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Psychological risk factors and the metabolic syndrome in patients with coronary heart disease: Findings from the Heart and Soul Study

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ABSTRACT

Psychological factors, such as depression and anxiety, are independently associated with an increased risk of both diabetes mellitus and cardiovascular disease, but the reasons for these associations are unknown. We sought to determine whether psychological factors were associated with a greater prevalence of the metabolic syndrome in patients with coronary heart disease, and the extent to which such an association may be explained by socioeconomic status, health behaviors, and biological mediators. We conducted a cross-sectional study of 1024 outpatients with stable coronary heart disease. Psychological factors, including depressive and anxiety symptoms, hostility, anger, and optimism–pessimism, were assessed using validated standardized questionnaires. The presence or absence of the metabolic syndrome was determined using the criteria outlined by the National Cholesterol Education Program, Adult Treatment Panel III. Higher levels of depression, anger expression, hostility, and pessimism were significantly associated with increased prevalence of the metabolic syndrome. These associations were explained by differences in socioeconomic status and health behaviors. Additional adjustment for potential biological mediators had little impact. Further research is needed to determine whether addressing socioeconomic and behavioral factors in people with depression or high levels of anger or hostility could reduce the burden of the metabolic syndrome.

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1. Introduction

Substantial evidence indicates that psychological factors are independent risk factors for chronic physical illness (Vitaliano et al., 2002). Many studies have found that depressive disorders are associated with increased incident cardiovascular events, re-hospitalizations, and cardiovascular mortality both in patients with overt cardiac disease and in the general population (Jiang et al., 2005; Shimbo et al., 2005). Depression is also an independent predictor of the development of Type II diabetes, and of poorer glycemic control among patients with existing diabetes mellitus (Eaton et al., 1996; Eaton, 2002; Katon et al., 2004; Brown et al., 2005; Sundaram et al., 2007). In addition to depression, other psychological factors such as anger, hostility, and anxiety have also been linked to increased risk of cardiovascular disease (Januzzi et al., 2000; Todaro et al., 2003; Rozanski et al., 2005).

Part of the connection between psychological factors and heart disease may be attributed to the clustering of several cardiovascular disease risk factors known as the *metabolic syndrome* (Vitaliano et al., 2002). Since individuals with the metabolic syndrome have greatly increased incidence of cardiovascular mortality and of diabetes, a better understanding of risk factors for the metabolic syndrome is needed to prevent its associated morbidity and mortality (Isomaa et al., 2001). Psychological factors have been linked to individual components of the metabolic syndrome, such as increased insulin resistance, hypertension, and abdominal obesity (Raikkonen et al., 1996; Kulkarni et al., 1998), and to the metabolic syndrome as a whole (Vaccarino et al., 2008). However, the association between psychological factors and the metabolic syndrome has never been studied in adults with established coronary heart disease, a group likely to be at highest risk of adverse cardiac outcomes. In addition, the mechanisms through which psychological factors elevate metabolic risk are unclear.

The aim of this study was to investigate the association between multiple psychological factors, including depression, stress, hostility, anxiety, and anger, and the metabolic syndrome in a large cohort of patients with stable coronary heart disease. We also explored the extent to which socioeconomic status, health behaviors, and markers of inflammation explained these associations.

2. Materials and methods

2.1. Participants

The Heart and Soul Study is a prospective cohort study of psychological factors and health outcomes in adults with stable coronary heart disease (CHD). A total of 1024

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ambulatory men and women with established CHD were enrolled between September 2000 and December 2002. Participants were recruited from two Department of Veterans Affairs Medical Centers (San Francisco Veterans Affairs Medical Center and the Veterans Affairs Palo Alto Health Care System), one university medical center (University of California, San Francisco), and nine public health clinics (Community Health Network of San Francisco). To be eligible, participants needed a history of a myocardial infraction, angiographic evidence of stenosis of 50% or greater in one or more coronary vessels, evidence of exercise induced ischemia (by treadmill electrocardiogram or stress nuclear perfusion), or a history of coronary revascularization. Individuals unable to walk one block or those planning to leave the area within 3 years were excluded. Informed consent was obtained from all participants, and appropriate institutional review boards approved the research protocol.

2.2. Psychological instruments

At the time of enrollment, participants completed a series of validated measures of psychological variables. Depressive symptoms were assessed with the validated nine-item Patient Health Questionnaire (PHQ) (Spitzer et al., 1999). The PHQ provides both a continuous and dichotomous measure of depressive symptoms. A score of 10 or higher has a sensitivity of 88% and a specificity of 88% for major depressive disorders (Kroenke et al., 2001). Hostility was measured using the Cynical Distrust Scale, which was factor-analytically derived from the Cook–Medley hostility scale, and shown to be a more specific measure of cynical distrust than the longer scale (Greenglass and Julkunen, 1989). This eight-item Likert-type scale has a four-point response format ranging from 1 to 4. Possible ranges of scores for this scale are between 0 and 24, and higher scores indicate a greater level of hostility.

Levels of anxiety were measured using the anxiety subscale of the Hospital Anxiety and Depression scale (HADS), which has been validated in psychiatric, primary care, and general population samples (Zigmond and Snaith, 1983; Herrmann, 1997; Bjelland et al., 2002). Questions from this seven-item scale are scored on a scale from 0 to 3. Scores range from 0 and 21, with higher scores indicating greater anxiety.

Anger was measured using the State-Trait Anger Expression Inventory (STAXI). The Anger-In scale is an eight-item scale that measures the frequency with which the respondent holds in or suppresses his or her anger. The Anger-Out scale is an eight-item scale that measures the frequency with which the respondent expresses his or her anger to other people or objects. All items are rated on a four-point scale, with scores ranging from 8 to 32. Higher scores represent higher levels of anger suppression/expression, and the STAXI has shown good convergent and divergent validity in prior studies (Spielberger et al., 1985; Spielberger, 1988).

Optimism–pessimism was measured using the Life Orientation Test (LOT) (Scheier et al., 1989). The LOT consists of six items that evaluate respondents' generalized expectations of negative and positive outcomes. The respondents were asked to rate the extent to which they agreed with the items on a four-point scale. Possible ranges of scores for this scale are between 0 and 24 with higher scores indicating greater optimism. The LOT has shown good construct validity and internal consistency in prior studies (Scheier et al., 1989).

2.3. Metabolic syndrome

The presence or absence of the metabolic syndrome was determined using the criteria outlined by the National Cholesterol Education Program, Adult Treatment Panel III. Individuals were considered to have the metabolic syndrome if they met three or more of the following criteria: abdominal obesity (waist circumference >40 in. for men, >35 in. for women); fasting serum triglycerides ≥150 mg/dL; low fasting serum high-density lipoprotein (HDL) cholesterol (<40 mg/dl in men, <50 mg/dl in women); systolic blood pressure ≥130 mmHg, diastolic blood pressure ≥85 mmHg; and fasting serum glucose ≥110 mg/dl or use of diabetic medications (Executive Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol In Adults, 2001). Because all subjects in our study sample had CHD, and the majority were taking antihypertensive and lipid-lowering statins for their cardiac protective effects, we did not consider use of these medications when evaluating hypertension or dyslipidemia (Spies et al., 2005; Ix et al., 2006).

2.4. Potential confounding and mediating variables

Age, race/ethnicity, annual household income, education, smoking status, alcohol use, and physical activity were obtained by self-report on baseline questionnaires (Lubbock et al., 2005). Participants brought their medication bottles to the baseline study visit, and research assistants recorded medication use. Height, weight, and waist circumference were measured at the baseline visit and body mass index (BMI) was calculated in kilograms per meter squared. Systolic and diastolic blood pressures were measured by sphygmomanometer. Participants were instructed to take their anti-hypertensive medications on the morning of the appointment and to not smoke or consume caffeine 5 h prior to the visit. Blood pressure measurements were recorded according to guidelines in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of Hypertension (Chobanian et al., 2003). Venous blood samples were obtained after a 12-h fast to measure total cholesterol, HDL, low-density lipoprotein (LDL), glycosylated hemoglobin, blood glucose levels, and inflammatory biomarkers (fibrinogen and tumor necrosis factor alpha (TNF-alpha), interleukin 6 (IL-6), and C-reactive protein (CRP)). The techniques used to measure these biomarkers have been described previously (Marcus et al., 2008; Shlipak et al., 2008).

2.5. Statistical analysis

The goal of this study was to examine the association of multiple psychological factors with the metabolic syndrome. Differences in characteristics between participants with and without the metabolic syndrome were compared with Student's *t*-test for continuous variables and chi-square tests for dichotomous variables.

We constructed separate logistic regression models for each psychological predictor variable, using diagnosis of metabolic syndrome as the outcome. Since each of our psychological questionnaires had a different range of scores, we determined the change in prevalence of the metabolic syndrome per standard deviation of continuous, normally distributed psychological questionnaire score.

To explore the effect of potential confounding and mediating variables on the association between psychological distress and the metabolic syndrome, we developed serially adjusted nested logistic regression models. In the primary model, we adjusted for potential confounding variables (age, sex, and race/ethnicity). In the second model, we also adjusted for socioeconomic status (income and education). The third model also adjusted for non-biological variables that may mediate this association (physical activity, smoking, alcohol use, and BMI). The fourth and final model also included potential biological mediators (antidepressant use, fibrinogen, TNF-alpha, log IL-6, and log CRP).

We ran additional sensitivity analyses entering these sets of mediators into the serially adjusted models in different orders. Potential confounding and mediating variables were selected based on their relevance to psychological factors and the metabolic syndrome in prior studies (Vitaliano et al., 2002; Spies et al., 2005; Ix et al., 2006). Although the majority of covariates were associated with the metabolic syndrome with *P*-values<0.20, this was not required for inclusion in the models. We also conducted a sensitivity analysis that excluded hypertension from the definition of the metabolic syndrome. Results from logistic regression models are reported as beta coefficients with 95% confidence intervals. We tested for interactions between the psychological predictors and the socioeconomic and behavioral covariates (income,

Table 1
Characteristics of participants according to presence or absence of the metabolic syndrome.[a]

	Metabolic syndrome	No metabolic syndrome	*P* value
	N=415	*N*=609	
Demographics			
Age, years	66±10	67±11	0.04
Male	317 (76)	523 (86)	0.0001
White	247 (60)	368 (61)	0.75
Income ($)			<0.0001
<20,000	232 (56)	266 (44)	
20,000–49,999	129 (31)	202 (33)	
>50,000	51 (12)	138 (23)	
Education			0.005
≤11 years	57 (14)	74 (12)	
High school graduate	237 (57)	299 (49)	
≥College graduate	119 (29)	236 (39)	
Health behaviors			
Body mass index	31±5	27±4	<0.0001
Smoking	77 (19)	124 (20)	0.45
Regular alcohol (≥4×/wk)	99 (24)	194 (32)	0.005
Physically active	232 (56)	417 (69)	<0.0001
Medication use			
Beta blockers	267 (64)	326 (54)	0.0006
Statins	276 (67)	381 (63)	0.20
ACE inhibitors/ARB	246 (59)	278 (46)	<0.0001
Aspirin	343 (83)	449 (74)	0.0008
Antidepressants	96 (23)	92 (15)	0.001
LABS			
Glycosylated hemoglobin	6.4±1.5	5.7±0.8	<0.0001
LDL-cholesterol	103±36	105±33	0.29
Fibrinogen	407±90	382±89	<0.0001
Log (IL-6)	1.1±0.7	0.9±0.7	0.0001
TNF-alpha	5.0±4.7	4.5±4.3	0.08
Log (CRP)	0.97±1.2	0.53±1.3	<0.0001
Metabolic syndrome components, *n* (%)			
Abdominal obesity	312 (77)	152 (26)	<0.0001
Elevated triglycerides	237 (57)	68 (11)	<0.0001
Low HDL-cholesterol	286 (69)	134 (22)	<0.0001
Hypertension	323 (78)	264 (44)	<0.0001
Hyperglycemia	322 (78)	168 (28)	<0.0001

[a] Values shown are means±S.D. or numbers of participants (percentages).

Table 2
Correlation of psychological predictor variables.

	Depression	Anger in	Anger out	Hostility	Anxiety	Pessimism
Depression		0.45	0.25	0.29	0.64	0.46
Anger in			0.32	0.38	0.52	0.41
Anger out				0.19	0.35	0.19
Hostility					0.26	0.38
Anxiety						0.44

education, BMI, smoking, regular alcohol use, and physical activity). All tests of significance were two-tailed (alpha = 0.05). Analyses were conducted using Statistical Analysis Software (version 8, SAS Institute, Cary, North Carolina).

3. Results

Table 1 shows the baseline characteristics of participants with versus without the metabolic syndrome and shows the prevalence of the five metabolic syndrome components. Individuals with the metabolic syndrome were younger, less likely to be male, and more likely to be of lower socioeconomic status. In addition, they had higher body mass index, glycosylated hemoglobin, and levels of inflammatory biomarkers. Participants with the metabolic syndrome were also less physically active, less likely to drink alcohol, and more likely to be taking cardioprotective medications.

Table 2 shows the correlation of the psychological factors, most of which showed low to moderate correlation. Correlations between the different psychological measurements ranged from 0.19 for hostility and anger to 0.64 for anxiety and depression. Table 3 compares the psychological characteristics of participants with and without the metabolic syndrome. Higher levels of depression, anger expression, hostility, and pessimism were significantly associated with increased prevalence of the metabolic syndrome. Adjustment for age, sex, and race/ethnicity weakened the association between psychological factors and the metabolic syndrome (Table 4). However, further adjustment for socioeconomic status and health behaviors virtually eliminated the association. Adjustment for possible biological mediators (use of antidepressant medications, fibrinogen, insulin, IL-6 and CRP) did not substantially change the results. Entering the sets of mediators in different orders or excluding hypertension from the metabolic syndrome criteria did not change our conclusions.

We found no evidence that the association between psychological variables and the metabolic syndrome differed by income, smoking, BMI, regular alcohol use, or physical activity. The association between pessimism and the metabolic syndrome seemed to be stronger in better educated participants (P for interaction = .009). Among patients with a college education, pessimism was strongly associated with an increased risk of the metabolic syndrome ($P = 0.004$). However, pessimism was not associated with metabolic syndrome in non-college educated patients, either with ($P = 0.12$) or without ($P = 0.46$) a high school degree.

Table 3
Psychological characteristics of participants according to presence or absence of the metabolic syndrome.

Psychological variable	Metabolic syndrome $N = 415$	No metabolic syndrome $N = 609$	P value
Depression (PHQ-9>=10), n(%)	95 (23)	104 (17)	0.02
Depression (PHQ-9 mean ± S.D.)	5.7 ± 5.8	4.8 ± 5.2	0.007
Anger in (mean ± S.D.)	14.6 ± 3.8	14.4 ± 4.1	0.38
Anger out (mean ± S.D.)	13.6 ± 3.2	13.2 ± 3.4	0.05
Hostility (mean ± S.D.)	3.2 ± 2.3	2.9 ± 2.3	0.05
Anxiety (mean ± S.D.)	5.7 ± 4.0	5.2 ± 3.9	0.07
Optimism–Pessimism (mean ± S.D.)[a]	14.7 ± 4.0	15.5 ± 4.0	0.002

[a] Higher scores indicate greater optimism.

Table 4
Unadjusted and adjusted associations of psychological variables with the metabolic syndrome.

	Unadjusted beta coefficient (95% CI)	Adjusted[a] beta coefficient (95% CI)	Adjusted[b] beta coefficient (95% CI)	Adjusted[c] beta coefficient (95% CI)
Depression (PHQ-9 score)	0.031[d] (0.01–0.06)	0.023 (−0.001–0.05)	0.016 (−0.01–0.04)	0.003 (−0.02–0.03)
Anger in	0.014 (−0.02–0.05)	0.006 (−0.02–0.04)	0.004 (−0.03–0.04)	0.006 (−0.03–0.04)
Anger out	0.038[d] (0.0003–0.08)	0.031 (−0.01–0.07)	0.033 (−0.01–0.08)	0.026 (−0.02–0.07)
Hostility	0.054[d] (0.0002–0.10)	0.060[d] (0.00–0.11)	0.033 (−0.02–0.10)	−0.014 (−0.08–0.06)
Anxiety	0.029 (−0.003–0.06)	0.012 (−0.02–0.05)	0.009 (−0.02–0.04)	0.014 (−0.02–0.05)
Pessimism	0.049[d] (0.02–0.08)	0.044[d] (0.01–0.07)	0.031 (0.00–0.06)	0.005 (−0.03–0.04)

A separate model was constructed for each psychological predictor.
[a] Adjusted for confounders: age, sex, race/ethnicity (white vs. non-white).
[b] Adjusted for above + SES (income, education).
[c] Adjusted for above + behavioral mediators (physical activity, smoking, regular alcohol use, BMI).
[d] $P \leq 0.05$.

4. Discussion

In a study of 1024 outpatients with stable coronary heart disease, we found that participants with greater levels of depressive symptoms, anger expression, hostility, and pessimism had a significantly higher prevalence of the metabolic syndrome. This association appeared to be explained by differences in socioeconomic status and health behaviors (physical inactivity, smoking, alcohol use, and BMI). Further adjustment for C-reactive protein and other inflammatory markers had minimal impact.

Previous investigations have found that depression, anxiety, stress, and lack of coping resources are associated with increases in individual components of the metabolic syndrome (Henry and Grim, 1990; Rosmond et al., 1996; Yancura et al., 2006). However, studies examining the association between psychological variables and the metabolic syndrome as a whole have yielded conflicting results. In a study of 3186 men and 3003 women, ages 17 to 39, who were free of coronary heart disease and diabetes, the prevalence of the metabolic syndrome was elevated among women with a history of depression but not among men (Kinder et al., 2004). Another study of 5691 men and women with a mean age of 31 did not find a significant association between the metabolic syndrome and depression or anxiety (Herva et al., 2006).

Studies in middle-aged and older adults have also shown varying associations between depression, anxiety, and the metabolic syndrome. In the Health, Aging, and Body Composition study of 2917 high-functioning elderly adults aged 70–79, depression was associated with the metabolic syndrome in whites, but not in blacks; and anxiety was associated with the metabolic syndrome in men, but not in women (Vogelzangs et al., 2007). In the Healthy Women Study, Räikkönen and colleagues followed 432 healthy white middle-aged women for an average of 15 years and found those who reported frequent feelings of anger, depression, and anxiety had a higher risk of developing the metabolic syndrome (Raikkonen et al., 2002, 2007). Whether these results are generalizable to other populations is unclear.

Whether psychological factors are associated with the metabolic syndrome in adults with established cardiovascular disease is unknown. Since patients with known cardiovascular disease are at high risk for adverse cardiac outcomes, this group represents an important target population for the initiation of potentially preventive

therapies. In a cross-sectional analysis of 1598 adults without established cardiovascular disease, but with at least one cardiovascular risk factor, Skilton and colleagues found that depression but not anxiety was associated with increased prevalence of the metabolic syndrome independent of age, socioeconomic status, and lifestyle factors (Skilton et al., 2007). In addition, the Women's Ischemia Syndrome Evaluation study showed an association between the metabolic syndrome and depression among women with suspected coronary artery disease, independent of lifestyle factors and functional status (Vaccarino et al., 2008). Our study expands this work by focusing on men and women with established coronary heart disease and by examining a wide array of psychological variables. While we found that many psychological variables were associated with an increase in the metabolic syndrome, in contrast to the prior studies, this association was not independent of socioeconomic and lifestyle factors. This may be due to differences in the covariates used in adjusted models. For example, prior studies did not adjust for income as part of socioeconomic status. Differences in the distribution of socioeconomic status or health behaviors in the study populations might also explain these discrepancies. However, in general, we did not find significant interactions between the psychological variables and socioeconomic status or health behaviors. The association between pessimism and the metabolic syndrome appeared to be limited to college graduates, but given the many interactions we tested, this could have occurred by chance.

Psychological factors may increase risk for the metabolic syndrome through multiple mechanisms. Individuals with high levels of depression, anger, or hostility could have unhealthy behaviors that increase metabolic risk, such as higher rates of smoking and illicit drug use (Breslau et al., 1998; Roeloffs et al., 2002). In our study, adjusting for such health behaviors, along with demographic and socioeconomic variables, explained most of the association between psychological variables and the metabolic syndrome. Psychological stressors may also lead to increased sympathetic nervous system activity and to elevated levels of cortisol and catecholamines, which can elevate risk for the metabolic syndrome (Brunner et al., 2002; Rosmond, 2005; Lamounier-Zepter et al., 2006). Studies have also shown that psychological risk factors are associated with higher levels of inflammatory markers such as interleukin-6 (Maes, 1995). Inflammatory markers, in turn, have been linked to a variety of metabolic abnormalities, including obesity, dyslipidemia, and hyperglycemia (Pradhan et al., 2001). However, additional adjustment for inflammatory markers did not affect the association between the metabolic syndrome and psychological measures in our study population. Finally, lifelong psychological *traits*, such as anger, hostility, and optimism, may act via different mechanisms than current *states*, such as anxiety and depression. It is also possible that lifelong traits may have stronger associations with metabolic syndrome than states since the cumulative exposure is presumably greater. In our analyses, adjustment for potential socioeconomic, lifestyle, and biological mediators had similar effects on the associations of traits and states with the metabolic syndrome. However, a detailed comparison of the influence of traits vs. states on metabolic risk is beyond the scope of our cross-sectional analyses.

Strengths of our study include the large sample size, ethnic and socioeconomic diversity of the population, and comprehensive measurements of potential confounding variables and mediators. In addition, this is the first study to examine psychological variables and metabolic syndrome in patients with known CHD, a group at highest risk of adverse cardiovascular outcomes. However, several limitations should be considered in interpreting the results. First, although our results extend the work of prior studies to an important and high-risk group, our study population consisted of mostly urban men with CHD, and our results may not generalize to other groups. Second, given their established CHD, all participants were likely to receive close management of the risk factors used as diagnostic criteria for the metabolic syndrome. This may have weakened our ability to find differences in the prevalence of the metabolic syndrome by level of psychological risk. Third, many facets of the metabolic syndrome are controversial, including appropriate cut-points for its components, whether it represents a true syndrome, and its clinical utility (Lawlor et al., 2004). Fourth, we included BMI in our adjustment for health behaviors, though it is an end result of health behaviors such as diet and exercise.

In summary, we found that multiple psychological factors were associated with an increased prevalence of the metabolic syndrome. This association was largely explained by differences in socioeconomic status and health behaviors. Further research is needed to determine whether modifying these factors in people with depression or high levels of anger or hostility could reduce the burden of the metabolic syndrome.

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