

Brain Health and Dementia Prevention in Ireland – A discussion paper

Joint discussion paper funded by the Alzheimer Society of Ireland and authored by the Institute of Public Health



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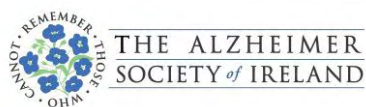


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June 2015



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Acronyms

ADI	Alzheimer's Disease International
APOE	Apolipoprotein E
ASI	Alzheimer Society of Ireland
BMI	Body Mass Index
CVD	Cardiovascular disease
DoH	Department of Health
EuroCoDe	European Collaboration on Dementia
FINGER	Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability
HSE	Health Service Executive
IPH	Institute of Public Health in Ireland
MAPT	Multidomain Alzheimer Preventive Trial
MRU	Memory Research Unit
NICE	National Institute for Health and Care Excellence
NICOLA	Northern Ireland Cohort Study for the Longitudinal Study of Ageing
NIH	National Institutes of Health (US)
PARs	Population Attributable Risks
PreDIVA	Prevention of Dementia by Intensive Vascular Care Study
RCTs	Randomised Control Trials
RRs	Relative Risks
TILDA	The Irish Longitudinal Study of Ageing
UK	United Kingdom
US	United States
VaD	Vascular Dementia
WHO	World Health Organization

Key points

- This discussion paper presents a rapid review of evidence on dementia prevention and presents estimates for the number of dementia cases that could potentially be preventable through modifying specific risk factors in Ireland. The paper focuses only on primary prevention which relates to delaying or preventing the onset of dementia.
- This paper also includes a preliminary exploration of how the public health community can respond to the evidence on dementia prevention in the areas of research, policy and practice.
- Current estimates suggest that there were nearly 48,000 people living with dementia in Ireland in 2011. The number of people with dementia in the population is expected to rise in the context of population ageing. Although dementia is more common among older people it is not a normal part of ageing.
- There is currently no known cure for dementia. The level of disability associated with dementia has significant implications for people with dementia, their families and the health and social care system.
- The publication of the *Irish National Dementia Strategy* has been significant in articulating a strategic approach and priority action areas. These include measures to promote a better understanding of dementia including modifiable risk factors.
- The *Irish National Dementia Strategy* proposes that effective preventive strategies to reduce the prevalence of dementia or delay the onset of clinical disease should

be guided by the Department of Health's Policy Frameworks for the Management of Chronic Disease.

- The evidence of what works in dementia prevention is unclear in many domains and there are many challenges in terms of interpretation. Not all cases of dementia can be prevented and risk is influenced by as yet poorly understood genetic factors.
- However, several evidence reviews now provide useful guidance in terms of the factors that may be important in modifying dementia risk at population level. These include health behaviour factors, cardiovascular factors, psychosocial factors and developmental factors.
- Health behaviours may be important in modifying dementia risk. Physical activity is beneficial to brain health and contributes to maintaining cardiovascular health, mental health and mobility in later years. Being physically active reduces some of the risk of developing dementia. This finding reinforces the need to support the implementation of the forthcoming *National Physical Activity Plan* and enhance the proportion of people who are physically active in all age groups.
- Smoking is associated with an increased risk of developing dementia. This would suggest that ongoing and enhanced investment in effective tobacco control, including focussed smoking cessation at all stages of life, may form a central component of prevention efforts. It is not yet clear to what degree use of e-cigarettes may negate against some of the toxic effects of inhaled tobacco smoke on the brain.

- Cardiovascular risk factors are associated with an increased risk of dementia including high blood pressure, mid-life obesity and Type 2 diabetes. The risk of dementia is particularly raised among those with existing cardiovascular disease or stroke. This would indicate that implementation of the governments cardiovascular strategy may be of particular importance in reducing the population risk of dementia in terms of enhancing the detection and management of cardiovascular risk factors and providing optimal comprehensive care for those with existing cardiovascular disease. It is not yet clear the degree to which enhanced early clinical intervention for cardiovascular and stroke events can modify the subsequent risk of dementia.
- Central adiposity (a large waist) and Type 2 diabetes are associated with an increase in dementia risk. However, there is not yet clear evidence to show that modification of these factors, once present, can reduce subsequent risk of dementia. Current trends in mid-life overweight and obesity in Ireland and the associated risk of diabetes may have negative implications for the future prevalence of dementia. Effective primary prevention of obesity may represent a viable goal within the primary prevention of dementia at population level.
- There is promising evidence to suggest that staying mentally active and socially engaged may reduce some of the risk of developing dementia. This would indicate the implementation of the *Positive Ageing Strategy*, the development of age-friendly communities and combatting social exclusion and isolation could be important in modifying dementia risk.
- Adverse socio-economic circumstances are also associated with an elevated risk of dementia. Social determinants of health, in particular income and education, are implicated in determining risk of dementia. In this regard, policies which prioritise addressing health inequalities may be of particular importance. Policies aimed at

minimising early school leaving and promoting life-long learning may therefore be significant in reducing dementia risk at population level.

- There are significant associations between sleep disturbance and the risk of dementia. It is not yet clear whether improvement of sleep patterns could result in lowered risk of dementia or to what degree the association with sleep disturbance merely reflects an early feature of dementia.
- Heavy alcohol consumption has been associated with dementia risk and cognitive decline. There is no convincing evidence of an association with moderate alcohol consumption. There is a significant level of heavy alcohol consumption in Ireland and ongoing public health measures to address binge drinking and excess consumption may contribute to reducing the risk of dementia in later life.
- Establishing the role of nutrition in determining the risk of dementia is inherently highly complex. The current evidence does not support a protective role for antioxidants in reducing risk of dementia although weak positive associations have been found in terms of eating a Mediterranean diet and fish.
- The risk of developing dementia is higher among those who experience adverse life events and psychological distress. There are associations between dementia and depression. However, the evidence does not yet provide clear guidance on what might be effective from a dementia prevention perspective in terms of the promotion of mental health or the care of those with an existing clinical diagnosis of depression.
- In the context of developmental factors, there is some evidence to suggest that adverse circumstances in foetal development, early years and childhood may be

associated with a consequent increased risk of dementia. However, establishing causality between early life factors and later life dementia is particularly difficult.

- This paper includes estimates of the effect of risk factor modification in Ireland based on similar international analyses. The analyses estimated the population attributable risk for seven risk factors (Type 2 diabetes, midlife hypertension, midlife obesity, physical activity, depression, smoking and low educational attainment) from the SLÁN survey and used these in the context of the 2011 dementia prevalence estimates. There are several significant caveats to consider in the interpretation of the analyses which are detailed in the main text of the paper.
- Based on the best available evidence, it was estimated that a 10% reduction in all the known modifiable risk factors (and taking into account the associations between these risk factors) could have resulted in 1084 fewer cases of dementia in 2011.
- While evidence is incomplete, there is now an opportunity to integrate brain health and dementia prevention perspectives within the core elements of national public health, disease prevention and health promotion policies and programmes.

Executive Summary

Dementia prevention and government policy

Approximately 47,849 people were living with dementia in Ireland in 2011. This number is expected to double by 2031 to about 90,000 as incident rates of dementia are set to rise with population ageing (Pierce et. al. 2014). Although much remains to be established at a causal level, epidemiological research indicates that there is scope for reducing dementia prevalence and age-specific incidence through addressing modifiable risk factors. There is a growing consensus for the mobilisation of public health approaches to attempt to reduce the prevalence of dementia through primary prevention.

The publication of the *Irish National Dementia Strategy* has been significant in articulating a strategic approach and priority action areas. These include measures to promote a better understanding of dementia including modifiable risk factors. The *Irish National Dementia Strategy* states that effective preventive strategies to reduce the prevalence of dementia or delay the onset of clinical disease should be guided by the Department of Health's *Policy Frameworks for the Management of Chronic Disease*. As reliable biological markers for dementia, agents to delay dementia onset and progression and a cure for dementia are not yet available, identifying effective preventative strategies remains important within the broader policy approach.

Aims and objectives

This discussion paper presents a rapid review of evidence on the primary prevention of dementia and presents estimates for the number of dementia cases that could potentially be preventable through modifying specific risk factors in Ireland. The paper focuses only on primary prevention which relates to delaying or preventing the onset of dementia.

Specifically, this discussion paper presents:

- *a rapid review of the current evidence-base on dementia prevention internationally*
- *estimates of the number of dementia cases that might be prevented by addressing modifiable risk factors*
- *considerations for integrating a brain health and dementia prevention perspective into public health research, policy and practice in Ireland*

What can be prevented and how?

Not all dementia can be prevented. Risk of dementia in later life is determined by several non-modifiable factors such as age, sex, learning disabilities and genetics. However, there is a growing body of evidence that other factors may be modified to reduce risk or delay the onset of dementia (Farrow, 2010). Modifiable factors can be categorised as lifestyle or health behaviour factors, cardiovascular factors, developmental factors, and psychosocial and mental health factors (ADI, 2014). The first aim of this paper was to conduct a rapid review of international evidence on modifiable risk and protective factors for dementia. The key findings from the review are outline below:

- Physical activity is beneficial to brain health as well as contributing to maintaining cardiovascular health, mental health and mobility in later years. Being physically active appears to reduce some of the risk of developing dementia.
- A number of studies show a relationship between smoking and dementia in later life.
- Heavy alcohol consumption has been associated with dementia risk and cognitive decline. There is no convincing evidence of an association with moderate alcohol consumption.
- There is promising evidence to suggest that staying mentally active and socially engaged may reduce some of the risk of developing dementia.
- There is consistent evidence to support an association between cardiovascular risk factors and dementia risk in later life.
- Hypertension, obesity and dyslipidaemia are more likely to act as risk factors in mid-life. Hypertension in mid-life increases the risk of dementia onset in late life

while Type 2 diabetes in later and probably mid-life increases the risk of dementia in later life. Mid-life obesity and dyslipidaemia may also increase risk in later life, although there is insufficient evidence on these associations at present.

- Addressing psychological distress, depression and sleep disturbance throughout the life course may confer significant benefit in later life. To date, there is insufficient evidence to support any particular interventions in targeting psychosocial factors to reduce dementia risk in later life; however this is a promising area for further research.
- In the context of developmental factors, brain development and consequent risk of dementia appears to be linked to adverse circumstances in foetal development, early years and childhood. However, determining causality between early life factors and later life dementia is particularly difficult.
- Establishing the role of nutrition in determining the risk of dementia is inherently highly complex. The current evidence does not support a protective role for antioxidants in reducing risk of dementia although positive associations have been found in terms of eating a Mediterranean diet and fish.

Although specific effective interventions have not yet been fully explored in randomised controlled trials (RCTs) these findings suggest that there is significant potential for public health interventions to reduce dementia prevalence through more effective prevention and control of these risk factors.

Estimates for preventable dementia in Ireland

The second aim of this paper was to estimate the effect of a reduction in the prevalence of key modifiable risk factors on the prevalence of dementia at a population level in Ireland. The population attributable risk for seven known modifiable risk factors for later life dementia was calculated based on the estimated 2011 dementia prevalence rate for Republic of Ireland ($n = 47,849$) and population prevalence of risk factors measured in the Survey of Lifestyle, Attitudes and Nutrition (SLÁN) 2007. It was estimated that a 10% reduction in all the known modifiable risk factors (and taking into account the associations between these risk factors) could have resulted in 1,084 fewer cases of dementia in 2011,

representing a reduction of 2.3% in the population prevalence. As further studies are required to firmly establish causality of risk factor exposure on dementia prevalence in later life, these estimates should be interpreted with care, and continually revised as further evidence emerges.

Implications for research and policy in Ireland

In order to develop effective policies it is important to ensure the actions are evidence based. While much evidence on dementia prevention is presented in this paper, further research is required to determine the causal pathways between modifiable risk factors and dementia. The development of epidemiological and intervention studies on dementia prevention is critical to inform appropriate prevention strategies in an Irish context. In addition to the enhancement of information systems to provide reliable data on dementia cases in Ireland, as recommended by Cahill et al (2012), the establishment of a comprehensive research and data programme linked with other public health policy indicators would clarify the linkages between health promotion action and prevention of dementia in an Irish context. Furthermore, there is much potential to examine the association between risk factors and dementia onset using data sources such as TILDA.

Although evidence is incomplete, there is now an opportunity to explore the potential of developing and implementing strategies to reduce dementia risk in Ireland. The concept of “brain health” is emerging as an important paradigm which could make a real contribution to addressing the challenge of dementia in Ireland. Within this paradigm brain health is the corner stone of public health action to address dementia prevention based on four explicit principles:

1. An emphasis on primary prevention
2. A community and population health approach
3. Evidence based actions
4. A commitment to eliminating disparities in dementia.

This approach acknowledges that the development of dementia occurs across the life course with factors accumulating, interacting and expressing themselves at different

periods. In addition, it encompasses action on social determinants of dementia which requires a whole-of-government approach as espoused in *Healthy Ireland – A Framework for Improved Health and Wellbeing 2013 – 2025* (Department of Health, 2013a). Overall, the evidence presented in this paper suggests that dementia prevention should be addressed as a public health issue in the same way as other chronic conditions and measures to prevent dementia may require embedding in core elements of major public health policies.

1. Introduction

1.1 Background

The Irish National Dementia Strategy was published in 2014 and articulates a strategic commitment towards addressing dementia at a policy level in Ireland. The Alzheimer Society of Ireland (ASI) and the Institute of Public Health in Ireland (IPH) welcomed the development of a more strategic and comprehensive approach to preventing, managing and caring for dementia in Ireland.

Dementia is a multifactorial syndrome or disorder, characterised by progressive global deterioration of cognitive abilities in multiple domains including memory and at least one additional area – learning, orientation, language, comprehension and judgement – severe enough to interfere with daily life (Daviglus et al., 2010). While cognitive impairment is a feature of dementia there are other causes of cognitive impairment. Dementia is an overarching term encompassing Alzheimer’s disease, vascular/ multi-infarct dementia, dementia with Lewy bodies, and other dementias including fronto-temporal dementias.

It is estimated that 47,849 people were living with dementia in Ireland in 2011 and this number is expected to almost double by 2031 to about 90,000 (Pierce et al., 2014). It is now well recognised that there is a significant need to mobilise evidence-informed action in the fields of prevention as well as in care and service planning. Evidence can be considered sufficient to justify sustained public health and policy actions across the life course, bringing dementia prevention into the frame of public health policy in addition to health and social care services. Within the ASI response to the Department of Health’s consultation on the *Irish National Dementia Strategy*, ASI advocated for priority to be afforded to dementia as one of the most significant public health issues in Ireland. The IPH response placed particular emphasis on a commitment to explore the development of a public health approach to dementia prevention (McDaid and McAvoy, 2012), echoing calls from the World Health Organization (World Health Organization, 2012).

'There is growing consensus that the scientific evidence is now sufficient to justify policy action across the life course and for further research to reduce modifiable risk factors for dementia and improve the population profile for recognised protective factors'
WHO, 2012

In 2014, a number of organisations and experts from across the UK dementia and public health community, including Ministers, researchers and practitioners, signed the Blackfriars Consensus Statement (Lincoln et al., 2014). The Statement highlights the need for focus on dementia risk reduction and the promotion of brain health. It set out a range of actions to advance this approach including:

- integration of dementia prevention into national policy
- greater collaboration between clinical practitioners, public health and prevention experts, researchers and policy makers concerned with dementia
- a focus on upstream population level actions as well as community and individual level interventions
- careful assessment of the potential impact of strategies and interventions to reduce the impact of health inequalities on dementia risk
- development of national policy guidelines to translate dementia prevention research into practice.

Public Health England recently recognised dementia risk reduction as one of its seven key public health priorities in 2014. The Alzheimer's Association and Centers for Disease Control and Prevention in the U.S. have developed a public health road map for dementia prevention (2013) based upon a population health approach. Similarly, the National Institute for Clinical Excellence (NICE) in the UK recently published draft evidence based guidelines on mid-life approaches to prevention of dementia, disability and frailty in later life. Finally, the most recent *World Alzheimer's Report* focused its attention on a comprehensive analysis of modifiable factors for dementia risk reduction and critically appraised the evidence in terms of its usefulness for public health (ADI., 2014).

Such modifiable factors are often conceptualised as delaying factors which postpone the onset of dementia rather than definitively preventing the condition or avoiding underlying neuropathology (Gatz et al., 2006).

1.2 Aims and objectives

Adopting a three stage approach to prevention of dementia has been recommended - primary prevention through health behaviour modification; secondary prevention to ensure timely diagnosis followed by appropriate intervention and treatment to delay the progression of dementia; and tertiary prevention to promote quality of life and optimum functioning and well-being of the individual as they live with their progressive condition (Prince et al., 2011). This discussion paper provides a platform for a range of stakeholders to consider the role of public health policy and practice in dementia prevention in Ireland in the domain of primary prevention. Primary prevention of dementia relates to modification of those factors shown to promote or reduce dementia risk.

The primary objectives of this discussion paper are to:

- 1. conduct a rapid review of the current evidence base on the primary prevention of dementia internationally*
- 2. develop estimates of the number of dementia cases that might be prevented by addressing modifiable risk factors*
- 3. consider the integration of a brain health and dementia prevention perspective into public health research, policy and practice in Ireland.*

1.3 An epidemiological transition - a policy challenge

An epidemiological transition is underway as a result of population ageing - this is characterised by an increase not just in chronic diseases such as heart failure, diabetes and respiratory disease but also in the context of neurodegenerative disorders (Broe, 2003).

Estimating dementia prevalence and incidence is challenging, particularly where national registries and large population studies are lacking. In Ireland, prevalence has been

estimated from studies undertaken in other European countries and applied to Irish Census data. Pierce et al. (2014) estimated that 47,849 people were living with dementia in Ireland in 2011 and projected that this number is expected to double by 2031 to about 90,000.¹ These projections are based principally on CSO fertility and migration assumptions and not related to data on the current or projected prevalence of modifiable risk factors.

A bio-psycho-social model is proposed based on determinants of health approach, recognising that it is the culmination of environment and behaviour affecting our biology, beginning before we are born and extending throughout our lives that determines much of our dementia risk in later life. This approach also encompasses the personhood of those with dementia which has not always been recognised (Barlett and O'Connor, 2007) and allows for a consideration of the potential effects of health inequalities on dementia prevalence and outcomes.

The impact of dementia on an individual's physical, psychological and emotional health is profound. Dementia is a leading cause of disability and reduced independence in later life with significant implications for quality of life as well as premature mortality (World Health Organization, 2012). Fitzpatrick et al (2005) estimated median survival from the point of a clinical diagnosis of Alzheimer's disease was 7.1 years (95% CI 6.7–7.5 years) and for vascular dementia 3.9 years (3.5–4.2 years). Evidence also supports the significant impact of caring for a relative with dementia which can include compromised health and wellbeing as well as social isolation and financial hardship (Brodaty, 2009).

In addition to the impact on individuals and their caregivers, the prevalence of dementia has significant economic implications for health and social care budgets. The cost of care for people with dementia draws significantly on a variety of public and private resources including the health services, social care services, families, and the voluntary sector (O'Shea, 2000). Connolly et al (2014) estimated the total cost of dementia in Ireland in 2011 at €1.69 billion, equating to €40,500 average cost per person with dementia per

¹ Estimates were based on the application of EuroCoDe dementia age and gender specific prevalence rates to the Irish census data for 2011.

annum. In the UK it has been found that the cost of care for people with dementia is relatively higher than those with stroke, heart disease or cancer, however resources allocated to dementia care continue to be substantially lower than each of these individual disease groups (Lowin et al., 2001, Trepel, 2012).

It has been argued that there is a research bias towards tackling conditions that add years to life, rather than life to years: A bibliometric study conducted in 2009 found an inverse correlation between research effort and more disabling conditions, including dementia (Prince and Jackson, 2009).

A recent review of key health promotion policy documents in Ireland (Pierce et al., 20-22 October 2014) found that the links between several modifiable risk factors and diseases other than dementia were frequently mentioned in 12 of the documents identified, but the links between modifiable risk factors and dementia were in contrast very rarely mentioned.

A combination of ageist and fatalistic assumptions around the potential for modifying disease risk and progression may instil hesitancy among policy makers to engage with the issue of dementia prevention as part of the chronic disease spectrum and indeed as part of wider public health policy approaches. Equally, policy makers may argue that releasing resource to the issue of dementia prevention is only contingent on strong evidence of effectiveness and that many of the potentially modifiable risk factors are already addressed within existing prevention approaches for cardiovascular, respiratory and other chronic disease strategies.

1.4 Dementia risk and the role of prevention

Risk of dementia in later life is determined by several factors including non-modifiable factors such as age, sex and genetics, as well as modifiable factors. Most dementia is age-related with the likelihood of incidence doubling every five years after the age of 65 (World Health Organization, 2012). However, although the risk of dementia increases with age, dementia is not a normal part of ageing. Certain individuals and subgroups are at high risk of early on-set dementia, in particular people with genetic predisposition

including those with Down's Syndrome (Cahill et al., 2012).

The APoE gene is considered a common genetic risk factor for non-familial, late onset Alzheimer's disease. It is a marker of susceptibility, meaning that it is neither sufficient nor necessary to cause disease (ADI., 2014). Although genetic factors cannot be modified, other risk factors for dementia can be modified to minimise other risks in those who have the APoE gene and identification and targeting of high risk sub-groups could confer some potential for prevention (ADI., 2014). The scope for this targeted approach remains unclear.

Dementia modifiable risk factors

Despite the impact of non-modifiable risk factors on dementia risk, other factors may be modified to reduce the risk of the disease or delay the onset of dementia (Farrow, 2010).

'It is generally accepted that people with better vascular health, who have been more physically, mentally and socially active, who adopt healthy eating habits, who don't smoke and who drink alcohol in moderation are significantly less likely on average to develop dementia in later life' (Farrow, 2010)

Before an overview of evidence on modifiable dementia risk factors is presented, it is important to highlight that risk pathways to dementia have not yet been fully determined. Many factors associated with increased dementia risk have yet to be established at a causal level. While causation cannot be attributed to any one factor it is generally considered that causal factors accumulate over the lifetime; referred to as a 'causal cascade' (Hachinski, 2008). Triggers of the causal cascade are not well understood. Several aetiological hypotheses have been proposed highlighting potential links of various risk factors to both vascular and neurodegenerative brain pathologies that can cause dementia (Mangialasche et al., 2012, Kivipelto and Solomon, 2009). These theories include the vascular hypothesis, inflammatory hypothesis, oxidative stress hypothesis, toxic hypothesis and psychosocial hypothesis (Qui and Fratiglioni, 2011).

The concepts of brain and cognitive reserve have been proposed to account for a person's ability to function in the context of dementia neuropathology. Such reserves, which develop in early life and represent a lifelong accumulation of exposures to mental stimulation, may buffer the expression of dementia symptoms in the presence of neurodegenerative disease in later life. The strength of association can vary at different times and it is also possible for risk factors in early or mid-life to become a consequence of the neurodegeneration process in later life, referred to as prodromal aspects of dementia.

Compression of cognitive morbidity – fewer years with dementia

There are currently no established diagnostic biomarkers of dementia-related brain damage (Frisoni et al., 2013). Prevention of dementia may thus correspond to a delay in symptomatic onset until death or at least a compression of time lived with the disease in later life, as referred to by Langa et al (2008) as 'the compression of cognitive morbidity'. If dementia is deferred into later old age and occurs closer to the end of life, fewer years will be lived with disease. Modelling studies suggest that even a small delay in the age of onset of dementia reduces population prevalence substantially.

Evidence from recent studies in several countries indicates that the incidence of age-specific dementia is already in decline with onset deferred into progressively older ages (Mathillas J et al., 2011, Matthews et al., 2013, Lobo et al., 2007, Langa KM et al., 2008, Qiu et al., 2011). This has been largely attributed to improved cardiovascular health. Improvements in the level of education achieved among successive generational cohorts have also been postulated as an influencing factor. In an Irish context the introduction of free primary school education as a national policy in the 1960's could conceivably have conferred significant gains for those generational cohorts that benefited (O'Sullivan, 2012). In addition, there has been a significant shift in cardiovascular morbidity in the Irish population over the past decade, attributed to both improved health behaviours and medical interventions (Bennett et al 2006). This would indicate that there may in fact be much to learn from retrospective analysis of a range of government policies in Ireland on dementia risk as well as a need to invest in comprehensive longitudinal studies into the future.

2. A Summary of Key Learning on Modifiable Factors from the International Literature

This section presents a synopsis of findings based on systematic reviews and meta-analyses. The recently published World Alzheimer Report (ADI., 2014) provides a comprehensive analysis of modifiable factors for dementia risk reduction internationally. Firstly, an overview of important methodological challenges in determining the effects of modifiable risk factors on dementia prevalence is outlined.

2.1 Interpretation of the dementia prevention evidence

Evidence relating to dementia prevention is intensely debated in the scientific literature. A report commissioned in 2010 by the National Institutes of Health (NIH) in the United States stated '*firm conclusions cannot be drawn about the association of any modifiable risk factor with cognitive decline or Alzheimer's disease*' (Daviglius et al., 2010). However, other studies have refuted the findings of this report arguing that the analytical approach applied in the review failed to take sufficient account of the life course perspective (Mangialasche et al., 2012). Alzheimer's Disease International recently commented that conclusions of the report may have led to unwarranted pessimism regarding the potential for primary prevention (ADI., 2014).

The majority of evidence on dementia risk is based on observational studies which are subject to issues of internal validity.² Such studies can provide evidence of associations but cannot adequately establish causality as they are subject to confounding and bias. The ADI report (2014) identified that many published systematic reviews have not adequately addressed issues of internal validity when critically appraising studies of prevention. In particular, issues of prodromal factors, reverse causality and bias are particularly pertinent.

Prodromal factors

Some observed exposures in epidemiological research may be acting as prodromal factors rather than independent predictors of dementia. This means that the observed associations reflect an expression of dementia neuropathology itself rather than a true

² Internal validity is the degree to which observed changes in a dependent variable can be attributed to changes in an independent variable.

cause of the disease. For example, where early pre-clinical effects of dementia may cause particular behavioural adjustments and be expressed as reduced physical activity or depression (ADI., 2014). To address this issue measurement of exposure status in disease-free individuals is required. However given the period of development between exposure and outcome over the life course and a lack of biological markers it is difficult to distinguish true risk factors from prodromal signs.

Reverse causality and bias

Establishing the direction of effect for risk and protective factors for dementia can be challenging and there is scope for potential reverse causality. Ideally, study designs should ensure adequate baseline measures for exposures well before old age and with a long period of follow up to establish the true direction of effect. Dementia risk research is vulnerable to particular biases:

- Participation bias where those with genetic susceptibility might be more inclined to participate in dementia research thereby affecting the representativeness of the sample and the transferability of results to the general population.
- Individuals with increased risk profiles for dementia also have increased risk for other conditions including cardiovascular disease and diabetes and are more likely to die prematurely. As such this can artificially deflate observed associations.
- Study participants who develop dementia can be more likely to drop out of studies, and also have recall issues in retrospective studies potentially biasing observed associations.
- Information bias can influence study outcomes if, for example, data on study participants is sourced from health care records. Healthier individuals, with less multimorbidity and need for healthcare consultations may be under-represented in such studies and as a consequence observed associations could be inflated.

Randomised Controlled Trials

Randomised Control Trials (RCTs) investigating the effect of removing or reducing the modifiable risk factors for dementia would provide the strongest evidence for the potential of dementia risk reduction. However very few RCTs have been conducted on

modifiable factors for dementia risk and such studies would be complex in many domains including the ethical dimension.

The gradual development of cognitive impairment which is often discovered far downstream from the onset of symptoms is also problematic for current research approaches. Given that symptom onset may not occur until many decades after initial biological expression of neuropathology, it is likely that the design of such RCTs would be inadequate to capture the true potential of risk reduction. RCTs are also subject to limitations:

- RCTs establishing causality for some common chronic conditions have excluded people with multimorbidity (co-existence of two or more chronic conditions in an individual) which is now common in older people (McDaid, 2014). Such RCTs are vulnerable to issues of external validity³ and may not be generalisable to older people.
- Risk exposures that occur in early or mid-life require long-term follow up to establish causal links and RCTs are not feasible given the need to maintain the intervention on a randomised basis for long enough to demonstrate an effect on risk reduction in later life.
- It would be unethical to randomise modification for several potentially modifiable risk factors for dementia since benefits have already been established for many other health conditions.

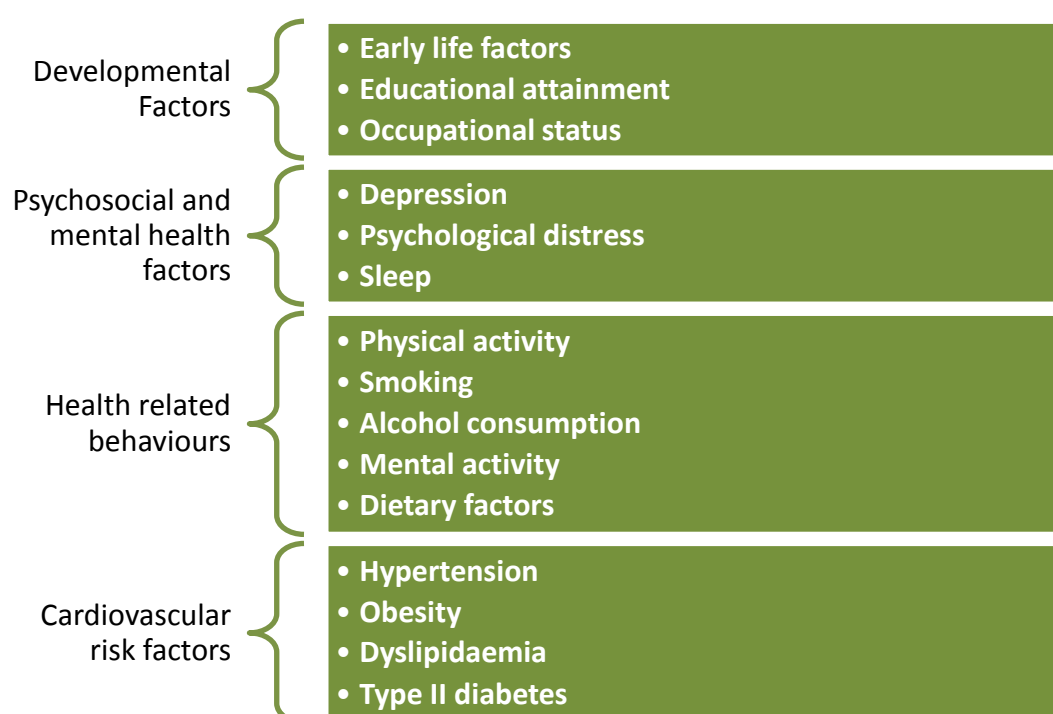
A wide range of research on dementia exists across many disciplines including laboratory based and clinical studies in neuroscience, health service settings as well as in the frame of sociology and longitudinal studies of ageing. No single discipline has yet achieved definitive answers on dementia risk. Additional insights may arise at the interface between public health, epidemiology, neuroscience and sociology as well as from more intensively tuning in to both the lived experience and the life history of those in the earlier stages of the disease.

³ External validity relates to the generalisability of research findings to and across various populations and settings.

2.2 Modifiable risk and protective factors

Modifiable factors can be categorised as developmental factors, psychosocial and mental health factors, health behaviour related factors and cardiovascular factors. Modifiable factors associated with dementia can be considered as risk or protective factors. Risk factors increase the likelihood of dementia in later life and protective factors confer increased protection from developing dementia in later life. While some factors may have an influence in early life, others may have an effect in mid-life and can interact with other factors over the life course to produce an effect in later life.

Figure 1. Summary of known modifiable protective and risk factors for dementia



Cardiovascular risk factors

Hypertension, dyslipidaemia, obesity, Type 2 diabetes and smoking are predisposing factors for cardiovascular disease including heart disease and stroke. Those who experience a stroke have approximately double the risk of developing dementia, with most of the increased risk concentrated in the three years following the stroke event (Savva and Stephan, 2010). It is thought that these factors increase risk of dementia through the increased risk of atherosclerosis and the inflammatory or thrombotic

components of vascular disease (ADI, 2014). Risk is not confined to vascular dementia and studies support an association between heart disease and Alzheimer's disease (Newman et al., 2005, Hayden et al., 2006).

Individuals show a reduced incidence of hypertension, obesity and hyperlipidaemia in advance of the clinical onset of dementia in later life; this can occur 5-15 years prior to clinical diagnosis (ADI, 2014). It is hypothesised then that cardiovascular risk factors may behave as prodromal indicators as well as risk factors for late-onset dementia, adding to the complexity in interpretation.

Hypertension

There is a significant association between hypertension and reduction in brain volume (Beauchet et al., 2013) as well as an association with an increased risk for dementia in later life. To date the evidence suggests that midlife hypertension is significant in determining dementia risk in later life (ADI, 2014). Late life hypertension may be inversely associated with dementia with an observed decline in blood pressure levels preceding the onset of disease in later life. To date, research has failed to demonstrate a beneficial effect of lowering blood pressure on incident dementia – however this may be attributable to the focus on hypertension reduction in later life. Reducing midlife hypertension may have value in reducing the dementia risk profile and further studies are necessary to establish the effectiveness of intervening in mid-life.

Obesity

Similar to hypertension, the evidence on risk related to obesity appears to be concentrated in midlife. Evidence on central obesity and dementia risk, using waist circumference measures, appear to be more consistent than those examining overall BMI (ADI, 2014). These findings indicate that the elevated risk of dementia associated with mid-life obesity may be principally mediated through insulin resistance and hyperinsulinaemia linked to Type 2 diabetes.

Dyslipidaemia

There are several hypotheses proposed to explain the associations observed between dyslipidaemia and dementia risk in later life. These hypothesis focus principally on the role

of cholesterol in neuronal plasticity and function. As with hypertension and obesity, the association between cholesterol levels and dementia risk in later life appears to be age dependent. Studies examining the effects of midlife dyslipidaemia on later life dementia risk demonstrate the most consistent findings. However, there is currently little evidence to demonstrate that the prevention or treatment of dyslipidaemia can reduce late-onset dementia risk. The evidence does not support a role for prescription of statins in the context of primary prevention of dementia.

Type 2 diabetes

There is consistent evidence of an association between Type 2 diabetes in later life and incident dementia risk in later life. Evidence also suggests that mid-life diabetes may have an equivalent if not a greater effect on dementia risk in later life suggesting that duration of disease may influence risk (ADI, 2014). The effect is stronger for vascular dementia compared to Alzheimer's disease with cerebrovascular disease likely to be an important mediating mechanism. Several underlying mechanisms have been proposed to explain this association but evidence on biological pathways is inconsistent. Few RCTs have been conducted to examine the potential beneficial effects of improved diabetes control on dementia risk. Both primary prevention of diabetes and appropriate management may be significant for altering the risk of dementia in later life.

Health behaviours

Several health related behaviours demonstrate a consistent association with dementia risk in later life. Clustering of unhealthy behaviours is an issue in assessment of the relative importance of these behaviours at a population level.

Physical activity

The beneficial effects of physical activity on brain health have been well demonstrated in epidemiological and animal- model studies (ADI, 2014). Physical activity contributes to a reduction in hypertension, dyslipidaemia, and obesity, thereby indirectly influencing dementia risk through intermediary cardiovascular risk factors. Physical activity is also associated with improved micro-structure and physiology of blood vessels in the cerebrovascular system. Given that functional impairment may proceed and gradually

progress after the onset of dementia pathology, investigations to establish the direction of the association between physical activity and dementia risk in later life requires well designed RCTs with long-follow up. Recent RCTs testing the short term effects of physical activity programmes and aerobic exercise on cognitive function have shown small but consistently positive results (ADI, 2014).

Mental activity

Experimental studies demonstrate measurable improvements from mentally stimulating activities for brain vascular health (Black et al., 1987, Saczynski et al., 2008), structure (Brown et al., 2003, Kempermann et al., 1997) and function (Cracchiolo et al., 2007, Cabeza et al., 2002). The effect of cognitive stimulation on dementia risk in later life is not easily discernible as a reduction in cognitive activity can be a prodromal sign of dementia disease. Prospective cohort studies have found a consistent effect of cognitive stimulation on both brain structure and function, although findings should be interpreted with caution as follow-up times may have been insufficient to adequately establish a causal rather than a prodromal effect. At present, although promising, there is insufficient evidence to support specific cognitive interventions to reduce dementia risk. RCTs which are currently underway could provide some useful findings to support interventions in this field.

Smoking

Tobacco smoke contains a myriad of chemical compounds including nicotine, carbon monoxide and heavy metals. There is strong evidence to support an association between current smoking behaviours and dementia risk. There is some evidence of a dose-response relationship, indicating that the more someone smokes, the higher their risk for developing dementia. It is proposed that tobacco smoking increases dementia risk through exerting direct oxidative stress and through inflammatory mechanisms as well as contributing to disease in the blood vessels of the brain. An association between second-hand smoke exposure and increased dementia risk has also been observed (McKenzie et al., 2014). There is some evidence to suggest that smoking may impair the brain's abilities in the domains of memory, learning and reasoning irrespective of neurodegenerative pathology. For example Dregan et. al. (2013) found a consistent association between smoking and measures of cognitive ability including memory and executive functioning.

Furthermore, tobacco smoke has been implicated in catalysing processes associated with the neuropathology of Alzheimer Disease, with some suggestion that nicotine plays an independent role (Swan and Lessov-Schlagga, 2007).

Ex-smokers do not appear to be at any increased risk, suggesting that quitting smoking may confer particular benefit in reducing dementia risk (ADI., 2014). Studies investigating the impact of smoking in later life are subject to bias – premature smoking-related mortality may be deflating observed effect sizes.

Alcohol consumption

The relationship between alcohol consumption and dementia risk in later life shows a J-shaped association, where moderate drinkers are at a lower risk of dementia than either abstainers or heavy drinkers (ADI., 2014).⁴ Studies of mortality risk from alcohol consumption have found that the ‘abstainer’ category in studies is a crude measure that combines a diverse mix of high and low risk groups. More sensitive categorisation based on reason for not drinking helps to explain more of the variance in mortality risk (Ancoli-Israel, 1997). This risk factor may be of particular relevance to the Irish context as the rate of alcohol consumption in Ireland is one of highest in Europe (Byrne, 2010; OECD, 2015). According to Long and Morgan (2010) more than half of Irish adults (54%) were classified as harmful drinkers (using the WHO AUDIT-C screening tool). This equates to approximately 1.4 million drinkers at harmful levels in Ireland in 2013. A recent study estimates that 2 in every 100 adults develop alcohol-related brain injury (ARBI) (McMonagle, 2015). ARBI refers to damage caused to the brain by excessive alcohol use and may results in structural or functional changes to the brain, which in turn leads to cognitive impairment (McMonagle, 2015). Further research to establish dose response patterns based on more developed measures of alcohol consumption will be important in establishing the true relationship between alcohol and dementia risk.

Dietary factors

Several dietary factors have been identified as conferring a protective effect on dementia risk in observational studies, particularly in the context of nutrient deficiency and

⁴ As with other risk factors, measurement of heavy drinking is not always well defined and it is not always clear what constitutes heavy drinking in studies.

supplementation, including B vitamins, antioxidants, Omega-3 and adherence to a Mediterranean diet. RCTs have shown consistent effects of vitamin B supplementation on a reduction in homocysteine levels, however further evidence is required to demonstrate whether this translates into a reduction in cognitive decline or dementia incidence. Higher fish consumption is associated with lower dementia risk. Modest evidence also exists on a positive association between adherence to a Mediterranean diet⁵ and reduced dementia risk (ADI, 2014). Further research is required to establish the causal mechanism conferring the protective effect of the Mediterranean diet on dementia risk in later life. Although biologically plausible that antioxidants may confer a protective effect on brain health by limiting the production of toxic substances and reducing damage by free radicals (Olanow, 1990), the current evidence base is insufficient to support a protective role for antioxidants in dementia risk (ADI, 2014).

Psychosocial and mental health factors

Depression

Depression is consistently independently associated with dementia in later life (ADI, 2014). However, the association is complex and there is insufficient evidence to fully disentangle the direction of effect. Most studies examining the issue have been based upon older people while studies focusing on earlier and mid-life are required to adequately establish a causal relationship rather than a prodromal effect for late-onset dementia. Few studies have examined the relationship between anxiety and dementia risk and establishing the true effect of anxiety disorders on dementia risk is problematic given that it so often co-occurs with depression.

Psychological distress

Psychological distress in adulthood has been found to be consistently independently associated with dementia risk in later life (ADI, 2014). Personality traits, which show stability throughout life, are thought to capture an individual's susceptibility to psychological distress (Wilson et al 2005). Those who display high neuroticism are more likely to be exposed to stressors (Bolger et al 1995), have less efficient coping strategies (Gunthert et al., 1999), report greater personal distress in the face of difficulties (Larsen

⁵ A diet consisting of a high intake of cereals, fruits, fish, legumes, and vegetables.

and Ketelaar, 1991) and experience a higher number of negative life events (Innes and Kitto, 1989). Studies have shown that the association between personality and dementia risk is more likely to be direct, rather than being mediated by lifestyle and health behaviours (Terracciano et al., 2014). The potential mechanism underpinning the relationship between psychological distress and dementia risk is not yet fully understood. As in childhood, it is thought to be linked to the HPA axis: sustained distress initiating a cascade of biological reactions that stimulate glucocorticoid secretion, mainly cortisol, leading to a number of physiologic responses associated with a poorer cardiovascular risk profile, unhealthy adaptive lifestyles and depressive symptomatology (Andrieu et al., 2011, Krieger, 1987, Lupien et al., 1998), which may all act as risk factors for dementia. In addition, psychological distress may exert a direct effect on dementia risk by impacting on the structure of the hippocampus (Lupien et al., 1998, Abercrombie et al., 2011).

The role of sleep

Sleep disturbance is a common occurrence among older people. In Ireland approximately 12% of people over 65 have trouble falling asleep and 17% experience waking up too early (TILDA, 2011). Quantity and quality of sleep are associated with memory, coordination and executive functions (Miller et al. 2013). For people with dementia, sleep disturbance can exacerbate early admission to residential care (Pollak et al., 1990). The relationship between sleep disturbance and dementia may be bidirectional but it has also been proposed that sleep problems may behave as a specific risk factor for cognitive decline (Peter-Derex et al., 2014). Cross-sectional studies find an association between particularly long or short sleep duration as well as poorer objective and subjective sleep quality with cognitive impairment (Blackwell et al., 2011, Bombois et al., 2010, Faubel et al., 2009). Longitudinal studies have also found associations between sleep disturbance and cognitive decline and dementia risk (Tworoger et al., 2006, Cricco et al., 2001, Jelicic et al., 2002, Potvin et al., 2012, Virta et al., 2013). Sleep disturbance is consistently associated with dementia risk even after controlling for sleeping pill use (ADI., 2014).

Developmental factors

Educational attainment

Evidence supports a protective effect of educational attainment on dementia risk in later life. The most recent meta-analysis conducted by ADI (2014) found consistent evidence across studies even after controlling for a range of important confounders. It is not yet known if there is a critical level of education that confers protection in later life. Many studies examining education and dementia risk rely on crude dichotomised measures of high versus low levels of educational attainment. Brain and cognitive reserve have become the dominant explanatory framework underpinning this effect. Greater brain volume (brain reserve) and more active qualitative conceptualisation (cognitive reserve) produces more efficient cognitive processing and helps compensate for dementia pathology in later life. Education is now widely applied as one proxy for cognitive reserve in research studies.

Occupational status

Higher occupational attainment across the life course has also been mooted as conferring a protective effect on dementia risk in later life (Caamaño-Isorna et al., 2006). The protective effect of occupational status could be as a result of life-long learning or represent an enhanced opportunity to build cognitive reserve. There are clearly associated links with higher socioeconomic status and consequent associations with other modifiable risk factors including harmful health behaviours. Educational and occupational attainment are closely correlated and associations with occupational attainment tend to attenuate after controlling for education suggesting an important influence of early life for the protective effect of brain and/or cognitive reserve (ADI., 2014). The concept of work complexity, in a small amount of studies, has shown a consistent independent protective effect on dementia risk but requires further clarification in cohort studies.

Early life factors

Conditions during gestation (in the womb), particularly during the 35th to 40th week of pregnancy influence brain and nervous system maturation and development (Cunnane and Crawford, 2003). Low birth weight and persistent under nutrition in early life are associated with lower cognitive levels in childhood and adulthood (ADI, 2014). In addition

brain size in early life is considered a valid marker for brain reserve and skull circumference in adulthood (ADI., 2014). However, there are relatively few studies examining the association between markers of early life development (i.e. brain circumference and leg length) and dementia risk.

Evidence suggests an association between childhood hardship (maltreatment or neglect) in early life and disruptions to brain growth and functioning (De Bellis, 2005, Anda et al., 1999) with a resulting susceptibility to dementia in later life. Studies point to the impact of child maltreatment and early life stress on brain development (De Bellis, 2002, De Bellis, 2005, DeBellis and M., 2006, Watts-English et al., 2006). Some evidence suggests an increased risk of dementia in later life for people who experienced early-parental death (ADI., 2014). However, determining causality between early life factors and later life dementia is particularly difficult.

3. Estimates of modifiable dementia risk reduction in an Irish context

Drawing on methodology used in studies by Barnes and Yaffe (2011) and Norton et al. (2014), estimates of population attributable risk for the seven leading modifiable risk factors for later life dementia in Ireland were developed. The potential effect of risk factor reduction on the prevalence of dementia was then calculated. Although this approach has a number of limitations, it gives some indication of the role of prevention in reducing dementia prevalence in Ireland.

3.1 Analytical approach to modelling modifiable dementia risk in Ireland

As section 2.1 demonstrated, there are many methodological challenges in identifying the causal effect of removing or reducing a risk factor for dementia. In the absence of Randomised Control Trials that more rigorously assess the effect of a risk factor on dementia prevalence, epidemiological research has focussed on estimating the potential benefit of risk factor primary prevention in reducing dementia prevalence and its age-specific incidence using population based data. It has been estimated that delaying the onset of Alzheimer's disease by one year would reduce the total worldwide number of people aged 60 years and over with dementia in 2050 by 11% (Brookmeyer et al., 2007).

Previous studies have estimated the effect of risk factor modification (Barnes and Yaffe, 2011, Norton et al., 2014) including estimates in the context of UK and Europe (Norton et al., 2014) on dementia prevalence. The approach adopted in these studies is to estimate the effect of risk factor reduction on dementia prevalence by calculating population attributable risks (PARs) and the number of dementia cases that might be prevented by addressing specific risk factors.

The PAR is the proportion of people with a disease in the population that can be attributed to a given risk factor, taking into account the strength of the association between the risk factor and the outcome as well as the prevalence of the risk factor (Barnes and Yaffe, 2011). PARs assume complete elimination of the risk factor.

Both Barnes and Yaffe, (2011) and Norton et al., (2014) examined the factors most consistently associated with dementia risk based primarily on findings from the US National Institute of Health (Daviglius et al., 2010), the most up to date review of the evidence at the time. The seven factors included in their analyses were: Type 2 diabetes, midlife hypertension, midlife obesity, physical inactivity, depression, smoking, and low educational attainment. In this paper a similar approach is adopted. According to Barnes and Yaffe (2011), while these types of analysis have some limitations (see section 3.4), they may help identify the risk factors that are likely to have the greatest effect on dementia prevalence.

3.2 Data and Sources

3.2.1. Risk factor prevalence

Three data sources were used to conduct this analysis. First, data from the Survey on Lifestyles and Attitudes to Nutrition (SLÁN) 2007 was used to provide a measure of population prevalence for each modifiable factor in Ireland. SLÁN is a representative sample of adults (18 years+) in Ireland and collects data on a wide range of health behaviours and chronic conditions. This data allowed for the inclusion of all seven risk factor identified in Norton et. al. (2014). Table 1 outlines the parameters of each of these

risk factors used in the analysis and allows for a comparison with those used in Norton's study.⁶

Table 1. Comparison of Norton et. al. (2014) Risk Factor Definition and SLÁN definition

Risk factor	Norton et al definition	SLÁN definition
Low educational attainment	The proportion of adults with an International Standard Classification of Education level of 2 or less (pre-primary, primary, and lower secondary education)	The proportion of adults aged 18+ years educated up to and including Junior certificate
Midlife obesity	Adult midlife prevalence of body-mass index greater than 30 kg/m ² between the ages of 35 years and 64 years	Proportion of adults aged 35-64 years with BMI greater than 30 kg/m ² (self-report)
Midlife hypertension	Adult midlife prevalence of hypertension between the ages of 35 years and 64 years	Self-reported clinically diagnosed hypertension in the previous 12 months (either treated with medication or untreated) in adults aged 35-64 years
Physical inactivity	Proportion of adults who <u>do not do</u> either 20 min of vigorous activity on 3 or more days or 30 min of moderate activity on 5 or more days per week	Proportion of adults aged 18+ years who are not regularly physically active and do not intend to be so in the next six months; and those who are not regularly physically active but are thinking about starting to do so in the next six months
Smoking	The proportion of adult smokers	Proportion of adults aged 18+ years who are Current Smokers
Diabetes	Adult prevalence of diagnosed diabetes mellitus between the ages of 20 years and 79 years	Self-reported clinically diagnosed diabetes in the previous 12 months or reported taking diabetes medication, in adults aged 20+ years
Depression	Lifetime prevalence of major depressive disorder using Diagnostic and Statistical Manual of Mental Disorders or International Classification of Diseases criteria	Proportion of adults aged 18+ years who responded YES to the question "During the past 12 months, was there ever a time when you felt sad, blue, or depressed for two weeks or more in a row?" (WHO Composite International Diagnostic Interview, Short Form)

3.2.2 Relative risks of dementia

A second data requirement to calculate PAR is information on the relative risk of dementia for each of the factors outlined in Table 1. Relative risks for each of the seven factors were obtained from Barnes and Yaffe (2011) with updated RRs from Norton et al (2014). Both of these studies used meta-data and the most up-to-date systematic reviews including Cochrane reviews.⁷

Table 2 presents the weighted prevalence of each risk factor taken from the SLÁN data and the Relative Risks taken from the meta-analysis carried out by Norton et. al. (2014).

Table 2. Population prevalence of seven modifiable factors and associated RRs

Modifiable risk factor	SLAN 2007 weighted prevalence %	Relative risk (95% CI)
Low education	37%	1.59 (1.35-1.86)
Mid-Life Obesity	12%	1.60 (1.34-1.92)
Hypertension	9%	1.61 (1.16-2.24)
Physical Inactivity	21%	1.82 (1.19-2.78)
Smoking	28%	1.59 (1.15-2.2)
Type 2 Diabetes	3%	1.46 (1.2-1.77)
Depression	11%	1.65 (1.42-1.92)

3.2.3 Number of people with dementia in Ireland

Finally, dementia prevalence rates were taken from Pierce et. al. (2014) which was principally an application of EuroCoDe dementia prevalence data rates to Irish Census data in 2011. Based on the best available evidence, the total number of people living with dementia in Ireland was taken as 47,849 (Pierce et al 2014).

⁷See Norton et al (2014) for detailed overview of the methodological approaches and appendix 4 for the specific data sources for the RRs.

3.3 Statistical analyses

There were four main steps undertaken in the analysis.

3.3.1 Individual PARs

Firstly, individual PARs were calculated. The PAR was calculated by applying the Levin Formula (Levin, 1953) to individual RRs for each of the seven individual risk factors.

$$PAR = [P_{RF} \times \frac{RR - 1}{1 + P_{RF} \times [RR - 1]}]$$

Where P_{RF} refers to the population prevalence of a risk factor and RR refers to the relative risk associated with that factor. The total number of dementia cases in Ireland attributable to a modifiable risk factor examined was estimated by multiplying the corresponding PAR estimated by the current prevalence of dementia. The individual PARs were used to determine the number of cases that could potentially be prevented if current risk factors were 10% lower. As risk factors were considered one at a time, the numbers of attributable cases may be overestimated.

3.3.2 Inter-relatedness of the risk factors

Secondly, an assessment of the inter-relatedness of the risk factors was undertaken. The communality for each risk factor was calculated from a principal components analysis of data from adults aged 18 years and over in the SLÁN survey 2007. Principal components analysis reduced a number of observed correlated variables into a smaller number of linearly uncorrelated variables called principal components that account for most of the variance in the data. The first three components displayed eigenvalues (the variances of the principal components) greater than 1 and accounted for 50.7% of the variance. The proportion of shared variance was 50.7%.⁸ Therefore, this approach is more conservative and realistic than estimates that assume independence between the risk factors (Norton et. al. 2014).

⁸ In total, 3 principal components with an eigenvalue of more than 1 were extracted.

3.3.3 Combined PAR

Thirdly, a combined PAR was estimated to assess the simultaneous effect of a reduction in all of the risk factors examined. Similar to Norton et. al. (2014), the principal component analysis of the inter-relatedness of the seven modifiable factors was incorporated into the calculation of a combined PAR. Without this adjustment the estimated combined effect of the seven factors is likely to be substantially over estimated given the complex clustering of unhealthy modifiable factors in certain population sub-group. For example, obesity, hypertension and diabetes are all highly correlated, and all are related to physical inactivity (Barnes and Yaffe, 2011).

The combined PAR was derived from the following formula, where w (weight) is $w=1$ minus the proportion of shared variance with the other risk factors (i.e. communality).

$$PAR_{\text{Adjusted Combined}} = 1 - \pi_1 - (w \times PAR_1)(w \times PAR_2) \dots (w \times PAR_7)$$

3.3.4 Number of potentially avoidable dementia cases

Finally the number of potentially avoidable dementia cases were calculated by applying the seven individual PARs and the combined PAR to the estimated number of dementia cases in Ireland. This could be done on the assumption that the risk factors are eliminated; here we do the calculations assuming the prevalence of each risk factor is reduced (relatively) by 10%.

3.4 Limitations of the analysis

A first limitation is that the relative risks (RRs) are taken from a wide variety of sources with differing populations. For example, the RRs are taken at particular age ranges but the interplay between the risk factors and dementia operate across the life course (Norton et. al. 2014). According to Norton et. al. (2014), in order to address this issue, future studies require data that draws on different points across the life span and in different generations.

The second limitation of the statistical approach adopted in this paper is that PAR estimates assume a direct causal relationship between risk factors and dementia, based on

relative risks. As many elements of the relationship between these risk factors and the outcome remain poorly understood, it is not certain that reduction of risk factors in the population would lead to a lower incidence of dementia. This is particularly the case as much of the evidence is based on observational data. A third limitation relates to the method used to eliminate the combined PAR.

A fourth limitation relates to the limitations inherent in providing an accurate overall estimate of dementia prevalence in Ireland. The prevalence figures used were based on application of EuroCoDe dementia prevalence rates to Irish Census data in 2011 (Pierce et al, 2014), but these estimates themselves rest on uncertain assumptions including aspects of demography and migration.

Finally, it is notable that several other factors shown to be associated with dementia in epidemiological studies were not included in this analysis, including psychological distress and diet. Including the full range of modifiable factors that impact on dementia risk in later life could result in a higher proportion of dementia cases attributable to modifiable risk factors.

Therefore, bearing in mind these limitations these estimates should be viewed as an indication of the possible implications of a 10% reduction in certain risk factors on dementia prevalence.

3.5 Findings

Table 3 presents a summary of the key results. The table includes overall population attributable risks (individual and combined) as well as the estimated number of potentially avoidable cases of later life dementia in Ireland in 2011 if risk factor prevalences were reduced by 10% in the population.

Firstly, with regard to PARs which estimate the number of cases which might be avoided by total elimination of that risk factor. Of all seven modifiable factors considered, the highest population attributable risk for dementia in Ireland was calculated for low education attainment. Table 3 shows that 17.9% of all cases of dementia in Ireland in 2011 could potentially be attributed to low educational attainment and 14.9% could be

potentially attributed to physical inactivity. Current smoking could be considered a significant factor in a further 14.3% of cases. The combined PAR adjusting for the inter-relatedness of the risk factors was 29.2%. This figure is similar to Norton et. al. (2014) estimates for the UK (30%).⁹

Secondly, with regard to what might result from a 10% reduction in the prevalence of modifiable risk factors, these findings indicate significant potential for a reduction in dementia prevalence. Taking into account the inter-relationship between the risk factors, if the prevalence of each of the risk factors was reduced by 10%, it is estimated that this could have resulted in 1084 fewer cases of dementia in 2011.

Table 3. Estimates of the number of potentially avoidable cases of dementia in Ireland (2011)

Risk factors	PAR	95% CI's	Number of potentially avoidable dementia cases in 2011 if risk factor prevalence was reduced by 10%	
		Corresponding to elimination of risk factors	N=47,849 (95% CIs)	
Low education	17.9%	(11.4 - 24.1)	715	(490 - 896)
Obesity	6.5%	(3.8 - 9.7)	294	(176 - 422)
Hypertension	5.4%	(1.5-10.3)	244	(69-447)
Physical inactivity	14.9%	(3.9-27.5)	615	(180 - 981)
Smoking	14.3%	(4.1 - 25.3)	594	(187 - 927)
Diabetes	1.3%	(0.6 – 2.2)	64	(28-105)
Depression	6.5%	(4.3 – 9.0)	294	(199 - 395)
COMBINED (adjusted)	29.2%	(14.4 – 43.3)	1084	(612-1344)

3.6 Discussion

This analysis applied RRs from systematic reviews and meta-analysis (applied in other similar international studies) to Irish data on risk factor prevalence and dementia prevalence. This allowed for the calculation of PAR and estimates of potentially attributable dementia cases to be calculated in an Irish context. Findings indicate the potential for reduction in dementia prevalence if modifiable risk factors were reduced. This suggests that public policies aimed at reducing smoking and enhancing physical activity as well as fostering educational attainment may have an important role in

⁹ The combined PAR without taking account of the non-independence of the risk factors was 51%. This compares with 52% found in the Norton et. al. (2014) study using the UK data.

addressing risk of dementia at population level. However, there are significant caveats principally based upon the limits of existing evidence on associations and on the return to dementia risk from any interventions. RCTs are the most robust way of assessing the causal relationship between risk factors and dementia, and further investment in this area is required to truly understand the effectiveness of prevention measures. Nevertheless, these types of estimates may provide policy makers with a guide to which dementia prevention strategies *may* impact on dementia prevalence (Barnes and Yaffe, 2011).

It should be noted that achieving a 10% reduction in each of the risk factors would represent a very significant challenge in the real world particularly in light of recent concerns in the prevalence of both obesity and depression. Positive changes in population prevalence of health behaviour risk factors of that magnitude rarely, if ever, occur over short periods of time. A 10% change in any one of the risk factors would represent unprecedented success for any strategic public health policy and intervention, but such change is not beyond the aspiration of some current public health policies. For example, Ireland's tobacco control policy *Tobacco Free Ireland* proposes to reduce the population prevalence of smoking from around 20% to under 5% between 2015 and 2025.

4. Exploring the potential of dementia prevention in current Irish research, policy and practice

4.1 Dementia Prevention Research in Ireland

Further investment in dementia prevention research specifically aimed at furthering understanding and establishing effective interventions is needed. However, development of our understanding of life course factors requires long-term studies which are expensive. The Irish Longitudinal Study on Ageing (TILDA) and other national health and well-being surveys should be utilised to their full extent to investigate the potentially modifiable risk and protective factors for dementia. TILDA to date has not been designed to include people with a dementia diagnosis in its sampling frame; nonetheless questions on cognitive impairment in the study provide useful insights. Of adults aged 80 and over, 35% have cognitive impairment compared to 4% of adults aged between 50 and 64 (O'Regan et al., 2011). Results on self-rated memory indicate a significant level of memory impairment in the first wave sample, particularly in older groups. Further research based on TILDA data highlights an important role between negative ageing perceptions and memory impairment in older Irish people (Robertson et al., Forthcoming). The wealth of information on health and social care utilisation, combined with data on social and economic circumstances and biological measures, places TILDA in a unique position to identify potentially important modifiable factors in an Irish context. However, the lack of longitudinal data in early and mid-adulthood may hamper understanding of the real contribution of risk factors at earlier stages in the life course, and a joined-up approach may bring greater insight.

Several ongoing research projects have considerable potential to inform a public health approach to dementia prevention in Ireland. The NEIL Programme in Trinity College Dublin collects comprehensive longitudinal data on a cohort of Irish adults aged 50 years and over. It runs in parallel with TILDA and provides additional testing for dementia intervention studies not possible in TILDA. The NEIL Programme is also leading out on a number of primary and secondary prevention research studies. Many of these studies focus on health behavioural interventions to delay cognitive decline including a focus on fitness and physical activity as well as cognitive activity and other modifiable factors that

contribute to brain health or dementia risk. The Social Determinants of Cognitive Decline study which commenced in 2014 will apply epidemiological approaches to TILDA and NICOLA data to assess the relationships between social factors and cognitive outcomes in older people both in Northern Ireland and the Republic of Ireland.

The In-MINDD project run in DCU is a three year funded research programme with the primary objective of delivering a robust dementia risk model for use in primary care to develop personalised strategies for individuals to take action to protect their brain health in mid-life. The In-MINDD trial is now underway across four primary care settings in Europe, including Ireland and may offer great potential to advance dementia risk reduction in primary care in Ireland in the future.

4.2 Dementia Prevention and Public Health Policies in Ireland

Adopting a ‘Brain health’ approach

While evidence is incomplete, there is now an opportunity to explore the potential of developing strategies to reduce dementia risk in Ireland. Broader public health approaches have begun to engage with the concept of “brain health” as an important paradigm which could bring together the neuroscience, clinical and public health disciplines to contribute to addressing dementia prevention. To date the concept of brain health has not been fully incorporated into broader public health or health promotion campaigns in Ireland. Drawing on The Healthy Brain Initiative: The Public Health Road Map for State and National Partnerships 2013—2018 (Alzheimer’s Association (US) and Centers for Disease Control and Prevention, 2013), it is suggested that a public health approach to dementia prevention be based on four explicit principles:

1. An emphasis on primary prevention
2. A community and population health approach
3. Evidence based actions
4. A commitment to eliminating disparities in dementia

In regard to the first principle outlined above, embedding a preventative approach into existing public health research, policy and practices is essential.

Secondly, in order to develop effective policies it is important to ensure the actions are evidence based. As already outlined, there is potential to build on the findings of this discussion paper to further examine the association between risk factors and dementia onset. The development of epidemiological and intervention studies on dementia prevention is critical to inform appropriate prevention strategies in an Irish context. In addition to the enhancement of information systems to provide reliable data on dementia cases in Ireland, as recommended by Cahill et al (2012), the establishment of a comprehensive research programme linked with relevant public health policy indicators would inform the prevention of dementia in an Irish context.

A population health approach to dementia risk reduction recognises the role of the broader determinants of health in shaping dementia risk. Many risk factors for dementia including level of education, health behaviours and vascular health display strong associations with social determinants.

Finally, policy actions must be committed to eliminating disparities in dementia prevention. Many modifiable risk factors for dementia cluster in population subgroups and display strong associations with social determinants. The extent of this clustering in Ireland has not yet been explored, although certain conclusions can be drawn from international evidence. Measures to address health disparities for other chronic conditions may also be effective in addressing dementia risk, particularly in early life. Fostering brain health from an early age and across the life course would likely confer substantial gains for at-risk population sub-groups and reduce disparities in dementia outcome in later life.

A dementia prevention approach within Irish public health policies

Public health policies are already addressing some of the modifiable factors associated with dementia risk, in particular in the domains of tobacco control and cardiovascular health. However, these policies are not yet integrated to take account of the potential benefits existing actions might confer on the dementia risk profile of Irish people. A key concern is how existing policy and actions can become better nuanced to take account of brain health. A cross-disciplinary, integrated, comprehensive life course approach to modifiable dementia risk factors should be further explored in public health policy and

practice. A co-ordinated approach that identifies synergies with existing public health strategies will be most effective. Actions arising from Healthy Ireland could be assessed to consider how they could incorporate elements of dementia prevention along with prevention of other chronic conditions in Ireland. In addition, the *National Policy Framework for Children and Young People; Better Outcomes, Better Futures* (Department of Children and Youth Affairs, 2014), *Tobacco Free Ireland* (Department of Health, 2013c) the *National Early Years Strategy* (Department of Children and Youth Affairs, 2013), the *National Positive Ageing Strategy* (Department of Health, 2013b), the forthcoming *National Physical Activity Plan* (Department of Health, forthcoming) and the *National Cardiovascular Health Strategy* (Department of Health and Children, 2010) present opportunities to advance dementia prevention at a policy level across the life course in Ireland.

In conclusion, the 'brain health' approach acknowledges that the development of dementia occurs across the life course and encompasses action on social determinants of dementia which requires a whole-of-government approach as espoused in *Healthy Ireland – A Framework for Improved Health and Wellbeing 2013 – 2025* (Department of Health, 2013a).

4.3 Dementia Prevention in Practice in Ireland

Developing appropriate preventative care practices is challenging. Currently, the evidence does not support the prescribing of statins, HRT, non-steroidal anti-inflammatory drugs or antioxidants in the primary prevention of late-onset dementia (NICE/ SCIE, 2006).

However, given the methodological issues outlined in this discussion paper in establishing an accurate evidence base on these interventions, it could be a case of modifying existing practice in health promotion and in clinical practice and screening towards influential periods for intervention across the life course, particularly in mid-life. The appropriate management of cardiovascular risk factors in primary care, particularly hypertension, atherosclerosis, diabetes and thromboembolic disease may be particularly important. Implementation of the primary prevention measures as detailed in the *National Cardiovascular Health Strategy*, may make a contribution to reducing the prevalence of dementia as well as coronary heart disease.

Dementia awareness programmes have been identified by the World Health Organisation as an important aspect of a public health approach to dementia prevalence (WHO, 2012). The Department of Health in Ireland have recently announced an initiative supported by Atlantic Philanthropies to develop GP training and raise awareness of dementia in the HSE. Hello Brain is a campaign to promote brain health, healthy ageing and brain research in Ireland run by the NEIL Programme in TCD¹⁰ and in 2013 ASI ran the Forget Me Knot campaign to increase awareness around measures to reduce dementia risk in the general population¹¹.

¹⁰<http://www.tcd.ie/Neuroscience/neil/interventions/hello-brain.php>

¹¹<http://www.alzheimer.ie/brain-health.aspx>

5. Conclusion

There is now sufficient evidence to explore the potential of dementia prevention as a public health policy issue. Findings on population attributable risks presented in this paper highlight the potential to address prevalence through modification of key risk factors at a population level in Ireland. Further research is required to adequately understand the mechanism of influence of health behaviour and environmental factors on cognitive decline and dementia risk in later life and to establish a robust evidence base to inform specific targeted interventions. To achieve answers, we need emphasis on appropriate research approaches including data synthesis, animal models and longitudinal studies over the life course to allow for evaluation of interaction effects of risk factors in later life outcomes (Anstey, 2014). Current epidemiological evidence highlights some important areas for public health intervention and ongoing research in an Irish context will aid development of interventions and inform public health actions to reduce dementia prevalence in the future.

There is growing support for action to expand our understanding on modifiable protective and risk factors and identify and test interventions. A brain health approach, embedded in a broader determinants and population health frame, should be the corner stone of public health action to address dementia prevention. This approach acknowledges that dementia pathology is a lifelong process with different periods of opportunity for prevention. In addition, it encompasses action on social determinants of dementia which allows for inclusion of a wide-ranging model of dementia prevention encompassing not just health and health services but also broader social, education and ageing policies.

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Appendix

Table 1x: Sources for Relative Risks

Risk factor	Norton et al 2014 Source
Low educational attainment	Caamano-Isorna F, Corral M, Montes-Martinez A, Takkouche B. (2006) 'Education and dementia: a meta-analytic study', <i>Neuroepidemiology</i> 2006; 26: 226–32
Midlife obesity	Barnes DE, Yaffe K. The projected effect of risk factor reduction on Alzheimer's disease prevalence. <i>Lancet Neurol</i> 2011; 10: 819–28
Midlife hypertension	Barnes DE, Yaffe K. The projected effect of risk factor reduction on Alzheimer's disease prevalence. <i>Lancet Neurol</i> 2011; 10: 819–28
Physical inactivity	Hamer M, Chida Y. Physical activity and risk of neurodegenerative disease: a systematic review of prospective evidence. <i>Psychol Med</i> 2009; 39: 3–11.
Smoking	Peters R, Poulter R, Warner J, Beckett N, Burch L, Bulpitt C. Smoking, dementia and cognitive decline in the elderly, a systematic review. <i>BMC Geriatr</i> 2008; 8: 36. Cataldo JK, Prochaska JJ, Glantz SA. Cigarette smoking is a risk factor for Alzheimer's disease: an analysis controlling for tobacco industry affiliation. <i>J Alzheimers Dis</i> 2010; 19: 465–80.
Diabetes	Cheng G, Huang C, Deng H, Wang H. Diabetes as a risk factor for dementia and mild cognitive impairment: a meta-analysis of longitudinal studies. <i>Intern Med J</i> 2012; 42: 484–91.
Depression	Gao Y, Huang C, Zhao K, et al. Depression as a risk factor for dementia and mild cognitive impairment: a meta-analysis of longitudinal studies. <i>Int J Geriatr Psychiatry</i> 2013; 28: 441–9. Diniz BS, Butters MA, Albert SM, Dew MA, Reynolds CF. Late-life depression and risk of vascular dementia and Alzheimer's disease: systematic review and meta-analysis of community-based cohort studies. <i>Br J Psychiatry</i> 2013; 202: 329–35.

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