The connection between cerebrovascular health and cognition has been of empirical interest to scientists for over a century. In 1894, Swiss neurologist Otto Binswanger, described an association between postmortem cerebrovascular changes, including atherosclerosis, and cognitive impairment preceding death in middle-aged and older adults.1 One-hundred and twenty years later, the field has evolved beyond Binswanger’s seminal work to include midlife systemic vascular health factors as potential mechanistic drivers in abnormal cognitive aging, including the most common form of dementia, Alzheimer’s disease.2,3

In this issue of Circulation, Yaffe and colleagues push the envelope further by reporting that longitudinal exposure to one or more vascular risk factors in early and midadulthood is associated with worse midlife cognitive performance.4 Participants from the Coronary Artery Risk Development in Young Adults (CARDIA) Study who were 18 to 30 years of age at baseline underwent vascular risk factor assessments every 2 to 5 years over a 25-year period. Cognitive assessment, conducted at the end of the follow-up period, included delayed episodic memory (Rey Auditory Verbal Learning Test), information processing speed (Digit Symbol Coding), and 1 key aspect of executive functioning (inhibition assessed by the Stroop Test).

In unadjusted models, cumulative exposure of each vascular risk factor (with the exception of total cholesterol) was individually associated with poorer performance on all 3 cognitive measures at midlife. However, in models adjusting for or excluding participants with incident cardiovascular events (eg, myocardial infarction, congestive heart failure) may act as a mediator variable in the association between vascular risk factors and poor cognitive outcomes (Figure A). That is, the presence of prevalent cardiovascular disease, rather than any 1 risk factor, drives observations between vascular risk factors and cognition. Most results from Yaffe et al remained statistically significant after adjusting for or excluding incident cardiovascular events, although effect sizes were reduced. Thus, their observed pattern of results supports an alternative explanation—a successive pathway of injury (Figure B). In this latter account, vascular risk factors, such as hypertension4 and diabetes mellitus,5 contribute an initial pathway of injury to cognition by disrupting the brain’s capillary ultrastructure. These initial basement membrane morphological changes (eg, pericytic degeneration)6 result in compromised blood-brain barrier permeability and microcirculation, which manifest as subtle cognitive changes. Over time, vascular risk factor burden can contribute to prevalent cardiovascular disease. Such interim cardiovascular events create a second, subsequent pathway of injury to the brain by further exacerbating...
levels) may have lower baseline cognitive performance levels (in comparison to peers with higher socioeconomic or literacy status). Just as the authors advocate for capturing exposure duration and intensity, it is similarly important to capture the shared effects of vascular risk factors on brain health. Another consideration is that increasing evidence supports APOEε4 as an effect modifier in the association between midlife vascular risk factor exposure and midlife, late-life cognition. Unfortunately, analytic models in the current study did not consider possible APOE genotype effects, perhaps because such data are unavailable in the cohort. Finally, in light of the extensive number of models analyzed, the absence of a correction factor could have yielded spurious findings, resulting in a type I error. Replication of these observations is essential.

Despite these modest limitations, the current work by Yaffe and colleagues is compelling and suggests that better vascular health in early life benefits cognitive aging in midlife. With respect to next steps, most essential is the need to unequivocally establish whether a causal connection exists between vascular risk factor exposure and worse cognitive trajectory (or whether these observations are explained by an epiphenomenon). If there is a causal connection, then the efficacy of therapeutic or lifestyle interventions in young adulthood and midlife can be determined. Once these essential aspects of the field are better understood, we can begin evaluating whether early screening coupled with more aggressive management of vascular risk factors in young adulthood is warranted to reduce the public health burden and associated costs of abnormal cognitive aging.

Disclosures
None.

References


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Vascular Risk Factors and Midlife Cognition: Rethinking the Exposure Window
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