The Relationship Between Psychological Risk Attributes and the Metabolic Syndrome in Healthy Women: Antecedent or Consequence?

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The metabolic syndrome is an important risk factor for major chronic diseases in women. A key component of the syndrome, central adiposity, is correlated with psychological risk factors associated with coronary artery disease in prior epidemiological studies. We evaluated if psychological risk factors predicted the metabolic syndrome and if the metabolic syndrome predicted psychological distress. A population-based cohort of 425 women who were middle-aged, and pre-, peri-, and postmenopausal was followed for an average 7.4 years. Psychological risk factors, including depression, anxiety, tension, current perceived stress, and anger, and biological components of the metabolic syndrome, including glucose, triglycerides, high-density lipoprotein (HDL)-cholesterol, waist circumference, and blood pressure (BP) were measured at baseline and at examinations 1 to 8 years postmenopause. Women were classified according to the National Heart, Lung, and Blood Institute (NHLBI) criteria for metabolic syndrome. Women who exhibited high levels of depression, tension, and anger at baseline, and increased in anger during the follow-up had elevated risk for developing the metabolic syndrome during follow-up, $P < .04$. The metabolic syndrome at baseline, in turn, predicted increasing anger and anxiety 7.4 years later, $P < .001$. Psychological risk factors affect the development of the metabolic syndrome. The association between anger and the metabolic syndrome is reciprocal. Reduction in the level of psychological distress may prevent the development of the metabolic syndrome in women.

THE METABOLIC SYNDROME is a cluster of metabolic, anthropometric, and hemodynamic disorders, including insulin resistance, hyperinsulinemia, glucose intolerance, dyslipidemia, central obesity, and hypertension. These factors independently and in combination increase the risk for cardiovascular disease and noninsulin-dependent diabetes mellitus.[1-4] In addition to behavioral lifestyle factors, such as physical activity, cigarette smoking, psychological traits, such as anger and depression may be involved in the etiology of the metabolic syndrome.[5,6] Available data are consistent with this psychosocial hypothesis, but are mainly based on individual components of the syndrome.[7-20] The cross-sectional nature of most data[7-11,13-16,19-23] raises the possibility that the psychological attributes are a consequence of the metabolic syndrome, not an antecedent factor. Indeed, in a lifestyle intervention trial on the effects of a low-fat diet, healthy premenopausal women significantly reduced lipid and glucose levels, weight, central obesity, and blood pressure (BP),[24,25] along with psychological distress.[26]

Here we report the associations between psychological attributes and the metabolic syndrome[3] in 425 middle-aged women participating in the Healthy Women Study (HWS)[27,28] across an average interval of 7.4 years. Prospective associations between the psychological attributes and BP, hypertension, and waist circumference taken separately have been reported elsewhere.[12,18,29] We expected that depression, anxiety, tension, current perceived stress, and anger, all related to risk for coronary artery disease,[30,31] would be associated with the development of the metabolic syndrome over the 7.4 years. We tested whether the metabolic syndrome would also predict changes in these psychological attributes across the study period.

MATERIALS AND METHODS

Subjects and Procedure

Participants in this study were drawn from the HWS, a prospective study of the changes in behavioral and biological characteristics of women during the climacteric. In 1983 to 84, 541 participants were recruited from a random sample of licensed drivers in Allegheny County, PA. Women eligible for the study met the following criteria: ages 42 to 50 years at study entry, menstruating within the past 3 months and not taking hormone replacement, diastolic BP < 100 mm Hg, not surgically menopausal, not diagnosed with diabetes or with hypertension, and not taking thyroid, lipid-lowering, or psychotropic medications. Of the sample, 90.6% were Caucasian (n = 490) and 8.9% (n = 48) African American (2 participants were Hispanic Americans and 1 was Indian American). The Institutional Review Board at the University of Pittsburgh approved this project; all subjects gave informed consent.

Eighty-nine percent of women who were contacted agreed to a telephone interview, and 60% of those who were eligible agreed to participate. Comparisons of the women who participated in the HWS and declined participation have been published previously[28]; participants were better educated and were employed in higher-paying jobs than either those who were ineligible or those who declined participation. Complete details of the HWS protocol can be found elsewhere.[27,28]

Women underwent clinic exams at study entry and within the next 3 years. Women returned cards monthly to indicate whether they had menstruated. Once classified as postmenopausal (defined as 12 successive months without menstruating), women returned for a follow-up examination, and then at years 2, 5, and 8 postmenopause.

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Since measurement of waist was added late to the study entry protocol (only n = 120, 22.2%, had their waists measured), the exam at an average 2.8 (SD = 0.6, range = 0.7 to 6.3) years from study entry evaluation was considered as the baseline for the present analyses. The study sample comprised of women who had data available simultaneously on metabolic, anthropometric, and hemodynamic measures at baseline (N = 475) and at least 1 of the follow-up exams across an average interval of 7.4 (SD = 2.2, range 0.6 to 10.6) years from baseline (N = 425). Through the eighth postmenopausal exam, 8 women had died and 52 had withdrawn from the study, the remaining not included in the analysis were missing a blood draw, typically because they moved out of the study area. Of the 425 women in the present analysis, 250, 63, and 112 were pre-, peri-, and postmenopausal, respectively, at baseline, and the follow-up exams were conducted 1 to 8 years postmenopause.

Measures

Metabolic syndrome. Blood draw was collected in the morning after a 12-hour fast. Glucose was analyzed by enzymatic assay (Yellow Springs Glucose Analyzer, Yellow Springs, OH), triglycerides and total high-density lipoprotein-cholesterol (HDL-C) were measured in the lipid laboratory of the Graduate School of Public Health, which has been certified by the Centers of Disease Control and Prevention, Atlanta, GA; waist was measured at the smallest circumference; BP was measured 3 times on 2 occasions 2 hours apart with a random zero muddler sphygmomanometer, the final overall reading being the average of the last 2 readings of these 2 assessments.

The metabolic syndrome was defined according to the NHLBI criteria[3] as the presence of 3 or more of the following: fasting glucose $\geq$ 110 mg/dL; triglycerides $\geq$ 150 mg/dL; HDL-C $<$ 50 mg/dL; waist circumference $>$ 88 cm; and systolic BP $\geq$ 135 and diastolic BP $\geq$ 85.

Standardized measures of psychological risk. The subjects completed the Beck Depression Inventory for depressive symptoms,[32] the Framingham Tension Scale for tension,[33] the Spielberger Trait Anxiety Questionnaire for anxiety,[34] the Cohen Perceived Stress Scale for current level of stress,[35] and the Spielberger Trait Anger Questionnaire for anger.[36] The scales have good internal consistency and good test-retest reliability.[32-36]

Measures of behavioral lifestyle factors. Cigarette smoking was measured by current status of smoking (yes/no) and alcohol intake by the amount of alcohol per day converted into grams of absolute alcohol (g/d). The Paffenbarger activity questionnaire was used to measure kilocalories per week spent in leisure-time activity.[37]

Statistical Analyses

Cross-sectional associations between the psychological attributes and the metabolic syndrome (the number of coexisting metabolic syndrome disorders served as the grouping factor) at baseline were tested using univariate analyses of covariance (ANCOVA). Cox proportional hazards models (assumptions tested and met) evaluated the risk for developing the metabolic syndrome during the 7.4-year follow-up period, first, in relation to the psychological attributes measured at baseline, and second, in relation to the change in the level of the psychological attributes until the date of meeting the metabolic syndrome criteria or until the endmost follow-up for those not meeting the criteria. ANCOVAs tested whether the metabolic syndrome status at the starting point of the current study predicted change in the psychological attributes until the date for those meeting the metabolic syndrome criteria and until the endmost follow-up for those who did not meet the criteria. In addition to behavioral lifestyle factors, the analyses took into account the potential confounding of age, menopausal status, use of hormone replacement therapy, and years of education as measured at baseline. Scaling corrections were computed for non-normally distributed variables where appropriate.

RESULTS

Criteria for the metabolic syndrome were met by 5.9% (n = 25) of the sample at baseline and 16.9% (n = 72) during the 7.4 years. Of the 72 women, 50 developed the metabolic syndrome during the follow-up, 22 met the criteria at both baseline and during the follow-up, and 3 at baseline only; 350 women remained free from the metabolic syndrome throughout the study. Not surprisingly, women who met the metabolic syndrome criteria at the baseline exhibited a higher level of the

Table 1. Characteristics of Women According to the Number of Risk Factors Comprising the Metabolic Syndrome at Baseline

	No. of Metabolic Syndrome Risk Factors					
	0 (n = 256)	1 (n = 109)	2 (n = 35)	3–5 (n = 25)	*P* Value*	*P* Value†
Fasting glucose (mg/dL)	85.2 (7.5)	87.6 (8.1)	91.6 (12.5)	111.3 (33.7)	< .001	< .001
HDL total cholesterol (mg/dL)	65.7 (11.4)	52.1 (12.4)	44.4 (8.0)	40.5 (7.2)	< .001	< .001
Triglycerides (mg/dL)	70.6 (26.9)	92.0 (43.8)	153.7 (66.1)	197.0 (69.5)	< .001	< .001
Waist (cm)	72.4 (7.3)	80.2 (9.9)	91.0 (14.0)	98.9 (11.8)	< .001	< .001
Systolic blood pressure (mm Hg)	105.2 (10.7)	109.1 (15.5)	113.7 (14.4)	121.6 (12.8)	< .001	< .001
Diastolic blood pressure (mm Hg)	72.0 (7.9)	73.8 (9.8)	77.5 (9.7)	79.8 (10.12)	< .001	< .001
Age (yr)	50.4 (1.4)	50.3 (1.7)	50.6 (1.6)	50.9 (1.6)	.16	.11
Years of education (% with high school or less)	22.7	33.0	42.9	48.0	.05	.01
Menopausal status (% postmenopausal)	24.2	25.7	40.0	32.0	.08	.01
Hormone replacement therapy (% yes)	8.6	14.7	20.0	4.0	.26	.32
Physical activity (kcal/wk)	1,783.4 (1,536.5)	1,477.7 (1,640.1)	1,250.7 (1,235.2)	1,177.2 (1,390.7)	.14	.05
Alcohol (g/d)	14.7 (14.6)	13.5 (13.0)	15.4 (16.6)	11.5 (13.0)	.31	.41
Smoking (yes %)	21.5	29.4	31.4	32.0	.40	.06

NOTE. Values are mean (SD) or %.

**P* values are from analyses comparing those with (3 to 5 risk factors) and without (0 to 2 risk factors) the metabolic syndrome.

†*P* values are from analyses testing whether a trend from 0, 1, 2 to 3, 4 or 5 risk factors is linear.

Table 2. Concurrent Associations Between Psychological Scores and the Number of Risk Factors Comprising the Metabolic Syndrome

	No. of Metabolic Syndrome Risk Factors					
	0 (n = 256)	1 (n = 109)	2 (n = 35)	3–5 (n = 25)	*P* Value*	*P* Value†
Beck Depression Inventory	4.3 (4.6)	4.5 (4.9)	6.5 (6.3)	7.1 (7.2)	.01	.002
Trait Anxiety	16.9 (4.7)	17.4 (4.6)	19.0 (5.6)	18.9 (4.8)	.08	.01
Framingham Tension	0.25 (0.30)	0.26 (0.29)	.34 (0.33)	0.38 (0.36)	.06	.02
Trait Anger	17.0 (3.9)	18.0 (4.3)	18.5 (4.3)	19.1 (4.9)	.05	.01
Cohen Perceived Stress	11.6 (3.7)	11.6 (4.4)	12.6 (4.2)	12.6 (3.7)	.32	.16

NOTE. Values are mean (SD) test scores.

*P value is from an ANOVA comparing those with (3 to 5 risk factors) and without (0 to 2 risk factors) the metabolic syndrome.

†P value is from an ANOVA testing whether a trend from 0, 1, 2 to 3, 4 or 5 risk factors is linear.

individual risk factors comprising the metabolic syndrome, spent fewer kilocalories per week in leisure-time activity (linear trend only), as well as had fewer years of education than did their counterparts (Table 1). Cox regression models showed that women who developed the metabolic syndrome during follow-up (n = 50 *v* 350) had fewer years of education (Hazards ratio = .78, 95% confidence interval [CI] = 0.6 to 1.0), were postmenopausal (hazards ratio = 1.6, 95% CI = 1.1 to 2.2), were on hormone replacement therapy (hazards ratio = 2.2, 95% CI = 1.0 to 4.7), and used less alcohol daily (hazards ratio = .97, 95% CI = 0.95 to 0.99) at baseline. When the significant effects were entered simultaneously into the regression equation, postmenopausal status ($P < .03$) and alcohol consumption ($P < .02$) remained significant independent predictors of the metabolic syndrome (data not shown). Menopausal status and hormone replacement therapy were not tested simultaneously because of their collinearity ($P < .0001$). Based on these analyses, years of education, menopausal status, physical activity, and alcohol consumption were used as covariates in the subsequent analyses.

Cross-Sectional Associations Between Psychological Attributes and the Metabolic Syndrome

Table 2 shows the cross-sectional associations of the psychological attributes and the metabolic syndrome at baseline. Women who met the criteria of the metabolic syndrome had higher scores on the Beck Depression Inventory; higher Trait Anxiety and Framingham Tension scores (linear trend only); and higher Spielberger Trait Anger scores, relative to women who did not meet the metabolic syndrome criteria. Cohen Perceived Stress scores were not significantly associated with the metabolic syndrome. Pearson correlations between the scores of depression, anxiety, tension, anger, and stress were significant and ranged between 0.37 to 0.63, $P < .001$.

Psychological Attributes and Development of the Metabolic Syndrome

Table 3 shows that women who had higher Beck depression, Framingham Tension, and Spielberger Trait Anger scores at baseline had elevated risk for developing the metabolic syndrome during the follow-up. The other psychological attributes measured at the current study starting point were not significantly associated with the risk for developing the metabolic syndrome.

Further, the risk for developing the metabolic syndrome during the 7.4 years was increased for women who experienced an increase in Spielberger Trait Anger (scores as standardized) from baseline to the follow-up exam (hazards ratio = 2.02, 95% CI = 1.50 to 2.72). Change in the other psychological attributes during the follow-up period did not predict the risk for developing the metabolic syndrome during the 7.4 years ($P > .07$; data not shown).

Metabolic Syndrome and Change in the Psychological Attributes

Spielberger Trait Anger and Trait Anxiety were the only significant psychological attributes that increased in response to the metabolic syndrome. Relative to women who did not have the metabolic syndrome, women who were classified as having the metabolic syndrome at baseline experienced a greater increase in Spielberger Trait Anger (M = −0.67 *v* 1.37, $P < .001$) and Trait Anxiety (M = −0.55 *v* 1.68, $P < .001$) across the follow-up. Figure 1 shows the percentage change in scores. The increase in the Spielberger Trait Anger and Trait Anxiety scores for women who exhibited 0 to 5 risk factors was linear, $P < .001$ for linear trends. Mean levels of follow-up minus baseline levels (controlling for the baseline levels), were, respectively, for Trait Anger and Trait Anxiety −0.95 and −0.59 for women with 0 risk factors, −0.25 and −0.46 for women with 1 risk factor, 0.05 and −0.57 for women with 2 risk factors, and 1.39 and 1.69 for women with 3 to 5 risk factors. There were no other significant associations between the metabolic syndrome and change in psychological risk attributes. Statistical controls for years of education, menopausal status, physical activity, or alcohol consumption did not alter the significant results (data not shown).

Table 3. Risk for Developing the Metabolic Syndrome Across the Follow-up According to Psychological Scores at Baseline

Psychological Scores	B	Hazards Ratio (95% CI)
Beck Depression Inventory	0.26	1.29 (1.03-1.62)
Trait Anxiety	0.02	1.02 (0.77-1.34)
Framingham Tension	0.28	1.31 (1.01-1.72)
Trait Anger	0.38	1.47 (1.14-1.89)
Cohen Perceived Stress	0.23	1.26 (0.96-1.66)

NOTE. B is unstandardized regression coefficient; psychological scores were standardized before entry to the Cox regression model.

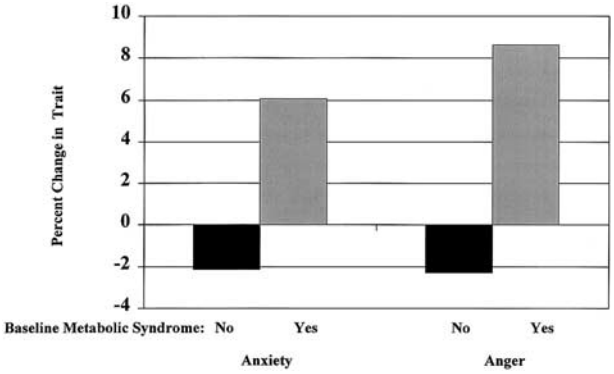

Fig 1. Metabolic syndrome status at baseline as a predictor of percent change in Trait Anger and Trait Anxiety scores across 7.4 years.

DISCUSSION

The present study tested the associations between psychological attributes and the clustering of cardiovascular risk factors, which comprise the metabolic syndrome among middle-aged women across an average of 7.4 years of follow-up. The longitudinal design of the study allowed us to address the potentially reciprocal nature of the associations, ie, whether the psychological risk factors predicted the risk for developing the metabolic syndrome during 7.4 years, and whether the metabolic syndrome, in turn, predicted increasing psychological risk.

We found that high baseline levels and/or increase across the average interval of 7.4 years in depression, tension, and anger predicted the risk for developing the metabolic syndrome during the 7.4 years. The metabolic syndrome did not, however, influence increasing depression or tension during the 7.4 years. However, feelings of anger both predicted and were predicted by the metabolic syndrome across the follow-up period. In addition, the results showed that while anxiety did not predict the risk for developing the metabolic syndrome, metabolic syndrome predicted increasing anxiety during the 7.4 years. The present study is, thus, the first one to test both the psychological influences on the development of metabolic syndrome as well as the reciprocal effect of the metabolic syndrome on psychological attributes.

The literature suggests multiple mechanisms that may account for the significant associations between psychological attributes and the metabolic syndrome cluster. The neuroendocrine dysregulation hypothesis proposes that unpleasant social conditions perceived as stressful trigger neuroendocrine and hemodynamic responses in preparation for coping.[5,6] One reaction is the well-known fight or flight reaction associated with the activation of the sympathetic nervous system. The other one is the defeat reaction characterized by apparent loss of control and is accompanied by increased activity of the hypothalamic-pituitary-adrenocortical (HPA) axis. The sensitized HPA axis is also reflected in elevated androgens in women and in altered secretion of sex-steroids and growth hormones.[38] Stress-initiated chronic neuroendocrine and sympathetic dysregulation may result over time in metabolic and anthropometric changes that characterize the metabolic syndrome.[5,6]

Alcohol intake, smoking, and decreased physical activity are also known to have sympathetic, endocrine, and metabolic-anthropometric consequences.[5,6,39,40] Thus, another possible pathway through which depression, tension, and anger may operate is the health-related behaviors. Statistical controls for alcohol and physical activity did not alter the significant associations, and smoking and the metabolic syndrome were not significantly associated in the current study, ruling out these as mediational influences in the present study. Finally, Bouchard et al[6] suggest that susceptibility to stress exposure and neuroendocrine dysregulation and their consequences on the metabolic syndrome profile are influenced by DNA sequence variation at a number of loci. Clearly, all possible pathways and predisposing factors need further, intense examination.

There are limitations to our study. The health of our population-based sample may have, at least to some extent, restricted the variance of the key variables. Consequently, the statistical power and significance levels of the associations may rather be reduced. Also, we conducted multiple statistical tests, perhaps increasing the possibility for type 1 error. However, the psychological attributes chosen for analysis were based on their associated risk for coronary artery disease.[30,31] Finally, the sample consisted of mostly Caucasians, limiting the external validity of the findings for other ethnic groups.

In conclusion, depression, anxiety, tension, and anger are associated concurrently with and/or predict the risk for developing the metabolic syndrome, defined via fasting glucose, triglycerides, HDL-C, central obesity, and BP in middle-aged women during an average follow-up interval of 7.4 years. The metabolic syndrome also led to increasing levels of anger and anxiety over time, suggesting that the association between psychological attributes and the metabolic syndrome may be reciprocal. A clinical implication of these findings is that interventions designed to reduce psychological distress may also prevent risk of developing the metabolic syndrome. Given the importance of the metabolic syndrome for women's health, such interventions may be particularly advantageous to women.

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