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Increased Heart Failure Risk in Normal-Weight People With Metabolic Syndrome Compared With Metabolically Healthy Obese Individuals

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Objectives The purpose of this study was to assess whether the metabolically healthy obese phenotype is associated with lower heart failure (HF) risk compared with normal-weight individuals with metabolic syndrome (MetS).

Background Obesity and MetS often coexist and are associated with increased HF risk. It is controversial whether obese individuals with normal insulin sensitivity have decreased HF risk.

Methods A total of 550 individuals without diabetes or baseline macrovascular complications were studied during a median follow-up of 6 years. Participants were classified by presence (n = 271) or absence (n = 279) of MetS and by body mass index (body mass index: <25 kg/m^2 = normal weight, n = 177; 25 to 29.9 kg/m^2 = overweight, n = 234; ≥ 30 kg/m^2 = obese, n = 139). MetS was diagnosed with the National Cholesterol Education Program Adult Treatment Panel III criteria. Left ventricular functional capacity, myocardial structure, and performance were assessed echocardiographically.

Results Body mass index was not associated with increased HF risk. The presence of MetS conferred a 2.5-fold higher HF risk (hazard ratio [HR]: 2.5, 95% confidence interval [CI]: 1.68 to 3.40). Overweight and obese individuals without MetS had the lowest 6-year HF risk (HR: 1.12, 95% CI: 0.35 to 0.33 and HR: 0.41, 95% CI: 0.10 to 1.31, respectively) compared with normal-weight individuals with MetS (HR: 2.33, 95% CI: 1.25 to 4.36, $p < 0.001$). From the individual components of MetS, impaired fasting glucose (HR: 1.09, 95% CI: 1.06 to 1.10), high BP (HR: 2.36, 95% CI: 1.03 to 5.43), low high-density lipoprotein cholesterol (HR: 1.88, 95% CI: 1.29 to −2.77), and central obesity (HR: 2.22, 95% CI: 1.02 to 1.05) were all associated with increased HF risk. Factors commonly associated with MetS such as insulin resistance and inflammation (high-sensitivity C-reactive protein and microalbuminuria) were also independently associated with HF incidence.

Conclusions In contrast to normal weight insulin-resistant individuals, metabolically healthy obese individuals show decreased HF risk in a 6-year follow-up study. (J Am Coll Cardiol 2011;58:1343–50) © 2011 by the American College of Cardiology Foundation

Heart failure (HF) is one of the leading causes of morbidity and mortality, and its prevalence continues to increase despite the decrease in cardiovascular death rates (1). Although prevention of HF is complex, several risk factors have been identified as consistently associated with its development, including age, sex, left ventricular (LV) hypertrophy and dysfunction, diabetes, hypertension, smoking, physical inactivity, dyslipidemia, and obesity. In addition to recent improvements in the management of classic cardiovascular risk factors, parameters such as obesity and insulin resistance are poised to play an important role in the development of future cardiovascular events. Although obesity is currently considered an established determinant of HF, the mechanisms by which it is translated into an increased HF risk are still unclear (2).

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Currently, there is strong interest in metabolically healthy obese people, who, despite their body fat, display a favorable metabolic profile characterized by high levels of insulin sensitivity and a favorable blood pressure (BP), glycemic, lipids, and inflammation profile (3). However, it remains controversial

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Abbreviations and Acronyms

BMI = body mass index
BP = blood pressure
CI = confidence interval
HF = heart failure
HR = hazard ratio
LV = left ventricular
MET = metabolic equivalent
MetS = metabolic syndrome

whether this healthier metabolic profile translates into a lower cardiovascular risk compared with normal-weight individuals with metabolic syndrome (MetS) (4).

We investigated the independent associations of MetS, insulin resistance, inflammatory markers, and lifestyle measures with incident HF beyond obesity and other established cardiovascular risk factors in a population without diabetes and baseline macrovascular complications.

Methods

Study population. The study population consisted of 550 of 944 individuals (58.3%) without diabetes enrolled in a prospective, community-based study designed to evaluate the impact of MetS on HF risk. Participants were recruited between 2003 and 2005. At baseline, inclusion criteria required that subjects were free of clinically apparent macrovascular disease. Therefore, we excluded all subjects with a history of chronic stable angina, echocardiographically documented acute and chronic HF, hemodynamically significant cardiac valvular disease, and peripheral vascular and cerebrovascular disease. Subclinical coronary artery disease was excluded at baseline in 454 participants (82.5%) who agreed to undergo quantitative coronary angiography. Patients with chronic kidney disease estimated by a glomerular filtration rate of <60 ml/min, infections, and acute or chronic inflammatory diseases were also excluded. This was further applied to patients treated with nonsteroidal anti-inflammatory medications or corticosteroids in the previous 3 months. The study was approved by the hospital review board, and all study participants gave written informed consent.

Baseline examination. Standardized questionnaires were used to obtain information about smoking and medication use. 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 was defined as a BMI ≥30 kg/m^2 and overweight as BMI 25 to 29.9 kg/m^2, respectively. Hypertension was defined as systolic BP ≥140 mm Hg and/or diastolic BP ≥90 mm Hg and/or use of antihypertensive medications.

Standardized physical activity questionnaires were used for the assessment of the average amount of time per week engaged in aerobic exercise activities and the energy expended for each activity in metabolic equivalent (MET) hours per week (MET-h/week) (5).

We classified participants into 3 groups of physical activity levels at each assessment: those engaged in <7.5 MET-h/week (equivalent to <150 min/week of moderate-intensity physical activity), the minimum recommended by the American Heart Association; 7.5 to <21 MET-h/week; and ≥21 MET-h/week (equivalent to ≥420 min/week of moderate-intensity activity) (6).

Fasting plasma glucose and insulin levels were measured at baseline. Insulin levels were determined by a radioimmunoassay method using the Biosure Human Insulin Specific RIA Kit (Biosure, Belgium). As an index of insulin resistance, the Homeostasis Model Assessment index was calculated using the formula (fasting glucose [mmol/l]) × (fasting insulin [μU/ml])/22.5 (7). Urinary creatinine and albumin were measured by radioimmunoassay (Pharmacia and Upjohn Diagnostics, Uppsala, Sweden) in a single 24-h urine collection after excluding proteinuria due to urinary tract infection by microscopic examination and culture. Participants were categorized into 2 groups based on the baseline urinary albumin (mg)/creatinine (g) ratio: 1) normal, ratio <30; and 2) microalbuminuria, ratio 30 to 299.9 (8). Glycated A1c hemoglobin was measured with a latex immunoagglutination inhibition method (Bayer HealthCare LLC, Elkhart, Indiana) with a nondiabetic range of 4.0% to 6.0%. High-sensitivity C-reactive protein was determined using ADVIA 1650 (Bayer HealthCare).

MetS was defined using the National Cholesterol Education Program Adult Treatment Panel III criteria (9). Participants with 3 or more of these criteria were considered to have MetS: abdominal obesity given as waist circumference (>102 cm in men and >88 cm in women), serum triglycerides >150 mg/dl, high-density lipoprotein cholesterol <40 mg/dl in men and <50 mg/dl in women, BP ≥130/85 mm Hg or use of antihypertensive medications, fasting glucose ≥100 mg/dl. The studied population was classified into 2 groups: those who met the MetS definition (n = 271, 54.2%) and those who did not (n = 279, 55.8%).

LV structure and function were determined by complete 2-dimensional, Doppler echocardiographic examination performed at baseline with a Hewlett-Packard Sonos 5500 Ultrasound System (Hewlett-Packard, Andover, Massachusetts).

Follow-up and outcome parameters. Median follow-up time was 6.0 years (interquartile range: 4.9 to 7.6 years). Each participant was contacted every 6 to 9 months to inquire about all interim hospital admissions, cardiovascular outpatient diagnoses, and deaths. Medical records and information were successfully obtained for the 487 subjects (83.2%). Subjects who were lost to follow-up (n = 52, 9.5%) were younger ($p = 0.01$) but did not differ in sex ($p = 0.70$) from those who were followed. Hospitalized cardiovascular event and outpatient cardiovascular diagnostic encounter information was successfully obtained for an estimated 98% of the participants.

The primary endpoint of this study was HF. Endpoint criteria were: 1) HF identified by the study physician on the basis of symptoms and signs (e.g., shortness of breath, fatigue, reduced exercise tolerance requiring initiation or an increase in dose if previously prescribed for another cause [i.e., hypertension] of a loop diuretic, angiotensin-converting enzyme inhibitor, or angiotensin II receptor blocker therapy, or evidence-

based beta-blocker therapy); and 2) objective evidence of structural or functional heart; disease defined as echocardiographic documentation of systolic dysfunction (LV ejection fraction (LVEF) <40%) or diastolic dysfunction (10). Diastolic dysfunction was defined as LV mass >88 g/m^2 in women and >102 g/m^2 in men, or E/A >1 or mitral (E wave) deceleration time <200 ms, or Tei index ≥0.40 (11).

Statistical methods. Statistical analyses were performed using programs available in the SPSS version 15.0 statistical package (SPSS Inc., Chicago, Illinois). Data are presented as mean ± SD or median (interquartile range) for continuous variables and number (percentage) for categorical variables. Differences in baseline characteristics of participants in whom HF developed or did not develop were tested with a Student *t* test (continuous variables with normal distribution) or chi-square test (categorical variables). Cox proportional hazards models were used to analyze the association of risk factors with incident HF. Two sets of models were used: model 1, unadjusted analysis, and model 2, adjusted for established risk factors of HF including age, sex, fasting glucose, hypertension, lipids, baseline LV hypertrophy and function, current cigarette smoking, and physical inactivity. Each novel risk factor was included in a separate model with the established risk factors in model 2.

Results of Cox proportional hazards models are reported as hazard ratios and 95% confidence intervals (CIs). All HRs are calculated and reported for 1 SD increase or decrease in continuous variables or transfer from 1 level to another of categorical variables, unless stated otherwise. Participants who were lost to follow-up (9.5%) were censored at the time of the last follow-up. Those who did not experience HF were censored at either 6 years or the last date of follow-up before 6 years. To evaluate how much of the association of obesity with incident HF was related to MetS, systemic inflammation and insulin resistance and vice versa, we compared the regression coefficient for obesity and MetS before and after adjusting for these variables.

Results

Baseline characteristics of the studied participants by BMI and the presence of MetS. At study entry, compared with normal-weight and overweight individuals, obese subjects had a higher incidence of MetS, were more likely to smoke cigarettes than overweight, but not more than normal-weight, individuals. The presence of inflammatory markers was significantly higher in obese compared with normal-weight and overweight subjects. MetS was strongly related to BMI, with 38.4% of individuals with a normal BMI having MetS compared with 45.7% among overweight and 69% among obese subjects. Mean systolic BP also correlated with BMI such that obese subjects had higher values than normal-weight subjects. However, the presence of high systolic BP was lower in obese than in normal-weight individuals (78.1% vs. 83.8%, p = 0.01). Obese subjects had pronounced central fat distribution, but lower high-density lipoprotein cholesterol levels, increased insulin resistance, and inflammation profile, except for microalbuminuria, compared with normal-weight and overweight individuals (Table 1).

Baseline LV structure and function. Because studied participants had no baseline history of heart disease, the frequency of individuals with abnormal LV structure and function was likely to be less than in the general population. Therefore, 95.4% of our studied population had LVEF ≥50%, and this proportion was 89.2% (n = 165) among the 185 participants in whom HF developed. On the other hand, among the 550 studied participants, 78 participants (14.1%) had LV hypertrophy, and among participants in whom HF developed, 48 participants (25.9%) had LV hypertrophy at baseline (Table 2). Moreover, among 106 patients for whom data on LV function at the time of HF diagnosis were available, 52 patients (49%) had LVEF ≥40%, and 54 participants (51%) had LVEF ≥50%.

Incident HF by levels of BMI and metabolic status. From the 550 participants studied, HF developed in 185 (80 male/73 female; age, 58.5 ± 7.9 years) during follow-up. Among the patients in whom HF developed, the presence of LV hypertrophy was significantly higher in all BMI groups with MetS compared with those without MetS (7.3% vs. 36.1%, p = 0.001). The presence of MetS also increased the percentage of patients in whom diastolic dysfunction with preserved LVEF developed in all BMI groups (5.2% vs. 46.4%, p < 0.001). The same was true for those in whom both diastolic and systolic dysfunction developed (1.8% vs. 9.1%, p = 0.001). Among the individuals without MetS, systolic dysfunction was present only in the normal-weight group.

Figure 1 separates drug-naïve patients in whom HF developed who required initiation of therapy as opposed to those in whom new HF symptoms, signs, and echocardiographic evidence developed while taking medication, according to BMI and MetS groups. The percentage of patients requiring initiation or adjustment of HF medication was significantly higher in all BMI subgroups with the presence of MetS.

At baseline, participants in whom HF developed were more likely to be older, obese with central fat distribution, current smokers or ex-smokers, hypertensive, and with impaired fasting glucose. Moreover, at baseline, the majority (44.3%) of those in whom HF developed expended <7.5 MET-h/week on physical activity, and only 3.8%, ≥21 MET-h/week. In contrast, among the population in whom HF did not develop, the majority (63.2%) had baseline moderate-intensity physical activity (7.5 to <21 MET-h/week). Finally, the prevalence of MetS at baseline was significantly higher in the studied population in whom HF developed (Table 2).

During the 6-year follow-up period, a consistent pattern was seen between BMI, MetS, and HF incidence. Among participants without MetS, HF incidence was 15.6% in those with a normal BMI, 14.2% in those overweight, and

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Table 1 Baseline Demographics and Clinical Characteristics of the Studied Cohort According to BMI and Metabolic Status

Characteristics	Normal (≤24.9 kg/m²) (n = 177)	Overweight (25–29.9 kg/m²) (n = 234)	Obese (≥30 kg/m²) (n = 139)	Normal Weight vs. Overweight, p Value	Normal Weight vs. Obese, p Value	Overweight vs. Obese, p Value
Age, yrs	60.3 ± 10.4	59.8 ± 9.0	60.0 ± 9.2	0.61	0.77	0.83
Female/male	103 (58.2)/74 (41.8)	135 (57.7)/99 (42.3)	74 (53.2)/65 (46.8)	1.00	0.46	0.49
MetS, yes/no	68 (38.4)/109 (61.6)	107 (45.7)/127 (54.3)	96 (69.0)/43 (31.0)	0.15	<0.001	<0.001
MetS: NCEP-ATP III score (0–5)*	3 (3–5)	4 (3–5)	4 (3–5)	0.03	<0.001	<0.001
Statins	65 (36.7)	43 (18.4)	46 (33.0)	0.07	0.97	0.04
ACEIs/ARBs	27 (15.3)	52 (22.2)	53 (38.1)	0.23	0.004	0.02
Smoking	30 (16.9)	21 (8.9)	22 (15.8)	0.02	0.84	0.02
Waist, cm	87.7 ± 9.3	97.4 ± 9.2	108.2 ± 8.6	<0.001	<0.001	<0.001
Glucose, mg/dl	103.5 ± 14.5	105.7 ± 13.6	110.4 ± 13.7	0.18	0.03	0.05
Triglycerides, mg/dl	127.4 ± 73.5	136.3 ± 66.7	156.7 ± 74.7	0.23	0.001	0.003
HDL cholesterol, mg/dl	49.0 ± 12.9	47.0 ± 12.4	44.3 ± 11.2	0.13	0.002	0.03
Systolic blood pressure, mm Hg	128.6 ± 18.6	132.6 ± 20.4	137.0 ± 19.4	0.05	<0.001	0.02
High waist	44 (24.8)	113 (48.3)	135 (97.1)	<0.001	<0.001	<0.001
High glucose	62 (35.0)	94 (40.2)	55 (39.6)	0.46	0.53	0.95
High triglycerides	56 (31.6)	81 (34.6)	58 (41.7)	0.45	0.06	0.13
Low HDL cholesterol	91 (51.4)	102 (43.5)	85 (61.2)	0.14	0.07	<0.001
High blood pressure	92 (51.9)	143 (61.1)	92 (66.2)	0.08	0.01	0.22
Total cholesterol, mg/dl	197.4 ± 44.4	195.9 ± 42.9	193.8 ± 42.6	0.74	0.48	0.62
LDL cholesterol, mg/dl	122.9 ± 37.5	121.6 ± 38.5	118.1 ± 37.1	0.80	0.23	0.24
Albumin, mg/24 h*	8.0 (3.0–218.6)	8.0 (3.0–139.3)	9.2 (2.9–175.0)	0.58	0.09	0.12
Microalbuminuria	31 (17.5)	51 (36.7)	57 (24.4)	0.10	<0.001	0.04
HOMA-IR*	2.74 (1.16–3.89)	3.11 (0.98–4.43)	3.96 (0.91–6.36)	0.10	<0.001	0.001
hs-CRP, mg/dl	3.13 ± 0.24	4.91 ± 0.52	5.50 ± 0.43	0.32	<0.001	0.001

Values are mean ± SD or as n (%). *Median values (interquartile range). High glucose is defined as fasting glucose ≥100 mg/dl; low HDL cholesterol is <40 mg/dl in men and <50 mg/dl in women; high blood pressure is ≥130/85 mm Hg or use of antihypertensive medications; NCEP-ATP-III score is the sum of the metabolic components; high waist defined as waist circumference >102 cm in men and >88 cm in women; high triglycerides defined as plasma triglycerides >150 mg/dl.

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; BMI = body mass index; HDL = high-density lipoprotein; HOMA-IR = Homeostasis Model Assessment for Insulin Resistance equation; hs-CRP = high-sensitivity C-reactive protein; LDL = low-density lipoprotein; MetS = metabolic syndrome; NCEP-ATP-III score = National Cholesterol Education Program Adult Treatment Panel III.

9.3% in those obese. These rates were much lower than those documented in patients with MetS (63.2%, 47.7%, and 54.2%, respectively). These relationships of MetS, but not BMI, being associated with HF incidence persisted and remained statistically significant after adjustment for age, sex, current smoking, physical inactivity, lipids, glycemic, and inflammation profile. Compared with participants without MetS, subjects with MetS who were normal weight, overweight, or obese with MetS had approximately 2.3, 2.6, and 2.1 times higher adjusted odds of having HF. Obese subjects without MetS had the lowest HF risk compared with normal-weight individuals with MetS (Table 3, Fig. 2).

Among the 5 criteria used in the definition of MetS, serum triglycerides were not significant predictors of incident HF. Fasting hyperglycemia, hypertension, and the presence of central obesity had the highest predictive value among MetS components. Inflammation markers were also significant predictors of incident HF in the studied population (Table 3).

Discussion

The main finding of the present study is that after adjustment for well-known cardiovascular risk factors, MetS was independently and significantly associated with an increased 6-year incidence of HF in a population without diabetes and baseline macrovascular complications. Obesity status or increased BMI were not independent predictors of 6-year HF-risk in this studied population. Moreover, obese participants without MetS displayed the lowest risk of incident HF compared with normal-weight participants with MetS. Finally, hypertension, central obesity, and inflammation were demonstrated as the strongest possible mediators of the independent association between MetS and 6-year incidence of HF.

The presence of obesity-related metabolic disturbances varies widely among obese individuals. Previous studies described a unique subset of obese individuals who seem to be protected or more resistant to the development of metabolic abnormalities associated with obesity. These individuals are known as metabolically healthy but obese, and, despite their body fatness, they display a favorable metabolic and inflammation profiles (3). In the present study, almost one-third of obese subjects did not have MetS, whereas a parallel proportion of normal-weight subjects (38.4%) had MetS. Compared with previous reports that used identical definition criteria in Mediterranean populations (12), our results probably indicate an increase in the prevalence of the different obesity phenotypes in the nondiabetic population.

Table 2 Distribution of the Baseline Characteristics of the Participants With and Without the Development of HF

	Without HF (n = 365)	With HF (n = 185)	p Value
Female/male	183 (50.1)/182 (49.9)	88 (47.6)/97 (52.4)	0.6
Age, yrs	55.4 ± 8.6	58.5 ± 7.9	<0.001
BMI, kg/m^2	27.9 ± 3.9	28.7 ± 4.3	0.04
Waist circumference, cm	97.0 ± 11.6	101.6 ± 11.7	<0.001
Normal weight (BMI <25 kg/m^2)	117 (32.1)	60 (32.4)	0.6
Overweight (BMI 25–29.9 kg/m^2)	165 (45.2)	69 (37.3)	0.04
Obesity (BMI >30 kg/m^2)	83 (22.7)	56 (30.3)	0.008
Cigarette smoking			
Current	38 (10.4)	28 (15.1)	0.2
Former	64 (17.5)	47 (25.4)	0.04
Never	263 (72.1)	110 (59.5)	0.007
Normal glucose (fasting <100 mg/dl)	148 (40.3)	26 (14.1)	<0.001
Hypertension	77 (21.0)	103 (56.0)	<0.001
Mean arterial pressure, mm Hg*	92.5 ± 12.3	99.4 ± 11.9	<0.001
Diastolic blood pressure, mm Hg	74.5 ± 10.6	78.4 ± 11.0	<0.001
Physical activity, MET-h/week	11.6 ± 5.9	9.1 ± 4.5	<0.001
<7.5 MET-h/week	80 (21.9)	82 (44.3)	<0.001
7.5 to <21 MET-h/week	231 (63.2)	96 (51.9)	0.014
≥21 MET-h/week	54 (14.9)	7 (3.8)	<0.001
Left ventricular mass, g/m^2	103.9 ± 13.3	115.5 ± 19.1	<0.001
Left ventricular hypertrophy, %	103 (28.2)	85 (45.9)	0.02
Left ventricular ejection fraction, %	65.3 ± 2.8	64.2 ± 2.6	0.01
MetS	138 (37.8)	149 (80.5)	<0.001

Values are n (%) or mean ± SD. *Impaired fasting glucose was defined as fasting glucose of 100 to 125 mg/dl. †Mean arterial pressure: 2/3·diastolic blood pressure + 1/3·systolic blood pressure.
BMI = body mass index; HF = heart failure; MET-h/week = metabolic equivalent hours per week.

Moreover, the presence of MetS in the normal-weight subgroup was associated with an increased incidence of central obesity, fasting hyperglycemia, hypertension, dyslipidemia, insulin resistance, and subclinical inflammation compared with the absence of MetS in the obese individuals. In accordance with previous reports (13), when compared with normal-weight individuals with MetS, a higher percentage of obese individuals with a healthy metabolic profile were nonsmokers and met the current physical activity guidelines.

Although 1 previous study that investigated the impact of MetS on incident HF in a cohort of older (70 years and older) adults failed to demonstrate a significant relationship between MetS and incident HF risk in the subgroup of subjects without a history of cardiovascular disease (14), we demonstrated a significant association between MetS and incident HF in a younger population (50 years and older). This is in accordance with another community-based study that also determined MetS as a significant and independent predictor of incident HF in a population of middle-aged men without a baseline cardiovascular disease history (15).

Although in the analysis of the MESA (Multi-Ethnic Study of Atherosclerosis) (16), after adjustment for known cardiovascular risk factors, only 2 components of MetS—abdominal adiposity and hyperglycemia—remained independent predictors of HF and MetS did not, we found independent associations among all MetS components and incident HF, except high serum triglycerides. This could be due to sex and ethnicity differences and partly due to the inclusion of patients with diabetes in the MESA study. Moreover, as previously suggested in epidemiological studies of type 2 diabetes and HF, insulin resistance may be more important in the development of idiopathic dilated cardiomyopathy than in the development of HF from ischemic heart disease (17,18). In other studies, insulin resistance accounted for >90% of the association between MetS and HF risk (19,20). In accordance with these previous reports, overweight and obese individuals without MetS in our studied population did not present an increased HF risk.

There are numerous potential pathophysiologic mechanisms underlying the relationship between insulin resistance and HF. The heart may become less energy efficient in the setting of insulin resistance, with decreased glucose use and increased free fatty acid use. This metabolic deregulation may increase susceptibility to injury, such as pressure overload or ischemia and thus promote deleterious renin-angiotensin-aldosterone system activation. Evidence of an insulin-resistant cardiomyopathy, independent of pressure or volume loading influences, is currently also emerging (21). Cardiac oxidative stress is often observed coincident with insulin resistance, and there is accumulating evidence that reactive oxygen species mediate deleterious effects in the insulin-resistant heart (22). Reduced mitochondrial oxidative capacity may also contribute to cardiac

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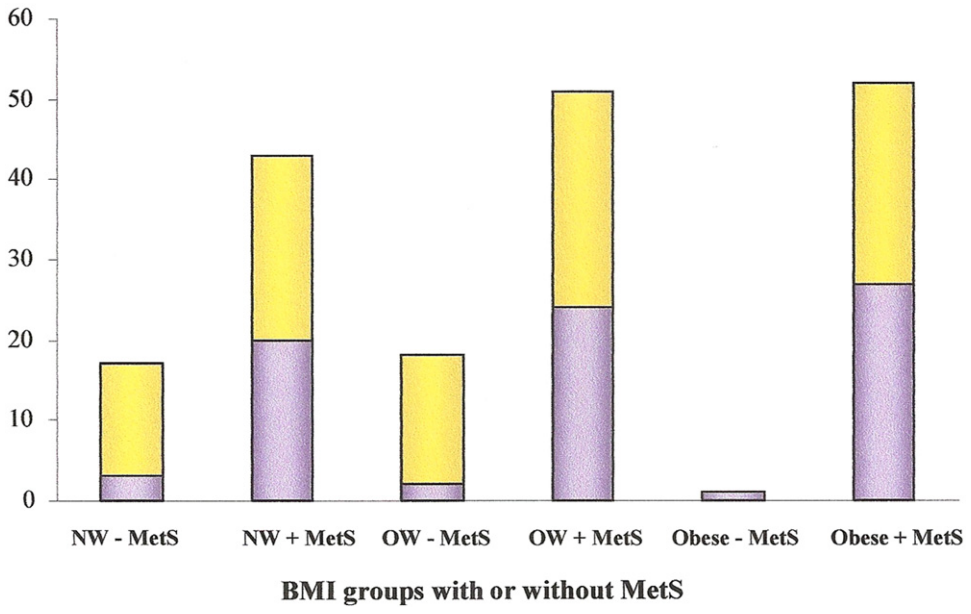

Figure 1 HF According to Obesity and Metabolic Status

The percentage of drug-naïve patients in whom heart failure (HF) developed requiring medication initiation **(yellow bars)** compared with those in whom new clinical symptoms, signs, and echocardiographic evidence of left ventricular dysfunction developed while taking medication **(purple bars)**. MetS = metabolic syndrome; NW = normal weight (BMI [body mass index]: <25 kg/m^2); OW = overweight (BMI: 25 to 29.9 kg/m^2); Obese: BMI >30 kg/m^2).

growth remodeling and dysfunction (23). Experimental data link both hyperglycemia and hyperinsulinemia with increased sympathetic nervous system activation, a key pathophysiologic mechanism in HF (24). Furthermore, the increased intramyocardial triglyceride content in patients with impaired glucose tolerance may lead to lipotoxicity and cardiomyocyte apoptosis, ultimately leading to cardiac dysfunction (25).

Inflammation mediators were significant and independent predictors of incident HF and were significantly associated with MetS in all BMI groups in our study population. In accordance with our findings, recent evidence suggests that the relationship between overweight/obesity and incident HF is mainly mediated by obesity-related metabolic, inflammatory (16,26), and hormonal (27) changes. Moreover, obesity is

Table 3 Relationship Among the 5 Metabolic Criteria Used in the Definition of MetS, the Presence of MetS, BMI, and HF Incidence During the 6-Year Follow-Up Period

Metabolic Components		n	HF Incidence, n (%)	Unadjusted HR	Adjusted HR*	95% CI	p Value
High fasting glucose		173	100 (57.8)	1.08	1.09	1.06–1.10	<0.001
High blood pressure		333	120 (36.0)	5.33	4.86	3.30–8.61	<0.001
High waist circumference		313	106 (33.8)	1.03	2.20	1.02–1.05	<0.001
Low HDL cholesterol		275	87 (31.6)	1.54	1.88	1.29–2.77	0.001
High triglycerides		199	53 (26.6)	1.11	1.18	0.74–1.66	NS
hs-CRP ≥1.5 mg/dl		103	43 (19.5)	1.55	1.52	1.31–1.82	<0.001
Microalbuminuria		139	63 (45.3)	2.49	2.51	1.66–3.74	<0.001
BMI Group	**MetS**		**Pre-Incidence of HF, n (%)**				
Normal	No	109	17 (15.6)	1.00	1.00	—	—
Normal	Yes	68	43 (63.2)	2.34	2.33	1.25–4.36	0.007
Overweight	No	127	18 (14.2)	0.90	1.12	0.35–1.33	0.36
Overweight	Yes	107	51 (47.7)	2.68	2.66	1.73–4.13	<0.001
Obese	No	43	4 (9.3)	0.26	0.41	0.10–1.31	0.49
Obese	Yes	96	52 (54.2)	2.02	2.13	1.29–3.17	0.002

*Adjusted for all the factors associated with HF incidence: age, sex, impaired glucose tolerance, dyslipidemia, hypertension, current cigarette smoking, physical inactivity, left ventricular hypertrophy and function on echocardiography. High fasting glucose level is ≥100 mg/dl; high blood pressure is ≥130/85 mm Hg; high waist circumference is >102 cm in men and waist >88 cm in women; low HDL cholesterol is <40 mg/dl in men and <50 mg/dl in women; high triglyceride level is >150 mg/dl; microalbuminuria is a urine albumin-to-creatinine ratio of 30 to 299.9 mg/dl.

CI = confidence interval; HR = hazard ratio; other abbreviations as in Tables 1 and 2.

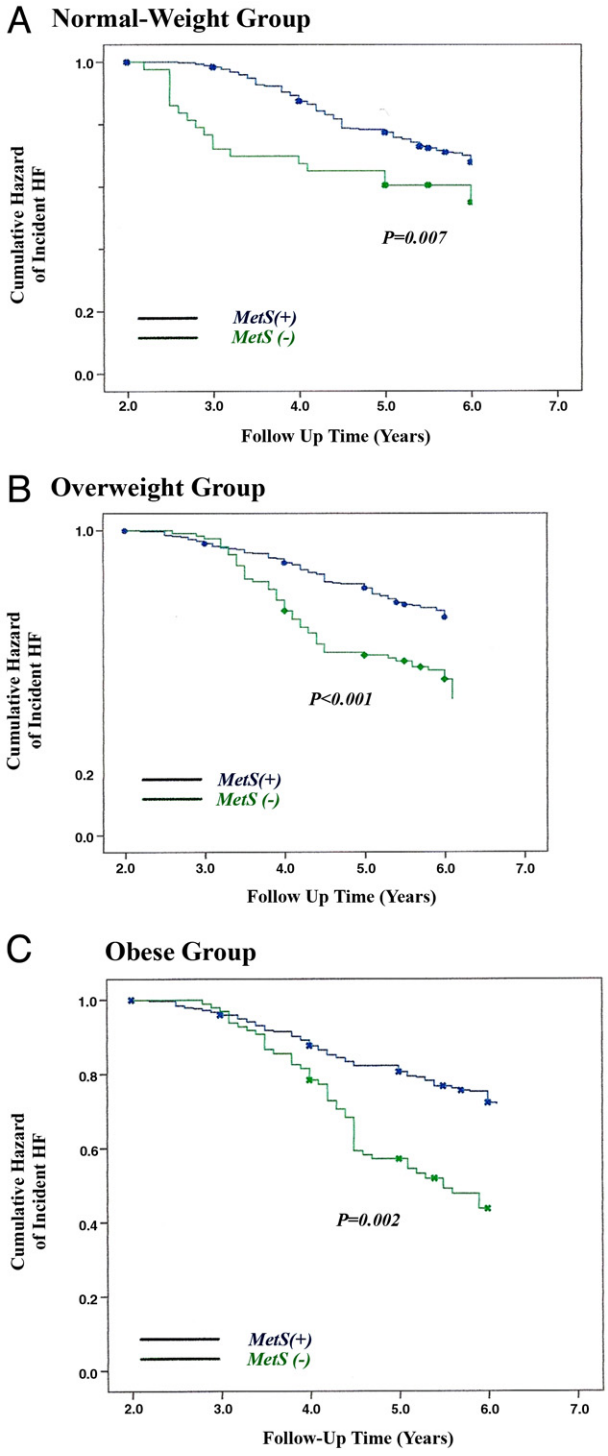

Figure 2 Kaplan-Meier Curves of Incident HF

(A) Kaplan-Meier curve of the 6-year incidence of heart failure (HF) in the normal-weight group. The presence of metabolic syndrome (MetS) (+) **(blue line)**, increased the incidence of HF compared with patients without MetS, MetS (−) **(green line)**. **(B)** Kaplan-Meier curve of the 6-year incidence of HF in the overweight group. The presence of MetS **(blue line)** increased the incidence of HF compared with patients without MetS **(green line)**. **(C)** Kaplan-Meier curve of the 6-year incidence of HF in the obese group. The presence of MetS **(blue line)** increased the incidence of HF compared with patients without MetS **(green line)**.

highly correlated with insulin resistance, which may in part potentiate the link between obesity and HF (15). Therefore, mechanisms beyond a positive caloric balance, such as inflammation and hormonal release, possibly determine the pathologic metabolic consequences in obesity.

Study limitations. A small number of patients had high-sensitivity C-reactive protein values ≥1.5 mg/dl and were included in the analysis. Therefore, the conclusions regarding the possible mechanistic role of systemic inflammation in the development of incident HF should be cautiously interpreted. Further studies are required for additional insights into this pathophysiologic link. Moreover, despite the longer median follow-up duration, compared with that of previous studies, the rather small number of patients in whom HF developed did not permit a separate cohort analysis that could have increased the study's statistical power. This may be explained by the exclusion from baseline of individuals with diabetes or macrovascular complications.

Conclusions

The emergence of HF as a global public health problem with a high prevalence, high morbidity, and extraordinary cost underscores the urgency of efforts to identify and modify risk factors for incident HF (17). The findings of the present study readdress the importance of MetS as a highly prognostic marker of future HF risk, whereas obesity alone appears to confer little independent value in cardiovascular risk stratification. Focus on the growing, interrelated epidemics of obesity and MetS is warranted because it is established that lifestyle interventions can decrease the risk of these syndromes. Furthermore, appropriate medical treatment of hypertension, dyslipidemia, and hyperglycemia in those at risk of HF is an essential component of prevention. Therefore, the evaluation of metabolic status with the National Cholesterol Education Program Adult Treatment Program III guidelines should be considered in cardiovascular risk stratification, regardless of weight status. Moreover, our findings indicate that normal-weight individuals with MetS have significantly increased risk of the development of HF. Similarly, overweight and obese people without MetS have a relatively low risk of the development of HF. As a result, a healthier overweight/obese metabolic profile may translate into a lower risk of cardiovascular morbidity and HF incidence. Despite the uncertainty regarding the exact degree of protection related to the metabolically healthy obese status, ongoing research on the identification of underlying factors and mechanisms associated with this phenotype will eventually enable us to understand the factors that predispose, delay, or protect individuals from future HF risk.

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REFERENCES

1. Vasan RS, Kannel WB. Strategies for cardiovascular risk assessment and prevention over the life course: progress amid imperfections. Circulation 2009;120:360–3.
2. Arnlöv J, Ingelsson E, Sundström J, et al. Impact of body mass index and the metabolic syndrome on the risk of cardiovascular disease and death in middle-aged men. Circulation 2010;121:230–6.
3. Primeau V, Coderre L, Karelis AD, et al. Characterizing the profile of obese patients who are metabolically healthy. Int J Obes (Lond) 2011;35:971–81.
4. Calori G, Lattuada G, Piemonti L, et al. Prevalence, metabolic features and prognosis of metabolically healthy obese Italian individuals: the Cremona Study. Diabetes Care 2011;34:210–5.
5. Lee IM, Paffenbarger RS Jr. Design of present day epidemiologic studies of physical activity and health. In: Lee IM, editor. Epidemiologic Methods in Physical Activity Studies. New York, NY: Oxford University Press; 2009:100–23.
6. Haskell WL, Lee IM, Pate RR, et al. American College of Sports Medicine, American Heart Association. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. Circulation 2007;116:1081–93.
7. Matthews DR, Hosker JP, Rudenski AS, et al. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412–19.
8. American Diabetes Association. Diabetic nephropathy. Diabetes Care 1997;20 Suppl 1:S24–7.
9. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report. Circulation 2002;106:3143–421.
10. Allen LA, Hernandez AF, O'Connor CM, Felker GM. End points for clinical trials in acute heart failure syndromes. J Am Coll Cardiol 2009;53:2248–58.
11. Voulgari C, Moyssakis I, Papazafiropoulou A, et al. The impact of metabolic syndrome on left ventricular myocardial performance. Diabetes Metab Res Rev 2010;26:121–7.
12. Iacobellis G, Ribaudo MC, Zappaterreno A, et al. Prevalence of uncomplicated obesity in an Italian obese population. Obes Res 2005;13:116–22.
13. Wildman RP, Muntner P, Reynolds K, et al. The obese without cardiometabolic risk factor clustering and the normal weight with cardiometabolic risk factor clustering: prevalence and correlates of 2 phenotypes among the US population (NHANES 1999–2004). Arch Intern Med 2008;168:1617–24.
14. Butler J, Rodondi N, Zhu Y, et al., Health ABC Study. Metabolic syndrome and the risk of cardiovascular disease in older adults. J Am Coll Cardiol 2006;47:1595–602.
15. Ingelsson E, Arnlöv J, Lind L, et al. Metabolic syndrome and risk for heart failure in middle-aged men. Heart 2006;92:1409–13.
16. Bahrami H, Bluemke DA, Kronmal R, et al. Novel metabolic risk factors for incident heart failure and their relationship with obesity: the MESA (Multi-Ethnic Study of Atherosclerosis) study. J Am Coll Cardiol 2008;51:1775–83.
17. Horwich TB, Fonarow GC. Glucose, obesity, metabolic syndrome, and diabetes relevance to incidence of heart failure. J Am Coll Cardiol 2010;55:283–93.
18. Voulgari C, Papadogiannis D, Tentolouris N. Diabetic cardiomyopathy: from the pathophysiology of the cardiac myocytes to current diagnosis and management strategies. Vasc Health Risk Manag 2010;6:883–903.
19. Li C, Ford ES, McGuire LC, et al. Association of metabolic syndrome and insulin resistance with congestive heart failure: findings from the Third National Health and Nutrition Examination Survey. J Epidemiol Community Health 2007;61:67–73.
20. Arnlöv J, Lind L, Sundström J, et al. Insulin resistance, dietary fat intake and blood pressure predict left ventricular diastolic function 20 years later. Nutr Metab Cardiovasc Dis 2005;15:242–9.
21. Witteles RM, Fowler MB. Insulin-resistant cardiomyopathy: clinical evidence, mechanisms, and treatment options. J Am Coll Cardiol 2008;51:93–102.
22. van Heerebeek L, Hamdani N, Handoko ML, et al. Diastolic stiffness of the failing diabetic heart: importance of fibrosis, advanced glycation end products, and myocyte resting tension. Circulation 2008;117:43–51.
23. Mellor KM, Ritchie RH, Delbridge LM. Reactive oxygen species and insulin-resistant cardiomyopathy. Clin Exp Pharmacol Physiol 2010;37:222–8.
24. Tentolouris N, Liatis S, Katsilambros N. Sympathetic system activity in obesity and metabolic syndrome. Ann N Y Acad Sci 2006;1083:129–52.
25. Szczepaniak LS, Victor RG, Orci L, et al. Forgotten but not gone: the rediscovery of fatty heart, the most common unrecognized disease in America. Circ Res 2007;101:759–67.
26. Gentile M, Panico S, Rubba F, et al. Obesity, overweight, and weight gain over adult life are main determinants of elevated hs-CRP in a cohort of Mediterranean women. Eur J Clin Nutr 2010;64:873–8.
27. Frankel DS, Vasan RS, D'Agostino RB Sr., et al. Resistin, adiponectin, and risk of heart failure: the Framingham Offspring study. J Am Coll Cardiol 2009;53:754–62.

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