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Psychosocial Factors and Cardiovascular Disease Risk: An Opportunity in Women's Health

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The reduction in cardiovascular disease (CVD) burden over the past half-century is one of the greatest public health successes in history¹. However, the gains in cardiovascular health have not been experienced equally across all groups. In addition to disparities by socioeconomic status, age, and race/ethnicity¹, differences by sex are also apparent². Overall reductions in CVD risk, as well as potential for benefit from existing cardioprotective strategies, appear greater among men than women². In addition, the clinical presentations of and several risk factors for CVD demonstrate sexual dimorphism². Therefore, ongoing work in CVD risk research has focused on potential paths to achieving better outcomes for women. A promising area is the domain of psychosocial factors, which have been associated with multiple biological processes that may be directly relevant to development of CVD. In this issue of *Circulation Research*, Chang and colleagues³ report on the association between a key psychosocial factor – social integration – with incidence of coronary heart disease (CHD) among mid-life and older women. They report that women with the highest levels of social integration (measured by an index of both content and frequency of social interactions) had nearly 50% lower risk of CHD when compared to those with the lowest levels of social integration. Interestingly, the differences were significant for both fatal and non-fatal events, but the relations of social integration to the latter appeared to be largely mediated by lifestyle and health behavior factors and were no longer statistically significant when those factors were included in the models.

The report by Chang et al.³ provides a branching off point for considering the evidence base regarding connections of CVD to psychosocial stressors, including specific conditions, such as depression and anxiety. First, it should be noted that many adverse psychological health states are substantially more common among women than men. For example, mood and anxiety disorders, including major depressive, panic and phobic disorders, have nearly two-fold higher lifetime prevalence among women compared to men⁴. Depression, anxiety and/or psychological distress have also been related to higher risk of coronary disease, sudden cardiac death, stroke, and all-cause mortality⁵⁻⁸. While the direct mechanisms are not completely understood, potential biological paths underlying these findings include altered neuroendocrine-stress response, accelerated telomere shortening, and higher levels of inflammation, oxidative stress, and insulin resistance⁹⁻¹¹. Social stress may also influence changes in gene expression levels via DNA methylation¹². Thus, social integration may have particular value as a predictor of CVD risk in women: it is both modifiable and may be protective to the extent that it enhances both biological and behavioral paths to resilience to the potential toxic effects of psychological stressors that are more prevalent in women.

The findings from Chang and colleagues also highlight that the relationship between psychosocial stressors and CVD may differ for fatal vs. non-fatal events. The authors noted a previous study by Eng et al.¹³ of social integration and CHD among men in which lower social integration was related to higher risk of fatal but not non-fatal CHD, and the present findings are consistent with that prior report. Indeed, Whang and colleagues⁶ previously found in this Nurses' Health Study (NHS) cohort that multivariable-adjusted associations of depression with fatal CHD, and particularly with sudden cardiac death (SCD), were strong but that relations to non-fatal myocardial infarction (MI) were greatly attenuated and no longer statistically significant after multivariable adjustment. Similarly, Albert et al.⁵ reported that high levels of phobic anxiety were associated with increased risk of SCD and fatal CHD but not of nonfatal MI. Therefore, it is plausible, as the authors of the present study posit, that relations of social integration to biological (e.g., autonomic, neuroendocrine) and behavioral (smoking, physical activity) factors may underlie the differing associations with fatal and non-fatal events in women.

Moreover, potential differences in the biological mechanisms involved in fatal vs. non-fatal events warrant further consideration. One possibility is that resilience enhancement via social integration may mitigate biological processes particularly relevant to acute cardiac crises, such as altered/reduced heart rate variability¹⁴, dysautonomia and the Takatsubo syndrome (a phenomenon of acute cardiomyopathy that occurs almost exclusively among women and typically follows sudden high-emotional valence events)¹⁵, which arise in settings of acute psychological stress, such as sudden bereavement, unexpected employment loss or other abrupt stressors. Furthermore, adjustment for lifestyle and behavioral factors would be *unlikely* to attenuate the association between social integration and *fatal* CVD, to the extent that social integration reduces risk of fatal events through influences on the above biologic processes; this may explain findings observed by the authors. However, with regard to non-fatal events, social integration may appear unrelated to the outcome, after accounting for lifestyle and health behaviors, such as smoking and physical activity. Notably, social integration may influence patients' behaviors that were unmeasured in the current study, including compliance with healthcare appointments and vascular risk treatments (e.g.,

antihypertensive agents, statins/cholesterol-lowering medications, etc.) that affect the likelihood of CVD events. Although many potential covariates were available in the analyses, treatment compliance was not explicitly measured or included.

Finally, the article by Chang and colleagues points to areas of future research activity. First, as has been stated by the authors and others elsewhere, there is a public health need to address persistent gaps in knowledge of women's CVD risk factors and disparities in women's cardiovascular outcomes. Addressing potential adverse impacts of psychosocial stress, especially on the risk of fatal CVD events in women, is an important public health research direction and opportunity for prevention. For example, future work is needed to understand whether efforts to optimize resilience to stress and psychological distress, such as through improved social integration, can yield benefits for CVD risk reduction in women. Second, the article reminds us of the importance of adequate characterization of potential explanatory lifestyle and health behavior variables, including treatment compliance, when considering relations of psychosocial factors to CVD risk. Finally, a continued target of research must be the differentiation of the individual and joint contributions of risk factors – genetic, biological, environmental, psychological, social, behavioral – for fatal versus non-fatal CVD events, and it is important for such efforts to consider sex as a biologic variable and concurrently to address disparities by socioeconomic factors and race/ethnicity.

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