Vascular risk interacts with amyloid levels to increase age-related cognitive decline

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Risk factors for heart disease and stroke appear to hasten the risk of cognitive decline in normal older individuals with evidence of very early Alzheimer's-disease-associated changes in the brain. Vascular risk factors increase the risk of cognitive impairment in older individuals and appear to have a negative synergistic effect with levels of brain amyloid-beta, the protein that aggregates into neurotoxic plaques in the brains of individuals with Alzheimer's disease. In their report published in *JAMA Neurology*, a team of Massachusetts General Hospital (MGH) investigators describes finding that the combination of increased vascular risk and higher brain amyloid levels predicted even faster cognitive decline in clinically normal older individuals than would be expected based on the independent effects of both factors.

"Our findings suggest that having vascular risk factors like diabetes, smoking, and high blood pressure may accelerate the rate of cognitive decline in normal older adults, and that the effect of vascular risk on decline is magnified in people with higher brain amyloid levels," says Jennifer Rabin, Ph.D., a clinical and research fellow in the MGH Department of Psychiatry, lead author of the paper. "Our findings support the rationale behind targeting modifiable vascular risk factors either alone or in combination with amyloid-lowering therapies to delay cognitive decline. Measures of vascular risk also may be able to complement existing biomarkers in identifying people at the greatest risk of cognitive decline."

Alzheimer's disease and cerebrovascular disease are probably the two most common causes of cognitive impairment in the elderly, but even though they often co-occur in individual patients, they are typically viewed as independent contributors. While the presence of amyloid plaques in the brain is considered a hallmark of Alzheimer's disease, some individuals with elevated amyloid levels never develop cognitive impairment. This has led to a search for additional markers beyond brain amyloid to help identify those at increased risk for cognitive decline.

The current study was designed to investigate whether the effects of increased brain amyloid and of vascular risk on cognitive decline are merely additive, reflecting a simple combination of the risks independently contributed by each factor, or synergistic, in which interaction of the two produces an even higher level of risk. Another goal was determining whether vascular risk remained a powerful predictor of cognitive decline, even when investigators also considered other cutting-edge measures of brain health derived from PET scans and MRIs.

The study analyzed data from 223 participants in the Harvard Aging Brain Study, an ongoing study of cognitively normal individuals ages 50 to 90 designed to improve understanding of brain changes affecting memory and cognition that occur with aging. Upon enrollment in the study, participants receive standard imaging biomarker studies, including PET scans with a compound that reveals amyloid deposits in the brain. Assessment of vascular risk is determined by the Framingham cardiovascular risk score, which is based on factors such as hypertension, body mass index, and histories of diabetes or smoking. Participants also receive standard tests of memory, attention and language, which are repeated at annual follow-up visits.

The results showed that both elevated brain amyloid levels and higher vascular risk, as measured upon study enrollment, were associated with more rapid cognitive decline, with the most rapid changes seen in participants with elevations in both factors. The extent of the interaction between the two measures suggested a synergistic, rather than simply an additive effect. Vascular risk remained a consistently strong predictor of cognitive decline, even after controlling for other biomarkers; and while the study did not

directly compare the contributions of brain amyloid levels and vascular risk to the rate of cognitive decline, the predictive power of both factors was statistically similar.

Senior and corresponding author Jasmeer Chhatwal, MD, Ph.D., of the MGH Department of Neurology, says, "Recent findings suggest elevated brain amyloid is necessary but perhaps not sufficient on its own to predict imminent cognitive decline. Therefore, we need to find additional, complementary measures to identify individuals at the highest risk for cognitive decline, as these are the people we want to enroll in Alzheimer's-disease-prevention clinical trials. Remarkably, vascular risk appears to be useful in identifying risk of cognitive decline above and beyond a full slate of MRI and PET measures of brain health. Perhaps more importantly, we can reduce vascular risk factors through medical treatments and lifestyle interventions, and reducing these vascular risk factors might reduce memory loss over time—especially in people with high brain amyloid."

Co-author Reisa Sperling, MD, of the Departments of Neurology at MGH and at Brigham and Women's Hospital (BWH) and the co-principal investigator of the Harvard Aging Brain Study, adds, "It's important to keep in mind that the Harvard Aging Brain Study enrolls pretty healthy older individuals who do not have very high levels of vascular disease. But even so, these results suggest that even relatively modest levels of vascular risk can interact with very early Alzheimer's disease pathology to hasten cognitive decline in normal older individuals." Sperling is a professor of Neurology, and Chhatwal an assistant professor of Neurology at Harvard Medical School.

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