

Metabolic Syndrome Modifies the Cardiovascular Risk Associated With Angiographic Coronary Artery Disease in Women

A Report From the Women's Ischemia Syndrome Evaluation

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Background—The metabolic syndrome, which is characterized by a constellation of fasting hyperglycemia, hypertriglyceridemia, low HDL cholesterol, hypertension, and/or abdominal obesity, is a risk factor for the development of coronary artery disease (CAD) and cardiovascular events. The interrelationship between metabolic status and CAD on cardiovascular risk in women is not known.

Methods and Results—We evaluated interrelationships between angiographic CAD, the metabolic syndrome, and incident cardiovascular events among 755 women from the Women's Ischemia Syndrome Evaluation (WISE) study who were referred for coronary angiography to evaluate suspected myocardial ischemia; 25% of the cohort had the metabolic syndrome at study entry. Compared with women with normal metabolic status, women with the metabolic syndrome had a significantly lower 4-year survival rate (94.3% versus 97.8%, $P=0.03$) and event-free survival from major adverse cardiovascular events (death, nonfatal myocardial infarction, stroke, or congestive heart failure; 87.8% versus 93.5%, $P=0.003$). When the subjects were stratified by the presence or absence of angiographically significant CAD at study entry, in women with angiographically significant CAD, the metabolic syndrome resulted in significantly higher risk of cardiovascular events than in women with normal metabolic status (hazard ratio 4.93, 95% CI 1.02 to 23.76; $P=0.05$), whereas it did not result in increased 4-year cardiovascular risk in women without angiographically significant CAD (hazard ratio 1.41, 95% CI 0.32 to 6.32; $P=0.65$).

Conclusions—These data suggest that in women with suspected myocardial ischemia, the metabolic syndrome modifies the cardiovascular risk associated with angiographic CAD. Specifically, the metabolic syndrome was found to be a predictor of 4-year cardiovascular risk only when associated with significant angiographic CAD. (*Circulation*. 2004; 109:714-721.)

Key Words: metabolic syndrome ■ coronary disease ■ inflammation ■ obesity ■ women

The metabolic syndrome is a constellation of lipid and nonlipid factors of metabolic origin associated with insulin resistance that places subjects at risk for diabetes and cardiovascular events.^{1,2} It has recently been defined by the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP-III),³ which suggests that the diagnosis be made when 3 or more of the following characteristics are present: high fasting glucose, high blood pressure, low HDL cholesterol, high triglycerides, and abdominal obesity. Several studies have shown an association

between the metabolic syndrome and increased cardiovascular events.^{1,2,4} Despite significant controversy, most experts appear to believe that the increased cardiovascular risk seen in these subjects is probably due to the clustering of known cardiovascular risk factors. However, even though there have been reports of an increased prevalence of coronary heart disease (CHD) in these subjects, these reports have used surrogate markers for CHD.⁵⁻⁷ In addition, the interrelationship between the metabolic syndrome and presence or absence of CHD and its effects on cardiovascular risk remains unknown. Accordingly, we sought to prospectively evaluate

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the potential relationships between the metabolic syndrome, presence of angiographically significant coronary artery disease (CAD), and incident cardiovascular events in a cohort of women with chest pain referred for coronary angiography.

Methods

Study Design

Women were enrolled in the Women's Ischemia Syndrome Evaluation (WISE) study if they had suspected myocardial ischemia that prompted clinical referral for coronary angiography at 1 of 4 sites (University of Alabama at Birmingham; University of Florida, Gainesville; University of Pittsburgh, Pittsburgh, Pa; and Allegheny General Hospital, Pittsburgh, Pa).⁸ Each woman underwent evaluation of demographic characteristics and medication use; quantitative coronary angiography⁹; and blood sampling for measurement of lipids, glucose, and inflammatory markers. All subjects provided written informed consent that was approved by the institutional review board at their local WISE clinical site. This report examines 755 WISE women in whom classification of metabolic status (normal, metabolic syndrome without diabetes, or diabetes with metabolic syndrome) was determined, as defined below.

Classification of Metabolic Status

The ATP-III criteria³ were used to classify 784 WISE women as being with or without the metabolic syndrome on the basis of the presence or absence of ≥ 3 of the following factors: (1) waist circumference >88 cm, (2) fasting triglycerides >150 mg/dL (measured by enzymatic assay at the WISE core lipid laboratory), (3) HDL cholesterol <50 mg/dL, (4) hypertension (systolic blood pressure ≥ 130 mm Hg, diastolic blood pressure ≥ 85 mm Hg or use of antihypertensive drug therapy), and (5) fasting glucose ≥ 110 mg/dL. The subset of 430 women who met the definition of the metabolic syndrome were subdivided into 2 study groups consisting of those with treated diabetes ($n=242$; diabetes group) and those without treated diabetes ($n=188$; metabolic syndrome group). Treated diabetes was defined as past or current use of oral hypoglycemic agents or insulin. Among the remaining 354 women, 29 had a history of diabetes but did not meet the definition of the metabolic syndrome at study entry. These women were excluded from the analysis, which left a third study group of 325 women with normal metabolic status and a total study cohort of 755 women.

The homeostasis model assessment (HOMA) was calculated as a measure of insulin sensitivity in the 311 subjects without diabetes who had data on fasting insulin that was measured by standard clinical techniques at the WISE core lipid laboratory. HOMA was calculated with the formula $\text{HOMA score} = [(\text{fasting glucose in units of mmol/L} \times \text{insulin in units of } \mu\text{U/mL}) / 22.5]$. Subjects with diabetes were excluded from the calculation because the score is not accurate in such patients.¹⁰

Measurement of Inflammatory Markers

Interleukin-6 (IL-6) levels were measured from plasma collected at study entry with a commercially available ELISA kit (Quantikine hs human IL-6, R&D Systems). The minimum limit of detection was 0.094 pg/mL, and the coefficients of variation of intra-assay and interassay precision were 3.8% and 9.9%, respectively. To confirm reproducibility, a random subset of 90 samples were assayed in duplicate. IL-6 levels in the duplicate samples had a correlation coefficient of 0.98. C-reactive protein (CRP) was measured by a high-sensitivity (hs) method on the Hitachi 911 analyzer with reagents from Denka Seiken and previously validated techniques.¹¹

Assessment of Angiographic CAD

Quantitative analysis of coronary angiograms was performed offline at the WISE angiographic core laboratory (Rhode Island Hospital, Providence, RI) by investigators blinded to all other subject data.⁹ Luminal diameter was measured at all stenoses and at nearby reference segments with an electronic cine projector-based cross-

hair technique (Vanguard Instrument Corp). The presence of 1 or more stenoses $\geq 50\%$ in diameter was considered significant CAD, maximum diameter stenosis 20% to 49% was considered minimal CAD, and $<20\%$ stenosis in all coronary arteries was considered no CAD.

Ascertainment of Cardiovascular Events

Follow-up for the occurrence of untoward cardiovascular events was obtained by annual telephone and/or mail contact. The primary clinical outcomes were death or the composite end point of major adverse cardiovascular events (MACE; death, nonfatal myocardial infarction, stroke, or congestive heart failure). Among the 715 women who did not die during 4-year follow-up, 87% had ≥ 1 -year follow-up, 81% had ≥ 2 -year follow-up, 66% had ≥ 3 -year follow-up, and 39% had ≥ 4 -year follow-up. The median length of follow-up was 3.5 years (interquartile range 2.8 to 4.7 years) among the 715 subjects who did not die during 4-year follow-up (94.7% of the total cohort) and 1.4 years for the 40 nonsurviving subjects (interquartile range 0.45 to 2.6 years).

Statistical Methods

Differences in baseline demographic and clinical characteristics were assessed by metabolic status (normal, metabolic syndrome without diabetes, diabetes with metabolic syndrome) with the Mantel-Haenszel χ^2 test for trend for categorical variables and ordered Jonckherre-Terpstra test for continuous variables. The latter non-parametric method was used owing to the relatively high skew of some baseline clinical variables, including inflammatory markers. The Kaplan-Meier method was used to estimate 4-year cumulative incidence rates of death and MACE, with the log-rank statistic used to assess differences by metabolic status. Participants who did not experience the clinical outcome of interest were censored at either 4 years or the last date of follow-up before 4 years. Proportional hazards regression analysis was used to estimate adjusted 4-year relative risks of death and MACE in relation to metabolic status. Covariates in adjusted models included age and race, as well as those with a probability value <0.20 , as determined by backward stepwise regression. In the initial variable selection process, inflammatory markers (IL-6 and hs-CRP) were not considered because they may be intermediate in the causal pathway between metabolic status and risk of cardiovascular events. However, after the final adjusted models were constructed (model 1), the log of hs-CRP was added in a separate model (model 2) to assess the extent to which the effects of metabolic status were attenuated by systemic inflammation. The proportional hazards assumption of invariant relative risk was tested and found to be satisfactory for all models constructed.

Results

Demographics

The mean age of the 755 subjects was 58 ± 12 years (range 21 to 86 years); 75% of the women were postmenopausal, 80% were white, and 34% were using postmenopausal hormone replacement therapy (HRT) at study entry.

Prevalence of Metabolic Factors by Metabolic Status

Among the 5 factors used to define the metabolic syndrome, the prevalence of hypertension was highest in the study cohort (79%), whereas fasting hyperglycemia was the least prevalent factor (40%; Table 1). With the exception of fasting glucose ≥ 110 mg/dL, which was considered present in all women with diabetes, the prevalence of the 4 remaining metabolic factors was higher in those with the metabolic syndrome than in those with diabetes. In women classified with normal metabolic status, the prevalence of metabolic factors ranged from 3% (fasting glucose ≥ 110 mg/dL) to 61% (hypertension).

TABLE 1. Prevalence of Metabolic Syndrome Risk Factors by Metabolic Status

Metabolic Syndrome Risk Factor	n	Prevalence at Study Entry, %			
		Normal* (n=325)	Metabolic Syndrome† (n=188)	Diabetes‡ (n=242)	All (n=755)
Waist circumference >88 cm	711	33.8	85.7	84.8	61.7
Triglycerides >150 mg/dL	720	16.6	75.0	57.2	43.3
HDL cholesterol <50 mg/dL	718	20.9	70.4	59.3	44.7
Systolic BP ≥130 mm Hg or diastolic BP ≥85 mm Hg or recent use of antihypertensive agents	747	61.2	91.8	92.3	78.7
Fasting glucose ≥110 mg/dL or history of treated diabetes	755	3.1	25.5	100.0	39.7

BP indicates blood pressure.

*Women without the metabolic syndrome.

†Women without treated diabetes yet with at least 3 of the 5 following factors present: (1) waist circumference >88 cm; (2) triglycerides >150 mg/dL; (3) HDL <50 mg/dL; (4) systolic BP ≥130 mm Hg or diastolic BP ≥85 mm Hg or recent use of antihypertensive agents; (5) fasting glucose ≥110 mg/dL.

‡Women with the metabolic syndrome and a history of treated diabetes, defined as use of oral agents and/or insulin. Note: 29 women with treated diabetes did not meet the definition of the metabolic syndrome and were excluded from the analysis.

Baseline Characteristics by Metabolic Status

Compared with women with normal metabolic status, those with the metabolic syndrome or diabetes were significantly older, were less likely to be white and current users of HRT, and were more frequent users of aspirin and antihypertensive drugs (Table 2). Women with diabetes were more likely to be taking statin therapy than nondiabetic women. Markers of systemic inflammation were lower in women with normal metabolic status than in those with the metabolic syndrome and diabetes. Interestingly, both the proinflammatory cytokine IL-6 and the nonspecific marker hs-CRP were as high in women with the metabolic syndrome as in women with diabetes (Table 2).

Prevalence of Angiographic CAD by Metabolic Status

At study entry, the prevalence of significant angiographic CAD (≥ 50% stenosis) was intermediate in women with the metabolic syndrome (33%) compared with women with normal metabolic status (26%) and those with diabetes (57%; Table 2; Figure 1). Similarly, 45% of women with normal metabolic status and 40% of women with the metabolic syndrome were considered to have no angiographic disease at study entry, compared with only 23% of women with diabetes.

Metabolic Status and Cardiovascular Outcome

Women with the metabolic syndrome had a significantly lower 4-year survival rate than women with normal metabolic status (94.3% versus 97.8%, $P=0.03$), whereas the rate was nonsignificantly higher than in those with diabetes (94.3% versus 89.4%, $P=0.07$; Figure 2, top). Similarly, when the composite end point of 4-year MACE was used, the event-free survival rate of 87.8% in women with the metabolic syndrome was lower than that observed in women with normal metabolic status (93.5% $P=0.003$) but significantly higher than in women with diabetes (76.5%, $P=0.03$; Figure 2, bottom). Thus, 4-year event-free survival rates in women with the metabolic syndrome were intermediate between those with normal metabolic status and those with diabetes.

Interaction Between Metabolic Status, Angiographic CAD, and Cardiovascular Outcome

Four-year survival rates in relation to metabolic status were evaluated by the absence or presence of significant angiographic CAD at study entry (Figures 3 and 4). Among women with significant angiographic CAD at study entry, 4-year survival rates were essentially identical between women with the metabolic syndrome and those with diabetes (86.2% versus 85.9%, $P=0.77$) and substantially lower than the 4-year survival rate of 96.9% observed in women with normal metabolic status (Figure 3, top). Similar results were observed with the composite end point of MACE (Figure 3, bottom). Thus, the 4-year risk of cardiovascular events in women with prevalent angiographic CAD at study entry was modified (substantially elevated) by the presence of the metabolic syndrome.

Among women without significant angiographic CAD at study entry, a different pattern of risk was observed in that those with the metabolic syndrome had similar survival as those with normal metabolic status (96.9% versus 98.1%, $P=0.65$) and similar 4-year freedom from MACE (91.4% versus 94.3%, $P=0.21$; Figure 4). There was a nonsignificant suggestion of lower event-free survival in women with diabetes compared with those with the metabolic syndrome (91.8% versus 96.9%, $P=0.16$), as well as lower rates of event-free MACE (85.8% versus 91.4%, $P=0.26$). Thus, in women without angiographic CAD at study entry, the 4-year risk of cardiovascular events in women with the metabolic syndrome was similar to the risk in women with normal metabolic status and was not statistically different from the risk in women with diabetes.

Adjusted Risk Estimates

Figure 5 presents 4-year adjusted hazard ratios (HRs) for death and MACE by metabolic status and presence or absence of angiographic CAD. As seen, among women with significant angiographic CAD at study entry, the adjusted 4-year risk of death for women with the metabolic syndrome (plotted on a logarithmic scale) was nearly 5-fold compared with women with normal metabolic status (HR 4.93, 95% CI

TABLE 2. Baseline Characteristics by Metabolic Status

Baseline Characteristic	Metabolic Status at Study Entry			P (Trend)
	Normal* (n=325)	Metabolic Syndrome* (n=188)	Diabetes* (n=242)	
Age, y, median	57	60	59	0.008
White race, %	86	84	69	<0.0001
Postmenopausal, %	71	76	79	0.03
HRT, %				
Ever	54	42	47	0.15
Current	40	31	28	0.002
Aspirin use, %	53	59	67	0.0008
Lipid-lowering statin use, %	23	21	35	0.002
Antihypertensive drug use, %	38	49	69	<0.0001
Cigarette smoking, %				0.22
Never	44	42	52	
Former	35	35	30	
Current	20	23	19	
History of CHF, %	6	7	16	0.0005
Family history of CAD, %	64	70	67	0.45
Body mass index, kg/m ² , median	26.1	30.2	31.3	NA†
Blood pressure, mm Hg, median				
Systolic	129	139	140	NA†
Diastolic	75	79	78	NA†
Cholesterol, mg/dL, median				
Total	188	197	191	NA†
HDL	56	47	47	NA†
LDL	108	106	102	NA†
Triglycerides, mg/dL, median	96	187	165	NA†
Inflammation, median				
IL-6, pg/mL	2.5	3.5	3.6	<0.0001
hs-CRP, mg/dL	0.28	0.64	0.54	<0.0001
Angiographic CAD, %				<0.0001
None (0–19% maximum stenosis)	45	40	23	
Minimal (20–49% maximum stenosis)	28	27	20	
Significant (≥50% stenosis)	26	33	57	

*As defined in Table 1.

†No statistical test performed because the baseline characteristic is directly or indirectly part of the definition for metabolic status.

1.02 to 23.76; $P=0.05$). Similar results were observed for the composite end point of MACE (HR=4.93, 95% CI 1.16–21.94; $P=0.02$). However, among women without significant angiographic CAD, the presence of the metabolic syndrome was not associated with increased risk of death (HR 1.41, 95% CI 0.32 to 6.32; $P=0.65$). A similar absence of heightened risk was observed for 4-year risk of MACE.

Given the higher levels of inflammatory markers at baseline in women with the metabolic syndrome and diabetes compared with normal metabolic status, we additionally sought evidence that hs-CRP might modify the associations seen between metabolic status and angiographic CAD in the 4-year adjusted HRs for death and MACE. In the model of women without significant angiographic CAD, hs-CRP did not significantly attenuate the effects of metabolic status on

mortality (HR 0.63, 95% CI 0.10 to 3.74; $P=0.61$). Similarly, in the model of women with significant angiographic CAD, there was only marginal attenuation by hs-CRP on the effects of metabolic status on mortality (HR 4.34, 95% CI 0.86 to 21.94; $P=0.08$). Similar results were observed when hs-CRP was added to the model with the combined end point of MACE.

Association Between Metabolic Status, Insulin Resistance, and Cardiovascular Events

Given that insulin resistance has been implicated as the underlying cause of the metabolic syndrome, we investigated whether a commonly used measure of insulin resistance (HOMA) was associated with the metabolic syndrome in the present study population. As anticipated, the distribution of

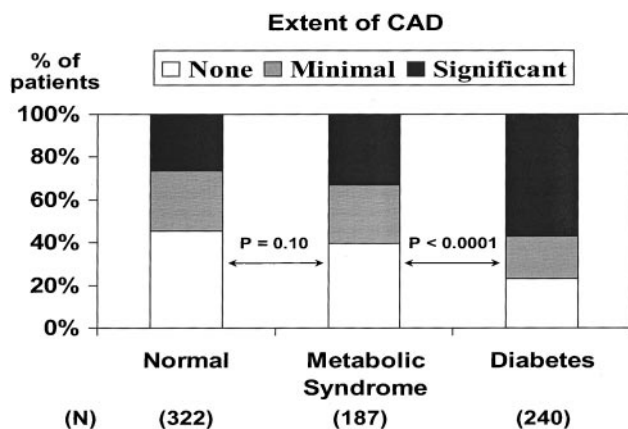


Figure 1. Extent of angiographic CAD at study entry in women with normal metabolic status (left), those with metabolic syndrome and without diabetes (middle), and those with both diabetes and metabolic syndrome (right).

HOMA scores were significantly higher in women with the metabolic syndrome (median 2.2, interquartile range 1.4 to 3.1) than in those with normal metabolic status (median 1.2, interquartile range 0.7 to 1.9; $P < 0.0001$). However, whereas metabolic status predicted 4-year risk of death in a gradient fashion (normal 2.2%, metabolic syndrome 7%, diabetic 10.6%), no such relationship was observed for the distribution of HOMA scores (lower tertile 3.4%, middle tertile 1.1%, upper tertile 5.8%).

Discussion

The results of this prospective study demonstrate that metabolic status is associated with angiographic CAD and cardiovascular risk in women with suspected myocardial ischemia. Furthermore, women with the metabolic syndrome or diabetes and angiographically significant CAD at study entry had significantly lower 4-year survival and event-free survival rates compared with women with normal metabolic status.

The present study supports previous reports suggesting that the metabolic syndrome is associated with CHD.⁵ However, in contrast to previous studies in which the presence of CHD has been defined by self-report of myocardial infarction or positive responses to the angina pectoris section of the Rose Questionnaire, the present study confirmed this association using angiographic CAD as the definition for CHD. In our study, there was a trend toward higher prevalence of angiographically significant CAD in women with the metabolic syndrome compared with women with normal metabolic status but lower than in women with diabetes. The results from our study of women referred for coronary angiography confirm prior reports that suggest that the risk of CHD that is associated with the metabolic syndrome is intermediate between that of individuals with normal metabolic status and that of those with diabetes.

In addition to predicting angiographic CAD, our study shows that the metabolic syndrome is a predictor of significant cardiovascular risk. Previous studies have suggested that the metabolic syndrome is associated with increased cardiovascular and total mortality in predominantly male cohorts.^{1,2} The present study confirms this association in an exclusively female cohort that is stratified by the presence or absence of significant angiographic CAD. It appears that the risk of mortality and 4-year MACE increased in a gradient fashion across the metabolic continuum in our cohort of women, with women with the metabolic syndrome having intermediate risk compared with women with diabetes and women with normal metabolic status. Importantly, 4-year survival and freedom from MACE were significantly lower in women with the metabolic syndrome compared with women with normal metabolic status. However, when subjects were stratified by the presence or absence of angiographic CAD at study entry, a different pattern of risk was observed. Specifically, in women with significant angiographic CAD at study entry, the 4-year risk of death or MACE was significantly higher in those with metabolic abnormalities as compared with those with normal metabolic status. In contrast, in women without angiographic CAD at study entry, the risk was low and not

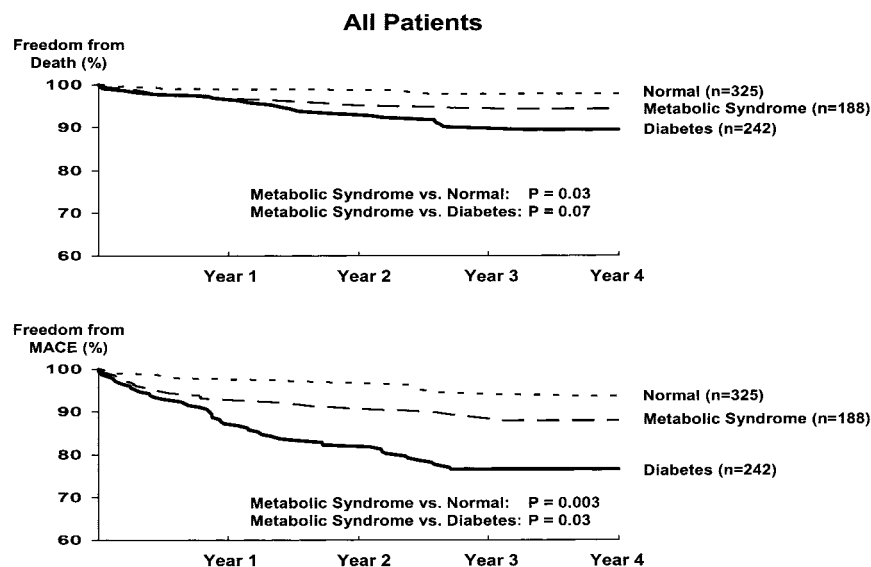


Figure 2. Four-year Kaplan-Meier plots of survival (top) and rates of freedom from MACE (death, nonfatal myocardial infarction, stroke, or congestive heart failure; bottom) by metabolic status at study entry.

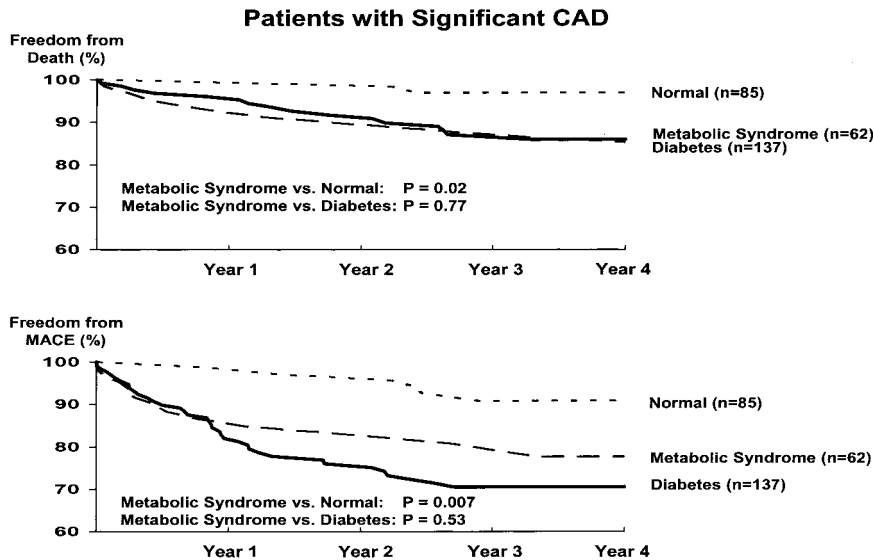


Figure 3. Among women with significant angiographic CAD at study entry (≥ 1 lesion $\geq 50\%$ stenosis), 4-year plots of survival (top) and freedom from MACE (death, nonfatal myocardial infarction, stroke, or congestive heart failure; bottom) by metabolic status at study entry.

significantly different among the 3 different groups. One possible explanation for these findings is the effect of insulin resistance on the coronary arteries. It is known that indices of insulin resistance predict atherosclerosis independently of other risk factors.¹² The present study confirmed that HOMA correlates strongly with the metabolic syndrome. However, our data suggest that the clinical definition of the metabolic syndrome is a more powerful predictor of adverse cardiovascular events than HOMA, which is a marker of insulin sensitivity. These findings suggest that insulin resistance may be the underlying cause of many, but not necessarily all, of the cardiovascular risks attributed to the metabolic syndrome.

Our findings improve the understanding of the effect of metabolic abnormalities on cardiovascular risk after stratification for the presence or absence of angiographic CAD and have important clinical implications. First, it appears that women with the metabolic syndrome who already have significant CAD are at very high risk of having adverse cardiovascular outcome. The increased risk approaches the cardiovascular risk conferred by diagnosed and treated dia-

betes. One possible explanation for this observation is that metabolic syndrome-associated inflammation may promote destabilization of preexisting atherosclerotic coronary artery plaques. Increased levels of inflammatory markers have been associated with increased cardiovascular events.^{4,11} The metabolic syndrome and diabetes are associated with systemic inflammation^{13,14} and a procoagulant state,¹⁵ which could result in increased propensity to plaque rupture and thrombosis^{16,17} and cardiovascular events.

Second, our study suggests, consistent with published expert opinions,¹⁸ that the absolute risk associated with the metabolic syndrome is variable. Specifically, we identified that there are metabolic syndrome patients who are at very high risk of adverse cardiovascular outcomes (such as the women with significant CAD), as well as those who are at only moderate or moderately high risk (such as the women with no significant CAD). However, we feel that regardless of the different pattern of risk based on the presence or absence of significant CAD in women, aggressive preventive therapy is warranted in women with metabolic abnormalities.

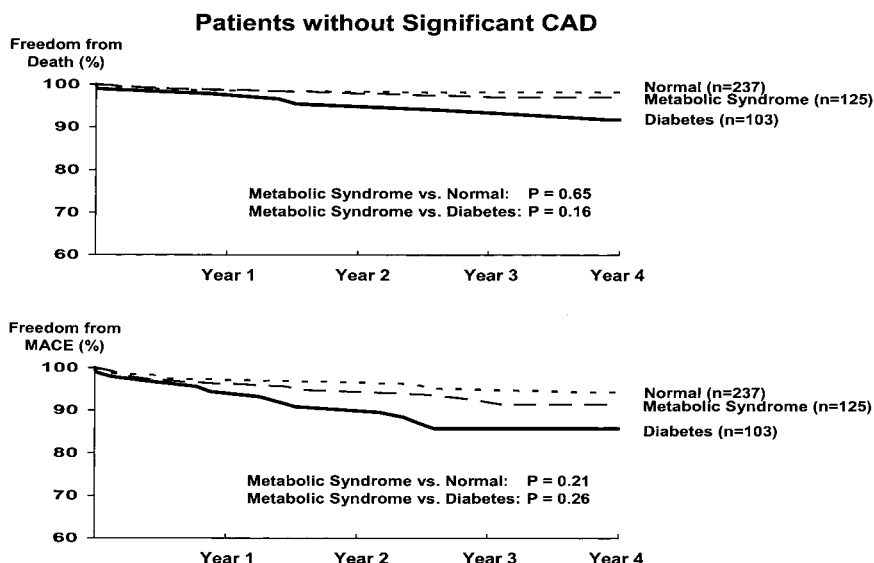


Figure 4. Among women without significant angiographic CAD at study entry (no lesion $\geq 50\%$ stenosis), 4-year plots of survival (top) and freedom from MACE (death, nonfatal myocardial infarction, stroke, or congestive heart failure) rates (bottom) by metabolic status at study entry.

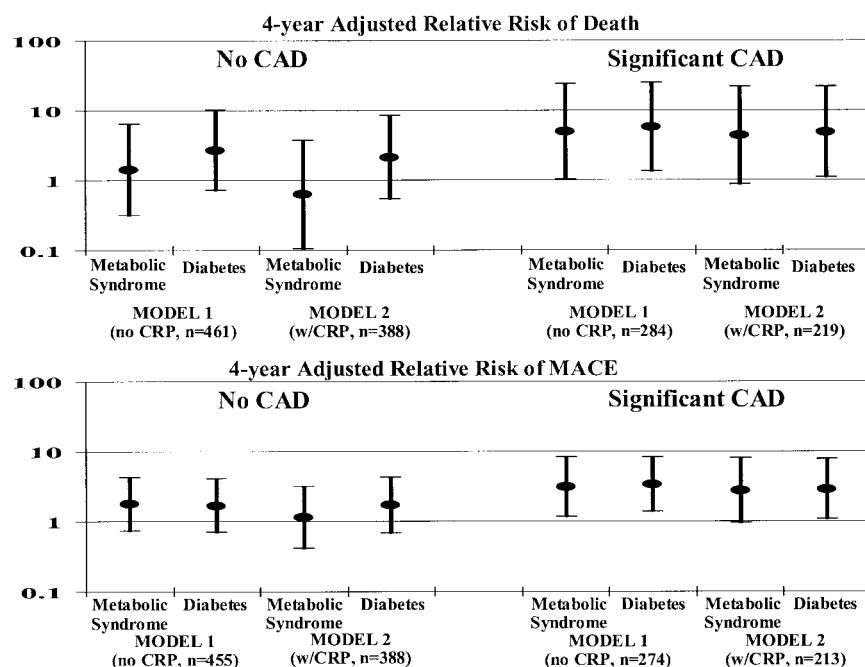


Figure 5. Four-year adjusted relative risks (bullets) and 95% CIs of death (top) and MACE (bottom) stratified by presence or absence of significant angiographic CAD ($\geq 50\%$ stenosis) at study entry, as by models without log hs-CRP (model 1) and with log hs-CRP (model 2) included. All models included adjustment for age and race, as well as various combinations of the following factors: history of CHF, use of lipid-lowering statins at study entry, use of aspirin at study entry, and use of antihypertensive drugs at study entry.

Study Limitations

The applicability of our results to the general population may be limited because our study involved a cohort of women with suspected myocardial ischemia that prompted coronary angiography. Furthermore, our subjects tended to be obese, with a high mean body mass index. This finding may explain the observation that levels of inflammatory markers in our study population were higher than those reported in some, but not all, previous studies of apparently healthy women.^{11,19} Although subjects in the present study tended to be obese, we did not control for body mass index in the statistical analyses because obesity is a central component of the definition of the metabolic syndrome. Rather, analyses were performed to evaluate the effect of the metabolic syndrome as a whole, not as the sum of its component factors. In addition, the prevalence of CAD in our population should not be used as an estimate of the prevalence of CAD in the general population because it is probably artificially high, especially compared with previous studies that used surrogate markers of CAD.⁵ All of our subjects had chest pain and were referred for coronary angiography, which may have introduced referral bias. However, we feel that rather than being a weakness, having information on the prevalence of angiographic CAD, the “gold standard” to diagnose CAD, is a significant strength of our study.

Conclusions

This study shows that the prevalence of angiographically significant CAD and the incidence of MACE increase in a gradient manner across the continuum of metabolic status from normal to the metabolic syndrome to diabetes in women with suspected myocardial ischemia. However, the influence of metabolic status on cardiovascular risk appears to depend on the presence or absence of angiographic CAD at study entry. In women with angiographically significant CAD at study entry, the metabolic syndrome significantly increases the risk of adverse cardiovascular outcomes, similar in magnitude to the effect of diabetes.

No such effect was seen in women without angiographically significant CAD at study entry. This finding should be hypothesis generating for future intervention studies testing different strategies to improve the risk associated with the metabolic syndrome in women both with and without angiographically significant CAD.

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References

- Lakka H-M, Laaksonen DE, Lakka TA, et al. The metabolic syndrome and total and cardiovascular mortality in middle aged men. *JAMA*. 2002; 288:2709–2716.
- Isomaa B, Almgren P, Tuomi T, et al. Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care*. 2001;24:683–689.
- Executive summary of the 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) *JAMA*. 2001;285:2486–2497.
- Ridker PM, Buring JA, Cook NR, et al. C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: an 8-year follow-up of 14, 719 initially healthy American women. *Circulation*. 2003;107:391–397.
- Alexander CM, Landsman PB, Teutsch SM, et al. NCEP-defined metabolic syndrome, diabetes, and prevalence of coronary heart disease among NHANES III participants age 50 years and older. *Diabetes*. 2003;52:1210–1214.
- Lindbald U, Langer RD, Wingard DL, et al. Metabolic syndrome and ischemic heart disease in elderly men and women. *Am J Epidemiol*. 2001;153:481–489.
- Wong ND, Sciammarella MG, Polk D, et al. The metabolic syndrome, diabetes, and subclinical atherosclerosis assessed by coronary calcium. *J Am Coll Cardiol*. 2003;41:1547–1553.
- Bairey Merz CN, Kelsey SF, Pepine CJ, et al. Women's Ischemia Syndrome Evaluation (WISE) study: protocol design, methodology and feasibility report. *J Am Coll Cardiol*. 1999;33:1453–1461.
- Sharaf B, Pepine CJ, Kerensky RA, et al. Detailed angiographic analysis of women with suspected ischemic chest pain (pilot phase data from the NHLBI-sponsored Women's Ischemia Syndrome Eval-

- uation [WISE] study angiographic core laboratory). *Am J Cardiol*. 2001;87:937–941.
10. 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;28:412–419.
 11. Ridker PM, Rifai N, Rose L, et al. Comparison of C-reactive protein and low density lipoprotein cholesterol levels in the prediction of first cardiovascular events. *N Engl J Med*. 2002;347:1557–1565.
 12. Hanley AJ, Williams K, Stern MP, et al. Homeostasis model assessment of insulin resistance in relation to the incidence of cardiovascular disease: the San Antonio Heart Study. *Diabetes Care*. 2002;25:1177–1184.
 13. Festa A, D'Agostino R Jr, Howard G, et al. Chronic subclinical inflammation as part of the insulin resistance syndrome: the Insulin Resistance Atherosclerosis Study (IRAS). *Circulation*. 2000;102:42–47.
 14. Saito I, Folsom AR, Brancati FL, et al. Nontraditional risk factors for coronary heart disease incidence among persons with diabetes: the Atherosclerosis Risk in Communities (ARIC) Study. *Ann Intern Med*. 2000;133:81–91.
 15. Juhan-Vague I, Thompson SG, Jespersen J, et al. Involvement of the hemostatic system in the insulin resistance syndrome. *Arterioscler Thromb*. 1993;13:1865–1873.
 16. Masseri A. Inflammation, atherosclerosis, and ischemic events: exploring the hidden side of the moon. *N Engl J Med*. 1997;336:1014–1016.
 17. Shah PK, Galis ZS. Matrix metalloproteinase hypothesis of plaque rupture. *Circulation*. 2001;104:1878–1880.
 18. Wilson PWF, Grundy SM. The metabolic syndrome: practical guide to origins and treatment: part I. *Circulation*. 2003;108:1422–1425.
 19. Haffner SM, Greenberg AS, Weston WM, et al. Effect of rosiglitazone treatment on nontraditional markers of cardiovascular disease in patients with type 2 diabetes mellitus. *Circulation*. 2002;106:679–684.