From Heart Health to Brain Health

Legacy of the North Karelia Project for Dementia Research

Miia Kivipelto*,†,‡, Tiia Ngandu*,‡

Helsinki and Kuopio, Finland; and Stockholm, Sweden

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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From the *National Institute for Health and Welfare, Helsinki, Finland; †University of Eastern Finland, Kuopio, Finland; and the ‡Karolinska Institutet, Stockholm, Sweden. Correspondence: M. Kivipelto (miia.kivipelto@ki.se).

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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

TABLE 1. Continued

Risk Factor	Findings
Biological parameters	
Vitamin E status [21]	The risk of cognitive impairment was lower in subjects in the middle tertile of the γ-tocopherol/cholesterol ratio than in those in the lowest tertile (OR: 0.27 [0.10 to 0.78]). Higher incidence of cognitive impairment was found in the middle (OR: 3.41; 95% CI: 1.29 to 9.06) and highest (2.89; 1.05 to 7.97) tertiles of the 5-NO2-γ-tocopherol/γ-tocopherol ratio. Risk of cognitive impairment was lower in subjects with higher levels of γ-tocopherol, β-tocotrienol, and total tocotrienols.
Vitamin B status [22]	Higher homocysteine levels in old age were associated with poorer performance in global cognition, relative difference: 0.90 (95% CI: 0.81 to 0.99); episodic memory: 0.87 (95% CI: 0.77 to 0.99); executive functions: 0.86 (95% CI: 0.75 to 0.98); and verbal expression: 0.89 (95% CI: 0.81 to 0.97) 7 years later. Increased holotranscobalamin levels were related to better performance on global cognition: 1.09 (95% CI: 1.00 to 1.19); executive functions: 1.11 (95% CI: 1.01 to 1.21); and psychomotor speed: 1.13 (95% CI: 1.01 to 1.26).
Psychosocial factors	
Living alone [23]	People cohabiting with a partner in midlife were less likely than single, separated, or widowed people to have cognitive impairment later in life. Those widowed or divorced in midlife and still so at follow-up had 3 times the risk compared with married or cohabiting people. Those widowed both at midlife and later life had an OR of 7.67 (1.6 to 40.0) for AD compared with married or cohabiting people. The highest AD risk was in ApoE ε4 carriers who lost their partner before midlife and were still widowed or divorced in late life.
Cynical distrust [24]	Those with the highest level of cynical distrust in late life had higher risk of dementia 8 years later (RR: 3.13; 95% CI: 1.15 to 8.55).
Hopelessness [25]	Higher levels of hopelessness in midlife were associated with cognitive impairment at follow-up; the adjusted OR for each step of the 5-level hopelessness scale was 1.30 (95% CI: 1.11 to 1.51) for any cognitive impairment and 1.37 (95% CI: 1.05 to 1.78) for AD.
Gene-environment interactions	More pronounced association observed among ApoE ε4 carriers for: • Alcohol • Smoking • Physical activity • Fat intake • Living alone More pronounced association observed among ApoE ε4 non-carriers for: • Poor physical fitness

AD, Alzheimer's disease; ApoE, apolipoprotein E; BMI, body mass index; CAIDE, Cardiovascular Risk Factors Aging and Dementia; CI, confidence interval; HR, hazard ratio; OR, odds ratio; RR, relative risk.

summary of the key findings from the CAIDE study is presented in Table 1.

We know today that cognitive impairment, dementia, and AD are multifactorial disorders, and evidence from observational studies shows that genetic, vascular, lifestyle-related, and other risk factors often co-occur in the same person and interact across the lifespan to determine the overall risk of developing dementia and AD [26] (Fig. 1). The CAIDE study has significantly contributed to the current level of evidence on the modifiable risk factors. The risk factors have been a focus of intensive research in the past years, and currently the evidence is strong regarding many of the risk factors (e.g., midlife hypertension, midlife obesity, smoking, depression, education, lack of physical activity), but still less consistent for other factors [27,28].

Age-dependent associations with dementia and AD have been suggested for several medical conditions. For example, hypertension, obesity and hypercholesterolemia at midlife (<65 years of age) have been associated with an increased risk of developing dementia and AD later on. On the other hand, low blood pressure, low body mass index, and low blood total cholesterol in late life (>75 years of age) have been also associated with subsequent development of dementia and AD [26]. This is probably due to the fact that those parameters decrease in the years before the onset of dementia, most likely also as a consequence of

the ongoing disease process, a concept defined as "reverse causality." Diabetes mellitus has been associated with increased risk of dementia and AD over all the adult life, with the risk being stronger when diabetes occurs in midlife than in late life [26].

Among genetic risk factors, the apolipoprotein E (ApoE) ε4 allele is a well-established risk factor for late-onset AD and dementia. Overall, approximately 15% to 20% of dementia cases are attributable to the ApoE ε4 allele, which increases the risk for AD in a dose-response manner: ε4-homozygous subjects have a higher risk than ε4-heterozygous individuals, who in turn have a higher risk than individuals with no ε4 copies [29]. In the CAIDE study we have shown that ApoE ε4 interacts with several lifestyle factors so that the effects of unhealthy lifestyle (e.g., smoking, excess alcohol consumption, physical inactivity, high saturated fat intake) factors are more pronounced among the ε4 carriers for subsequent dementia/AD risk [30].

The pathways and mechanisms leading from different risk factors to dementia and AD are not fully understood, but several etiological hypotheses have been proposed: the vascular hypothesis, inflammatory hypothesis, oxidative-stress hypothesis, toxic hypothesis, and psychosocial hypothesis [29]. These theories highlight potential links of various risk factors to both the vascular and the neurodegenerative brain pathologies that can cause dementia. AD and cerebrovascular disease are often co-occurring in persons with cognitive impairment/dementia, and this is in line with the evidence that both diseases share several risk factors.

THE CAIDE RISK SCORE: A PRACTICAL TOOL FOR ASSESSING DEMENTIA RISK

Risk scores have been developed to predict the risk of cardiovascular events, diabetes, and mortality [31−33]. As the evidence of the dementia risk factors started to accumulate, it became possible to develop a risk score also for the prediction of dementia. The CAIDE risk score was the first instrument developed for this purpose [34]. This risk score includes the following risk factors: high age, hypertension, hypercholesterolemia, physical inactivity, obesity and low education. Based on these risk factors measured at midlife the CAIDE Dementia Risk Score gives an estimate of the risk of developing dementia 20 years later (Table 2). The CAIDE Dementia Risk Score was also externally validated in a large multiethnic population in the Kaiser Permanente study in the United States [35]. We have also shown that the CAIDE risk score is associated with dementia-related brain changes 30 years later [36]. Rather than providing exact risk prediction, the main utility of the tool is to identify individuals at increased risk for dementia, who can benefit from preventive interventions to reduce the risk [34]. Another important benefit of the risk score is that it can be used to distribute easily understandable information about risk factors to the general population. Currently the CAIDE risk score is widely used (e.g., by the Finnish Alzheimer Association) and is currently available as an app in several languages [37].

FROM OBSERVATION TO ACTION: FINGER TO PREVENT COGNITIVE IMPAIRMENT

After identification of risk factors in observational studies, the next step to successful prevention of cognitive impairment is randomized controlled trials (RCT). Previous prevention studies have yielded mainly negative results [28]. These studies had often several methodological limitations. Some positive results have been reported by single-domain lifestyle interventions with physical activity, cognitive training, diet, and use of antihypertensive medications, although evidence is too limited to formulate clear recommendations [26,38].

We have learned many important lessons from the previous prevention trials. The key methodological issues that need to be considered when conducting dementia prevention trials include: 1) Timing: Previous trials have been conducted in old populations or among already cognitively impaired people. As the pathologic disease process starts even decades before the first cognitive symptoms appear, starting the prevention trial earlier may lead to better effects. 2) Target group: Conducting a trial among a healthy, young population will require long follow-up times, large sample sizes, and considerable financial resources. An option may be to target the interventions to a higher risk group. 3) Outcome measures: At the current time there is no gold standard for an outcome measure in cognitive impairment/dementia prevention trials. However, use of compound batteries including several validated cognitive tests has been recommended [39]. 4) Ethical issues are also important, as placebo-controlled trials for high blood pressure and cholesterol are not possible due to their known protective effects for cardio- and cerebrovascular disease. 5) It is also becoming clear that targeting several risk factors simultaneously and for a sufficiently long duration is needed for optimal preventive effect. The FINGER (Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability) study (NCT01041989) is the first large long-term multidomain intervention trial reporting results of the intervention on cognition [40,41].

The FINGER study is following in the footsteps of the North Karelia Project and the Finnish Diabetes Prevention study, utilizing the knowledge and multidisciplinary expertise accumulated in these lifestyle interventions. The FINGER study is a multicenter RCT that included 1,260 participants 60 to 77 years of age. The participants were recruited among persons previously participating in population-based surveys (the North Karelia study and its successor the National FINRISK study, and FIN-D2D [Finnish type 2 diabetes] population study). This gave us extensive background information of the participants that is not usually available in RCTs. We were able to invite persons that had an increased risk of dementia based on

their risk factor profile (data from the earlier population surveys). The inclusion criteria were CAIDE Dementia Risk Score ≥6 points indicating presence of modifiable risk factors, and cognitive performance at the mean level or slightly lower than expected for age. Persons with clear cognitive impairment were excluded.

Participants were randomized (1:1) to a 2-year multidomain intervention (diet, exercise, cognitive training and social activities, vascular and metabolic risk factor monitoring), or to a control group receiving general health advice. The FINGER study showed a significant intervention effect on the primary cognitive outcome (the neuropsychological test battery [NTB] total score), on the main cognitive secondary outcomes (the NTB domain scores for executive functioning, processing speed), as well as on the complex memory score tasks [41] (Fig. 2). The control group had 30% increased risk for cognitive decline (odds ratio: 1.31; 95% confidence interval: 1.01 to 1.71) after 2 years compared to the intervention group. The intervention benefitted also other factors (body mass index, dietary habits, and physical activity), which are linked to healthy aging. The adherence to the intervention was high, with a low dropout rate, indicating that this multidomain approach is feasible, safe, and effective in older adults [41]. Currently, an extended follow-up of the FINGER study is ongoing to investigate the effect of the multidomain intervention also on the incidence of dementia and AD and several secondary outcomes.

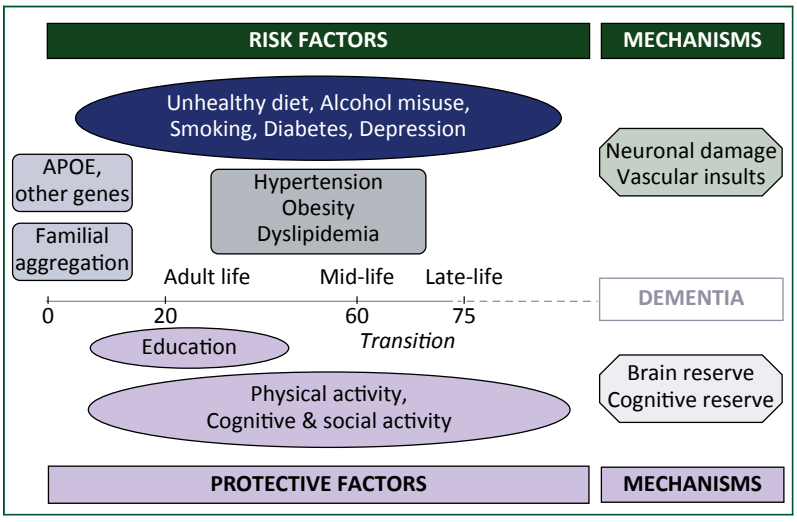

FIGURE 1. Risk factors for dementia and Alzheimer's disease during life course. APOE, apolipoprotein E.

TABLE 2. The CAIDE dementia risk score

Risk Factor	Points	Dementia Risk Percentage
Age, yrs		
<47	0	
47–53	3	
>53	4	
Education, yrs		
≥10	0	
7–9	2	
<7	3	
Sex		
Female	0	
Male	1	
Blood pressure, mm Hg		
≤140	0	
>140	2	
Body mass index, kg/m^2		
≤30	0	
>30	2	
Total cholesterol, mmol/l		
≤6.5	0	
>6.5	2	
Physical activity		
Yes	0	
No	1	
Total score		
0–5		1.0%
6–7		1.9%
8–9		4.2%
10–11		7.4%
12–15		16.4%

CAIDE, Cardiovascular Risk Factors Aging and Dementia.

MULTINATIONAL PREVENTION INITIATIVES AND PRAGMATIC PREVENTION PROGRAMS

Currently, there are also several other preventive trials ongoing. Two European trials, PreDIVA (Prevention of dementia by intensive vascular care) and MAPT (Multidomain Alzheimer Preventive Trial), are testing multicomponent interventions in older adults, and their results are expected shortly [26]. These trials differ in terms of target groups and intervention content, and together the FINGER study and the other trials will provide more information on what kind of interventions will be most effective in different groups of individuals. For the prevention of vascular cognitive impairment, multicomponent RCTs implementing medications and lifestyle changes are being tested in subjects with ischemic stroke: in the PODCAST (Prevention of Decline in Cognition after Stroke Trial) study intensive lowering of blood pressure and lipids levels is compared to standard care; the ASPIS (Austrian Polyintervention Study to Prevent Cognitive Decline After Ischemic Stroke) RCT promotes adherence to evidence-based vascular treatments (lipid-lowering, antihypertensive, antiaggregants, diabetes therapy), and includes lifestyle modifications (diet, exercise, cognitive training).

Another line of preventive RCTs is trials testing drugs targeting underlying AD pathology. Despite huge international efforts, no cure or disease modifying drugs for AD

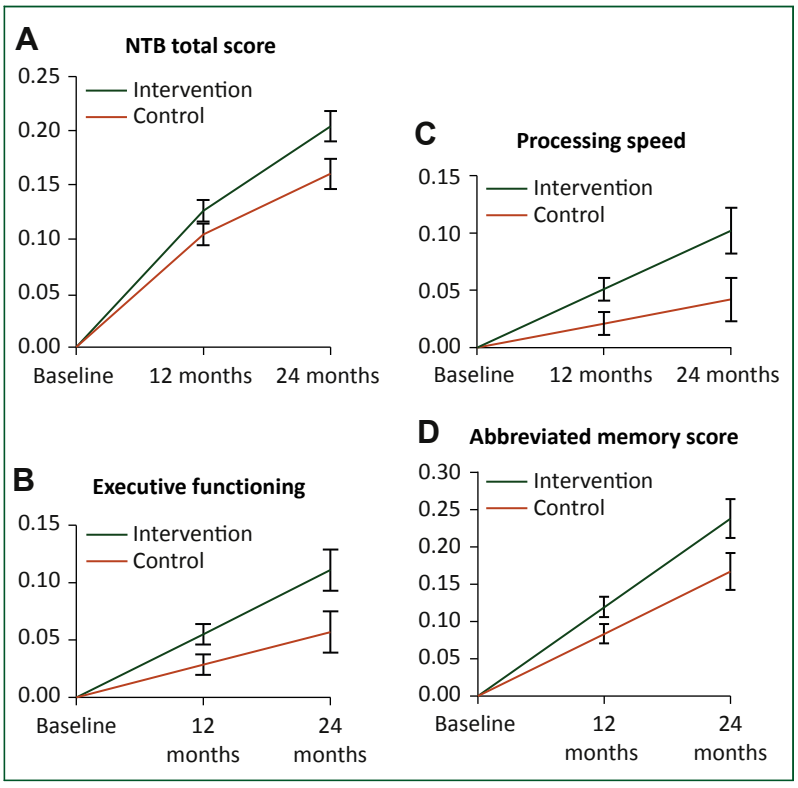

FIGURE 2. Change in cognitive performance during a 2-year multidomain lifestyle intervention, the FINGER (Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability) study [41]. Difference between intervention and control groups per year. **(A)** Neuropsychological test battery (NTB) total score: 0.022 (95% confidence interval [CI]: 0.002 to 0.042; p = 0.03). **(B)** Executive function: 0.027 (95% CI: 0.001 to 0.052; p = 0.04). **(C)** Psychomotor speed: 0.030 (95% CI: 0.003 to 0.057; p = 0.03). **(D)** Abbreviated memory score: 0.038 (95% CI: 0.002 to 0.073; p = 0.04). Lines indicate estimates for cognitive change from baseline to 12 and 24 months, higher scores indicate better performance, error bars indicate standard errors, and p values indicate difference in trajectories over time between groups.

are currently available and failure rate in RCTs has been very high during the last 10 years [42]. The new approach is to start also the drug interventions earlier and to enroll individuals prior to the onset of cognitive symptoms or with very mild symptoms but who are at high risk of AD (e.g., carriers of autosomal-dominant mutations for AD) or presence of strong risk factors for AD (i.e., ε4-homozygous and evidence of brain amyloid accumulation). Drugs currently investigated mainly target the amyloid-β cascade, but even the other hallmark pathological features of AD are targeted (e.g., tau, inflammation) and also drugs already used for other indications are being tested (e.g., statins, insulin, antioxidants).

Given the heterogeneity of risk profiles in the older populations, it is likely that different lifestyle and/or pharmacologic interventions are most beneficial in different subgroups. Identification of these optimal individually tailored interventions requires large, multinational RCTs. International preventive initiatives have been launched that target population-based and clinical-based groups of at-risk persons [26]. The European Dementia Prevention Initiative (EDPI) is a network between ongoing multidomain RCTs in Europe (FINGER, MAPT, PreDIVA) and pooled data will provide valuable information about the best strategies to prevent cognitive impairment and plan future multinational prevention trials. The MIND-AD (Multimodal preventive trials for Alzheimer's Disease: towards multinational strategies) project (www.mind-ad.eu) is a recently launched initiative aiming to test multidomain intervention based on the FINGER study among persons with mild Alzheimer and to harmonize and optimize methodologies for multinational and multimodal prevention RCTs. The HATICE (Healthy Aging through Internet Counselling in the Elderly) trial (www.hatice.eu) is a large European trial testing the possibility to utilize modern technology in prevention of vascular disorders and cognitive impairment.

SUMMARY

In aging populations, it is a great public health challenge to bring as much health and well-functioning years into life as possible. Dementia is the leading cause of disability among elderly persons and prevention is increasingly recognized as the key element in managing the dementia epidemic.

The CAIDE study has been 1 of the pioneers in identifying modifiable risk factors for dementia/AD and indicating that observational studies need to start early and have a long duration to identify windows of opportunity for effective interventions. It has also shown that building on existing infrastructures and cohorts developed for other chronic diseases allows optimizing the use of resources.

Based on several observational studies, it has been recently estimated that about 30% of AD cases worldwide are potentially attributable to following 7 modifiable risk factors: low educational attainment, smoking, physical inactivity, midlife hypertension, midlife obesity, diabetes, and depression. A reduction in the prevalence of those risk factors by 10% to 20% per decade would reduce worldwide AD prevalence by 8% to 15% in 2050 (between 8.8 and 16.2 million cases) [43]. Even smaller risk reduction or just the possibility to delay the clinical expression of dementia with some years would have a huge impact on public health.

Interestingly, some recent studies have suggested that dementia incidence (or age-specific prevalence) have been decreasing in several Western countries [1]. This may be linked with reduced stroke incidence, better management of vascular risk factors, healthier lifestyle, and higher education. These results give additional evidence that dementia prevention may be at least partly possible in the similar way as for many other chronic diseases. However, it is important to notice that in the last few decades there has been a widespread increase in the prevalence of obesity and diabetes mellitus. Updated knowledge about risk factor

distributions in different populations is crucial to obtain reliable estimates of the effects of preventive interventions on future dementia prevalence, thus aiding health education and community planning. Public health efforts promoting healthier lifestyles in midlife have great potential to improve both brain and general health status in advanced age.

The North Karelia Project was at the forefront of prevention of cardiovascular diseases. Now its heritage lives on in the field of dementia research with the CAIDE and FINGER studies. The FINGER study indicates that a multidomain lifestyle-based intervention is effective also against cognitive impairment and provides a pragmatic model that can be further tested and adapted in various settings and populations. The FINGER study together with the ongoing multinational trials, will pave the way for pragmatic prevention/risk reduction programs and integrated interventions (e.g., with cardiovascular diseases and diabetes). With these results and the new ongoing multinational initiatives, we are several steps closer of having evidence-based answers to the global dementia challenge.

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