Vascular Risk Factors and Midlife Cognition:
Re-thinking the Exposure Window

Running title: Jefferson; Cumulative vascular risk factors

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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 post-mortem cerebrovascular changes, including atherosclerosis, and cognitive impairment preceding death in middle-age 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 (AD).\(^2,3\)

In this issue of *Circulation*, Yaffe and colleagues push the envelope further by reporting that longitudinal exposure to one of more vascular risk factors in early and mid-adulthood 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 two to five 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 one key aspect of executive functioning (inhibition assessed using the Stroop Test).

In unadjusted models, cumulative exposure of each vascular risk factor (except total cholesterol) was individually associated with poorer performance on all three cognitive measures at midlife. However, in models adjusting for or excluding participants with incident cardiovascular events (e.g., myocardial infarction, coronary revascularization, congestive heart failure), findings were less consistent, and significant effects that remained were diminished. Normal levels of each risk factor (defined by American Heart Association guidelines\(^5\)) were unrelated to midlife cognitive performance in models adjusting for age, sex, race, and education. Yet, when models included the same key demographic covariates, elevated systolic blood
pressure, diastolic blood pressure, and fasting blood glucose were each individually associated with poorer cognitive performance.

Collectively, results suggest that longitudinal exposure to one or more vascular risk factors across early and middle adulthood may have modest effects on midlife cognitive performance. Recent literature indicates the pathogenesis of AD unfolds decades before late-life clinical symptom manifestation. For example, post-mortem evidence of abnormal phosphorylated tau (i.e., a precursor to neurofibrillary tangles associated with AD) can be found in children and young adults age 4 to 29 years. Neuroimaging evidence suggests infant ε4 carriers of the apolipoprotein E genotype (APOEε4, a susceptibility gene for AD) have structural brain differences in comparison to their APOEε4 negative counterparts. Thus, it is similarly plausible that the intersection of vascular risk exposure and initial changes in brain structure may occur much earlier than previously appreciated, though such effects may not clinically manifest until midlife or late adulthood. The current findings by Yaffe and colleagues highlight this possibility.

The authors speculate that a diverse number of causal mechanisms account for the reported associations, including ischemia (especially of a subcortical nature), alterations in amyloid production or clearance, inflammatory or oxidative stress-induced neuronal injury, or gene-environment interactions. The underlying mechanism(s) are likely complex and may or may not reflect a causal pathway.

If a causal mechanism exists, there are at least two fundamental pathways through which vascular risk factors negatively impact cognition. First, prevalent cardiovascular disease (e.g., myocardial infarction, congestive heart failure) may act as a mediating variable in the association between vascular risk factors and poor cognitive outcomes (Figure 1a). That is, the presence of
prevalent cardiovascular disease, rather than any one 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, though effect sizes were reduced. Thus, their observed pattern of results supports an alternative explanation - a ‘successive pathway’ of injury (Figure 1b). In this latter account, vascular risk factors, such as hypertension and diabetes, contribute an initial pathway of injury to cognition by disrupting the brain’s capillary ultrastructure. These initial basement membrane morphological changes (e.g., pericytic degeneration) 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 small vessel changes (and perhaps affecting larger vessels, too) with corresponding cognitive decline.

Alternatively, it is plausible that no such causal pathway exists, and any reported connection between vascular risk factors and abnormal cognitive aging is epiphenomenological in nature. One confounding variable that could explain this phenomenon is age. Vascular risk factors and prevalent cardiovascular disease increase with age as does the prevalence of cognitive impairment. Shared age-related biological change(s) not adequately captured by chronological age could reasonably account for the results reported by Yaffe and colleagues (Figure 1c). Another possible epiphenomenon (or confound) is socioeconomic status or any one of its complex correlates like literacy, nutrition habits, or environmental enrichment versus impoverishment. Individuals from lower socioeconomic backgrounds or with lower literacy levels (compared to peers with higher socioeconomic or literacy levels) may have lower baseline cognitive performance levels and engage in poorer health choices, thereby increasing
vascular risk factor burden. Prior studies from the CARDIA cohort\textsuperscript{11} and others\textsuperscript{13} have shown that lower socioeconomic status is a major predictor of poorer cardiovascular health outcomes. However, the current study design does not take into account the potential impact of socioeconomic status or literacy level on results, and the absence of baseline cognitive testing precludes evaluation of the potential confounding effects of inter-individual differences in literacy or socioeconomic status within the cohort.

Much of the existing vascular risk factor and cognitive aging literature focuses on risk exposure at a single time-point, likely inadequately capturing risk development and burden over the life course. In contrast, Yaffe and colleagues leverage longitudinal data from eight examinations spanning 25 years across early adulthood and midlife. While the reported effects are small and the clinical significance is unclear, a key strength of the study is its emphasis on cumulative temporal exposure to one or more risk factors. Unfortunately, cognitive assessment is restricted to a single evaluation at the end of the follow-up period, which precludes inferences about how cumulative burden of each risk factor affects cognitive trajectory.

There are a few additional caveats to consider with respect to the results put forth by Yaffe and colleagues. First, the analytical models consider each risk factor individually without statistical consideration of the inter-correlated nature of these variables (e.g., examining fasting blood glucose without adjusting for the potential confounding role of systolic blood pressure). 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 \textit{APOE}\textsuperscript{4} as an effect modifier in the association between midlife vascular risk factor exposure and midlife\textsuperscript{14} and late-life cognition.\textsuperscript{15} Unfortunately, analytical models in the current study did not consider possible \textit{APOE} genotype
effects, perhaps because such data is 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.

**Conflict of Interest Disclosures:** None.

**References:**


Figure Legend:

**Figure 1.** Hypothetical pathways that may account for the association between worse vascular health and abnormal cognitive changes with age.
A. Mediating Pathway

vascular risk factors → prevalent cardiovascular disease → worse cognitive performance

B. Successive Pathway of Injury

vascular risk factors → Initial injury → worse cognitive performance → Subsequent injury → prevalent cardiovascular disease

C. Epiphenomenon or Confound

aging, low literacy, low socioeconomic status, or other variable → vascular risk factors or disease → worse cognitive performance
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