alzheimer's research&therapy

REVIEW

Dementia prevention: current epidemiological evidence and future perspective

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Abstract

Dementia, a major cause of disability and institutionalization in older people, poses a serious threat to public health and to the social and economic development of modern society. Alzheimer's disease (AD) and cerebrovascular diseases are the main causes of dementia; most dementia cases are attributable to both vascular and neurodegenerative brain damage. No curative treatment is available, but epidemiological research provides a substantial amount of evidence of modifiable risk and protective factors that can be addressed to prevent or delay onset of AD and dementia. Risk of late-life dementia is determined by exposures to multiple factors experienced over the life course, and the effect of specific risk/protective factors depends largely on age. Moreover, cumulative and combined exposure to different risk/protective factors can modify their effect on dementia/AD risk. Multidisciplinary research involving epidemiology, neuropathology, and neuroimaging has provided sufficient evidence that vascular risk factors significantly contribute to the expression and progression of cognitive decline (including dementia) but that active engagement in social, physical, and mentally stimulating activities may delay the onset of dementia. However, these findings need to be confirmed by randomized controlled trials (RCTs). A promising strategy for preventing dementia is to implement intervention programs that take into account both the life-course model and the multifactorial nature of this syndrome. In Europe, there are three ongoing multidomain interventional RCTs that focus on the optimal management of vascular risk factors and vascular diseases. The RCTs include medical and lifestyle interventions and promote social, mental, and physical activities aimed at increasing the cognitive reserve. These studies will provide new insights into prevention of cognitive impairment and dementia. Such knowledge can help researchers plan larger, international prevention trials that could provide robust evidence on dementia/AD prevention. Taking a step in this direction, researchers involved in these European RCTs recently started the European Dementia Prevention Initiative, an international collaboration aiming to improve strategies for preventing dementia.

Introduction

Dementia is an acquired disabling syndrome characterized by progressive deterioration in multiple cognitive domains and is severe enough to interfere with daily functioning. Alzheimer's disease (AD) is the most common cause of dementia, but increasing evidence from population-based neuropathological and neuroimaging studies shows that mixed brain pathologies (neurodegenerative and vascular) account for most dementia cases, especially in very old people [1,2].

Both prevalence and incidence of dementia rise exponentially with advancing age, and 70% of all dementia cases occur in people who are at least 75 years old [3]. The worldwide increase in the number of older adults, more pronounced in those who are at least 80 years old, explains the epidemic proportions assumed by dementia. Because dementia is a major cause of disability in and institutionalization of older people, the increased prevalence of this syndrome places enormous pressures on health-care systems and society. The *World Alzheimer Report* estimates that, in 2010, the number of people with dementia worldwide was 35.6 million and that this will increase to 65.7 million by 2030 and 115.4 million by 2050 unless effective means of reducing the incidence of this disease are introduced [4]. In 2010, the total estimated worldwide costs of dementia were USD $604 billion, including the costs of informal care (unpaid care provided by family and others), direct costs of social care (provided by community care professionals and in residential home settings), and the direct costs of medical care (the costs of treating

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dementia and other conditions in primary and secondary care) [4].

No curative treatment is available, but epidemiological research provides substantial evidence of modifiable risk and protective factors that can be addressed to prevent or delay AD and dementia onset. In this review, we summarize the evidence supporting dementia/AD prevention and discuss key aspects that need to be considered when planning preventive strategies.

Prevention of dementia: current evidence from observational studies

Over the last decades, the etiology of dementia has been extensively studied with the aim of identifying efficacious prevention and treatment strategies. These efforts have led to the broad consensus that dementia is a multifactorial disorder caused by several interrelated mechanisms in which the interaction of genetic and environmental factors plays the major role (Table 1).

The pathways that lead from different risk factors to dementia are not fully understood, but several etiological hypotheses have been proposed: the vascular hypothesis, inflammatory hypothesis, oxidative stress hypothesis, toxic hypothesis, and psychosocial hypothesis [5,6]. These theories highlight potential links of various risk factors to both the vascular and the neurodegenerative brain pathologies that can cause dementia, justifying the validity of dementia syndrome as target for prevention [7,8].

A recent report commissioned by the National Institutes of Health (NIH) and issued by the Agency for Healthcare Research and Quality (AHRQ) concluded that current research evidence on many risk and protective factors for cognitive decline and AD is not of sufficient strength, thus recommendations for preventing these conditions cannot be made [9,10]. Another previous review yielded similar conclusions [11]. These negative perspectives have been criticized since epidemiological evidence that the use of antihypertensive medications, cessation of smoking, and increasing physical activity produce cognitive benefits in older adults is not inadequate [12], and the analytical strategy used in the evidence-based review did not take into account the life-course perspective [13]. In fact, observational longitudinal studies clearly show that the risk of late-life dementia is determined by exposures to multiple factors experienced over the life span and that the effect of specific risk/protective factors depends largely on age. Thus, a life-course perspective is relevant for chronic disorders (such as dementia) that have a long latent period. It allows the identification of time windows when exposures have their greatest effect on outcome and assessment of whether cumulative exposures could have multiplicative or additive effects over the life course [6].

Age-dependent associations with dementia/AD have been suggested for several aging-related medical conditions. For example, elevated blood pressure, body mass index (BMI), and total cholesterol levels at a young age and in middle age (<65 years) are associated with an increased risk of dementia and AD, and having lower values in late life (>75 years) is also associated with subsequent development of dementia/AD [14-19]. Diabetes mellitus has been associated with increased risk of dementia and AD over adult life, but the risk is stronger when diabetes occurs in mid-life than in late-life [20]. Current smoking is another major risk factor for dementia and AD, and, given the worldwide prevalence of smoking, about 14% of all AD cases are potentially attributable to this risk factor [21]. Although it is not entirely clear whether depression is a risk factor for or a preclinical symptom of dementia, studies with long-term follow-up support the risk factor hypothesis [22].

Protective factors for dementia and AD have also been identified; these include high education and socio-economic status in early life as well as a number of factors in adult life: high work complexity, rich social network, social engagement, mentally stimulating activity, non-smoking, and regular physical exercise [5,23,24]. Living with a partner during mid-life has been associated with reduced risk of cognitive impairment and dementia later in life, suggesting that being in a relationship entails cognitive and social challenges that can increase the cognitive reserve [25]. Even at old ages, the active engagement in mental, physical, and social activities may postpone the onset of dementia, possibly by increasing the cognitive reserve [26].

In addition, several follow-up studies reported a decreased dementia risk associated with healthy dietary patterns and nutritional factors, such as high adherence to a Mediterranean diet or dietary intake of antioxidants (for example, vitamins E and C) and ω-3 polyunsaturated fatty acid (PUFA) (often measured as fish consumption) [27-31].

Cumulative and combined exposure to different risk factors can lead to modified effects on dementia/AD risk (Table 1). In the Finnish CAIDE (Cardiovascular Risk Factors, Aging and Incidence of Dementia) study, the risk of dementia has been evaluated in relation to a score (CAIDE Dementia Risk Score) combining mid-life risk factors, including low education and cardiovascular factors (that is, hypertension, obesity, hypercholesterolemia, and physical inactivity). The risk of dementia increased as the score increased in a dose-response trend, making it possible to identify individuals who can greatly benefit from preventive intervention that targets vascular risk factors [32]. Similar findings have been reported for late-life exposures: in the Swedish Kungsholmen Project, the cumulative effect of vascular risk factors

Table 1. Risk and protective factors for dementia and Alzheimer's disease

Risk factors	Protective factors	Combined effects
Genetic	Psychosocial factors	Increased
ApoE ε4	High education and socioeconomic status	1. Genetic and environmental factors in mid-life
Familial aggregation	High work complexity	ApoE ε4 magnifies the effect of high alcohol intake, smoking, physical inactivity, and high intake of saturated fat.
Vascular	Rich social network and social engagement	2. Vascular factors in mid-life
Cerebrovascular lesions	Mentally stimulating activity	Hypertension, obesity, hypercholesterolemia, and physical inactivity have an additive effect when they co-occur.
Cardiovascular diseases		3. Vascular factors/diseases in late life
Diabetes mellitus and prediabetes	Lifestyle	Higher risk in individuals with brain hypoperfusion profile: chronic heart failure, low pulse pressure, and low diastolic pressure
	Physical activity	Higher risk in individuals with atherosclerosis profile: high systolic pressure, diabetes mellitus or prediabetes, and stroke
Positive association in mid-life but negative association in late life		Decreased
Hypertension	Diet	1. Genetic and environmental factors in mid-life
High BMI (excessive weight and obesity)	Mediterranean diet	High education reduces the negative effect of ApoE ε4.
High serum cholesterol	Polyunsaturated and fish-related fats	Physical activity counteracts the risk due to ApoE ε4.
	Vitamins B_6 and B_{12} and folate	2. Environmental factors in mid-life
Lifestyle	Antioxidant vitamins (C and E)	High work complexity modulates the increased dementia risk due to low education.
Smoking		
High alcohol intake		
Diet		
Saturated fats		
Homocysteine		
Others		
Depression		

ApoE, apolipoprotein E; BMI, body mass index.

and vascular diseases on dementia/AD risk has been investigated in people who are at least 75 years old. These factors were aggregated according to two pathophysiological hypotheses: the brain hypoperfusion profile, defined by chronic heart failure, low pulse pressure, and low diastolic pressure, and the atherosclerosis profile, which included high systolic pressure, diabetes mellitus or prediabetes, and stroke. In both profiles, dementia/AD risk increased with increasing scores in a dose-response manner, suggesting a synergy of vascular risk factors in promoting dementia/AD also in advanced age [33]. The American Cardiovascular Health Cognition Study developed a Late-life Dementia Risk Index and also a brief version, which groups older adults in the three categories of low, moderate, and high risk of developing dementia. Both versions of the index support the cumulative effect of different factors in determining the risk of dementia after the age of 65 years. These indices include information from different domains, including demographic factors (age), genetics (presence of the apolipoprotein E (ApoE) ε4 allele), lifestyle (BMI of less than 18.5 and lack of alcohol consumption), comorbid vascular conditions (internal carotid artery thickening,

angina, coronary artery bypass surgery, stroke, and peripheral artery disease), evidence of brain abnormalities shown by magnetic resonance imaging (white matter diseases or enlarged ventricles), cognitive test scores, and physical performances [34,35].

The combined effect of genetic-environmental or environmental-environmental joint exposures may also lead to the attenuation of the dementia risk. Population-based studies suggest an effect modification for the ApoE ε4 allele, the most important genetic risk factor for sporadic AD. ApoE ε4 carriers seem more vulnerable to risk factors like alcohol drinking, smoking, physical inactivity, and high intake of saturated fat, indicating that people with genetic susceptibility may reduce their initial AD risk by lifestyle interventions (that is, physical activity, sufficient intake of PUFA, and avoiding excess alcohol drinking and smoking) [36]. Furthermore, it has been shown that high education may reduce dementia risk among ApoE ε4 allele carriers [37]. In regard to the interactions among modifiable risk factors, results from the Kungsholmen Project suggested that complexity of work with data and people was related to a decreased dementia risk and that the highest level of work

complexity may modulate the increased dementia risk due to low education [23].

In conclusion, even though for some risk and protective factors the role in dementia and AD needs to be clarified, evidence from observational studies points at different modifiable factors that can be managed in order to prevent or delay dementia onset. Moreover, epidemiological findings strongly suggest that the life-course approach model and the multifactorial nature of dementia and AD should be considered when planning any preventive strategy.

Prevention of dementia: current evidence from interventional studies

Interventional studies on dementia and AD prevention have tested different medications, including statins, antihypertensive drugs, estrogens alone or in combination with progestin (hormone replacement therapy, or HRT), non-steroidal anti-inflammatory drugs (NSAIDs), and nutraceuticals (folate, Ginkgo biloba, and vitamins B_{12}, C, and E). For all of these compounds, the protective effects suggested by observational studies have not been confirmed in randomized controlled trials (RCTs), the results of which are inconsistent or even suggest a detrimental effect on cognition (for example, NSAIDs and HRT) [38-41]. Few interventional studies implementing non-pharmacological approaches have been carried out. Among them, some RCTs on cognitive training and physical activity provided encouraging results, which need confirmation [38,42]. It is possible that the negative results from the RCTs done so far reflect the real inefficacy of the tested strategies in preventing dementia and AD. However, the apparent contradiction of results from observational and interventional studies could be explained by several factors:

1. The intervention was done outside the time window during which management of a risk factor would reduce dementia risk: several risk factors exert their effect mainly during mid-life, whereas RCTs have been done in older adults. This is the case for vascular risk factors, which seem to be more relevant when the exposure occurs during mid-life. Moreover, the HRT research suggests that estrogens may have beneficial, neutral, or detrimental effects on the brain depending on age at treatment, type of menopause (natural versus medically or surgically induced), or stage of menopause [43]. This concept, called the 'window of opportunity hypothesis', is in agreement with the life-course approach model. There is evidence of neuroprotective effects of estrogens in women before the age of natural menopause and in the early postmenopausal stage (50 to 60 years), whereas estrogens initiated in late post-menopause (65 to 79 years) increase the risk of cognitive impairment and dementia [43,44]. Two RCTs

are ongoing and both are due to be completed this year; one is testing the effect of HRT in early post-menopause (Kronos Early Estrogen Prevention Study, or KEEPS; ClinicalTrials.gov identifier NCT00623311) and the other is comparing the effects of HRT in early and late postmenopause (Early Versus Late Intervention Trial With Estradiol, or ELITE; ClinicalTrials.gov identifier NCT00114517).

2. Short treatment and follow-up: many studies were of relatively short length. Thus, interventions have been implemented for a period that is not long enough to determine a neuroprotective effect, and the limited follow-up duration of many RCTs would not allow detection of differences in dementia incidence.

3. The statistical power was inadequate since some RCTs had small samples and dementia has been considered a secondary endpoint in most clinical trials (for example, antihypertensive therapy).

4. The choice of compounds tested in RCTs using nutra-ceuticals was not optimal: although several products have been tested, supplement composition is still a debated issue. For instance, whereas observational studies suggested that a balanced intake of different forms of vitamin E can be important for reducing dementia/AD risk, only one form (α-tocopherol) has been tested in RCTs, and the findings were conflicting [29,30,45,46]. Moreover, intake of high doses of α-tocopherol supplements has been associated with increased hemorrhagic stroke and mortality risk [47].

5. Despite the multifactorial nature of dementia and the importance of combined risk exposures, most studies were based on a mono-intervention approach, almost always testing single agents or lifestyle interventions. In multifactorial conditions, a small reduction in multiple risk factors can substantially decrease overall risk.

In summary, despite the discrepancies between findings of observational and interventional studies and the disappointing results of intervention studies on dementia and AD, methodological issues of the RCTs carried out thus far suggest that a valid evaluation of the efficacy of preventive measures has yet to be undertaken.

Prevention of dementia: ongoing multidomain intervention studies

The knowledge derived from the previously described observational and interventional studies paved the way for some ongoing RCTs on the prevention of cognitive decline and dementia. In Europe, there are three large ongoing RCTs: the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER), the Multidomain Alzheimer Preventive Trial (MAPT), and the Prevention of Dementia by Intensive Vascular Care (PreDIVA) study [48,49]. The common denominator

of these studies is the multidomain approach, which aims to simultaneously target several risk factors for dementia in older adults, mainly by promoting lifestyle changes and adherence to medical treatments for vascular risk factors and vascular diseases. All RCTs exclude individuals with dementia and use clinical evaluation and neuropsychological tests to detect cognitive changes and dementia incidence as main outcomes. Furthermore, secondary outcomes include functional status, mood disorders, quality of life, adherence to the intervention programs, and utilization of health resources. The latter two aspects are essential from a public health perspective since they provide information on feasibility and cost-effectiveness of prevention strategies. Additionally, both FINGER and MAPT include ancillary studies on neuro-imaging (morphological and functional), cerebrospinal fluid, and blood markers related to AD pathophysiology in order to investigate the effect of the interventions on brain morphology and metabolism, clarify mechanisms underlying preventive measures, and identify biomarkers that can be used to monitor effects of interventions.

FINGER (ClinicalTrials.gov identifier NCT01041989) is a multicenter RCT aiming to prevent cognitive impairment, dementia, and disability in 60- to 77-year-olds. The study population is represented by 1,200 individuals who are at increased risk of dementia and who were selected according to the CAIDE Dementia Risk Score and the CERAD neuropsychological test battery [32,48]. The 2-year multidomain intervention includes nutritional guidance, physical activity, cognitive training, increased social activity, and intensive monitoring and management of metabolic and vascular risk factors (hypertension, dyslipidemia, obesity, and impaired glucose tolerance). Individuals in the reference group are given general public health advice on lifestyle and vascular risk factors. FINGER participants are recruited from previous population-based observational surveys (that is, FINRISK and FIN-D2D) with detailed retrospective information on lifestyle and vascular factors [48]. Thus, differences in these variables can be taken into account and this is normally not possible in RCTs. The primary outcome is cognitive decline measured by a sensitive Neuropsychological Test Battery and the Stroop and Trail-making tests, which can depict early cognitive impairment typical for AD and vascular dementia (VaD). The planned 7-year extended follow-up will allow detection of differences in dementia/AD incidence.

MAPT (ClinicalTrials.gov identifier NCT00672685) is a French multicenter RCT evaluating the efficacy of isolated supplementation with ω-3 fatty acid, isolated multidomain intervention, or their combination in the prevention of cognitive decline in frail individuals who are at least 70 years old. One thousand six hundred eighty community-dwelling participants have been enrolled by

using a frailty definition that includes three components: presence of memory complaints, limitation in one instrumental activity of daily living, and slow walking speed. The 3-year multidomain intervention consists of group training sessions (physical exercise, cognitive training, and nutritional advice) and yearly personalized preventive consultations that aim to identify dementia and frailty risk factors (vascular risk factors, nutritional problems, sensory deficits, mood disorders, and walking difficulties) and promote their management in collaboration with the general practitioner. Follow-up is 5 years, and the main outcome measure is the 3-year change in cognitive function assessed with a neuropsychological test (Grober and Buschke) [48,50].

The PreDIVA study (Controlled-Trials.com identifier ISRCTN29711771) is a Dutch multicenter, open, cluster RCT comparing standard and intensive care of cardiovascular risk factors in preventing dementia and disability in older people. The study includes 3,534 community-dwellers who are 70 to 78 years old and who were recruited from primary care practices. The standard care is based on guidelines for Dutch general practice, whereas the multicomponent intensive vascular care addresses hypertension, hypercholesterolemia, smoking habits, excessive weight, physical inactivity, and diabetes mellitus, which are strictly controlled with medication and lifestyle interventions. Study duration is 6 years, and primary outcomes are incident dementia assessed according to standard criteria and disability as measured with the Academic Medical Center Linear Disability Scale [49].

Researchers involved in these large European trials (FINGER, MAPT, and PreDIVA) recently started the European Dementia Prevention Initiative (EDPI), an international collaboration to improve preventive strategies against dementia [51]. Collaboration and data sharing within the EDPI will allow refining of methodological aspects of prevention trials, including identification of target populations, improvement of intervention methods (that is, type, intensity, and duration), and development and standardization of relevant outcome measures and prognostic and monitoring tools that can be easily implemented in large populations. This will help planning larger, international prevention trials able to provide robust evidence on dementia/AD prevention.

Conclusions

Although the pathogenesis of dementia is not fully elucidated, primary prevention seems possible as most factors involved in dementia onset and progression are modifiable or amenable to management. The recent AHRQ/NIH report shows that development of successful preventive strategies requires a more refined knowledge of risk and protective factors for dementia and AD as well as a validation of the observational studies with large

intervention studies [7]. AD and VaD share several risk factors, and most dementia cases are attributable to both vascular and neurodegenerative brain damage. Furthermore, population-based neuropathological studies have shown that both subclinical neurodegenerative (amyloid plaques, neurofibrillary tangles, and Lewy bodies) and vascular lesions (and their co-occurrence) are common in the brains of cognitively normal older individuals [52]. In light of this, preventive strategies aiming to postpone the onset of dementia syndrome have great potential.

Epidemiological research suggests that the most effective strategy may be to encourage the implementation of multiple preventive measures throughout the life course, including high educational attainment in childhood and early adulthood, active control of vascular factors and disorders over adulthood, and maintenance of mentally, physically, and socially active lifestyles during middle age and later in life. It has been estimated that half of AD cases worldwide are potentially attributable to modifiable risk factors, and a 10% to 25% reduction in these factors could potentially prevent 3 million AD cases worldwide, and a reduction in all risk factors would have the greatest impact on dementia prevalence [21]. However, RCTs are indispensable to confirm the effect of risk reduction strategies targeting multiple risk factors. Multidomain interventional RCTs are ongoing and will provide new insights into prevention of cognitive impairment and dementia. Full implementation of the life-course approach is more challenging because of the difficulties of carrying out RCTs over many decades. Such long-term studies would require very large sample sizes and huge financial resources, and a pragmatic way to assess the effect of long-term interventions within an RCT has not yet been established. Furthermore, for ethical reasons, several risk and protective factors are not appropriate for intervention trials. Thus, evidence about these factors relies on conducting rigorous observational studies (for example, placebo-controlled trials for high blood pressure or cholesterol are not possible, because such treatments are known to protect against cardiovascular/cerebrovascular diseases) [9]. Methodological alternatives to RCTs have been proposed to obtain robust evidence on AD and dementia prevention [11,53]. The ongoing RTCs on dementia prevention will have to take into account the 'window of opportunity hypothesis' when evaluating the results of interventions. In fact, efficacy of preventive actions may vary by age. Thus, implementation of interventions at the appropriate time in the life course is crucial for successful prevention. Refining of prognostic tools, which can be used for early detection of subjects at risk of dementia in the general population, will also help to better plan intervention studies. Also, when older individuals are targeted, the frequent coexistence of chronic diseases needs to be considered since it can negatively impact cognitive performance and limit adherence to preventive interventions. On the other hand, appropriate management of morbidity can help improve cognitive performance and delay dementia onset. For instance, although stroke is a known risk factor for dementia, it has been recently reported that about 25% of stroke patients discontinued one or more of their prescribed secondary prevention medications within 3 months of hospitalization for acute stroke [54-56]. Improving long-term adherence to post-stroke treatment can prevent recurrent cerebrovascular diseases and contribute to preventing or delaying clinical expression of dementia syndrome. Additionally, there is evidence of inadequate management of hypertension and hypercholesterolemia in older adults [49]. Similar situations exist for heart failure, which increases the risk of dementia among older adults [56], and diabetes mellitus, which accelerates the progression from mild cognitive impairment to dementia by more than 3 years [57]. Preliminary results from the PreDIVA study showed that 87% of the study participants have at least one modifiable risk factor amenable to intervention, proving the presence of a window of opportunity for improved risk management [49].

In conclusion, prevention of dementia is now moving from observational to interventional studies to verify hypotheses and define tools that can be applied in the general population. Epidemiological and preclinical studies will continue to provide new information on risk/protective factors and pathological mechanisms. The international collaboration among research teams involved in ongoing multidomain RCTs will allow the sharing of experiences and discussions on methodological aspects of these studies. This can help in interpretation of results, identification and solution of problems related to intervention strategies, and refinement of preventative approaches.

Since a cure for dementia is not yet available, finding effective preventive strategies is essential for a sustainable society in an aging world. As dementia, cardiovascular diseases, stroke, and diabetes mellitus – all major public health problems – share several risk factors, public health efforts promoting a healthier lifestyle have the potential to enhance health status in advanced age.

Abbreviations
AD, Alzheimer's disease; AHRQ, Agency for Healthcare Research and Quality; ApoE, apolipoprotein E; BMI, body mass index; CAIDE, Cardiovascular Risk Factors, Aging and Incidence of Dementia; EDPI, European Dementia Prevention Initiative; FINGER, Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability; HRT, hormone replacement therapy; MAPT, Multidomain Alzheimer Preventive Trial; NIH, National Institutes of Health; NSAID, non-steroidal anti-inflammatory drug; PreDIVA, Prevention of Dementia by Intensive Vascular Care; PUFA, polyunsaturated fatty acid; RCT, randomized controlled trial; VaD, vascular dementia.

Competing interests
The authors declare that they have no competing interests.

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