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Novel Metabolic Risk Factors for Incident Heart Failure and Their Relationship With Obesity

The MESA (Multi-Ethnic Study of Atherosclerosis) Study

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Objectives The objectives of this study were to determine the associations of the metabolic syndrome, inflammatory markers, and insulin resistance with incident congestive heart failure (CHF), beyond established risk factors, and to examine whether these risk factors may provide the link between obesity and CHF.

Background Recently, increasing interest has emerged on the potential role of novel risk factors such as systemic inflammation, insulin resistance, and albuminuria in the pathophysiology of CHF and their relationship with obesity.

Methods The MESA (Multi-Ethnic Study of Atherosclerosis) study is a community-based multicenter cohort study of 6,814 participants (age 45 to 84 years, 3,601 women) of 4 ethnicities: Caucasians, African Americans, Hispanics, and Chinese Americans. Participants were recruited between 2000 and 2002 from 6 U.S. communities. Median follow-up time was 4 years. Participants with history of symptomatic cardiovascular disease were excluded. Cox proportional hazards models were used to analyze the associations of the metabolic syndrome, inflammatory markers, insulin resistance, and albuminuria with incident CHF, independent of established risk factors (age, gender, hypertension, diabetes mellitus, left ventricular hypertrophy, obesity, serum total cholesterol, and smoking), an interim myocardial infarction, and baseline magnetic resonance imaging parameters of left ventricular structure and function.

Results A total of 79 participants developed CHF during follow-up, and 26 participants (32.9%) had a myocardial infarction prior to CHF and 65% of the cases had CHF with preserved function (left ventricular ejection fraction ≥40%). In multivariable analyses, serum interleukin-6 (hazard ratio [HR] for 1 standard deviation 1.50, 95% confidence interval [CI] 1.10 to 2.03) or C-reactive protein (HR for 1 standard deviation 1.38; 95% CI 1.01 to 1.86) and macroalbuminuria (HR 4.31, 95% CI 1.58 to 11.76) were predictors of CHF, independent of obesity and the other established risk factors. Although obesity was significantly associated with incident CHF, this association was no longer significant after adding inflammatory markers (interleukin-6 or C-reactive protein) to the model.

Conclusions Inflammatory markers and albuminuria are independent predictors of CHF. The association of obesity and CHF may be related to pathophysiologic pathways associated with inflammation. (J Am Coll Cardiol 2008;51: 1775–83) © 2008 by the American College of Cardiology Foundation

Congestive heart failure (CHF) is one of the leading causes of morbidity and mortality (1–7) and its prevalence continues to rise in the U.S. (6), despite the decline in cardiovascular death rates (5). Although the prophylaxis of heart failure is complex, several risk factors have been identified as consistently associated with the development of CHF, including age, male sex, left ventricular hypertrophy (LVH), diabetes mellitus, valvular heart disease, hypertension, myocardial infarction (MI), LV dysfunction, and obesity. The associations of dyslipide-

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Abbreviations and Acronyms

BMI = body mass index
CHF = congestive heart failure
CI = confidence interval
CPH = Cox proportional hazards
CRP = C-reactive protein
ECG = electrocardiography
HOMA = homeostasis model assessment
HR = hazard ratio
IL = interleukin
IR = Insulin resistance
LV = left ventricle/ventricular
LVEF = left ventricular ejection fraction
LVH = left ventricular hypertrophy
MI = myocardial infarction
MRI = magnetic resonance imaging
UACR = urinary albumin-to-creatinine ratio

mia and cigarette smoking with CHF have been less consistent in the literature (7–13).

Among the established risk factors for CHF, obesity merits special attention, due to the rapidly growing obesity pandemic. Indeed, along with the recent improvements in the control of hypertension and hyperlipidemia, factors such as obesity and insulin resistance (IR) are poised to play a more important role in the development of cardiovascular events in the future. Although obesity is currently considered as an established determinant of CHF, the mechanisms by which it is translated into an increased risk for CHF remain unclear.

More recently, strong interest has emerged on novel risk factors for CHF such as systemic inflammation (10,14,15), IR (16–19), and albuminuria (20,21). These metabolic risk factors are recently clustered as part of the metabolic syndrome, which has been defined as the concurrence of some or all of abdominal obesity, hypertension, impairment of glucose metabolism, lipid disturbances, and albuminuria (22,23). The metabolic syndrome has been associated with LV dysfunction (24), CHF (25), and other cardiovascular events (26,27). Also, the pro-inflammatory state that characterizes the metabolic syndrome (28), which is indexed by markers such as C-reactive protein (CRP) (14,29) and interleukin (IL)-6 (30,31), may be associated with incident CHF through pathways that do not necessarily include obesity or IR. On the other hand, diabetes and IR are frequent comorbid conditions in both obese and nonobese patients with CHF (32). The relative importance of these factors in the general population and their role in the increased risk of CHF that is associated with obesity are largely unknown. These risk factors may play a direct role in the increased risk of CHF associated with obesity, or may instead be markers of other underlying conditions (18).

We investigated the independent associations of the metabolic syndrome, inflammatory markers, albuminuria, and IR with incident symptomatic CHF beyond obesity and other established risk factors for CHF in a multi-ethnic population. We also determined whether these risk factors predict CHF independent of an interim MI during follow-up. Finally, we explored whether the associations of obesity with incident CHF could be partially explained by these novel inflammatory and metabolic risk factors.

Methods

Study population. The MESA (Multi-Ethnic Study of Atherosclerosis) study is a multicenter cohort study of 6,814 men and women (age 45 to 84 years, 3,601 women) who have defined themselves as Caucasian (38%), African American (28%), Hispanic (22%), or Chinese American (12%). Participants were recruited between 2000 and 2002 from 6 U.S, communities in Maryland, Illinois, North Carolina, California, New York, and Minnesota. The exclusion criteria included the presence of clinically apparent cardiovascular disease at baseline. The design of the MESA study has been described in detail elsewhere (33). The study was approved by the institutional review boards at all participating centers and all participants gave informed consent.

Baseline examination. Standardized questionnaires were used to obtain information about smoking and medication use (34). Body mass index (BMI) was calculated as BMI = weight (kg)/ height^2 (m^2) from weight measured to the nearest 0.5 kg and height to the nearest 0.1 cm. Obesity and overweight were defined as BMI $\geq$30 kg/m^2 and 25 $\leq$ BMI $<$30 kg/m^2, respectively. Hypertension was defined as systolic blood pressure $\geq$140 mm Hg and/or diastolic blood pressure $\geq$90 mm Hg and/or use of antihypertensive medications. Diabetes was defined as fasting glucose $>$126 mg/dl or use of hypoglycemic medication.

Fasting plasma glucose and insulin levels were measured at baseline. Insulin levels were determined by a radioimmunoassay method using the Linco Human Insulin Specific RIA Kit (Linco Research, Inc., St. Charles, Missouri). As an index of IR, homeostasis model assessment (HOMA) index was calculated using the formula HOMA = (fasting glucose [mmol/l])(fasting insulin [μU/ml])/22.5 (35). Urinary creatinine and albumin were measured using the Vitros 950IRC instrument (Johnson & Johnson Clinical Diagnostics, Inc., Rochester, New York) and the Array 360 CE Protein Analyzer (Beckman Instruments, Inc., Fullerton, California), respectively. Participants were categorized into 3 groups based on baseline urinary albumin (mg)/creatinine (g) ratio (UACR): 1) normal: UACR $<$30; 2) microalbuminuria: UACR 30 to 300; and 3) macroalbuminuria: UACR $>$300 (36).

The metabolic syndrome was defined using the Adult Treatment Panel III criteria (22). Participants with 3 or more of these criteria were considered as having metabolic syndrome: abdominal obesity, given as waist circumference ($>$102 cm in men and $>$88 cm in women); serum triglycerides $\geq$150 mg/dl; high-density lipoprotein cholesterol $<$40 mg/dl in men and $<$50 mg/dl in women; blood pressure $\geq$130/$\geq$85 mm Hg or use of antihypertensive medications; fasting glucose $\geq$110 mg/dl or use of hypoglycemic medications. Serum levels of IL-6, CRP, and fibrinogen were measured as markers of systemic inflammation. Levels of IL-6 were determined by ultrasensitive ELISA (Quantikine HS Human IL-6 Immunoassay, R&D Systems, Minneapolis, Minnesota), and CRP levels were

measured by the BNII nephelometer (N High Sensitivity CRP, Dade Behring Inc., Deerfield, Illinois). The BNII nephelometer (N Antiserum to Human Fibrinogen; Dade Behring Inc.) was used to determine fibrinogen.

Left ventricular structure and function were determined by magnetic resonance imaging (MRI) at baseline in 5,004 participants (73.4%) who agreed to undergo MRI. The MRI protocol and analysis methods have been previously described (37). In addition to LV mass measured by MRI, data regarding LVH in electrocardiography (ECG) were collected in all participants.

Follow-up and outcome parameter. Median follow-up time was 4.0 years (interquartile range: 3.1 to 4.2 years), resulting in 25,107 person-years of observation. A telephone interviewer contacted each participant (or representative) every 6 to 9 months to inquire about all interim hospital admissions, cardiovascular outpatient diagnoses, and deaths. Medical records and information were successfully obtained on an estimated 98% of hospitalized cardiovascular events and 95% of outpatient cardiovascular diagnostic encounters. Two physicians reviewed all records for independent end point classification and assignment of event dates.

The end point for this study was symptomatic CHF. End point criteria included symptomatic CHF diagnosed by a physician and patient receiving medical treatment for CHF and 1) pulmonary edema/congestion by chest X-ray, and/or 2) dilated ventricle or poor LV function by echocardiography or ventriculography, or evidence of LV diastolic dysfunction. Participants who had a physician's diagnosis of CHF were classified as having CHF. Myocardial infarction was diagnosed based on combinations of symptoms, ECG, and cardiac biomarker levels.

Statistical methods. Data are presented as mean ± standard deviation (SD) or median (interquartile range) for continuous variables and number (percentage) for categorical variables. Logarithmic transformation was performed for serum insulin, HOMA index, serum IL-6, and CRP to reduce the skewness in the distributions. Differences in baseline characteristics of participants who developed and did not develop CHF were tested with Student *t* test (continuous variables with normal distribution) or chi-square test (categorical variables).

Cox proportional hazards (CPH) models were used to analyze the association of risk factors with incident CHF. Three sets of models were used: Model 1: unadjusted analysis; Model 2: adjusted for established risk factors of CHF, which include age, gender, hypertension, diabetes, LVH in ECG, obesity, serum total cholesterol, and current cigarette smoking; and Model 3: adjusted for the established risk factors included in Model 2 plus baseline LV function. Each novel risk factor was included in a separate model with the established risk factors in Models 2 and 3. Due to collinearity between different parameters of LV function, we only included left ventricular ejection fraction (LVEF) in Model 3, because LVEF had the strongest association with incident CHF (highest hazard ratio [HR] for 1 SD change in the predictor) in univariable analysis. The most parsimonious models were defined using a stepwise backward elimination in which age and gender were retained in the models and elimination was based on p values and likelihood ratio test.

To evaluate whether these risk factors predicted CHF independent of an interim MI during the follow-up, we performed an additional analysis in which we added interim MI as a time-varying covariate to Model 3. Using interim MI as a time-varying covariate allowed participants who developed CHF following an interim MI to contribute to person-times at risk for "CHF without prior interim MI" before they had MI and to person-times at risk for "CHF with prior interim MI" after they experienced MI. We also performed 2 ancillary analyses: 1) multivariable analysis in a subsample without participants with interim MI during follow-up, and 2) CPH model analyses in which patients with interim MI were censored at the time of MI diagnosis.

Results of CPH models are reported as HRs and 95% confidence intervals (CIs). All HRs are calculated and reported for 1 SD increase in continuous variables or transfer from 1 level to another of categorical variables, unless stated otherwise. Proportionality of hazards was checked by visually examining "log-log" plots. Participants who were lost to follow-up (<11%) were censored at the time of the last follow-up. To evaluate how much of the association of obesity with incident CHF was related to systemic inflammation and IR, we compared the regression coefficient for obesity before and after adjusting for these variables. Missing values were handled based on our a priori analysis plan, that is, only participants who had missing data on a variable needed for a particular model were excluded from the analysis. This method was used to maximize the statistical power, and in view of the negligible percentage of missing data to control for intercenter variability, study center was included as a categorical variable in the multivariable models. Cumulative hazards of CHF were illustrated in Nelson-Aalen plots and were compared using the log-rank test. Statistical analyses were performed using Stata version 8.2 for Windows (StataCorp, College Station, Texas).

Results

Seventy-nine out of 6,814 MESA participants developed CHF during follow-up (incidence rate: 3.1 per 1,000 person-years). Participants who developed CHF were more likely to be older, male, obese, current smoker, hypertensive, and diabetic (Table 1). Although the absolute risk of CHF in nonobese participants was 10 per 1,000, obese participants had a risk of 16 per 1,000 for developing CHF (attributable risk: 6 per 1,000; 95% CI 0.0004 to 0.012). The attributable risks associated with hypertension and diabetes were 11 per 1,000 (95% CI 0.006 to 0.017) and 19 per 1,000 (95% CI 0.008 to 0.030), respectively. Of the 79 participants who developed CHF during follow-up, 26

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Table 1 Distribution of Baseline Characteristics of the MESA Participants by Gender*

Characteristic	Men (N = 3,213)	Women (N = 3,601)
Demographic and anthropometric characteristics		
Age, yrs	62.2 ± 0.2	68.3 ± 1.2
Ethnicity, n (%)		
African Americans	1,261 (39.2)	1,363 (37.8)
Hispanics	718 (22.4)	774 (21.5)
Caucasians	844 (26.3)	1,051 (29.2)
Chinese Americans	390 (12.1)	413 (11.5)
Body mass index, kg/m^2	27.9 ± 0.1	28.8 ± 0.1
Waist circumference, cm	99.3 ± 0.2	97.1 ± 0.3
Established risk factors for CHF		
Obesity	903 (28.1)	1,294 (35.9)
Overweight	1,447 (45.0)	1,217 (33.8)
Cigarette smoking, n (%)		
Never	1,301 (40.7)	2,125 (59.3)
Former	1,427 (44.7)	1,037 (29.0)
Current	465 (14.6)	420 (11.7)
Diabetes classification, n (%)		
Normal	1,645 (51.4)	2,281 (63.6)
IFG†	1,055 (32.9)	840 (23.4)
Diabetes	503 (15.7)	466 (13.0)
Hypertension, n (%)	1,497 (46.6)	1,754 (48.7)
Mean arterial pressure (mm Hg)‡	92.0 ± 0.2	88.4 ± 0.2
Diastolic blood pressure (mm Hg)	75.0 ± 0.2	69.1 ± 0.2
LVH in electrocardiography, n (%)	46 (1.4)	22 (0.6)
LV mass index (g)	85.8 ± 0.3	70.8 ± 0.2
Metabolic syndrome	994 (30.1)	1,338 (38.0)
Incident symptomatic CHF	52 (1.6)	27 (0.8)
Myocardial infarction during follow-up, n (%)	59 (1.8)	19 (0.5)

For continuous variables, mean values ± standard errors are shown. Percentages for continuous variables are shown in parentheses. *All participants with symptomatic CHF or any other kind of cardiovascular disease at baseline were excluded from the study. †IFG was defined as fasting glucose 100 to 125 mg/dl. ‡Mean arterial pressure = 2/3 × diastolic blood pressure + 1/3 × systolic blood pressure

CHF = congestive heart failure; IFG = impaired fasting glucose; LV = left ventricle; LVH = left ventricular hypertrophy; MESA = Multi-Ethnic Study of Atherosclerosis.

(32.9%) had an interim MI, and 3 (3.8%) participants had a clinical MI after being diagnosed as CHF.

Metabolic syndrome, insulin resistance, and inflammatory markers. The metabolic syndrome was observed in 2,362 participants (34.7%) at baseline. In unadjusted models, participants who met Adult Treatment Panel III criteria for the metabolic syndrome at baseline were at higher risk of developing CHF (HR 2.04). The absolute risks of CHF were 17 per 1,000 and 9 per 1,000 in participants with and without the metabolic syndrome, respectively (attributable risk ≈9 per 1,000; 95% CI 0.003 to 0.015). Among the 5 criteria used in the definition of the metabolic syndrome, serum triglyceride and high-density lipoprotein cholesterol were not significant predictors of incident CHF.

Markers of systemic inflammation were significant predictors of CHF. Among these markers, IL-6 was the strongest predictor in the unadjusted models (HR of 1.84 for each SD increase in log serum IL-6). The absolute risks for CHF were 21 per 1,000 among participants at top quartile of serum IL-6 and 8 per 1,000 among those in the lower three quartiles (attributable risk: 13 per 1,000; 95% CI 0.005 to 0.20). A serum CRP ≥5 mg/dl was also significantly associated with an 87% increase in the risk of CHF (HR 1.87; 95% CI 1.16 to 3.00) and an increase in absolute risk from 10 per 1,000 to 18 per 1,000 (attributable risk: 8 per 1,000; 95% CI 0.001 to 0.016). Figure 1 illustrates the cumulative hazard of CHF by metabolic risk factors.

Higher fasting glucose levels were associated with a high risk of incident CHF. Participants with a HOMA score ≥95th percentile (4.8 U) were at a marginally higher risk of CHF compared to those with HOMA scores <95th percentile (HR 2.00, p = 0.06). On the other hand, both macroalbuminuria (UACR >300) and microalbuminuria (UACR: 30 to 300) were significant predictors of CHF (HR 9.47 and 4.40, respectively). The absolute risk for CHF increased from 8 per 1,000 in participants with normal UACR to 38 and 79 per 1,000 in those with micro- and macroalbuminuria, respectively.

Baseline LV structure and function and incident CHF. Because MESA participants had no history of heart disease at baseline, the frequencies of individuals with abnormal LV structure and function were likely to be less than in the general population. In this regard, 98.7% of MESA participants had LVEF ≥50%, and this proportion was 84.8% (67 participants) among the 79 participants who developed CHF. On the other hand, among the 6,814 participants of MESA, 505 participants (10.1%) would be considered to have LVH by Framingham criteria, and among participants who developed CHF, 17 participants (32.1%) had LVH at baseline. As shown in Table 2, LVEF, LV mass index, LV end-diastolic volume, LV end-systolic volume, and LV mass to end-diastolic volume ratio at baseline were all significant predictors of incident CHF. Among different parameters of LV function, LVEF had the strongest independent association with incident CHF, and therefore, we used LVEF as a covariate in multivariable CPH models (Table 2, column 3). Moreover, among 60 cases for which data on LV function at the time of CHF diagnosis were available, 52 patients (87%) had LVEF ≥30%, 39 participants (65%) had LVEF ≥40%, and 33 participants (55%) had LVEF ≥50%.

Adjustment for established risk factors and baseline LV structure and function. The results of the multivariable CPH models are shown in Table 3. Serum levels of IL-6, CRP, and fibrinogen as well as presence of microalbuminuria and/or macroalbuminuria were significant predictors of CHF, independent of established risk factors and LV function at baseline. The metabolic syndrome and HOMA index were not significantly associated with CHF in Models 2 and 3, after adjustment for established risk factors and LV function. Among the different metabolic syndrome criteria, plasma glucose and abdominal obesity were the strongest predictors of incident CHF (Table 3). Note that lack of association between CHF and high blood pressure in Models 2 and 3 is probably due to inclusion of LVH, which

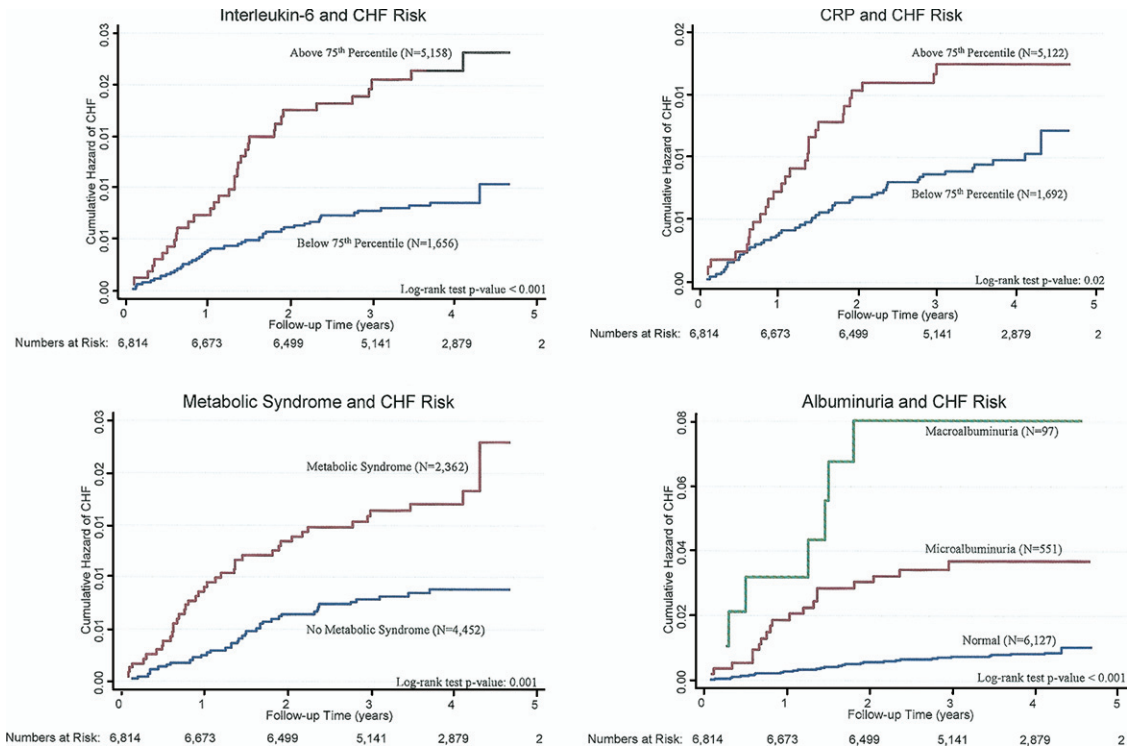

Figure 1 **Cumulative Hazards of CHF by Categories of Inflammatory Markers, Metabolic Syndrome, and Albuminuria**

Nelson-Aalen plots of cumulative hazards for congestive heart failure (CHF) in the MESA (Multi-Ethnic Study of Atherosclerosis) study by categories of interleukin (IL)-6, C-reactive protein (CRP), metabolic syndrome, and albuminuria. The 75th percentiles for IL-6 and CRP were 1.9 and 4.3 mg/dl, respectively.

is closely related to hypertension, in these models. Albuminuria, included in the World Health Organization criteria for the metabolic syndrome (23), was also a significant predictor.

Although obesity was a significant predictor of CHF, adding inflammatory markers (IL-6 or CRP) to any of the CHP models, which included obesity (or BMI), resulted in a considerable reduction in the magnitude of the association between obesity and incident CHF, and this association was no longer significant. For example, when IL-6 or CRP were added to the univariable analyses, the HR for obesity changed from 1.65 ($p = 0.03$) to 1.16 ($p = 0.53$) and 1.38 ($p = 0.18$), respectively. Similarly, the HR associated with obesity in Model 2 changed from 1.83 ($p = 0.01$) to 1.50 ($p = 0.11$) and 1.58 ($p = 0.06$), respectively, when IL-6 and CRP were added to Model 2. Substitution of obesity for BMI as a continuous variable yielded similar results.

Table 2 **Unadjusted and Adjusted Hazard Ratios of CHF in Relation to MRI-Defined LV Structure and Function at Baseline in the MESA Study (N = 5,004)**

Parameters of LV Structure and Function	Hazard Ratios (95% Confidence Interval)*	
	Unadjusted	Adjusted for Established Risk Factors†
LVEF (per 7.4% decrement)	1.89 (1.49–2.27)	1.69 (1.37–2.08)
LVEF ≤50%	14.92 (7.88–28.26)	8.30 (4.26–16.17)
End-diastolic volume index‡ (per 13.6 ml/m^2)	1.76 (1.46–2.13)	1.71 (1.40–2.08)
End-systolic volume index‡ (per 8.1 ml/m^2)	1.71 (1.53–1.90)	1.63 (1.44–1.87)
Stroke volume index‡ (per 9.0 ml/m^2)	0.98 (0.74–1.29)	1.11 (0.86–1.44)
LV mass index‡ (per 16.3 g/m^2)	1.87 (1.67–2.09)	1.84 (1.56–2.18)
LV mass/volume ratio (per 0.25 g/ml)	1.64 (1.39–1.96)	1.21 (0.96–1.51)

*Hazard ratios are calculated for 1 standard deviation increase in continuous variables or transfer from 1 level to another of categorical variables. †Age, gender, hypertension, diabetes mellitus, LV hypertrophy, obesity, serum cholesterol, and current cigarette smoking. ‡Absolute volumes and LV mass were indexed to body surface area.

MRI = magnetic resonance index; other abbreviations as in Table 1.

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Table 3 Unadjusted and Adjusted Hazard Ratios for Symptomatic CHF in Relation to Novel Metabolic Risk Factors in the MESA Study (n = 6,814)

Characteristic†	Hazard Ratios (95% Confidence Interval)*		
	Model 1: Unadjusted	Model 2: Adjusted for Established Risk Factors‡	Model 3: Adjusted for Established Risk Factors and LV Function at Baseline§
Established risk factors			
Age	1.97 (1.55–2.50)	1.96 (1.50–2.56)	2.07 (1.49–2.89)
Male gender	2.16 (1.35–3.44)	2.09 (1.27–3.42)	1.92 (0.99–3.69)
Obesity (BMI ≥30 kg/m^2)	1.65 (1.05–2.57)	1.83 (1.14–2.92)	1.58 (0.87–2.87)
Diabetes mellitus	3.17 (1.98–5.08)	2.06 (1.25–3.39)	1.99 (1.08–3.68)
Hypertension	2.88 (1.76–4.72)	1.49 (0.87–2.54)	1.69 (0.88–3.25)
LVH in electrocardiography	14.23 (7.09–28.54)	8.38 (4.05–17.31)	6.91 (2.93–16.29)
Current smoking (vs. never smoking)	1.85 (1.0–3.41)	2.74 (1.45–5.17)	3.91 (1.80–8.52)
Serum cholesterol (per 35.7 mg/dl)	1.01 (0.80–1.26)	1.21 (0.97–1.50)	1.45 (1.13–1.87)
Metabolic syndrome			
Metabolic syndrome‖	2.04 (1.31–3.17)	1.08 (0.63–1.86)	1.60 (0.89–2.87)
Abdominal obesity¶	1.82 (1.13–2.93)	2.06 (1.25–3.41)	1.73 (0.97–3.08)
High plasma glucose (≥110 mg/dl)	3.24 (2.07–5.05)	2.30 (1.45–3.64)#	3.06 (1.74–5.37)¶
High blood pressure (≥130/≥85 mm Hg)	2.66 (1.57–4.50)	1.32 (0.75–2.33)#	1.54 (0.79–3.02)#
Low serum HDL cholesterol**	0.94 (0.59–1.50)	0.79 (0.49–1.29)	0.95 (0.53–1.70)
High serum triglycerides (≥150 mg/dl)	1.11 (0.69–1.78)	0.97 (0.58–1.57)	1.11 (0.61–2.00)
Glucometabolic factors			
Fasting plasma glucose (per 30.9 mg/dl)	1.28 (1.13–1.45)	1.20 (1.04–1.38)	1.31 (1.12–1.54)
Fasting plasma insulin (per 0.64 log U/ml)	0.96 (0.77–1.20)	0.75 (0.58–0.96)	0.78 (0.57–1.07)
HOMA insulin resistance index (per 0.73 log unit)	1.14 (0.85–1.54)	0.74 (0.57–0.98)	0.80 (0.58–1.10)
HOMA insulin resistance index ≥95th percentile	2.00 (0.96–4.15)	1.30 (0.59–2.88)	1.30 (0.43–3.93)
UACR			
Normal (UACR <30)	1.0 (reference)	1.0 (reference)	1.0 (reference)
Microalbuminuria (UACR: 30 to 300)	4.40 (2.59–7.46)	2.73 (1.56–4.78)	1.80 (0.83–3.86)
Macroalbuminuria (UACR >300)	9.47 (4.28–20.93)	5.27 (2.30–12.11)	4.81 (1.76–13.10)
Markers of systemic inflammation			
Interleukin 6 (per 0.66 log pg/ml)	1.84 (1.48–2.28)	1.64 (1.31–2.06)	1.44 (1.09–1.92)
CRP (per 1.16 log mg/dl)	1.36 (1.09–1.70)	1.35 (1.06–1.73)	1.41 (1.06–1.87)
Serum fibrinogen (per 73.9 mg/dl)	1.37 (1.14–1.66)	1.25 (1.02–1.53)	1.26 (0.99–1.61)

*Hazard ratios are calculated for 1 standard deviation increase in continuous variables or transfer from 1 level to another of categorical variables. †Novel risk factors were included in Models 2 and 3 one at a time, that is, each model included 1 novel risk factor plus established risk factors for Model 2 and established risk factors and LVEF for Model 3. ‡Age, gender, hypertension, diabetes mellitus, LVH, obesity, serum cholesterol, and current cigarette smoking. Values for established risk factors are from the multivariable model including only established risk factors. §Left ventricular ejection fraction determined by MRI at baseline was used as a parameter of LV function. ‖Defined as the presence of 3 or more of the 5 criteria for the metabolic syndrome (22). ¶Waist circumference >102 cm in men and >88 cm in women. #In Models 2 and 3 for high blood glucose and high blood pressure (as 2 criteria for metabolic syndrome), we did not include the variables diabetes and hypertension, respectively, as independent variables (due to high correlations with the dependent variables). However, using medications for diabetes and hypertension were included in these models. **High-density lipoprotein cholesterol <40 mg/dl in men and <50 mg/dl in women.

BMI = body mass index; CRP = C-reactive protein; HDL = high-density lipoprotein; HOMA = homeostasis model assessment; UACR = urinary albumin-to-creatinine ratio; other abbreviations as in Tables 1 and 2.

MI during follow-up and the association of obesity with incident CHF. Interim MI during follow-up was associated with a significant increase in the risk of CHF (HR 112.24; 95% CI 69.20 to 182.03). Even though CRP remained associated with CHF (HR 1.42; 95% CI 1.05 to 1.92) after adding interim MI to Model 3 (including established risk factors and LV function), the metabolic syndrome and obesity were no longer significant predictors. However, in the model including interim MI, microalbuminuria remained associated with incident CHF (HR 2.40; 95% CI 1.13 to 5.08).

When the analyses were limited to the subsample of participants without interim MI, obesity, inflammatory markers, metabolic syndrome, and macroalbuminuria were significantly associated with incident CHF. Using Model 3 (adjusted for baseline LV function) in the subpopulation without interim MI, age, CRP, obesity, serum cholesterol, LVEF, current or former smoking, and LVH were significant predictors of CHF.

Finally, in another set of ancillary analyses, the patients with interim MI were censored (at the time of diagnosis of MI). The results of univariable analyses (Model 1) as well as Models 2 and 3 in these sets of models were similar to the results of the analysis in which interim MI was treated as a time-varying covariate. However, the magnitude of the association between obesity and CHF was higher in Model 1 (HR 2.7; 95% CI 1.6 to 4.7). Novel risk factors significantly associated with CHF in univariable analyses included the metabolic syndrome, macroalbuminuria, microalbuminuria, IL-6, CRP, and fibrinogen. Using Model 3 in this set of analyses, serum CRP, age, gender, obesity, cigarette smoking, serum cholesterol, LVH, and baseline LVEF were significant predictors of CHF.

Discussion

This study reports on the associations of obesity and the metabolic syndrome with incident CHF in a multi-ethnic population in which baseline LV structure and function were carefully assessed by MRI. We demonstrate strong associations of inflammatory components of the metabolic syndrome and albuminuria with incident CHF, even after adjustment for established risk factors, LV dysfunction, and interim MI. Moreover, the results indicate that inflammation may play an important role in the association between obesity and incident CHF.

Even though the metabolic syndrome represents a constellation of several risk factors for cardiovascular disease, this constellation has been recognized as a risk factor for cardiovascular morbidity and mortality (25–27). However, there are only a few previous studies that have specifically evaluated the association of the metabolic syndrome with incident CHF and whether the concurrence of these specific factors puts any given individual at a risk beyond what is expected based on the known associations of each risk factor with CHF. Our results show that although the metabolic syndrome is strongly associated with incident CHF, this association is largely explained by its specific risk factor components. Also, among the 5 criteria that are used for the diagnosis of the metabolic syndrome, high levels of plasma glucose, abdominal obesity, and hypertension were the strongest predictors of incident CHF.

Obesity, inflammation, and incident CHF. This study extends our knowledge of the association between systemic inflammation and CHF by showing that this strong association is independent of both interim MI during follow-up and baseline LV systolic function measured by MRI. Also, our results suggest that inflammation might be involved, directly or as a marker of other underlying conditions, in the pathologic pathways that link obesity to LV dysfunction and ultimately CHF. Previous studies have shown that IL-6, IL-2, CRP, and tumor necrosis factor-alpha are associated with CHF (14,38,39) and subclinical LV dysfunction (40–42). Experimental studies have also shown that IL-6 and tumor necrosis factor-alpha are associated with progressive LV dysfunction, LV remodeling, myocyte hypertrophy, and myocyte apoptosis (43–45). Some mechanisms suggested for these associations include immune activation, myocardial biosynthesis of inflammatory markers, underperfusion of systemic tissues, absorption of endotoxins from the edematous intestines, and neurohormonal activation/stabilization (43). However, it remains unclear whether the association between inflammatory markers and CHF is causal or indirectly related to other local or generalized inflammatory states.

Obesity was an independent risk factor for CHF in our study. However, obesity was not significantly associated with CHF after adjustment for baseline LV systolic function or for inflammatory markers. These findings suggest that the association of obesity with CHF is mediated by LV systolic dysfunction and might be at least in part explained by pathways related to inflammation. Inflammation, on the other hand, could theoretically be linked to incident CHF through pathways related to, or independent of, LV systolic dysfunction.

Impaired glucose metabolism, albuminuria, and incident CHF. In the MESA community-based population, although high fasting glucose was a significant predictor of CHF, the association of high HOMA index (above 95th percentile) with CHF was only marginally significant in univariable analysis and not significant in multivariable analysis. These results are different from those of a previous study (18) of 1,187 Swedish men in which the HOMA index was an independent risk factor for CHF. Another factor that is closely related to impaired metabolism of glucose (46) is albuminuria; our study shows that both micro- and macroalbuminuria are strong predictors of CHF. In previous studies, we have documented that progressive regional myocardial systolic or diastolic dysfunction is associated with renal dysfunction in a subset of MESA participants (21). The association of albuminuria with CHF has been previously demonstrated in the HOPE (Heart Outcomes Preventive Evaluation) study (20). Albuminuria is considered as a marker of microvascular and macrovascular disease (47), and it has been associated with several cardiovascular risk factors and inflammatory markers (44,48).

Strengths and limitations. The strengths of this study include the large ethnically diverse population, detailed clinical and metabolic characterization of the cohort, and precise measurements of LV structure and function by MRI. There are, however, some limitations to this study. Because inflammatory markers and obesity were measured at the same time, the conclusions regarding the possible mechanistic role of systemic inflammation in the association of obesity with CHF should be interpreted cautiously. Further specific studies are required for additional insights into this pathophysiologic link. Moreover, the median follow-up time was 4 years, and considering the low incidence of CHF, a longer follow-up duration could have increased the study's statistical power. Conversely, however, the fact that the associations of the novel risk factors, for example, inflammatory factors and albuminuria, with CHF were significant during this relatively short period might also reflect the strength of these associations. Our study had 94% power to detect a HR of 1.5 associated with the presence of a risk factor in 10% of the population. The power was lower for multivariable as opposed to univariable models and higher for risk factors with prevalence rates greater than 10% and for continuous variables.

Conclusions

Inflammatory markers and albuminuria are independent predictors of CHF beyond traditional risk factors and the development of an interim clinical MI. The presence of the

metabolic syndrome is associated with a higher risk for CHF, and this association is mainly related to impaired glucose metabolism, hypertension, abdominal obesity, and the pro-inflammatory state that characterizes the metabolic syndrome. The association of obesity and CHF may be related to pathophysiologic pathways associated with inflammation. Further studies are needed to elucidate the importance of these novel risk factors in the prophylaxis of progressive LV dysfunction and CHF.

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APPENDIX

A full list of participating MESA investigators and institutions can be found at http://www.mesa-nhlbi.org.