PUBLIC HEALTH CENTER OF EXCELLENCE
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DEMENTIA RISK REDUCTION

Cardiovascular Risk Factors, Cognitive Decline, and Dementia:

What's Good for the Heart Is Good for the Brain

What Is Already Known

There is substantial evidence for a relationship between vascular risk factors and brain disorders, including cognitive decline and dementia. Up to 80% of people with Alzheimer's disease (AD) have significant vascular pathology in the brain. This evidence is remarkably consistent and spans the translational spectrum from basic biology to epidemiologic and clinical trial science.

Background and Evidence Base

Mechanistic evidence

Beta-amyloid (Aβ), a protein that accumulates in the brains of those with Alzheimer's disease, produces oxidative stress that in turn causes neurovascular injury by constricting capillaries in the brain. This constriction can lead to chronic hypoperfusion, exacerbating neurodegeneration and cognitive dysfunction. There is evidence for a synergistic interaction between the accumulation of Aβ and vascular damage in the brain. However, it is unclear whether vascular decline precedes amyloid accumulation or vice-versa.

Another mechanism that could explain the link between vascular and cognitive health is arterial stiffness. The brain, heart, and kidneys are especially vulnerable to arterial stiffness, and all three organs show age-related changes in physiology associated with organ system failure. Arterial stiffness increases pulse wave velocity, and the increased transmission of a larger forward wave may expose peripheral small arteries and microvessels to damaging levels of pulsatility, particularly in the brain. Such damage may contribute to the microvascular disorders that are common in aging in these organs.

Evidence from population studies

There is substantial evidence that chronic hypertension over the lifespan is the most prevalent risk factor for cognitive impairment in aging, with midlife hypertension strongly associated with later cognitive deficits.

- Midlife vascular factors, particularly hypertension, were associated with 25-year incident dementia in the diverse Atherosclerosis Risk in Communities (ARIC) observational cohort.
- The AGES-Rejyavik Study documented the joint importance of mid- and late-life blood pressure on subsequent cognitive decline.
- A 2014 review and meta-analysis reported associations between arterial stiffness, cerebral small vessel disease, and cognitive impairment.
- The Harvard Aging Brain Study reported interactive associations among vascular risk, Aβ burden, and cognitive decline in clinically normal older adults.
- In a British birth cohort study, Insight 46, vascular risk across adulthood was associated with late-life brain pathology.
- In the Coronary Artery Risk Development in Young Adults (CARDIA) study, cumulative blood pressure exposure over time, beginning in young adulthood, was associated with mobility and cognitive function in midlife.
- Most recently, a study used UK Biobank data from more than 200,000 participants to determine the relative causal contributions to dementia of individual biological and lifestyle factors that tend to cluster together in midlife. The results showed that, of the biological factors (i.e., systolic blood pressure, LDL cholesterol level, and hemoglobin A1c level), only systolic blood pressure in midlife was an independent predictor of incident dementia later in life.

Evidence supporting vascular risk treatment to reduce the risk of later dementia

The most recent evidence that reduction of a cardiovascular (CVD) risk factor could minimize the risk for clinically significant cognitive decline came from the Systolic Blood Pressure Intervention Trial (SPRINT). Participants were randomized to either a standard blood pressure management goal (systolic blood pressure <140 mm Hg) or to an intensive blood pressure management goal (systolic blood pressure <120 mm Hg). Participants assigned to the lower systolic blood pressure goal had a 19% lower risk for developing mild cognitive impairment (MCI), a precursor stage of dementia, compared with those assigned to the systolic blood pressure goal of <140 mm Hg. Participants also had a 17% lower risk for developing

dementia, but this reduction was not statistically significant as fewer cases of dementia than of MCI developed during the follow-up period. (It should be noted that this trial terminated early because of the cardiovascular benefits of treatment identified in the overall SPRINT trial.) Participants assigned to the lower blood pressure goal also had reduced development of abnormal white matter lesions in their brains, indicating a possible mechanism for the observed preservation of cognitive function.

Evidence for the effects of statins on reducing the risk of cognitive decline and dementia is equivocal. While it is known that clinical and subclinical cardiovascular disease increases the risk of cognitive impairment and dementia and that the antihypertensive drugs statins reduce rates of ischemic stroke (a significant contributor to vascular dementia), the role of statins in preserving cognition is unclear. This gap in knowledge led to the development of the PREVENTABLE study, a new trial that is testing the hypothesis that statins could reduce the occurrence of the composite endpoint of death, dementia, and persistent disability among 20,000 community-living adults aged 75 years and older without cardiovascular disease or dementia at baseline. The secondary hypothesis is that statins could reduce the occurrence of the composite endpoint of MCI and dementia and a composite cardiovascular outcome. Results of this trial, due in 2027, will provide evidence for whether treatment with statins can protect against cognitive decline in aging.

Implications for Public Health

There is a vascular component in most cases of ADRD, with increasing evidence that hypertension in midlife is strongly associated with dementia in older adulthood. Hypertension is thus a modifiable risk factor for dementia and should be a target for prevention strategies. Public health efforts should focus on populations with the lowest rates of controlled hypertension: older adults and Black, indigenous, and other people of color. There is substantial epidemiologic evidence for a link between long term hypertension and ADRD incidence and therefore an additional target population for prevention should be middle-aged adults.

Nearly six million people in the United States aged 75 years or older met the criteria for inclusion in the SPRINT trial. This age group is rapidly growing and at the greatest risk for cognitive decline and dementia and would therefore be a prominent subgroup to target for meeting blood pressure goals as a way to quickly reduce the risk of cognitive dysfunction.

Discussion

Evidence shows that vascular health and cognitive health are closely related. Chronic hypertension is the most prevalent risk factor for cognitive impairment in aging, and the incidence of high blood pressure increases with age; by age 75, up to 80% of individuals will have been diagnosed with and/or treated for hypertension. Prevention is always the most effective way to change the course of a disease and the scientific evidence is strong for treating hypertension is an effective means to reducing the risk of cognitive dysfunction in older age. Importantly, there are many existing treatments for doing so. However, despite the wide availability of such antihypertensive treatments, access to those treatments is a major concern for underrepresented populations, many of which have higher rates of hypertension and dementia. Public health programs should target these populations with hypertension prevention and treatment strategies to reduce the risk of, or delay the development of, cognitive decline in later life.

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