Prevention of Alzheimer's Disease: Intervention Studies

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1. Introduction

The aging of the population is a worldwide phenomenon, and studying age-related diseases has become a relevant issue from both a scientific and a public health perspective. Dementia is a syndrome characterised by loss of cognitive abilities in multiple domains that results in impairment in normal activities of daily living and loss of independence [1]. Both prevalence and incidence of dementia rise exponentially with advancing age, and 70% of all dementia cases occur in people aged 75+ years [2]. The worldwide increase in the number of older adults, more pronounced in the 80+ age group, explains the epidemic proportions assumed by dementia. According to the World Alzheimer Report, there were 35.6 million people living with dementia worldwide in 2010, a number that will increase to 65.7 million by 2030 and 115.4 million by 2050 unless effective means reducing the disease incidence are introduced [3]. Dementia is a major cause of disability and institutionalization of elderly people and because of its increased prevalence this disorder is becoming an emerging public health issue not only in developed countries but also in less developed regions of the world. The total estimated worldwide costs of dementia were US$604 billion in 2010, 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 dementia and other conditions in primary and secondary care) [3].

Alzheimer's disease (AD) is considered the most common cause of dementia, accounting for 60–70% of all dementia cases. The hallmarks of AD neuropathology in the brain are the presence of extracellular plaques composed of amyloid-β (Aβ) and intracellular neurofibrillary tangles (NFTs) composed of hyperphosphorylated aggregates of the microtubule-associated tau protein [4].

Vascular dementia (VaD), mainly due to cerebrovascular diseases (CVD), is the second most frequent type of dementia [5, 6]. This current classification of dementia types is being reconsidered in light of recent neuropathological and neuroimaging studies, which have shown a range of dementia-associated brain abnormalities from pure vascular lesions at one end to pure AD pathologies at the other, with most dementia cases being attributable to both CVD and AD. In fact, AD and CVD-related changes often coexist in the brain of older adults with dementia and mild cognitive impairment (MCI) [7, 8]. Also, both types of lesions are detected in the brain of cognitively normal elderly people, highlighting the importance of mixed pathologies in increasing the risk of late-life dementia [9]. The co-occurrence of AD and CVD is consistent with the evidence that AD and VaD share several risk and protective factors, including cardiovascular and lifestyle related factors. Overall, this implies that dementia syndrome is a valid target for prevention, especially from the public health perspective.

Prevention is traditionally divided into three levels: primary, secondary, and tertiary prevention. Primary prevention aims to reduce the incidence of the disease by eliminating or treating specific risk factors, which may decrease or delay the development of dementia. Secondary prevention aims to early detection of the disease, before any symptom has emerged, when treatment could stop its progression. Tertiary prevention aims to reduce the impact of complications and disability of long-term diseases.

Regarding primary prevention, both observational and interventional epidemiological studies have been conducted for dementia and AD. On the other hand, in the field of AD the development of pharmacological interventions has been mainly limited to a tertiary prevention level, since the diagnostic criteria currently in use for AD (National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association, NINCDS-ADRDA - criteria) identify the presence of the disease only when AD is severe enough to cause a dementia syndrome [10]. Thus, the majority of anti-AD drugs have been tested in subjects already in the symptomatic stage of the disease, and so far no drug has shown the ability to stop the disease progression (i.e. disease-modifying effect) [11]. However, several studies have shown that the pathophysiological process of AD begins years, if not decades, before the diagnosis of Alzheimer's dementia and individuals generally experience a gradual impairment of cognitive functions, which can progress to a dementia syndrome [12-14].

Recent advances in neuroimaging, cerebrospinal fluid (CSF) assays, and other techniques now provide the ability to detect evidence of the AD pathophysiological process in vivo, but the diagnostic criteria currently in use do not take into account these biomarkers. Three international workgroups promoted by the American National Institute of Aging (NIA) and the American Alzheimer's Association recently proposed new diagnostic guidelines to identify dementia due to AD, MCI due to AD, and preclinical AD [15-17]. These new criteria formalize the different clinical stages of AD and incorporate biomarkers (genetic, biochemical, neuroimaging) that can be detected in vivo and are believed to reflect AD pathology. These diagnostic criteria are now being validated and can be revised as long as new findings from research on biomarkers in AD will clarify the link between AD pathophysiology and the AD clinical syndrome. These criteria offer the opportunity to identify subjects who can be target of

secondary prevention in order to halt the progression of the brain damage and prevent or delay the onset of cognitive symptoms. A step in this direction has been done by planning randomized controlled trials (RCTs) testing anti-amyloid drugs in older adults with evidence of brain amyloid accumulation. The same type of intervention will also be tested in subjects at risk of early onset AD due to genetic mutations associated with familial AD.

This chapter summarizes the major findings concerning primary prevention of late onset dementia and AD, based on current epidemiological evidence from observational and interventional studies. Preventive strategies for early onset AD are also mentioned. Although many aspects of the dementias are still unclear, some risk and protective factors have been identified. It is also possible to delineate some preventative strategies. Ongoing interventional studies testing the effect of preventive measures for dementia and AD are discussed, and methodological challenges in designing dementia prevention trials are summarized.

2. Observational studies

Several community-based prospective studies of aging and health have been carried out in different countries since the 80s'. These studies have provided relevant information on the aetiology of dementia and AD, and have led to the identification of possible preventive strategies. Evidence from these observational studies has shown 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 [18, 19]. These theories highlight potential links of various risk factors to both the vascular and the neurodegenerative brain pathologies that can cause dementia, supporting the validity of dementia syndrome as target for prevention [6, 20].

2.1. Non-modifiable risk factors for Alzheimer's disease

Both modifiable and non-modifiable risk factors have been identified for dementia and AD, and while for some factors the scientific evidence is quite robust, for others the results are still inconclusive.

2.1.1. Age

Increasing age is a well-established risk factor for dementia, which is a common disorders after 75 years of age, but rare before age 60. The incidence rates of dementia increase exponentially with advancing age. In Europe, approximately two per 1,000 person-years become demented among people aged 65-69 years, and the incidence increases to 70 to 80 per 1,000 person-years for people 90 years or over [21, 22]. It is still unclear if the incidence of dementia continues to increase even in the oldest old or reaches a plateau at a certain age. The Cache County Study found that the incidence of dementia increased with age, peaked, and then started to decline

at extreme old ages for both men and women. However, some meta-analyses and large-scale studies in Europe provided no evidence for the potential decline in the incidence of dementia among the oldest old [21, 22].

Risk factors	Protective factors	Combined effects
Age	**Genetic**	**Increased risk**
	APP	*Genetic and environmental factors in midlife*
Genetic		APOEε4 magnifies the effect of high alcohol intake, smoking, physical inactivity and high intake of saturate fat
Familial aggregation	**Psychosocial factors**	
APOE ε4	High education and SES	
APP	High work complexity	
GSK3β	Rich social network and social engagement	*Vascular factors in midlife*
DYRK1A	Mentally stimulating activity	Hypertension, obesity, hypercholesterolemia and physical inactivity have an additive effect when they co-occur
Tau		
CLU	**Lifestyle**	
TOMM40	Physical activity	
PICALM		*Vascular factors/diseases in late-life*
CR1	**Diet**	Higher risk in individuals with brain hypoperfusion profile: chronic heart failure, low pulse pressure, low diastolic pressure
	Mediterranean diet	
Vascular	Polyunsaturated (PUFA) and fish-related fats	
Cerebrovascular lesions	Vitamin B$_6$, B$_{12}$, folate	Higher risk in individuals with atherosclerosis profile: high systolic pressure, diabetes mellitus or prediabetes, stroke
Cardiovascular diseases	Antioxidant vitamins (A, C, E)	
Diabetes mellitus and pre-diabetes	Vitamin D	
Midlife positive association but late-life negative association		
Hypertension	**Drugs**	**Decreased risk**
High BMI (overweight and obesity)	Statins	*Genetic and environmental factors in midlife*
High serum cholesterol	Antihypertensive drugs	High education reduces the negative effect of *APOE*ε4
	HRT	
Lifestyle	NSAIDs	Physical activity counteracts the risk due to *APOE*ε4
Smoking		
High alcohol intake		
		Environmental factors in midlife
Diet		High work complexity modulates the increased dementia risk due to low education
Saturated fats		
Homocysteine		
		Genetic and environmental factors in late-life
Others		Active leisure activities or absence of vascular risk factors reduces the risk due to *APOE*ε4
Depression		
Occupational exposure		
Traumatic brain injury		
Infective agents (Herpes Simplex Virus Type I, Clamydophila pneumoniae, Spirochetes)		

APOE: apolipoprotein E. BMI: body mass index. *CLU*: clusterin. *CR1*: complement component receptor 1. *DYRK1A*: dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 1A. *GSK3β*: glycogen synthase kinase-3beta. HRT: hormone replacement therapy. NSAIDs: nonsteroidal anti-inflammatory drugs. *PICALM*: phosphatidylinositol binding clathrin assembly protein. PUFA: polyunsaturated fatty acid. SES: socioeconomic status. *TOMM40*: translocase of outer mitochondrial membrane 40 homolog.

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

2.1.2. Familial aggregation

Familial aggregation is another important risk factor for late life dementia and AD. First-degree relatives of AD patients have a higher lifetime risk for developing AD than relatives of non-demented people or the general population (Table 1) [21, 22]. It is likely that shared genetic and environmental factors contribute to the familial aggregation. The amount of risk of AD that is attributable to genetics is estimated to be around 70% [25].

2.1.3. Genes

The Apolipoprotein E *(APOE)* ε4 allele is the only established genetic risk factor for both early- and late-onset AD; it is a susceptibility gene, being neither necessary nor sufficient for the development of AD. The risk of AD increases with increasing number of the ε4 alleles in a dose-dependent manner, but the risk effect decreases with increasing age. Individuals with two *APOE* ε4 alleles have a more than seven times increased risk of developing AD compared with those with *APOE* ε3 alleles and approximately 15 to 20 percent of AD cases are attributable to the *APOE* ε4 allele [25-28].

Other genes have been related to increased risk of late life AD, but the association is less consistent. These are mainly genes involved in the metabolism and processing of the amyloid precursor protein (APP) and Aβ, as well as tau protein, including the *GSK3β*, *DYRK1A, Tau*, and *CLU* genes [25]. Until now, mutations in APP have not been implicat-ed in the late-onset form of AD, with the exception of the rare variant, N660Y, which was recently identified in one case from a late-onset AD family [29]. A recent study identi-fied a mutation in the *APP* gene that can be protective against AD and age-related cognitive decline. This mutation is associated with a reduced production of amyloidogenic pepti-des [30]. Other genes that have been associated with increased risk of AD are *TOMM40*, *CR1* and *PICALM*. The *TOMM40* gene is located in a region of chromosome 19, which is in linkage disequilibrium with *APOE*, and its polymorphism affects the age on onset of AD in subjects with an *APOE* genotype [31]. *CR1* is involved in the complement cascade, while *PICALM* encodes a protein that is involved in clathrin-mediated endocytosis, an essential step in the intracellular trafficking of proteins and lipids such as nutrients, growth factors and neurotransmitters [32].

Several aspects challenge the identification of genetic risk factors for late life AD, including the fact that risk conferred by a single gene is generally small, and for some genes is the combination of risk alleles that is relevant for a significant change of the overall risk. Also, the heterogeneous and mixed nature of brain pathology causing dementia, particularly coexisting CVD, makes it more difficult to identify genetic risk factors for AD. Nevertheless, the identi-fication of genetic risk factors for late onset AD can have implication for preventive and therapeutic strategies. In fact, it has been shown that the *APOE ε4* allele can modulate the effect of lifestyle related risk factors [33] and influence the effect of pharmacological treatment for AD [34]. It is thus possible that future preventive and therapeutic measures will be tailored according to specific genetic risk profiles.

2.2. Modifiable risk and protective factors for Alzheimer's disease

Different modifiable factors have been proposed to play a role in late life dementia and AD, including nutritional factors (i.e., diet and nutritional supplements), social or economic factors, medical conditions and lifestyle related factors (e.g., smoking habit, physical activity, etc.) (Table 1). A report commissioned by the National institute of Health (NIH) to the Agency for Healthcare Research and Quality (AHRQ) was published in 2010, and 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 [35, 36]. Another previous review yielded similar conclusions [37]. These negative perspectives have been criticized, since there is consistent and robust epidemiological evidence that use of antihypertensive medications, cessation of smoking and increasing physical activity produces cognitive benefits in older adults [38]. Furthermore, the analytical strategy used in the Evidence Based Review carried out by the AHRQ did not take into account the life-course perspective [39]. Observational longitudinal studies have shown that the risk of late-life dementia and AD is determined by exposures to multiple factors experienced over the life-span and that the effect of specific risk/protective factors largely depends on age [39]. Thus, a life-course perspective is relevant for chronic disorders with a long latent period (such as dementia). 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 [40]. Age-dependent associations with 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) have been associated with an increased risk of dementia and AD, whereas having lower values in late life (age >75 years) has been also associated with subsequent development of dementia/ AD [41-46].

2.2.1. Risk factors

1. **Vascular risk factors and disorders**: An association of elevated blood pressure in midlife with an increased risk of dementia and AD later in life has been reported in several population-based studies [41, 47], while follow-up studies of late-life blood pressure and risk of dementia yield mixed results, largely depending on the length of follow-up. The short-term follow-up studies (e.g., less than 3 years) often found no association or even an inverse association between blood pressure and risk of dementia and AD [41]. However, studies of very old people (i.e., 75 + years) with a longer follow-up period (i.e., more than 6 years) also revealed an increased risk of dementia associated with low blood pressure [48], suggesting that among very old people low blood pressure may also contribute to the development of dementia, possibly by influencing cerebral blood perfusion.

    For BMI, the bidirectional association with dementia and AD has been shown in several studies, and longitudinal studies of elderly people have associated accelerated decline in BMI with subsequent development of dementia. This implies that low BMI and weight loss in advanced age can be interpreted as markers for preclinical dementia [45, 46, 49-55].

Regarding serum total cholesterol, the importance of the pattern of change in cholesterol levels after midlife has been shown by two studies with a long follow-up, reporting that a decline in plasma total cholesterol after midlife may be associated with the risk of cognitive decline, dementia and AD in late life [56, 57]. These findings suggest that high total serum cholesterol in midlife seems to be a risk factor for dementia and AD in advanced age, while decreasing serum cholesterol after midlife may reflect ongoing disease processes and represent a marker of early stages in the development of dementia and AD. The use of statins (cholesterol-lowering drugs) in relation to dementia has been investigated in several community studies, with mixed findings. Some observational studies suggest a protective effect, while others did not, and clinical trials using statins for prevention of cognitive decline or dementia mainly reported no effects [6, 58]. 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 [59]. Also pre-diabetes, impaired glucose regulation, and impaired insulin secretion have been associated with and increased risk of dementia and AD [60].

Cerebrovascular lesions and cardiovascular diseases have been shown to be risk factors for dementia and AD. Several population-based studies reveal an approximately two- to four-fold increased risk of incident dementia associated with clinical stroke (post-stroke dementia) [61, 62]. It is probable that an association of clinical stroke with AD is rarely reported due to the fact that a history of stroke is part of the current criteria for excluding the diagnosis of AD. However, asymptomatic cerebrovascular lesions such as silent brain infarcts and white matter lesions have been associated with an increased risk of dementia and AD [63, 64], although the association with AD is likely to be due to the inclusion of mixed dementia cases. The Cardiovascular Health Study found that cardiovascular disease was associated with an increased incidence of dementia, with the highest risk seen among people with peripheral arterial disease, suggesting that extensive peripheral atherosclerosis is a risk factor for dementia [65]. Atrial fibrillation, heart failure, and severe atherosclerosis measured with ankle-to-brachial index are also associated with the increased risk of dementia and AD [66-69].

2. **Environmental and other factors**: Current smoking is another major risk factor for dementia and AD, and based on the worldwide prevalence of smoking, about 14% of all AD cases are potentially attributable to this risk factor [70]. 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 [71]. Other conditions have been proposed as risk factors for dementia and AD, but the evidence is still sparse. These include occupational exposure, traumatic brain injury and infections. Occupational exposure to heavy metals such as aluminum and mercury has been suggested to be a risk factor for AD; even high consumption of aluminum from drinking water has been associated with an elevated risk of AD and dementia [6, 72]. In addition, occupational exposure to extremely-low-frequency electromagnetic fields (ELF-EMFs) has been related to an increased risk of dementia and AD [73, 74].

Traumatic brain injury has been extensively investigated as a possible risk factor for AD. The meta-analysis of case-control studies supported an association between a history of head injury and the increased risk of AD [75]. In contrast, some longitudinal studies found that AD was not associated with head trauma or only associated with severe traumatic head injury [76]. The role of viral and bacterial organisms in the development of chronic neurodegeneration is long established. Thus, Treponema pallidum and HIV, in particular, have been associated with the development of dementia. Other infections in the central nervous system (CNS), particularly Herpes Simplex Virus Type 1, Chlamydophila pneumoniae and several types of Spirochetes, have been suggested as possible aetiological agents in the development of sporadic AD, but with little consistent evidence. It has also been suggested that peripheral infections may have a role in accelerating neurodegeneration in AD by activating already primed microglial cells within the CNS [77].

2.2.2. Protective factors

1. **Psychosocial factors**: Protective factors for dementia and AD have also been identified, including high education and socioeconomic status (SES) 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 [6, 78, 79]. 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 [80]. 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 [81].

2. **Lifestyle and diet**: In addition, several follow-up studies reported a decreased risk of dementia and AD associated with healthy dietary patterns and nutritional factors, such as high adherence to a Mediterranean diet or dietary intake of antioxidants (e.g., vitamins E and C) and ω-3 polyunsaturated fatty acid (PUFA, often measured as fish consumption) [82-86], although some negative results have been also reported [87-90]. Light-to-moderate alcohol intake (e.g., 1-3 drinks per day) has been associated to a reduced incidence of dementia and AD [6, 91, 92], while heavy alcohol consumption at midlife has been associated to an increased risk of dementia/AD, especially among *APOE* ε4 carriers [93]. Alcohol may have beneficial influences on several cardiovascular factors, including lipid and lipoprotein levels, inflammatory and hemostatic factors. Indeed, moderate alcohol drinking has been related to a reduced risk of cardiovascular diseases, and may be associated with fewer brain infarcts [6]. However, it has been also suggested that the apparent cognitive benefits of light-to-moderate alcohol intake could be due to potential biases that result from methodological limitations of the observational studies such as information bias, confounding of socioeconomic status and healthy lifestyles, and inconsistent approaches of alcohol assessments [6].

3. **Vitamins**: The micronutrient vitamin E is the main lipid-soluble, chain-breaking, non-enzymatic antioxidant in the human body [94], and is essential for normal neurological functions [95]. Vitamin E includes eight natural congeners: four tocopherols and four

tocotrienols, named as α, β, γ, and δ [96]. Each congener shows different biological properties potentially relevant for neuroprotection. These include antioxidant and anti-inflammatory activity and modulation of signaling pathways involved in neurodegeneration [96, 97]. Most investigation of vitamin E in relation to dementia and AD has focused primarily only on α-tocopherol, with conflicting findings. Overall, studies investigating vitamin E intake only from supplements found no association with dementia/AD risk [89, 98-101], or a reduced incidence was found only for the combined use of vitamin E and C supplements [102, 103]. On the other hand, studies examining vitamin E dietary intake consistently report a reduced risk of dementia/AD in individuals with high vitamin E intake [84, 85, 104-106]. This might be explained by the fact that while vitamin E supplements contain only α-tocopherol, dietary intake can provide a balanced combination of different forms of vitamin E, which can be more relevant for neuroprotection. Recent studies seem to support this hypothesis: a multicenter European study found that both AD and MCI were associated with low plasma tocopherols and tocotrienols levels [107]. Further, in the Swedish Kungsholmen Project a decreased AD risk was found in subjects with high plasma levels of total tocopherols and total tocotrienols [108].

Vitamin B12 and folate are essential micronutrients that are part of the homocysteine metabolic cycle, and both vitamin B12 and folate deficiencies can result in increased total homocysteine levels, which may lead to a variety of disorders including cardiovascular and cerebrovascular conditions. Several studies reported and increased risk of dementia/AD, worse cognitive functioning and structural brain changes in individuals with low levels of vitamin B12, holotranscobalamin (the biologically active fraction of vitamin B12) or folate, or high levels of total homocysteine [109-115]. Other studies did not confirm these findings, but methodological differences (e.g., different follow-up duration, implementing the study after mandatory folic acid fortification, etc.) could account for the discrepancy [116-119]. Reviews of RCTs concluded that supplementations of folic acid and vitamin B12 had no benefits on cognition in healthy or cognitively impaired older people, although they were effective in reducing serum homocysteine levels [120, 121]. A more recent RCT testing the efficacy of B vitamins (B6, B12, folate) in subjects with MCI reported beneficial effects of the supplementation, in terms of reduced rate of brain atrophy and cognitive decline, which were more evident in subjects with elevated homocysteine levels [122, 123].

Vitamin D is a secosteroid hormone that is suggested to have neuroprotective effects that include regulation of neuronal calcium homeostasis, as well as antioxidant, neurotrophic and anti-inflammatory properties. Few recent longitudinal studies found a reduced risk of cognitive decline or AD in subjects with higher blood levels or higher dietary intake of vitamin D [124-126]. Despite the epidemiological evidence is still weak vitamin D is already being tested as a therapeutic agent in AD [127].

2.2.3. Combined effect

Cumulative and combined exposure to different risk factors can lead to modified effects on dementia/AD risk (Table 1). In the Finnish Cardiovascular Risk Factors, Aging, and Dementia

study (CAIDE), 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 (i.e., hypertension, obesity, hypercholesterolemia, 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 [128]. Similar findings have been reported for late-life exposures: in the Swedish Kungsholmen Project, the cumulative effect of vascular risk factors and vascular diseases on dementia/AD risk has been investigated in people aged 75+ years. 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 [129]. The American Cardiovascular Health Cognition Study developed a Late-life Dementia Risk Index, and also its 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), genetic (presence of the *APOE* ε4 allele), lifestyle (BMI<18.5, lack of alcohol consumption), comorbid vascular conditions (internal carotid artery thickening, angina, coronary artery by-pass surgery, stroke, peripheral artery disease), evidence of brain abnormalities showed by magnetic resonance imaging (MRI) (white matter diseases or enlarged ventricles), cognitive test scores and physical performances [130, 131].

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 saturate fat, indicating that people with genetic susceptibility may reduce their initial AD risk by lifestyle interventions (i.e., physical activity, sufficient intake of PUFA, and avoiding excess alcohol drinking and smoking) [33]. The protective effect of lifestyle in *APOE* ε4 carriers seem to be present also in advanced age: in the Swedish Kungsholmen Project, subjects aged 75+ years who were *APOE* ε4 carriers, but with high education, active leisure activities, or good vascular health (i.e., absence of vascular risk factors), had a reduced risk of dementia and AD, as well as a delayed time of onset of the disease [132]. Further, it has been shown that high education may reduce dementia risk among *APOE* ε4 allele carriers [133].

Regarding 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 [78].

In conclusion, even though the evidence for some risk and protective factors in dementia and AD is still scarce, and their role needs to be further clarified, findings 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.

3. Interventional studies

3.1. Current evidence

Different medications, including statins, antihypertensive drugs, estrogens alone or in combination with progestin (hormone replacement therapy, HRT), nonsteroidal anti-inflammatory drugs (NSAIDs), and nutraceuticals (vitamin B12, C, E, folate, Ginkgo biloba) have been tested as primary or secondary prevention measures for dementia and AD in subjects with normal cognition or MCI. In general, for all these compounds the protective effects suggested by observational studies have not been confirmed in RCTs, the results of which are inconsistent or even suggest a detrimental effect on cognition (e.g., NSAIDs, HRT) [120, 134-136]. 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 further confirmation [134, 137]. 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 when 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 [138]. 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 (50-60 years), while estrogens initiated in late postmenopause (65-79 years) increase the risk of cognitive impairment and dementia [138-142]. The large-scale RCT of the Women's Health Initiative Memory Study (WHI-MS) showed that estrogens therapy alone or in combination with progestin was associated with a two-fold increased risk for dementia and MCI [139, 140]. The WHI-MS study enrolled women aged 65-79 years, who were given the HRT many years after the onset of natural or surgical menopause. In contrast, the Kronos Early Estrogen Prevention Study (KEEPS) tested the HRT in recently menopausal women (mean age 53 years; enrolment within three years after menopause), reporting beneficial effects [141]. In fact, the use of the HRT in the KEEPS participants has been associated with the improvement of markers of cardiovascular risk, anxiety and depression, without adverse effects on

cognition [141]. Overall these results suggest that the role of the HRT in age-related cognition and dementia needs to be further investigated, taking into account the time-window when the treatment is administered.

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 (e.g., antihypertensive therapy), in which clear benefits for primary endpoints (e.g., coronary heart disease and stroke) are shown usually in a short period of observation.

4. The choice of compounds tested in RCTs using nutraceuticals was not optimal: although several products have been tested, supplements 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, with conflicting findings [84, 85, 107, 108, 143]. Moreover, intake of high doses of α-tocopherol supplements has been associated with increased hemorrhagic stroke and mortality risk [144]. Regarding the studies on vitamins B, while the majority of RCTs done so far did not find evidence of benefit [120, 121], a recent RCT reported favourable effects in subjects with MCI, especially individuals with elevated homocysteine levels. In this latter RCT supplementation was done using a combination of vitamins B (B6, B12, folate) at high doses, suggesting that refining the type of supplements (i.e. composition, concentration) might increases the possibility to achieve beneficial effects in selected populations [122, 123].

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 conclusion, 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.

3.2. Ongoing multidomain intervention studies

The disappointing results of previous trials, testing the effects of mono-intervention strategies in cognitively normal elderly or already cognitively impaired persons, have pointed out some key issues: i) timing – starting earlier may lead to better effects; ii) target group – a healthy, young population would require long follow-up times, large sample sizes and considerable financial resources; iii) lack of consistent and uniformly applied definitions of MCI has lead to enrolment of heterogeneous groups underpowering the studies; iv) outcome measures – cognitive impairment may be a better endpoint than conversion to dementia; v) ethical issues

are also important, as placebo-controlled trials for high blood pressure and cholesterol are not possible due to their known protective effects regarding cardio- and cerebrovascular disease. Furthermore, a critical aspect that needs to be taken into account when planning preventive measures for dementia and AD, is the multifactorial nature of these disorders, which require multiple prevention approaches. Intervention studies combining several different approaches have not been conducted for AD so far, and the knowledge derived from the previously described observational and interventional studies has paved the way for some ongoing RCTs on prevention of cognitive decline and dementia. In Europe there are three large ongoing RCTs: FINGER, MAPT and PreDIVA [145, 146] (Table 2). The common denominator of these studies is the multidomain approach, which aims to target simultaneously several risk factors for dementia and AD 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 or substantial cognitive decline, and use clinical evaluation and neuropsychological tests to detect cognitive changes and dementia incidence as main outcomes. Further, secondary outcomes include functional status, mood disorders, quality of life, adherence to the intervention programs and health resources utilization. These two latter 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 neuroimaging (morphological and functional), CSF 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.

The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER, NCT01041989) is a multicenter RCT aiming to prevent cognitive impairment, dementia and disability in 60-77 year-old people. The study population is represented by 1282 individuals at increased risk of dementia, selected according to the CAIDE Dementia Risk Score and the CERAD neuropsychological test battery [128, 145]. 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, 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 (i.e., FINRISK, FIN-D2D) with detailed retrospective information on lifestyle and vascular factors [145]. Thus, differences in these variables can be taken into account, which is normally not possible in RCTs. The primary outcome is cognitive decline measured by a sensitive Neuropsychological Test Battery (NTB) and the Stroop and Trail Making tests, which can depict early cognitive impairment typical for AD and VaD. The planned 7-year extended follow-up will allow detection of differences in dementia/AD incidence. Two earlier intervention trials in Finland were important sources of inspiration for the FINGER study. The Diabetes Prevention Study (now completed) is a landmark RCT showing the effectiveness and feasibility of physical exercise and dietary interventions as preventive measures in people with impaired glucose tolerance. In this RCT lifestyle intervention in people at high risk for type 2 diabetes resulted in sustained lifestyle changes and a reduction in diabetes incidence, which remained after the

individual lifestyle counselling was stopped [147, 148]. The four-year exercise and dietary intervention study Dose-Responses to Exercise Training (DRs EXTRA) had a drop-out rate of only 8% after two years, and preliminary results suggested a potential benefit of higher physical fitness on cognition [149].

RCT Country	FINGER Finland	MAPT France	Pre-DIVA Netherlands
Sample size	1282	1680	3534
Main inclusion criteria	Dementia Risk Score >6 and mild degree of cognitive impairment	Frail elderly people (subjective memory complaint, slow walking speed, limitation in IADL)	All elderly within GP practices, non demented (MMSE >23)
Age at enrolment, yrs	60 -77	≥ 70	70-78
Study design	Multi-center, randomized, single-blind, parallel-group	Multi-center, randomized, controlled trial	Multi-site, open, cluster-randomized parallel group
Multi-domain intervention	Nutritional guidance, physical activity, cognitive training, increased social activity and intensive monitoring and management of metabolic and vascular risk factors	Vascular care, nutritional advice, exercise advice, cognitive training, and/or DHA 800 mg/day	Nurse-led vascular care including medical treatment of risk factors, diet advice, exercise advice
Intervention period	2 yrs	3 yrs	6 yrs
Follow-up period	7 yrs	5 ysr	6 yrs
Primary outcome	Neuropsychological test battery, Trail Making test, Stroop test, Dementia	Change in cognitive function (Grober and Buschke memory test)	Dementia, Disability
Study Completion	2013	2013	2016

DHA: docosahexaenoic acid acid. IADL: Instrumental Activities of Daily Living. MMSE: Mini Mental State Examination

Table 2. Ongoing multi-domain prevention RCTs on dementia

The Multidomain Alzheimer Preventive Trial (MAPT, NCT00672685) is a French multicenter RCT evaluating the efficacy of isolated supplementation with ω-3 fatty acid, isolated multi-

domain intervention, or their combination in the prevention of cognitive decline in frail individuals aged ≥70 years. 1680 community-dwelling participants have been enrolled, using a definition of frailty that includes three components: presence of memory complaints, limitation in one instrumental activity of daily living (IADL) 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, 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) [145, 150].

The Prevention of Dementia by Intensive Vascular Care (PreDIVA) study is a Dutch multi-center, open, cluster-RCT comparing standard and intensive care of cardiovascular risk factors in preventing dementia and disability in elderly people. The study includes 3534 community-dwellers aged 70-78 years, recruited from primary care practices. The standard care is based on guidelines for Dutch general practice, while the multi-component intensive vascular care addresses hypertension, hypercholesterolemia, smoking habits, overweight, 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 AMC Linear Disability Scale (ALDS) [146].

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 [151]. Collaboration and data sharing within the EDPI will allow refining methodological aspects of prevention trials, including identification of target populations; improvement of intervention methods (i.e., type, intensity, 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 and international prevention trials able to provide robust evidence on dementia/AD prevention.

3.3. Presymptomatic Alzheimer's disease treatment: Anti-amyloid drugs

Presymptomatic (or preclinical) AD treatments have been defined as "those interventions that are initiated before apparent cognitive decline and are intended to reduce the chance of developing AD-related symptoms" [152]. The proposed term refers to an intervention whether it is started before or after biological evidence of the underlying disease, and whether it postpones the onset, partially reduces the risk of, or completely prevents symptomatic AD [153]. The progress on the knowledge about the AD phenotype, particularly on the biomarkers which have been incorporated in the new diagnostic criteria for dementia and MCI due AD, as well preclinical AD, has provided the basis for intervention studies evaluating pharmacological interventions in asymptomatic subjects who are at risk of AD, because of an established biomarker burden or a specific genetic profile. Three RCTs are planned to start in 2013 to verify

safety and efficacy of anti-amyloid drugs as preventive measure in AD (Table 3). The Alzheimer's Prevention Initiative (API) and the Dominantly Inherited Alzheimer's Network (DIAN) studies will enrol subjects who carry genetic mutations for dominantly inherited AD: mutations in the *APP*, presenilin-1 (*PSEN1*), and presenilin-2 (*PSEN2*) genes can cause early-onset familial AD that accounts for no more than 5 percent of all cases [154].

Data from the DIAN study have shown that different phenotypic changes can be detected several years before the onset of cognitive symptoms in individual with autosomal dominant AD: it has been shown that CSF levels of Aβ42 decline 25 years before expected symptom onset, and brain deposition of Aβ can be detected 15 years before. Further, increased concentrations of tau protein in the CSF and brain atrophy are visible 15 years before expected symptom onset, while cerebral hypometabolism can be observed 10 years before [155]. The API RCT will focus on the world largest early-onset AD kindred in Antioquia, Columbia. Of about 5000 individuals in this kindred, approximately 1500 carry a mutation in the *PSEN1* gene (E280A) causing early onset AD (mean age of onset: 45 years) [156, 157]. The trial will also include a small number of individuals in the United States, recruited in collaboration with researchers from the DIAN study [158]. The drug used in the API study is the anti-amyloid antibody crenezumab, which has been chosen based on the evidence of its ability to remove from the brain different forms of Aβ and its safety profile (low risk of cerebral vasogenic oedema and microhaemorrhages) [157]. The trial within the DIAN cohort will include people with mutations in any of the three genes linked to early-onset AD: *PSEN1*, *PSEN2*, and *APP*. Three different anti-amyloid compounds will be evaluated in the first phase of the study (2 years): the beta-secretase inhibitor LY2886721, which limits the production of Aβ; and two anti-amyloid antibodies (Gantenerumab, Solanezumab) which promote Aβ removal from the brain. The more effective drug(s) will be further tested in a 3 years extension phase of the study. A third trial, the Anti-Amyloid Treatment of Asymptomatic Alzheimer's (A4) RTC, aims to prevent sporadic AD and will evaluate the effect of an anti-amyloid compound in older adults with evidence of brain amyloid accumulation at neuroimaging evaluation. The study is sponsored by the Alzheimer's Disease Cooperative Study, and also in this case the drug candidate still needs to be identified among anti-amyloid compounds. The study is expected to detect differences in the rate of cogntive decline, while it has not enough statistical power to detect a difference in dementia incidence. The A4 study will also include an ethics arm examining the psychological impact of disclosing information to individuals about their risk of developing AD [157].

Overall, these studies provide the opportunity to test the efficacy of AD-modifying treatments in an earlier stage of AD compared to the pharmacological RCTs done so far. While testing these compounds in young, healthy individuals would require enormous financial resources and too long follow up, the recruitment strategies implemented in these studies allow testing the benefit of anti-amyloid drugs earlier than otherwise possible. This approach provides also the opportunity to further verify the amyloid hypothesis, which has been reconsidered many times over the past decades and criticized in light of the recent failures of RCTs testing anti-amyloid drugs in subjects with mild-to-moderate AD. A possible interpretation of these failures is that the anti-amyloid therapies have missed their "window of opportunity", since

they have been provided too late. The preventive RCTs on anti-amyloid drugs are based on the assumption that an earlier interference on amyloid accumulation, before irreversible brain damage occurs, would exert a significant disease-modifying effect. These prevention studies will also allow determining the ability of different biomarkers to predict a clinical benefit, information needed to help qualify biomarker endpoints for use in prevention trials. These studies offer great hope, but also safety concerns, since anti-amyloid compounds will be tested in subjects with no cognitive problems and the long-term risk associated with the use of anti-amyloid drugs is yet unknown.

RCT	API Alzheimer's Prevention Initiative	DIAN Dominantly Inherited Alzheimer Network	A4 Anti-Amyloid Treatment of Asymptomatic AD
Sample size	300 members of Colombian families. A small number of individuals from USA (collaboration with the DIAN network) will also be included	240 members of families with early-onset AD	1500 older adults with no cognitive impairment
Main inclusion criteria	Carriers of a mutated *PSEN1* gene. Non-carriers will also be included, to ensure double-blinding about the genetic status	Carriers of mutation in *PSEN1*, or *PSEN2*, or *APP*. Non-carriers will also be included, to ensure double-blinding about the genetic status	Evidence of brain amyloid accumulation. Subject with no evidence of amyloid burden will also be included
Age at enrolment, yrs	≥ 30	NA	≥ 70
Study design	Randomized, double blind, placebo controlled trial	Randomized, double blind, placebo controlled trial	Randomized, double blind, placebo controlled trial
Intervention	Anti-amyloid antibody Crenezumab (Genentech)	Three anti-amyloid therapies: the beta-secretase inhibitor LY2886721 (Lilly), and the anti-amyloid antibodies Gantenerumab (Roche) and Solanezumab (Lilly)	One anti-amyloid therapy (to be determined)
Duration	5 yrs, (interim analysis at 2 yrs)	2 yrs + 3 yrs extension	3 yrs + 2 yrs extension
Outcomes	Primary: cognitive function Secondary: biomarkers, including brain amyloid load and brain atrophy	Initial phase (2 yrs): biomarkers analysis, to identify the most promising drug candidate Follow-up phase (3 yrs): cognitive function	Primary: cognitive function Secondary: biomarkers

APP: amyloid precursor protein. *PSEN1*: presenilin 1. *PSEN2*: presenilin 1

Table 3. Alzheimer's prevention trials based on anti-amyloid treatments

4. Conclusion

Prevention is a newer area in dementia/AD research, and the shift from observation to action has occurred only in the last decade, with several intervention studies now ongoing, and other RCTs starting soon. 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 on risk and protective factors for dementia and AD, as well as a validation of the observational studies with large intervention studies [19]. 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, Lewy bodies) and vascular lesions are common in the brains of cognitively normal elderly individuals, as is their co-occurrence [9]. 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 10-25% reduction in these factors could potentially prevent 3 million AD cases worldwide, with a reduction in all risk factors having the greatest impact on dementia prevalence [70]. However, RCTs are indispensable to confirm the effect of risk reduction strategies targeting multiple risk factors. Multidomain interventional RCTs are now ongoing and will provide new insights into prevention of cognitive impairment and dementia. Full implementation of the life-course approach is more challenging, due to 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 a RCT has not yet been established. Furthermore, several risk and protective factors are not appropriate for intervention trials, due to unethical reasons, thus evidence about these factors rely on conducting rigorous observational studies (e.g., placebo-controlled trials for high blood pressure or cholesterol are not possible because such treatments are known to protect against cardio/cerebrovascular diseases) [35]. Methodological alternatives to RCTs have been proposed to obtain robust evidence on AD and dementia prevention [37, 159].

Platforms for early intervention could be established by incorporating the classical clinical trial approach to disease into a public health model, with long-term longitudinal databases including large populations. Establishing comprehensive databases for studies on aging can create the opportunity to formulate and validate tools for early detection of people who are at increased risk of late-life cognitive impairment, to identify important targets (risk factors) for preventive interventions, and to test such interventions in RCTs.

The first initiatives with an international perspective have already been established, for example the Leon Thal Symposia [160], Prevent Alzheimer's Disease by 2020 (PAD2020, http://www.pad2020.org), and the European Dementia Prevention Initiative (EDPI, http://www.edpi.org). It has been suggested that a worldwide database could be built by integrating and expanding already existing cohorts and registries [160].

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 targeting elderly individuals, 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 [161-163]. 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 the older adults [146]. Similar situations exist for heart failure, which increases the risk of dementia among older adults [68], and diabetes mellitus, which accelerates the progression from mild cognitive impairment to dementia by more than 3 years [164]. 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 [146].

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. The multidomain intervention RCTs are at one end of the current spectrum of intervention trials in AD/cognitive impairment. At the other end are RCTs testing disease-modifying drugs (i.e. anti-amyloid therapy) in genetically at-risk groups or those with established biomarker burden. The shift towards pre-symptomatic and pre-dementia stages of AD has brought prevention and treatment RCTs much closer to each other than before. 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 healthier lifestyle have the potential to enhance health status in advanced age.

Acknowledgements

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