

## Poor Health Behaviors Largely Explain Link Between Depression and Cardiovascular Events

Whooley MA, de Jonge P, Vittinghoff E, et al. Depressive symptoms, health behaviors, and risk of cardiovascular events in patients with coronary heart disease. *JAMA* 2008;300:2379–88.

### Study Overview

**Objective.** To understand the association between depressive symptoms and increased risk of cardiovascular events.

**Design.** Prospective cohort study.

**Setting and participants.** A total of 1024 patients with stable coronary heart disease were recruited between September 2000 and December 2002 from 12 outpatient Veterans Affairs, university, and public health clinics in the San Francisco Bay area and were followed through January 2008. Patients were eligible for enrollment if they had a history of myocardial infarction, prior exercise-induced ischemia on an exercise or pharmacologic stress test,  $\geq 50\%$  stenosis in  $\geq 1$  coronary vessels, history of coronary revascularization, or diagnosis of coronary artery disease documented by an internist or cardiologist. Of the initial participants who completed the baseline examination, 7 could not be reached for follow-up, leaving 1017 for evaluation. Participants completed the intake examination, fasting blood draw, psychiatric interview, depression questionnaire, echocardiogram, 24-hour ambulatory electrocardiogram, and 24-hour urine collection.

**Main outcome measures.** Proportional hazards models were used to evaluate the extent to which baseline cardiovascular disease (CVD) and biologic and behavioral mediators explained the association between depressive symptoms and cardiovascular outcome events. Depressive symptoms were assessed with the 9-item Patient Health Questionnaire (PHQ) and the Computerized Diagnostic Interview Schedule for DSM-IV. Cardiovascular events were defined as heart failure hospitalizations, nonfatal myocardial infarctions, stroke, transient ischemic attacks, or death.

**Main results.** Overall, a total of 341 cardiovascular events occurred over 4876 person-years of follow-up. Mean follow-up was 4.8 years. Of the 1017 patients, 199 (19.6%) had depressive symptoms as determined by PHQ scores  $\geq 10$ . The age-adjusted annual rate of cardiovascular events was 10% in patients with depressive symptoms compared with 6.7% in those without depressive symptoms (hazard ratio [HR], 1.50 [95% confidence interval {CI}, 1.16–1.95];  $P = 0.002$ ).

Patients with depressive symptoms were more likely to be female, younger, smokers, less physically active, less adherent to medications, have a higher body mass index, have more comorbidities, use more antidepressants, and have greater urinary norepinephrine excretion, higher C-reactive protein (CRP) levels, and lower omega-3 fatty acid levels. After adjusting for CVD severity and other comorbid conditions, depressive symptoms were still associated with a 31% higher rate of cardiovascular events (HR, 1.31 [95% CI, 1.00–1.71];  $P = 0.04$ ). Further adjustment for CRP somewhat attenuated this relationship (HR, 1.24 [95% CI, 0.94–1.63];  $P = 0.12$ ), and subsequent adjustment for smoking, medication nonadherence, and physical inactivity completely eliminated the relationship between depressive symptoms and cardiovascular events (HR, 1.05 [95% CI, 0.79–1.40];  $P = 0.75$ ). In the final overall model, physical inactivity was associated with a 44% higher rate of cardiovascular events (HR, 1.44 [95% CI, 1.14–1.82];  $P = 0.002$ ), adjusting for depressive symptoms, age, disease severity, comorbid conditions, CRP, smoking, and medication adherence.

**Conclusion.** In patients with stable coronary heart disease, those with depressive symptoms at baseline had a 50% greater rate of subsequent cardiovascular events. Health-related behaviors, such as physical inactivity, explained much of the association between depressive symptoms and future cardiovascular events.

### Commentary

The connection between depression and CVD has been long recognized but poorly understood. Major depressive disorder is a risk factor for the development of new coronary disease events in healthy patients and recurrent cardiovascular events in patients with established disease [1]. Depression is present in 20% to 30% of outpatients with CVD but remains underrecognized and undertreated [1]. Furthermore, it remains unclear whether the link between depression and CVD is mediated by patient health behaviors such as physical inactivity and smoking, or biologic factors such as high catecholamine excretion, low heart rate, worse cardiac disease severity, or even antidepressant toxicity.

The present study by Whooley et al aimed to understand

what factors among depressed patients lead to worse cardiovascular outcomes. After adjusting for disease severity and other comorbidities, the relationship between depression and cardiovascular events was found to be largely mediated by health-related behaviors, particularly physical inactivity. Other factors such as high CRP, smoking, and medication nonadherence played a smaller role.

This study was a well-conducted prospective cohort study that included detailed, well-validated biologic and psychosocial measures. Few patients were lost to follow-up, and the sample sizes in each group gave the study adequate power to detect differences. The study's comprehensive assessment of cardiovascular events was also notable.

A few limitations deserve mention. First, the directionality of the relationship between physical inactivity and depression is unclear because they were both assessed only at baseline. Most likely, these 2 factors influence each other in a bidirectional fashion and thus causation cannot be deduced from this study. To the extent that inactivity precedes depressive symptoms, it may be a confounder as opposed to a mediator. It is also possible that physical inactivity could have resulted from more severe CVD, although the authors went to great lengths to adjust for this possible confounding.

Second, the attenuation of the relationship between depression and CVD by CRP is not completely explained by the study. After adjusting for disease severity and comorbidities, the addition of CRP to the model statistically nullified the relationship (as the lower 95% CI crosses 1). Smoking, nonad-

herence, and physical inactivity each decreased the already statistically insignificant HR further toward 1. Although the change in effect size of the association between depression and cardiovascular event was largest for physical inactivity, large differences were also seen for CRP level, disease severity, and comorbidities. How much to make of the further changes in HR after statistical insignificance was reached is debatable. It is also unclear from the study whether CRP represents a marker for more severe disease, a separate link between depression and CVD, or part of the pathway between physical inactivity and worse cardiovascular outcomes. Finally, the majority of participants were older white men, potentially limiting the generalizability of the findings.

### Applications for Clinical Practice

The link between depression and recurrent cardiovascular events may be explained in large part by health-related behaviors, particularly physical inactivity. While we wait for the results of ongoing prospective trials of exercise therapy, clinicians have yet another reason to consider recommending a safe and monitored exercise regimen to their patients with stable coronary heart disease who also have a history of depression.

—Review by Asaf Bitton, MD

### Reference

1. Whooley MA. Depression and cardiovascular disease: healing the broken-hearted. *JAMA* 2006;295:2874–81.

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