INVITED ARTICLE

Brain Health—Curbing Stroke, Heart Disease, and Dementia

The 2020 Wartenberg Lecture

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Abstract

There is no health without brain health, which is threatened by rising curves of stroke, ischemic heart disease, and dementia (the triple threat). The fastest growing and intractable threat has been dementia. Focusing on finding a drug to stop Alzheimer disease has yielded growing knowledge but no treatments, partly because in the elderly, cognitive impairment results from multiple interactive pathologies aggravated by fragility and tempered by resilience on the advancing background of aging. The concept of vascular cognitive impairment (VCI) cuts pragmatically through this complexity. VCI is any cognitive impairment caused by or associated with vascular factors. It spans the spectrum of undetected cognitive impairment to full-blown dementia. The vascular component represents the only major current, treatable, and preventable contributor to dementia and offers the possibility of delaying, mitigating, or preventing more dementias in the near future. The triple threat conditions share the same protective and treatable risk factors and can be prevented together. The approach needs to be comprehensive, identifying all relevant environmental, socioeconomic, health care, and individual factors; targeted, as risks and protective factors differ among populations and individuals; and and investment valued, yielding worthwhile returns in terms of money, effort, or time. The World Stroke Organization's proclamation calling for the joint prevention of stroke and potentially preventable dementias has been endorsed by 23 international, regional, and national brain and heart organizations, including the American Academy of Neurology. We need to develop joint prevention programs to curb the triple threat. Millions of brains depend on it.

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Glossary

AD = Alzheimer disease; **CTIV** = comprehensive, targeted investment value approach; **MoCA** = Montreal Cognitive Assessment.

In 1948, the WHO defined health as "A state of complete physical, mental and social well-being and not merely the absence of disease or infirmity." Who we are, what we think and feel, and what we do are all mediated through the brain. It is important not only to have a healthy lifestyle and manage illnesses: brain health is key to functioning in an increasingly digitized, complex, and demanding world.

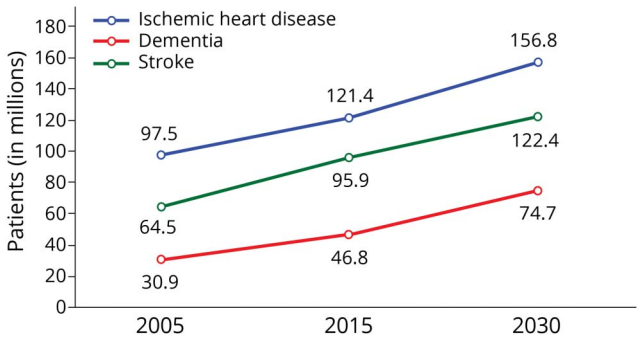
Although brain health matters throughout the life cycle, it is becoming more difficult to maintain with increasing age. Aging of the world's population, urbanization, and Westernization are driving a global pandemic of stroke, ischemic heart disease, and dementia (the triple threat) (figure 1). Although the triple threat conditions will be considered together, the emphasis will be on dementia.

Background

In the 1950–1970s, the prevalent view of dementia in the elderly held that hardening of the brain arteries with aging resulted in a slow strangulation of the brain's blood supply, causing ischemia and neuronal death. Atherosclerotic dementia or hardening of the arteries became near synonymous with dementia of old age.

By the end of the 20th century, it was Alzheimer disease (AD) that became near equivalent with dementia. Now we are at a stage of sophisticated confusion, of bewildering complexity that follows discovery, but precedes true understanding. As David A. Bennett and colleagues concluded after extensive review of their multiple studies, "there is much greater heterogeneity in the comorbidity and cognitive impact of age-related neuropathologies than currently appreciated, suggesting an urgent need for novel therapeutic approaches that embrace the complexity of disease to combat cognitive decline in old age."[1]

Figure 1 Worldwide Number of People With Ischemic Heart Disease, Stroke, and Dementia (Million)



Current Approaches

The bulk of the efforts to prevent dementia so far have been in finding a drug that would stop the Alzheimer process. This approach has advanced science but not therapeutics. So far, no anti-amyloid or anti-tau agent has proven effective.

The idea of focusing on a single mechanism to stop complex pathophysiologic processes has precedents. The belief that stiffened and clogged arteries caused most dementias of old age spawned a whole industry of alleged brain vessel vasodilators. If true, brain arteries would be maximally dilated from accumulated metabolites and could not dilate any further with CO_2. We showed that patients with alleged atherosclerotic dementia and primary degenerative dementia dilated equally well to CO_2 inhalation.[2] We concluded that when vascular disease caused dementia, it was through small or large infarcts: multi-infarct dementia.[3] This concept implies that most strokes are preventable and hence some dementias should be.

Some drug companies confronted with the growing evidence that vasodilators lacked rationale tried to hang on to their markets by relabeling their products "brain oxygenators." Despite these efforts, the market for vasodilators slowly constricted and died. This did not deter another set of pharmaceutical companies a few years later betting on single mechanisms of neuroprotectant drugs in acute stroke. All the trials failed, for several reasons,[4] perhaps the main one reflecting the fact that the complex cascade of multiple interactive mechanisms triggered by acute ischemia cannot be arrested by targeting just one.

Dementia of late onset is no less complex and unlikely to yield to a drug aimed at a single mechanism. Up to 8 pathologies account for what is diagnosed as "Alzheimer disease" and explain 2/3 of dementia. Tellingly, 1/3 of the dementia cannot be attributed to them,[5] leaving ample room to discover new pathologies and mechanisms and understand resilience, whereby with the same pathologic load some patients develop dementia and others do not. Moreover, we need to make our interpretations within a larger and more dynamic context.[6]

From Complexity to Practicality

The continuous attempts to impose diagnostic criteria on AD brings to mind a song by the rock band Rush: "You can bend perceptions; reality won't budge." The reality is that dementia of late onset is not a disease, but a syndrome.

In the elderly, after excluding specific entities such as frontotemporal dementia, Lewy body dementia, and Parkinson disease, we are left with a cognitive impairment syndrome resulting from multiple interactive pathologies aggravated by

fragility and tempered by resilience on the advancing background of aging.[7] To cut through the Gordian knot of the complexity of a syndrome with multiple pathologies pragmatically, we suggested the concept of vascular cognitive impairment[8,9]—that is, any cognitive impairment caused by or associated with vascular factors. It spans the whole spectrum from undetected cognitive impairment to fully developed dementia. It often coexists with neurodegenerative conditions to different degrees. It rests on the premise that it is the vascular component that is most amenable to treatment and prevention. One way of identifying the vascular component is applying an ischemic score.[2,10,11]

The evidence for vascular contributions to dementia has become uncontestable. All major dementias have a vascular component, ranging from 61% in frontotemporal dementia to 80% in AD. The presence of a vascular component doubles the chances of developing dementia.[12]

Similarly, at least a quarter of asymptomatic elderly have Alzheimer pathology, but if they also have a vascular component, that doubles the chances that the individual will develop dementia.[7]

A stroke doubles the chances of developing dementia.[13] Moreover, after a first stroke, cognitive decline accelerates,[14] suggesting that a stroke triggers or interacts with a neurodegenerative process.

An international, multidisciplinary group has laid out the epidemiologic, pathophysiologic, clinical, and therapeutic scientific bases for considering and preventing stroke and dementia together.[15]

Personalized Medicine

The encouraging news is that the age-adjusted incidence of ischemic heart disease and stroke is falling and dementia incidence is decreasing in high-income countries.[16] Something positive must be happening or we must be doing something right. We need to find out what and do more, particularly in dementia prevention. Specific interventions are beginning to yield positive results.

Intensive treatment of lifestyle factors (diet, exercise), cognitive training, and management in a 2-year randomized study showed a small cognitive decline.[17] Anticoagulation of patients with atrial fibrillation reduces the risk of developing dementia by 48%.[18] Treating patients at risk of vascular disease blood pressure to a target of 120 mm Hg compared to 140 mm Hg resulted in a reduction of mild cognitive impairment of 19%.[19] The study also showed less increase in white matter hyperintensities in the 120 vs the 140 mm Hg targeted group. This is encouraging, given that some of the earliest changes later associated with cognitive impairment arise in the white matter. Prevention of white matter disruption represents a promising and underexplored area of therapeutics.[20] However, not all white matter lesions have the same origin.

Although on average, lower blood pressures seem better for the brain, lower blood pressure could be harmful to some individuals. The human brain contains 2 complementary systems: a high-pressure and a low-pressure system: the ambibaric (2 pressures) brain.

Blood pressure below a critical threshold of the individual could result in ischemic damage in the low-pressure *Homo sapiens* brain. This holds particularly true if high blood pressure is treated too rapidly. The brain's blood flow autoregulatory plateau has turned out to be much more dynamic and narrower than we thought. Instead of 100 mm Hg, it is closer to 10 mm Hg. Moreover, its effectiveness decreases with age and conditions such as hypertension[21] and diabetes. One of the most important questions in personalized medicine is "What is the optimal blood pressure for my brain?" We need to develop techniques that can be used widely, as high blood pressure represents one of the most powerful and prevalent treatable risk factor for the triple threat.

Personalizing: Matching the Individual With Growing Databases

When a patient presents with a cognitive problem, a precise diagnosis might be a problem. A limitation of current approaches arises from the diagnostic criteria that put a patient in a category in which only some of the items apply. One means of developing personalized evidence-based criteria consists of agreeing to record a minimum set of clinical, neurophysiologic, imaging, and other relevant data recorded as individual items. These can be set into provisional criteria that can be refined with increasing knowledge and made comparable among studies.[22] This would make studies comparable and in addition, in the world of electronic records and artificial intelligence, much could be discovered through the core data generated by routine clinical practice and comparing them with data from longitudinal studies and clinical trials on an item-by-item basis so that the individual can be matched as closely as possible for diagnostic treatment and prognosis. Patients can then be screened by the Montreal Cognitive Assessment instrument (MoCA) and the additional half hour or 1 hour battery administered if warranted by the MoCA results.[22] Using the MoCA for screening in daily practice would create a wealth of comparable data. The Indian Council of Medical Research has commissioned a large multicenter collaborative study to develop a testing battery based on the recommended standards.[22] Similar studies are underway in other counties, including Korea and China. Like all neuropsychological tests, the MoCA has limitations.[23,24] However, it is offered as a core minimum to be complemented by other tests, depending on the sophistication of the study.

If the patient shows signs of cognitive impairment, tailored interventions can be carried out, including looking for evidence for a vascular component to the cognitive impairment. A simple screening for the latter is the use of an ischemic score.[2]

As shown in the table,[11] the original 13 items have been reduced to 5 questions that do not require a neurologic examination.

Table Ischemic Score With 5 Composite Items[a]

Item number	Item description	Score if answer is yes
1/2	Abrupt onset or stepwise deterioration	Scored electronically
3/4	Fluctuating course or nocturnal confusion	Scored electronically
6/8	Depression or emotional incontinence	Scored electronically
9/11	History of hypertension or atherosclerosis	Scored electronically
10/12	History of stroke or focal neurologic symptoms	Scored electronically
Total		Scored electronically

[a] A vascular component of cognitive impairment may be indicated after electronic computation.

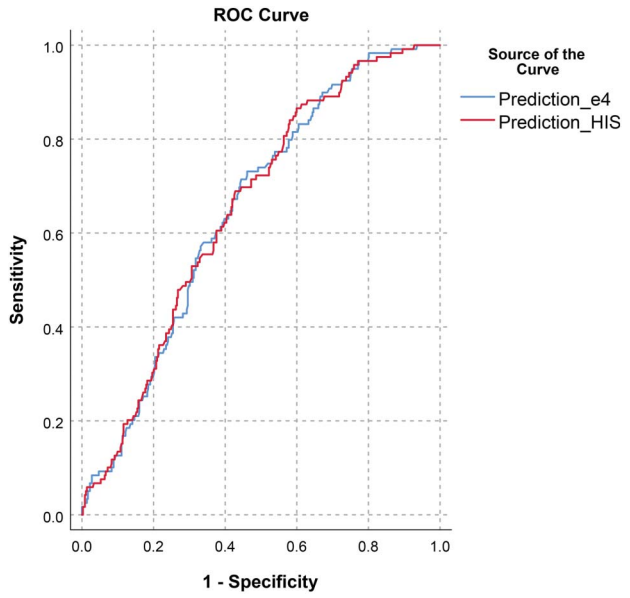
The ischemic score does not differ in power in predicting progression to dementia in 5 years compared to *APOE* ε4 (figure 2)[25.]

The higher the score, the greater the likelihood of progressing to dementia. Genetics represents one of the most promising areas of progress, but in the meantime, we cannot change our genes, whereas most of the items of the ischemic score are modifiable.[2,11]

Cognitive testing should be part of every initial neurologic examination. This applies particularly to individuals at high risk, such as patients with TIAs or minor strokes. We showed that 5% had decreased memory within the limits of normative data for age and sex. However, 39% had executive dysfunction.[26]

Executive function is particularly sensitive to hypertension. We found that in individuals presenting with memory problems, hypertension had no role as to whether they progressed to dementia in 5 years. However, if patients presented with executive dysfunction, then 58% of hypertensive patients but only 28% of normotensive patients progressed to dementia in 5 years. In principle, half of progressions could have been prevented.[27]

Figure 2 Receiver Operating Characteristic (ROC) Curves of Ischemic Score and *APOE* E4 Dementia Prediction Scores



Hypertension should be targeted early and vigorously but cautiously, as it affects the frontotemporal networks and executive function in healthy middle-aged individuals (44–69 years).[28] All hypertensive patients deserve cognitive screening to identify risk early and give the patient the extra motivation that treatment of hypertension will yield benefits immediately in preserving cognition.

Targeting Population Health

The personalized approach needs to be complementary by population-level strategies. Most events related to a risk factor do not occur in the high-risk groups, but in the mild and moderate risk groups. This sounds counterintuitive, but was demonstrated well by Geoffrey Rose.[29]

To use a simplified theoretical example: Let us suppose that the high blood pressure group has a 50% chance of developing a stroke and the mild/moderate hypertensive group has only a 10% chance of developing a stroke. Typically, the high-risk group represents 10%–15% of a population at risk, so that roughly 5 strokes will result in the high-risk group and about 9 in the mild/moderate group. Many in the mild/moderate group do not know that they have the risk factors and if they do see a doctor, both might become falsely reassured because the risk is low.

Small differences at the population level make larger differences than large differences at the individual level. A decrease of 2 mm Hg in blood pressure for the individual is barely meaningful. However, it has been calculated that a 2 mm Hg decrease at the population level would reduce the incidence of stroke by 24.2%.[30]

This principle is well understood in business. You can earn a large profit margin on individual customers, but you can earn

much more with a small profit margin on a very large number of customers. This principle underlies the success of chains like Walmart.

Knowledge accrues in pieces, but is understood in patterns. We need to retrieve and integrate currently known but dispersed facts. Specialization accounts for the explosive growth of information and to a lesser extent, knowledge. Knowledge implies understanding, but many pieces of information that could contribute to explanatory patterns remain stranded behind professional, specialized, and terminologic walls. Similarly, although most risk and protective factors for dementia, stroke, and ischemic heart disease are the same, seldom have the respective organizations come together for a joint prevention effort. Figure 3 illustrates the relationships among the triple threat and the commonality of risk and protective factors.[15,31]

A number of pathophysiologic mechanisms linking vascular disease and AD have been described,[15] including glymphatics. Moreover, connections among the triple threat continue to be discovered, such as shared proteomic effects of cerebral atherosclerosis and AD in the human brain.[32]

Control of common risk and protective factors could also help prevent certain types of retinal and kidney conditions. The least explored is the vascular–bipolar link that holds great promise, as the relationship is strong and the prevention studies scant.[33] Neuropsychiatric sequelae of stroke offer another promising area for treatment and prevention.[34]

An encouraging development has been that the World Stroke Organization Proclamation on the joint prevention of stroke and potentially preventable dementia has been endorsed by Alzheimer Disease International, the World Federation of Neurology, the International Brain Research Organization, and 20 other international, regional, and national organizations.[35,36] The World Stroke Organization and the World Heart Federation have made further commitments to work together.[37] In the United States, the Proclamation has been endorsed by the Alzheimer Association, the American Heart/Stroke Association, and the American Academy of Neurology.

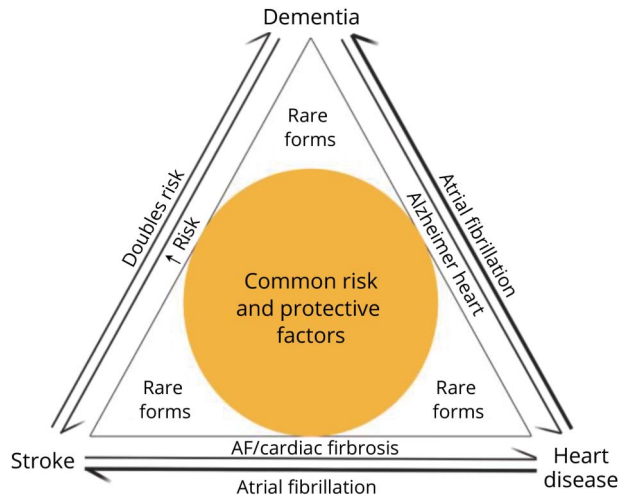
It has long been recognized that environmental, socioeconomic, and health care factors contribute to dementia, stroke, and ischemic heart disease. However, the literature is specialized, fragmented, and dispersed. To have a full understanding of the problem and potential solutions, all factors need to be considered at once (figure 4).

We showed that in step with the implementation of the different components of a stroke strategy from 2002 to 2013, the incidence of stroke declined by 32% and that of dementia by 7% in the province of Ontario, Canada (population 14 million).[38] We aimed to find out why and help apply the lessons across Canada and beyond.

We propose to:

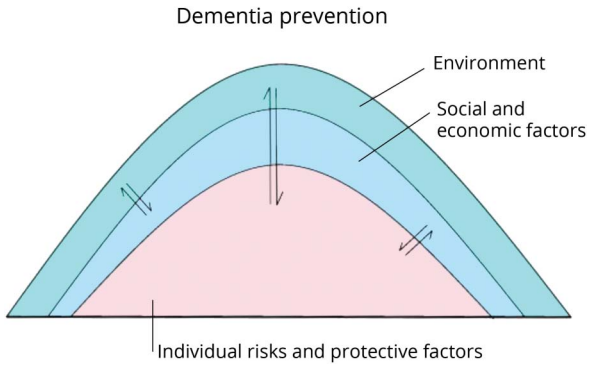
1. Produce a unique Canada heat map of cognitive impairment and dementia and identify high and low stroke and heart disease incidence and determine what accounts for the differences and what lessons can be learned and applied
2. Identify known risk and protective factors and discover new ones through a combination of standard, contextual, and artificial intelligence analyses
3. Develop comprehensive, targeted, investment value models of dementia prevention depending on what the most relevant factors are for a particular jurisdiction or individual

Figure 3 Reciprocal Relationships Among Stroke, Dementia, and Heart Disease



AF = atrial fibrillation.

Figure 4 Schematic Representation of Categories of Risk and Protective Factors for the Triple Threat and Showing That They All Interact



A comprehensive, targeted investment value approach (CTIV) will first take a comprehensive approach to identify all relevant factors, realizing that small differences in many small factors might make as large a difference as a large difference in a single factor; then, it will target the factors with the greatest potential for prevention for different populations and among individuals according to age, sex, ethnicity, and other factors; and finally, assure that the solutions are investment valued: that is, what would be the payoff? Policymakers need to know what they will receive in return from investing in specific actions so the solutions have a chance of being implemented in competition with many other worthy causes. Individuals likewise need to know what to expect in return for effort and time to motivate themselves and others to implement the targeted recommendations.

Our ultimate aim should not only be the prevention, delay, or mitigation of disease, but the promotion of brain health. The World Brain Alliance (wfneurology.org/world-brain-alliance) was founded in 2011 on 3 premises:

1. The brain is key to health and wellness. There is no health without brain health.
2. Brain health begins with the mother's and the child's and their education.
3. Our brains are our future.

In the digital age, we need to optimize our brain health to cope with an increasingly complex world, adapt to new jobs and settings, and enjoy the full capacities to think, feel, and create.

Norway has introduced a national brain health plan and the European Brain Council, the European Network of Neurologic Associations, and the European Academy of Neurology have an initiative of making brain health the top health priority in the European Community and an international effort in this direction is gaining ground.

No agreed-upon definition of brain health exists, but a definition of health does. The WHO Constitution (1948) defines health as "A state of complete physical, mental and social well-being and not merely the absence of disease or infirmity." Similarly, we could define brain health as a state of complete physical, mental, and social well-being through full, balanced, ongoing development and exercise of the brain.[39] After all, as Hippocrates recognized about 2,500 years ago, "From the brain and from the brain only, arise our pleasures, joys, laughter and jests as well as our sorrows, pains, griefs and tears. Through it…we think, see, hear, and distinguish the ugly from the beautiful, the bad from the good."

Discussion

Brain health is the world's ultimate wealth and guarantee of well-being. This goal is undermined by the aging of the population that is leaving in its wake stroke and heart disease and dementia (the triple threat). Considerable progress has been made in the prevention of stroke and heart disease. However, the bulk of efforts to prevent dementia have been on stopping the accumulation or enhancing the clearance of amyloid or tau protein, without applicable results. No one magic bullet drug will stop "Alzheimer disease" in the elderly because it is not a disease but a syndrome. We can begin preventing some dementias by adopting the vascular cognitive impairment approach: identify the vascular component of cognitive impairment and treat it or prevent it.

Dementia, stroke, and heart disease share the main modifiable risk and protective factors and joint prevention strategies need to be developed together by the organizations that are already committed to their joint prevention.

We need to develop a CTIV approach to assure optimal prevention and maximal brain health and curb the triple threat, taking us closer to the ideal of a brain healthy world.

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