



**Alzheimer's Disease  
International**

*The global voice on dementia*

# World Alzheimer Report 2014

## Dementia and Risk Reduction

AN ANALYSIS OF PROTECTIVE AND MODIFIABLE FACTORS

**EXECUTIVE SUMMARY**



SUPPORTED BY



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# Foreword

Dementia, including Alzheimer's disease, remains one of the biggest global public health challenges facing our generation. The number of people living with dementia worldwide today is estimated at 44 million, set to almost double by 2030 and more than triple by 2050. The global cost of dementia was estimated in 2010 at US \$604 billion, and this is only set to rise.

Given this epidemic scale, and with no known cure, it's crucial that we look at what we can do to reduce the risk or delay the onset of developing the disease. We believe that Alzheimer's disease and other forms of dementia must become a national and international public health priority. Governments must develop adequate strategies to deal with the epidemic holistically – including tackling both reduction in risk for future generations, and adequately caring for people living with the condition and supporting their friends and family.

As the only worldwide international federation of Alzheimer associations and global voice on dementia, and the largest international provider of specialist dementia care, we are committed to changing the way the world thinks about dementia. One way we will do this is by campaigning for national dementia plans which have greater emphasis on improved brain health, as well as enabling those who have dementia to live well.

To make this happen, and lessen the impact of dementia on individuals and society, there is enormous possibility in a comprehensive approach from all sectors, including health, business, academia, foreign affairs, NGOs and others, to work together to reduce the risks associated with dementia, as well as promote the interventions to manage the quality of life of those living with it and their relatives.

Our World Alzheimer Report 2014 examines the latest existing evidence associated with dementia risk factors, ranging from smoking to socialising, and provides an analysis of interventions that have been trialled to create change around the world. We believe this is an invaluable resource. It provides the basis upon which to campaign for change, and opens the door for more research in the area.

We're committed to addressing global dementia risk reduction and care – tackling one of the toughest challenges in healthcare, together.



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# **World Alzheimer Report 2014**

## **Dementia and Risk Reduction**

**AN ANALYSIS OF PROTECTIVE AND MODIFIABLE FACTORS**

### **EXECUTIVE SUMMARY**

This brief report provides a synopsis of the findings of detailed evidence-based reviews presented by the authors in the full World Alzheimer Report 2014. In the interests of brevity, all tabulated data and references from the full report have been omitted in this summary version. The full version of the report includes, as well as data and references, a more detailed exposition and discussion of results. It can be downloaded from [www.alz.co.uk/worldreport2014](http://www.alz.co.uk/worldreport2014)

## **The Global Observatory for Ageing and Dementia Care**

The Global Observatory for Ageing and Dementia Care, hosted at the Health Service and Population Research Department, King's College London, was founded in 2013.

Supported by Alzheimer's Disease International, and King's College London, the Observatory has a tripartite mission:

1. To build upon ADI's 10/66 Dementia Research Group program of population-based and intervention research in low and middle income countries, maximising the impact that research findings from our data can have upon policy and practice.
2. To developing, evaluate, and promote primary care and community interventions for people with dementia.
3. To synthesise global evidence for policymakers and public, in particular, continuing and developing our role in the preparation of high impact evidence-based reports for Alzheimer's Disease International (World Alzheimer Reports 2009, 2010, 2011 and 2013, and Nutrition and dementia), the World Health Organization (Dementia: a public health priority, 2012) and other relevant intergovernmental organisations.

The World Alzheimer Report 2014 was independently researched and authored by Prof Martin Prince, Prof Emiliano Albanese, Dr Maëlynn Guerchet and Dr Matthew Prina on behalf of the Global Observatory for Ageing and Dementia Care, with contributions from others as listed. The evidence reported in Chapters 1-6, and the inferences drawn, are the responsibility of the authors alone. The key messages were developed by Alzheimer's Disease International and the Global Observatory.

# Contents

## CHAPTER 1

### **Background** 4

Dementia 4

Epidemiological concepts 4

Prevention 4

Life course approach 5

## CHAPTER 2

### **Developmental and early-life risk factors** 6

Leg length and head circumference 6

Early-life events 6

Education and occupation 6

## CHAPTER 3

### **Psychological factors** 7

Depression 7

Psychological distress: personality and life events 8

Sleep disorders 8

## CHAPTER 4

### **Lifestyle** 9

Smoking 9

Alcohol 9

Physical activity 10

Cognitive stimulation 10

Diet 10

## CHAPTER 5

### **Cardiovascular risk factors** 12

Hypertension 12

Obesity 12

Cholesterol (Dyslipidaemia) 13

Diabetes 13

## CHAPTER 6

### **Summary and conclusion** 14

Summary of findings 14

Contextualising these findings with other research 18

Implications - Where do we go from here? 19

## CHAPTER 1

# Background



### Introduction

- Dementia is a syndrome due to disease of the brain, usually chronic, characterized by a progressive, global deterioration in intellect including memory, learning, orientation, language, comprehension and judgment. It mainly affects older people but, 2 to 10% of all cases are estimated to start before the age of 65 years. After this, the prevalence doubles with every five year increment in age. Dementia is one of the main causes of dependence and disability at older ages.
- Dementia syndrome is linked to a very large number of underlying brain pathologies. Alzheimer's Disease (AD), vascular dementia (VaD), dementia with Lewy bodies and frontotemporal dementia are the commonest. Senile plaques and neurofibrillary tangles have been then recognized to be the two core pathological hallmarks of Alzheimer's Disease. The second common form of dementia after AD, vascular dementia (VaD) is characterized by multifocal or diffuse lesions (lacunes to microinfarcts) resulting from cardiac, and local large and small vessel disease, which affect neural networks.
- Clinico-pathological correlation studies examining the agreement between the diagnosis made in life and the pathology evident in the brain post-mortem have tended to indicate that mixed pathologies are much more common than 'pure' forms of dementia (particularly for AD and VaD, and AD and dementia with Lewy bodies).
- Brain pathology likely starts decades before the onset of clinical dementia, which could be seen as a transition point in the accumulation of brain damage over time. Modifiable risk factors may influence the rate of development of the underlying neuropathologies, or they may counteract in various ways the detrimental effects of brain pathology on cognitive function.

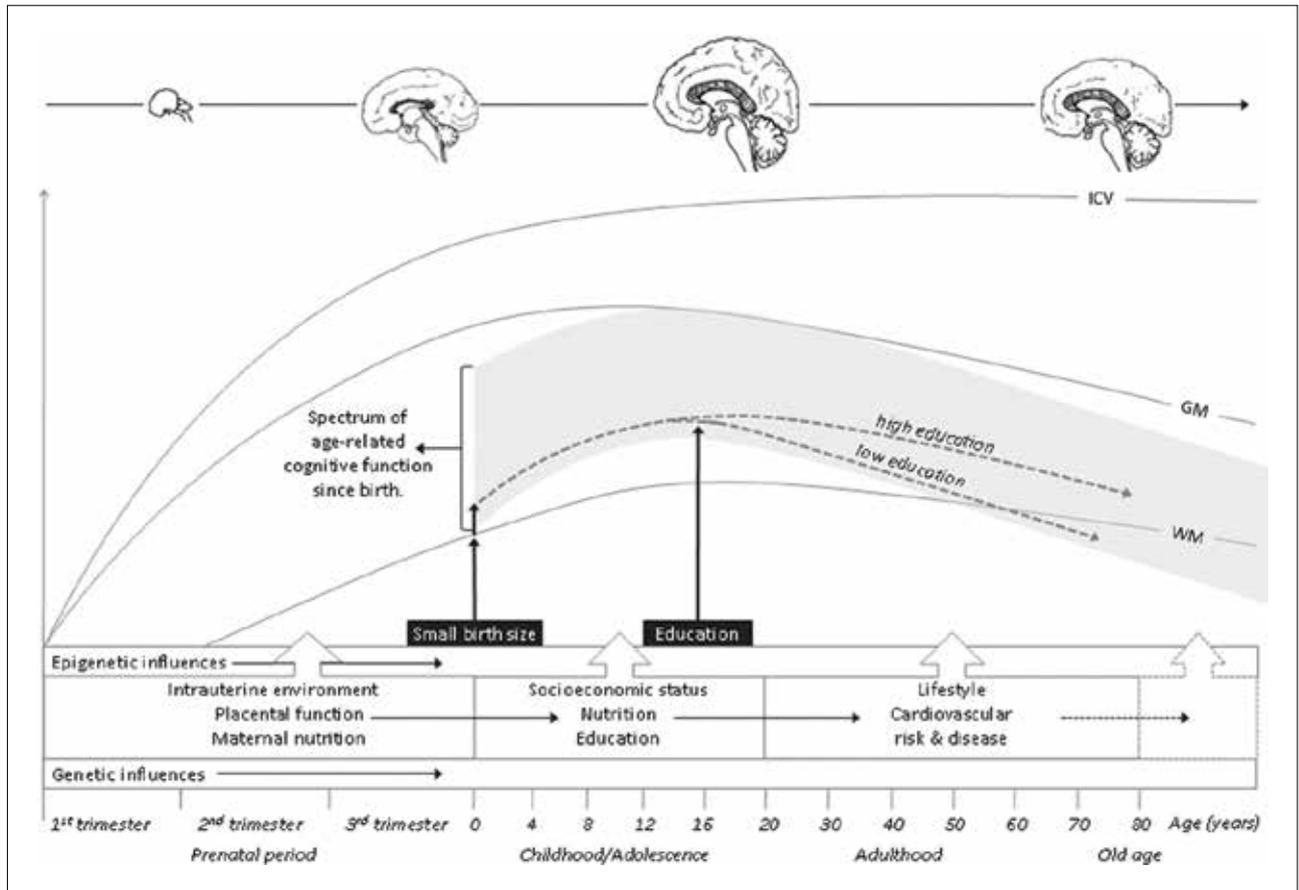
### Epidemiological concepts

- Epidemiology is the discipline that studies the distribution, the causes and impact of ill health in populations. Epidemiology is mainly concerned with the estimation of the number of those affected by a certain health condition or trait in the population, and with the identification of risk factors for disease. It aims to inform policy decisions including preventive strategies based on knowledge about causes.
- Two main types of study designs are used to investigate the causes of diseases: observational studies where the onset of a disease in a population is studied as a function of exposure to a hypothesised cause, and experimental studies (like randomized controlled trials (RCTs)) which are conducted by randomly exposing or not, two groups of people to an intervention (typically a treatment, like a drug, or the removal of a risk exposure e.g by smoking cessation programs) to determine whether disease incidence varies under experimentally controlled conditions. Experimental studies are considered to provide much stronger evidence about causes than observational studies, although observational studies are an indispensable investigational tool, not least because in many cases it would not be ethical or practical to manipulate a potential risk exposure under experimental conditions.

### Prevention

- Dementia has an insidious onset typically characterized by an initial subtle decline in one or more cognitive functions including memory and reasoning. Because the mechanisms that link dementia-related brain damage to the expression of dementia symptoms are not fully understood, prevention of dementia is commonly conceived as the delay of the clinical onset of the disease rather than a slowing or avoidance of the development of the underlying neuropathology. An average five year delay in the age of onset would tend to reduce population prevalence by 50%, hence greatly reducing its impact in the general population.
- The current focus on modifiable risk factors is justified by their potential to be targeted for prevention. However, non-modifiable risk factors (age, gender and genetic factors) are also very important. Although at present genetic factors cannot be modified they might be used to identify those at higher risk who may be targeted for subgroup prevention programs.

Figure 1.1  
Hypothesized model of the origins and life course of brain aging – From Muller M et al. 2014



## Life-course approach

- Certain risk factors may operate at critical periods with varying strengths of association observed at different time periods. Even the direction of association can vary over time, as a factor that was a risk factor for the onset of dementia in turn becomes influenced by the dementia disease process (reverse causality) before and after the clinical onset of the condition.
- Brain and cognitive reserve, developed early in life, and consolidated in midlife may buffer the expression of symptoms of dementia in the presence of neurodegenerative disease.
- Dementia risk and protective factors are best studied using a life course approach (see model proposed by Muller et al. (FIGURE 1)). The key purpose of life course epidemiology is to provide clues to the aetiology of diseases, building and testing theoretical models of pathways between exposures across the life course and outcomes in late life. The timing and duration of exposures are considered key. Long follow ups are needed to relate lifelong exposures to dementia risk in late-life, which complicates the conduct of such research.

## CHAPTER 2

# Developmental and early-life risk factors



### Introduction

- Possible early-life risk factors include perinatal factors (birth weight, intrauterine environment, number of siblings and birth order) and also factors influencing the growth and development of the brain or body, such as nutrition. Socio-economic conditions, environmental enrichment and education in the first years of life have also been suggested as having an effect on the risk of dementia.

### Leg length and head circumference

- Brain reserve, the number of neurons and synapses (for which brain size might be a marker) may buffer the effects of dementia related neuropathology and explain the variability of the expression and severity of dementia clinical symptoms in people with the same levels of neuropathology. Conditions during foetal life and the first two years after birth are important for determining final brain size. Measurement of skull circumference made in adulthood reflect the size of the brain in early-life, and skull dimensions can be considered as a stable marker.
- Persistent insufficient nutrient intake in early infancy slows growth and causes low height for age that results in shorter legs for total height. Having shorter legs relative to total height in adulthood is a valid proxy of early life inadequate nutritional level.
- The association between head circumference, leg length and dementia has been investigated in few

studies to date. The little available evidence seems consistent, showing an association of shorter legs and smaller heads with prevalent and incident dementia in diverse geographical regions of the world.

- Early-life development therefore appears to be of possible relevance to the risk of dementia and Alzheimer's disease. Weaknesses in the current evidence base include the paucity of prospective studies, and lack of long-term cohort studies with contemporary assessment of developmental indicators in childhood.

### Early-life events

- Experiencing negative events might cause stress reactions, which could affect the brain structure through a complex neuro-endocrine process regulated by the 'HPA axis'. Evidence is less extensive for the first period of life, and often focused on the death of a parent during childhood. Such stressors have been shown to impact health into adulthood and to predict decreased longevity.
- Evidence from longitudinal studies shows an increased risk of dementia or Alzheimer's disease for people who experienced early-parental death (and/or a crisis after early parental death), with the possibility of different critical periods for paternal and maternal death. The association seems to be weaker when the widowed parent remarries during the index person's childhood. However, the evidence relies for now on very few longitudinal studies. Linkage of clinical data with population database could allow more rigorous testing of this hypothesis in large epidemiological population-based studies.

### Education and Occupation

- Years of formal education may raise one's level of "intellectual reserve" and thus exert a protective effect against developing dementia, a large number of studies have investigated this association. Higher occupational attainment has also been highlighted as a potentially protective factor against risk of developing dementia. This could either be a result of lifelong opportunity to build Cognitive Reserve; a result of the "use it or lose it" principle whereby continued mental exercise helps forestall cognitive decline, or as a result of higher socioeconomic status being associated with superior health care and health behaviours. Education and occupational status are likely to be closely related, and adjusting for educational level in studies on occupational status may help clarify to what extent effects operate independently of one another.
- Early reviews identified that education was likely to be a protective factor for dementia, across study

designs and outcome definitions. Despite some inconsistencies, cohort studies from the developed countries showed that higher levels of education and occupational attainment were associated with a lower incidence of dementia. Our new systematic review and meta-analysis included updated evidence from longitudinal studies, including, for the first time, those conducted in low and middle income countries. and confirmed a protective effect of education against developing dementia later in life (RR for high vs. low educational level =0.58). Adjusted and unadjusted pooled effect sizes were comparable to those reported in previous reviews. Most individual studies found a protective effect for higher levels of education, even after controlling for important confounders.

- While there appears to be some association between occupational attainment and dementia, adjustment for confounders appears to substantially reduce the effect size. There was heterogeneity in the confounders adjusted for in our meta-analysis, and residual confounding may well account for the remaining effect
- Education, at least in early life, appears to be an important potential protective factor against dementia. Cognitive reserve seems to be the best current model for explaining this effect, but the effects of the quality, quantity, type and timing of education remain to be clarified.

## CHAPTER 3

# Psychological factors



## Depression

- Depression is one of the most common mental health conditions in adults. It is associated with high levels of disability, reduced quality of life and adverse hospital outcomes. Cognitive disorders and depression often co-occur, however, the nature of this association is still not entirely understood. Various explanations for the association have been proposed: depression could be a consequence of dementia, represent a very initial phase (or prodrome) of, or an independent risk factor for, dementia.
- We conducted a review to update previously meta-analysed evidence on the relationship between depression and subsequent onset of dementia. The latest published studies seem consistent with earlier work, and accordingly strengthen the evidence that depression may increase dementia risk, with a pooled estimate of 1.97 (95% CI: 1.67-2.23). Most studies, with only a few exceptions, reported positive associations, even after adjusting for potential confounding variables.
- While our analysis clarifies the strength of the association between depression and the subsequent onset of dementia, it still does not distinguish clearly between the two most plausible explanations for this association – that is, whether depression is a prodrome of dementia, or an independent causal risk factor. Unfortunately, relatively few studies (4 of 32) carried out follow-ups of longer than 10 years. There is a trend towards smaller effect sizes in studies with longer follow-up, which would be consistent with expectations if depression were part of the prodrome of dementia (a manifestation of neurodegenerative processes underlying dementia, or a psychological

reaction to the experience of cognitive impairment). Studies that have specifically focused on late-onset depression and explored latency in the onset of dementia reported positive associations only with shorter follow-ups, in line with the prodromal hypothesis.

- The incidence and prevalence of depression may be reduced through population primary prevention and improved coverage of evidence-based pharmacological and psychological treatments should be effective in shortening episodes of depression and reducing relapses. These are public health priorities in their own right, but their effectiveness in reducing and delaying dementia onset is open to doubt.
- There is currently too little evidence on the relationship between anxiety and incident dementia to conclude whether this may be an independent risk factor. Further research is required, particularly exploring the impact of the extensive comorbidity with depression.

### Psychological distress: personality and life events

- Psychological distress is a state or feeling of pressure or strain. Psychological distress is very common in most populations, and because it can be modified and improved with lifestyle, environmental and even pharmacological interventions, it may be a target for preventive strategies. The association of prolonged psychological distress with dementia seems biologically plausible.
- Indirect measures of sustained psychological distress may be used in epidemiological studies. For instance, self-reported exposure to stressors, negative life events and difficulties has been found to be associated with cognitive impairment and increased dementia risk in large population-based samples. Personality traits, which tend to remain stable throughout adult life, are often used as a proxy for individual lifelong proneness to experience psychological distress. Personality measures have been consistently found to be related to dementia. This body of evidence would support the hypothesis that higher psychological distress may increase dementia risk.
- As with potential risk factors discussed in other chapters, associations between personality traits and dementia may be accounted for by reverse causality (pre-clinical dementia leading to changes in personality) if personality is not assessed before old age and the follow-up time to dementia diagnosis is short. Personality may be less stable than assumed, and is markedly impacted by the emergence of symptoms of dementia. Only part of the available

evidence comes from studies with long follow-ups and in which personality measures were assessed in mid-life.

- In conclusion, at present the evidence remains insufficient to support wider scale preventive interventions in the general population. Demonstration of reduced incidence of cognitive decline in randomised controlled trials of evidence-based interventions for those prone to high levels of stress would add to proof of concept.

### Sleep disorders

- Sleep disturbances are a collection of conditions strongly related to behavioural changes present in people with dementia. Symptoms such as increased time to fall asleep, increased number of awakenings, early awakening, diurnal naps and alterations in the circadian rhythm, which are commonly reported by older people, are exacerbated in people with dementia.
- Evidence suggests that the relationship between sleep disturbances and dementia may be bidirectional. Impairment of the neural pathways involved in the sleep-wake cycle caused by dementia might result in sleep disorders; but the reverse is also possible, where sleep problems might also be a risk factor for cognitive decline.
- There are few well-designed cohort studies of the association of sleep disturbances with dementia incidence, and variation in the types of exposure studied (sleep-disordered breathing, sleep duration, snoring, apnoea) make it difficult to synthesise the available evidence. The use of sleeping pills has been associated with an increased risk of dementia in several studies. However those studies in which the use of sleeping pills was accounted for in the analysis, the association between sleep disturbance and dementia remained significant, hinting at two potential pathways or mechanisms. Despite mechanistic evidence from animal models, it is still not clear whether changes in sleep are a cause or consequence of dementia and the underlying brain pathology that may precede its onset.

### Overall conclusion

- More research is needed, in particular on the relationship between anxiety, sleep disorders and dementia, but also on the potential impact of mid-life psychological interventions to reduce risk or delay the onset of dementia. Although the effect of these interventions on dementia risk is not clear, addressing psychological problems throughout the life course is nonetheless of public health importance, as the social, medical and financial burden of these conditions is extremely high.

## CHAPTER 4

# Lifestyle



### Introduction

- Potential relationships between lifestyle factors and dementia risk are highly salient since lifestyles and behaviours are modifiable and constitute typical targets of preventive programs and interventions.
- Lifestyles, such as diet, physical activity, alcohol and smoking habits are strongly correlated with each other, and to the metabolic syndrome, and are the target of existing preventive programs that aim to improve health, particularly through the reduction of cardiovascular risk. There is, therefore, some potential overlap and synergy between factors considered in this chapter, and the ‘cardiovascular risk factors’ considered in chapter 5.

### Smoking

- Tobacco smoke contains a myriad of toxic substances favoring oxidative stress and inflammation, which potentially exacerbate AD pathology. In animal models cigarette smoke increases amyloidogenesis, neuroinflammation and tau phosphorylation. An increased risk of atherosclerosis, ischaemic heart disease and stroke has been clearly demonstrated.
- Our systematic review and meta-analyses indicate that current smokers, compared to never smokers have a higher risk for the incidence of AD, with a non-significant trend in this direction for incident any dementia and VaD. Ex-smokers are at a similar risk to never smokers for the incidence of all types of incident dementia. There is inconsistent evidence for a dose response effect among current smokers, with an increased risk of AD (and, possibly, any dementia) with increasing pack-years exposure up to, but not including very heavy consumption (>55 pack-years). There is insufficient evidence to determine whether

or not the association of smoking with incident dementia or AD is modified by APOE genotype.

- There is now quite strong and consistent evidence to support an association between current smoking and the incidence of AD, with tentative evidence for a similar association with vascular dementia. Conversely, ex-smokers do not appear to be at increased risk. This is an encouraging finding for dementia prevention, suggesting, as with other adverse impacts of smoking, that the increased risk of dementia can be avoided by quitting smoking.
- It will be important to further clarify the nature and extent of this association both to quantify more accurately the total burden of disease and societal economic impact attributable to smoking, and to model the potential changes in future dementia incidence in different world regions where the prevalence of smoking has been decreasing (most high income countries), or increasing (many low and middle income countries) in recent years.

### Alcohol

- The deleterious effects of alcohol in the brain are well known. It produces cerebral volume loss, especially from the white matter that is related to memory processing and visuospatial functioning. The mechanisms involved in brain damage include nutritional factors that can exacerbate ethanol neurotoxicity, such as thiamine deficiency (vitamin B1).
- The potential neuroprotective effects of moderate alcohol consumption could be explained by different mechanisms (increases in the insulin-sensitive glucose transporters, significant reduction in plasma viscosity, reduction in fibrinogen concentration, flavonoids and resveratrol that have antioxidant and anti-inflammatory effects, stimulation of acetylcholine in the hippocampus).
- We conducted a new systematic review of population-based cohort studies, to update the evidence, and were more conservative in how we combined data, distinguishing studies that had a more standard way of categorizing moderate and heavy, from those including much lighter categories for moderate drinking. Our pooled estimates show that compared to abstainers, drinkers and moderate drinkers are at lower risk of AD and any dementia, while heavy/excessive drinkers are at similar risk. There is no clear evidence that drinking wine is associated with a lower AD and/or dementia risk. There is no evidence that the association between alcohol consumption and dementia is modified by APOE genotype.

- The comparison with abstainers is not helpful, since this group is recognized to be highly heterogeneous, including recovering alcoholics and those who do not drink for health reasons. As a group, they are well recognized to have an increased risk of poor health outcomes, including mortality. A more helpful comparison would be between different levels and patterns of alcohol consumption.
- Despite much research activity, currently available evidence on the impact of alcohol consumption on dementia incidence is largely irrelevant to the formulation of public health policy. More research is needed, and this should focus upon a) lifetime histories of alcohol consumption, distinguishing lifetime abstainers (and their reasons for abstaining) from those who have given up drinking, b) reasons for changes in alcohol consumption, including reasons for stopping drinking, and c) more, and better studies of dose response effects among drinkers, seeking to identify risk conferring levels and patterns of drinking.

## Physical activity

- The independent association of physical activity with lower dementia risk is plausible and has received growing attention in recent years. Epidemiological research, and animal models and basic research provide sound observational and mechanistic evidence that physical activity can be beneficial for brain health.
- Physical activity can help control hypertension, diabetes, hypercholesterolemia and obesity and thus indirectly reduce dementia risk. Physical activity is also beneficial for the structure and function of blood vessels, including those of the cerebrovascular system. Animal models suggest direct effects including reduction of amyloid burden, improvement and consolidation of neuronal structure, and enhancement of neurotransmitter synthesis.
- There are a very large number of observational studies that have explored the association between physical activity and dementia. Conversely, there are no RCTs that specifically tested the potential protective effect of physical activity programs to reduce dementia risk. The evidence from observational studies is inconsistent. Although the results of available studies seem to suggest that physical activity may be associated with up to a 40% reduction in dementia risk, more recent studies with longer follow-up report consistently negative results. This suggests the possibility that reverse causality could account for these findings.
- Although the evidence from the numerous RCT that tested the short term effects of physical activity programs and aerobic exercise on cognitive function showed small but mainly encouraging results, such evidence cannot be generalised to support physical activity as an effective way to prevent or delay the onset of dementia. More longer-term RCTs are warranted, and the type, intensity and duration of the physical activity interventions should be carefully considered.

## Cognitive stimulation

- There is great interest in whether engaging in cognitive stimulating activities may exert benefits on the brain and preserve, or even improve cognitive function. The simple idea that cognitive activities may be as beneficial for brain function as exercise is for physical health is indeed biologically plausible. However, dementia has a significant impact on all leisure activities, due to the progressive difficulties caused by cognitive impairment and to early manifestations of neuropsychiatric symptoms including apathy and depression.
- Cognitive activity programs are components of multi-domain interventions of recently completed, or still ongoing randomised controlled trials designed to test their potential to reduce risk of incident dementia in older adults at higher risk. Although evidence from prospective cohort studies is limited, consistent results from a large number of observational studies that measured cognitive activity in late-life seem to support the hypothesis that this may be beneficial for both brain structure and function. However the current evidence on cognitive activity and risk of dementia should be interpreted with caution. The observed lower cognitive activity levels in those who will go on to show clinical symptoms of dementia may well be a prodromal sign of the disease.
- Evidence from randomised controlled trials that are been conducted on both cognitively healthy subjects and on people at greater risk of dementia will help to elucidate this unresolved issue, and support the development and implementation of primary and secondary prevention interventions.

## Diet

- In cross-sectional studies, compared to adults with dementia, healthy older people tend to have a healthier diet, richer in fruits and vegetables, rather than meat, processed carbohydrates and fats. Because dementia alters dietary habits, these initial studies have been useful in generating hypotheses but could not prove any causal link. Prospective cohort studies with long follow-up intervals are needed to clarify the direction of the association under study and inform dietary recommendations to reduce risk of dementia in populations.

## B – Vitamins

- The association between B vitamins and cognition has been the subject of several recent systematic reviews and since the latest reviews a number of new studies have been published. Cohort studies have produced inconclusive evidence on the association between vitamin-B deficiency and cognitive decline, but have seemed to confirm that high levels of homocysteine are associated with poorer cognition.
- Some new randomised controlled trials have also been published in the past couple of years with mixed results. More encouraging findings have been reported in individuals with higher homocysteine levels at baseline, suggesting that those with clear and defined deficiencies may be the ones who could benefit from vitamin supplementation.

## Antioxidants

- There is currently insufficient evidence from either longitudinal studies or randomised controlled trials to support a role for antioxidants in cognition. The only consistent associations were reported in studies that have assessed vitamin E status using food frequency questionnaires, rather than biochemical measures, suggesting that more work is needed to better understand these nutrients and their relationship with dementia.

## Omega-3

- The evidence on the beneficial effects of fish consumption to prevent dementia incidence is overall conflicting, but a protective role does not seem to exist. Healthy lifestyles and life circumstances (including socio-economic and educational level) that are associated both with higher fish consumption and lower dementia risk may explain the positive results found by some studies. Evidence from experimental studies on the beneficial effects of omega-3 PUFA supplementation is insufficient to recommend their use in populations either for the prevention, or treatment or amelioration of dementia.

## Mediterranean diet

- There is moderate evidence from observational studies suggesting a positive link between adherence to the Mediterranean diet and reduced dementia risk. Not all the studies did, however, report positive findings, in particular regarding cognitive decline.
- Only one randomised trial has attempted to test this association in an experimental design, by comparing a nutritional Mediterranean diet intervention supplemented with either extra- virgin olive oil (EVOO) or mixed nuts, with a low-fat control diet. The intervention, lasting 6.5 years showed encouraging results; participants that supplemented

Mediterranean diet with EVOO but not with mixed nuts, had better cognitive function, and less incident mild cognitive impairment (MCI) than the control group. Implementing such an intervention on a large scale, and in a sustainable way, would be challenging. More intervention studies are needed to identify the active ingredients for improving cognitive function and reducing dementia risk.

## Conclusion

- There is currently insufficient evidence to confirm a relationship between the micro- and macro-nutrients described above (vitamin B6, vitamin B12, folate, vitamin C, vitamin E, flavonoids, omega-3, Mediterranean diet) and dementia incidence. Although some studies have shown positive results, particularly those using cross-sectional designs, the findings have not been consistently supported in prospective cohort studies, and preventive interventions have generally failed the critical test of randomised controlled trials.

## CHAPTER 5

# Cardiovascular risk factors



## Introduction

- Dyslipidaemia (an abnormal amount of cholesterol/fat in the blood), hypertension, diabetes, smoking and obesity are the major modifiable risk factors for cardiovascular diseases (CVDs) including heart disease and stroke. These cardiovascular risk factors (CVRF) are already common by midlife, and their prevalence increases with increasing age thereafter. Associations between CVRF and dementia are plausible, first, because hypertension, dyslipidaemia, obesity and type 2 diabetes all predispose to ischaemic heart disease and cerebrovascular disease, including cortical and sub-cortical infarcts, and white matter lesions. Cerebrovascular disease may interact with other neurodegenerative pathologies, including AD, to predispose to the onset of dementia. Other mechanisms, specific to particular CVRF, may initiate or exacerbate neurodegenerative pathologies, particularly AD.

## Hypertension

- Hypertension can be prevented by attention to lifestyle factors, particularly diet, weight and physical activity, and controlled with antihypertensive medication. These efforts must be sustained across the adult life course, since the adverse effects of hypertension are apparent well into old age.
- Hypertension decreases the vascular integrity of the blood–brain barrier, leading to cell damage, a reduction in neuronal or synaptic function, and apoptosis (cell death). It may also increase the accumulation of insoluble A $\beta$ , contributing directly to AD pathology. Studies show a significant association

of higher blood pressure levels and/or hypertension with total or regional reduction in brain volume.

- There is strong and consistent evidence for an association of mid-life hypertension and the incidence of any dementia in late-life. This is likely accounted for mainly by the even stronger association observed between midlife hypertension and incident vascular dementia. An association of midlife hypertension with incident AD has not yet been convincingly demonstrated, and the size of possible effects has probably been over-estimated.
- Hypertension in late-life is not associated, or is even inversely associated with incident dementia because of the decline in blood pressure levels that precedes the clinical onset of dementia, particularly of the Alzheimer type. However, late-life hypertension is associated with an increased risk of VaD in some studies.
- The failure, experimentally, to demonstrate a benefit of blood pressure lowering in RCTs that are conducted in late-life is likely to be explained by the specific salience of exposure to hypertension in midlife. Reducing this exposure through improved prevention, detection and control of hypertension is likely to have a substantial impact on the future prevalence of all forms of dementia.

## Obesity

- While larger birth weight and high (optimal) body size in childhood may be associated with better cognition, overweight and obesity from an excess of nutrient/energy intake and/or reduced physical activity level are notoriously harmful for health. Evidence also suggests that they may contribute to neurodegenerative and cerebrovascular changes underlying late-life dementia, through both vascular and metabolic pathways.
- Adiposity may have direct adverse effects on brain tissue through production of inflammatory cytokines, Advanced Glycosylation End Products (AGEs), and hyperinsulinaemia, some of which factors may be directly implicated in the promotion of AD pathology.
- The association between adiposity and ensuing dementia is biologically plausible. However, similar to hypertension, any excess risk seems to relate to obesity in midlife, with those going on to develop dementia experiencing greater relative decline in body mass up to a decade before clinical onset. There is currently inadequate evidence to confirm an association between midlife obesity and incident dementia. Problems arising from uncontrolled confounding, and bias have not been adequately highlighted in previous reviews. Decline in BMI from mid- to late-life appears to be a stronger predictive factor than mid-life obesity, although it is unclear

whether this represents a causal association or a prodromal aspect of dementia.

- The possibility that central obesity in midlife (e.g. waist circumference), rather than total obesity (e.g. BMI) better encapsulates the relationship between adiposity and future dementia risk warrants further research. An improved understanding of the critical pathways that may lead from high adiposity to greater dementia risk could have a significant impact on targeting of primary prevention strategies.

## Cholesterol (Dyslipidemia)

- Lipids comprise triglycerides, free fatty acids, sterols (cholesterol and cholesterol-related compounds) and phospholipids. Dyslipidaemia occurs when levels of triglycerides or total cholesterol are high. Dyslipidaemia is an important independent risk factor for ischaemic heart disease and stroke.
- Lipids are the basic structural component of neuronal (nerve) cell membranes, and constitute the majority of brain dry weight. The brain is the most cholesterol-rich organ, containing 30% of the body's total cholesterol. Cholesterol is an essential component of neuronal cell membranes and plays a crucial role in the development and maintenance of neuronal plasticity and function.
- Findings on the association between cholesterol level and dementia are inconsistent. Studies where the exposure is assessed in midlife, are more likely to report a positive association than short latency studies where exposure is assessed in late-life shortly before the onset of dementia. Similar to body weight and blood pressure, cholesterol levels may decline more rapidly from midlife to late-life in those who go on to develop dementia, particularly AD.
- The most recent review of prospective studies of cholesterol as a risk factor for dementia concluded that "consistent associations between high midlife TC and increased risk of AD... and any dementia were found". In fact, the evidence reported in that review was inconsistent, and the support for this conclusion has been weakened further with the publication of findings from more long-term cohort studies. Positive findings for an association between midlife TC and late-life AD come principally from two Finnish Cohort studies. It remains possible, therefore, that there is a genuine association, but that increased risk for AD is concentrated at very high levels of midlife TC.
- The most consistent finding across cohorts is that a more rapid decline in TC from mid- to late-life predicts the onset of AD, and, possibly, dementia and cognitive decline. Elucidation of the underlying mechanisms may improve our understanding of the neurobiology of AD.

- The evidence accumulated to date does not support the hypothesis that preventing or treating dyslipidaemia will help to prevent cognitive decline, AD or other forms of dementia. However, there are several important caveats. The possible benefits of statin treatment for preventing or treating vascular dementia have been little studied. Dyslipidaemia is an important risk factor for stroke, and there may yet be therapeutic benefits through this mechanism. Effective primary and secondary prevention of dyslipidaemia, initiated in midlife, may yet help to prevent AD or dementia. There is some evidence for example, from pharmacoepidemiologic studies that longer term treatment with statins is associated with a greater protective effect. Interesting findings from genetic research, animal models and in vitro studies that strongly suggest an important role for brain cholesterol metabolism and transport in AD neuropathology. This research may yet help to identify novel therapeutic targets.

## Diabetes

- Type 2 diabetes is one of the commonest common chronic conditions worldwide. In contrast to type 1 diabetes, most cases are brought on by lifestyle factors and are therefore preventable; taking exercise, losing weight, cutting fat and sugars in the diet, reducing alcohol consumption and stopping or avoiding smoking should all reduce risk. Diabetes can be treated with diet, oral hypoglycaemic drugs or insulin. The high prevalence of diabetes makes it potentially one of the most important modifiable risk factors for dementia.
- There are several possible mechanisms by which diabetes may act to increase the risk of dementia and AD. As has been noted, diabetes is an important component of the metabolic syndrome and increases risk for vascular disease. Advanced glycation endproducts (AGEs) provide a particularly plausible link between diabetes and AD pathology. AGEs are elevated in diabetes, and are strongly implicated in end-organ damage. AGEs are also elevated in AD brains where they can stimulate beta-amyloid production.
- Our new meta-analysis of population-based cohort studies confirms a particularly strong and consistent association between diabetes in late-life and the subsequent onset of dementia. This is in contrast to the pattern observed for hypertension, obesity and dyslipidaemia, where the increased risk, if it exists, is only apparent for midlife exposures. Clearly this may have important implications for prevention. However, in contrast to other CVRF, relatively few randomised controlled trials have been conducted to assess if improved diabetes control results in a lower incidence of dementia.

- Evidence from health record linkage studies also suggests that diabetes in midlife may have an equivalent or even greater effect, and it may be that the duration of diabetes is an important risk determinant. The primary prevention of diabetes should also therefore be targeted.
- Diabetes seems to be a much stronger risk factor for vascular dementia than for Alzheimer's disease, and cerebrovascular disease is likely to be an important mediating mechanism, although other processes may also be involved. Improved understanding of causal mechanisms will help to shape diabetes treatment and prevention strategies to prevent dementia. In the meantime, the rising and overlapping epidemics of diabetes and dementia mean that older persons with diabetes are increasingly likely to have cognitive impairment, affecting their self-care, and posing a challenge for healthcare systems worldwide.

## CHAPTER 6

# Summary of findings and conclusion



## Summary of findings

- To inform health promotion and disease prevention strategies, we have examined critically the evidence for the existence of modifiable risk factors for dementia. We have accessed systematic reviews, and assessed their quality, making a point of reading the full text of all included studies. We have updated the evidence contained in those reviews, and where necessary conducted new fully systematic reviews (of the effects of education, occupation, depression, smoking, alcohol consumption, and diabetes).
- We have, throughout, addressed brain health promotion and dementia prevention from developmental and life course perspectives. One of the key issues to be considered was whether, for certain risk factors, there might be critical life periods during which the factor exerted the greatest impact on future risk of dementia.
- Summarizing the evidence in Table 6.1, we have provided information on the general direction of the observed association, the extent and adequacy of the evidence-base to inform policy and practice (yes/no), the consistency of the evidence between studies (high, moderate, low), and the overall strength of the evidence (robust, moderate, insufficient).
- The strongest evidence for possible causal associations with dementia (plausible, consistent, strong associations, relatively free of bias and confounding) are those of low education in early life, hypertension in midlife, and smoking and diabetes across the life course. There is also consistent evidence from several studies for an inverse

Table 6.1.a and b

**Summary of evidence for risk factors of dementia.** ↓ signifies decreased risk with higher levels of exposure ↑ signifies increased risk → signifies varying risk, or null findings

	Direction of Association	Sufficient number of cohort studies to draw meaningful conclusions	Consistency across studies	Evidence type (robust, moderate, insufficient)	Notes
<b>Developmental factors</b>					
Nutrition (growth and development)	↓	No	Moderate	Insufficient	Indirect evidence from proxies for early life nutrition and development (leg length and skull circumference inversely associated with dementia prevalence)
Education	↓	Yes	Moderate	Robust	Consistently protective effect, but with a variable effect size, in a large number of cohort studies, across cultures
Occupational status	↓ →	Yes	Low	Moderate	Effects are attenuated when controlling for education, hence apparent protective effect may not be causal
Early life events	↑	No	Moderate	Insufficient	Suggestive evidence that death of a parent may increase dementia incidence, but few studies, and potential for recall bias

	Direction of Association	Sufficient number of cohort studies to draw meaningful conclusions	Consistency across studies	Evidence type (robust, moderate, insufficient)	Notes
<b>Psychological factors – midlife</b>					
Depression	↑	No	n/a	Insufficient	Metaregression indicates smaller effect sizes (closer to the null) for studies with longer follow-up periods. However, limited evidence on midlife exposure
Anxiety	↑	No	n/a	Insufficient	One cohort study suggesting possible increased risk
Sleep disorders	↑	No	n/a	Insufficient	Very few long-term cohort studies
Psychological distress	↑	No	High	Insufficient	Indirect evidence using personality type as a lifelong stable proxy for the likely intensity and duration of stress response. Neuroticism positively associated and conscientiousness negatively associated with dementia/ AD risk
<b>Psychological factors – late life</b>					
Depression	↑	Yes	High	Moderate	A strong and consistent association observed across many studies. However, this may reflect reverse causality (see midlife above)
Anxiety	→	No	n/a	Insufficient	One case-control and one cohort study – no association observed
Sleep disorders	↑	No	n/a	Insufficient	Suggestive evidence from a small number of cohort studies. Various self-reported exposures. Short follow-up. Reverse causality not excluded.
Psychological distress	↑	No	n/a	Insufficient	See midlife (above)

Table 6.1.c

**Summary of evidence for risk factors of dementia.** ↓ signifies decreased risk with higher levels of exposure ↑ signifies increased risk → signifies varying risk, or null findings

	Direction of Association	Sufficient number of cohort studies to draw meaningful conclusions	Consistency across studies	Evidence type (robust, moderate, insufficient)	Notes
<b>Lifestyle factors – midlife</b>					
Smoking	↑	No	Low	Moderate	Late-life studies include retrospective assessment of lifetime smoking history, and support hypothesis. Midlife exposure in long-term cohort studies may underestimate effect due to mortality/ competing risk
Alcohol	→	No	n/a	Insufficient	Very few studies
Micro- and macronutrient deficiency	→	No	n/a	Insufficient	Very few studies
Physical activity	↓→	No	High	Insufficient	Only three long-term cohort studies with mixed results
Cognitive stimulation	↓	No	n/a	Insufficient	Supportive evidence from case-control studies, prone to bias. Only one long-term cohort study, with high attrition and imprecise exposure measures
<b>Lifestyle factors – late life</b>					
Smoking	↑	Yes	Moderate	Moderate	Dose response effect for incidence of AD. Possible effect on VaD and any dementia.
Alcohol	→	No	Moderate	Insufficient	Moderate drinkers have a lower risk of dementia and AD than abstainers. Unclear if this is causal or reflects confounding by reason for abstaining. Upper safe limit of 'moderate' drinking and impact of heavy drinking is unclear
Micro- and macronutrient deficiency	→	Yes	Moderate	Insufficient	With the exception of Mediterranean diet (one positive trial), suggestive evidence from observational cohort studies has not been confirmed in supplementation trials. However, RCTs are few in number and often of poor quality. They do not always focus on those with micronutrient deficiencies
Physical activity	↓→	Yes	High	Insufficient	Duration of follow-up is a major determinant of heterogeneity of effect, with inverse association seen mainly in short follow-up studies. High probability of reverse causality. RCTs needed to clarify this
Cognitive stimulation	↓	Yes	High	Insufficient	Consistent risk reduction associated with performance of cognitively stimulating activities. Reverse causality remains to be excluded. RCTs needed to clarify this.

Table 6.1.d

**Summary of evidence for risk factors of dementia.** ↓ signifies decreased risk with higher levels of exposure ↑ signifies increased risk → signifies varying risk, or null findings

	Direction of Association	Sufficient number of cohort studies to draw meaningful conclusions	Consistency across studies	Evidence type (robust, moderate, insufficient)	Notes
<b>Cardiovascular risk factors - midlife</b>					
Hypertension	↑	Yes	High	Robust	Consistent evidence from 5 studies across four cohorts. Evidence stronger for any dementia, and VaD, than for AD.
Obesity	↑ →	No	Low	Insufficient	Inconsistent findings for association with midlife BMI. Problems with bias and residual confounding. Possibly more consistent association with central obesity.
Cholesterol	↑	No	Low	Insufficient	Inconsistent findings. Hypothesis supported mainly by two Finnish long-term cohort studies
Diabetes	↑	No	Moderate	Moderate	Evidence is somewhat indirect, from health care record linkage studies, and subject to bias. However, longer duration of diabetes is associated with higher dementia risk. Only one long-term cohort study, with no association.
<b>Cardiovascular risk factors – late life</b>					
Hypertension	↓ →	Yes	High	Robust	Cross-sectional studies show lower BP level in people with dementia and AD relative to controls. Decline in BP predicts the onset of dementia and AD, but this is unlikely to be causal. RCTs suggest no cognitive benefit or harm associated with the treatment of hypertension in older people in general, or those with dementia.
Obesity	→	Yes	High	Robust	Several studies. No association. However, decline in BMI from mid- to late-life predicts dementia onset but this is unlikely to be causal.
Cholesterol	→	Yes	Moderate	Moderate	No effect of cholesterol lowering with statins on cognitive outcomes. No association of total cholesterol (TC) with incident dementia, but effects of cholesterol subfractions need to be explored further. However, decline in TC from mid- to late-life predicts dementia onset.
Diabetes	↑	Yes	High	Robust	Highly consistent evidence for a strong association between diabetes and the incidence of any dementia, AD and VaD. Particularly strong effect on VaD. Possibly mediated through poor glycemic control. Mixed evidence for cognitive benefits of optimising glycemic control

association between both physical and cognitive activity and dementia incidence –however, reverse causality has not been excluded, and indeed is a very plausible explanation for the observed associations.

- Two important general mechanisms may be in operation. The first is cognitive, or possibly brain reserve. Education and occupational attainment may have positive effects on brain structure or function, or both, that modify the impact of neurodegenerative brain damage in late-life. The second is vascular pathology, through which the effects of midlife hypertension, smoking and diabetes may be mediated. The associations of midlife hypertension and diabetes with incident any dementia and VaD are generally stronger than those with AD. This pattern is not so apparent for smoking, although the cardiovascular disease risks of smoking are very clearly established. Associations with obesity and dyslipidaemia were less clear cut, but these are important risk factors for hypertension and diabetes, and contribute independently to cardiovascular risk.

## Contextualising these findings with other research

- The US National Institutes of Health (NIH) conducted a state-of-the-science conference review in 2010 to provide an assessment of currently available data on prevention of AD and cognitive decline. Their headline finding that “firm conclusions cannot be drawn about the association of any modifiable risk factor with cognitive decline or Alzheimer’s disease” may have led to unwarranted pessimism regarding the potential for primary prevention. It is true that very few primary prevention randomised controlled trials (RCTs) have been conducted, and that their results do not support potential for risk reduction. However, many of these trials recruited older people, and follow-up periods were relatively short. Given that neurodegeneration may precede the onset of dementia by several decades, this may have been a case of ‘too little too late’. As we have shown in this report, there is strong evidence from population-based cohort studies attesting to the potential risk reduction benefits of better cardiovascular health and more education, and, possibly physical activity and cognitive stimulation.
- Following the NIH state-of-the-science review, another group conducted systematic reviews into the epidemiological evidence for risk reduction focusing on seven risk factors for which there was strong evidence of independent effects on the incidence of Alzheimer’s disease; diabetes, midlife hypertension and obesity, depression, physical inactivity, smoking and low education. Having meta-analysed the evidence base to estimate the relative risk, they combined this with the population prevalence of the risk factor to compute a population attributable risk – the proportion of cases of AD that might be prevented if the risk factor could be removed entirely. The most promising strategies for prevention were the elimination of physical inactivity (12.7% of AD cases prevented), smoking (13.9%) and low education (19.1%), since these factors are both relatively common and strongly associated with incident AD. The authors modeled the effect of a 10% or 20% reduction in the prevalence of the risk exposures on the prevalence of dementia through to 2050 – an 8.3% reduction in AD prevalence assuming a 10% reduction in exposure prevalence, and a 15.3% reduction assuming a 20% reduction in exposure prevalence.
- There is an underlying assumption in all such calculations that the associations observed in the epidemiological research studies that the risk factor has caused the onset of dementia. This may not be the case. Confounding may have occurred; other factors associated with, for example, midlife obesity may have been the true causal risk factor; under these circumstances, eliminating obesity would have no preventive effect. Bias may also be a problem, arising from selective patterns of mortality or other losses to follow-up ; from an increased likelihood in health care record linkage studies of detection of dementia in the presence of chronic diseases requiring long-term health care ; or from information bias where recall of exposure may be affected by the coming onset of dementia. The early pre-clinical effects of dementia may induce depression, or reduce physical or cognitive activity – hence the disease may cause the ‘risk factor’ rather than the risk factor causing the disease (reverse causality).
- These aspects have been given insufficient attention in many previous systematic reviews, which have been insufficiently critical of the internal validity of the observed associations. The causality of the observed associations of incident dementia with depression, physical and cognitive activity, and midlife obesity are either thinly evidenced, and/ or open to considerable doubt.
- It is for these reasons that policymakers and advisors (such as the recent NIH state-of-the-science expert panel) are reluctant to act on the basis of epidemiological evidence alone. Randomised controlled trials of the effects of removing or reducing the risk factor are considered to provide the strongest evidence. However, these are sometimes difficult if not impossible to conduct given the long latency between the period over which the risk factor exerts an influence on the underlying mechanisms that lead to dementia (early to mid-life), and the onset of dementia in late life. This stricture applies to the possible effects of education (which is not, in any

case, amenable to experimental control), and mid-life hypertension and midlife hypercholesterolaemia (where placebo-controlled trials would, in any case, no longer be ethical).

- One of the complicating factors for interventions in this area is that evidence suggests that while hypertension, raised cholesterol, and obesity in midlife increase the risk for later onset of dementia, blood pressure levels, cholesterol and body mass index fall progressively before the onset of the disease. Hence people with dementia have lower blood pressure levels, cholesterol and body mass than others. Therefore, early primary prevention may be the most effective intervention. Preventive trials indicate that statins, and antihypertensive treatment, do not seem to lower the incidence of dementia when initiated in older people, but there have been, and can no longer be any long-term trials from midlife onwards.

## Implications - Where do we go from here?

### Randomised controlled trials

- There are outstanding questions highlighted in this review, that would, in principle, be testable in randomized controlled trials involving experimental manipulation of lifestyles and control of risk factors among older people at risk for dementia. These relate to the effects of cognitive and physical activity in late-life, and to the potential benefits of correction of established micronutrient deficiency, and optimised glycaemic control in those with diabetes
- Aggregated cardiovascular risk indices incorporating hypertension, diabetes, hypercholesterolaemia and smoking incrementally increase risk for dementia incidence whether exposure is measured in midlife or a few years before dementia onset. Multi-component prevention trials are currently underway in several European countries under the umbrella of the European Dementia Prevention Initiative (EDPI - <http://edpi.org/>). The FINGER trial in Finland (Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability), comprising multi-domain life-style intervention including nutritional guidance, exercise, cognitive training, increased social activity, and intensive monitoring and management of metabolic and vascular risk factors for 60-77 year old persons at an increased dementia risk has recently demonstrated cognitive benefits at the 2-year interim endpoint, and will now go on to assess impact on dementia incidence over seven years.
- The examples suggested above all refer to risk exposures that might have an impact in late-life. Given the difficulties in gathering relevant experimental evidence from RCTs for exposures

operating over a much longer time period, we must, therefore, explore other sources of evidence.

### Enhancing the quality and relevance of evidence from observational studies

- We identified errors in many of the published systematic reviews that we accessed. These included; inclusion of studies that were not relevant; misinterpretation and/or incorrect reporting of study designs and findings; incorrect transcription and reporting of effect sizes; incorrect referencing, and untraceability of included studies. As the number of systematic reviews increase, journal editors may struggle to find peer reviewers who can allocate sufficient time to give each submitted review the detailed scrutiny it requires. Given the complex and time consuming nature of the task when done properly, reviewers may need to be paid for their work, and provided with a complete set of electronic copies of included publications.
- Existing evidence should be documented in an authoritative publicly accessible archive. Such an initiative has been attempted for genetic and environmental risk factors for Alzheimer's disease, through the AlzRisk consortium (<http://www.alzrisk.org/>).
- Much of the relevant evidence generated in well-conducted studies could not be included in meta-analyses because of the non-harmonisability of exposures and/or outcomes. A collaborative network of relevant cohort studies could be established, to share existing data and work together on re-analysis using common exposure definitions. Such an approach has been of tremendous value in clarifying risk associations in the cardiovascular disease field.
- Many studies look at risk factors for 'any dementia' and AD and VaD subtypes. A relatively large number of studies only assess risk factors for AD. A few studies focus on VaD alone. In the domain of public health, dementia, regardless of cause or subtype is the most relevant outcome. Atherosclerosis and AD are likely to be linked disease processes, with common pathophysiological and aetiologic underpinnings. They may also be directly interactive through damage to the vascular integrity of the blood brain barrier. A radical, but evidence-based view would be that AD pathology and cerebrovascular disease are best considered as independent but interactive risk factors for dementia, rather than necessary or sufficient causes, or defining characteristics of distinct subtype entities. Therefore, it would be helpful if future epidemiological studies always included 'any dementia' as an outcome, in addition to AD and/or VaD.

### Modelling the 'real world' effect of changes in putative risk exposures on the incidence and prevalence of dementia.

- Our best hope of ascertaining the likely impact of increasing levels of education, and improvements in cardiovascular health may be to observe populations in which such trends are prominent, to see whether these are associated with a decline over time in the age-specific incidence of dementia. Detection and treatment of diabetes and hypertension, reduction in levels of obesity, smoking cessation, increased physical activity, and better education are already public health priorities for most countries worldwide. Nevertheless, the message that dementia, alongside heart disease, stroke and cancer may be prevented through increased adoption and more effective implementation of these public health strategies is one that policymakers and public need to hear.
- All current projections of the scale of the coming dementia epidemic assume that the age- and gender-specific prevalence of dementia will not vary over time, and that population ageing alone (increasing the number of older people at risk) drives the projected increases. However, each generation is better educated than the one before. Although trends differ between countries, genders, age groups and time periods, there has been a general trend in high income countries towards less smoking, falling total cholesterol and blood pressure levels, and increasing physical activity. On the other hand, the prevalence of obesity and diabetes has been increasing in most developed countries. After a lag period, to the extent that these factors are genuinely causally associated with dementia, one would expect to see corresponding changes in the incidence of dementia.
- In 2009, what very few data was available from certain high income countries did not suggest any clear pattern of a decline or increase over time in either the incidence or prevalence of dementia. Just a few years later, and linked to a greatly increased interest in the potential for prevention of dementia by targeting modifiable risk factors, the quality and extent of the evidence has expanded greatly.
- A near one-third (30%) reduction in the prevalence of dementia was observed between two phases (1990-1993, CFAS I; 2008-2011, CFAS II) of the MRC Cognitive Function and Ageing Study (MRC CFAS) in England, adjusting for differences in age, sex and socioeconomic status. A similar trend towards declining prevalence was observed in a study from Zaragoza, Spain, although this has not been replicated in all other studies of this type. More compelling evidence comes from the long-term USA Health and Retirement Survey, in which there was a substantial decline in the prevalence of cognitive impairment between survey waves conducted in 1993 and 2004, accompanied by a higher relative mortality risk for those who had developed cognitive impairment. There is also evidence consistent with a recent decline in incidence in Sweden and the Netherlands. Preliminary findings from two important studies were presented at the Alzheimer's Association International Conference in July 2014. In the US Framingham study dementia incidence was tracked over thirty years in four five-year periods. Compared to the first five-year period, incidence had fallen by 17%, 32% and 42% respectively. Reductions were largest in the younger age groups, suggesting that dementia incidence was being delayed or deferred to older ages. The second study used claims data of the largest German public health insurance company to track the incidence and mortality of dementia in 2007-2010, compared with 2004-2007. Age-specific incidence fell by around 20% in only five years, while mortality among those with dementia had increased for women but remained stable in men.
- Evidence from these studies presents a more consistent pattern of declining incidence, with onset of dementia deferred to progressively older ages. If the onset of dementia occurs close to the end of the natural life span, fewer years will be lived with dementia. Langa described this phenomenon as 'the compression of cognitive morbidity', a desirable outcome for public health and individual quality of life, resulting in longer, healthier lives, with fewer years spent in a state of reduced independence and needing care.
- The authors of the UK MRC CFAS study noted that observed reduction in prevalence was "in line with major reductions in risk factors in higher income countries, which have been modified by societal changes such as improvements in education, and prevention and treatment strategies in recent decades". In the Framingham study the decline in the incidence of dementia over a 30-year period was accompanied by improvements in educational status, more use of antihypertensive and statin medication, lower blood pressure and cholesterol levels, and reductions in prevalence of smoking, heart disease and stroke, whereas the prevalence of obesity and diabetes had increased.
- While cardiovascular health is improving in many high income countries, it is deteriorating elsewhere. Evidence from China and other east Asian countries suggests a worrying trend toward an increase in the prevalence of dementia over the last 20 years. Many low and particularly middle income countries show a pattern of increasing stroke and ischaemic heart disease morbidity and mortality, linked to an epidemic of obesity, and increasing blood pressure levels.

- The future course of the global dementia epidemic, through to 2050, will depend crucially upon the success or otherwise of continuing efforts to improve public health. Those who will be old in 2050, were born around the 1970s, and have already received their basic education. They are now in their third and fourth decades of life, a crucial 'sensitive period' where, evidence suggests, efforts to prevent, detect and control obesity, hypertension, diabetes and dyslipidaemia (high cholesterol) are likely to have maximum positive impact upon brain health and dementia risk in late-life.
- Observe and correlating actual changes in risk factor profiles and disease incidence over time, is a well-established modeling approach in the cardiovascular disease field where it has contributed greatly to our understanding of the potential for prevention, and the attribution of changes in disease incidence to specific factors. Between 1980 and 2000, age standardised ischaemic heart disease mortality rates nearly halved in the USA, nearly three-quarters of the deaths prevented or postponed being among those aged 65 years and over. This was evenly attributed to improvements in medical care and reduced risk factor exposure, despite increases in obesity and diabetes. In the late 1960s, ischaemic heart disease mortality among Finnish men was the highest in the world. Risk factor trends have been monitored since 1972 in the North Karelia Project, over which period there has been a remarkable decline in serum cholesterol levels, a decline in blood pressure level, which levelled off in 2002, a decrease in smoking among men but an increase among women, and an increase in body mass index in both sexes. Given knowledge of risk associations, the decline in cholesterol among men would have been predicted to result in around a 40% reduction in mortality, the decline in BP around a 20% reduction, and the changes in smoking habit around a 15% reduction. The combine defect of the risk factor changes would be a 60% reduction in mortality. In fact the observed mortality reduction for men was a remarkable 80%. Observed and predicted mortality reductions tracked each other closely until the mid 1980s. The subsequent additional decline in mortality over and above that predicted was attributed to the increased availability of secondary prevention and invasive revascularization procedures for coronary patients.
- Similar studies could, in the future, be carried out to monitor the impact of prevention programs on the future scale of the dementia epidemic. To do this, renewed efforts would need to be made in all regions to monitor trends in incidence and prevalence of dementia and to associate these with changes in public health, and in medical and social care. Unfortunately, studies of the prevalence of dementia have been conducted less frequently in high income

countries since the 1990s. For the purposes of the risk modeling exercises described above, risk exposures should ideally be assessed in the same population sample. Governments need to commit to the funding of such monitoring activities, over the longer term.

## **An integrated approach to the prevention of dementia and other chronic diseases**

- Numbers of people with dementia are increasing worldwide, and there is growing evidence that suggests that attention to 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. In September 2011 the United Nations General Assembly discussed the global impact of non-communicable diseases (NCDs). In the adopted political declaration mental and neurological disorders including Alzheimer's disease are mentioned as important contributors to the global NCD burden. The declaration states the importance of recognising that these conditions share common risk factors, including tobacco use, harmful use of alcohol, an unhealthy diet, and lack of physical activity that can benefit from common prevention responses targeting priority NCDs (cancer, diabetes, cardiovascular disease and chronic respiratory diseases).
- The current agenda for chronic disease prevention prioritises a simple five-point plan with the potential to reduce the risk of dying from one of the four main NCDs by 25% by 2025. The plan focuses, mainly, on primary prevention through population-level interventions -
  - A 40% reduction in tobacco use, achieved through full implementation of the WHO Framework Convention on Tobacco Control
  - Reduction in population levels of salt consumption (to reduce population blood pressure)
  - A 10% relative reduction in per capita adult alcohol consumption; achieved by interventions to make alcohol more expensive and less available.
  - A 10% relative reduction in adult inactivity levels (a challenging target requiring engagement with non-health sectors such as transport, energy, and urban planning)
  - An increase in the coverage of multidrug therapy, preferably fixed dose combination therapy, to at least 50% of people older than 50 years whose risk of a heart attack or stroke in the next 10 years

is 30% or more, or for anyone who has already had a heart attack or stroke.

- While dementia prevention was not a prime consideration in developing this strategy, it is well suited to this purpose. Given the support that it has received from governments worldwide, and intergovernmental agencies such as WHO and the UN, what more now needs to be done?

## **Towards a dementia-focused prevention strategy**

- An important component of the dementia prevention message is that 'it is never too late' to change habits and lifestyles. The NCD prevention strategy focuses upon middle-aged persons, and the prevention of 'premature mortality'. However, evidence presented in our report suggests that control of diabetes, smoking cessation, and, possibly, increases in physical and cognitive activity, have the potential to reduce the risk of dementia even in late-life.
- The current NCD prevention agenda focuses mainly upon population level interventions, particularly the use of legislation, fiscal measures, and voluntary agreements with industry to achieve its desired ends. Much less attention is given to health promotion activities. In the past, such programmes have proved to be remarkably effective in improving cardiovascular health. People over the age of 55 years fear the onset of dementia more than any other condition, including cancer, hence there may be untapped potential to boost older people's motivation to make and maintain changes in their life habits.
- There is also little emphasis in the NCD strategy on the role of the health sector in providing accessible and equitable treatment for the primary and secondary prevention of cardiovascular disease. The detection, treatment and control of hypertension and diabetes is currently inadequate among older people, particularly, but not exclusively in low and middle income countries. Trials such as the Finnish FINGER trial described above, may, over time, develop an evidence-base that will reinvigorate interest in the targeted intensive treatment of at risk individuals in later-life, to promote brain health, and preventing cognitive decline and dementia.
- While the message is becoming clearer, the optimal prevention strategy, and the 'messaging' to achieve the desired objectives remain obscure. We are at the foothills with a mountain to climb, in particular in comparison to the evidence-base developed over the last 50 years to guide cardiovascular disease prevention and health promotion. Alzheimer's Disease International intends to follow-up this report with a selection of 'early adopter' case studies of brain health promotion and dementia prevention programmes, in an attempt to learn from these experiences, and understand which approaches are most likely to gain traction.
- If we can all enter old age with better developed, healthier brains we are likely to live longer, happier and more independent lives with a much reduced chance of developing dementia. With an estimated global societal economic cost of dementia of over \$600 billion, and rising, the stakes could hardly be higher.



## Alzheimer's Disease International

*The global voice on dementia*

### About ADI

Alzheimer's Disease International (ADI) is the international federation of Alzheimer associations throughout the world. Each of our 84 members is a non-profit Alzheimer association supporting people with dementia and their families.

ADI's vision is an improved quality of life for people with dementia and their families throughout the world. ADI aims to make dementia a global health priority, to build and strengthen Alzheimer associations, and to raise awareness about dementia worldwide. Stronger Alzheimer associations are better able to meet the needs of people with dementia and their carers.

### What we do

- Support the development and activities of our member associations around the world.
- Encourage the creation of new Alzheimer associations in countries where there is no organization.
- Bring Alzheimer organizations together to share and learn from each other.
- Raise public and political awareness of dementia.
- Stimulate research into the prevalence and impact of Alzheimer's disease and dementia around the world.
- Represent people with dementia and families in international platforms at the UN and WHO

### Key activities

- Raising global awareness through World Alzheimer's Month™ (September every year).
- Providing Alzheimer associations with training in running a non-profit organization through our Alzheimer University programme.
- Hosting an international conference where staff and volunteers from Alzheimer associations meet each other as well as medical and care professionals, researchers, people with dementia and their carers.
- Disseminating reliable and accurate information through our website and publications.
- Supporting the 10/66 Dementia Research Group's work on the prevalence and impact of dementia in developing countries.
- Support global advocacy by providing facts and figures about dementia and monitor as well as influence dementia policies.

ADI is based in London and is registered as a non-profit organization in the USA. ADI was founded in 1984 and has been in official relations with the World Health Organization since 1996. You can find out more about ADI at [www.alz.co.uk](http://www.alz.co.uk).



### About Bupa

Bupa's purpose is longer, healthier, happier lives.

As a leading international healthcare group, we offer health insurance and medical subscription products, run care homes, retirement villages, hospitals, primary care centres and dental clinics. We also provide workplace health services, home healthcare, health assessments and long-term condition management services.

We have over 22m customers in 190 countries. With no shareholders, we invest our profits to provide more and better healthcare and fulfil our purpose.

We employ more than 70,000 people, principally in the UK, Australia, Spain, Poland, New Zealand and Chile, as well as Saudi Arabia, Hong Kong, India, Thailand, and the USA.

For more information, visit [www.bupa.com](http://www.bupa.com).

### About Bupa's social care services around the world

During any given year, Bupa cares for more than 65,000 people in nearly 460 care homes and retirement villages in the UK, Spain, Australia, New Zealand and Poland.

We are the leading international provider of specialist dementia care. Of our care home residents, around three quarters have dementia.

In the UK, Bupa Care Services is providing care to nearly 29,000 residents during 2014 in 287 homes.

In Australia, Bupa Aged Care Australia is the largest private operator of residential aged care facilities. Caring for around 8,000 residents across 62 homes.

In New Zealand, Bupa Care Services New Zealand cares for more than 4,600 people in 48 homes, 21 care villages. It also operates 25 retirement villages and seven brain rehabilitation sites and provides support via a personal medical alarm network to over 14,000 people.

In Spain, Bupa (Sanitas Residencial) is one of the biggest geriatric care companies. It now has 41 care homes, caring for around 6,700 residents during 2014.

In Poland, Bupa (LUX MED) has a large nursing and residential care home.

We combine experience and expertise to care for our residents living with the dementia, providing a safe, comfortable and stimulating environment in our care homes. Our expertise in dementia care includes an innovative 'Person First' approach where our care revolves around each person's own needs and life history.

Alzheimer's Disease International:  
The International Federation  
of Alzheimer's Disease and  
Related Disorders Societies, Inc.  
is incorporated in Illinois, USA,  
and is a 501(c)(3) not-for-profit  
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