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Healthy Young Hearts Sharper Older Minds Make

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The “Simple 7” – eating a healthy diet, not smoking, being physically active, maintaining normal blood pressure, blood glucose, total cholesterol levels and body weight – have a potent impact on cardiovascular (CV) mortality¹. Over the past quarter century, it has become clear that at least several of the Simple 7 also influence brain health. In this issue of the *Annals of Neurology*, investigators representing the Coronary Artery Risk Development in Young Adults (CARDIA) study evaluated the impact on midlife cognition of adherence to the 7 CV metrics in young adulthood².

Reis et al report that individuals, who between the ages of 18-30 years exhibited a higher number of healthy CV metrics, had better cognition 25 years later². The relationships were seen with two tests of attention and executive function as well as a verbal memory task. In general, the greater the number of healthy metrics achieved, the better the cognitive outcome. Those participants who maintained higher adherence to the CV metrics at the 25 year follow-up also had better cognition than those who had fewer. While midlife diabetes, hypertension and other CV risk factors have been shown to be risk factors for late life cognitive decline³⁻⁸, the CARDIA study provides novel longitudinal observations of young adults through midlife who were far younger than in any prior studies. It may never be too late to “get with the program” and adopt a healthy lifestyle, but the deleterious effects of failing to do so are already operative in the third or fourth decade of life.

Why is CV health relevant to the brain? If better CV health promotes better cerebrovascular health, which in turn reduces atherosclerosis and arteriolosclerosis and reduces the probability of macroscopic and microscopic cerebral infarcts, then better cognitive functioning in later life would result. From a public health perspective, that would be very good news because attaining some of the 7 metrics such as stopping smoking, maintaining a healthier diet, exercising more regularly and losing weight are feasible for anyone, in principle. While “in principle” glosses over major challenges for implementation, campaigns to avoid smoking, reduce obesity and increase physical fitness in teenagers and young adults will pay dividends in the future by reducing the burden of late life cognitive impairment and dementia.

However, there are alternative interpretations of the impact of CV risk factors on cognition that make interventions look less feasible. First, because cognition was not measured in CARDIA participants at baseline, it is possible that cognition at the baseline visit was already lower in those with poorer adherence to CV health metrics. If cognition had a graded relationship to the number of healthy CV metrics at baseline, causality would be reversed: poorer intellectual development would lead to poor life choices, and more dysfunctional health behaviors. Improving CV health in young adulthood might still have CV benefits, but there might be no cognitive benefits. And then there is the impact of opportunity to access

educational opportunities and health care. In the CARDIA cohort, socio-economic status is strongly tied to CV health⁹. If low socio-economic status drives poorer intellectual development and unhealthy lifestyle choices, improving cognitive health through manipulation of CV health will require massive educational and social policy initiatives by governmental entities that most Americans might not accept.

While retaining skepticism but not nihilism, we should accept that it is possible that improved cardiovascular health beginning in young adulthood could improve brain health lifelong. One of the attractive conceptual features of the Simple 7 is that the formulation recognizes that many of the CV risk factors are intertwined. While it is sometimes helpful from an investigational viewpoint to focus on one, eg diabetes, it is essential from an interventional perspective to link dietary and exercise efforts to management of hyperglycemia, hyperlipidemia and adiposity.

Exactly how might early life CV risk factors influence cerebral physiology? There is no consensus on the sequence of events, but promotion of microvascular disease is a leading candidate. Brain microvascular disease is caused by intimal fibromuscular hyperplasia and lipohyalinosis¹⁰⁻¹². One consequence is the eventual obliteration of the lumen of the vessel, leading to a microinfarct. A few microinfarcts might have no impact on cognitive functioning, but the gradual accumulation of microinfarcts throughout the cerebral hemispheres over 30 or 40 years would take a toll. Microvascular disease is associated with loss of brain volume¹³. If microvascular pathology is paired with a second pathophysiological process such as multiple larger infarcts or a degenerative process such as β -amyloidosis, tauopathy or α -synucleinopathy, there are much higher odds of overt cognitive impairment¹³⁻¹⁶. A second possible pathophysiological mechanism by which CV risk factors impact the brain is by promoting neurodegenerative disease. An underrecognized consequence of cerebral arteriolar disease is interference with the protolymphatic functions of the physically contiguous Virchow- Robin (perivascular) spaces that accompany every cerebral microvessel¹⁷. The Virchow-Robin spaces are involved in the transport of β -amyloid and other damaged proteins out of the neuropil and into the cerebrospinal fluid¹⁸. Microvascular disease could facilitate perivascular accumulation of β -amyloid^{19,20}. A second non-ischemic consequence of damage to the penetrating cerebral arterioles might be alterations in regulation of inflammatory functions that utilize the perivascular spaces²¹. The ischemic and non-ischemic mechanisms are not mutually exclusive. To the contrary, they could easily co-occur.

The study by Reis et al² is unique because of the young age at which individuals were first assessed, the thoroughness of the cardiovascular assessment in young adulthood, and the cognitive assessment that occurred in later life. It is unfortunate that cognition was not measured at the time of enrollment. The failure to do so represented the prevailing unawareness of relationships between cardiovascular disease and cognitive health that existed 25 years ago. But, CARDIA also represents a wonderful example of how that divide has been breached.

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