Alzheimer's Disease International

# Policy brief

# Risk factors for dementia

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**Policy recommendations by Alzheimer's Disease International**

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# Policy brief - Risk factors for dementia

## Introduction

On the 19th and 20th of September 2011 the United Nations General Assembly met at the level of Heads of State and Government to discuss the global impact of non-communicable diseases (NCDs). In article 18 of the adopted political declaration[1] mental and neurological disorders, including Alzheimer's disease, are mentioned as important causes of morbidity and contributing to the global NCD burden and for which there is a need to provide equitable access to effective programmes and health-care interventions. The declaration states the importance of recognising that these diseases share common risk factors namely tobacco use, harmful use of alcohol, an unhealthy diet, and lack of physical activity that can benefit from common responses to NCDs. Even some NCDs themselves, such as cardiovascular disease, are suspected risk factors for dementia. Consequences of poor health are personally, socially and financially devastating. The World Economic Forum (WEF) recently published a report[2] identifying NCDs as one of the top threats to worldwide development, as they are driving up health-care costs, disabling workers, and burdening households with financial tolls. The medical and social costs for mental health and dementias were not included in this report. For dementia alone, Alzheimer's Disease International (ADI) estimated the global cost in 2010 at $604 billion or 1% of the global GDP[3]. The economic and social impact of dementia will be enormous as the number of people living with dementia worldwide will increase from 35.6 million in 2010 to 65.7 million by 2030 to 115.4 million in 2050. Nearly two-thirds live in low and middle-income countries, where the sharpest increases in numbers are set to occur.

The number of individuals with dementia is increasing worldwide and there is growing evidence that suggests that a number of lifestyle and health factors may substantially reduce the risk of developing dementia. Combining efforts to tackle the global burden and threat of non-communicable disease is important and will contribute to efficient use of resources and funds. The goal of this paper is to provide information to set priorities for the promotion of risk factor reduction as a follow up on the NCD Summit.

First, an overview of conclusions from recent literature reviews on risk factors and prevention of dementia will be given followed by highlighting some of the generic difficulties and limitations in the field of dementia risk factor and prevention research. The second part of the paper presents an overview of the scientific evidence available on modifiable risk factors for Alzheimer's and other dementias and an overview of ongoing dementia prevention studies. The paper concludes with policy recommendations based on this overview as proposed by Alzheimer's Disease International.

## Conclusions from reviews on risk factors and prevention of dementia

*Systematic review of health behavioral risks and cognitive health in older adults* (Lee et al, International Psychogeriatrics 2010)[4]: A review of studies on community representative samples aged 65+, with prospective cohort design and multivariate analysis. The outcome was cognitive health - ranging from cognitive decline to dementia and the health behaviours included physical activity, smoking, drinking alcohol, body mass index and diet and nutrition. The studies were categorised from quality level A to C

based on a variety of criteria and only A quality studies were considered in the analysis. The review demonstrates accumulating evidence supporting health behavioural effects in reducing the risk of cognitive decline and dementia. Results indicate potential benefits of healthy lifestyles, especially in midlife, in protecting cognitive health in later life.

*Targets for the prevention of dementia* (Middelton and Yaffe, Journal of Alzheimer's Disease 2010)[5]: Cognitive, physical and social activity, vascular risk factors and diet are associated with the likelihood of dementia in many observational studies however the best strategy to prevent dementia is still unclear. Given that risk factors are largely correlated it may be that living a healthy, engaged life is the best way to prevent dementia and that one single factor is insufficient to prevent the disease.

*National Institutes of Health State-of-the-Science Conference Statement - Preventing Alzheimer Disease and Cognitive Decline* (Daviglus etal, Annals of Internal Medicine 2010)[6]: Review of the literature did not find any evidence of even moderate scientific quality to support the association of any modifiable factor with reduced risk for Alzheimer's disease. Efforts to examine these associations to date are hampered by numerous problems, including limited follow up, methodological differences across studies in measurement of exposures and over reliance on single measurements of exposure variables[7].

*The projected effect of risk factor reduction on Alzheimer's disease prevalence* (Barnes & Yaffe, The Lancet Neurology 2011)[8]: The article provides a summary of evidence regarding seven potentially modifiable risk factors for Alzheimer's disease: diabetes, midlife hypertension, midlife obesity, present smoking, depression, cognitive inactivity or low educational attainment and physical inactivity. A 25% reduction in all seven examined risk factors could reduce the number of cases of Alzheimer's disease by up to 3 million worldwide. Fratiglioni and Qui (2011) argue that the estimates reported in this review are only theoretical because all the projected effects are based on observational studies and the Alzheimer's disease diagnosis is uncertain[9].

*Dementia Etiology and Epidemiology - a systematic review* by The Swedish Council on Technology Assessment in Health Care[10] (SBU, 2008): Based on an extensive review of the literature the authors conclude that: Age is the primary risk factor for developing dementia (Evidence Grade 1); Among people older than 85, a greater percentage of women than men have Alzheimer's disease (Evidence Grade 2); Although known genetic changes that cause Alzheimer's disease are rare, the Apolipoprotein E (ApoE) e4 allele is known to increase the risk (Evidence Grade 1); Currently there is no specific preventive treatment for dementia, but blood pressure monitoring in middle age reduces the risk of developing it later in life (Evidence Grade 2); Treatment with antihypertensive medication reduces the risk of developing vascular dementia later in life (Evidence Grade 2); The progression of dementia can be delayed among older people who continue to lead active lives (Evidence Grade 2).

*Formative Assessment to Inform the Revision of the National Public Health Road Map for the Maintenance of Cognitive Health: A review of Recent Literature on Protective Factors for Cognitive Health* (Reed and Johnston, 2010): Conclude that the evidence is most consistent to support the protective effects of cognitive engagement, physical activity and healthy eating related to lower fat intake and the adverse contribution of vascular risk of diabetes. Protective factors viewed to have relatively strong evidence

include the influence of general healthy eating particularly for the Mediterranean Diet and the specific risk of high blood pressure. Regarding vascular risk and weight conclusion cannot be drawn due to inconsistency of findings.

**Difficulties and limitations in dementia risk factors and prevention research**

The review conclusions reflect controversy in opinions reflecting the generic difficulties and limitations in field of dementia risk factor and prevention research.

The 'golden standard' of a randomised controlled clinical trial is unfeasible to conduct for many exposures. Assigning for example a head trauma, smoking or long-term diets is unethical and undoable. Therefore observational studies, meaning studies in which the investigators have no control over the exposure status of their participants, are the main study design of choice. When properly designed, conducted and analysed both observational and prevention trials can produce valid findings. However observational cohort studies do have their weaknesses, particularly confounding and reverse causation. Confounding refers to the situation where other factors can be related to both the exposure and the outcome, leading to a spurious association between the two[11]. In the situation of reverse causality the early dementia symptoms (for example, being less active) actually cause the risk factor rather then the risk factor causing the disease. Another challenge in conducting valid dementia risk factor and prevention research is that many relevant exposures have a long latency period exerting an influence on the underlying mechanisms that increase the risk of dementia and the onset of dementia in late life. These limitations of observational studies are as valid for research of risk factors of dementia as for other NCDs. Other designs described to be useful in assessing the cause of chronic multifactoral diseases are population based follow-up studies and evaluating evidence from a life course perspective but these have rarely been done[12]. It is beyond the scope of this review to assess all articles individually on the methodological quality of their studies. The articles referred to have been published in independent peer-reviewed journals on whose quality of scientific judgment this paper relies. A specific challenge that needs to be addressed when comparing dementia studies is the lack of consistent and uniformly applied definitions and highly reliable consensus based diagnostic criteria for cognitive decline, mild cognitive impairment, Alzheimer's disease and other dementias. Research has shown a range of dementia-associated brain abnormalities from pure vascular lesions at one end to pure Alzheimer's pathologies at the other, with most dementia cases being attributable to both vascular disease and neurodegeneration[13]. For this review we use the disease definitions as proposed by each individual research study and rely on the validity of the independent researcher's diagnostic and peer reviewed criteria.

Furthermore, to access the impact of existing public health interventions it is necessary to monitor changes in incidence over time and take into consideration that all suggested risk factors and linked prevention strategies are already being prioritised for other NCDs.

## Overview of risk factors for dementia

Non-modifiable risk factors:

Age: greatest risk factor
Genes
Family history
Down's syndrome

Modifiable risk factors:

Vascular risk factors: People with vascular risk factors are at higher risk not only for vascular dementia (VaD) but also for Alzheimer's disease (AD). Both share risk factors (such as smoking, high cholesterol, hypertension, physical inactivity, obesity and diabetes) and pathological features (as inflammatory markers and protein misfolding) with cardiovascular disease[14]. The construct of Vascular Cognitive Impairment (VCI) has been introduced to capture the entire spectrum of cognitive disorders associated with all forms of cerebral vascular brain injury ranging from mild cognitive impairment through to fully developed dementia. Dysfunction of the neurovascular unit and mechanisms regulating cerebral blood flow are likely to be important components of the pathophysiological processes underlying VCI[15].

Current smoking: Smoking is a well-recognised cardiovascular risk factor and mediated by oxidative stress, inflammation and atherosclerosis known to increase the risk for neurodegeneration[16]. A meta-analysis of 19 prospective studies assessed the association of smoking with dementia and cognitive decline and concluded that elderly smokers have increased risks of dementia and cognitive decline[17]. The same study found that former smoking is not associated with AD risks. Lee et al (2010) found 4 observational studies of A quality and all 4 studies reported on the negative effect of smoking on dementia and AD. It was predominantly current smoking, not past smoking, that increased the risk of dementia and the association was stronger the higher the number of pack-years. Rusanen et al (2010) analysed a large multiethnic cohort to investigate the long-term association between the amount of smoking in midlife and the risk of dementia, AD and VaD. Their study suggests that heavy smoking in middle age increases the risk for dementia, AD and VaD for men and women across different race groups[18]. Barnes and Yaffe (2011) calculated that nearly 14% (4.7 million) of AD cases worldwide are potentially attributable to smoking. A 10% reduction in smoking prevalence could possible lower AD prevalence by about 412,000 cases. A 25% reduction in smoking prevalence could potentially prevent more than 1 million cases worldwide[19].

Midlife obesity: The findings on obesity and dementia are difficult to interpret. Lee et al (2010) found 6 level A quality studies. Four of the six studies found being overweight or obese to contribute to incident dementia and cognitive decline but they varied in outcome measures for dementia, AD and VaD and showed gender and age differences. A recent article by Sellboom[20] concludes that to date there is evidence for increased dementia risk, specific cognitive impairment, and corresponding neurological alterations in obese persons across the lifespan, as well as preliminary evidence that obesity-associated cognitive dysfunction may be reversible with weight loss. Barnes and Yaffe (2011) conclude on the basis of the available evidence that there is an association

between midlife obesity and increased risk AD. They calculated that about 2% of AD cases are potentially attributable to midlife obesity taking into consideration that rates vary between gender (higher in women) and country. A 10% reduction would prevent 67,000 cases worldwide, a 25% reduction about 167,000.

Midlife hypertension: High blood pressure is one of the most important controllable risk factors for stroke, which in turn can result in vascular dementia. Also there is increasing evidence of an association between AD and hypertension. The AlzRisk AD Epidemiology Database of the Alzheimer Research Forum on blood pressure[21] working in parallel with Powell et al[22] found that the available data fail to indicate a consistent relationship between blood pressure and AD. While the data suggest that there may be an age-dependent relationship between blood pressure and AD, i.e. hypertension may be harmful in midlife and protective in late-life, the current data are limited and are therefore insufficient to draw firm conclusions. Few studies have specifically considered the association between midlife blood pressure and AD, and it is possible that that bias (in particular reverse causation or selection bias) might account for any protective association in late-life. Despite the uncertainty regarding the relationship between blood pressure and risk of AD, AlzRisk does promote that the benefits of blood pressure control on cardiovascular risk are sufficient to justify current treatment standards. Barnes and Yaffe (2011) conclude that given the available literature from epidemiological studies and randomised controlled trials (RCTs) only midlife, not late life hypertension is associated with an increased risk of AD and dementia. According to their calculations about 5% (1.7 million) of AD cases worldwide are potentially attributable to midlife hypertension. A 10% decrease in midlife hypertension prevalence would reduce the number of AD cases by 160,000 and a 25% reduction would be associated with 400,000 fewer AD cases[23].

Midlife hypercholesterolemia: Evidence is growing that monitoring cholesterol levels is just as important for a person's brain as for his or her heart[24]. A number of observational trials have examined whether stain therapy might reduce the risk of AD and dementia but the results were not convincing[25].

Diabetes Mellitus (DM): The AlzRisk AD Epidemiology Database of the Alzheimer Research Forum on diabetes mellitus[26] presents a modest number of reports whose results, taken collectively, suggest an association between DM and increased risk for both AD and other dementias. However they write, there are methodological issues as few reports distinguish type 1 from type 2 diabetes and some informational gaps and ambiguities remain. A review by Biessels etal (2006) identified 14 eligible longitudinal population-based studies of variable methodological quality. They concluded that the risk of dementia is, in general, increased in patients with diabetes mellitus and this increased risk seems to include both Alzheimer's disease and vascular dementia—although the limitations of clinical diagnostic criteria in the classification of dementia by pathological subtype should be considered, especially in a complex disorder such as diabetes. Therefore, rather than focusing the discussion on which subtypes of dementia are associated with diabetes, it might be more pragmatic to try and identify which diabetes-related factors, or comorbid conditions, primarily drive the association between diabetes and dementia. Vascular disease and alterations in glucose, insulin, and amyloid metabolism may underlie the pathophysiology, but which of these mechanisms are clinically relevant is unclear. Pasqueler (2006) found evidence in prospective and cross-sectional studies for an elevated risk of both vascular dementia and AD in patients

with type 2 DM, albeit with strong interaction of other factors such as hypertension, dyslipidaemia and ApoE genotype. This study also found DM type 2 to be an independent predictor of post-stroke dementia[27]. A review by Reed and Johnston (2010) commissioned by the Alzheimer's Association and CDC found 8 studies considering diabetes (the review does not distinguish between type 1 and type 2) a potential risk factor for dementia of which 6 provided supporting evidence (all large longitudinal studies) and 2 found no association (a cohort study and small retrospective study). They conclude that despite the evidence of the studies that found no association, on balance the results of the supportive studies provide strong evidence for a link not only to cognitive function and cognitive decline but also vascular dementia and Alzheimer's disease[28]. Barnes and Yaffe (2011) found several studies to show an association between diabetes and an increased risk of AD and dementia but not all showed a significant increase. They calculated that if diabetes prevalence were 10% lower about 81,000 cases and if 25% lower 203,000 cases of AD could be prevented. Biessels (2006) concludes that there is still a need for studies on large population-based cohorts of elderly people with diabetes and longitudinal studies of at-risk populations that examine the progress of vascular disease, metabolic syndrome, diabetes, and cognition[29].

Metabolic syndrome: Vascular risk factors often occur in clusters. A cluster of 3 or more vascular risk factors (hypertension, hyperglycemia, abdominal obesity and/or low high density lipoprotein) is referred to as metabolic syndrome. People with metabolic syndrome were found to have augmented risk of cognitive decline and each vascular risk appeared to be additive[30]. Several possible mechanisms may explain an association between the metabolic syndrome and cognitive decline including micro-vascular and macro-vascular disease, inflammation, adiposity, and insulin resistance[31]. Interestingly one study found that metabolic syndrome was associated with slower cognitive decline in the oldest old. Why this is so is unclear but Middleton (2010) suggests this may reflect selective survival in the very old. Luchsinger (2009) also makes the case that the potential mechanisms linking the continuum of adiposity, hyperinsulinemia, and type 2-diabetes are multiple, overlapping, and highly correlated. Therefore to elucidate that a single mechanism is the culprit is difficult and public health interventions would impact all potential mechanisms. That is, weight loss through lifestyle interventions or medications alters adipokine activity, improves hyperinsulinemia, inflammation, glucose tolerance, blood pressure, lipids, and the risk of cerebrovascular disease[32].

Physical inactivity: Multiple studies show a relationship between physical *activity* and the development and progression of dementia. These findings suggest that midlife physical activity may be associated with a reduced risk of AD or vascular dementia in later life[33]. Even mild activities, such as walking, were found to be protective. In Lee et al's review (2010), of 9 observational studies rated of level A quality, 8 exhibited significant associations between physical (in)activity and dementia, AD and cognitive decline[34]. Physical activity is thought to enhance cognitive function by increasing cardiovascular fitness and cerebral perfusion and possibly by stimulating neurogenesis[35]. The AlzRisk AD Epidemiology Database of the Alzheimer Research Forum on physical activity[36] concluded that overall, the evidence suggests a modest protective role for physical activity in the development of AD and cognitive decline. Some ambiguities remain regarding the association; areas warranting further research include the optimal duration, intensity, timing during lifespan, and the durability of the effect of physical activity. Nevertheless, physical activity is a potentially modifiable protective factor with

established collateral benefits, such as the prevention of cardiovascular disease and diabetes. Barnes and Yaffe (2011) calculated that a 10% reduction in prevalence of physical inactivity could potentially prevent about 380,000 AD cases worldwide and a 25% reduction potentially around a million cases of AD. The Alzheimer Society of Canada examined the impact of an intervention that focuses on increasing physical activity by 50% for all Canadians (65+) without dementia who are already moderately to highly active. This scenario shows a significant reduction in the number of individuals diagnosed with dementia in the short and long term[37].

Diet and Nutrition: Numerous studies investigated the effect of various nutrients on cognition. Lee et al (2010) found 15 studies that they categorised as level A. Mediterranean diet, vegetables and fatty fish consumption were found to lower dementia risk. Three studies found a negative effect for high saturated fat intake. Studies on Vit E, niacin and folate were inconsistent. No association was found for Vit C, carotenes, Vit B12 and flavonoids. Tangney et al (2011)[38] investigated whether adherence to a Mediterranean dietary pattern or to the Healthy Eating Index–2005 (HEI-2005) is associated with cognitive change in older adults. They concluded that the Mediterranean dietary pattern as captured by the MedDiet scoring system may reduce the rate of cognitive decline with older age.

Sodium intake: Sodium intake is of great interest due to its association with blood pressure regulation and heart disease. National and international groups, including the World Health Organization (WHO), have set out to promote reductions in sodium intake at the population level to reduce the incidence of cardiovascular disease. Fiocco etal (2011) [39] assessed the association between sodium intake and global cognitive function over 3 years of follow-up in older adults (a subgroup of the Canadian NuAge cohort). This study suggests that sodium intake reduction, especially in low physical activity older adults, may further improve brain health in late life. Importantly, the present findings suggest that the impact of sodium intake on cognitive function may be dependent on level of physical activity. They conclude by emphasising the importance of addressing multiple lifestyle factors rather than a single domain effect on brain health.

Alcohol consumption: Moderate consumption of wine (250–500 ml/day versus a smaller or larger amount) is found to be associated with a reduced risk of subsequent dementia, including Alzheimer's disease[40]. The idea is that by increasing HDL cholesterol levels and fibrinolytic factors that lower platelet aggregation, insulin sensitivity is enhanced, reducing inflammatory response and preventing oxidative damages in the brain[41]. In Lee et al's review (2010) several studies demonstrated beneficial effects of moderate drinking though there were differences between gender and ApoE4 carriers. Harmful effects of alcohol have also been noted. A U-shaped relationship was suggested where non-drinkers and frequent drinkers showed an increased risk.

Depression: Barnes and Yaffe (2011) assessed several studies looking at the relationship between depression and dementia and found that people with a history of depression had about a two-time risk of dementia compared to those without depression. They also describe several RCTs finding that treatment of depression in elderly adults results in improved cognitive function though some show no improvement at all and typically the results remain below normal levels in these patients. Additionally some types of anti-depressant medication (especially those with anti-cholinergic properties) can worsen cognitive function. According to their calculation more then 10%

of AD cases are potentially attributable to depression. A 10% reduction will result in 326,000 fewer AD cases worldwide and a 25% reduction could prevent 827,000 AD cases.

Cognitive inactivity or low educational attainment: Barnes and Yaffe (2011) identified several reviews and meta-analyses assessing so-called 'brain reserve'. Brain reserve refers to the capacity of the brain to withstand the effects of pathological changes by recruiting alternative neurological pathways. The review concludes that the risk for dementia is lower for those with higher education, occupational attainment, intelligence or IQ and mentally stimulating leisure activities. These observational findings are supported by results from RCTs, which found that cognitive interventions in healthy older adults are associated with domain-specific improvements in cognitive function. Based on these findings they calculated that a 10% reduction would lower the prevalence of AD by 534,000 cases worldwide and a 25% reduction could lower the prevalence by 1.375 million[42].

Other factors (low quality or controversial evidence):
Low social support: loneliness in individuals age 65+ has been linked to a higher risk of dementia[43]
Estrogens
Non-Steroid Anti Inflammatory Drugs (NSAIDs)
Coronary artery bypass surgery
Exposure to environmental toxins
Head trauma in early adulthood
Gender

Clustering of multiple risk factors increasing dementia risks further imply synergistic effects[44].

**New risk factors which have been identified and which need to be addressed**

Apart from the previously described risk factors, which have been identified and examined, to a greater or lesser extent, there are other risk factors for Alzheimer's disease and cognitive decline more generally which have been clearly identified, but not yet addressed in controlled studies. An example is subjective cognitive impairment (SCI, also referred to as subjective cognitive complaints), which occurs in the absence of measurable cognitive impairment on either psychological tests or clinical examinations. SCI has been clearly shown in several recent studies to be an early risk factor for cognitive decline and / or dementia, generally Alzheimer's disease[45, 46, 47]. In a recent study, the hazard ratio for increased cognitive decline in persons with subjective cognitive impairment, after controlling for socio-demographic and other variables, was 4.5[47]. Furthermore, this condition of subjective cognitive impairment has been shown to be prevalent even in some of the most remote regions of the world[48]. Addressing this condition may provide an opportunity for substantial dementia and Alzheimer's disease reduction worldwide.

## Ongoing dementia prevention studies

Currently several large European dementia prevention studies are targeting cardio-vascular and lifestyle related risk factors:

- The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER)
- The Prevention of Dementia by Intensive Vascular Care (PreDIVA)
- The Multidomain Alzheimer Preventive Trial (MAPT)

By collaborating in the newly founded 'European Dementia Prevention Initiative' (www.edpi.org) longitudinal data in over 6,000 elderly people without dementia becomes available and will allow a comprehensive exploration of optimal target population, intervention and outcome measures, which are currently unknown. The combined scientific and logistic experience of the three research groups can set the stage for future large-scale European studies.

## ADI Policy Recommendations

Randomised control trials (RCTs) are considered to provide the strongest evidence for prevention or reducing risk factors in chronic disease. However, such trials are difficult to conduct because of the long time between exposure to risk factors and the onset of the disease, as well as for ethical and practical reasons. Not unlike other chronic diseases, dementia risk factor and prevention research therefore relies mainly on well-constructed observational cohort studies. When properly designed, conducted and analysed both observational and prevention trials can produce valid findings though potential weaknesses, as confounding and reverse causation needs to be taken into account.

More research is needed to investigate strategies to maintain cognitive function in individuals at risk for decline, identify factors that may delay the onset of Alzheimer's disease and other dementias among those at risk and identify factors that may slow the progression among people in whom the condition is already diagnosed so public health campaigns targeted at risk factor modifications can be developed.

With the current knowledge, we recommend reducing risk factors for dementia by increasing access to education and measures against risk factors for vascular diseases, diabetes, (midlife) hypertension, obesity, smoking and physical inactivity. Many of these measures relate to suggested policies for other non-communicable diseases: implementation of policies to reduce smoking, salt reduction, combination therapy for cardiovascular diseases and measures to stimulate physical exercise.

We also recommend more research into the prevalence and incidence of dementia in both higher and lower and middle-income countries, so we can monitor the increase of the global dementia epidemic and measure the impact of policies and programmes[49].

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