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Behavioral Mechanisms, Elevated Depressive Symptoms, and the Risk for Myocardial Infarction or Death in Individuals With Coronary Heart Disease

The REGARDS (Reason for Geographic and Racial Differences in Stroke) Study

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Objectives The aim of this study was to determine whether behavioral mechanisms explain the association between depressive symptoms and myocardial infarction (MI) or death in individuals with coronary heart disease (CHD).

Background Depressive symptoms are associated with increased morbidity and mortality in individuals with CHD, but it is unclear how much behavioral mechanisms contribute to this association.

Methods The study included 4,676 participants with a history of CHD. Elevated depressive symptoms were defined as scores ≥4 on the Center for Epidemiologic Studies Depression 4-item Scale. The primary outcome was definite/probable MI or death from any cause. Incremental proportional hazards models were constructed by adding demographic data, comorbidities, and medications and then 4 behavioral mechanisms (alcohol use, smoking, physical inactivity, and medication non-adherence).

Results At baseline, 638 (13.6%) participants had elevated depressive symptoms. Over a median 3.8 years of follow up, 125 of 638 (19.6%) participants with and 657 of 4,038 (16.3%) without elevated depressive symptoms had events. Higher risk of MI or death was observed for elevated depressive symptoms after adjusting for demographic data (hazard ratio [HR]: 1.41, 95% confidence interval [CI]: 1.15 to 1.72) but was no longer significant after adjusting for behavioral mechanisms (HR: 1.14, 95% CI: 0.93 to 1.40). The 4 behavioral mechanisms together significantly attenuated the risk for MI or death conveyed by elevated depressive symptoms (−36.9%, 95% CI: −18.9 to −119.1%), with smoking (−17.6%, 95% CI: −6.5% to −56.0%) and physical inactivity (−21.0%, 95% CI: −9.7% to −61.1%) having the biggest explanatory roles.

Conclusions Our findings suggest potential roles for behavioral interventions targeting smoking and physical inactivity in patients with CHD and comorbid depression. (J Am Coll Cardiol 2013;61:622–30) © 2013 by the American College of Cardiology Foundation

In recent years, there has been considerable interest in the negative impact of depression on outcomes among patients with coronary heart disease (CHD) (1). It is estimated that approximately 20% of individuals with CHD meet criteria for major depression, and up to 40% experience some depressive symptoms (2,3). Furthermore, the presence of depression or elevated depressive symptoms in individuals

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with CHD has consistently been shown to be associated with a markedly increased risk of adverse events including death and myocardial infarction (MI) (2–7). Because of this, national guidelines have recommended screening and treatment of depression in individuals with CHD (1). However, the evidence for improving cardiac outcomes by treating depression has been limited, and trials of interventions to improve depression thus far have shown equivocal results with regard to improving cardiac risk (8–10).

A better understanding of mechanisms by which depression conveys cardiac risk might suggest alternative approaches for improving outcomes in individuals with concomitant depression and CHD. Recent studies have noted the potential role of behavioral mechanisms that are associated with both depression and cardiac risk. For instance, smoking (2), physical inactivity (2,11), and medication non-adherence (12) have all been shown to explain part of the increased risk for adverse cardiac outcomes conveyed by depression. However, most studies focused on different individual behavioral mechanisms in selected populations, limiting their generalizability. In the current study, we sought to clarify the collective contribution of behavioral mechanisms to the increased cardiac risk conveyed by elevated depressive symptoms in individuals with CHD. Specifically, we examined the explanatory role played by alcohol use, smoking, physical inactivity, and medication non-adherence in the association between depressive symptoms and MI or death in participants with CHD enrolled in the REGARDS (REason for Geographic and Racial Differences in Stroke) study.

Methods

Details on the REGARDS study have been published previously (13). In brief, the REGARDS study is a population-based cohort study of stroke incidence and cognitive decline with the incidence of CHD being investigated through an ancillary study. The study enrolled adults ≥45 years of age from the continental United States. Potentially eligible participants were identified from commercially available lists of U.S. residents and sent an initial mailing that provided details of the study. This mailing was followed by a telephone call and a subsequent in-home visit, during which time participants were enrolled. Between January 2003 and October 2007, 30,239 African-American and white adults were enrolled. The current analysis was limited to 5,346 participants with a history of CHD (as defined in the following text) at baseline. Of these participants, 26 did not complete depression screening at baseline, and 92 were missing follow-up data for outcomes. Additionally, we excluded 520 participants who were missing covariate information. After these exclusions, the analysis included 4,676 participants with complete data. The REGARDS study protocol was approved by the institutional review boards at the participating centers, and all participants provided informed consent.

Abbreviations and Acronyms

BMI = body mass index
CHD = coronary heart disease
CI = confidence interval
HR = hazard ratio
MI = myocardial infarction

Data collection. The REGARDS study baseline data collection included a computer-assisted telephone interview, an in-home examination, and self-administered questionnaires. Trained research staff conducted telephone interviews to collect demographic data and data on education; income; cigarette smoking; physical activity; aspirin and thienopyridine use; and use of antihypertensive, anti-glycemic, and cholesterol-lowering medications. During the in-home study visit, trained and certified health professionals conducted a physical examination and collected biological samples. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Blood pressure was measured 2 times following a standardized protocol (14). On the basis of the average of the 2 blood pressure measurements, hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, and/or self-reported use of antihypertensive medication. Diabetes was defined as a serum glucose ≥126 mg/dl for participants who had fasted ≥8 h before their in-home study visit, serum glucose ≥200 mg/dl for those who had not fasted, or self-report of a prior diagnosis of diabetes with current use of insulin or oral hypoglycemic medications. A history of MI and stroke were identified via self-report. Also, during the in-home visit, participants were asked to provide all medications they had taken in the past 2 weeks, and medication names were recorded and subsequently coded into drug classes. During the in-home examination, an electrocardiogram was performed. A history of CHD at baseline was defined as a self-reported history of MI or coronary revascularization procedure (percutaneous coronary intervention or coronary artery bypass surgery) or evidence of MI on the study electrocardiogram.

For the current analysis, we focused on 4 behavioral mechanisms: alcohol use, smoking, physical inactivity, and medication non-adherence. On the basis of prior published data, light/moderate and heavy alcohol consumption was defined as consuming >0 to 14 and ≥15 alcoholic beverages/week, respectively, for men and >0 to 7 and ≥8 alcoholic beverages/week, respectively, for women (15,16). Current smoking was determined by affirmative responses to both of the following yes/no questions: "Have you smoked at least 100 cigarettes in your lifetime?" and "Do you smoke cigarettes now, even occasionally?" Physical inactivity was assessed through a single question: "How many times per week do you engage in intense physical activity, enough to work up a sweat?" with response options of "none," "1 to 3 times per week," and "4 or more times per week." Medication non-adherence was assessed with the 4-item Morisky Medication Adherence Scale. Each item has a yes/no response option. One point is assigned to each "yes" response, and points are summed (totaling 0 to 4),

with score of 3 or 4 indicating high risk of medication non-adherence (17,18).

Depressive symptoms. The brief, 4-item Center for Epidemiologic Studies Depression Scale was used to assess the presence of depressive symptoms, by asking how often over the prior week the participant: 1) felt depressed; 2) felt lonely; 3) had crying spells, and 4) felt sad, with response options of <1 day (no points), 1 to 2 days (1 point), 3 to 4 days (2 points), and 5 to 7 days (3 points). Elevated depressive symptoms were defined as having a summed score ≥4, which had been reported to have 79.2% sensitivity and 86.4% specificity for meeting a previously established threshold for having clinically significant depressive symptoms as assessed by the full 20-item Center for Epidemiologic Studies Depression Scale (19,20).

Outcomes. The outcomes for the current study included definite/probable MI or death from any cause. Outcome data through December 31, 2008 were used in this analysis. Participants were contacted twice yearly by telephone to identify potential events, subsequent to the REGARDS in-home examination. When a cardiac-related hospital stay was reported, medical records were retrieved and reviewed by a team of trained physicians with a standardized protocol (21). Records were examined for the presence of signs or symptoms suggestive of ischemia, typical rise and fall of cardiac enzymes, and electrocardiogram changes consistent with ischemia or MI, guided by the Minnesota code (22,23). The MIs were adjudicated as being definite, probable, or possible on the basis of published guidelines (22). For participants who were unable to be contacted for their bi-annual interviews, an interview was conducted with the next of kin listed on study forms, and when deaths were reported, the date of death was confirmed through the Social Security Death Index, death certificates, or the National Death Index. Follow-up time was recorded as the number of days from the baseline in-home visit to confirmed date of death of participant, occurrence of a definite or probably MI, or their last REGARDS study telephone contact before December 31, 2008, whichever occurred first.

Statistical analyses. Characteristics of REGARDS study participants with a history of CHD were calculated by depressive symptom status and compared via *t* tests and chi-square tests, as appropriate. With the Kaplan-Meier approach, the cumulative incidence was calculated for participants with and without depressive symptoms, separately, for: 1) the primary outcome of definite/probable MI or death; 2) definite/probable MI (fatal or nonfatal); and 3) death from any cause. Next, the hazard ratio (HR) for the primary outcome associated with depressive symptoms was calculated in 3 nested models. The first model (Model 1) included adjustment for demographic data (age, sex, race), education, income, and BMI. The next model (Model 2) included additional adjustment for comorbid conditions (hypertension, diabetes mellitus, self-reported history of stroke, and self-reported history of MI) and cardiovascular medication use (aspirin, beta blockers, thienopyridines, ACE-inhibitors/angiotensin receptor blockers, statins, and antidepressants). The final model (Model 3) included additional adjustment for behavioral mechanisms, including alcohol use, cigarette smoking, physical inactivity, and medication non-adherence. For physical activity, because those who reported "1 to 3 times per week" and "4 or more times per week" had similar HRs as compared with the reference group of those who reported "none," the final model considered physical activity as a dichotomous variable, where participants who answered "none" were classified as physically inactive. We also repeated, as a sensitivity analysis, the aforementioned analysis after excluding probable MI (fatal or nonfatal) from the outcome.

To quantify the amount of association between elevated depressive symptoms and CHD risk that is explained by behavioral risk factors (24), we used the bootstrap method recommended by Preacher and Hayes (25,26). Specifically, with the model that included age, sex, race, education, income, and BMI, the percentage of the association between depressive symptoms and the primary outcome explained by comorbidities, medication use, and behavioral mechanisms was calculated. To do so, we used a 1,000-iteration bootstrap; each iteration included 4,676 observations chosen at random from the original dataset with replacement. For each iteration, we modeled the primary outcome with and without adjustment for the explanatory variables (β_{after} and β_{before}, respectively) and calculated the percentage change in the beta coefficient between the 2 models ($[\beta_{after} - \beta_{before}]/\beta_{before}$). The median difference was used as the percentage attenuation with the 2.5th and 97.5th percentiles as empirical 95% confidence intervals (CIs). Analyses were conducted with SAS version 9.2 (SAS Institute, Cary, North Carolina).

Results

Baseline characteristics. Of 4,676 REGARDS participants included for analysis, 638 (13.6%) had elevated depressive symptoms. Compared with 4,038 (86.4%) participants without elevated depressive symptoms, those with elevated depressive symptoms were younger, less likely to be male, more likely to be black, less likely to have graduated from high school, more likely to have annual income <$20,000, and more likely to have higher BMI (Table 1). Participants with depressive symptoms were more likely to have hypertension, diabetes mellitus, and a self-reported history of stroke. Participants with depressive symptoms were also more likely to be taking thienopyridines and antidepressants and less likely to be taking statins at baseline.

For behavioral mechanisms, participants with elevated depressive symptoms were more likely to report no alcohol use and less likely to report either light-to-moderate or heavy alcohol use ($p < 0.001$ for overall comparison). Those with elevated depressive symptoms were more likely to be current smokers (27.6% vs. 13.8%; $p < 0.001$) and to report

Table 1 Baseline Characteristics of Participants With Coronary Heart Disease

	No Elevated Depressive Symptoms (n = 4,038)	Elevated Depressive Symptoms (n = 638)	p Value
Demographic data			
Age, mean (SD), yrs	68.9 ± 8.8	65.5 ± 9.5	<0.001
Male	63.1	43.3	<0.001
Black	32.5	49.2	<0.001
High school graduate	85.3	71.3	<0.001
Income <$20,000	20.8	47.0	<0.001
BMI, mean (SD)	29.2 ± 5.8	30.7 ± 6.8	<0.001
Comorbidities			
Hypertension	71.3	80.1	<0.001
MI*	71.4	73.5	0.260
Stroke*	11.2	17.1	<0.001
Diabetes mellitus	31.8	41.5	<0.001
Medication use			
Aspirin	70.2	67.1	0.110
Beta blocker	47.1	50.9	0.073
Thienopyridine	15.1	18.8	0.015
Ace-inhibitor/angiotensin receptor blocker	50.5	52.4	0.384
Statin	59.6	51.3	<0.001
Antidepressants	13.0	30.9	<0.001
Behavioral risk factors			
Alcohol use			
None	63.7	73.7	<0.001
Light-to-moderate	33.2	23.5	
High	3.1	2.8	
Current smoking	13.8	27.6	<0.001
Physical inactivity			
None	36.1	51.9	<0.001
1+ times/week	63.9	48.1	
Morisky scale for medication non-adherence			
0 (best adherence)	69.0	58.8	<0.001
1	24.3	26.7	
2	4.4	8.7	
3 or 4 (worst adherence)	2.3	5.8	

By elevated depressive symptoms (Center for Epidemiologic Studies Depression Scale score ≥4). Values are % except otherwise specified. *History of myocardial infarction (MI) and stroke as identified by self-report.
BMI = body mass index.

physical inactivity (51.9% vs. 36.1%; $p < 0.001$). Participants with elevated depressive symptoms reported worse levels of medication adherence (Morisky scale score of 3 or 4, 5.8% vs. 2.3%; $p < 0.001$).

Clinical events, elevated depressive symptoms, and behavioral mechanisms. Over a median 3.8 years of follow up, 125 (19.6%) of 638 participants with elevated depressive symptoms experienced the primary outcome of definite/probable MI or death, compared with 657 (16.3%) of 4,038 participants without (Fig. 1, top panel). After adjusting for demographic data, education, income, and BMI (Table 2, Model 1), the HR for MI or death associated with depressive symptoms was 1.41 (95% CI: 1.15 to 1.72). After further adjustment for medical comorbidities and medications used (Table 2, Model 2), the HR remained statistically significant but decreased to 1.25 (95% CI: 1.02 to 1.52). Finally, in the full model including all 4 behavioral mechanisms (Table 2, Model 2), the HR for MI or death associated with elevated depressive symptoms was further attenuated and was no longer statistically significant (HR: 1.14, 95% CI: 0.93 to 1.40). For individual behavioral mechanisms, both smoking (HR: 2.06, 95% CI: 1.71 to 2.47) and physical inactivity (HR: 1.47, 95% CI: 1.27 to 1.71) were associated with a higher risk of MI or death in the fully adjusted model (Table 2, Model 3), whereas levels of alcohol use and medication non-adherence were not.

Only 14.0% (95% CI: −2.5% to −44.3%) of the excess risk for MI or death associated with elevated depressive symptoms was due to medical comorbidities including hypertension, history of MI, history of stroke, and diabetes mellitus (Table 3). Medication use did not significantly attenuate the HR for elevated depressive symptoms (HR: −27.4%, 95% CI: −12.7% to 86.1%). In contrast, inclusion of all 4 behavioral mechanisms into the model attenuated more than one-third of the risk for MI or death associated with elevated depressive symptoms (HR: −36.9%, 95% CI:

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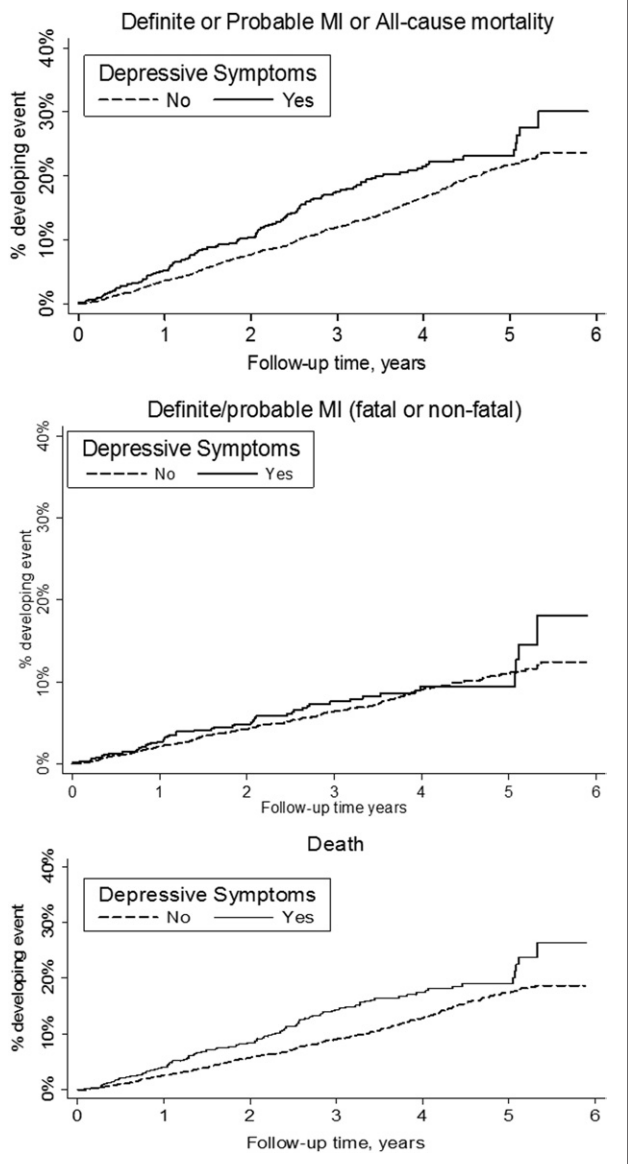

Figure 1 **Kaplan-Meier Curves for Adverse Events**

Cumulative incidence of definite/probable myocardial infarction (MI) or death; definite/probable MI (fatal or nonfatal); or death from any cause, for REGARDS (REason for Geographic and Racial Differences in Stroke) participants with and without elevated depressive symptoms.

−18.9% to −119.1%), with smoking and physical inactivity having the biggest impact (Table 3).

Individual outcomes and sensitivity analyses. As a secondary analysis, we further explored the role of behavioral mechanisms in explaining the association between elevated depressive symptoms and the individual components of the primary outcome (definite/probable MI and all-cause mortality, separately), with the same incremental proportional hazards models specified in the preceding text. During the follow-up period, 101 (15.8%) of 638 participants with elevated depressive symptoms died, compared with 504 (12.5%) of 4,038 participants without elevated depressive symptoms; 50 (7.8%) of 638 participants with elevated depressive symptoms and 314 of (7.8%) 4,038 participants without experienced a definite/probable MI (Fig. 1, middle and bottom panels). The results of proportional hazards models for death were consistent with the findings from the primary analyses: the HR for elevated depressive symptoms was 1.48 (95% CI: 1.18 to 1.85) in the model containing demographic covariates and BMI only but was no longer statistically significant (HR: 1.20, 95% CI: 0.96 to 1.50) in the fully adjusted model containing behavioral mechanisms. For definite/probable MI, a similar trend was observed, although none of the HRs met statistical significance (Fig. 2). In sensitivity analysis excluding probable MI events, the findings were similar.

Discussion

In this analysis of a large cohort of participants from across the continental United States enrolled in the REGARDS study, we found that self-reported behavioral mechanisms explained a substantial proportion of the excess risk of MI or death associated with elevated depressive symptoms in individuals with CHD. Of the 4 behavioral mechanisms that were assessed, smoking and physical inactivity were the most substantial contributors, each accounting for approximately one-fifth of the relationship between elevated depressive symptoms and cardiac risk. We also confirmed that elevated depressive symptoms are associated with an increased risk of MI or death in individuals with CHD, a relationship that was mainly driven by the increased risk of death.

Our results are consistent with and extend the findings of prior studies in this field (2,11). In an analysis of 5,888 participants enrolled in the Cardiovascular Health Study, Win et al. (11) reported that physical inactivity accounted for 25% of the increased risk for cardiovascular mortality associated with depression. We observed an effect size of a similar magnitude for physical inactivity in our cohort but also considered other behavioral mechanisms, such as smoking, alcohol use, or medication non-adherence, which were not accounted for in the Cardiovascular Health Study. Our results are also similar to that from the Heart and Soul Study, which found that self-reported physical inactivity explained approximately 30% and smoking approximately 10% of the association between depressive symptoms and increased cardiovascular events, whereas the contribution of medication non-adherence was similarly of borderline significance as observed in our cohort (2). The prevalence of elevated depressive symptoms was slightly lower in our cohort (13.6%), compared with these prior studies, which might be due to our study sample being population-based as well as our use of a different measure and threshold for defining elevated depressive symptoms. However, our larger sample size and the robust bootstrapping method we used go further to support the role of smoking and physical

Table 2 Association Between Elevated Depressive Symptoms and Definite/Probable MI or Death

	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)
Elevated depressive symptoms	1.41 (1.15–1.72)	1.25 (1.02–1.52)	1.14 (0.93–1.40)
Age, per 10 yrs	1.52 (1.39–1.65)	1.53 (1.40–1.67)	1.64 (1.50–1.80)
Male	1.44 (1.22–1.69)	1.46 (1.24–1.72)	1.54 (1.31–1.82)
Black	1.11 (0.94–1.30)	1.00 (0.85–1.18)	0.97 (0.82–1.14)
High school graduate	0.87 (0.73–1.05)	0.94 (0.78–1.13)	0.97 (0.80–1.16)
Annual household Income <$20K	1.53 (1.28–1.83)	1.45 (1.21–1.73)	1.30 (1.09–1.56)
BMI, per 5 kg/m^2	0.94 (0.88–1.01)	0.89 (0.83–0.95)	0.91 (0.84–0.97)
Hypertension	*	1.20 (0.99–1.43)	1.21 (1.01–1.44)
MI†	*	1.35 (1.14–1.60)	1.31 (1.11–1.55)
Stroke†	*	1.43 (1.19–1.72)	1.34 (1.11–1.61)
Diabetes mellitus	*	1.58 (1.35–1.84)	1.55 (1.33–1.80)
Aspirin	*	0.90 (0.77–1.05)	0.89 (0.76–1.05)
Beta blocker	*	1.18 (1.02–1.37)	1.18 (1.02–1.36)
Thienopyridine	*	1.36 (1.13–1.64)	1.35 (1.12–1.63)
ACE-inhibitor/ARB	*	1.04 (0.89–1.21)	1.05 (0.90–1.22)
Statin	*	0.73 (0.63–0.85)	0.75 (0.64–0.87)
Antidepressant use		1.29 (1.07–1.56)	1.20 (0.99–1.45)
Alcohol use	*	*	
None			1.00 (ref)
Light-to-moderate			0.93 (0.79–1.09)
High			0.69 (0.43–1.11)
Current smoking	*	*	2.06 (1.71–2.47)
Physical activity	*	*	
Any			1.00 (ref)
None			1.47 (1.27–1.71)
Morisky scale for medication adherence	*	*	
0 (best adherence)			1.00 (ref)
1			1.15 (0.97–1.35)
2			1.23 (0.90–1.67)
3 or 4 (worst adherence)			0.80 (0.51–1.25)

Association between elevated depressive symptoms (Center for Epidemiologic Studies Depression Scale score of ≥4 vs. <4) and definite/probable myocardial infarction (MI) or death. Models also included adjustment for geographic region of residence. *Not included in regression model. †History of MI and stroke as identified by self-report.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BMI = body mass index.

inactivity as key behavioral mechanisms that explain the association between elevated depressive symptoms and the risk of MI or death.

In our study, alcohol use and medication non-adherence did not attenuate the relationship between elevated depressive symptoms and MI or death. There are several potential explanations. The precise impact of alcohol consumption on cardiovascular risk remains under debate (16,27), and it has been proposed that physical activity might be a confounder for epidemiological observations that link light-to-moderate alcohol use with decreased number of cardiac events (28). Supporting this, alcohol consumption was not associated with MI or death in the full model that included physical activity in our study and thus would not be expected to explain the association between elevated depressive symptoms and cardiac outcomes. For medication non-adherence, although we used the 4-item Morisky scale rather than a single-item assessment as was done in the Heart and Soul Study, underreporting of medication non-adherence is a known challenge for assessments based on self-report (29). It is possible that more objective measurement tools would demonstrate a more important role for medication non-adherence. Consistent with this, a study of 168 patients with acute coronary syndrome has previously shown that aspirin non-adherence measured with electronic pill-bottles accounted for a substantial amount of the risk for increased death or major adverse cardiovascular events associated with elevated depressive symptoms (12).

In our analysis, we found that the association of elevated depressive symptoms with death was significant, whereas that between elevated depressive symptoms and MI was not. A similarly nonsignificant association between elevated depressive symptoms and MI was also seen in the Heart and Soul Study, which also showed that the relationship between elevated depressive symptoms and other cardiovascular events such as stroke and heart failure was more pronounced (2). A meta-analysis by van Melle et al. (30) noted a stronger link between depression and death in post-MI patients than that between depression and cardiovascular events including recurrent MI. Therefore, there is a

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Table 3 Attenuation in Association Between Elevated Depressive Symptoms and Definite/Probable MI or Death, After Addition of Clinical and Behavioral Variables

	% Attenuation HR (95% CI)
Hypertension/MI/stroke/ diabetes mellitus	−14.0% (−2.5% to −44.3%)
Medications (aspirin, beta blockers, ACE-I/ARBs, thienopyridine, statins, antidepressants)	−27.4% (−12.7% to 86.1%)
Alcohol use	0% (4.8% to 3.0%)
Current smoking	−17.6% (−6.5% to −56.0%)
Physical inactivity	−21.0% (−9.7% to −61.1%)
Medication non-adherence	−3.6% (2.5% to −16.1%)
All behavioral mechanisms	−36.9% (−18.9% to 119.1%)

Attenuation in the association between elevated depressive symptoms (Center for Epidemiologic Studies Depression Scale of ≥4 vs. <4) and definite/probable MI or death, after addition of clinical and behavioral variables. Baseline model is Model 1 in Table 3 and includes adjustment for age, race, sex, geographic region of residence, income, education, and BMI.

Abbreviations as in Table 2.

possibility that, in patients with CHD, depression increases the risk for death through causes other than recurrent myocardial infarction, potentially via mechanisms for which smoking and physical inactivity are contributors (3,31).

Our study also has, in addition to these mechanistic insights, important implications for future research and potential interventions for patients with CHD and elevated depressive symptoms. Given that prior studies of pharmacological and counseling approaches of depression treatment demonstrated only limited efficacy in reducing cardiac risk in that patient population (8–10), our results suggest that there might be a role for intermediary interventions that explicitly target health behaviors. Despite clear guidelines, many individuals with CHD and especially those with depressive symptoms still do not meet current recommendations for smoking cessation and exercise (32). The recently published UPBEAT (Understanding the Prognostic Benefits of Exercise and Antidepressant Therapy) trial demonstrated that a 4-month exercise intervention was able to reduce depressive symptoms in patients with CHD, but the trial was not powered to find differences in cardiac outcomes (33). Given our findings that behavioral risk factors explain a substantial part of the association between elevated depressive symptoms and the risk of MI or death, future trials of interventions targeting these particular behaviors to improve cardiac outcomes in patients with CHD and elevated depressive symptoms are urgently needed.

There are several strengths in our study. The REGARDS study includes a large number of women and African Americans and recruited adults from across the continental United States, supporting the generalizability of our findings. Furthermore, we used the statistical approach of bootstrapping to quantify the amount of attenuation of the relationship between elevated depressive symptoms and the risk of MI or death after behavioral mechanisms were considered, which allowed us greater confidence in the robustness of our results. Finally, although we used brief, self-reported items to measure behavioral mechanisms and depressive symptoms at a single point in time, their ease-of-use and positive associations with outcomes suggest a potential role for broader application in clinical and research settings.

Study limitations. As stated in the preceding text, the measures of behavioral risk factors including smoking, physical inactivity, alcohol use, and medication non-adherence in our study were self-reported, and their exact prevalence might be underestimated. The REGARDS study did not assess other potential biological factors, such as endothelial dysfunction and heart rate variability, which have been proposed to explain the association between depressive symptoms and cardiac risk (1,34). Prior studies,

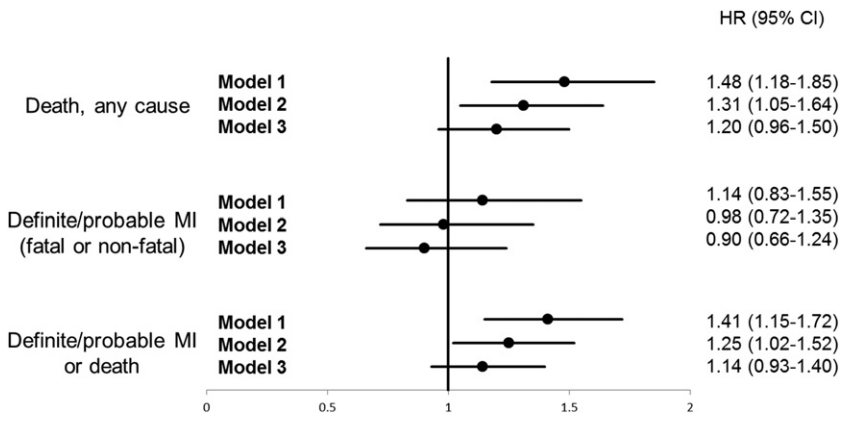

Figure 2 HRs for Elevated Depressive Symptoms in Incremental Proportional Hazard Models

Hazard ratios (HRs) for elevated depressive symptoms in incremental proportional hazard models, with the outcomes of death from any cause; definite/probable myocardial infarction (MI) (fatal or nonfatal); or the composite of both endpoints. Model 1: adjusted for demographic data, education, income and body mass index. Model 2: adjusted for all covariates in Model 1, with additional adjustment for comorbidities and medication use. Model 3: adjusted for all covariates in Model 2, with additional adjustment for behavioral mechanisms (alcohol use, current smoking, physical inactivity, and medication non-adherence).

however, suggest that the role played by these biological mechanisms might be modest (2,7,35,36). It is also possible that there is a survivor bias, because those individuals with elevated depressive symptoms and who are at the highest risk for death would not have survived to be enrolled in our study. However, this would tend to bias our results toward the null and thus would only underestimate the associations that we have identified between elevated depressive symptoms, clinical events, and behavioral mechanisms. Finally, causality cannot be ascertained in our observational study. For instance, it is possible that physical inactivity and depressive symptoms are both markers of disease severity rather than causal determinants of cardiac risk. Future studies, possibly with a cross-lagged path design (37), might help to clarify the complex relationships between depressive symptoms, cardiac risk, and behavioral mechanisms such as physical inactivity and smoking.

Conclusions

In summary, we found that in a large cohort of participants from across the continental United States enrolled in the REGARDS study, elevated depressive symptoms are associated with increased risk of MI or death in individuals with a history of CHD. Furthermore, a substantial proportion of the relationship between elevated depressive symptoms and the risk for MI or death was explained by behavioral mechanisms, the most important of which were smoking and physical inactivity. These findings add to our understanding of the mechanisms by which elevated depressive symptoms might convey increased risk for adverse cardiovascular outcomes for individuals with CHD and suggest that behavioral interventions to target smoking cessation and increase physical activity could reduce the excessive cardiac risk associated with depression in CHD patients.

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