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EDITORIAL COMMENT

Coronary Artery Calcification

A Canary in the Cognitive Coalmine*

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In this cognitive study cohort from the Cardiovascular Health Study (CHS) in this issue of the *Journal*, Kuller et al. (1) examine coronary artery calcification (CAC), a measure of subclinical cardiovascular disease, as a predictor of incident dementia and coronary events among individuals without a baseline history of clinical cardiovascular events who were predominantly 80+ years of age. The study extends previous findings by examining dementia incidence prospectively over a longer follow-up duration. The results suggest that for people who live into their 8th decade without a cardiovascular event, dementia is a more likely incident impediment to healthy longevity than a heart attack or stroke; dementia affected 64% of participants before their deaths. However, the findings do not imply a lesser role for atherosclerosis—in fact, quite the opposite—CAC was a risk factor for incident dementia as well as incident coronary events.

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The prospective association between CAC and dementia is consistent with cross-sectional analyses from the AGES (Age, Gene/Environment Susceptibility)-Reykjavik Study, wherein CAC was associated with poorer cognitive performance and dementia (2). In that study, brain magnetic resonance imaging markers, including cerebral infarcts and microbleeds, volumes of grey and white matter and white matter hyperintensities, collectively accounted for the association. Therefore, CAC may be related to dementia due to strokes, brain atrophy, and abnormalities of the small cerebral blood vessels leading to small chronic hemorrhages and lesions to the white matter (3). Microinfarcts correlated with cognitive impairment in autopsy studies (4) also likely contribute.

In general, CAC occurs when atherosclerotic lesions are present, and it reflects plaque burden. It is an active process regulated similarly to bone formation, which occurs both in the vascular intima and media (5). Clinical correlates of intimal calcification include aging, hyperlipidemia, diabetes, hypertension, osteoporosis, male gender, smoking, and inflammation. Calcific vasculopathy of the tunica media tends to be associated with aging, diabetes, and chronic kidney disease, contributing to arterial stiffness. Risk factors for CAC are also risk factors for dementia (**Table 1**). Accordingly, the findings of the CHS Cognitive Study may in part reflect the cumulative burden of these risk factors, although relationships with CAC were not shown. In the coronary arteries, CAC weakens vasomotor responses and elasticity, worsens ejection fraction, hypertrophy and ischemia, and affects plaque stability.

In the present study, black men and women had lower levels of CAC, consistent with previous

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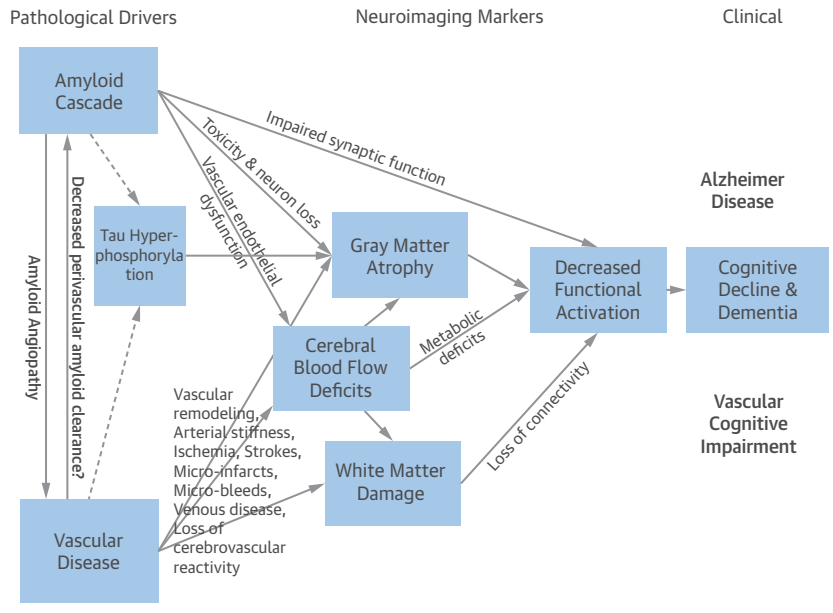
TABLE 1 Modifiable Clinical Risk Factors for Stroke, Heart Disease, and Dementia

Hypertension
Diabetes
Hyperlipidemia
Obesity
Depression
Poor sleep quality
Sedentary behavior
Smoking
Excessive alcohol intake
Dietary salt, saturated fat, and sugar intake
Hyperhomocysteinemia
Inflammation

findings from the Multi-Ethnic Study of Atherosclerosis (6). In white men, CAC was a risk factor for mortality; however, when found in women, CAC was a more portentous risk factor for dementia. CAC did not predict dementia in men (probably due to a small comparison group with low CAC scores), or mortality in women (significant only at trend level $p = 0.110$), but these findings likely reflect the sample size and the distribution of CAC more than a true lack of effect.

Kuller et al. (1) emphasize the importance of determining whether preventing atherosclerosis will also prevent Alzheimer disease (AD). The question is germane because AD is the most common dementia diagnosis, and the clinical risk factors for AD are also risk factors for atherosclerosis. However, how exactly AD and vascular disease may be cocontributors or causally related remains unclear (**Figure 1**). White matter hyperintensities, presumed to indicate cerebral small vessel disease (3,7), are correlated with brain atrophy and cognition in AD (8), and with progression of amyloid burden (9). The findings agree with suggestions that perivascular drainage pathways may help clear amyloid-β (10). Amyloid-β deposition occurs both interstitially in the brain, and in the cerebral vasculature, where it contributes to angiopathy often seen as microbleeds in lobar brain regions, particularly posteriorly (11). In particular, the amyloid-$\beta_{1\text{-}40}$ fragment damages cerebrovascular endothelial cells, impairing vasodilation and blood flow regulation during active brain processes (12). Glucose utilization during brain activation plus impaired blood flow may result in metabolic deficits, oxidative stress, and brain cell loss. Insulin resistance associated with type 2 diabetes, also a risk factor for CAC and dementia, may exacerbate this process. Aortic calcification and stiffness may transfer pulsatility further downstream to the smaller vessels perforating the substantia innominata, including the

FIGURE 1 Common Cocontributing Drivers of Dementia



Possible relationships between vascular- and Alzheimer-related pathologies and their contributions to neuroimaging markers and clinical cognitive outcomes.