Reviewer’s report

Title: Depression as a Risk Factor for Adverse Outcomes in Coronary Heart Disease

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Reviewer: Monika Safford

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This opinion piece seeks to present the methodologic challenges that need to be overcome in order to conclude whether there is a causal relationship between depression and CHD, and what the directionality of that relationship is. The authors have written a well-organized and thoughtful essay that is well supported by the literature. They summarize a lot of the key controversies in this field. I thought it was logically and convincingly presented and have only minor suggestions that could strengthen the arguments even further. These comments fall into the discretionary revisions category.

Background: The authors restrict the topic to the relationship between depression and outcomes among individuals with CHD. They state the controversy clearly: is there a causal link? Is depression modifiable in CHD patients, and does treatment of depression improve cardiac event-free survival? The objective is clearly stated, i.e., they will discuss some of the challenges and controversies in the literature.

Defining and measuring depression. The authors outline the issue of whether features that resemble depression in CHD patients are “real” depression. Supporting this concern is that some symptoms of depression are nonspecific and could be symptomatic of disorders other than depression. Is this only true of depression in CHD, though? The cited example is fatigue. This is certainly present in depression without CHD, and similar issues about overlap or nonspecificity of symptoms challenge physicians treating the increasing number of people living with multiple chronic medical conditions, not just CHD. The authors argue that the proposition to leave out fatigue as part of the constellation of symptoms of depression for patients with CHD is difficult to defend, and their argument is persuasive. The exposition of the challenges in diagnosis are well presented, logical and lead to a deeper understanding of the complexity of the issues related to diagnosis in the setting of CHD. Table 1 could be strengthened by including the positive predictive value of thresholds of the self-report questionnaires and DSM diagnoses in CHD populations, if this is available. At least including the Sn and Sp of these instruments would be helpful. Is the CES-D really not used in this literature? This is a very widely used instrument.

Subtypes of depression. The authors present the controversy surrounding whether distinct symptom complexes are more or less deleterious, specifically mentioning the cognitive vs. somatic distinction that has gained attention in the behavioral cardiology literature. They point out that this literature is challenging to
interpret and clearly expound why this is, and how the literature is inconclusive. The statement that “some studies have shown that somatic symptoms are better predictors of cardiac outcomes than are cognitive symptoms, but other studies have not found this difference” would be stronger if it were referenced.

Time factors. The authors point out the long time period between subclinical disease development and overt disease manifestation, with many people not surviving their initial presentation. This necessarily limits inferences that can be drawn about the role of depression prior to overt disease presentation and its role in subsequent outcomes after the initial event. The authors discuss important challenges such as recall bias when attempting to construct a depression history preceding cardiac events, and the heterogeneity in studies of how the “initial” cardiac event is defined, resulting in inclusion of individuals who are in fact along a broad continuum of atherosclerotic disease progression. This further complicates the interpretation of findings across studies and attempts to draw conclusions about the temporal nature of the relationship between depression and CHD outcomes.

An additional factor that could play a very important role in the temporal issue relates to diagnosed vs. undiagnosed depression. A lot of depression remains undiagnosed, thus attempting to construct a lifetime history of depression is made even more challenging. The authors do not mention this point, which could strengthen their argument that teasing apart temporal relationships is fraught with challenges.

Causal model/mechanisms. The authors do a nice job of laying out the current thinking on causal mechanisms. However, when discussing measures of the symptomatic or functional severity of heart disease, they stray into the realm of heart failure by citing a study that examined NYHA functional class and depression. Was this study limited to individuals with ischemic cardiomyopathy? Heart failure is less and less related to ischemic disease and more and more often related to diastolic compliance, which is a completely different pathophysiology. While this blurring of disease states does occur in the literature, it does little to advance the study of the relationship between depression and CHD of an atherosclerotic etiology. Pointing this out could strengthen the author’s position. The conclusion that complex relationships that include aspects of multiple causal models may be operating is convincing.

Treatment research. This literature is synopsized very well and thoughtfully critiqued. A major challenge in trials to date has been the modest success in treating depression. It would strengthen this discussion to have some thoughts from the authors why this might be. Depression trials in general populations show more success with SSRIs or CBT for moderate depression, with the greatest success for both used in combination. What could have led to the low success rates in the CHD trials? Were more severely depressed patients selected? Are there signals for more resistance to treatment in CHD patients? A bit more information on these intriguing questions would strengthen this segment.

Summary. The final sentence is a bit wishy-washy. Do the authors think that at this time we can conclude neither that there is a causal relationship between depression and CHD, nor what the directionality of this relationship is? A more
definitive statement about which side of the debate the authors are on would strengthen the conclusion.

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests