incident HF over 16 years’ median follow-up of the ARIC cohort. The magnitudes and patterns of the associations were similar for all 3 measures, and there was evidence of a graded relation for all race and gender groups. Furthermore, an adverse association existed between adiposity and incident HF even for those who were overweight compared with normal weight, although this finding was less consistent across stratified analyses. Analyses of receiver operating characteristic curves found no important differences in the prediction of incident HF for the 3 measures. This implies that measures of WHR and waist circumference are not superior to BMI in the prediction of HF. This is contrary to our hypothesis that measures of central adiposity will be more closely associated with HF due to their closer association with diabetes, a known HF risk factor. This suggests that beyond the metabolic derangements associated with central adiposity, other mechanisms associated with generalized adiposity, must play a role in mediating the relationship between obesity and HF.

Several previous studies with BMI measures have found similar associations to those observed here. The Framingham Heart Study found that overweight and obesity as measured by BMI were associated with an increased risk for HF over 14 years’ median follow-up; multivariable adjusted HRs were 1.34 (95% CI, 1.08 to 1.67) and 2.04 (95% CI, 1.59 to 2.63), respectively. In these models, the Framingham study adjusted for diseases along the causal pathway between obesity and HF. As they note, adjustment for factors along the causal pathway may underestimate the effect of adiposity with HF. Study differences between the Framingham study and ours include that the outcome of HF from the Framingham study was validated using Framingham criteria. The Framingham Heart Study is a primarily white population from a single community that is approximately a third the size of the ARIC study. Because the ARIC study included blacks and whites...
from 4 US communities, one might expect to find more heterogeneity in the findings between these 2 studies. Instead, the robustness of these findings supports a lack of differences in this association by race.

The Renfrew-Paisley study, a community-based study from Scotland, observed an association of obesity (as defined by BMI) with HF (men: HR, 2.16; 95% CI, 1.57 to 2.57; women: HR, 1.37; 95% CI, 1.00 to 1.88). The First National Health and Nutrition Examination Survey studied the association of excess BMI and incident HF,2 using a dichotomous cut point for BMI (men: 27.8 kg/m²; women: 27.3 kg/m²): their findings were similar to that observed in our overweight group despite the differing cut points used.

To date, studies of central obesity and HF have involved less generalizable populations. For example, the Health, Aging, and Body Composition Study (Health ABC) is a longitudinal cohort study of those aged 70 to 79 without CHD, in which multiple metrics of overweight/obesity and body composition were measured.16 This study had a limited number of HF events (n = 166), in part due to the exclusion of those with CHD, a common HF precursor.25 Despite the small sample size, BMI, waist circumference, and waist/thigh ratio were all positively associated with HF incidence. In contrast, a study of participants with CVD from the Heart Outcomes Prevention Evaluation study did not find an association between obesity and incident HF (n = 297 HF events) for BMI or WHR, except there seemed an effect for WHR in women (HR, 2.30; 95% CI, 1.25 to 4.21).17

We also describe risk groups using the cross-classification of 2 anthropometric measures, BMI and WHR. We find that incidence rates increase across categories of BMI stratified by WHR; however, the receiver operating characteristic analysis does not support better prediction of incident HF with this cross-classification of BMI and WHR when compared with these measures alone.

Further support for the association of obesity with HF comes from echocardiographic studies. Specifically, results from the Framingham Heart Study found positive correlations between obesity (BMI >30 kg/m²) and echocardiographic measures of left ventricular mass, which were also associated with increase in left ventricular internal dimensions, and wall thickness.26 A small study in normotensive men reported a small study in normotensive men reported that cardiovascular function improved with loss of excess BW.27 Recently, McGavock et al.28 found that cardiac steatosis as seen with magnetic resonance spectroscopy occurs with impaired glucose tolerance even before the development of type 2 diabetes mellitus and/or left ventricular dysfunction.

Obesity’s role in the development of HF may be through either direct and/or indirect mechanisms. The indirect mechanisms are those in which obesity causes other diseases, such as diabetes,29 hypertension,30 or CHD, which are themselves risk factors for HF.35 A direct mechanism might be that cardiac adaptation to excess body fat can result in decreased cardiac function.31 This has been termed “obesity cardiomyopathy.”32,33 A novel hypothesis is that an increase in inflammatory cytokines from excess adipocytes may increase the risk of HF.32,33 Also, several mechanisms from animal models have been proposed for the cardiotoxic effect of fat cells.34 However, true obesity cardiomyopathy is uncommon and usually occurs in cases of extreme obesity (BMI >40 kg/m²) of >10 years’ duration.

The main limitation of this study is our definition of HF. We included hospitalized and fatal HF, as we did not have data on outpatient HF; however, community surveillance reports have indicated that 74% of outpatient HF cases are hospitalized within 1.7 years.39 To address this limitation, we performed a sensitivity analysis to explore the effect of nondifferential outcome misclassification on our findings. As would be expected with outcome misclassification, we found it should bias our findings toward the null and increase our uncertainty about the true magnitude of the association.

This study is relevant and important to the understanding of the etiology of HF for 3 reasons. First, the ARIC study is the largest population-based cohort study to evaluate the association between WHR and waist circumference and incident HF. Furthermore, this is a well-characterized cohort with a long period of follow-up for which standardized methodology was used. Because it is a large biracial study, we were able to describe this association stratified by race and gender.

In conclusion, we observed that obesity was associated with incident HF and there was a graded relation with body size. This association did not vary by race or gender. Selecting the best anthropometric for the prediction of HF could have implications for the screening and prevention of HF. The current study does not support the superiority of WHR or waist circumference over BMI for the prediction of HF.

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Disclosures

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References


CLINICAL PERSPECTIVE

This is an important contribution to the literature on heart failure (HF) from a large population-based bi-ethnic cohort study with a median of 16 years of follow-up for incident HF. This article adds to the existing literature by providing estimates for the association of adiposity, as measured by 3 different anthropometric measures (body mass index [BMI], waist-hip ratio, and waist circumference) with incident HF for blacks as well as whites. In most clinical settings, BMI is the sole adiposity metric that is measured. This study evaluated whether these other measures were superior to BMI for the determination of HF risk. In fact, our findings do not support waist circumference, waist-hip ratio, or even further stratification of BMI into high and low categories of waist-hip ratio as superior to BMI for the purpose of determining HF risk. Therefore, the potential clinical impact is that measurement of waist circumference or waist-hip ratio is not necessary to improve determination of HF risk. This was true for both races (whites and blacks) and across gender.
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