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COMMENTARY

Pathways linking hypertension and depression with mild cognitive impairment in older adults

Mild cognitive impairment (MCI) is a cognitive state intermediate between normal cognitive aging and dementia, and therefore, it is a critical target for clinical interventions designed to reduce further cognitive decline. Moreover, because MCI is prospectively associated with Alzheimer's disease and related dementias (ADRD), we have an opportunity to identify and target key modifiable risk factors for MCI and thus promote healthy cognitive aging across late life. Among these risk factors, cardiovascular risk factors (CVRFs), including hypertension, diabetes, and smoking, have long been implicated in risk for MCI and ADRD. However, few studies have systematically accounted for the prevalence of lifetime major depressive disorder (MDD), which frequently co-occurs with both CVRFs and MCI. In a recent paper in *International Psychogeriatrics*, Karameh *et al.* (2022) address this open question and report findings that substantiate the role of lifetime history of hypertension in the development of MCI, independent of lifetime MDD.

Karameh *et al.* grouped a cohort of older adults according to current MCI diagnosis and history of MDD and compared these groups in terms of select CVRFs, including history of hypertension, history of diabetes, and smoking status. Additionally, they examined associations between these CVRFs and neuropsychological performance among six domains of executive functioning. Results demonstrated that older adults with MCI showed greater prevalence of hypertension compared to older adults without MCI. By contrast, older adults with a history of MDD did not show greater prevalence of hypertension, and MDD history was not associated with CVRFs in comorbid patients. Finally, across the patient cohort, a history of hypertension was associated with poorer neuropsychological performance, consistent with prior studies and meta-analyses (Gifford *et al.*, 2013).

A novel finding of the study by Karameh *et al.* and somewhat inconsistent with prior studies, was that a lifetime history of MDD was not associated with increased prevalence of hypertension. The authors suggested this discrepancy may have been attributable to including older adults with lifetime MDD, as opposed to including older adults with late-life MDD only. This interpretation is supported by previous literature indicating that cerebrovascular dysfunction has long been implicated in the pathogenesis of late-life MDD (Taylor *et al.*, 2013), whereas the determinants of MDD emerging earlier in life may comprise a larger variety of factors that may not necessarily involve CVRFs. The study by Karameh et al., did not explore the clinical characteristics of the cohort with lifetime MDD, in particular the age of onset and the lifetime number of depressive episodes (Butters *et al.*, 2008). Such clinical factors could be useful terms of more concretely testing the hypothesis that CVRFs (including hypertension) are linked to late-life MDD and MCI but not to MDD with earlier onset in this cohort (Armstrong *et al.*, 2018).

The findings by Karameh *et al.* add to an established literature demonstrating that modifiable CVRFs such as hypertension are associated with MCI in older adults. The next frontier is to identify how these and other CVRFs influence brain health to promote cognitive decline across the life course. Beyond the direct effect of CVRFs on brain health and cognitive function, it is also unclear how resilience to these CVRFs and their effects on the brain can stave off age-related cognitive decline. To address these open questions, we argue that future studies could benefit from examining putative biological and neurophysiological pathways that may mediate the lifetime influence of hypertension and other CVRFs on brain health. Such work may identify pathways that can be targeted with treatment or otherwise may identify factors that promote resilience to CVRFs and their influence on brain and cognitive aging.

A key pathway through which CVRFs may increase risk of MCI broadly involves the impact of biological mediators of CVRFs on brain health. There are various markers of brain health, including gray matter structure, white matter integrity, cerebral blood flow, and cerebral glucose metabolism, all of which show distinct patterns of age-related changes throughout the life course (Grady, 2012). Among these, markers of poor brain health, in particular poor cerebrovascular function, have long been implicated in the pathogenesis of MCI

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(Luchsinger *et al.*, 2009). Hypertension is associated with various markers of poor brain health in midlife and late life, including reduced gray matter volume, increased white matter hyperintensities, and reduced cerebral blood flow (Jennings *et al.*, 2021). Hence, multiple mechanisms may link a history of hypertension with poor brain health and risk for MCI. To this end, a growing line of research leverages large-scale cohorts along with multimodal neuroimaging methods (e.g., magnetic resonance imaging, positron emission tomography) to better understand how hypertension and other CVRFs may impact patterns of age-related changes in brain health to prospectively influence MCI risk (Paus, 2010).

The results of Karameh *et al.* point to the importance of maintaining blood pressure levels within a healthy range throughout the life course as a potential strategy for reducing risk of MCI. Thus, understanding the behavioral and physiological determinants of hypertension will be critical to reducing risk for hypertension, and by extension, risk for later cognitive decline. In addition to smoking, key behavioral risk factors for hypertension include insufficient sleep, physical inactivity, poor diet, and excessive alcohol consumption. Moreover, key physiological pathways thought to mediate the impact of these and other behavioral factors on vascular function include activation of the sympathetic nervous system and alterations in the renin–angiotensin system, as well as elevated proinflammatory signaling (Savoia and Schiffrin, 2006). We note that psychosocial factors including stress, anxiety, loneliness, and neuroticism have long been linked to hypertension and cardiovascular disease risk through these behavioral and physiological pathways (Steptoe, 2000). Indeed, acute and chronic stressors alter sympathetic outflow and peripheral vasoconstriction by activating threat-related brain circuits implicated in peripheral physiological control (Andreescu *et al.*, 2019; Kraynak *et al.*, 2018). And, exaggerated stressor-evoked cardiovascular responses are prospectively associated with hypertension during adulthood (Matthews *et al.*, 2004). Accordingly, chronic experiences of psychological stress and other forms of psychosocial adversity may over time impact peripheral vascular health via the brain to promote a hypertensive state, which over the life course may feedback to influence central aspects of brain health and thereafter increase risk for MCI. How this lifelong bidirectional brain-body loop unfolds across the life course and across populations, however, is not fully understood. To address this knowledge gap, future studies should examine the above behavioral and psychosocial factors in the context of CVRFs, MCI, and intermediary neuroimaging measures of brain health.

Similarly, we note that the reported associations between hypertension and related CVRFs and risk of MCI do not occur in a vacuum, but that broader environmental and psychosocial factors are likely to play an important role in producing and modifying these associations. For example, Karameh *et al.* reported that the association between history of hypertension and MCI was attenuated when adjusting for age, sex, and education. It is unclear which of these factors played the predominant role in attenuating effect sizes. Regarding the latter factor, however, we note that indicators of socioeconomic disadvantage, including lower educational attainment, have been linked to elevated risk of hypertension and MCI (Fernández-Blázquez *et al.*, 2021; Leng *et al.*, 2015). In addition, markers of socioeconomic position have been linked to reduced cortical gray matter thickness (Gianaros *et al.*, 2017) and reduced cerebral blood flow (Hackman *et al.*, 2018) during midlife, neuroimaging markers of brain health which have in turn been associated with MCI (Beishon *et al.*, 2017). Future studies incorporating multimodal neuroimaging assessments might test whether socioeconomic disparities and other psychosocial factors relate to elevated MCI risk via their impact on CVRFs and neuroimaging measures of brain health.

In conclusion, the study by Karameh *et al.* in *International Psychogeriatrics* adds to the growing literature indicating hypertension as a key risk factor for brain aging and cognitive decline. Indeed, some of the presumed cognitive effects of hypertension are already apparent in this cohort, as evidenced by the reported association between hypertension history and neuropsychological performance across patients. Future research may identify critical timepoints during the life course when biological mediators of CVRFs impact brain health, and moreover may characterize how this process varies across populations and life circumstances. To address this question as well as other questions related to the long-term effect of depression on brain health addressed in the current issue of International Psychogeriatrics, future studies leveraging measures of peripheral biological pathways, depressive phenotypes and neuroimaging markers of brain health can elucidate the time course of processes that link hypertension, depression and related CVRFs to poorer brain health and risk for cognitive decline.

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Conflicts of interest

The authors have no conflicts of interest to declare.

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