Psychosocial Variables Are Associated With Atherosclerosis Risk Factors Among Women With Chest Pain: The WISE Study

THOMAS RUTLEDGE, PHD, STEVEN E. REIS, MD, MARIAN OLSON, MS, JANE OWENS, PHD, SHERYL F. KELSEY, PHD, CARL J. PEPINE, MD, NATHANIEL REICHEK, MD, WILLIAM J. ROGERS, MD, C. NOEL BAIREY MERZ, MD, GEORGE SOPKO, MD, CAROL E. CORNELL, PHD, AND KAREN A. MATTHEWS, PHD

Objective: We investigated associations between atherosclerosis risk factors (smoking behavior, serum cholesterol, hypertension, body mass index, and functional capacity) and psychological characteristics with suspected linkages to coronary disease (depression, hostility, and anger expression) in an exclusively female cohort. **Methods:** Six hundred eighty-eight middle-aged women with chest pain warranting clinical investigation completed a comprehensive diagnostic protocol that included quantitative coronary angiography to assess coronary artery disease (CAD). Primary analyses controlled for menopausal status, age, and socioeconomic status variables (income and education). **Results:** High depression scores were associated with a nearly three-fold risk of smoking (odds ratio (OR) = 2.8, 95% confidence interval (CI) = 1.4–5.7) after covariate adjustment, and women reporting higher depression symptoms were approximately four times more likely to describe themselves in the lowest category of functional capacity (OR = 3.7, 95% CI = 1.7–7.8). High anger-out scores were associated with a four-fold or greater risk of low high-density lipoprotein cholesterol concentration (<50 mg/dl; OR = 4.0, 95% CI = 1.4–11.1) and high low-density lipoprotein cholesterol concentration (>160 mg/dl; OR = 4.8, 95% CI = 1.5–15.7) and a larger body mass index (OR = 3.5, 95% CI = 1.1–10.8) after covariate adjustment. **Conclusions:** These results demonstrate consistent and clinically relevant relationships between psychosocial factors and atherosclerosis risk factors among women and may aid our understanding of the increased mortality risk among women reporting high levels of psychological distress. **Key words:** coronary artery disease, women, psychosocial risk factors.

BDI = Beck Depression Inventory; BMI = body mass index; CAD = coronary artery disease; CI = confidence interval; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; OR = odds ratio; WISE = Women's Ischemia Syndrome Evaluation.

INTRODUCTION

There is compelling literature to support the associations between specific psychosocial characteristics and the incidence and prognosis of CAD (1–4). Reviews of this research (5–7) cite particularly strong evidence for four psychological factors: depression, hostility, and two types of anger expression (ie, anger-in and anger-out). The predictive value of these four factors has been demonstrated across both cross-sectional and prospective studies of CAD, in cohorts of healthy subjects as well as subjects with disease, and the effects have proven robust after controlling for more established risk factors, such as age, family history, and disease severity (8–10).

The rationale for the relationship between psychosocial variables and CAD commonly takes one of two forms. First, a series of recent findings support adverse psychophysiological effects relevant to CAD, such as increased responsiveness of the sympathetic nervous system (ie, increased blood pressure and heart rate activity) and hypothalamic-pituitary axis (eg, hypercortisolemia) under conditions of mental stress (11, 12). Second, psychological variables may impact the course of coronary disease through behavioral mechanisms, for example, by fostering negative health behaviors such as smoking, decreased fitness or physical activity, poor diet, and reduced adherence to treatment (13).

Although many previous psychosocial studies of coronary disease have included measures of behavioral and physiological risk factors (ie, cholesterol levels and BMI) as covariates, with the possible exception of hypertension (14, 15), less is known about direct associations between psychosocial variables and major coronary risk factors among traditionally understudied female groups (16–18). In light of evidence from male patient groups suggesting that psychosocial effects on cardiovascular disease may be in part mediated by atherosclerosis risk factors (19), it is important to examine this issue in women.

To evaluate the relationship between psychosocial traits and atherosclerosis risk factors, we studied women undergoing evaluation for suspected myocardial ischemia enrolled in the National Heart, Lung,

From the University of Pittsburgh (T.R., S.E.R., M.O., J.O., K.A.M.), Pittsburgh, Pennsylvania; University of Florida at Gainesville (S.F.K., C.J.P.), Gainesville, Florida; Allegheny General Hospital (N.R.), Pittsburgh, Pennsylvania; University of Alabama at Birmingham (W.J.R., C.E.C.), Birmingham, Alabama; Cedars-Sinai Medical Center (C.N.B.M.), Los Angeles, California; and National Heart, Lung, and Blood Institute (G.S.), Bethesda, Maryland.

Address reprint requests to: Thomas Rutledge, PhD, c/o WISE Coordinating Center, 127 Parran Hall, 130 DeSoto St., Pittsburgh, PA 15261. Email: dr.tom@musclemail.com

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and Blood Institute–sponsored multicenter WISE study (20). Participants completed a psychosocial battery that included measures of cynical hostility, depression, and anger expression in addition to undergoing blood tests (serum cholesterol levels), physical examination (BMI), quantitative coronary angiography, and questionnaire assessments of atherosclerosis risk factors (smoking status, existing or prior hypertension diagnosis, and functional capacity).

METHODS

Participant Recruitment and Entrance Criteria

Women were eligible for participation in WISE if they were older than 18 years of age and were referred for coronary angiography to evaluate suspected myocardial ischemia. Exclusion criteria included current pregnancy, cardiomyopathy, recent myocardial infarction or revascularization procedure (percutaneous transluminal coronary angioplasty or coronary artery bypass grafting), language barrier preventing completion of the questionnaires, and a history of congenital heart disease (20). The study population consisted of 688 women who completed the angiogram procedures and core diagnostic protocol. Because of the staggered start in recruitment during 1996–1997 (recruitment for WISE began approximately 1 month before development of the psychosocial battery) and because of changes in the psychosocial battery during the pilot phase of data collection, 200 participants completed the anger expression measures and 495 completed the depression and hostility questionnaires. All participants who completed the anger expression measures also completed the depression and cynical hostility questionnaires.

Psychosocial and Risk Factor Measurement

Depression, cynical hostility, and anger expression were each assessed using measures with demonstrated predictive validity for cardiovascular disease outcomes (5, 6, 10, 15). The BDI (21) assesses symptoms related to sadness, feelings of guilt, and perceptions of self-worth, among others. The Cook-Medley Hostility Scale (22) measures a stable lack of trust and bitterness toward others. The Spielberger Anger Expression Scale (23) measures anger-in and anger-out, that is, a respondent's tendency to inhibit or repress signs of anger vs. making outward (vocally or physically) displays of anger. Following are example items from each scale: 1) depression: "I feel worthless compared with other people" and "I am sad all the time"; 2) hostility: "It makes me impatient to have people ask my advice or otherwise interrupt me when I am working on something important" and "When someone does me wrong I feel I should pay him back if I can, just for the principle of the thing"; 3) anger-out: "I often say nasty things when I'm angry" and "If someone annoys me, I'm apt to tell them how I feel"; and 4) anger-in: "I keep things in when I'm angry" and "I boil inside, but I don't show it."

Major coronary risk factors include age, obesity, low levels of physical activity, hypertension, and a high cholesterol level. We focused on relationships between psychosocial variables with major coronary risk factors measured as follows: 1) smoking status, rated as current smoker or current nonsmoker; 2) HDL-C, <50 or >50 mg/dl (24); 3) LDL-C, <160 or >160 mg/dl; 4) hypertension status, history of positive or negative diagnosis; 5) BMI, <27.0 or >27.0; and 6) functional capacity. The functional capacity score was aggregated from the 12-item Duke Activity Status Index, which assesses a patient's ability to perform a variety of activities ranging from basic self-care to strenuous exercise and is associated with physical fitness levels (25). Based on the total functional capacity score, we categorized patients as healthy (upper 75% of distribution) or impaired (lower 25% of distribution). The Duke Activity Status Index is scored such that *higher* scores equal *lower* functional capacity. Patients taking cholesterol-lowering medications (approximately 20% of the sample) were excluded from analyses involving the LDL-C and HDL-C end points.

Control variables included patient's age, menopausal status (a dichotomous yes/no variable), and socioeconomic variables (education and patient's family income). The objective of including these covariates was to demonstrate psychosocial relationships independent of standard atherosclerosis risk factors like age, hormonal activity, and variables of socioeconomic status that are known to be linked to both atherosclerosis risk and psychological characteristics in women (26, 27). Socioeconomic variables in particular were included as potential mediators of the psychosocial relationships (19).

Statistical Analyses

We assessed relationships between psychosocial factors and coronary risk factors using logistic regression methods. Using each of the risk factors as a separate outcome, control variables were force-entered at step one of each equation, followed by entrance of significant univariate psychosocial predictors at step two. All psychosocial measures were examined in quartiles in the logistic equations. The first quartile served as the reference category in the calculation of ORs. Power analyses, calculated using $\alpha = 0.05$ and a minimum N value of 200, indicated that our probability to detect large effects (eg, ORs > 2.0) was $>99\%$ and that power levels were smaller but also acceptable (0.75) for effects of moderate size (eg, ORs > 1.5). Notably, this analytic scheme produced 24 relationships (four psychosocial measures by six atherosclerosis risk factors), suggesting that at least one significant association could be expected due to chance alone.

Because of the potential for selection bias among the WISE participants, we also tested the possibility that psychological factor–CAD risk factor associations could be affected by the severity of underlying coronary disease by including a dichotomous disease severity variable ($0 = \leq 49\%$ maximum stenosis, $1 = \geq 50\%$ maximum stenosis) as an additional covariate and by testing for the presence of interactions between psychological factors and severity of CAD. These terms had no statistical effect on the results of the psychosocial analyses and are not reported.

RESULTS

Descriptive Summary

Means and standard deviations for the psychosocial, atherosclerosis risk factor, and control variables for the WISE sample are shown in Table 1. Scores from the four psychological scales were significantly intercorrelated, with Pearson r values ranging from 0.18 (for depression and anger-out scores) to 0.54 (for depression and anger-in scores), with most values (four of six relationships) between 0.20 and 0.30 (all p values $<$ .01). Interrelationships among the atherosclerosis risk factors were also present. Hypertension was associated with larger BMI scores ($r = 0.17$), smoking ($r = 0.10$), and poor functional capacity ($r = 0.22$, all p values $<$

TABLE 1. A Description of Psychosocial, Coronary Risk Factor, Demographic, and Control Variables Across Patients Categorized by Angiographic Severity of CAD (N = 688)

	Mean (SD)
Age (y)	59.6 (11.6)
LDL-C (mg/dl)	114.3 (40.3)
HDL-C (mg/dl)	53.0 (12.8)
Current smokers (%)	19.7
BMI	30.2 (6.7)
Functional capacity (range 12–48)	24.8 (5.6)
Postmenopausal (%)	83.4
Race (%)	
White	80.4
Black	18.3
Other	1.3
Annual income > $20,000 (%)	64.2
Completed high school (%)	79.8
Cynical hostility[a]	5.0 (3.4)
Depression[b]	10.7 (8.1)
Anger-in[c]	15.1 (4.1)
Anger-out[c]	13.2 (3.5)

[a] Measured using the Cook-Medley Hostility Scale (N = 490).
[b] bMeasured using the BDI (N = 490).
[c] Measured using the Spielberger Anger Expression Scale (N = 200).

.05). Larger BMI scores and smoking were also correlated with lower HDL-C values (r values = −0.16, p values < .01). Finally, poorer functional capacity scores were associated with larger BMI values (r = 14, p < .05). No risk factor predicted LDL-C.

Psychosocial Predictors of Atherosclerosis Risk Factors

Unadjusted correlation values between the psychosocial variables and atherosclerosis risk factors are shown in Table 2. Because of the dichotomous nature of the smoking and hypertension status variables, point biserial (rather than Pearson r) correlation coefficients were calculated to assess interrelationships with these two terms. Psychosocial scores were associated with each of the risk factors. In several cases variations in sample size caused minor variations in the magnitude of the correlation coefficients required to meet significance criteria. Lower HDL-C values were associated with higher anger-out, cynical hostility, and depression scores, whereas higher LDL-C scores were associated with high anger-out scores. Current smokers were more likely to report symptoms of anger-in, cynical hostility, and depression, and lower functional capacity was related to higher depression and cynical hostility scores. A history of hypertension was associated with greater cynical hostility, and larger BMI scores were associated with higher anger-out scores.

TABLE 2. Univariate Correlations Between Atherosclerosis Risk Factor Status and Measures of Depression, Hostility, and Anger Expression

	Anger-in	Anger-out	Hostility	Depression
HDL-C	0.12	0.23**	0.10*	0.12**
LDL-C	0.07	0.15*	0.04	0.05
Current smoking status[a]	0.14*	0.10	0.14**	0.19***
Functional capacity	0.03	0.04	−0.19***	−0.29***
Hypertension status[a]	0.04	−0.02	0.11*	0.08
BMI	−0.02	0.18**	−0.03	−0.02

[a] 0 = no; 1 = yes.
* p <.05; ** p <.01; *** p <.001.

Table 3 presents a breakdown of participant's risk factor status across quartiles of the reliable psychosocial predictors. Values from this table reinforce the correlational findings by highlighting clinically meaningful differences in risk factor profiles based on psychosocial standing. For example, in comparison with those with the lowest depression scores, participants in the upper quartile of depression symptoms were approximately 2.5 times more likely to smoke (34.1% vs. 13.0%) and nearly 3 times more likely to endorse the lowest category of functional capacity (32.5% vs. 11.1%). Current smokers were also more than twice as likely to fall in the upper quartile of anger-in (26.5% vs. 13.0%) and cynical hostility scores (28.7% vs. 13.1%).

Furthermore, low HDL-C and high LDL-C status were each roughly twice as frequent among the highest quartile of anger-out scorers relative to those with the lowest scores on this instrument (HDL-C, 62.2% vs.

TABLE 3. Atherosclerosis Risk Factor Status as a Function of Standing on Statistically Significant Psychosocial Predictor Variables

	Quartile			
	1	2	3	4
Depression				
HDL-C <50 mg/dl (%)	32.4	34.5	45.6	45.8
Functional capacity (% in most impaired group)	11.1	13.7	18.3	32.5
Current smokers (%)	13.7	12	14.4	34.1
Anger-in				
Current smokers (%)	13.0	20.0	24.2	26.5
Anger-out				
HDL-C <50 mg/dl (%)	31.4	42.5	52.1	62.2
LDL-C >160 mg/dl (%)	20.0	32.5	30.0	40.5
Body mass index (% >27.0)	60.0	60.5	72.0	83.3
Cynical hostility				
HDL-C <50 mg/dl (%)	34.1	36.7	42.9	47.5
Current smokers (%)	13.1	15	15.1	28.7
Functional capacity (% in most impaired group)	13.1	15.1	22.1	27.0
Hypertension (%)	53.4	52.3	57.0	65.6

31.4%; LDL-C, 40.5% vs. 20.0%). The breakdown of other risk factors across the psychosocial groups were not as striking but also showed a consistent (and statistically reliable) increase in the presence of risk factors with higher reported psychosocial symptoms.

Covariate-adjusted odds ratios are shown in Table 4. High anger-out scores remained predictive of an elevated risk of low HDL-C status (OR = 4.0, 95% CI = 1.4–11.1), high LDL-C status (OR = 4.8, 95% CI = 1.5–15.7), and greater BMI (OR = 3.5, 95% CI = 1.1–10.8). Similarly, scores in the highest depression quartile demonstrated an elevated risk of smoking (OR = 2.8, 95% CI = 1.4–5.7) and low functional capacity (OR = 3.7, 95% CI = 1.7–7.8) in comparison to participants with the lowest depression scorers after adjusting for covariates. Finally, the association between cynical hostility and hypertension was nonsignificant after controlling for covariates (OR = 1.4, 95% CI = 0.80–2.5). Exploration of this latter change revealed that the socioeconomic covariate terms seemed to mediate the effects of cynical hostility on blood pressure status (ie, socioeconomic status was associated with both cynical hostility and hypertension, and its presence in the regression equation decreased the association between cynical hostility and hypertension).

DISCUSSION

We investigated relationships between known atherosclerosis risk factors and empirically supported psychosocial measures in a moderately large, exclusively female cohort. The literature indicates that psychosocial factors may increase the prospective risk of developing coronary disease (5, 6) and may undermine the prognosis for those with existing disease (28, 29). However, the precise pathophysiological mechanisms through which psychosocial factors may translate into coronary disease outcomes remain undefined. Among female groups there is evidence that psychosocial distress is prospectively associated with increased risk of disease and premature mortality from cardiovascular events (30, 31). Studies have demonstrated relationships between low socioeconomic status and coronary risk factors (26, 27), but there is comparatively little evidence addressing risk factor profiles among female patients with higher levels of psychological distress. Evidence for such relationships would strengthen the proposed connection between psychological factors and coronary disease by showing associations with behavioral and physiological factors that are believed to directly influence disease risk.

TABLE 4. Covariate-Adjusted Logistic Regression Results Presenting Multivariate Psychosocial Predictors for HDL-C and LDL-C Status, BMI Values, Hypertension Status, Smoking Status, and Functional Capacity Levels[a]

	β	β Error	OR	95%CI	p
Low HDL-C					
Anger-out(4)[a]	1.4	0.53	4.0	1.4–11.1	.009
High LDL-C					
Anger-out (2)	1.4	.58	4.1	1.3–13.0	.02
Anger-out (4)	1.6	.60	4.8	1.5–15.7	.009
Smoking status					
Depression (4)	1.0	.36	2.8	1.4–5.7	.003
Low functional capacity					
Depression (4)	1.3	.39	3.7	1.7–7.8	.001
Hypertension status					
Hostility (4)	0.35	.29	1.4	0.80–2.5	.20
BMI					
Anger-out (4)	1.2	.58	3.5	1.1–10.8	.03

[a] Covariates included age, menopause status, and socioeconomic status. Numbers in parentheses represent quartile group compared with quartile 1.

We observed a pattern of associations between atherosclerosis risk factor variables and psychosocial measures. Anger expression, particularly high anger-out scores (a style characterized by a more outward expression of aggression and angry emotions), was the strongest predictor of unfavorable blood cholesterol levels and larger body mass, and higher cynical hostility and depression scores were each linked to an increased risk of smoking, a reduced ability to perform tasks related to self-care and exercise, and to lower HDL-C levels. These results were bolstered by two criteria: first, the atherosclerosis risk factor profile assessed here included both physiological and behavioral variables, and second, the relationships remained significant after controlling for CAD-relevant covariates.

Although the correlations illustrated in Table 3 were modest in size, a breakdown of risk factor status across the psychosocial measures suggested a consistent dose-response relationship between increased psychosocial distress symptoms and a less favorable risk factor status. The covariate-adjusted logistic equations further supported the potential importance of the psychosocial measure–risk factor associations by revealing ORs of clinically relevant magnitude. Although the cross-sectional design used here prevents us from disentangling causal directions in these relationships, our findings indicate a need for prospective trials to evaluate the effects of behavioral modification on atherosclerosis risk factors and cardiac events.

Depression and anger-out scores proved to be the most robust psychosocial predictors of atherosclerosis risk factor status. Depressive symptoms among WISE participants were assessed using the BDI, an instrument that has received criticism in some heart disease trials because of the possibility that certain item content (eg, items referring to recent appetite, weight

changes, or sexual activity) could reflect disease severity rather than features of depression. However, use of the BDI also provides two important advantages: 1) practicality in comparison to lengthy interviews required for formal psychiatric diagnoses and 2) proven value as a predictor of premature mortality among patients with CAD (6). It is estimated that >20% of CAD patients may meet criteria for a major mood disorder (5). BDI scores alone do not permit the diagnosis of a major mood disorder. Based on the distribution of BDI scores observed here, however, scale norms indicated that approximately 16% of WISE women had scores indicating at least subclinical levels of depression (BDI scores ≥17). Because even subclinical depressive symptoms are associated with increased mortality among CAD patients (27), the consistent link between depression and atherosclerosis risk factors found here deserves attention as a potential explanation for higher mortality rates.

We observed some limited support for the role of socioeconomic variables as an explanatory factor in the relationship between psychosocial variables and atherosclerosis risk factors. Specifically, the association between cynical hostility and hypertension, although independent of age and menopause status, was no longer significant after controlling for socioeconomic status. As noted earlier (26), socioeconomic status is a powerful epidemiological predictor of atherosclerosis risk in women and is also linked to higher levels of psychological distress. More sophisticated attempts to model interrelationships between psychological variables, socioeconomic status, and atherosclerosis risk factors (eg, Ref. 27) are less common (32), but they represent a potentially valuable avenue to advance our understanding of psychological effects on coronary health.

In addition to suggesting a more routine inclusion of socioeconomic variables in psychosocial factor–atherosclerosis risk analyses, the pattern of relationships described here raise a number of interesting questions for future research: Are relationships between smoking and cynical hostility a product of higher smoking incidence rates among this population or of higher relapse rates (33)? What manner of behavioral (eg, dietary or physical activity) or physiological (eg, metabolic changes) mechanisms explain associations between anger expression and blood lipid profiles? Given the known interrelationships among psychosocial measures and among atherosclerosis risk factors (eg, the metabolic syndrome), can these associations be better characterized through the use of factor analytic or structural modeling techniques that are capable of deriving solutions based on oblique variable sets? Thus, the current results offer statistically and possibly clinically significant interrelationships between psychosocial variables and major coronary risk factors, but additional research is needed to understand the direction and nature of these associations.

Study Limitations

Cross-sectional relationships must be carefully tested against the threat of confounding. For example, it is plausible that symptoms of depression are spuriously related to decreased activity and smoking as a result of cohorts differing on factors such as age and socioeconomic status. Although we took steps to control for such competing explanations by covarying these factors in our analyses, we cannot rule out the effects of unmeasured third variables or interactions among several variables that may have influenced psychosocial variable–risk factor associations observed here.

The relatively unique nature of the WISE sample also deserves comment. This group represents women referred for angiography on the basis of atherosclerosis risk factors, clinical presentation, and positive results on exercise testing among other criteria. The WISE cohort, however, should not be construed to represent a random sample of women undergoing cardiac catheterization or of women with atherosclerosis. Symptoms of angina are themselves associated with psychological characteristics such as anxiety and depression (34, 35), for example, and therefore likely affect probability of referral. The relatively high levels of depression reported here (mean BDI score = 10.7) may offer direct support for a potential referral bias due to psychological distress. Similarly, previous publications based on the WISE sample (20) have shown that <50% of participants had evidence of significant atherosclerosis (ie, stenosis ≥70%) based on angiography. Although lower concordance rates between clinical presentation and risk of atherosclerosis among women in comparison with men are well documented (36, 37), the potential confounding of clinical symptoms and referral rates on the basis of psychological characteristics requires caution in generalizing these findings to general female populations or to male samples.

CONCLUSIONS

This study demonstrated a consistent pattern of relationships between psychosocial factors and atherosclerosis risk factors. We found that anger expression was related to dyslipidemia and larger body mass, whereas both cynical hostility and depression symptoms were associated with an increased likelihood of smoking, lower levels of functional capacity, and

lower HDL-C levels. All associations were in the direction of increased disease risk. These findings are consistent with those in the broader literature linking psychosocial factors with clinically expressed CAD and may also be valuable in understanding observations of increased morbidity and mortality among psychologically distressed women after cardiac events. Although we noted the limitations inherent in this study due to the cross-sectional methodology and selected nature of the sample, the findings have implications for the understanding of coronary disease and reinforce efforts to examine psychosocial factors in women.

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