ORIGINAL ARTICLE

Depression Symptom Severity and Reported Treatment History in the Prediction of Cardiac Risk in Women With Suspected Myocardial Ischemia

The NHLBI-Sponsored WISE Study

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Background: Depression is associated with clinical events and premature mortality among patients with established coronary artery disease (CAD). Typically, however, studies in this area focus only on baseline symptom severity and lack any data concerning symptom duration or symptom history.

Objectives: To describe and compare the relationships between 2 measures of depression—assessed in the form of depression symptom severity and reported treatment history—with atherosclerosis risk factors and major clinical events in a sample of women with suspected myocardial ischemia.

Design: Follow-up study of women who completed a diagnostic CAD protocol, including cardiac symptoms, coronary angiography, ischemic testing, and assessments of depression symptom severity and reported treatment history.

Setting: The Women's Ischemia Syndrome Evaluation (WISE), a National Heart, Lung, and Blood Institute (NHLBI)–sponsored multicenter study assessing cardiovascular function using state-of-the-art techniques in women referred for coronary angiography to evaluate chest pain or suspected myocardial ischemia.

Participants: Five hundred five women (mean age, 53.4 years) enrolled in WISE and followed up for a mean of 4.9 years.

Main Outcome Measures: Incidence of cardiac events, including myocardial infarction, stroke, and heart failure, and total mortality.

Results: Relative to those with no or less stable depression symptoms, women with elevated depression symptoms and a reported treatment history showed higher rates of smoking, hypertension, and poorer education and an increased incidence of death and cardiac events (multivariate-adjusted risk ratio, 3.1; 95% confidence interval, 1.5-6.3; $P = .001$).

Conclusions: Among women with suspected myocardial ischemia, a combination of depressive symptom severity and treatment history was a strong predictor of an elevated CAD risk profile and increased risk of cardiac events compared with those without depression or with only 1 of the 2 measured depression markers. These findings reinforce the importance of assessing mental health factors in women at elevated CAD risk. Focusing only on baseline depression symptom severity may provide an incomplete picture of CAD risk.

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Depression is among the most robust psychosocial predictors of coronary artery disease (CAD) incidence, progression, and mortality.[1-5] Prevalence data indicate that depression is common among patients with CAD, with most studies estimating rates of depression disorders between 20% and 40% among samples of cardiac patients.[6-8] Depression symptoms are also associated with pathophysiology linked to CAD—notably reduced heart rate variability, hypercortisolemia, suppressed immune system functioning, and increased platelet adhesion, among others—along with higher rates of low physical activity and smoking, behavioral risk factors known for chronic diseases.[2,9,10] This combination of factors is often cited as the basis of a biobehavioral model to explain associations between psychosocial factors and coronary events.

In most studies, relationships between depression and cardiac outcomes are based on acutely measured mental health symptoms, most commonly in the form of a diagnostic interview or questionnaire assessment of baseline symptom severity. These baseline assessments are often

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treated as indicators of stable mental health symptomology.[7,8] However, treatment experience shows that the course of depression is complex, sometimes remitting without treatment. This raises many clinically important and unanswered questions. Is the risk of clinical events for a patient experiencing a first-time episode of major depression in the aftermath of myocardial infarction (MI) the same as for a patient with a history of stable or recurrent depression? Does this relationship differ for women, among whom rates of depression disorders are substantially higher?[11-13] In chronic diseases such as CAD—a condition with clinical manifestations that can unfold across decades—preliminary evidence suggests that more recurrent depression symptoms may confer greater risk of CAD in women.[14]

In this report, we provide new data regarding the assessment of depression symptom patterns in CAD risk among a cohort of women with suspected myocardial ischemia. As part of the protocol, patients completed standardized questionnaires of depression symptom severity and a self-reported history of treatment for depression. We stratified patients by their responses to these measures, hypothesizing that patients with a combination of high levels of depression symptoms at baseline and histories of treatment for depression would experience the most significant risk for mortality and clinical events during a study follow-up period approaching 5 years.

The goals of the current study were 2-fold: (1) to examine associations between depression symptom patterns and the incidence of MI, stroke, congestive heart failure, and total mortality in women with suspected myocardial ischemia; and (2) to compare atherosclerosis risk factors, survival, and clinical event rates among women having a more recurrent pattern of depression characterized by a combination of elevated baseline symptoms *and* reported treatment histories with those of women having no depression symptoms and those of women having *either* elevated baseline symptoms or reported treatment histories.

METHODS

PARTICIPANT ELIGIBILITY CRITERIA

The Women's Ischemia Syndrome Evaluation (WISE) is a National Heart, Lung, and Blood Institute–sponsored multicenter study assessing cardiovascular function using state-of-the-art techniques in women referred for coronary angiography to evaluate chest pain or suspected myocardial ischemia.[15] Participating sites included the University of Florida, Gainesville; University of Pittsburgh, Pittsburgh, Pa; University of Alabama at Birmingham; and Allegheny General Hospital, Pittsburgh. The WISE cohort included a total of 955 women, with pilot study enrollment beginning in 1996-1997; however, psychological testing was not part of the initial protocol. The results presented here are based on 505 women (mean age, 53.4 years) with complete depression symptom information and completed follow-up data.

WISE eligibility required being older than 18 years and having a coronary angiogram. Exclusion criteria included current pregnancy, cardiomyopathy, a recent MI or revascularization procedure (percutaneous transluminal coronary angioplasty or coronary artery bypass graft), a language barrier preventing questionnaire completion, and a history of congenital heart disease. The WISE protocol was approved by each participating site's institutional review board, and all participating women signed informed consent.

MEASUREMENT OF CAD, CARDIAC EVENTS, AND MORTALITY

All women were followed up for new cardiovascular events, hospitalizations, and death during a mean of 4.9 years. For this report, the cause of death was not classified in primary analyses owing to insufficient numbers. Follow-up was conducted by telephone interview at 6 weeks and then yearly thereafter. Follow-up consisted of a scripted interview by an experienced nurse or physician. Each patient was queried about hospitalizations and the reason for hospitalization. No participants with depression data were lost to follow-up. Cardiac events were defined as hospitalization for unstable angina, MI, congestive heart failure, stroke, other vascular events, and death. When a major cardiovascular event was identified, the referring physician was contacted for confirmation, dates, and documentation of the event. In the case of death, we obtained a death certificate.

Coronary artery disease (anatomic) severity was based on angiogram results using the participant's raw maximum stenosis score. In all, 343 participants completed 1 or more detailed noninvasive tests for myocardial ischemia, including exercise and pharmacologic stress testing with or without echocardiographic or radionuclide imaging.

Major CAD risk factors included body mass index, smoking, cholesterol, diabetes mellitus history, and hypertension status. The assessment of smoking, diabetes, and hypertension was based on participants' self-report of diagnosis and treatment history. All testing was performed in accordance with institutional guidelines.

PSYCHOSOCIAL MEASURES

As part of the baseline self-report battery, 505 participants completed the Beck Depression Inventory (BDI).[16] The BDI is a widely used, 21-item instrument for assessing a variety of depression symptoms and has been shown to predict outcomes among cardiovascular patients.[2] The BDI provides continuous scores. Previous research suggests that scores of 17 or greater indicate the presence of clinically significant depression. Thus, we defined elevated depression symptoms as a BDI score of 17 or greater.

As part of their baseline examination, WISE participants answered a separate mental health history question regarding whether they had ever received treatment for depression. This question did not query the type or duration of treatment, the outcome of the intervention, or whether they were currently being treated for depression. Participants also completed the Social Network Index,[17] a validated measure of social network size.

STATISTICAL ANALYSES

Using the depression questionnaire and treatment history responses, we categorized women into 3 symptom patterns: (1) those with neither elevated baseline symptoms nor a reported treatment history; (2) those with baseline symptoms *or* a reported treatment history; and (3) those with elevated baseline symptoms *and* a treatment history. This method placed each participant into 1 of 3 independent groups.

Preliminary results compared means and standard deviations of CAD risk factors and demographic variables for participants in the depression groups using analysis of variance. In the case of statistically significant F test values, we com-

Table 1. Demographic and CAD Risk Factors Among Depression Groups in WISE*

	Depression Groups (N = 505)		
	No Depression† (n = 322)	High BDI Scores or Treatment History (n = 145)	High BDI Scores and Treatment History (n = 38)
Age, y‡	60.4 (11.1)	56.5 (11.3)	56.0 (9.1)
BMI	29.8 (6.6)	29.3 (6.6)	29.3 (5.1)
HDL cholesterol level, mg/dL	54.1 (12.0)	54.4 (12.1)	54.7 (15.7)
LDL cholesterol level, mg/dL	116.0 (37.0)	111.3 (45.0)	118.1 (42.9)
Social network size, No. of persons‡	6.6 (1.8)	6.1 (1.7)	5.8 (1.8)
Completed high school, %‡	83.5	81.4	64.9
Hypertensive, %‡	55.3	54.2	75.7
Diabetic, %	20.8	22.1	24.3
Current smoker, %‡	12.8	26.9	35.1
Married, %	65.2	58	56.8
Maximum stenosis score§	35.8 (35.9)	35.2 (33.4)	35.9 (35.5)
Positive myocardial ischemia test, %	45	41	31

Abbreviations: BDI, Beck Depression Inventory; BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); CAD, coronary artery disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; WISE, Women's Ischemia Syndrome Evaluation.

SI conversion factors: To convert cholesterol to millimoles per liter, multiply by 0.0259.

*Values are expressed as mean (SD) unless otherwise indicated.

†No depression indicates patients with low baseline depression and no reported history or treatment.

‡Groups differ at $P<.05$ compared with the no-depression group.

§Stenosis scores can range from 0 to 100, with a higher score indicating more severe atherosclerosis.

pleted follow-up multiple comparisons using the Tukey honestly significant difference method. Where unequal variances occurred between cells, we used the Dunnett C multiple comparisons test. In subsequent outcome assessments, we used the mental health groupings as predictors in Cox proportional hazards regression analyses to predict combined clinical outcomes—consisting of death, stroke, congestive heart failure, and MI—during the follow-up interval. We assessed mortality separately and combined mortality with clinical outcomes categories to provide adequate numbers of events. We performed regression equations in 2 levels: age adjusted and multivariate adjusted for age and measured CAD risk factors (cholesterol, CAD severity, diabetes, education, hypertension, smoking, and body mass index). All analyses were computed as 2-tailed tests. We completed all analyses using SPSS version 10.0 statistical software (SPSS Inc, Chicago, Ill).

RESULTS

Table 1 is an overview of the demographic characteristics, biomedical risk factors, and psychosocial characteristics of our cohort across the categories of depression symptoms. Despite the high rates of cardiac symptoms and suspected myocardial ischemia, we observed a low prevalence of clinically significant CAD based on coronary angiography. Similarly, rates of documented myocardial ischemia by laboratory testing were less than 50% for the cohort.

To assess the risk of selection bias, we compared the 505 women with valid depression information with those without these data on rates of ischemia and clinical events, angiogram results, and major coronary risk factors (data not shown). We observed no differences on CAD risk factors, including smoking, cholesterol, diabetes, hypertension, body mass index, or rates of clinical events during follow-up ($P>.05$ for all comparisons). However, WISE participants without depression data did show more severe CAD on angiogram relative to women with valid depression information (mean maximum angiographic severity, 47.6 vs 35.7, respectively; $P=.008$), as well as higher rates of myocardial ischemia (rates of positive tests, 51% vs 43%, respectively; $P=.04$).

Based on self-reported baseline symptoms and treatment histories, depression was common. Of the 505 participants, 183 (36.2%) had either baseline depression or a treatment history. More than one quarter (129 [25.6%]) reported a history of depression treatment alone, while 93 (18.4%) reported BDI scores of 17 or greater. Despite the relatively high prevalence of depression symptoms, the combination of a treatment history and baseline depression symptoms proved infrequent. A total of only 38 participants (7.5%) reported a combination of elevated depression symptoms and history of treatment for depression.

The results in Table 1 show that depression was associated with a pattern of elevated CAD risk. In all cases, women with elevated BDI scores and a history of depression treatment showed the worst risk factor profiles. Those with both depression markers had significantly lower levels of education, higher rates of hypertension, smaller social networks, and a greater prevalence of smoking compared with those free of depression. Women with high BDI scores and a reported treatment history also differed significantly from those with only 1 of the depression measures on education histories and hypertension rates.

PREDICTION OF MORTALITY AND CLINICAL OUTCOMES

Table 2 describes the results of Cox proportional hazards regression analyses in which the depression symptom categories were used to predict the occurrence of mortality and mortality events combined with stroke, MI,

Table 2. Cox Regression Analyses Predicting Mortality and Combined Clinical Outcomes During Follow-up Using Depression Symptom Patterns in 505 Women*

Regression No. and Description by Depression Group	RR (95% CI)	*P* Value
1. Mortality outcomes: age-adjusted relationships		
High BDI scores or treatment history	1.9 (1.0-3.6)	.06
High BDI scores and treatment history	2.9 (1.2-7.1)	.02
2. Mortality outcomes: age- and CAD risk factor–adjusted relationships†		
High BDI scores or treatment history	1.5 (0.7-2.9)	.27
High BDI scores and treatment history	2.5 (1.0-6.3)	.04
3. Combined outcomes: age-adjusted relationships		
High BDI scores or treatment history	1.6 (1.0-2.6)	.03
High BDI scores and treatment history	2.6 (1.4-4.9)	.003
4. Combined outcomes: age- and CAD risk factor–adjusted relationships†		
High BDI scores or treatment history	1.5 (0.9-2.6)	.10
High BDI scores and treatment history	3.1 (1.5-6.3)	.001

Abbreviations: BDI, Beck Depression Inventory; CAD, coronary artery disease; CI, confidence interval; RR, risk ratio.

*Clinical outcomes were stroke, myocardial infarction, congestive heart failure, or death. The no-depression group served as the reference category for all models.

†Adjusted for age, cholesterol, maximum stenosis score, history of smoking, diabetes, education, hypertension, and body mass index.

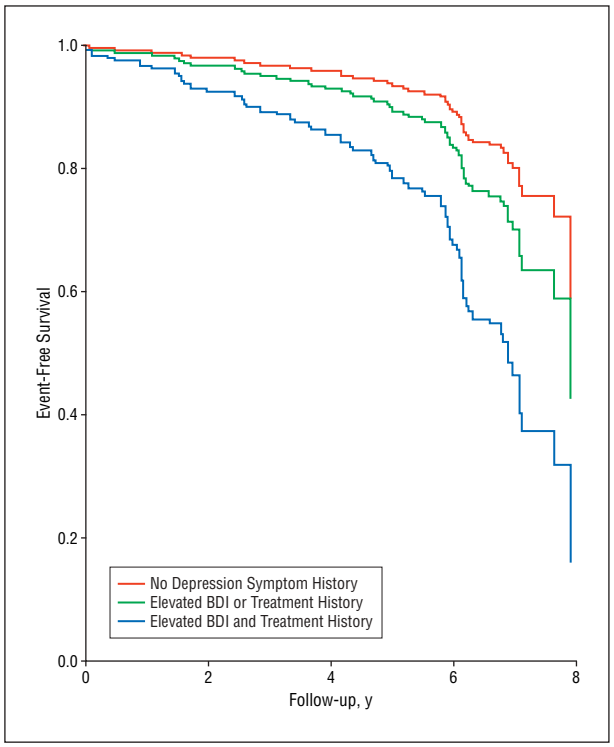

Figure. Multivariate-adjusted survival curves predicting combined clinical outcomes (death, congestive heart failure, myocardial infarction, or stroke) in the Women's Ischemia Syndrome Evaluation using participants' self-reported depression symptom patterns. BDI indicates Beck Depression Inventory.

congestive heart failure, and death during follow-up. There were 44 deaths (8.7%) and 92 clinical events (18.2%) among the patients with depression data. Participants who experienced multiple events (eg, death due to MI) counted for only 1 event. For both depression models, participants with neither a history of treatment nor elevated baseline depression symptoms served as the reference category.

In the depression groups, we found an association between symptom patterns and clinical outcome categories. Participants with a combination of elevated BDI scores and a reported history of treatment were nearly 3 times more likely to die during follow-up relative those with no depression (risk ratio [RR], 2.9; 95% confidence interval [CI], 1.2-7.1) after age-adjustment; this remained robust after the inclusion of CAD risk factors (RR, 2.5; 95% CI, 1.0-6.3). Participants with high baseline depression symptoms or a reported treatment history showed a trend toward elevated mortality risk in the age-adjusted model, but this effect was attenuated by CAD risk factors.

Combining mortality with additional cardiovascular outcomes produced a stronger pattern of relationships. Regressions 3 and 4 of Table 2 illustrate age- and multivariate-adjusted effects for the combined clinical outcomes. Compared with those with no depression, women with any marker of depression were at an elevated risk for events. However, those with a combination of elevated BDI scores and a reported treatment history again showed the strongest pattern, with a nearly 3-fold event risk that remained significant after adjustment. The **Figure** illustrates the survival outcomes for the combined clinical outcome among the 3 depression subgroups. The survival curves for the depression groups differed significantly from those with no depression.

We also compared women having elevated BDI scores and a history of depression treatment with those having only high BDI scores or a treatment history by using the latter group as the reference category. The latter test suggested outcome differences between the groups but did not meet significance criteria (multivariate RR, 2.1; 95% CI, 0.9-4.9; $P=.07$). These results were likely a result of the loss of power caused by removing the participants with no depression, because the overall death and event rates showed a graded trend toward increasingly worse outcomes across the depression groups. The women without depression experienced an event rate of 0.15 and a death rate of 0.07 during follow-up, compared with rates of 0.21 and 0.11 (for all events and death, respectively) among women with elevated BDI scores or a treatment history, and rates of 0.32 and 0.16, respectively, among women with both depression markers. Assessed independently, continuously measured BDI scores were a significant predictor of multivariate adjusted events (RR, 1.03; 95% CI, 1.00-1.06; $P=.05$), as was depression treatment history (RR, 1.9; 95% CI, 1.3-2.9; $P=.01$).

COMMENT

We combined depression symptom information from questionnaires and self-reported treatment history in an attempt to distinguish between depression symptom patterns in the prediction of CAD risk factors and clinical outcomes in a prospective study of women with sus-

pected myocardial ischemia and detailed cardiovascular assessment. This is a relatively novel report in the behavioral medicine literature, which typically relies heavily on baseline severity measures or single-period diagnostic interviews of mental health characteristics. Our objective was to combine measures of past and present depression to approximate a definition of recurrent depressive symptoms in the WISE cohort.

Using self-reported treatment histories for depression, in combination with scores from validated symptom questionnaires, we categorized women into 1 of 3 categories: those with no evidence of clinically significant depression based on no reported history of treatment and low symptom severity at study outset; women reporting either a history of treatment or high BDI scores at baseline but not both; and women with a more recurrent depression presentation based on a combination of a history of treatment and elevated symptoms at baseline. We then compared these symptom pattern groups on an array of established predictors of CAD risk and for differences in the rates of clinical outcomes during the follow-up interval.

For women separated by our depression classification, distinguishing participants with a combination of depression markers revealed an additional tier of risk. Women with both high baseline symptoms and a treatment history were at significantly greater CAD risk and had a nearly 3-fold risk of death and clinical events during follow-up. Although not statistically significant, women with a combination of baseline depression and treatment history also showed trends toward worse outcomes compared with those with only 1 depression marker (ie, elevated BDI scores or a history of treatment).

Our results extend observations by others. Agatisa and colleagues[14] reported a similar pattern of findings in linking Structured Clinical Interview for *DSM-IV*–assessed recurrent depression to the risk of aortic calcification in a sample of healthy middle-aged women. The recurrent depression group was compared with those who experienced no depression or a single episode of depression, indicating that recurrent depression was associated with a greater than 3-fold risk of high aortic calcification measured by electron beam tomography. Recurrent depression has likewise been linked to decreased baroreflex sensitivity[18] and appears to be a common depression subtype among women with CAD risk factors.[19] These results are also consistent with more than a decade of laboratory studies linking depression symptoms with CAD pathophysiological states, such as changes in heart rate variability, platelet dysfunction, and increased production of cortisol.[2,3,9] The pathophysiology of depression may present different kinds of risk at different stages of CAD. Over periods of years or decades, recurrent depression symptoms may increase women's risk for developing atherosclerosis through inducing and maintaining pro-CAD states, such as increased platelet reactivity and hypercortisolemia, while stable depression symptoms in the aftermath of a cardiac event may promote secondary events through an imbalance of sympathetic and parasympathetic systems with resultant reductions in vagal tone.[2]

There is a need to study methods of depression assessment in relation to cardiovascular events.[20] Depression comprises a complex and often individual array of physical and psychological symptoms, many of which can be influenced or directly produced by CAD.[21,22] Symptoms change over time—sometimes spontaneously—while others may appear. Depression can appear as an acute or single episode, can be recurrent, or can be stable for lengthy periods (eg, dysthymia); for reasons that are no doubt in part sociocultural, the prevalence of nearly all forms of depression has increased in recent decades. Women maintain a greater than 2-fold risk of depression relative to men.[23] This requires a continued focus on women by health scientists as a traditionally understudied population in heart disease research. Clarifying depression diagnoses and symptom patterns may help us to identify patients at greatest risk and provide an improved guide for intervention efforts. Results from the Sertraline Antidepressant Heart Attack Randomized Trial (SADHART), for example, showed that recurrent depression was particularly responsive to a sertraline hydrochloride intervention among patients with prior MI.[24] Although the methodologies of the WISE and SADHART studies differ greatly, a possibly emergent theme between the two is that patients who are most likely to respond to a selective serotonin reuptake inhibitor are perhaps also those who face the highest risk of subsequent health complications.

A recent editorial[8] in a leading behavioral medicine journal cited these reasons in calling for researchers to pay increased attention to depression definitions in cardiac research. Our results are consistent with the notion that distinguishing symptom patterns can provide additional insight into the depression–heart disease relationship. Future research can expand on these findings in several directions. As indicated, there is a need to replicate these findings using a validated assessment method for recurrent depression. Furthermore, extending the differentiation of depression to samples with clinically significant CAD or alternative measures of CAD severity, such as intravascular ultrasound or electron beam tomography, is an important next step. Finally, our findings suggest that prospective studies of depression and CAD could benefit from including depression measures at multiple time points to track the stability and course of depression symptoms in relation to health event risk.

Although the WISE study contains both cross-sectional and prospective components, the method and sample composition differ in important ways from most previous cardiovascular studies in behavioral medicine. The WISE study was designed to identify factors that could improve the prediction of atherosclerosis in women. Participants were identified and referred by physicians on the basis of suspected myocardial ischemia. As such, this was a highly symptomatic sample—showing comparatively higher levels of physical symptoms and psychosocial distress in relation to a healthy community sample—but was also a group that proved to have relatively low rates of clinically significant CAD on the basis of angiogram results.[15]

Because of these characteristics, our results cannot be generalized to samples with more advanced CAD, with

a history of cardiac events, or of healthy women. It is also possible that psychosocial characteristics of WISE participants affected their symptom presentation and likelihood of study referral. In fact, this theory—that physicians may have been more likely to refer women for cardiac testing if they were reporting greater levels of emotional distress—was described in previous reports from WISE showing that an anxiety treatment history was actually linked to less severe atherosclerosis.[25] The same relationship may also be true of depression, supported here by the statistical trend toward lower rates of ischemia seen among women with high baseline depression and a treatment history compared with other groups. Anxiety and depression symptoms are usually strongly correlated, and the conditions share an important quality in that individuals with these characteristics are frequently highly somatic and body focused, reporting elevations of many types of physical health symptoms in addition to emotional symptoms.[26]

An additional limitation concerns the method by which we defined our depression groups. The use of questionnaires is common in behavioral medicine research for the assessment of mental health characteristics, but it is a poor substitute for detecting the presence of true disorders by using validated interviews. We did not query for *DSM-IV* conditions in WISE, and even our questions concerning mental health history concerned treatment and not diagnosis. Furthermore, we did not assess important factors such as the length of time since treatment, the type of treatment, symptom duration (which could have ranged from months to decades), the effects of treatment based on a review of treatment history reports, or participants' current use of depression treatments at study baseline. We also cannot discount the possibility that selective use of depression treatments during the study could have mitigated the prospective findings.

Finally, statistical power was limited in this study by the combination of the sample size and the low rate of clinical events. This limited somewhat the number of covariates we were able to include in our survival analyses and contributed to the imprecision of the presented CIs. Our statistical models also did not include other potentially important factors, such as peripheral vascular disease or chronic obstructive pulmonary disease, which could have produced some degree of unmeasured confounding.

In summary, this report highlights the need for further research clarifying the definition and diagnosis of depression in women at increased risk for CAD. On the basis of simple and easily administered self-reports, a combination of elevated depression symptoms and a history of depression treatment was associated with significant increases in CAD risk profile and cardiac event rates compared with those having no depression or less stable depression patterns. Our results suggest that depression is highly prevalent in women who are at risk for CAD and reinforce the need for primary care providers to carefully screen for depressive symptoms when assessing CAD risk. More research is needed to confirm these findings using improved clinical methods for diagnosing depression subtypes, and to extend the findings to populations with higher rates of CAD.

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