RESEARCH REPORT

Association of metabolic syndrome and insulin resistance with congestive heart failure: findings from the Third National Health and Nutrition Examination Survey

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J Epidemiol Community Health 2007;61:67–73. doi: 10.1136/jech.2006.048173

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Accepted 22 May 2006

Objective: Congestive heart failure (CHF) has been associated with insulin resistance, but few studies have examined its relationship with metabolic syndrome (MetS). Little is known about whether insulin resistance explains the association between MetS and CHF.

Design: Population-based, cross-sectional surveys.

Setting: Third National Health and Nutrition Examination Survey (NHANES III).

Participants: Data from 5549 men and non-pregnant women aged ≥ 40 years in NHANES III were analysed.

Results: About 4% of men and 3% of women had CHF between 1988 and 1994 in the US. The age-adjusted prevalence of CHF was significantly higher in African Americans (4.1%), in Mexican Americans (8.5%) and in those of other ethnic origin (6.7%) than in white people (2.5%). People with MetS had nearly twice the likelihood of self-reported CHF (adjusted odds ratio 1.8; 95% confidence interval 1.1 to 3.0) after adjustment for demographic and conventional risk factors such as sex, ethnicity, age, smoking, total cholesterol, left ventricular hypertrophy, and probable or possible myocardial infarction determined by electrocardiography. However, this association was attenuated after further adjustment for insulin resistance as measured by the homoeostasis model assessment (HOMA). $>90\%$ of the association between MetS and CHF was explained by the HOMA.

Conclusions: MetS was associated with about a twofold increased likelihood of self-reported CHF and it may serve as a surrogate indicator for the association between insulin resistance and CHF.

Metabolic syndrome (MetS), a cluster of cardiovascular risk factors according to the National Cholesterol Education Program expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (NCEP ATP III), affected about 64 million Americans in 2000.¹ MetS has been associated with increased risk of type 2 diabetes,^{2,3} cardiovascular morbidity and mortality,^{4,5} and stroke.^{6,7} Little is known, however, about the association between MetS and congestive heart failure (CHF).

CHF is a major public health problem in the US. Among Americans aged ≥ 65 years, nearly 5 million have heart failure.^{8–10} Conventional risk factors for CHF include hypertension, coronary heart disease, left ventricular hypertrophy (LVH), cigarette smoking, obesity, dyslipidaemia and diabetes.^{11–14} Insulin resistance has also been associated with CHF independent of the other established risk factors.^{15,16} As identification of insulin resistance is complex and detection is difficult in clinical settings,¹⁷ MetS may be used as its surrogate indicator, in that insulin resistance has been proposed as a possible mechanism underlying MetS.¹⁸

In this study, we examined the association of CHF with MetS and insulin resistance among the participants of the Third National Health and Nutrition Examination Survey (NHANES III) conducted in the US between 1988 and 1994. We also investigated whether the association between MetS and CHF could be explained through insulin resistance.

METHODS

Study population

A representative sample of the civilian non-institutionalised US population was recruited into NHANES III (1988–94) by means of a multistage, stratified sampling design.¹⁹ Participants were invited to attend one of three examination sessions: morning, afternoon or evening. Response rates were 86% for the household interviews and 78% for the medical examinations.²⁰

Sampling weights had been calculated to account for unequal probabilities of selection resulting from the sample design, from non-response and from planned oversampling of certain subgroups.²⁰ In this study, 5549 men and non-pregnant women aged ≥ 40 years were analysed, who had fasted at least 8 h and who had complete data for MetS and insulin resistance. The weighted sample reflects the general US population as of the early 1990s (46.8% men; ethnicity: 80.1% white, 9.4% African American, 3.5% Mexican American and 7.0% other).

Measurements

People were defined as having CHF if they answered “yes” to the question “Has a doctor ever told you that you had congestive heart failure?” MetS was assessed on the basis of two working definitions proposed by the NCEP ATP III and the International Diabetes Federation (IDF). According to the NCEP ATP III report, people who have three or more of the following five criteria were defined as having MetS^{21,22}:

1. Abdominal obesity: waist circumference >102 cm in men and >88 cm in women;
2. Concentration of triglycerides ≥ 150 mg/dl (1.7 mmol/l);
3. Concentration of high-density lipoprotein cholesterol <40 mg/dl (1.02 mmol/l) in men and <50 mg/dl (1.29 mmol/l) in women;
4. Systolic blood pressure ≥ 130 mm Hg or diastolic blood pressure ≥ 85 mm Hg;

Abbreviations: CHF, congestive heart failure; ECG, electrocardiography; HOMA, homoeostasis model assessment; IDF, International Diabetes Federation; LVH, left ventricular hypertrophy; MetS, metabolic syndrome; NCEP ATP III, National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults; NHANES III, Third National Health and Nutrition Examination Survey

5. Fasting glucose ≥ 100 mg/dl (5.6 mmol/l).

In addition, persons currently using drugs to correct hypertension were counted as having high blood pressure, and those using drugs to control diabetes (insulin or oral agents) were considered to have diabetes.

According to the IDF definition,²³ people who have central obesity and two or more of the following four components have MetS:

1. Raised levels of triglycerides;
2. Reduced levels of high-density lipoprotein cholesterol;
3. Raised blood pressure;
4. Raised fasting plasma glucose concentration or previously diagnosed type 2 diabetes.

Diabetes status was determined on the basis of an affirmative answer to the question "Have you ever been told by a doctor that you have diabetes or sugar diabetes?" The IDF document provides ethnicity-specific values for waist circumference to define central obesity.²³ For Europeans, sub-Saharan Africans, Eastern Mediterranean and Middle Eastern (Arab) populations, central obesity is defined as waist circumference ≥ 94 cm for men and ≥ 80 cm for women, for South Asians, Chinese and ethnic South and Central Americans, as ≥ 90 cm for men and ≥ 80 cm for women, and for Japanese, as ≥ 85 cm for men and ≥ 90 cm for women.

In our study, waist circumference was measured at the high point of the iliac crest at minimal respiration to the nearest 0.1 cm. Serum triglyceride concentration was measured enzymatically after hydrolysis to glycerol. High-density lipoprotein cholesterol was measured on a Hitachi 704 Analyzer (Boehringer Mannheim Diagnostics, Indianapolis, USA) after the precipitation of other lipoproteins with a heparin-manganese chloride mixture. Plasma glucose concentration was measured by using an enzymatic reaction (Cobas Mira Chemistry System; Roche Diagnostic Systems, Montclair, New Jersey, USA). Plasma insulin concentration was measured by a Pharmacia Insulin radioimmunoassay kit (Pharmacia Diagnostics, Uppsala, Sweden). Details of the laboratory procedures for all these tests are published previously.²⁰ The averages of the second and the third systolic blood pressure and diastolic blood pressure readings were used in the analyses. The homeostasis model assessment (HOMA) was used to measure insulin resistance. It has been shown to be a reliable estimate and is calculated as²⁴

$$\text{HOMA} = (\text{Glucose (mmol/l)} \times \text{insulin } (\mu\text{U/ml})) / 22.5$$

Quartiles of the HOMA were used in the logistic regression analyses, and the log-transformed HOMA values were used to examine the association between mean levels of the HOMA and number of MetS components. The fourth quartile value of the HOMA was used as a cut-off point to define the insulin resistance (HOMA-IR or IR) in our study.

LVH was determined by a combination of possible LVH, defined according to the Minnesota Code criteria, and probable LVH, as determined by left ventricular mass index,²⁵ on the basis of electrocardiography (ECG) records. Probable myocardial infarction was determined by the Minnesota Code on the basis of ECG records. Demographic and other covariates such as age (years), sex, race or ethnicity (white, African American, Mexican American or other) and smoking status (never, former or current) were self-reported by the participants.

Statistical methods

We directly adjusted our statistics to the US population aged ≥ 40 years in the year 2000 (weights: 0.358, 0.348 and 0.294 for the age groups 40–49, 50–64 and ≥ 65 years, respectively). Contrasts were used to test for the linear trends of prevalence of

CHF for variables with ≥ 3 levels. The differences in the age-adjusted prevalence of CHF by MetS, demographic variables and other risk factors were compared among those with complete data for both CHF and MetS ($n = 4922$). Participants with missing data for any of the covariates were excluded ($n = 513$). The odds ratios (ORs) and 95% confidence intervals (CIs) were estimated in logistic regression models in a common restricted subsample with complete data ($n = 4409$). The proportions of men, Mexican Americans, current smokers and people with MetS, diabetes or LVH were similar between the sample with complete data and that with missing data ($p = 0.23$ – 0.88). The proportions of African Americans, older adults (aged 60–69 years) and people with myocardial infarction or CHF were higher in the sample with missing data than in that with complete data ($p < 0.01$).

All analyses were conducted using the SUDAAN software (Research Triangle Park, North Carolina, USA) to account for the complex sampling design.²⁶ We used the sampling weight to calculate estimates that were representative of the civilian non-institutionalised US population.^{19, 20}

RESULTS

Age-adjusted prevalence of CHF

We observed significant differences between men and women in the prevalence of CHF among people aged 70–79 years ($p = 0.04$), among those with three components of MetS by the IDF definition ($p = 0.04$), and among those with the highest quartile of total cholesterol ($p = 0.05$) or with LVH ($p < 0.01$; table 1). Mexican Americans had a significantly higher prevalence of CHF than white people ($p < 0.01$). We found a significantly increasing trend in the prevalence of CHF for the number of components of MetS ($p < 0.01$). People with diabetes, LVH, or probable or possible myocardial infarction had a higher prevalence of CHF than their counterparts (all $p < 0.01$). People with the highest quartile of the HOMA had a higher prevalence of CHF than those who had the lowest quartile ($p < 0.001$).

We found significant differences in the prevalence of CHF between people with and without MetS among African American women ($p < 0.01$) by the NCEP ATP III definition, and among white men ($p < 0.01$) and African American women ($p = 0.03$) by the IDF definition (fig 1).

Unadjusted and adjusted OR of MetS

MetS as defined by the NCEP ATP III was associated with twice the likelihood of having CHF (table 2). This association persisted even after adjustment for demographic variables and conventional risk factors. However, when the HOMA was included in the model, the OR of MetS significantly decreased and was no longer significant ($p > 0.10$).

HOMA was significantly associated with CHF (Wald $\chi^2 = 7.4$; $p < 0.01$ for a linear trend). A comparison of the regression coefficients for MetS on CHF in the logistic regression model with ($\beta = 0.05$; standard error (SE) 0.33) and without ($\beta = 0.54$; SE 0.25) the HOMA suggests that about 90.7% ($((0.54 - 0.05)/0.54)$) of the association between MetS and CHF could be explained by the HOMA. This percentage was 85.7% for white people, 32.7% for African Americans and 95.7% for Mexican Americans when separate analyses were conducted by race or ethnicity.

Association between MetS and HOMA

The number of MetS components defined by the NCEP ATP III and the IDF was highly correlated with the HOMA for men ($r = 0.62$, $p < 0.001$; $r = 0.61$, $p < 0.001$, respectively) and for women ($r = 0.63$, $p < 0.001$; $r = 0.60$, $p < 0.001$, respectively). We found a significantly increasing trend in the mean levels of the logarithm of the HOMA for the increasing number of MetS components defined by the NCEP ATP III definition for both men ($p < 0.001$) and women ($p < 0.001$; fig 2).

Table 1 Age-adjusted prevalence of congestive heart failure among participants from the Third National Health and Nutrition Examination Survey (aged ≥ 40 years) by demographic characteristics and risk factors, 1988–94

	Total			Men			Women			p Value for sex differences
	n	%	SE	n	%	SE	n	%	SE	
Total	5549	3.6	0.3	2696	4.1	0.6	2853	3.1	0.3	0.14
Demographic characteristics										
Race/ethnicity										
White	2741	3.0	0.3	1314	3.7	0.5	1427	2.5	0.3	0.07
African American	1342	4.3	0.6	633	4.7	0.9	709	4.1	0.7	0.56
Mexican American	1248	7.5	0.7	652	6.5	1.3	596	8.4	1.5	0.44
Other	218	6.9	2.0	97	7.2	3.6	121	6.7	2.6	0.92
Contrast: Mexican American v white	p<0.001			p=0.06			p<0.001			
Age (years)										
40–49	1500	0.3	0.1	712	0.2	0.1	788	0.2	0.1	0.52
50–59	1067	2.9	0.9	499	3.9	1.7	568	2.0	0.8	0.35
60–69	1288	5.8	0.7	666	6.3	1.0	622	5.6	1.0	0.61
70–79	973	8.1	1.4	470	10.8	2.2	503	5.9	1.4	0.04*
≥80	721	7.8	1.2	349	6.1	1.4	372	8.7	1.5	0.18
Linear trend	p<0.001			p<0.001			p<0.001			
Risk factors										
MetS (NCEP ATP III)										
None	644	1.2	0.4	359	1.7	0.6	285	0.7	0.6	0.35
1	1246	2.7	0.6	645	2.7	0.8	601	2.7	0.9	0.99
2	1228	3.6	0.9	607	5.3	1.8	621	2.2	0.6	0.12
3	980	4.2	0.7	443	5.6	1.5	537	3.1	0.7	0.16
4	599	4.9	0.9	277	5.1	1.5	322	4.5	1.2	0.74
5	225	5.9	1.6	86	6.6	2.2	133	5.7	1.9	0.62
Linear trend	p<0.01			p<0.01			p<0.01			
MetS (IDF)										
None	384	1.3	0.7	230	1.3	0.7	154	1.2	1.2	0.96
1	1047	2.1	0.6	532	2.5	0.7	515	1.9	0.9	0.60
2	1331	3.1	0.7	608	3.7	1.4	723	2.6	0.6	0.52
3	1157	3.8	0.7	558	5.7	1.4	599	2.3	0.5	0.04*
4	725	5.5	0.9	365	6.3	1.4	360	4.6	1.2	0.36
5	278	5.9	1.5	124	5.5	1.8	154	5.9	1.8	0.86
Linear trend	p<0.001			p<0.01			p<0.01			
Smoking status										
Current	1269	4.1	0.9	742	4.7	1.5	527	3.5	1.0	0.52
Former	1830	3.9	0.5	1209	4.4	0.6	621	3.1	0.7	0.09
Never	2450	2.8	0.4	745	2.5	0.6	1705	2.9	0.5	0.62
Linear trend	p=0.12			p=0.76			p=0.22			
Total cholesterol (quartile)										
Q1	729	3.2	0.8	411	2.4	0.8	318	4.4	2.5	0.51
Q2	1127	4.3	0.9	592	5.8	1.7	535	2.7	0.7	0.09
Q3	1625	3.3	0.4	823	3.2	0.7	802	3.4	0.7	0.84
Q4	1885	3.7	0.4	798	5.0	0.9	1087	2.9	0.5	0.05*
Linear trend	p=0.86			p=0.21			p=0.61			
Diabetes										
No	5001	3.2	0.3	2450	3.7	0.5	2551	2.7	0.3	0.16
Yes	540	8.0	1.5	243	8.9	2.5	297	7.7	1.9	0.68
Contrast: yes v no	p<0.01			p=0.05			p=0.01			
LVH by ECG										
No	4013	2.6	0.3	2026	2.9	0.5	1987	2.2	0.3	0.29
Yes	894	6.1	0.8	393	10.1	2.0	501	4.2	0.6	0.007**
Contrast: yes v no	p<0.001			p<0.01			p<0.01			
Probable or possible MI by ECG										
No	4796	2.8	0.3	2326	2.9	0.6	2470	2.6	0.4	0.61
Yes	158	22.7	4.5	111	26.8	5.6	47	13.6	7.5	0.19
Contrast: yes v no	p<0.001			p<0.01			p<0.15			
HOMA quartiles (median)										
Q1 (1.12)	1024	2.1	0.4	477	1.4	0.4	547	2.5	0.7	0.28
Q2 (1.76)	1328	2.3	0.4	645	3.2	0.7	683	1.7	0.5	0.08
Q3 (2.65)	1532	3.5	0.8	763	4.7	1.4	769	2.5	0.6	0.14
Q4 (5.29)	1497	6.2	0.8	729	6.0	1.2	768	6.4	1.2	0.81
Linear trend	p<0.001			p<0.01			p<0.01			

ECG, electrocardiography; HOMA, homeostasis model assessment; IDF, International Diabetes Federation; LVH, left ventricular hypertrophy; MetS, metabolic syndrome; MI, myocardial infarction; NCEP ATP III, National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults.

* $p < 0.05$; ** $p < 0.01$.

Association between MetS and CHF stratified or combined by diabetes and insulin resistance

In stratified analyses, MetS was significantly associated with CHF among people with diabetes (OR 2.2; 95% CI 1.3 to 3.8)

but not among those without diabetes (OR 0.9; 95% CI 0.3 to 2.7), indicating a possible effect of modification between MetS and diabetes on CHF (fig 3A). By contrast, MetS was not significantly associated with CHF among people with insulin

Figure 1 Age-adjusted percentages of congestive heart failure (CHF) among participants from the Third National Health and Nutrition Examination Survey (age ≥ 40 years) by metabolic syndrome (MetS), sex, and race or ethnicity, 1988–94; n=4922 with complete data for both CHF and MetS. IDF, International Diabetic Federation; NCEP ATP III, National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults.

resistance (≥ 75 th centile of the HOMA; OR 0.7; 95% CI 0.3 to 1.5) and among those without insulin resistance (< 75 th centile of the HOMA; OR 1.4; 95% CI 0.7 to 2.7), indicating that the effect of MetS on CHF was mediated through insulin resistance.

In the analyses of joint effects, compared with people having no MetS and diabetes, people with MetS only (OR 1.2; 95% CI 0.7 to 2.2) or diabetes only (OR 0.9; 95% CI 0.3 to 2.7) had no significant association with CHF; however, those with both MetS and diabetes (OR 2.6; 95% CI 1.4 to 4.9) had increased likelihood of CHF. By contrast, compared with people with no MetS and insulin resistance, those with insulin resistance only (OR 3.6; 95% CI 1.3 to 9.9) or both MetS and insulin resistance (OR 2.4; 95% CI 1.3 to 4.5) had increased likelihood of CHF (fig 3B).

Relative importance of MetS components for CHF

High blood pressure, high fasting glucose and central obesity were significantly associated with CHF in univariate logistic regression analyses (table 3; model 1). High blood pressure was the only variable that remained significant when all five components were included in the model (model 2). The effects of all five MetS components on CHF decreased markedly after adjustment for demographic variables (model 3), conventional risk factors (model 4) and finally the HOMA (model 5).

DISCUSSION

Our study found that people with MetS, by either the NCEP ATP III or the IDF definition, had about twice the likelihood of self-reported CHF. This association persisted after adjustment for conventional risk factors such as sex, race or ethnicity, age, smoking, total cholesterol, LVH, and probable or possible myocardial infarction as identified by ECG. The association weakened dramatically after including the HOMA in the final model. Nearly 90% of the association between MetS by the NCEP ATP III definition and CHF was explained by insulin resistance. We found a significant dose-response trend for the HOMA in the CHF

prevalence. We also found that the number of MetS components was highly correlated with the HOMA in both men and women.

Our findings add further support to an association between CHF and insulin resistance independent of other conventional risk factors. Indeed, a higher level of insulin resistance as manifested by the HOMA quartiles was associated with a higher prevalence of CHF in a dose-response fashion. In previous longitudinal studies,^{15–16} insulin resistance predicted CHF independent of established risk factors. The exact mechanism for the observed association of insulin resistance with CHF is unknown. Two hypotheses are as follows: (1) hyperinsulinaemia may lead to decompensation in people with subclinical myocardial dysfunction^{15–16} or sympathetic nervous system activation²⁷; and (2) insulin may act as a growth factor in the myocardium and thus hyperinsulinaemia may increase myocardial mass and decrease cardiac output as shown in animal studies.²⁸ On the other hand, several previous studies have shown that CHF predicts the development of type 2 diabetes.^{29–30} Increased adrenergic drive³¹ or raised levels of circulating tumour necrosis factor α ³⁰ may lead to increases in free fatty acid oxidation and subsequent insulin resistance in patients with CHF. Given the cross-sectional nature of our study, we could not confirm whether insulin resistance is a primary or secondary phenomenon in patients with CHF. Most previous studies were based on highly selected hospital settings or patients selected from clinical trials. Such people may not reflect the spectrum of CHF in the general population. By contrast, our findings were derived from a national representative sample and the relationship of insulin resistance to CHF may be generalisable to the whole population studied.

Insulin resistance has been proposed as a possible underlying mechanism for MetS.¹⁸ As measuring insulin resistance is complex and difficult to perform in clinical practice,³² it is useful to consider MetS as a surrogate indicator for insulin resistance in predicting the risk and prognosis of cardiovascular diseases.^{4–7}

Table 2 Odds ratio of congestive heart failure in relation to demographic characteristics and risk factors among participants (n=4409) from the Third National Health and Nutrition Examination Survey (aged ≥40 years), 1988–94

	Unadjusted		Adjusted for demo		Adjusted for demo +risk factors		Adjusted for demo +risk factor+HOMA	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
MetS (NCEP ATP III)								
No	1.0	—	1.0	—	1.0	—	1.0	—
Yes	2.2**	1.3 to 3.6	1.8*	1.1 to 3.1	1.7*	1.1 to 2.8	1.1	0.5 to 2.0
Sex								
Female	1.0	—	1.0	—	1.0	—	1.0	—
Male	1.4	0.9 to 2.1	1.6*	1.1 to 2.5	1.3	0.8 to 2.2	1.3	0.8 to 2.0
Race or ethnicity								
White	1.0	—	1.0	—	1.0	—	1.0	—
African American	1.3	0.9 to 2.0	1.7*	1.1 to 2.5	1.5†	1.0 to 2.2	1.4	0.9 to 2.0
Mexican American	1.8***	1.2 to 2.6	2.4***	1.5 to 3.6	2.6***	1.7 to 3.9	2.4**	1.6 to 3.6
Other	2.3	0.7 to 7.3	3.2*	1.0 to 9.8	3.5*	1.2 to 10.9	3.5*	1.2 to 10.4
Age (10-year increments from 40 years)	1.8***	1.5 to 2.0	1.8***	1.6 to 2.1	1.7***	1.5 to 2.0	1.7***	1.5 to 2.0
Smoking status								
Never	1.0	—	...	...	1.0	—	1.0	—
Former	1.6*	1.0 to 2.7	...	...	1.6†	0.9 to 2.8	1.5	0.8 to 2.7
Current	1.4	0.7 to 3.1	...	...	2.0†	0.9 to 4.5	2.1†	1.0 to 4.7
Total cholesterol (quartiles)								
Q1	1.0	—	...	...	1.0	—	1.0	—
Q2	2.3*	1.0 to 5.1	...	...	2.2†	0.9 to 5.6	2.3†	1.0 to 5.4
Q3	1.4	0.7 to 3.2	...	...	1.2	0.5 to 2.8	1.2	0.5 to 2.8
Q4	1.8†	0.9 to 3.6	...	...	1.5	0.7 to 3.2	1.6	0.8 to 3.1
LVH by ECG								
No	1.0	—	...	...	1.0	—	1.0	—
Yes	3.7***	2.3 to 5.7	...	...	2.2**	1.3 to 3.6	2.2**	1.3 to 3.6
Probable or possible MI by ECG								
No	1.0	—	...	...	1.0	—	1.0	—
Yes	10.8***	5.8 to 19.9	...	...	5.8***	2.7 to 12.2	5.7***	2.7 to 12.3
HOMA quartiles (median)								
Q1 (1.12)	1.0	—	...	...	...	...	1.0	—
Q2 (1.76)	1.5	0.7 to 3.1	...	...	...	...	1.5	0.7 to 3.3
Q3 (2.65)	2.5**	1.2 to 5.2	...	...	...	...	2.2†	0.9 to 5.2
Q4 (5.29)	4.7***	2.6 to 8.5	...	...	...	...	3.9**	1.6 to 9.9

demo, demographic variables; ECG, electrocardiography; HOMA, homeostasis model assessment; LVH, left ventricular hypertrophy; MetS, metabolic syndrome; MI, myocardial infarction; NCEP ATP III, National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults; —, reference group; ..., not included in the model.

Demographic variables are sex, race or ethnicity, and age. Conventional risk factors are smoking, total cholesterol, LVH and MI.

*p<0.05; **p<0.01; ***p<0.001; †p<0.1 for all logistic regression analyses.

Few studies have examined the association of CHF with MetS and insulin resistance. Levantesi *et al*³³ assessed the role of MetS as a risk factor of cardiovascular events in patients who have had a myocardial infarction. They found that diabetes rather than

Figure 2 Mean levels of homoeostasis model assessment (HOMA) and number of metabolic syndrome (MetS) components among participants from the Third National Health and Nutrition Examination Survey (aged ≥40 years) by sex, 1988–94; n=4409 with complete data for the HOMA and all components of MetS by the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (NCEP ATP III) criteria. $r=0.62$ for men ($p<0.001$) and 0.63 for women ($p<0.001$); $p<0.001$ for a linear trend for both men and women.

MetS was associated with increased risk of hospitalisation for patients with CHF. Diabetes has often been studied as a risk factor for CHF.^{11–34} Yet, a more detailed characterisation of the associations among diabetes, MetS, insulin resistance and subsequent CHF is still lacking. We found that diabetes alone was not markedly associated with increased likelihood of CHF. Diabetes may increase the risk of CHF in combination with MetS or in combination with MetS and insulin resistance.

Our study provides further evidence that MetS could act as a surrogate indicator for insulin resistance in relation to CHF, because about 90% of the association between MetS and CHF could be explained by the HOMA. As suggested in our analyses, MetS may be a better predictive measurement than its single components in relation to CHF. Among the five components of MetS, high blood pressure seemed to be a relatively stronger factor than other components of MetS in relation to CHF. However, the effect of hypertension was attenuated after further adjustment for demographic variables and conventional risk factors. By contrast, MetS was persistently related to CHF even after adjustment for the same set of covariates as for the single components.

The two definitions of MetS (NCEP ATP III²² and IDF²³) yielded similar patterns in overall patterns and magnitudes in the prevalence of CHF and mean levels of log HOMA with regard to the number of MetS components. This finding is consistent with the prevalence estimates of MetS by the two definitions using the most recent national data from US adults.³⁵ The prevalence of MetS was about 5% higher with the IDF definition than with the NCEP ATP III definition. This

Figure 3 (A) Relationship of metabolic syndrome (MetS) with congestive heart failure (CHF), stratified by diabetes mellitus (DM) or homeostasis model assessment insulin resistance (HOMA-IR). (B) Joint effects of MetS with DM and HOMA-IR on CHF, OR and 95% CI were estimated in logistic regression models adjusted for sex, race or ethnicity, age, smoking status, total cholesterol, left ventricular hypertrophy and myocardial infarction.

observed difference seemed to be largely attributable to cut-off criteria used to define central obesity with the NCEP ATP III (waist circumference >102 cm in men and >88 cm in women)²² versus IDF (waist circumference ≥ 94 cm or

≥ 90 cm or 85 cm for men and ≥ 80 cm or ≥ 90 cm for women, depending on ethnicity) criteria.²³ One exception in our study was that central obesity defined by the IDF seemed to be a persistent factor in relation to CHF after adjustment for demographic and conventional risk factors. The observation suggests that central obesity with lower cut-off criteria as defined by the IDF could be an independent risk factor associated with increased likelihood of CHF.

The strengths of our analysis include the use of a national representative sample with a large sample size to obtain accurate estimates of CHF prevalence. We also determined MetS by two definitions using reliable laboratory and examination data.²⁰ On the other hand, a limitation of our study was the cross-sectional design that did not allow us to determine causality. Self-reported CHF without validation by medical records or local adjudication might have introduced misclassification bias. In fact, the Women's Health Initiative study showed a moderate agreement (positive predictive value 65%; $\kappa = 0.48$) between self-report and local adjudication for CHF.³⁶ Resulting misclassification was likely to be non-differential with respect to the objective measures of MetS, and would therefore bias the estimates of association towards the null. Hence, the prevalence of CHF and its association with MetS might have been underestimated in our study.

Our findings are relevant for clinical practice and intervention. As CHF is potentially preventable,⁸ it is important to identify predictors or correlates of CHF occurrence or progression. A diagnosis of MetS can be made easily by a doctor in a primary care setting according to either the NCEP ATP III or the IDF definition. Therefore, ascertaining the presence of MetS, particularly among people with diabetes, may be useful for the prediction, prognosis and prevention of CHF. Aggressive treatment for conventional risk factors such as hypertension has also been effective in the prevention of CHF.³⁷ New therapeutic strategies aimed at treating MetS as a disease entity may provide further insight for the prevention of CHF.

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Table 3 Relative importance of components of the metabolic syndrome for congestive heart failure among participants ($n = 4409$) from the Third National Health and Nutrition Examination Survey (aged ≥ 40 years), 1988–94

	Model 1		Model 2		Model 3		Model 4		Model 5	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
NCEP ATP III definition										
Central obesity	1.7*	1.1 to 2.7	1.2	0.7 to 2.1	1.4	0.8 to 2.7	1.6	0.8 to 3.1	1.2	0.6 to 2.3
Low HDL	1.7†	1.0 to 2.9	1.4	0.7 to 2.6	1.5	0.8 to 2.9	1.3	0.7 to 2.5	1.2	0.6 to 2.3
High triglyceride	1.8†	1.0 to 3.3	1.3	0.6 to 2.5	1.3	0.7 to 2.5	1.4	0.8 to 2.6	1.2	0.7 to 2.2
High blood pressure	2.6**	1.5 to 4.6	2.2**	1.2 to 4.0	1.4	0.8 to 2.5	1.2	0.7 to 2.1	1.1	0.6 to 2.0
High fasting glucose	1.9**	1.2 to 3.0	1.3	0.8 to 2.2	1.0	0.6 to 1.7	1.1	0.7 to 1.8	0.8	0.5 to 1.3
IDF definition										
Central obesity	2.3**	1.4 to 3.8	1.6	0.9 to 3.1	1.8†	0.9 to 3.6	2.1*	1.0 to 4.3	1.6	0.8 to 3.3
Low HDL	1.7†	1.0 to 2.9	1.3	0.7 to 2.6	1.5	0.8 to 2.9	1.3	0.7 to 2.4	1.2	0.6 to 2.2
High triglyceride	1.8†	1.0 to 3.3	1.2	0.6 to 2.4	1.3	0.7 to 2.5	1.3	0.7 to 2.5	1.2	0.7 to 2.1
High blood pressure	2.6**	1.5 to 4.6	2.1**	1.2 to 3.8	1.4	0.8 to 2.4	1.2	0.7 to 2.1	1.1	0.6 to 2.0
High fasting glucose	2.0**	1.3 to 3.2	1.4	0.9 to 2.4	1.2	0.7 to 1.9	1.2	0.8 to 1.9	0.9	0.6 to 1.5

HDL, high-density lipoprotein; HOMA, homeostasis model assessment; IDF, International Diabetes Federation; NCEP ATP III, National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults.

For all components, 1 = yes, 0 = no.

Model 1 was unadjusted; model 2 was adjusted for all five components listed in the table; model 3 was further adjusted for demographic characteristics such as sex, race or ethnicity, and age on the basis of model 2; model 4 was further adjusted for conventional risk factors such as smoking, total cholesterol, left ventricular hypertrophy, and probable or possible myocardial infarction on the basis of model 3; model 5 was further adjusted for the HOMA on the basis of model 4.

* $p < 0.05$; ** $p < 0.01$; † $p < 0.1$.

What is already known

- Metabolic syndrome (MetS) has been associated with increased risk of type 2 diabetes, cardiovascular morbidity and mortality, and stroke.
- Conventional risk factors for congestive heart failure (CHF) include hypertension, coronary heart disease, left ventricular hypertrophy (LVH), cigarette smoking, obesity, dyslipidaemia and diabetes.
- Insulin resistance has been associated with CHF independent of the other established risk factors.

What this paper adds

- MetS is associated with almost twice the likelihood of CHF.
- The association persists even after adjustment for conventional risk factors such as sex, race or ethnicity, age, smoking, total cholesterol, LVH, and probable or possible myocardial infarction as identified by electrocardiography.
- Nearly 90% of the association between MetS and CHF was accounted for by the homeostasis model assessment insulin resistance.

Policy implications

- As measurement of insulin resistance is complex in clinical settings, yet a diagnosis of MetS can be made easily by a primary care physician, ascertaining the presence of MetS, particularly among people with diabetes, may be useful for the prediction, prognosis and prevention of CHF.

Competing interests: None.

The findings and conclusions in this article are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

Contributors: CL had full access to all of the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis. Study concept and design: CL, ESF. Acquisition of data: CL, ESF. Analysis and interpretation of data: CL, ESF, LCMcG, AHM. Drafting of the manuscript: CL. Critical revision of the manuscript for important intellectual content: CL, ESF, LCMcG, AHM. Statistical analysis: CL, ESF. Administrative, technical, or material support: CL, ESF, AHM. Study supervision: ESF, AHM.

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