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EDITORIAL COMMENT

Depression and Incident Cardiovascular Disease*

Lisa Pennells, BSc, MSc, PhD,[a,b] C. G. Nicholas Mascie-Taylor, MA, PhD, ScD[a,b]

In their research paper published in this issue of *JACC: Asia*, Senoo et al[1] quantify the association between clinically diagnosed depression and cardiovascular disease (CVD) incidence by using more than 4 million data records from a Japanese health insurance claims database. Focusing on individuals who were initially free of CVD, Senoo et al[1] found a persistent association between clinical depression and incident CVD after accounting for several other CVD risk factors, with a markedly greater association in women than in men.

As Senoo et al[1] remark, conclusions about causality cannot be drawn from observational data, but this study adds to the body of evidence indicating an important link that requires understanding and awareness in clinical practice and primary prevention of CVD.[2-5] It also adds to contrasting evidence on whether associations are similar in men and women, by providing large-scale evidence of a greater effect in women. This finding has particular relevance to efforts to broaden awareness of CVD risk and improve cardiovascular event outcomes among women.[6] The current study may be large (perhaps the largest yet), but how robust are these findings to biases often present in observational studies? To answer this question, it is helpful to consider various aspects of the data and analysis.

First, was appropriate adjustment applied for CVD risk factors that are correlated with both depression and CVD? Many key clinical risk factors were taken into account, but some were measured in a way that could result in incomplete adjustment and residual impact. For example, cholesterol, blood pressure, and body mass index were not included as continuous measurements but as binary classifications of dyslipidemia, hypertension, and above/below 26 kg/m^2, respectively. Similarly, physical activity was defined as active/inactive and alcohol consumption and smoking habits as current/not current, thus ignoring the degree of use and former use. This simplistic binary inclusion of CVD risk factors could have resulted in incomplete adjustment because many of these risk factors are known to have continuous linear associations with CVD risk.[7-9] Furthermore, sleep habits/problems, diet, education, and income/socioeconomic factors were not recorded. The more important question is whether "incomplete" adjustment could have explained the greater association observed in women. Many of the included risk factors may have different associations with CVD in men and women,[6,10] and so their simplistic inclusion could have led to sex differences in the degree of incomplete adjustment. Similarly, a lack of allowance for effect modification in associations by sex may have led to further sex differences in adequacy of adjustment. This issue perhaps warrants further investigation.

A second consideration is whether the severity of depression experienced may be correlated with CVD risk. A previous multicohort individual participant data meta-analysis revealed a linear dose-response relationship between depressive symptoms and CVD risk.[3] If women, as Senoo et al[1] discuss, are more prone to severe depression, then this finding could partially explain the stronger associations observed among women vs men. Given that the binary depression diagnosis used by Senoo et al[1] included several conditions (with separate International Classification of Diseases, 10th revision codes) from mild to severe and included both single and recurrent depression episodes, this diagnosis could potentially be broken down by severity to test this theory.

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From the [a]British Heart Foundation Cardiovascular Epidemiology Unit, Department of Public Health and Primary Care, University of Cambridge, Cambridge, United Kingdon; and the [b]Victor Phillip Dahdaleh Heart and Lung Research Institute, University of Cambridge, Cambridge, United Kingdom.

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A third aspect, also mentioned by Senoo et al,[1] is the tendency for CVD risk among women to increase in response to hormonal changes during the menopause.[11] It would be interesting to investigate whether there were additional diagnoses of depression during the same time period[12] that could have somewhat explained the association for women, perhaps investigating whether results varied by hormone replacement therapy use or age at depression diagnosis.

A fourth factor is the ascertainment of CVD endpoints. Along with myocardial infarction and stroke, both the baseline exclusion criteria and the endpoint choice included additional CVDs such as angina and atrial fibrillation. The latter "softer" conditions may have gone undiagnosed at baseline, thereby potentially leading to reverse causation (underlying, undetected CVD causing depression and subsequently manifesting as a diagnosed CVD event during follow-up). Conversely, undiagnosed endpoints (ie, incomplete outcome ascertainment) may have diluted the magnitude and precision in observed associations. Importantly, if there were discrepancies in detection rates by sex,[6] underdiagnosis could have had a different impact on the observed associations for women vs men. A further point is that linkage between data records with death registries appears not to have been completed. Events included in the insurance claims database are presumably only nonfatal, leading to some missing endpoints, possibly preferentially among men who, at the included age range, experience higher incidences of both nonfatal and fatal CVD.[13] Again, this factor could have induced sex differences in observed associations.

A final consideration is whether cultural habits and stigma associated with mental health may have affected the tendency of individuals to seek professional help for depressive symptoms. In particular, if there were sex differences in attitudes toward mental health, compounded by sex differences in health care–seeking behaviors more generally, this may have led to greater underdiagnosis in men vs women.[14] Hence, this could have diluted the observed association between depression and CVD more for men vs women. Research has shown that stigma associated with mental health disorders among the Japanese population is not insubstantial,[15] so this is another avenue worthy of further understanding.

Sex differences and methodologic considerations aside, associations between depression and CVD have been repeatedly found across multiple settings by using various methods, and these associations do not appear to attenuate substantially on adjustment for several CVD risk factors that could either confound or mediate the association.[4,5] Similarly, exclusion of CVD events occurring in the years immediately after baseline appears not to attenuate the observed association, thus shedding doubt on the theory of reverse causality.[3] Furthermore, observational associations have been broadly confirmed by Mendelian randomization studies, some of which have indicated a causal link between depression and CVD that is not found in the reverse direction.[16,17] Although such studies have shown that smoking, cardiometabolic factors, and hypertension represent important mediators of this association, some independent causal impact of depression on future CVD incidence has not been ruled out.[16] Several potential mechanisms have been suggested, including altered brain and neuronal function affecting neuroendocrine pathways, autonomic nerve dysfunction, immune responses, platelet activation, and thrombosis.[4,5] Evidence from clinical trials on the impact of treatment for depression on future CVD is limited, not least because substantial follow-up is often needed to assess CVD risk properly, and this is not the primary endpoint for such trials.[16]

Whether or not depression is an independent causal risk factor for CVD development, the observed increase in CVD risk in patients with depression appears clinically significant. Depressive disorders affect the lives of >200 million individuals worldwide and rank in the top 5 causes of years lived with disability.[18] Any secondary impact on other health conditions therefore is potentially important. Paying attention to both hearts and minds when caring for patients and considering cardiovascular health can only lead to benefits. Potential beneficial pathways activated on reducing depression are multiple, including improved adherence to lifestyle advice and prescribed treatment. This benefit has been recognized by clinical advisory bodies around the world, with guidelines highlighting the relevance of acknowledging and tackling mental health as a valuable part of CVD prevention.[5,19-21] The current analysis affirms this approach. Whether associations are greater for women than for men perhaps remains unclear, and further untangling of this observation may be needed as part of efforts to better understand the mechanisms underlying the observed associations.

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ADDRESS FOR CORRESPONDENCE: Dr Lisa Pennells, British Heart Foundation Cardiovascular Epidemiology Unit, Department of Public Health and Primary Care, University of Cambridge, Victor Phillip Dahdaleh Heart and Lung Research Institute, Papworth Road, Cambridge CB2 OBB, United Kingdom. E-mail: lamp2@medschl.cam.ac.uk.

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