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EDITORIAL COMMENT

Navigating the Intersection of Sex, Vascular Risk Factors, and Cognitive Decline

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Cerebral small vessel disease, defined as a disorder of the small penetrating blood vessels in the brain leading to white and deep gray matter damage, is a major contributor to cognitive impairment and dementia.[1] It is well established that vascular risk factors such as hypertension, hyperlipidemia, diabetes, obesity, cigarette smoking, and atrial fibrillation contribute to cerebrovascular disease, including cerebral small vessel disease (CSVD), and increase the risk of vascular cognitive impairment and dementia.[2] Prior literature suggests that CSVD is more severe in males compared to females,[3] though female sex is associated with the progression of CSVD and accompanied cognitive decline.[4] Whether sex differences exist in the contribution of individual vascular risk factors to cognitive decline is less well established. Given the growing burden of CSVD, cognitive impairment, and dementia in the aging population, evaluating sex differences in the impact of vascular risk factors on cognition is crucial to providing individualized preventive care.

In this issue of *JACC: Advances*, Kaur et al[5] report on sex differences in the association between vascular risk factors and cognitive decline in the UK Biobank, a prospective cohort study of >500,000 adults aged 40 to 69 years at the time of enrollment. The authors compared cognitive function in domains typically implicated in CSVD among males (n = 9,689) and females (n = 9,378) at baseline in 2014 and again in 692 males and 608 females who had repeat cognitive testing in 2019. Although males were slightly older (60.9 vs 61.5 years, $P < 0.001$) and had more prevalent vascular risk factors, females had lower cognitive performance across all domains tested (executive function, memory, and processing speed) at baseline. Females demonstrated a significant decline in executive function (matrix pattern completion) compared to males over the 5-year study period; however, in the multivariable analysis adjusted for vascular risk factors, this sex difference in cognitive decline was no longer statistically significant. Importantly, the main finding of the study was the increased effect of high low-density lipoprotein, high blood pressure, and lower education status on worse cognitive decline in executive function among females compared to males. There were no sex differences in the effect of vascular risk factors on memory or processing speed domains. These findings suggest there may be sex-specific differences in the mediation of cognitive decline by vascular risk factors, which has clinical implications for an individualized approach to preventive strategies. How does this fit with the current literature and understanding of pathophysiological mechanisms linking biological sex differences, vascular risk factors, and cognitive impairment?

In the prospective TRACE-VCI (Utrecht-Amsterdam Clinical Features and Prognosis in Vascular Cognitive Impairment) study of 860 memory clinic patients with possible vascular cognitive impairment, investigators demonstrated that there were no sex differences in baseline or follow-up cognitive performance across 5 domains; however, the type of vascular injury (cortical infarcts, lacunar infarcts, white matter hyperintensities on brain imaging), vascular risk factors, and social characteristics differed by sex.[6] Men were more likely to have

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cortical and lacunar infarcts, while women were more likely to have white matter hyperintensities, a common marker of CSVD. Moreover, in a community-based study of aging (n = 1,453), postmortem examination revealed that, compared to males, females had significantly greater Alzheimer disease pathology and had 28% greater odds of severe arteriosclerosis (another marker of CSVD) after adjusting for age and education level.[7] Given the study design, however, these results were not assessed in the context of cognitive performance. Conversely, in a large systematic review and meta-analysis of 36,910 total participants with clinical or silent CSVD, males had more moderate-severe CSVD compared to females, and there was a higher male-to-female sex ratio for cognitive CSVD.[3] However, there was insufficient sex-stratified data to assess whether vascular risk factors were driving sex-specific effects on the severity and characteristics of CSVD.

In terms of the sex-specific effects of vascular risk factors, women with hypertension, diabetes, and smoking have a relatively higher risk of cardiovascular disease than men with the same risk factors.[8] Similarly, in a prior UK Biobank study comparing the effect of traditional vascular risk factors between men and women, women with hypertension, smoking, and lower socioeconomic status had a higher risk of any stroke; women with diabetes had a higher risk of ischemic stroke; and women with atrial fibrillation had a higher risk of hemorrhagic stroke compared to men.[9] Additionally, various studies have shown the increased effect of mid-late life hypertension, type-2 diabetes, and obesity on the risk of vascular cognitive impairment in women compared to men.[10] Furthermore, there seems to be a protective effect of estrogen on vascular risk factors (stroke, diabetes, mid-life obesity, and hypertension),[10] and observational studies have suggested that the initiation of hormone replacement therapy early (<5 years) after menopause may lower the risk of dementia (the so-called "critical window hypothesis").[11]

The present study is the first to show the interaction of sex and individual vascular risk factors on cognitive decline in otherwise healthy individuals, highlighting the greater impact of high low-density lipoprotein, high blood pressure, and lower education status on executive function in women compared to men. Although this has major clinical implications for individualized approaches to vascular and cognitive health and prevention strategies, there remain many unknowns as to the underlying mechanisms and mediators of this observed trend. Social determinants of health, for instance, have a major impact on brain health and cognitive trajectories and were not fully assessed in this study, except for education status. The degree of vascular risk factor control and the use of guideline-recommended therapies for vascular risk factor control may also impact cognitive trajectories and were not assessed in this study. Furthermore, the present study did not assess CSVD imaging biomarkers (such as white matter hyperintensities, cerebral microbleeds, and lacunar infarcts on brain imaging), which may also be associated with cognitive trajectories.

In summary, the present literature suggests that there are sex differences in the distribution of vascular risk factors, CSVD, and cognitive impairment, and that vascular risk factors may have a differential impact on cardiovascular disease, stroke, and cognition in women compared to men. What is not well understood is whether vascular risk factors mediate the occurrence and progression of CSVD pathology (and neurodegenerative pathology) among women and men differently and the impact these potential sex differences may have on cognitive trajectories. Further research should focus on the underlying biological mechanisms contributing to these observed sex differences to develop and implement more precise and individualized treatment and prevention strategies for vascular risk factors and cognitive decline. The MarkVCID (Biomarkers for Vascular Contributions to Cognitive Impairment and Dementia) Consortium, STROKOG (Stroke and Cognition Consortium), Small Vessel Diseases-At-Target, Heart Brain Connection consortia, and the ongoing DISCOVERY study (Determinants of Incident Stroke Cognitive Outcomes and Vascular Effects on Recovery; NCT04916210) may provide more insight on vascular contributions to cognitive impairment and dementia, including sex-specific differences and mechanisms.

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