Understanding the relationship between cardiovascular markers and cognitive decline

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In recent years, there has been greater awareness of the heart-brain connection, or the impact of cardiovascular function on brain health and cognition.

However, the relationships between circulating cardiovascular markers—which are substances that are released into the blood when the heart is damaged or stressed, and cerebrovascular function—which refers to the ability of the cerebral blood vessels to deliver oxygen and nutrients for neural activity, for underlying cognitive decline are not yet fully understood.

At the same time, brain free-water is a novel imaging marker that is useful for detecting early and subtle cerebrovascular dysfunction. Detected by diffusion MRI, free water is defined as water molecules that are free to diffuse and do not experience restriction or hindrance, which makes it easy to detect biomarkers in the image relevant to a patient's diagnosis. This could provide valuable insights into disease progression and response to therapy.

Homing in on the relationship between cardiovascular markers and cerebrovascular function, Associate Professor Helen Zhou from the Center for Sleep and Cognition in NUS Medicine, and Director, Center for Translational MR Research at the Yong Loo Lin School of Medicine, National University of Singapore (NUS Medicine), and Dr. Mitchell Lai from the Department of Pharmacology and Principal Investigator at the Memory, Aging and Cognition Center at NUS Medicine, led a study to investigate the neural mechanism guiding the relationship between cardiovascular dysfunction and cognitive decline in the Singaporean elderly.

The study was conducted on the elderly with normal cognition, mild cognitive impairment and dementia. The researchers found that three blood cardiovascular biomarkers were associated with higher brain free-water, indicating a higher change of decline in neural function. The paper is published in *Neurology*.

To understand the relationship between cardiovascular biomarkers and

different brain functions, researchers measured the free-water in gray and white matter of the brain separately. They found that the blood cardiovascular biomarkers were associated with higher free-water in widespread regions of white matter, which serves to transmit signals to other regions of the brain, and in specific gray matter networks including the default mode (active when the brain is at wakeful rest, such as during daydreaming and mind-wandering), executive control (engaged in high-level cognitive tasks), and somatomotor networks (used in performing and coordinating motor tasks).

The researchers found that cardiovascular dysfunction could lead to alterations in brain vasculature, affecting small arteries, arterioles, and capillaries, as well as causing neurovascular changes. These changes can instigate cerebrovascular dysfunction processes, which may lead to neuronal damage, synaptic loss, and neurodegeneration, ultimately resulting in dementia and cognitive decline.

Moreover, free-water, which captured the processes of cerebrovascular dysfunction, in widespread white matter and network-specific gray matter, were found to fully explain the associations of blood biomarkers with longitudinal cognitive decline over five years. Specifically, higher free-water in the executive control network was responsible for executive function impairment, such as the capacity to plan ahead and meet goals, display self-control, among others, while free-water in the default mode network mediated the relationship with memory dysfunction.

Thus, their findings suggest the role of brain free-water in linking cardiovascular dysfunction to longitudinal cognitive decline. Free-water alterations might be one of the early underlying mechanisms of brain network degeneration in dementia patients, which eventually influences domain-specific cognitive functions.

"The prevalence of dementia will double every 20 years. At the same time, there is a high prevalence of cerebrovascular disease (CeVD) among patients with mild cognitive impairment (MCI) and dementia in Singapore. CeVD often appears together with vascular dementia or Alzheimer's disease (AD). AD with CeVD is the most common type of dementia in Asia, including Singapore," said Associate Professor Zhou.

Clinically, the assessment of free-water in specific brain networks together with the blood test of cardiovascular biomarkers could be helpful for the personalized prediction of cardiovascular and cerebrovascular disease progression and domain-specific cognitive decline.

The team will continue developing brain imaging and blood-based tests, to pave the way for precision and preventive medicine which can be helpful especially for middle-age and relatively healthy Singaporeans.

More information: Fang Ji et al, Associations of Blood Cardiovascular Biomarkers With Brain Free Water and Its Relationship to Cognitive Decline: A Diffusion-MRI Study, *Neurology* (2023). DOI: 10.1212/WNL.0000000000207401

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