

## EDITORIAL COMMENT

# A Sum Greater Than its Parts

## A Composite Psychological Distress Score and Cardiovascular Risk\*



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Chronic psychological stress has a similar degree of risk for cardiovascular disease (CVD) compared to traditionally recognized risk factors.<sup>1</sup> Individuals with coronary heart disease (CHD) may suffer the greatest consequences of chronic stress in terms of their future CVD risk.<sup>2</sup> Putative mechanisms include lifestyle and behavioral factors and biological pathways that include increased sympathetic nervous system activity, stress hormone disruption, inflammation, and thrombosis.<sup>3</sup> Nevertheless, psychological stress has remained challenging to quantify in the clinical setting, and, despite clinical overlap between symptoms related to stress, many pre-existing studies have only leveraged assessments of individual psychological constructs (eg, depression, anxiety, perceived stress, anger) to evaluate associations with CVD.<sup>4</sup> The relationship between measures of psychological stress and CVD risk beyond traditional risk factors also remains incompletely defined. Furthermore, there remains a dearth of evidence regarding effective therapies to reduce psychological stress that also meaningfully impact CVD. As such, while psychological factors, especially depression, are discussed in documents from professional societies in the United States, societies continue to avoid identifying stress

as an independent risk factor for CVD and do not recommend screening or treatment for patients with high stress and CVD.<sup>5-7</sup> Accordingly, additional research is needed to identify an effective assessment of psychological stress that accounts for a range of psychological constructs, independently associates with risk for CVD, and is modifiable by therapies.

The paper by Garcia et al<sup>8</sup> in this issue of *JACC: Advances* begins to address these gaps. The authors report an investigation into the relationship between a composite index of psychological distress on adverse CVD outcomes and the contribution of this index to CVD risk prediction in participants with CHD. The investigators leveraged a cohort of 891 individuals who were previously recruited at a single institution for 1 of 2 studies: the MIPS (Mental Stress Ischemia Prognosis Study), which provided 611 subjects with documented stable CHD (based on a clinical event or imaging), and the MIMS2 (Myocardial Infarction and Mental Stress Study 2), which provided 280 individuals with prior myocardial infarction.<sup>9,10</sup> These individuals were evaluated at baseline with questionnaires regarding symptoms of depression, anxiety, post-traumatic stress disorder, perceived stress, and anger. Within each cohort, results were ranked for each questionnaire, averaged, and split into tertiles. The tertile determination was then pooled for the combined cohort to create an overall rank for the distress score to overcome different cohort sizes and the resulting variation in raw rankings. Individuals were followed for a median of 5.9 years for first or recurrent events including cardiac death, nonfatal myocardial infarction, and heart failure hospitalization.

Individuals in the highest tertile of composite psychological distress score had a significantly increased risk of a first or recurrent CVD event compared to those in the lowest tertile in each cohort

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separately (adjusted HR in MIPS of 1.47 and in MIMS2 of 2.38) and in the combined cohort (adjusted HR of 2.11). These results remained significant after adjustment for several important demographic (eg, age, sex, race, family income) and clinical (eg, CVD risk factors and prior CVD events) variables and remained significant when heart failure hospitalizations were excluded from the outcome measures. The results were not substantially impacted when separate measures of psychological stress were evaluated individually (aside from being attenuated for the anger assessment) or when the analyses using the composite psychological distress score were stratified by demographic or clinical factors. Furthermore, when the composite psychological distress score was added to models that included demographic and clinical risk factors, there was an improvement in the C-statistic (by 5%), category-free net-reclassification index (improved risk classification by 46%), and integrative discrimination index. Collectively, these results suggest that the composite self-reported measure of psychological distress may improve risk stratification in patients with CHD and that it is noninferior to the individual assessment of each psychological construct.

There are notable strengths to these data. First, the included individuals had a spectrum of baseline psychological health, as those with depression, anxiety, and post-traumatic stress disorder and those on antidepressant medications were included unless they had features of psychosis. Additionally, the authors accounted for many important demographic and clinical confounders in their analyses. All events were stringently adjudicated by 3 investigators. The implemented psychological distress score equally weighted several different factors related to chronic psychological stress and provided a broader assessment than that used by many prior studies. Notably, a previous study used a similar composite psychological distress score in the context of a combined cardiac rehabilitation and stress management intervention and demonstrated that an improvement in the score was associated with a lower risk of adverse CVD events.<sup>11</sup> Accordingly, such a score may offer a brief and inexpensive clinical assessment that provides insights into CVD risk and serves as an actionable measure that may yield CVD benefits.

The study has several limitations that should also be discussed. Participants came from a single institution, and all had pre-existing CHD. While it is possible that disease itself is an important stressor

that drives downstream disease, it is also possible that reverse causation contributed to these findings among individuals with more severe CHD, which led to both greater psychological distress and CVD risk. The authors attempted to account for this possibility by adjusting for CVD events that occurred prior to study entry. Additionally, given that this study retrospectively evaluated individuals from pre-existing studies, all potential confounders, including key lifestyle factors, could not be assessed.

The study offers important findings related to the risk of psychological distress and CVD, and it provides an actionable and feasible way to assess psychological distress as a CVD risk factor in clinical practice. Additional work remains to broaden clinical attention to identifying and treating psychological distress in patients with or at risk for CVD. These findings should be replicated in additional diverse populations from multiple institutions and include individuals without baseline CVD as well as a spectrum of psychological stress to determine whether the composite risk score effectively predicts CVD risk in a broad population. These studies should be designed to assess potential confounders prospectively and comprehensively. Additionally, prospective research to link the composite psychological stress score to biomarkers of stress, such as measures of inflammation and neural activity that have been linked to stress and stress-associated CVD, should be performed.<sup>3</sup> Interventional studies targeting stress and healthy lifestyle should include similar composite measures of distress to determine the effect of interventions on this measure as well as stress-associated biomarkers and CVD endpoints. Finally, randomized studies are needed to explore the role of screening for and treating individuals with high CVD risk and increased levels of psychological distress to determine the impact on a range of outcome variables.

Among a population derived from 2 prospective studies of CHD patients, a composite assessment of psychological distress was independently associated with risk for index and subsequent CVD events and improved the reclassification of CVD risk. These results take an important step towards increasing screening and treatment of psychological distress in individuals with CHD. Further study is needed to determine the utility of this composite assessment in a broad population and to evaluate whether treatments modify the composite assessment of distress and whether changes in the score are associated with beneficial CVD outcomes.

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## REFERENCES

1. Rosengren A, Hawken S, Ounpuu S, et al. Association of psychosocial risk factors with risk of acute myocardial infarction in 11,119 cases and 13,648 controls from 52 countries (the INTERHEART study): case-control study. *Lancet*. 2004;364:953-962.
2. Kivimaki M, Steptoe A. Effects of stress on the development and progression of cardiovascular disease. *Nat Rev Cardiol*. 2018;15:215-229.
3. Osborne MT, Shin LM, Mehta NN, Pitman RK, Fayad ZA, Tawakol A. Disentangling the links between psychosocial stress and cardiovascular disease. *Circ Cardiovasc Imaging*. 2020;13:e010931.
4. Davidson KW, Alcantara C, Miller GE. Selected psychological comorbidities in coronary heart disease: challenges and grand opportunities. *Am Psychol*. 2018;73:1019-1030.
5. Lichtman JH, Bigger JT, Blumenthal JA, et al. Depression and coronary heart disease. *Circulation*. 2008;118:1768-1775.
6. Levine GN, Cohen BE, Commodore-Mensah Y, et al. Psychological health, well-being, and the mind-heart-body connection: a scientific statement from the American Heart Association. *Circulation*. 2021;143:e763-e783.
7. Smith SC Jr, Benjamin EJ, Bonow RO, et al. AHA/ACC secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation endorsed by the World Heart Federation and the Preventive Cardiovascular Nurses Association. *J Am Coll Cardiol*. 2011;58:2432-2446.
8. Garcia M, Moazzami K, Almuwaqqat Z, et al. Psychological distress and the risk of adverse cardiovascular outcomes in patients with coronary heart disease. *JACC: Adv*. 2024;3(2):100794.
9. Hammad M, Al Mheid I, Wilmot K, et al. The mental stress ischemia prognosis study: objectives, study design, and prevalence of inducible Ischemia. *Psychosom Med*. 2017;79:311-317.
10. Vaccarino V, Sullivan S, Hammad M, et al. Mental stress-induced-myocardial Ischemia in young patients with recent myocardial infarction: sex differences and mechanisms. *Circulation*. 2018;137:794-805.
11. Blumenthal JA, Sherwood A, Smith PJ, et al. Enhancing cardiac rehabilitation with stress management training: a randomized, clinical efficacy trial. *Circulation*. 2016;133:1341-1350.

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