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Review

Future directions in Alzheimer's disease from risk factors to prevention

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ABSTRACT

The increase in life expectancy has resulted in a high occurrence of dementia and Alzheimer's disease (AD). Research on AD has undergone a paradigm shift from viewing it as a disease of old age to taking a life course perspective. Several vascular, lifestyle, psychological and genetic risk factors influencing this latent period have been recognized and they may act both independently and by potentiating each other. These risk factors have consequently been used to derive risk scores for predicting the likelihood of dementia. Despite population differences, age, low education and vascular risk factors were identified as key factors in all scoring systems. Risk scores can help to identify high-risk individuals who might benefit from different interventions. The European Dementia Prevention Initiative (EDPI), an international collaboration, encourages data sharing between different randomized controlled trials. At the moment, it includes three large ongoing European trials: Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER), Prevention of Dementia by Intensive Vascular Care (preDIVA), and Multidomain Alzheimer Prevention study (MAPT). Recently EDPI has developed a "Healthy Aging through Internet Counseling in Elderly" (HATICE) program, which intends to manage modifiable risk factors in an aged population through an easily accessible Internet platform. Thus, the focus of dementia research has shifted from identification of potential risk factors to using this information for developing interventions to prevent or delay the onset of dementia as well as identifying special high-risk populations who could be targeted in intervention trials.

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1. Background

Dementia is a devastating syndrome affecting an ever-increasing number of people due to the aging of populations all around the world. According to Alzheimer's Disease International (ADI), 24.3 million people were living with dementia in 14 World Health Organization (WHO) regions in 2001, and this will reach 81.1 million by 2040, with the numbers doubling every 20 years [1]. If we consider the values for the year 2010 in all regions of the world, then global prevalence of dementia was 4.7% in people older than 60 years with regional prevalence of 2.6% in Africa, 4.0% in Asia, 6.2% in Europe and 6.9% in North America [2]. The Global Burden of Disease has estimated that dementia accounts for 11.2% of disability years in people >60 years of age, a value higher than the disability years attributable to stroke (9.5%), cardiovascular diseases (5.0%), musculoskeletal disorders (8.9%) and all forms of cancer (2.4%) [3]. These facts and figures emphasize the importance of prevention of this debilitating disease to reduce the burden on society as well as easing suffering of those affected and their families.

The etiopathogenesis of Alzheimer's Disease (AD), the most common cause of dementia (60–80% of cases), has been an area of active research since the 1960s. While the genetic and non-genetic risk factors of the disease started to become unraveled in the 1990s [4], recent research has concentrated on the disease development and this has revealed the complexity of the pathology in late-onset AD. Identification of multiple modifiable life-style related risk factors has resulted in the transformation of dementia from an untreatable almost inevitable aspect of aging into a potentially preventable affliction. The pre-clinical phase of AD may last more than 20 years before the onset of clinical symptoms. The long prodromal phase is highlighted also in the recently proposed AD criteria by the National Institute on Aging and Alzheimer's Association (NIA-AA) and International Working Group criteria (IWG) [5]. This shift toward presymptomatic and preclinical stages of AD has opened new horizons for early interventions.

This review provides an overview of modifiable risk factors for dementia/AD with a special focus on dementia risk scores that can help to identify high-risk individuals who might benefit from intensive lifestyle/pharmacological interventions, and ongoing dementia prevention studies and initiatives.

2. Risk factors for dementia and AD

The characterization and association of multiple environmental risk factors has changed our approach to dementia prevention. The strict differentiation between AD and vascular dementia (VaD) has vanished due to mixed findings from autopsy, and epidemiological and biological evidence for a vascular component in AD pathology [6]. AD is now increasingly recognized as a complex multifactorial disease attributable to several interrelated and interacting genetic and environmental factors.

2.1. Cardiovascular risk factors

The cardiovascular risk factors for both AD and VaD include diabetes, hypertension and high cholesterol levels. These factors predispose an individual to a cognitive decline in their own right and also by potentiating each other.

Four longitudinal studies have identified an aggregation of midlife cardiovascular risk factors that can increase the risk of cognitive decline/dementia in late life after 15, 21, 23, and 27 years of follow up [7–10]. The midlife risk for stroke as measured by Framingham stroke risk profile in a British cohort resulted in an increased risk of dementia 10 years later [11]. Vascular risk factors increased the risk of incident AD in a longitudinal cohort study in a dose dependent manner with a mean 5.5 years of follow up [12]. The control of midlife vascular risk factors including blood pressure, total cholesterol, BMI, has been associated with a reduction in white matter lesions (WML) in late life, which can decrease the risk of AD [13]. A longitudinal study in late middle aged participants' associated cardiovascular risk factor especially diabetes and hypertension to the cognitive decline, implying that early treatment of these cardiovascular risk factors might reverse the situation [14].

2.1.1. Hypertension

Hypertension, a risk factor for cardiovascular diseases, has been associated with dementia/AD in multiple studies, but the association appears to be age-dependent. High blood pressure (BP) in midlife has been linked with an increased risk of dementia/AD in several longitudinal studies [15,16]. High BP even late in life may increase the risk [17] but the inverse association has been described in many studies among elderly persons; this may in part be explained by reverse causality. One recent study provided further support for this hypothesis by indicating that midlife hypertension was associated with a thinner cortex in several brain areas, including the insular cortex which is known to be involved in BP regulation [18]. Interestingly, among elderly individuals with a thinner insular cortex, there was a continuous decline in systolic BP after midlife. This may reflect ongoing Alzheimer or vascular pathological processes, at least partly initiated by the presence of midlife hypertension.

High blood pressure may increase the risk of dementia/AD through stimulation of the neurodegenerative process/atrophy/or by enhancing the damage inflicted by cerebrovascular insults [19]. A recent study in the Honolulu Asian Aging cohort reported that high diastolic blood pressure in midlife was linked with a decline in the plasma amyloid beta (Aβ) level and an increase in the risk of AD 15 years later in life. The reduced plasma Aβ level corresponded with elevated cortical deposition, decreased Aβ clearance, cerebral amyloid angiopathy, and a high risk of incident AD [20].

2.1.2. Cholesterol

High total serum cholesterol in midlife has been linked with an increased risk of dementia and of the AD [15]. This association may

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be mediated at least via two different mechanisms; first, high cholesterol concentrations cause atherosclerosis resulting in a high risk of cardiovascular and cerebrovascular diseases while on the other hand, a high cholesterol level has been associated with greater amounts of amyloid deposition in brain [21,22]. The association between cholesterol and AD seems to be bidirectional and the inverse association encountered in old age may be explained by the effect of AD process on cholesterol levels and metabolism [22].

2.1.3. Body mass index (BMI)

The association between body mass index (BMI) and dementia/AD seems also to be bidirectional, with high BMI in midlife linked with an increased risk of dementia/AD, while the reverse is evident in old age [23,24]. This has been attributed to the fact that dementia/AD in itself causes weight loss as early as 10 years before its onset and consequently a low BMI value in old age can be a sign of dementia, (reverse causality). Adiposity leads to insulin resistance, advanced glycosylation end products, high levels of adipokines and cytokines, all of which have been associated with an increased risk of AD [25,26].

2.1.4. Diabetes

Diabetes Mellitus (DM) has been linked with an increased risk of dementia and clinical AD in several studies [27]. DM may exert its role in clinical manifestation of AD via interaction with other vascular risk factors as smoking, hypertension and APOE ε4-allele through an increase in cerebral infarcts and other vascular lesions [28]. This might be mediated by the development of cerebral micro-vascular disease due to chronic hyperglycemia resulting in a 1.5–2 fold increase in risk of dementia among elderly with type2 diabetes [29]. DM is responsible for small vessel disease resulting in white matter hyper-intensities and lacunae formation, along with a disruption of the blood brain barrier due to damage to endothelial cells leading to neuroinflammation and degeneration. The reduction in insulin signaling in DM evokes a decrease in the synthesis of Insulin degrading enzyme (IDE) contributing to the accumulation of Aβ and hyperinsulinemia, which in turn activates glycogen synthase kinase 3 beta (GSK-3b) activity with an increase in phosphorylation of tau [30–32]. High fasting plasma glucose levels, even within the so-called normal range, have also been associated with hippocampal atrophy [33]. In a prospective cohort study, DM and poor glucose control over 9 years were associated with a cognitive decline, implying that the severity of DM contributes to the speed of cognitive decline [34].

2.2. Lifestyle related risk factors

The modifiable part of AD pathology also includes lifestyle related risk factors such as education, physical activity, smoking and alcohol intake, dietary factors and social interactions.

2.2.1. Education

Education, a marker of cognitive reserve along with occupation has been associated with a reduction in the risk of incident dementia [35,36]. Better education confers protection against the clinical manifestation of dementia/AD even in individuals with an unfavorable genetic background i.e. APOE ε4 carriers [37,38]. A study of the impact of White Matter Lesions (WML) on the risk of Mild Cognitive Impairment (MCI) and dementia was conducted on a cohort of 500 elderly over 7 years. It found that subjects with higher education were resistant to the harmful effects of WML on cognition [39]. Another trial concluded that high cognitive reserve protected against the progression from normal cognition to the onset of clinical symptoms independent of amyloid levels in CSF but was associated with low levels of t-tau and p-tau [40]. A study in 3 population cohorts reported higher education to reduce the risk of dementia; not due to any reduction in dementia-related neuropathology, but rather to an increase in the threshold at which these pathological changes would manifest themselves clinically [41]. Structural MRI analysis for cortical thickness and brain volume in a multicenter longitudinal study cohort found more years of education to increase the threshold before which brain atrophy became manifest clinically among patients with AD, a phenomenon explained by increased cognitive reserve [42].

2.2.2. Physical activity

Physical activity in midlife decreased the risk of dementia studied 26 years later which can be explained by the decline in the cardiovascular risk profile and a reduction in brain tissue loss [43]. High and moderate intensity physical activity decreased the risk of cognitive decline in healthy individuals by up to 38 and 35% respectively [44]. Aerobic exercise reduced the risk of cognitive impairment and dementia which can be explained by either a direct neurotrophic effect of exercise or by an improvement in the cerebrovascular and cardiovascular risk profiles [45]. In a prospective study with healthy participants, a Mediterranean diet and a higher level physical activity seemed to protect against AD [46]. In the Cardiovascular Aging and Dementia study cohort (CAIDE), leisure time physical activity but not work related physical activity measured at midlife was related to a 50% reduced risk of late life AD and dementia [47,48]. The association between leisure time physical activity and the reduced AD risk was more pronounced among APOE ε4 carriers than in non-carriers [47]. With respect to the leisure time activities, cognitively stimulating exercises but not physical activities were associated with a decrease in vascular cognitive impairment [49].

2.2.3. Smoking and Alcohol

Studies on the association of smoking and alcohol intake with cognition have yielded inconsistent results. Previous research has claimed nicotine to be a neuroprotective agent and thus the harmful association of heavy smoking on increased risk of AD might be attributable to the other 4000 substances present in cigarette smoke which are known to trigger oxidative stress, neuronal degeneration and plaque formation [50]. Heavy midlife smoking in a large multi-ethnic cohort predicted dementia, AD and VaD in a dose dependent manner more than two decades later. This association was not affected even after controlling for stroke, a disease for which smoking is a well-established risk factor. Instead it pointed to an independent association between smoking to VaD and AD not restricted to the cerebrovascular insults [51]. In another large cohort of CAIDE, midlife smoking increased the risk of dementia and AD among APOE ε4 allele carriers, but not among non-APOE ε4 carriers. This indicates that there is complicated gene environment interplay between smoking and dementia risk [52]. Data about another indulgence–alcohol depicts that mild-moderate alcohol intake is protective against dementia while excessive consumption increases the risk of cognitive decline and dementia [53–57].

2.2.4. Dietary patterns

Saturated fats have been found to increase the risk of AD, while healthy dietary patterns such as diets rich in fruits and vegetables, adherence to a Mediterranean diet, intake of antioxidants and omega 3 fatty acids have been found to decrease the dementia risk [58–61].

2.2.5. Social characteristics

Social characteristics refer to a wide range of attributes. For example, high social networking, purpose in life, high education and socioeconomic position, involvement in cognitively challenging

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tasks and being in a relationship have all been claimed to be protective against AD [41,62–65].

2.3. Genetic risk factors

There are genetic risk factors for AD. For example, carriers of the APOE ε4 allele are susceptible to develop this disease in a dose dependent manner and this is related to triggering of cerebral amyloid pathology [66]. On one hand, APOE ε4 potentiates the effect of high alcohol and saturated fat intake, physical inactivity and smoking on the risk of AD, while on other hand, high education and physical activity have been shown to counteract the negative impact of APOE ε4 on the AD risk [38,67]. While APOE ε4 is the strongest genetic risk factor, genome-wide association studies have identified many other susceptibility genes but with lower impacts [68–71] (Table 1)

3. Risk scores for dementia

Risk scores have been developed to predict the risk of cardiovascular events, diabetes, and mortality [72–74]. Risk scores have generally included only a few known risk factors that are easily measurable and which can be used to calculate the subsequent risk of an event or disease within a given time frame. The long preclinical state of dementia/AD and the fact that cumulative and combined exposure to different vascular and environmental factors can modify the risk have complicated the development of dementia risk scores in different populations. The first scoring system for dementia was formulated in 2006 based on the CAIDE study in Finland [75]. Since then, four other scoring systems have been derived [75–81]. The different risk scores are summarized in Table 2. The main use of risk scores is to target the preventive measures to those individuals most at risk of developing the disease. Another important benefit is to publicize easily understandable information about risk factors to the general population.

3.1. CAIDE Dementia Risk Score

The first dementia risk scoring system was devised by Kivipelto et al. in 2006 based on the midlife risk profile in a community dwelling population (n = 1409) recruited from the Cardiovascular Aging and Dementia (CAIDE) cohort [75]. The aim was to develop a simple method for the prediction of the risk of late-life dementia in middle aged individuals on the basis of their risk profiles. Several midlife (baseline mean age 50 years) vascular risk factors were studied to create the scoring tool. The score values were estimated on the basis of β coefficients and the dementia risk score was the sum of these individual scores (range 0–15). In the CAIDE risk score, future dementia was predicted by high age, low education, hypertension, hypercholesterolemia, obesity, and physical inactivity. The dementia risk score predicted dementia well with an area under the curve value of 0.77; 95% CI 0.71–0.83. The risk of dementia according to the categories of the dementia risk score was 1.0% for those with a score of 0–5, 1.9% for a score of 6–7, 4.2% for a score of 8–9, 7.4% for a score of 10–11, and 16.4% for a score of 12–15. When the cut-off value of 9 points or more was applied the sensitivity was 0. 77, the specificity was 0.63, and the negative predictive value was 0.98. Inclusion of APOE status in a separate analysis did not significantly improve the predictive value.

In summary, the CAIDE risk score provided a quantitative estimation of the probability of developing dementia with the ultimate aim being to devise effective preventive strategies in the future. It included simple, easy to assess variables, and provided a good possibility to detect people at risk of developing dementia 20 years later in life.

The external validity of the CAIDE dementia risk score was recently assessed in a diverse, large population of 9480 participants from the Kaiser Permanente Cohort (baseline age range 40–55 years). The CAIDE score worked well in this population, stratifying subjects into those with a low (9%) and high (29%) risk for dementia over 40 years of life span [77]. Additional midlife variables were analyzed in an attempt to improve the predictive value of the CAIDE dementia risk score; these included a history of head trauma, central obesity, depressed mood, poor pulmonary function, and diabetes. The additional variables did not alter the validity of the CAIDE score and c statistic value for this refinement cohort was 0.75, which is very similar to the CAIDE cohort value of 0.77.

The outcome of these two studies indicate that a score created by combination of the mostly modifiable risk factors in midlife is highly predictive for the likelihood of dementia 2–3 decades later and emphasizes the importance of maintaining vascular health in the primary prevention and delay of dementia.

3.2. Dementia risk prediction in the elderly

A prediction of dementia in 3375 older adults (baseline mean age 76 years) over 6 years was performed in a large, biracial population enrolled in the Cardiovascular Health Cognition Study (CHS). This score was devised using intricate neurological and cardiovascular risk assessments for accurately stratifying older adults into low, moderate and high risks of developing dementia. It had a high predictive accuracy of 0.81. With this score, older age and poorer cognitive performance at baseline were associated with a high risk of dementia [78]. The difference in the predictive accuracy of this late-life risk score and former midlife based risk scores could well have been explained by the simple and easily available measures used in the latter scoring system or perhaps dementia prediction might become easier closer to symptom onset.

3.3. LOAD risk score

The risk score for Late Onset Alzheimer's disease (LOAD) after 4 years was formulated from data obtained from 1051 community dwelling older individuals with a mean age of 75.6 years at baseline. This score added diabetes and a complete clinical and neuropsychological evaluation along with vascular risk factors. Old age, low level of education, APOE genotype, history of diabetes, hypertension or smoking, high waist-to-hip ratio and low HDL-C levels at baseline were predictive of dementia. Those individuals with the highest scores were at a 20.5-fold elevated risk (measured as Hazard Ratio) of developing dementia compared to those with the lowest score (their risk was designated as 1) [79].

3.4. Risk score for primary care settings

Dementia prediction among 3055 old adults (mean age 80.1 years) in a primary care setting was assessed in the German study

Table 1
Main proposed risk factors for dementia and AD.

Risk Factors	
	1. Cardiovascular risk factors: **Hypertension**, Hypercholesterolemia, Obesity, Diabetes Mellitus, Homocysteine, Cardiovascular diseases, Cerebrovascular diseases
	2. Life style related risk factors: **Low** education, Physical inactivity, Smoking, Excessive alcohol intake, Diet rich in saturated fats, Low vitamins and antioxidants intake, Social inactivity
	3. Genetic: **APOE** epsilon 4-allele, Familial aggregation

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Table 2
Dementia Risk scores.

Title	Country/year	Mean age at baseline	Study/number of participants/ follow up years	Variables included in scoring	Accuracy
Prediction of dementia risk in 20 years based on midlife risk profile [75]	Finland/2006	50.4 years	CAIDE based longitudinal/1409/20 years	Age, education, sex, BMI, SBP, total cholesterol, physical activity ApoE ε4 carrier in a separate analysis	Prediction accuracy (AUC), c statistic 0.78 PPV 9% NPV 98%
Midlife risk score for prediction of dementia four decades later [77]	USA/2013	At baseline, start of dementia ascertainment and end of follow up 46.1, 73.1, 82.2 years respectively	Members of KPNC who participated in voluntary Multiphasic Health Checkups (MHC)/9480/40 years	CAIDE dementia risk factors Additional variables: head trauma, central obesity, depressed mood, poor pulmonary function, diabetes mellitus and smoking	c statistic for specialist confirmed dementia diagnosis in refinement cohort was (0.75) which is quite comparable to original CAIDE cohort (0.78)
Dementia risk prediction in older adults within 6 years [78]	USA/2009	76 years	CHS study/ 3375/ 6 years	Age, education, race, MMSE, digital symbol substitution score, bypass surgery, time to put on and button shirt, current alcohol consumption, BMI, enlarged ventricles and white matter disease on MRI, internal carotid artery thickness, apo lipoprotein E genotype	Prediction accuracy (AUC) 0.81 PPV 57% for individuals scoring in top 5% of the prediction score
Risk score for prediction of AD in elderly [79]	USA/2010	75.66 years	Community based longitudinal cohort of Medicare recipients/ 1051/ 4.2 years	Age, sex, education, ethnicity, diabetes, hypertension, current smoking, HDL-C, waist to hip ratio, APO E genotypes	High risk score (>28) had HR (95% CI) 20.47 (8.38–49.99) among probable and possible LOAD cases
Dementia prediction in Primary Care Patients [80]	Germany/2011	80.1 years	Based on (AgeCoDe) study/ 3055/ 3.81–6.14 years	Age, sex, verbal fluency, subjective memory impairment (SMI), IADL, depressive symptoms by GDS, education, smoking, family history of dementia, living status, MMSE	Prediction accuracy (AUC) was 0.84 in first cohort and 0.79 in test cohort
Prediction of 10 year dementia risk in individuals with type 2 diabetes [76]	USA/2013	70.6 years	Based on KPNC diabetes registry/ 29,961/ 10 years External validation cohort 2413 people> 60 years with type 2 diabetes and members of Pathway study cohort, USA	Age, education, microvascular disease, diabetic foot, cerebrovascular disease, cardiovascular disease, acute metabolic event, depression	C statistic for development cohort was 0.736 for validation cohort was 0.746
Cognitive decline prediction by comparing dementia risk score with two Framingham vascular risk scores [81]	UK/2013	55.2/55.6 in Framingham CVD vs. dementia risk score (comparison 1) and Framingham stroke vs. dementia risk score (comparison 2) respectively	Framingham general cardiovascular disease risk score and Framingham stroke risk score compared with CAIDE dementia risk score for cognitive decline in a British cohort /10 years/ Comparison 1 (4374) Comparison 2 (5175)	CAIDE: age, sex, education, SBP, BMI, total cholesterol, physical activity Framingham risk scores: age, sex, SBP, antihypertensive medication use, diabetes, current smoker, total cholesterol, HDL cholesterol, history of heart disease, atrial fibrillation, left ventricular hypertrophy	CVD risk score was associated with -0.06 SD (95% CI = −0.08, −0.05) decline in global cognitive scores while dementia risk score was associated with -0.03 SD (95% CI = −0.04, −0.01) decline

Abbreviations: CAIDE (cardiovascular risk factors, dementia and aging study), SBP (systolic blood pressure), DBP (diastolic blood pressure), BMI (body mass index), AUC (area under curve), MMSE (mini mental scale examination), MRI (magnetic resonance imaging), HDL (high density lipoprotein), SIDAM (structured interview for diagnosis of dementia of alzheimer type), SISCO (), IADL (impairment in daily life activities), GDS (geriatric depression scale), CVD (cardiovascular diseases), KPNC (Kaiser Permanente northern California),PPV (positive predictive value), NPV (negative predictive value).

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on Aging, Cognition and Dementia (AgeCoDe) study which had 4–6 years of follow up. The study population was randomly split into two separate cohorts, one to devise the risk score and other to test it. Two cut off values of the score were defined, one to sensitively identify the individuals at risk while the other was utilized to identify the high-risk group with high specificity. The score was successful in detecting dementia in a low prevalence setting. The predictive accuracy of this score was 0.79 with 79.6% sensitivity at the first cut off ($\geq$9 points) and 92.6% specificity at the second cut off value ($\geq$15) in the test cohort. In this score, subjective memory complaints along with poor MMSE score and Impairment in Activities of Daily Living (IADL) were strong predictors of dementia [80].

Subjective memory complaints proved to be a more accurate tool in predicting AD before its onset than objective neuropsychological tests in the primary care setting [80]. This is in agreement with the previous research reporting an association between subjective complaints and future dementia/AD [82–84].

3.5. Type 2 diabetes-specific dementia risk score (DSDRS)

The DSDRS risk score was devised for prediction of dementia over 10 years in 29,961 individuals with type2 diabetes and a mean age of 70.6 years, from the Kaiser Permanente Northern California diabetes registry. The predictive accuracy of the demographic characteristics, detailed assessments of diabetes-related pathologies from medical records, medication history from prescription records and glycated hemoglobin measurements were assessed. The final score consisted of age, education, micro-vascular disease, diabetic foot, cerebrovascular disease, cardiovascular disease, acute metabolic event and depression. The external validation of this score was performed in a cohort of 2413 patients (age $\geq$ 60 years) from the Pathways study, Washington, USA, with type 2 diabetes with the same selection criteria as in the development cohort. Both the development cohort and the validation cohort displayed predictive accuracies of 0.74 and 0.75 respectively, and an increase in the risk score increased the dementia risk in a dose-dependent manner. The DSDRS score contains information that is easily available to a clinician or nurse, either from patient records or from a brief interview with the patient [76].

3.6. Framingham risk scores and prediction of cognitive decline in a British cohort

The predictive accuracy of cognitive decline in a British cohort in late middle age was assessed by comparing two Framingham vascular risk scores and the CAIDE dementia risk score. In this comparison, a high score on Cardiovascular Disease and the stroke risk profile were associated with a rapid decline in the global cognitive score, semantic fluency and in all tests except memory, while the CAIDE risk score predicted a faster decline in reasoning, vocabulary and global cognitive score. The presence of diabetes in two Framingham scores and education in the CAIDE dementia score most strongly predicted a cognitive decline over 10 years [81]. The fact that the CAIDE dementia risk score was developed to predict the risk of clinically manifest dementia 20 years later and the Framingham study focused on cognitive decline during 10 years of follow-up, may explain some of the differences. So, it is not possible to compare the scores, as both scores highlight the relevance of vascular factors for cognitive decline/dementia.

3.7. Summary of the risk scores

Different sets of populations, age groups, follow-up times and risk and predictive factors have been used to develop the different risk scores. Interestingly, all of them have good predictive values for dementia or cognitive decline. Age was the strongest risk factor for dementia in all scoring systems; followed by low education and vascular risk factors. It is important to notice that risk profiles at midlife and late life may differ; while vascular risk factors (high BP, cholesterol level, BMI) are important at midlife, cardiovascular and cerebrovascular conditions (that may be due to vascular risk factors in midlife) are often more strongly related to dementia risk at late-life and during short follow-up. When moving closer to dementia onset, other predictors like cognitive complaints, cognitive tests, and brain MRI findings can be included to increase the predictive value. However, the predictive accuracy of both midlife and late-life scores was quite similar. On the basis of previous research: age, education, diabetes, obesity, hypertension and APO E genotype seem to be the key predictors of dementia risk. Few of the risk scores (mentioned in Table 2) have been validated in separate cohorts. It includes: (1) score developed to predict dementia in primary care patients [80], where risk score was developed and tested in separate subsamples of same cohort; (2) risk score for prediction of 10 year dementia risk in individuals with type 2 diabetes was validated in another study cohort from USA [76]; (3) The CAIDE risk score was developed in Finnish cohort and it has also been validated in a multi-ethnic US cohort [75,77]. Thus, further validation work is necessary to confirm the generalizability of other risk scores mentioned in Table 2.

Overall, the risk scores may form the basis of an effective and easily used tool to assess those at risk of cognitive decline, both in midlife and late life, and to concentrate prevention at targeted population groups. The scores can be used as educational and motivational tools but importantly, these scores should not be used "to label" individuals as being at risk of dementia. This is an important point since misuse of these tools may lead to an over-diagnosis of dementia, resulting in adverse emotional and financial consequences from fear of putative dementia at both the individual and the community level. Moreover resources would be directed from those with incident dementia toward presymptomatic individuals who may or may not develop dementia [85]. Thus, those at high-risk should be closely monitored by offering them detailed advice on lifestyle modifications and extensive diagnostic efforts should be employed when indicated.

4. From observation to action in dementia prevention

As described above, there is increasing evidence from epidemiological studies linking several modifiable risk factors to dementia and AD. However, evidence is still partly inconclusive and the National Institutes of Health (NIH) report recently highlighted the need for high-quality randomized controlled trials (RCTs) to verify the effectiveness of interventions targeting modifiable risk factors [86]. As dementia/AD has a multifactorial etiology, conducting RCTs with multidomain interventions was also recommended. This recommendation is further supported by the fact that previous single domain RCTs aiming to prevent dementia/AD have yielded inconclusive or negative results (e.g. statins, NSAIDs, nutraceuticals) [87]. For non-pharmacological factors, there is some evidence from RCTs that physical and cognitive activities may have positive effects on cognition. However, the effects sizes have been relatively modest and implications for dementia prevention still remain to be proven.

Other important lessons learnt from previous studies include timing of the intervention (starting earlier may lead to better results, 'critical time window' for some interventions), target populations (targeting at risk individuals may be the most effective approach), and the importance of long follow-up and realistic power calculations. Importance of international collaboration is increasingly highlighted to facilitate planning and conducting effective dementia prevention trials. The first initiatives with an

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international perspective have already been established, including the European Dementia Prevention Initiative (EDPI, http://www.edpi.org) [88–90].

In Europe, there are three large ongoing RCTs on dementia prevention: Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) [91], Multidomain Alzheimer prevention study (MAPT) [92], and Prevention of dementia by intensive vascular care (preDIVA) [93] (for details see Table 3). The common factor in these studies is the multi-domain approach which aims to simultaneously target several proposed vascular and lifestyle related risk factors for dementia and targeting older 'at risk' adults. As an example, the FINGER study (ClinicalTrials.gov identifier: NCT01041989) targets 60–77-year old individuals selected according to the CAIDE Dementia risk score (6 point or higher), and the CERAD neuropsychological test battery (cognitive performance at the mean level or slightly lower than expected for age according to Finnish population norms) [91]. The 2-year multi-domain intervention includes nutritional guidance, cognitive training, increased social activity, and monitoring and management of metabolic and vascular risk factors. The primary outcome is cognitive decline measured by a sensitive Neuropsychological Test Battery and the Stroop and Trail Making tests. Extended follow-up for at least 7 years is planned to detect differences in dementia/AD incidence and in secondary outcomes. Several ancillary studies on neuroimaging and blood/CSF markers are included to clarify mechanisms underlying preventive measures.

Researchers involved in these large European trials have started The European Dementia Preventive Initiative (EDPI), an international collaboration to improve preventive strategies against dementia [89]. Collaboration and data sharing among different RCTs will allow refining of methodological aspects of prevention trials including identification of ideal target populations and improvement in intervention methods and outcome measures. This will facilitate determining the optimal study design for future multi-national dementia prevention trials.

Recent progress by EDPI is the European Union-funded project 'Healthy Aging Through Internet Counseling in the Elderly' (HATICE, www.hatice.eu). HATICE project started January 2013 and aims to support management of vascular and life-style related risk factors in older adults, through an easily accessible Internet platform, with readily available nurse-support. The main goal of HATICE is improvement of cardiovascular risk profile and prevention of dementia and cardiovascular disease in the elderly. To investigate the efficacy of the platform, within HATICE a randomized controlled clinical trial among 4600 elderly is planned (starting 2015).

5. Summary and Future directions

Long-term epidemiological studies have linked several vascular and lifestyle related factors to dementia and AD and highlighted the importance of multi-domain approaches and life-course perspective in dementia/AD prevention. Available drug treatments

Table 3
Characteristics of RCTs with Multidomain interventions for prevention of cognitive impairment, dementia and Alzheimer's disease.

RCT	preDIVA[93]	Finger[91]	MAPT [92,98]
Objective of study	Prevention of dementia by intensive vascular care	To prevent/delay dementia in elderly at increased risk of cognitive decline through multidomain intervention	To prevent AD by multidomain interventions
Country	Netherlands	Finland	France
Number of participants	3700	1200	1680
Age	70–78 years	60–77 years	70 years and above
Study design	Multisite, open, cluster randomized parallel group study	Multicenter, randomized, controlled trial	Multicenter, randomized, placebo controlled study
Inclusion criteria	Non demented elderly from GP practices	Elderly with CAIDE risk score >6 and further screening by CERAD neuropsychological battery depicting mild cognitive impairment	Frail elderly people (defined by having subjective memory complaint, limitation in one IADL, slow walking speed)
Intervention	Control group: intensive management of vascular risk factors by practice nurse SC group: participants would receive regular care according to Dutch general practice	Control Group: Intensive intervention in nutrition, physical exercise, cognitive training and vascular risk factors Other group: Regular health advice	All participants sub grouped into 4 groups, 3 based on treatment options (omega 3 alone, multidomain intervention alone, both combined) and one placebo group
Follow up	6 years on whole IVC group: every 4 month visit with practice nurse for life style and medical interventions, then 2,4 and final 6 years follow up SC group: 2,4 years follow up and final 6 years visit	2 years Both groups meet study nurse 3 times and final visit with physician in 2 years Control group in addition undergoes intensive monitoring in each domain through frequent visits	3 years Cognitive and functional assessments conducted at baseline, 6 months and then annually Supplement distribution, compliance at 6,12,18,24,30 and 36 months
Primary outcome	Incident dementia and disability measured by ALDS	Cognitive performance evaluated by mNTB, Stroop and Trail making test	Change in cognition over 3 years determined by Grober and Buschke test
Secondary outcome	Overall mortality, incidence of vascular events as MI, peripheral vascular disease, mood (GDS), cognitive decline (MMSE, VAT)	Dementia, cognition, vascular risk factors, disability, falls, depression, cardio and cerebrovascular morbidity and mortality, health service utilization, neuroimaging and other AD biomarkers	Biological and neuroimaging markers to assess efficacy of intervention, body composition changes on frailty and cognitive decline
Current status	Ongoing, will be completed in 2015	Ongoing, intervention will be completed in 2014 when a 5 year extended follow up will begin	Ongoing, will be completed in 2014 and then undergo 2 year extended follow up

Abbreviations: preDIVA, prevention of dementia by intensive vascular care; GP, general practitioner; SC, standard care; IVC, intensive vascular care; ALDS, AMC linear disability scale; MI, myocardial infarction; GDS, geriatric depression scale; MMSE, mini mental scale examination; VAT, visual association test; FINGER, finnish geriatric intervention study to prevent cognitive impairment and disability, CAIDE, cardiovascular risk factors; aging and incidence of dementia study; mNTB, modified neuropsychological test battery; MAPT, the multidomain alzheimer prevention trial; IADL, instrumental activities of daily living.

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in AD are symptomatic, and no new drugs have been introduced since 2002. The shift toward pre-symptomatic/pre-dementia AD stages has narrowed the gap between prevention and treatment RCTs. Prevention is now increasingly highlighted as the main therapeutic goal, and evidence-based effective interventions are urgently needed.

The dementia risk scores have provided practical tools to estimate the risk of dementia and target interventions for those at the highest risk. CAIDE risk score has been recently validated in a multi-ethnic population and is currently tested in the FINGER intervention study. Further refining and validating of the risk scores in different target populations, such as samples from memory clinics and general population-based samples is crucial and will help to better plan further intervention studies. Given that dementia, cardiovascular risk factors, stroke, and diabetes mellitus–all major public health problems – share several risk factors, joint risk scores and integrated interventions could be planned. For cardiovascular diseases and diabetes prevention, there are already several successful studies/initiatives indicating the efficacy of interventions targeting lifestyle and vascular risk factors [94]. For dementia/AD, validation of the observational findings with large intervention studies is still needed and experiences from previous preventive programs in other chronic diseases should be utilized.

Results from the ongoing/planned dementia prevention studies (e.g. FINGER, MAPT, pre-DIVA, HATICE) can open new avenues for interventions in persons at risk of cognitive decline/dementia. Through multi-domain interventions, the studies will provide healthy lifestyle recommendations for preventing cognitive decline and disability, and information on how adherence to lifestyle changes can be improved. Such recommendations are urgently needed for health education and clinical practice. Full implementation of the life-course approach is more challenging because of the difficulties in conducting RCTs over many decades. Also, ethical issues need to be recognized when designing RCTs (e.g. vascular risk factors cannot be left untreated in the control group). Thus, evidence about some early life/midlife vascular risk factors relies on rigorous observational studies.

Supporting the observational findings concerning modifiable risk factors for dementia/AD, some recent studies have indicated a decline in dementia prevalence and/incidence [95,96]. As an example, recent data from the Medical Research Council Cognitive Function and Aging Study (MRC CFAC) in three areas of England has identified that there has been a decline in the prevalence of dementia taking place during the past two decades among individuals 65 years and older. This 1.8% decline in prevalence of dementia in this older population would be observed in future generations if putative efforts are employed in effective primary prevention of risk factors for dementia in conjunction with an improvement in protective factors such as better levels of education and more physical activity [97]. Given the rapid aging of the population and the fact that obesity, diabetes and sedentary lifestyle have been reported to increase in several countries, it is important to continuously follow the trends. Identification of efficacy of preventive strategies to prevent or postpone dementia/AD onset would have a major impact on patients, caregiver, public health and health economic.

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