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The Role of Cardiovascular Disease in Cognitive Impairment

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Abstract

Purpose of the Review With no disease-modifying treatments for Alzheimer's disease (AD) currently established, a priority for public health is prevention of cognitive decline and dementia. Treatment and prevention of cardiovascular disease (CVD) may provide such an opportunity.

Recent Findings While the pathology of athero- and arteriolosclerotic cerebrovascular disease was once thought of as distinct from AD pathobiology, accumulating evidence suggests that there is more overlap in vascular and AD-related pathologies than previously recognized. CVD and its risk factors are associated with cognitive decline and dementia, in multiple studies. Given that CVD is prevalent among older adults, understanding the contributions of vascular disease to dementia is an important area of research.

Summary While the exact relationship remains to be defined, several mechanisms linking CVD to dementia have been proposed: [1] CVD and dementia have shared risk factors, which might alter clearance of brain toxins or otherwise increase neurodegeneration; [2] CVD might lead to clinical or subclinical strokes, leading to cognitive impairment; and [3] CVD might directly alter cerebral perfusion. Most prior work has focused on risk factors for CVD, but the relationship between end-organ CVD itself and dementia is of extreme importance in considering prevention. Earlier intervention might be the most beneficial since CVD risk appears to have strongest relationships with cognition when measured years before the onset of dementia. The practicing physician should see such evidence as an impetus to aggressively address both symptomatic CVD and CVD risk factors, not only in their elderly patients but importantly in those of middle age.

Keywords Cognitive impairment · Vascular cognitive impairment · Geriatrics · Ischemic stroke · Dementia

Introduction

One of the most difficult diagnoses for a patient and his or her family to receive is that of dementia. Alzheimer's disease (AD) is the leading cause of dementia and remains without a cure. Projections suggest that compared to the 50 million people worldwide who have dementia currently, by 2050, this number will have risen to 132 million [1]. The last decade has seen the AD clinical and research focus turn toward prevention, with a growing body of literature suggesting a link between cardiovascular disease (CVD) and both prevalent and incident cognitive impairment. Vascular contributions to cognitive impairment and dementia (VCID) are increasingly recognized as very common and important contributors to cognitive impairment, often occurring simultaneously or at least in conjunction with neurodegenerative diseases such as AD and importantly often preceding these neurodegenerative changes. VCID has been recognized as the second most common type of dementia and has most simply been defined as cognitive impairment or dementia that can be attributed at least partially to vascular disease [2]. Distinguishing the relative contributions of VCID and AD is challenging, especially given the frequency of mixed pathologies and the relatively high prevalence of both AD and vascular pathologies [3,4]. Pathology-based studies suggest that the majority of dementia cases have evidence of both ischemic lesions as well as known features of AD, such as amyloid plaques and neurofibrillary tangle pathology [3]. Importantly, while the symptoms of dementia do not usually develop until later in life, the underlying

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brain pathology appears to develop years earlier making it even more imperative that this relationship is understood [5]. Furthermore, the long preclinical period for AD is a primary reason why many disease-modifying therapies to date have been unsuccessful as the pathologic cascades leading to cognitive decline and dementia take decades to occur [6].

There have been several mechanisms suggested by which CVD and its risk factors might increase AD pathology. It may be that recurrent hypoxia-ischemia from chronic hypertension could upregulate amyloid-beta production, which by leading hypotheses is a major pathogenic step in the development of AD, or reduce its removal, resulting in accumulation. It has also been suggested that cerebral hypoperfusion resulting from CVD might accelerate neuronal injury and worsen AD pathology [7,8]. While the precise mechanisms linking VCID and AD remain unclear, and the underlying biology demonstrating links and exploring mechanisms linking the two is beyond the scope of this review, the hope remains that there is a potential for preventing dementia with aggressive prevention and treatment of CVD. In this manuscript, we will review the best evidence to date regarding the intertwining relationship of cognitive impairment and CVD. Specifically, we will address the cognitive ramifications of symptomatic cerebral ischemic stroke, the relationship between specific cardiovascular disease conditions, and the cognitive impairment (including impacts on brain microvascular disease) and finally highlight the importance of both the presence and control of vascular risk factors in the development of cognitive decline and dementia. With the recent release of pivotal studies, such as SPRINT-MIND, any physician of an older adult can anticipate questions from their patients and families about dementia preventive strategies [9••]. We aim to facilitate further understanding of this relationship and provide citations for future reference in this rapidly developing field.

Cardiovascular Disease and Ischemic Stroke

The morbidity and mortality associated with stroke are well understood, but what may go unrecognized are the resulting cognitive impairments. Some deficits may be subtle or completely missed on initial testing, or focused cognitive testing may never be performed during the acute post-stroke period. Furthermore, the cognitive consequences of stroke are best studied over time, since early after stroke, there are acute changes, some of which may resolve and could cloud the ability to detect more subtle decline in cognition. While this review discusses both, it is important to recognize that cognitive deficits related to an acute stroke can be distinct, although related to any changes in long-term cognitive trajectories and risk for dementia and AD that occur in the months and years after a clinical stroke. There remains a major gap in understanding of the early recovery period and how cognition changes over this time period impact longer-term cognitive trajectories [10].

Before describing cognitive impairment post-stroke, it is important to recognize the frequent preexisting cognitive impairment that occurs in patients who develop stroke. In fact, lower cognition has even been identified as a risk factor for stroke, which may reflect the shared risk factors to be discussed in more detail below [11]. Up to 26% of patients with ischemic stroke or intracerebral hemorrhage had either mild cognitive impairment or dementia in one study, and since most studies of post-stroke cognitive impairment do not include an evaluation for baseline preexisting cognitive status, estimates of post-stroke impairment are likely to overestimate true rates and report "incident" rates when actually reporting prevalence rates [12]. Patients with preexisting cognitive impairment *before* a stroke may be less likely to receive adequate acute rehabilitation, further worsening the likelihood that cognition might further decline in this population [13]. There is not a consensus on whether cognitive impairment also impacts secondary stroke prevention measures and medication adherence, since patients with cognitive difficulties often solicit help of family members, but theoretically a further increased risk of recurrent stroke in individuals with post-stroke cognitive impairment could also worsen cognitive trajectories for this population [14].

The focal cognitive deficits seen in the acute period after stroke depend strongly on the location of the infarcted brain tissue. It is estimated that 15% to a third of all patients with stroke develop language impairment, or aphasia, and up to 40% of right hemisphere strokes experience hemispatial neglect [15]. Tests of global cognitive function are often distinct from those used acutely to evaluate specific cognitive deficits post-stroke, such as aphasia and neglect, without a widely accepted single test. Thus, the estimated percentage of patients with a cognitive deficit varies widely depending on the type of cognitive assessment administered, the population tested, the timing of the administration of the test, or the definition of impairment using distinct assessments [16]. In 1 study of 95 ischemic and hemorrhagic stroke patients with a mean admission NIHSS of 4.7 who were evaluated within 3 weeks of an acute stroke, two-thirds of patients had cognitive impairment using a comprehensive neurocognitive battery. In this study, the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA), two measures of global cognitive function, were also both administered, and the MoCA was found to be highly sensitive (97%) but less specific (42%) for cognitive dysfunction, whereas the MMSE was less sensitive, at 66%, but more specific (97%). Using different cutpoints for both of these tests shifted the test characteristics, emphasizing the lack of consensus on best test or best use in this setting [17,18]. The heterogeneity in reports of cognitive dysfunction in the acute setting illustrated by the above contributes to a major gap in what is understood about

rates of impairment and its implications on long-term cognitive outcome.

In studies of cognitive impairment after the early recovery period, similar inconsistencies arise, reflecting differences in tools, timing of administration, and in definitions used to define cognitive impairment. The MMSE identified 25% of patients with cognitive impairment, but studies that utilized more detailed neuropsychological assessments at 3 months post-stroke identified approximately 70% of patients with cognitive deficits in at least one domain [19]. The modified Rankin Scale (mRS) is widely utilized to determine successful recovery and favorable outcomes post-stroke, but this scale does not incorporate or focus on cognitive deficits. The MoCA identified 65% of patients as having post-stroke cognitive impairment at 3 months, with attention and executive deficits and word recall the most commonly impaired. It also compared favorably to a more detailed cognitive battery in stroke caused by small vessel disease at 3 months [16,20]. The MoCA has been seen as a strong tool to use when evaluating vascular patients as executive functioning and visual construction tasks are particularly assessed, and these are commonly impaired in anterior circulation strokes, but use of the MoCA post-stroke is not common in standard clinical practice, and determining the optimal cutoff score is variable, with most studies suggesting 26 [21,22]. Similar to the acute setting, the lack of consensus in the field regarding the best screening tool, the best cutpoint for the available tools, and the best timing to use these tools make it challenging to compare rates of cognitive impairment across studies. An ideal tool could be easily administered early post-stroke, administered acutely, and before discharge to stroke patients, as well as provide the opportunity for comparison to a more thorough but still easily implementable assessment tool that can be repeated over time to track cognitive performance.

When standardizing the way that cognitive decline is evaluated and monitored overtime, the timing of the assessment and the duration of follow-up cannot be overemphasized. The trajectory of cognitive symptoms after initial stroke is recognized to vary across individuals, with both dementia and cognitive impairment commonly occurring post-stroke, but equally common is that a large proportion of initially impaired patients experience some degree of improvement. It has been postulated then that cognitive function will improve among individuals without dementia pre-stroke, unless they have concurrent cerebrovascular disease and/or develop further cerebral infarction [23]. In the REGARDS study, cognition declined acutely after stroke but had a longer and persistent decline extending over 6 years post-stroke, emphasizing the need to follow patients not only in the months after stroke but in the years that follow [24••]. In the TABASCO study, only 20% of patients had cognitive impairment 2 years post-stroke, while in another study, over 80% of patients had impairment 4 years post-stroke [25,26].

When cognitive decline does persist, most patients post-stroke demonstrate deficits across multiple cognitive domains, with the most commonly impaired being executive function and processing speed, attention, visual perception, and verbal memory [27]. These complex skills are associated with the proper functioning of complicated networks involving multiple cortical, subcortical, and infra-tentorial structures. Therefore damage to any one or more of these areas may result in discrete cognitive impairments [15].

The presence of comorbid vascular disease, particularly carotid artery disease, appears to play a role in the severity of cognitive impairment after stroke. Recent studies have suggested a higher risk of cognitive impairment post-stroke if the patient is also found to have severe carotid artery disease or stenosis regardless of if the patient specifically presents with symptoms of carotid artery disease [28,29]. Because carotid artery stenosis increases risk for ischemic stroke or TIA, and is often asymptomatic until the inciting event, understanding the cognitive sequelae of carotid stenosis may help elucidate its role in stroke patients. Even after adjusting for large artery stroke and other vascular risk factors, participants with a high degree of carotid stenosis showed a significantly higher frequency of cognitive impairment at 1 year post-stroke compared to those with < 70% stenosis [30]. Although some groups, in case series or observational studies, report that surgical intervention for symptomatic internal carotid disease may protect patients from cognitive decline, not just stroke, when compared to controls without surgical management, there is lack of consensus in the field without a clinical trial demonstrating this benefit [31,32]. The ongoing CREST-2 randomized trial will provide important information on cognitive trajectories after medical, surgical, and endovascular management of carotid stenosis [33].

There is also evidence that the subtype of stroke may matter when considering the cognitive outcomes and trajectory of ischemic stroke patients. Perhaps the most well-recognized association between cognitive impairment and stroke is damage to the deeper structures of the cortex from long-standing cerebral small vessel disease. If symptomatic and sudden in onset, it will manifest as ischemic stroke in the territory of a single deep penetrating artery or a so-called lacunar stroke. If asymptomatic, then it may manifest as white matter disease or white matter hyperintensities (WMH), usually incidentally diagnosed on brain magnetic resonance imaging.

Despite the initial belief that acute lacunar infarcts do not result in cognitive deficits, more recent literature has revealed cognitive deficits in up to 57% of patients during the acute phase post-lacunar stroke, spanning a range of cognitive domains [34]. Furthermore, accumulation of lacunar infarcts over time is also important for cognitive decline, as 41% of those with cognitive deficits had a previous lacunar infarct. Difficulty with executive function has been postulated as the most common cognitive domain impaired in lacunar stroke

due to lack of blood flow to the white matter and deep gray matter of the frontal lobes [35]. This supports other research suggesting that not only the location of the lacunar infarct but the number of lacunar infarcts increases the likelihood of cognitive impairment [35].

While damage to the structures that are fed by the small vessels might be more prevalent in patients with vascular cognitive impairment per autopsy studies, recent large epidemiology cohort studies suggest that cardioembolic stroke (CS) patients fare worse than their counterparts with ischemic strokes of other etiologies [36]. Leveraging the REGARDS study, Levine et al. identified that CS was associated with an acute decline in global cognition with notably a faster rate of decline in the years post-stroke compared to strokes of other etiologies [24]. Similarly, delayed recall and executive function deficits have been documented as most prevalent post-CS [37]. The morbidity associated with CS is high, with patients having the highest long-term rates of mortality as well as hospital readmission rates [38]. A higher degree of stroke severity in CS, older age, the presence of comorbid CVD, and more post-stroke complications have all been postulated as possible reasons, but the magnitude of the contribution of each factor, particularly when considering cognitive decline, is poorly understood [39].

The impact of CVD on cognitive ability is not limited to injury through clinically symptomatic stroke alone. VCID in particular has been recognized as a spectrum of different manifestations of vascular injury, to include not only focal ischemic injury but more widespread atherosclerosis, arteriolosclerosis, or diffuse ischemic changes [40]. The microvascular integrity of both the cortex and the deep white matter may be impaired from either shared risk factors (see subsequent section), or it may be the direct result of pathological changes that have been shown to lead to cognitive impairment. These subclinical changes, including silent lacunar infarcts, as described above, as well as other silent infarcts, microhemorrhages, and white matter hyperintensities, appear to be highly important in the development and progression of cognitive decline and dementia [41]. In the Rotterdam Scan Study, the presence of silent, nonclinically detected infarcts was associated with an over two times higher risk of incident dementia [42]. Because silent ischemia, or white matter disease, shares risk factors with stroke, and these risk factors are independently important for cognitive impairment, it is often difficult to delineate effects of stroke or small vessel disease (white matter hyperintensities, lacunar infarcts, and microhemorrhages) from the individual-level factors that caused a person to have that stroke or silent ischemia in the first place.

Vascular Risk Factors and Cognitive Decline

A separate publication would be required to do justice to the topic of the relationship between vascular risk factors and cognitive decline, but no manuscript on CVD and dementia would be complete without a discussion, albeit brief, of this incredibly dense topic (see also Table 1).

Hypertension is the most widely recognized risk factor for dementia, with evidence suggesting that midlife exposure to elevated blood pressure is especially important in subsequent adverse cognitive trajectories and risk of dementia [43,44••]. Several different large epidemiological cohorts have further supported that untreated hypertension at younger ages is associated with increased risk for cognitive decline in older age with evidence for impairments in executive functioning, processing speed, verbal fluency, and poorer working memory all reported [45–47]. It is notable that late-life hypertension alone does not appear to be a sufficient risk factor for incident AD but rather both the trajectory of the blood pressure over a life span and the age of onset seem to play a role [48]. Sustained hypertension in midlife to late-life as well as midlife hypertension and late-life hypotension was recently found to be associated with increased risk of dementia compared to normotension [49]. The highly anticipated SPRINT MIND trial was designed to test the effect of more intensive BP control (systolic blood pressure target < 120 versus < 140) on cardiovascular (primary end point), renal, and cognitive outcomes in persons without diabetes or preexisting stroke [9]. The study, which was stopped early and thus had a relatively short duration of follow-up, did not show that treating systolic blood pressure more aggressively resulted in a reduction in dementia but did result in a lower risk of mild cognitive impairment in secondary analysis. These findings, combined with the observational data demonstrating strong associations with midlife hypertension and later-life cognition, suggest that blood pressure management is likely still an important risk factor to consider to prevent adverse cognitive outcomes.

The literature on the relationship between diabetes mellitus (DM) and cognitive decline show a similar trend to that of blood pressure, where both the presence of DM and the degree of blood sugar control appear to play a role in onset of dementia. The attributable risk of diabetes to dementia in the Rotterdam Study was reported at 8.8% [50]. A longitudinal cohort study of 16,667 participants with DM suggested that a history of severe hypoglycemic events was associated with a greater risk of dementia and with a graded increase in risk in the frequency of episodes [51]. On the opposite side of the spectrum, higher average glucose levels within the preceding 5 years was related to an increased risk of dementia [52]. The risk of DM is also intertwined with the risk of obesity and metabolic syndrome with separate work demonstrating that metabolic syndrome is associated with an increased incidence of MCI and progression to dementia [53].

Nutrition has also been an area of interest when defining modifiable risk factors for cognitive decline. The data have been mixed with some suggestion that intake of dietary cholesterol has no impact on dementia risk while intake of one serving a week of dietary fish was associated with decreased

Table 1 Overview of modifiable risk factors for dementia*

Risk factor	Aspects of risk factor that increase risk	Citation numbers
Hypertension	Trajectory of hypertension, untreated hypertension, and age of onset (younger > older)	43–49, 9
Diabetes mellitus	Having diabetes and poorly controlled blood sugars (both hypo- and hyperglycemia), increased risk of cardiovascular disease through metabolic syndrome	50–53
Dietary cholesterol	Conflicting evidence with no clear association	54
Mediterranean diet, fish intake	Some suggestion of benefit with increased fish consumption, adherence to a Mediterranean diet	55, 56
Tobacco abuse	Age of onset of smoking, current smoking, history of smoking	2, 57–58
Markers of cardiovascular risk	Elevated composite risk scores (Framingham), elevated coronary artery calcium, higher baseline high sensitivity troponin T, higher levels of pro-brain natriuretic peptide	59, 72–74, 83, 85–86

*This is not meant to be an extensive list but rather a summary of some of the most important modifiable risk factors referenced in the text, along with the supporting citations

risks of dementia [54,55]. Adherence to a Mediterranean diet was not associated with incident dementia risk, although there was suggestion of fewer errors on the MMSE [56].

Tobacco use or cigarette smoking is one of the strongest risk factors for CVD and has been associated with cognitive decline, independent of other risk factors. Current smokers are more likely to experience cognitive decline than former smokers or nonsmokers with a relative risk estimate of 1.4 [2]. A history of smoking was one of the main predictors found in the conversion to mild cognitive impairment, while not smoking was found to be a significant baseline variable associated with maintaining cognitive function [57,58]. There was an increased risk of dementia in later life among those who were smokers during midlife, defined as 44 to 66 years old, suggesting that even earlier interventions targeting cessation of smoking might be the most impactful [58].

When reviewing these risk factors, it is important to also acknowledge that composite measures of vascular risk have shown even stronger associations with cognitive decline than individual risk factors. Accumulation of risk factors, such as those defined using the Framingham Stroke Risk Profile Score, which includes age, systolic blood pressure, hypertension medication, diabetes, cigarette smoking, CVD history, and atrial fibrillation, has been shown to be associated with a worse cognitive trajectory among those who are dementia-free at baseline [59]. Additionally, an increasing number of midlife, but not late-life, vascular risk factors was found to be associated with elevated late-life brain amyloid deposition, an important pathological feature of AD, using florbetapir positron emission tomography (PET) [43]. This has similarly been supported by pathology, with cerebrovascular changes most apparent in patients with Alzheimer's disease and multiple vascular risk factors, suggesting that there is a cumulative effect in the vascular contributions to dementia [60].

Cardiac Disease and Cognition

A consideration of the impact of cardiovascular disease itself on cognition must appreciate the shared risk with the above-described vascular risk factors, which are important for stroke, and cardiac disease, as well as cognitive decline and dementia. Although cardiac disease is often a more severe consequence of long-standing risk factors, there is evidence that end-organ cardiac disease itself can independently increase risk for cognitive decline and dementia. Representing one end of this spectrum is heart failure (HF), which, as with stroke, represents a significant public health problem with the healthcare-related costs for HF alone anticipated to rise to more than $70 billion by 2030 as a result of the population aging and growing [61]. The Atherosclerosis Risk in Communities Study (ARIC) has shown that around 915,000 incident cases of HF occur each year in the USA, with the same cohort demonstrating that participants with the lowest cognitive scores at baseline as well as those with the greatest change in scores over 6 years had a higher risk of subsequent incident HF. Furthermore, the existence of HF itself is associated with higher incidence of mild cognitive impairment and dementia [62–64], with a reported odds ratio of 1.67 (1.15–2.42) for cognitive decline in participants with HF versus non-HF [65].

It is acknowledged that HF patients have an elevated vascular risk factor profile, which again makes teasing apart the exact causal mechanisms difficult. If HF is to be thought of as causal, it has been postulated that new clinical infarction, subclinical cerebral sequelae of long-standing HF, potentially from undiagnosed atrial fibrillation (AF), or hypoperfusion might be possible explanations [66–68]. Similarly, elevations in inflammatory markers have been associated with cognitive impairment in HF [69]. It may be possible that with either appropriate medical treatment of decompensated heart failure or avoidance of heart failure complications, such as

hospitalization or progression to heart transplantation, cognitive performance might be improved [70,71].

Coronary artery disease (CAD), in the form of a history of coronary artery bypass graft surgery, and even elevated coronary artery calcium (CAC) have been associated with increased risk of dementia [72,73]. Notably, higher baseline CAC was significantly associated with this risk, even after controlling for incident stroke and other vascular risk factors. Although traditionally thought of as a marker for CAD, this surrogate for atherosclerotic disease might serve as a useful tool in understanding the link between vascular disease and dementia, above and beyond predicting CVD [74]. Additionally, those with more severe angina pectoris in midlife had poorer cognitive performance in late-life, among those with preexisting HD, suggesting that it is not only the presence of disease but also the severity of the disease process that makes a difference on cognitive trajectory [75].

The increased risk of cognitive impairment with atrial fibrillation (AF) has been well documented [76]. AF is certainly associated with increased risk of ischemic stroke and other cardiac conditions, such as heart failure, that increase risk of dementia, but if the effect of AF on cognition is mediated entirely through these pathways or if there is a more direct mechanism by which AF impacts, cognition is unknown [77]. There has been a suggestion that AF may impact brain volumes via cerebral hypoperfusion or cerebral emboli, with permanent AF more strongly associated with global brain atrophy than paroxysmal AF, suggesting a cumulative effect, but other work saw such associations disappear after adjusting for vascular risk factors [78,79]. There may also be a multihit phenomenon with literature suggesting that patients with AD, the APOE Ɛ4 allele, and permanent AF have lower MMSE scores and the highest risk of cognitive deterioration when compared with individuals with only some of these features [80].

Overt manifestations of CVD may not be the only way that cardiac disease contributes to cognitive decline but more subtle changes or subclinical CVD may also be associated with cognitive decline. Drops in blood pressure during cardiopulmonary bypass surgery have been associated with decline in cognitive performance, and similarly lower cardiac ejection fraction is also associated with worse cognitive performance, especially if concurrent blood pressure is low [81,82]. Other markers of subclinical cardiac disease have been associated with cognitive performance in individuals from community-based cohorts without clinical CVD: higher baseline high sensitivity cardiac troponin T (hs-cTnT) was associated with lower baseline cognition as well as increased dementia hospitalization risk [83]. Because one mechanism by which subclinical cardiac disease may act on cognition is via clinical or subclinical cerebrovascular injury, or even other cerebral structural changes, studies demonstrating associations with these brain changes also further support a role of subclinical cardiac disease in cognitive decline and dementia [84]. A difference of 25 g in higher left ventricular mass was associated with significantly lower hippocampal volume and higher degrees of cerebral white matter disease, while higher levels of pro-brain natriuretic peptide (NT-proBNP) and hs-cTnT were associated with cortical cerebral microinfarcts among a cohort seeking treatment for memory complaints [85,86]. Such literature may suggest that frank disease states are not necessary for a change in cognitive trajectory, but more subtle signs of CVD may be sufficient.

Conclusions

Recognizing that frank CVD as well as subclinical cardiac dysfunction serve as potential risk factors for cognitive decline is an important first step to prevention of dementia. It may be that tailored interventions, targeting both the prevention and manifestation of CVD, are one mechanism by which dementia, or at least cognitive impairment, might be averted. We have discussed that the causal relationship between the two is complicated by shared risk factors contributing to pathology within both organs. Major vascular risk factors, such as elevated blood pressure and smoking, especially when measured in midlife, and diabetes, even when assessed only later in life are known to predict, years later, both dementia and AD specifically. Nevertheless, it is plausible that cardiac dysfunction might directly lead to brain injury (including cognitive decline and dementia), either in the form of new clinical infarcts, new subclinical infarcts, the progression of WMH, or via a flow phenomenon such as hypoperfusion. Future studies should also take into account the intensity, duration, and timing of the vascular risk factor, because exposures may be more influential and interventions more effective during critical or sensitive periods throughout life. With education of the lay public and increased awareness of the treating physician, a multidomain and multidisciplinary approach to treatment of the medical conditions associated with CVD may be the key to identifying individuals at risk for dementia, offering a window before it is too late to treat the disease effectively.

Compliance with Ethical Standards

Conflict of Interest Dr. Gottesman reports her role as Associate Editor of American Academy of Neurology's Neurology journal.

Dr. Johansen reports grants from American Heart Association, outside the submitted work.

Dr. Langton-Frost declares no conflict of interest.

Human and Animal Rights and Informed Consent There are several references for the ARIC study, which is a longitudinal cohort study that has answered many of the questions raised by this article. It is human subjects research and both Dr. Johansen and Dr. Gottesman have done work with this group.

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