

## Connecting Cardiovascular Disease and Dementia: Further Evidence

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Cognitive impairment is highly prevalent in the elderly, and it accounts for a large part of the burden of disability and of the use of healthcare resources. The major types of dementia are Alzheimer disease and vascular dementia.<sup>1</sup> For many years, atherosclerosis was not considered to play a role in Alzheimer disease. Etiologically, both dementias may, however, not be as different as has been proposed in clinical classifications of dementia.<sup>2</sup> Indeed, Haring et al,<sup>3</sup> in the article published in this issue of *JAHA*, reported that women aged 65 to 79 years with cardiovascular diseases (CVD) enrolled in the Women's Health Initiative Memory Study (WHIMS), after a median follow-up time of 8.4 years, tended to be at increased risk for cognitive decline compared to those free of CVD. Vascular disease, atrial fibrillation, and heart failure were ascertained via self-reporting.

Specifically, women with myocardial infarction or other vascular diseases, such as peripheral artery disease, and invasive procedures, including coronary bypass surgery or carotid endarterectomy, were at higher risk. On the other hand, no significant relationships were found for either atrial fibrillation or heart failure. Hypertension and diabetes were observed to increase the risk of cognitive decline in women without CVD, while no significant trend was seen for adiposity. After excluding women with incident stroke or transient ischemic attack (TIA) events after baseline, the authors found that a history of myocardial infarction and angina remained strongly associated with cognitive decline.

The authors did not report any etiological diagnosis of dementia (ie, vascular or degenerative), but they assessed the

incidence of mild cognitive impairment (MCI) and probable dementia (PD). Since there has been a significant evolution in defining the features of cognitive syndromes associated with risk factors for CVD and their manifestations, it would have been useful to know the type of dementia, in order to assess properly the association of each disease with its risk factors. Moreover, neuroimaging data were not reported, so that the presence of parenchymal brain lesions remained unknown. Since vascular disease may represent vascular or degenerative processes, neuroimaging could have detected infarcts, white matter degeneration, and deep or lobar microbleeds that would have helped in identifying small vessel disease and cerebral amyloid angiopathy.<sup>4</sup> Despite these limitations, the study was performed using appropriate neurocognitive and neuropsychiatric examinations with an adequate follow-up.

Coronary artery disease has been identified in previous studies as an independent risk factor for vascular dementia<sup>5</sup> and computed tomography–based coronary artery calcium, a measure of severity of coronary atherosclerosis, has been associated with a higher risk of cognitive impairment.<sup>6</sup> However, adjustment for white matter lesions, silent brain infarcts, cerebral microbleeds, and brain volumes has attenuated the observed association between coronary artery calcium and cognition, suggesting that other vascular mechanisms play a role.<sup>7</sup> For these reasons, it would have been particularly interesting to have neuroimaging data on the patients reported by Haring et al. Also, patients who had other vascular diseases, such as peripheral artery disease, or who had undergone invasive procedures, including coronary bypass surgery or carotid endarterectomy, were at higher risk for cognitive decline. The possible connection between carotid atherosclerosis and dementia has been previously emphasized, leading to potential explanations, including the contribution of carotid atherosclerosis to silent or symptomatic cerebrovascular events, or to chronic cerebral hypoperfusion.<sup>8</sup> Additionally, the presence of peripheral arterial disease, evaluated with the ankle-brachial index or with carotid-femoral pulse wave velocity, has a confirmed association with lower cognitive function.<sup>9–11</sup>

Regarding vascular risk factors such as systolic hypertension and diabetes mellitus, a relationship with cognitive decline seems more obvious. Systolic hypertension is an important modifiable risk factor for late-life cognitive decline,

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mild cognitive impairment, and vascular dementia, although some studies have reported a J- or U-shaped relation.<sup>4,12</sup> Observational studies point to some benefit from antihypertensive treatment in order to reduce the concomitant development of Alzheimer disease.<sup>4</sup> Chronic hyperglycemia, metabolic syndrome, and diabetes are associated with cognitive decline, in relation to vascular and neural damage, with functional changes in cerebral blood flow and neural damage following recurrent episodes of hypoglycemia.<sup>13</sup>

A meta-analysis has shown that a high waist-hip ratio is associated with a greater risk of dementia in all studies.<sup>14</sup> Conversely, Haring et al did not report a correlation between adiposity and cognitive decline. The Framingham Offspring Study found a correlation between waist-hip ratio and lower cognitive function, strengthening the possibility of an association between hypertension and dementia in the highest quartile of waist-hip ratio, but also suggesting an important role for confounding factors.<sup>15</sup>

Haring et al, did not report a correlation between the presence of atrial fibrillation or heart failure and cognitive decline. Previous studies have reported that a subclinical decrease in cardiac output is associated with lower cognitive function,<sup>16</sup> which may be due to reduced systemic perfusion affecting cerebral perfusion homeostasis.<sup>17</sup> These differences between past versus Haring et al studies are probably due to the fact that while a wide range of confounding factors were considered in the present study, residual confounding factors were present, but not evidenced. Indeed, the relative number of incident cases of MCI and PD may have limited the power of the analysis. Furthermore, relatively healthy postmenopausal women were included, which may have underestimated the real association present in the general population between specific cardiovascular disease, such as atrial fibrillation or heart failure, and cognitive decline.

The final message conveyed by the study of Haring et al is that generalized atherosclerosis and its risk factors play a pivotal role in the etiology of dementia, while a decrease in cardiac output seems less critical. Several plausible mechanisms that underlie this relationship have been hypothesized, including ischemic lesions affecting specific neuronal networks, or ischemia triggering an inflammatory host response leading to neuronal degeneration.<sup>2,18,19</sup> The prevention of chronic vascular disease by identifying and treating all modifiable risk factors may thus help reduce the overall incidence of mild cognitive impairment and subsequent dementia.

## Disclosures

None.

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