From Heart Health to Brain Health

Legacy of the North Karelia Project for Dementia Research

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ABSTRACT

Cognitive impairment is very common in advanced age, with dementia representing the main cause of disability in older adults. Over the past 20 years, several modifiable risk factors have been identified for dementia and Alzheimer's disease (AD), and many of them are shared with cardiovascular diseases. Given that the pathologic changes leading to dementia may start decades before dementia is diagnosed, it is crucial to adopt a life course approach when investigating risk factors for dementia. The CAIDE (Cardiovascular Risk Factors, Aging and Dementia) study is one of the first and still very few existing observational studies to have investigated the role of midlife risk factors for the subsequent development of dementia and AD in late life. The CAIDE study is built on the North Karelia Project, enabling risk factor assessment 20 to 30 years before the dementia diagnosis. The CAIDE study has revealed that late-life dementia and AD are heterogeneous and multifactorial disorders, suggesting that multidomain interventions targeting several risk factors simultaneously may be needed for optimal preventive effects. The FINGER (Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability) study is the first large long-term multidomain lifestyle intervention showing effect on prevention of cognitive impairment in at-risk elderly people. The study is conducted within the existing framework and builds on multidisciplinary prevention expertise following the North Karelia Project and CAIDE study. The FINGER study will, together with the ongoing multinational preventive initiatives, pave the way for pragmatic prevention programs and integrated interventions to facilitate healthy brain aging. This paper summarizes major findings on risk and protective factors for dementia and AD, and reviews key aspects and future directions in preventative strategies.

The number of people living to old age is increasing exponentially. This is accompanied by a dramatic increase in disorders that are common in old age. Cognitive impairment is among the most frequent chronic conditions in elderly persons and dementia, its most severe expression, represents the main cause of disability in older adults, with large human, economic, and societal burdens.

Dementia, and its most common form, Alzheimer's disease (AD) are reaching epidemic proportions in many countries, with an estimate of 1 new case every 3 s, and about 47 million cases worldwide in 2015. Driven by population aging, this number is predicted to double every 20 years [1] unless effective preventive and therapeutic means are found. The global economic costs of dementia were estimated to be 818 billion USD in 2015 [1], which is an enormous economic impact for a single group of disorders. The World Health Organization and G8 Dementia Summit have recently described dementia as a global public health priority and prevention as 1 of the key elements in addressing dementia epidemic, in a similar way as it is for other major noncommunicable disorders such as cardiovascular disease [2,3].

The pathological processes leading to AD start decades before the first symptoms appear [4,5]. This emphasizes the importance of a life-course approach when investigating the risk factors and preventive strategies for dementia and AD. For a long time, old age and family history were the only known risk factors for dementia and AD. This provided very little means for prevention. The first longitudinal cohort studies investigating the risk factors were conducted among elderly persons, and had relatively short follow-up times. Although these studies have been an important first step, it was very challenging to separate true risk factors from spurious associations caused by reverse causality.

FROM NORTH KARELIA TO DEMENTIA RISK FACTORS

In the late 1990s a research project to investigate the risk factors of dementia, the CAIDE (Cardiovascular Risk Factors, Aging and Dementia) study, was initiated in the Eastern Finland. The unique feature of the project was that the participants were the former participants of the North-Karelia Project and FINMONICA studies in 1972, 1977, 1982 or 1987. They were invited for re-examinations within the CAIDE study, where also their cognitive status was thoroughly evaluated and dementia was diagnosed [6,7].

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TABLE 1. Key risk factors for dementia from the CAIDE study

Risk Factor	Findings
Vascular risk factors	
Hypertension [8]	High systolic blood pressure (≥160 mm Hg) in midlife increased risk of AD in later life (OR: 2.3; 95% CI: 1.0 to 5.5). No association with diastolic blood pressure.
Hypercholesterolemia [8,10]	High serum total cholesterol (≥6.5 mmol/l) in midlife increased risk of AD in later life (OR: 2.1; 95% CI: 1.0 to 4.4). A moderate decrease in total cholesterol from midlife to late life (0.5 to 2 mmol/l) was associated with a more impaired late-life cognitive status.
Obesity [9,11]	Obesity at midlife (BMI >30 kg/m^2) was associated with the risk of dementia and AD (OR: 2.1; 95% CI: 1.0 to 4.6) Decrease in BMI from midlife to late life was associated with higher risk of dementia (HR: 1.14 [95% CI: 1.03 to 1.25] for 1-unit decrease) and AD (HR: 1.20 [95% CI: 1.09 to 1.33]).
Lifestyles	
Alcohol [12]	The apolipoprotein E (ApoE) ε4 carriers had an increased risk of dementia with increasing alcohol consumption: compared with ApoE ε4 non-carriers who never drank, the OR for carriers who never drank was 0.6, for infrequent drinkers it was 2.3, and for frequent drinkers 3.6 The ApoE ε4 non-carriers had similar risk for dementia irrespective of alcohol drinking frequency.
Smoking [13]	Smoking in midlife increased the risk of dementia (OR: 4.93; 95% CI: 1.51 to 16.11) and AD (6.56; 1.80 to 23.94) among the ApoE ε4 carriers, but not among the ApoE ε4 non-carriers.
Physical activity [14,15]	Leisure-time physical activity at midlife was associated with a reduced risk of dementia and AD (OR: 0.48; 95% CI: 0.25 to 0.91 and 0.38; 0.17 to 0.85, respectively). The associations were more pronounced among the ApoE ε4 carriers. Maintaining high level of physical activity (HR: 0.16; 95% CI: 0.06 to 0.41) or increasing physical activity (HR: 0.19; 95% CI: 0.09 to 0.40) after midlife was associated with lower dementia risk.
Physical fitness [16]	Poor physical fitness at midlife was associated with increased dementia risk (HR: 1.5; 95% CI: 1.1 to 2.0). A decline in fitness after midlife was also associated with dementia (OR: 3.0; 95% CI: 1.7 to 5.1)
Healthy diet [17–19]	Moderate intake of polyunsaturated fats at midlife decreased the risk of dementia (second quartile vs. first quartile OR: 0.40, CI: 0.17 to 0.94), whereas saturated fat intake was associated with an increased risk (second quartile OR: 2.45, CI: 1.10 to 5.47). The associations were seen only among the ApoE ε4 carriers. Coffee drinkers at midlife had lower risk of dementia and AD later in life compared with those drinking no or only little coffee The lowest risk (65% decreased) was found in people who drank 3 to 5 cups per day. Persons with a healthy diet (healthy-diet index >8 points) had a decreased risk of dementia (OR: 0.12; 95% CI: 0.02 to 0.85) and AD (OR: 0.08; 95% CI: 0.01 to 0.89) compared with persons with an unhealthy diet (0 to 8 points).
Medical history	
Asthma and chronic obstructive pulmonary disease [7]	Midlife chronic obstructive pulmonary disease (HR: 1.85; 95% CI: 1.05 to 3.28), asthma (HR: 1.88; 95% CI: 0.77 to 4.63), and both pulmonary diseases combined (HR: 1.94; 95% CI: 1.16 to 3.27) increased the later risk of cognitive impairment. Pulmonary diseases diagnosed later in life were inversely related to cognitive impairment (both pulmonary diseases combined HR: 0.42; 95% CI: 0.19 to 0.93).
Heart diseases [20]	Atrial fibrillation in late life was risk factor for dementia (HR: 2.61; 95% CI: 1.05 to 6.47) and AD (HR: 2.54; 95% CI: 1.04 to 6.16). Late-life heart failure, but not coronary artery disease, tended to increase the risks as well. Heart diseases diagnosed at midlife did not increase the risk of later dementia and AD.

(continued)

This design made it possible to analyze the risk factors in midlife (around 50 years of age) and subsequent development of dementia and AD 20 to 30 years later. The first results from the CAIDE study showed that vascular factors, including hypertension, hypercholesterolemia and obesity at midlife increased the risk of dementia and AD in late life [8,9]. Since then, a wide range of lifestyle-related, psychosocial, and medical factors have been investigated. A