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Depressive Symptom Clusters as Predictors of Incident Coronary Artery Disease Events: A 15-Year Prospective Study of Older Adults

Misty A.W. Hawkins, PhD, **Christopher M. Callahan, MD**, **Timothy E. Stump, MA**, and **Jesse C. Stewart, PhD**
Department of Psychology, Kent State University (M.A.W.H.), Department of Psychology, Indiana University-Purdue University Indianapolis (J.C.S), Department of Medicine, Indiana University School of Medicine (T.E.S, C.M.C), Indiana University Center for Aging Research, Indiana University School of Medicine (C.M.C.), Regenstrief Institute, Inc. (C.M.C.), Indianapolis, IN

Abstract

Objective—Because it is not known whether particular clusters of depressive symptoms are more cardiotoxic than others, we compared the utility of four clusters in predicting incident coronary artery disease (CAD) events over 15 years in large cohort of older primary care patients.

Methods—Participants were 2,537 primary care patients aged ≥ 60 years who were screened for depression between 1991–1993 and had no existing CAD diagnosis. Depressive symptoms clusters scores (depressed affect, somatic symptoms, interpersonal distress, and positive affect) were computed from responses on the Center for Epidemiologic Studies Depression Scale administered at baseline. CAD events, defined as the occurrence of a nonfatal acute myocardial infarction or CAD death during the follow-up period, were identified using electronic medical record and National Death Index data.

Results—There were 678 CAD events. In separate fully-adjusted Cox proportional hazard models (controlling for demographics and cardiovascular risk factors), the depressed affect (*HR* = 1.11, 95% *CI*: 1.04–1.20), somatic (*HR* = 1.17, 95% *CI*: 1.08–1.26), and positive affect (*HR* = 0.88, 95% *CI*: 0.82–0.95) clusters each predicted CAD events. When the depressive symptom clusters were entered simultaneously into the fully-adjusted model, however, only the somatic cluster remained predictive of CAD events (*HR* = 1.13, 95% *CI*: 1.03–1.23).

Conclusions—Our findings suggest that the longitudinal relationship between overall depressive symptom severity and incident CAD events may be driven primarily by the somatic cluster.

Keywords

Coronary artery disease; depression; depressive symptoms clusters; elderly; primary care; prospective study

Address Correspondence and Reprint Requests to: Jesse C. Stewart, PhD, Department of Psychology, Indiana University-Purdue University Indianapolis, 402 North Blackford Street, LD 100E, Indianapolis, IN 46202. Phone: (317) 274-6761. Fax: (317) 274-6756. jstew@iupui.edu.

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Introduction

Prospective epidemiologic evidence amassed over the past three decades indicates that depressive disorders and elevated depressive symptoms independently predict incident coronary artery disease (CAD) events (1). Depression was treated as a unidimensional construct in most of these investigations; however, depression is multidimensional, consisting of affective, cognitive, behavioral, and somatic symptom clusters (2). There is now a small but growing body of literature comparing the relative importance of depressive symptom clusters in predicting CAD-related outcomes among adults initially free of cardiovascular disease; however, results have been inconsistent. In approximately half of these studies, the somatic cluster was found to be the most predictive of CAD-related outcomes (3–5), whereas other studies reported similar results for the cognitive (6–8) and affective (9) clusters. Given the dearth of investigations and the conflicting findings, it remains unknown whether particular depressive symptom clusters are stronger predictors of incident CAD than are others.

Addressing this knowledge gap could have significant scientific and clinical implications. Determining which clusters are the most cardiotoxic could help to identify the mechanisms underlying the depression-CAD relationship by increasing the plausibility of some candidate mediators while decreasing that of others (10). In addition, systematically targeting the most cardiotoxic clusters and the corresponding mechanisms could result in more effective and efficient CAD prevention efforts. Finally, such findings could provide clues as to why past depression clinical trials have not observed the anticipated cardiovascular benefits (11). For instance, if somatic symptoms are found to have the greatest cardiotoxicity but a particular depression intervention is more efficacious for the affective and cognitive symptoms, it would not be surprising if that intervention had little effect on the likelihood of future CAD events. Consistent with this notion is evidence indicating that the somatic symptoms of depression are often residual or emergent symptoms after depression treatment (12, 13), although other evidence suggests that both antidepressants and psychotherapy have similar treatment effects on various symptom clusters (14–16). Given the high costs and long duration of prospective cohort studies, reanalysis of investigations in which depression was initially treated as a unidimensional construct could be instrumental in determining which clusters are the strongest predictors of incident CAD events (17).

Accordingly, our objective was to compare the utility of four depressive symptom clusters in predicting incident CAD events in large cohort of older primary care patients with no existing CAD diagnosis. We previously reported that, among 2,728 patients initially free of cardiovascular disease, elevated overall depressive symptom severity was associated with a 46% greater risk of acute myocardial infarction or CAD death over a 15-year period (18). In this report, we extend these past findings by determining which clusters – depressed affect, somatic symptoms, interpersonal problems, and/or (lack of) positive affect – are driving this longitudinal relationship.

Method

Participants

Participants were 2,537 older men and women screened for depression by research assistants during regularly scheduled primary care appointments in an urban public health setting in Indianapolis, IN, between 1991 and 1993. Details regarding the screening process are available elsewhere (19–21). All primary care patients aged 60 years and older (N = 4,413) were approached for screening, of whom 115 patients refused, 57 could not complete the screener due to severe cognitive impairment, and 284 were not eligible because they did not speak English, were institutionalized, or had a hearing impairment. No other eligibility

criteria were used. Of the remaining 3,957 patients, 190 individuals were excluded from our analyses who were unable to answer more than four of the CES-D items. For the current study, an additional 1,039 patients were excluded because, at baseline, they had an existing diagnosis of CAD, congestive heart failure, cerebrovascular accident, or atherosclerotic vascular disease. We determined the presence of these conditions using physician diagnoses as recorded in the electronic medical record (18). From the resulting sample of 2,728 primary care patients, we selected those who had complete data for each of the depressive symptom subscales yielding a final sample of 2,537 patients.

Measures and Procedures

Depressive Symptoms Clusters—To assess depressive symptom clusters, we used the 20-item Center for Epidemiologic Studies Depression Scale (CES-D), which has demonstrated good internal consistency, test-retest reliability, and construct validity (22). Our previous exploratory factor analysis using principal component analysis with oblique rotation in this cohort (21) generated a four-factor solution: depressed affect (Items 1, 3, 6, 10, 14, 17, 18), somatic symptoms (Items 2, 7, 11, 13, 20), interpersonal distress (Items 15 and 19), and positive affect (Items 4, 8, 12, 16). Similar, though not identical, four-factor structures have been reported by others (2, 23). The “mind” and “failure” items were excluded because they did not load on any factor in our previous factor analysis, and the “bothered” item was included in the depressed affect subscale (21). Thus, we computed subscale scores using 18 items and summed the items that loaded on each factor. Analyses with the CES-D total score used all 20 items.

Coronary Artery Disease Events—Our outcome variable was incident CAD events, defined as the occurrence of a nonfatal myocardial infarction (MI) or CAD death after the depression screen date. Nonfatal MI was defined as a serum creatine kinase-myocardial band isoenzyme test value > 3.0 ng/mL or a serum troponin test value > 0.3 μg/L as recorded in the Regenstrief Medical Record System. Providers at each site of the targeted health system electronically record all diagnoses, test results, procedures, and prescribed medications. This information is stored in a searchable database, the Regenstrief Medical Record System, which has been frequently utilized for clinical epidemiologic research (24). CAD death was determined using National Death Index data. A death was classified as CAD death if ischemic heart disease (ICD-9 codes: 410–414, ICD-10 codes I20-I25) was the first-listed cause on the death certificate. Patients were censored at the time of non-CAD death or the end of the observation period (December 31, 2006). Because screening began in January 1991 and ended in May 1993, patients had 13–16 years of follow-up. For presentation proposes, we refer to the follow-up period as being 15 years.

Covariates—Information regarding our primary covariates, including demographic factors (age, sex, and race) and cardiovascular risk factors (diabetes, hypertension, smoking, hyperlipidemia, and excess body weight), were extracted from the Regenstrief Medical Record System (24) at the time of depression screening. We also included the following secondary covariates in an exploratory model: years of education, cancer, anemia, chronic obstructive pulmonary disease (COPD), arthritis, hypoalbuminemia, alcohol problems, and cognitive functioning. If a patient’s physician ever diagnosed the patient with diabetes, hypertension, cancer, anemia, COPD, or arthritis or indicated that a patient was a smoker before the screening date, we coded that patient as having a positive history of the respective condition at baseline. Hyperlipidemia was defined as a total cholesterol level > 200 mg/dL. As in our previous report (18), patients whose weight was in the highest quartile of our sample were coded as having excess body weight. Hypoalbuminemia was defined as a serum albumin level < 3.5 g/dL. Alcohol problems (defined as a score ≥ 2) were assessed

using the CAGE (25), and cognitive functioning was assessed using the Short Portable Mental Status Questionnaire (26).

Statistical Analyses

We first conducted independent samples *t* tests and chi-square tests to compare the depression groups on the baseline characteristics. Then, we evaluated the internal consistency of and bivariate correlations among the depressive symptom measures. To compare the relative importance of depressive symptom clusters in predicting incident CAD events, we performed three sets of Cox proportional hazards regression models – demographics-adjusted, fully-adjusted, and simultaneous entry. To facilitate comparisons of effect sizes, depressive symptom measures were converted to *z* scores. Covariates in demographics-adjusted models were age, sex, and race; additional covariates in the fully-adjusted models were cardiovascular risk factors (diabetes, hypertension, smoking, hyperlipidemia, and excess body weight). In the demographics-adjusted and fully-adjusted models, each CES-D score was entered into a separate model as the predictor variable. In the simultaneous-entry models, all of the CES-D subscale scores were forced into the same model along with the covariates of the demographics-adjusted models (Model #1) or the fully-adjusted models (Model #2) to determine which subscales were unique predictors of CAD events.

We also constructed an exploratory model that contained the four CES-D subscales, demographic factors, cardiovascular risk factors, and secondary covariates (education, cancer, anemia, COPD, arthritis, hypoalbuminemia, alcohol problems, and cognitive functioning) to determine whether any observed effects remained after adjusting for a marker of socioeconomic status and other health-relevant factors. For CES-D subscales found to be unique predictors of CAD events, survival curves (adjusted for age, sex, race, diabetes, hypertension, smoking, hyperlipidemia, excess body weight and all other CES-D subscale scores) were created by stratifying model effects by ≥ +1 *SD* and < +1 *SD* above the mean of the selected subscale score. These subscale cut points were designed to be analogous to the CES-D total clinical cut point of ≥ 16 (22). Lastly, for CES-D subscales found to be unique predictors, we examined the individual items in separate exploratory models (adjusted for demographic factors, cardiovascular risk factors, and the other CES-D subscales) to determine which items might drive the association between that subscale and CAD events.

Results

Depressed patients were younger and more likely to be female and to have a history of smoking but were less likely to be African American and to have a history of hypertension than nondepressed patients (Table 1). The mean CES-D total score was in the subclinical range (Table 2). Although the CES-D total score and depressed affect subscale had adequate internal consistency (Cronbach's $\alpha \geq .70$), the other three subscales fell short of this cut point. The CES-D subscales were moderately to weakly correlated in the expected directions. The combined endpoint of acute MI or CAD death occurred in 678 (26.7%) patients, and among these individuals, the mean time to event was 8.4 years (*SD* = 4.0).

Demographics-adjusted Cox models revealed that CES-D total score was a predictor of CAD events ($p < .001$) such that a 1-*SD* increase in the score was associated with a 17% greater risk of an event (Table 3). Each subscale score, except interpersonal distress ($p = .23$), also predicted CAD events (depressed affect: $p = .003$; somatic symptoms: $p < .001$; positive affect: $p < .001$). A 1-*SD* increase in the depressed affect and somatic symptoms scores was associated with an 11% and 17% increase in risk, whereas the same change in the positive affect score was associated with a 12% decrease in risk. Adjusting for

cardiovascular risk factors did not alter the results. However, in the simultaneous entry model adjusted for demographics (Model #1), only the somatic symptoms (p = .011) and positive affect (p = .044) scores remained predictors of CAD events. Furthermore, the somatic symptoms score (p = .011), but not the positive affect score (p = .075), remained predictive of events in the simultaneous entry model adjusted for all covariates (Model #2). Variance inflation factor values for all of the predictor variables in the simultaneous-entry models were all ≤ 1.70, indicating that multicollinearity was not an issue.

In an exploratory model containing the four CES-D subscales, demographic factors, cardiovascular risk factors, and secondary covariates (education and other health-relevant factors), the somatic symptoms subscale remained predictive of CAD events (*HR* = 1.12, 95% *CI*: 1.02–1.23), whereas no other subscale was a predictor (all *p*s ≥ .10). Figure 1 displays survival curves (adjusted for demographic factors, cardiovascular risk factors, and the other CES-D subscales) illustrating the time to CAD event among patients with (≥ +1 *SD*) and without (< +1 *SD*) elevated somatic symptoms. As can be seen, patients with somatic symptoms scores ≥ +1 *SD* above the mean (n = 371; 15% of the sample) were more likely to experience a CAD event over the 15-year period than those with scores < +1 standard deviation above the mean (n = 2,166; 85% of the sample). These percentages are comparable to the 16% of patients classified as depressed (CES-D total ≥ 16) in our original report (18). When the individual somatic items were examined as predictors of CAD events in separate models (adjusted for demographic factors, cardiovascular risk factors, and the other CES-D subscales), the following two items were predictive of CAD events: “I did not feel like eating; my appetite was poor” (*HR* = 1.11, 95% *CI*: 1.03–1.21, p = .008) and “I felt that everything I did was an effort” (*HR* = 1.11, 95% *CI*: 1.03–1.20, p = .005). The other three items – “I talked less than usual” (p = .90), “I could not get going” (p = .52), and “My sleep was restless” (p = .66) – were not predictors of CAD events.

Discussion

In a large sample of older primary care patients initially free of CAD diagnosis, we found that the depressed affect, somatic, and positive affect clusters of depressive symptoms each predicted incident CAD events over a 15-year period. Only the somatic cluster, however, remained predictive of CAD events after adjusting for cardiovascular risk factors and the other depressive symptom clusters. Further adjustment for education and other health-relevant factors did not alter these results. Our findings suggest that the longitudinal relationship between overall depressive symptom severity and incident CAD events that we previously reported in this cohort (18) was driven primarily by the somatic cluster, although a lack of positive affect contributed to a lesser extent. Exploratory item-level analyses revealed that the somatic items assessing poor appetite and activities requiring high effort drove the association between somatic symptoms and CAD events. Although it is likely that the poor appetite item specifically assesses hypophagia, the high effort item could reflect depression-related fatigue, anhedonia, and/or psychomotor retardation. However, because other subscales and items assessing anhedonia (positive affect subscale) and psychomotor retardation (talk less item) did not independently predict CAD events, the predictive utility of this item may stem from its assessment of fatigue.

There are several possible explanations for why the somatic cluster was found to be a stronger predictor of CAD events. One possible explanation may be the older age of our sample. The majority of studies observing that the somatic symptoms were the most predictive of CAD-related outcomes involved adults aged ≥ 50 years (4, 5), whereas most studies reporting similar results for the affective or cognitive symptoms involved middle-aged adults (6, 8, 9). As compared to middle-aged adults, older adults tend to report more somatic and fewer cognitive symptoms of depression (27). Greater endorsement of the

somatic symptoms could, in turn, result in improved sensitivity and/or increased variability of the somatic cluster, properties that could increase its ability to predict CAD outcomes. In addition, older adults may be more likely than middle-aged adults to suffer from vascular depression (28), in which depressive symptoms are thought to be a consequence subclinical cerebrovascular disease. This could also increase the somatic cluster's utility in predicting CAD events, given that the extent of atherosclerosis in one vascular bed is indicative of disease in other beds (29). Thus, for a portion of our sample, elevated somatic symptoms may have reflected greater subclinical cardiovascular disease in general, thereby placing these individuals at elevated risk for incident CAD events.

Another explanation is that the somatic cluster may have been the most predictive of incident CAD events because the somatic symptoms may be more strongly linked to the mechanisms thought to underlie the depression-CAD relationship. For example, we previously observed that the somatic-vegetative symptoms of depression, but not the cognitive-affective symptoms, predicted 6-year increases in interleukin-6 (5), a proinflammatory cytokine predictive of future CAD (30). Next, the somatic cluster may be more strongly associated than the other clusters with a third factor potentially predictive of both depression and CAD, such as genetic variants related to systemic inflammation (31). Lastly, elevated somatic symptoms may be a marker of other medical conditions that may promote the development of CAD. Results of our exploratory model do not support this notion, as the somatic cluster remained predictive of CAD events after adjusting for many medical conditions, health behaviors, and other health-relevant factors. However, because we could not adjust for all possible medical confounders, this explanation remains a possibility. For instance, certain sleep disorders, such as sleep apnea and insomnia, could lead to an elevation in the somatic symptoms of depression and contribute to the development of CAD (32, 33). There is a clear need for future studies to evaluate each of these possibilities.

One potential limitation of this study is our measure of depressive symptoms. Although the CES-D has strengths (e.g., strong psychometric properties and a well-defined factor structure), it does not assess all facets of the depression construct, such as thoughts of death/dying. In addition, the internal consistency of some CES-D subscales in our sample fell below the adequate cut point, which could in part explain the lack of association of the interpersonal distress cluster with incident CAD events. It should be noted, however, that the internal consistency of the somatic subscale, which predicted CAD events in all models, was comparable to that of the interpersonal distress subscale. A second potential limitation is our use of nonfatal MI or CAD death only to identify incident CAD events. Although this definition has high specificity, it also has lower sensitivity, as incident CAD cases identified via exercise testing or cardiac catheterization only, for example, would not be captured. A final limitation is that we did not obtain data regarding antidepressant use from this cohort. Thus, we cannot determine whether the use of antidepressants with known adverse cardiovascular effects, such as tricyclic antidepressants (34), is partially responsible for the observed relationship between depressive symptoms and incident CAD events.

To conclude, the present results indicate that the longitudinal relationship between overall depressive symptom severity and incident CAD events among older adults may be driven primarily by the somatic symptoms of depression. Our results, combined with similar findings, could inform the development of interventions designed to simultaneously treat depression and reduce CAD risk among older men and women. Specifically, our findings suggest that such interventions should have demonstrated efficacy for the somatic symptoms of depression, particularly reduced appetite and fatigue, if cardiovascular benefits are to be expected. Existing depression interventions that may be good candidates and worthy of

further evaluation include appetite-stimulating antidepressants, such as mirtazapine (35), and exercise training (36).

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Glossary

CAD	coronary artery disease
CES-D	Center for Epidemiologic Studies Depression Scale
HR	hazard ratio
MI	myocardial infarction

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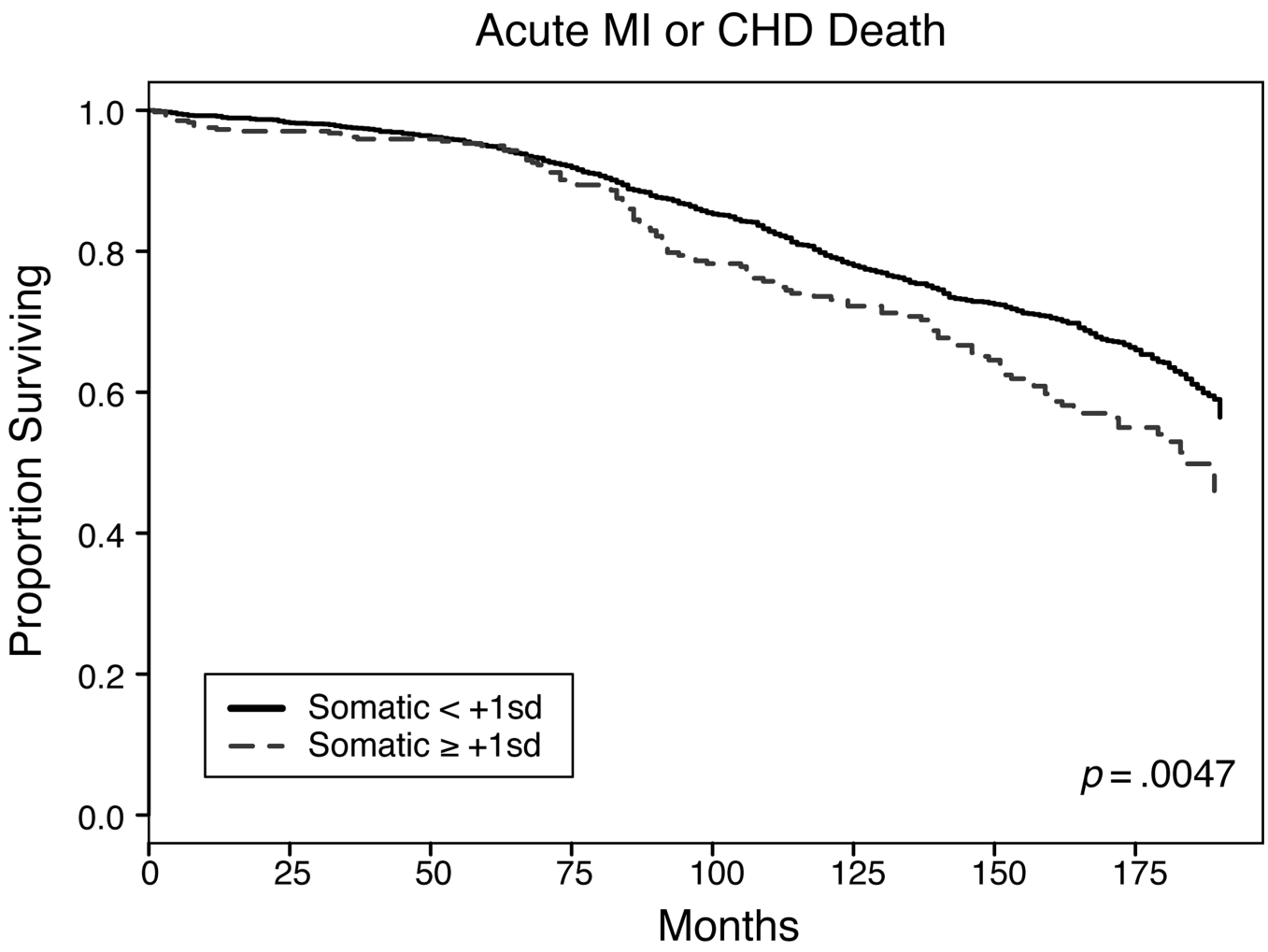

Figure 1.
Survival curves illustrating the time to coronary artery disease (CAD) event over the 15-year follow-up period among primary care patients with (≥ +1 *SD*) and without (< +1 *SD*) elevated somatic symptoms of depression. Survival curves are adjusted for age, sex, race, diabetes, hypertension, smoking, hyperlipidemia, excess body weight, and the three other CES-D subscale scores.

Table 1

Baseline Characteristics of Participants (N = 2,537)

	Depression Status[a]	
	Nondepressed (*n* = 2,151)	**Depressed (*n* = 386)**
Demographic Factors		
Age, mean (*SD*)	67.6	66.1*
Female, %	70.5	76.7*
African American, %	69.3	52.1*
Cardiovascular Risk Factors		
Diabetes, %	20.5	23.8
Hypertension, %	62.3	56.0*
History of Smoking, %	27.5	32.6*
Hyperlipidemia, %	48.8	51.6
Excess Body Weight (highest quartile), %	25.6	23.3

[a] Primary care patients with a Center for Epidemiologic Studies Depression Scale (CES-D) score ≥ 16 were classified as depressed, whereas patients with a CES-D score < 16 were classified as nondepressed (22).

* Independent *t* tests for continuous variables and chi-square tests for categorical variables indicate that the depressed group value differs from nondepressed group value ($p < .05$).

Table 2

Descriptive Statistics for and Correlations among the Depressive Symptom Measures

Measure (possible range)	*M* ± *SD*	Cronbach's α	1.	2.	3.	4.
1. CES-D Total (0–60)	8.1 ± 8.3	0.84	---			
2. Depressed Affect (0–21)	2.6 ± 3.5	0.77	.87	---		
3. Somatic Symptoms (0–15)	3.0 ± 3.1	0.63	.79	.53	---	
4. Interpersonal Distress (0–6)	0.3 ± 0.9	0.58	.40	.30	.18	---
5. Positive Affect (0–12)	1 10.3 ± 2.4	0.59	−.71	−.49	−.38	−.22

Note. N = 2,537. All correlations $p < .01$. CES-D = Center for Epidemiologic Studies Depression Scale.

Table 3

Cox Proportional Hazard Models Predicting Coronary Artery Disease (CAD) Events

	Demographics-Adjusted Models[a]	**Fully-Adjusted Models**[b]	**Simultaneous-Entry Model #1**[a,c]	**Simultaneous-Entry Model #2**[b,c]
	***HR* (95% *CI*)**	***HR* (95% *CI*)**	***HR* (95% *CI*)**	***HR* (95% *CI*)**
CES-D Total	1.17** (1.09–1.26)	1.17** (1.09–1.26)	---	---
Depressed Affect Subscale	1.11** (1.04–1.20)	1.11** (1.04–1.20)	1.01 (0.91–1.11)	1.01 (0.92–1.11)
Somatic Symptoms Subscale	1.17** (1.08–1.26)	1.17** (1.08–1.26)	1.13* (1.03–1.23)	1.13* (1.03–1.23)
Interpersonal Distress Subscale	1.04 (0.97–1.12)	1.05 (0.98–1.13)	1.00 (0.93–1.08)	1.01 (0.94–1.09)
Positive Affect Subscale	0.88** (0.82–0.94)	0.88** (0.82–0.95)	0.92* (0.84–1.00)	0.93 (0.85–1.01)

Note. *N* = 2,537 (678 CAD events). CES-D = Center for Epidemiologic Studies Depression Scale. HR = hazard ratio. CI = confidence interval.

[a] Adjusted for age, sex, and race.

[b] Adjusted for age, sex, race, diabetes, hypertension, smoking, hyperlipidemia, and excess body weight.

[c] Adjusted for all other CES-D subscale scores.

* $p < .05$

** $p < .01$