

TARGETING BRAIN, BODY AND HEART FOR COGNITIVE HEALTH AND DEMENTIA PREVENTION

**CURRENT EVIDENCE AND
FUTURE DIRECTIONS**

PAPER 29
SEPTEMBER 2012

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ISBN 978-1-921570-22-3

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ABN 79 625 582 771 ARBN 066 779 557

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ACKNOWLEDGEMENTS

Acknowledgements:

The authors would like to thank Professor Kaarin Anstey and Associate Professor Michael Woodward for reviewing this paper and providing helpful feedback.

This work was supported by funding from the Australian Government, under the Dementia Collaborative Research Centres and the Chronic Disease Prevention and Service Improvement Fund.

Suggested citation:

Farrow M, O'Connor E. Targeting brain, body and heart for cognitive health and dementia prevention. *Alzheimer's Australia Paper 29*. 2012. Alzheimer's Australia: Canberra.

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FOREWORD

Most Australians want to know how they can keep their brain sharp as they get older – what things should they do and not do to keep their brain healthy. People affected by dementia and their families and friends are anxious to know how to slow down the cognitive decline that defines the illness.

In general, Australians have a low level of awareness of the research evidence that shows that health and lifestyle strategies can reduce the risk of cognitive decline and dementia. Statistics reveal that only 51% of Australians believe it is possible to reduce their risk and there is a widespread lack of knowledge that what's good for the heart is also good for the brain.

The objective of this paper is to provide an updated review of the evidence for dementia risk reduction strategies. Modifiable risk and protective factors are detailed and the current evidence presented for each one. Major reviews of the scientific literature are discussed and controversial findings are addressed. Current and future research projects that will address remaining questions and pave the way for improved advice about what people can do to reduce their dementia risk, are also reviewed.

An increasing body of evidence suggests that a range of lifestyle and health factors has the potential to reduce the risk of cognitive decline and dementia. Higher levels of mental, social and physical activity are associated with lower risk of developing dementia while cardiovascular risk factors such as diabetes, high blood pressure and high cholesterol are associated with increased risk.

It seems midlife is a critical time to address these modifiable risk factors, but it is never too late to develop good brain health habits. Evidence is emerging that these same beneficial factors can influence the rate of cognitive decline in someone with dementia and that by keeping the person engaged, and effectively managing other medical conditions, their quality of life can be improved.

Dementia is not a normal part of ageing. The changes it causes in brain function are the result of brain disease for which there is unfortunately as yet no cure. However, evidence gathered in recent years suggests that modifiable risk factors do influence disease progression. While the search for disease-modifying drug treatments continues, we must capitalise on the available evidence for health and lifestyle interventions that may reduce risk, as this provides us with the best hope of delaying or slowing down dementia.

Studies reviewed in this paper estimate that significantly fewer – many thousands in fact – will develop dementia if we address modifiable risk factors now. Conversely, if we do nothing, numbers will increase rapidly from 280,000 in 2012 to almost one million in 2050. Of course, there are no guarantees for any person. Some risk factors for dementia, including older age and genetics, cannot be modified.

Increased funding for research is essential. In the past 10 years, scientific research has resulted in new hope for dementia prevention but much more is needed. Additional investment in research to consider the prevention, early intervention and treatment of dementia, is pivotal in addressing the looming epidemic. Dementia research in Australia is significantly underfunded compared with other chronic diseases such as cancer, cardiovascular disease and diabetes.

The publication of this paper coincides with the launch of Alzheimer's Australia's new brain health program, *Your Brain Matters: A guide to healthy hearts and minds*, which we hope will encourage all Australians to look after their brain, body and heart, in order to maintain brain health and reduce their risk of dementia. We believe it is everyone's responsibility to do this. Alzheimer's Australia is committed to conveying this message throughout Australia and will continue to develop resources to help people understand and apply the current evidence.

I commend this paper to all people who are interested in what can be done now to address dementia prevention for the Australian community. My thanks to the authors for their efforts to provide this overview of the state of the evidence and promising future directions.



Ita Buttrose AO, OBE
President, Alzheimer's Australia

September 2012

EXECUTIVE SUMMARY

CAN DEMENTIA BE PREVENTED?

Prevention of dementia is the ultimate aim of a large, albeit under resourced, international research effort. The success of this effort would have enormous benefits for millions of people and save billions of dollars in health care costs. Conversely, the status quo will see the number of Australians living with dementia soar in coming years. Many more people will experience and seek help for mild cognitive impairment.

There are many different forms of dementia, a syndrome caused by brain disease and characterised by declining cognitive function that impairs daily activities. Dementia can affect memory, language, attention, judgement, planning, behaviour, mood and personality. Mild cognitive impairment does not significantly impair daily activities, but often represents an earlier stage of cognitive decline.

There is no cure for the common forms of cognitive decline and dementia, including the most common, Alzheimer's disease. A cure may only be achieved by prevention, because the diseases that cause dementia begin many years before symptoms become apparent and gradually damage the brain until it can no longer function normally. Intervening early to stop or slow disease progression, before cognitive impairment emerges, offers the best hope of preventing dementia.

Is this achievable? It requires breakthroughs in early detection and intervention.

New diagnostic technologies have been developed that can detect the presence of abnormal protein accumulations in the brain that characterise Alzheimer's disease. The disease can now be detected by brain scans or cerebrospinal fluid tests in the preclinical stage, before any cognitive changes occur.

Several clinical trials of potential drug therapies against Alzheimer's disease have been conducted in recent years. None have been successful. Despite promising evidence that these drugs can impede the protein accumulations that characterise Alzheimer's disease, when tested with people with Alzheimer's, they have failed to provide clinical benefits.

Researchers are now asking whether this is in part due to intervening too late in the disease process. Trials will soon begin to involve people

who are in the preclinical phase of Alzheimer's disease. This research offers new hope, however, a breakthrough is likely many years away. Therapies also need to be found for other forms of dementia, which often coexist with Alzheimer's contributing to cognitive impairment.

In the meantime, there is much interest in what other strategies might help to prevent or slow down cognitive decline and dementia. The available evidence indeed supports potential benefits of healthy, active lifestyles. These cannot definitely prevent dementia, but until curative therapies are found, preventative health approaches offer hope of reducing risk and delaying onset of dementia.

HEALTH AND LIFESTYLE STRATEGIES FOR PREVENTION

Higher levels of mental activity throughout life are consistently associated with better cognitive function and reduced risk of cognitive decline and dementia. Almost one in five cases of cognitive impairment or dementia may be attributable to low levels of mental activity, more than any other risk factor, including the major genetic risk factor for Alzheimer's disease. Complex mental activity across the lifespan may contribute to brain reserve, allowing normal cognitive function to continue for longer in the face of underlying disease. It may also reduce the protein accumulations seen in Alzheimer's disease.

Higher engagement in social activity is associated with reduced risk of cognitive decline and dementia. Social engagement has been found to have benefits for other health factors related to cognitive functioning, such as vascular conditions and depression. Social activity is cognitively stimulating and may contribute to building brain reserve that protects against cognitive decline and dementia.

Moderate alcohol consumption is associated with better cognitive function and reduced risk of dementia. However, excessive amounts over time may increase the risk. The benefits of moderate alcohol consumption include reducing inflammation, increasing HDL ("good") cholesterol, increasing brain blood flow, and antioxidant properties, all of which have positive effects on brain health. In contrast to the potential benefits of moderate alcohol consumption, heavy use can lead to brain damage.

What we eat is also likely to be important for cognitive health, but the evidence is not yet conclusive. Dietary choices affect risk for cardiovascular disease, high blood pressure, diabetes, high cholesterol and obesity, all of which in turn are associated with increased risk of cognitive impairment and dementia. Dietary patterns characterised by higher intake of fruits, vegetables, fish, nuts and legumes, and lower intake of meats, high fat dairy and sweets seem to be associated with lower risk of cognitive impairment and dementia.

Regular physical exercise is associated with better brain function and reduced risk of cognitive decline and dementia. Even simple exercise like walking has been shown to be beneficial. Physical activity increases brain blood flow, stimulates the growth of new neurons and synapses, is associated with larger brain volume, and reduces the risk of cardiovascular conditions associated with increased risk and severity of cognitive decline and dementia.

There is a U-shaped relationship between midlife body weight and the risk of developing dementia later in life, with increased risk found for those who are underweight as well as those who are obese. Obesity is also associated with increased risk for high blood pressure, diabetes, cardiovascular disease and cerebrovascular disease, which affect brain health and increase the risk of dementia.

Smoking has been demonstrated to be a risk factor for dementia and cognitive decline. Former smokers do not appear to be at increased risk compared to never-smokers, suggesting quitting smoking may be beneficial for reducing dementia risk. Smoking may affect dementia risk via its negative effects on the cardiovascular system, increased oxidative stress, atherosclerosis and inflammation.

Untreated hypertension (high blood pressure) increases risk for vascular disease, stroke, and related cognitive impairment. Hypertension in midlife may also be associated with an increased risk of Alzheimer's disease, however, hypertension in old age is not. Hypertension may contribute to both vascular damage in the brain and Alzheimer's disease pathology, both of which in turn contribute to cognitive impairment. Treatment of midlife hypertension has been found to reduce dementia risk.

Untreated high total cholesterol at midlife is associated with an increased risk of developing dementia, especially Alzheimer's disease. Cholesterol levels may decline in the preclinical stages of Alzheimer's disease, so late-life high cholesterol is not associated with increased risk. Treatment of high cholesterol with statins has

been associated with reduced risk of dementia in several studies. High midlife cholesterol levels may accelerate the protein accumulations of Alzheimer's disease and contribute to vascular disease, especially atherosclerosis, both of which can contribute to cognitive impairment.

Type 2 diabetes and pre-diabetes syndromes such as insulin resistance appear to be risk factors for cognitive impairment and dementia. Few studies have examined the effect of treatment of diabetes on dementia risk and the results are mixed. Prevention of diabetes, through early screening for glucose tolerance and insulin resistance and lifestyle modifications for those at risk, could reduce the incidence of mild cognitive impairment and dementia. Insulin resistance and diabetes may accelerate the protein accumulations of Alzheimer's disease and contribute to cerebrovascular disease.

YOUR BRAIN MATTERS: A GUIDE TO HEALTHY HEARTS AND MINDS

Of the factors that evidence indicates are associated with brain health and dementia risk, the ten health and lifestyle factors highlighted here are the most amenable to modification. They form the basis of *Your Brain Matters*, a new program from Alzheimer's Australia designed to raise awareness that cognitive decline is not an inevitable part of ageing, that everyone can do something to reduce their risk, and that preventative strategies are critical at midlife.

The evidence base for this program indicates that a life-course approach to dementia prevention will reap the most benefit. Many of the associations with late life dementia risk are strongest when the risk factor is measured at midlife. Brain pathology that causes dementia likely develops gradually from midlife and evidence is emerging that modifiable factors influence this pathology. Taken together, there is compelling evidence to suggest lifestyle and medical interventions in midlife can slow down the progression of brain disease and resultant cognitive decline.

Some experts cautiously suggest there is not yet enough evidence to make firm recommendations, but there is consensus that long standing preventative approaches that are good for the heart will also be good for the brain, and that raising awareness of this is important.

Alzheimer's Australia's vision is for a society committed to the prevention of dementia, while valuing and supporting people living with dementia. An active, healthy lifestyle and effective treatment of cardiovascular risk factors may also benefit people diagnosed with dementia, helping to slow cognitive decline.

Your Brain Matters: A guide to healthy hearts and minds provides Australians with three key messages that encourage a holistic approach to looking after your brain, body and heart at all ages:

- Keeping your brain active matters
- Being fit and healthy matters
- Looking after your heart matters

The table below summarises *Your Brain Matters*. For more information, visit yourbrainmatters.org.au.

Health or lifestyle factor	Risk for cognitive decline and dementia
BRAIN	
Mental activity	Higher mental stimulation through education, occupation or leisure is associated with lower risk.
Social activity	Higher social interaction in late life is associated with lower risk.
BODY	
Diet *	Findings for individual nutrients are inconsistent. Higher intakes of fruits and vegetables and fish seem to be associated with lower risk.
Physical activity	Regular physical exercise at all ages is associated with lower risk.
HEART	
Blood pressure	Untreated midlife high blood pressure is associated with increased risk.
Cholesterol	Untreated midlife high cholesterol is associated with increased risk.
Diabetes	Type 2 diabetes is associated with increased risk.
Smoking	Current smoking is associated with increased risk, former smoking is not.
Weight	Midlife obesity and underweight are associated with increased risk.

* Moderate alcohol consumption is associated with lower risk, but comes with a warning – alcohol consumption can cause other health problems.

1. INTRODUCTION

In September 2012, Alzheimer's Australia launches its new brain health and dementia risk reduction program, *Your Brain Matters: A guide to healthy hearts and minds*. This community program aims to educate Australians about the lifestyle and health factors that could help them maintain brain health into old age and reduce their risk of dementia. There is compelling evidence that a healthy, mentally stimulating and physically active lifestyle and prevention or control of cardiovascular risk factors are associated with better cognitive function and lower dementia risk. Nonetheless, it is important that there is increased investment in dementia research to further build the evidence base. This paper outlines current evidence and research directions.

1.1 COGNITIVE IMPAIRMENT AND DEMENTIA

Dementia is an umbrella term, used to describe a syndrome that can have many different causes. The syndrome is characterised by gradual decline in cognitive abilities and neuropsychiatric symptoms. The causes are most commonly brain disease including Alzheimer's disease, Lewy body disease, cerebrovascular disease and frontotemporal lobar degeneration. These diseases begin to damage the brain many years before symptoms become apparent and cause a progressive decline in functioning as more of the brain is damaged. In new diagnostic criteria to be published in 2013, the term dementia will be replaced by 'major neurocognitive disorder' to reflect the severity of cognitive impairment at this stage of disease [1].

Because conditions such as Alzheimer's disease have a gradual onset, many affected people begin to experience cognitive problems that are not severe enough to significantly interfere with daily functioning, and so do not meet criteria for dementia. This is currently termed mild cognitive impairment (MCI) or cognitive impairment – no dementia (CIND). In the new diagnostic criteria to be published in 2013, these terms will be replaced by 'minor neurocognitive disorder' [1]. Criteria specifically for Alzheimer's disease label this stage as prodromal Alzheimer's disease [2].

There is also an initial stage of disease in which cognitive function remains normal. In this earliest stage, pathology begins to build up in the brain, but is not yet sufficient to cause any changes in brain function. New neuroimaging techniques and measures of proteins in cerebrospinal fluid allow this preclinical phase to be detected for Alzheimer's disease. It is this preclinical stage

that future therapies may target, to stop the disease before it affects cognitive function. Even therapies that could slow down the progression of the pathology and its effects on function would be enormously beneficial.

Such therapies do not yet exist and drug discovery research and clinical trials are continuing. In the meantime, there is much community interest in what other strategies might help people to avoid or at least slow down cognitive decline and dementia, and much research is happening in this area. The available evidence supports the potential of healthy active lifestyles to reduce the risk of cognitive decline and dementia.

1.2 WHY IS RISK REDUCTION IMPORTANT?

It is estimated that almost 280,000 Australians currently live with dementia. Without a significant medical breakthrough, that is expected to soar to almost 1 million by 2050 [3]. There are many more older people with some degree of cognitive impairment impacting on their lives [4]. Cognitive impairment and dementia already place significant burden on the health system and economy and this impact is set to rapidly increase as the population ages.

While dementia remains incurable, preventative health approaches offer some hope of reducing this impact. Reducing dementia risk factors has the potential to reduce risk and delay onset of dementia for individuals, and reduce the incidence of dementia in the population. Barnes and Yaffe recently estimated that up to half of Alzheimer's disease cases are potentially attributable to seven risk factors (diabetes, midlife hypertension, midlife obesity, depression, physical inactivity, smoking and cognitive inactivity) [5]. They further estimated that 3 million cases of Alzheimer's disease could be prevented worldwide by reducing by 25% the incidence of these risk factors. Another study estimated that a one year delay in the average age of onset of Alzheimer's disease through preventative strategies would result in nearly 12 million fewer cases worldwide by 2050 [6].

It is also estimated significant impacts can be achieved by modifying the risk factor profile in the Australian population. For example, a decline in the physical inactivity rate by 5% every 5 years would reduce dementia prevalence by 11% in 2051 [7]. That equates to around 100,000 fewer Australians living with dementia, as a consequence of addressing just one risk factor.

Addressing health and lifestyle risk factors in those already living with cognitive decline or dementia may also be beneficial. Treatment of hypertension, high cholesterol, diabetes and depression, and maintaining cognitive, physical and social activities may help slow cognitive decline, or at least ensure cognitive impairment is not exacerbated [8].

While research into therapies that can stop the diseases that cause dementia continues, we can do something now to inform Australians about the potential benefits of risk reduction strategies.

1.3 DEMENTIA RISK REDUCTION AWARENESS

Despite a growing body of research evidence for lifestyle and health strategies that may reduce dementia risk, Australians have a low level of awareness of these strategies. A review of community surveys found that only 51% of Australians believed risk reduction is possible, while 20% believed nothing can be done to reduce dementia risk and the remainder were unsure [1]. When asked how risk could be reduced, or when presented with factors and asked which would reduce risk, mental activity was nominated by more people than any other strategy, followed by a healthy diet and physical exercise. However, the majority of people did not agree that reducing cardiovascular risk factors (smoking, high blood pressure and high cholesterol) could reduce dementia risk.

Survey findings also revealed that few people are currently taking steps to reduce their dementia risk and many lack motivation to do so [9].

Evaluation of Alzheimer's Australia's Mind your Mind program (the predecessor to Your Brain Matters) revealed that providing information about dementia risk factors and risk reduction strategies, via community presentations or a website, was able to significantly increase

people's knowledge and their motivation to improve their brain health related behaviours [10,11].

1.4 YOUR BRAIN MATTERS

Your Brain Matters: A guide to healthy hearts and minds is an Alzheimer's Australia program that provides Australians with three key messages about the modifiable risk and protective factors for cognitive decline and dementia.

- Keeping your brain active matters
- Being fit and healthy matters
- Looking after your heart matters

The program aims to educate people that there is more to maintaining cognitive function than doing crossword puzzles, that in fact a holistic approach looking after their brain, body and heart will give them the best chance of cognitive health into old age. It also aims to raise awareness that what is good for the heart is good for the brain. The 'Brain' component of the program includes advice that those who are more mentally and socially active have better cognitive function and lower dementia risk. The 'Body' component provides advice that healthy choices related to alcohol consumption, diet and exercise are associated with better cognitive function and lower dementia risk. And the 'Heart' component encourages abstinence from smoking, maintaining a healthy weight, regular health checks and good control of diabetes, high blood pressure and high cholesterol to reduce the risk of vascular contributions to dementia. For more information about the program, visit yourbrainmatters.org.au.

The evidence for the association of each of these modifiable lifestyle and health factors with brain health and dementia risk is summarised in this paper.

2. NON-MODIFIABLE RISK FACTORS FOR DEMENTIA

2.1 AGE

Older age is the most important risk factor for cognitive decline and dementia. The prevalence of dementia increases exponentially with age. 1 in 30 Australians aged 70 to 74 are estimated to have dementia, increasing to 1 in 8 of those aged 80 to 84 and 1 in 3 of those aged 90 to 94 [3].

Age is a risk factor that cannot be modified and has been referred to as 'the elephant in the room' [12]. Because the modifiable risk factors for dementia overlap with those of heart disease and other chronic illnesses, perhaps the assumed prevention of dementia through addressing lifestyle risk factors would be attenuated by increased survival of the population to older ages [12]. However, if addressing modifiable risk factors reduced the number of people developing dementia at all ages, there would be less people living with the illness even though they lived longer.

Despite the important impact of age on the risk of developing dementia, research clearly indicates there are factors that protect older people from developing the illness. Older people with better vascular health, who have been more physically, mentally and socially active, who don't smoke and who drink alcohol in moderation are significantly less likely on average to develop dementia.

The modifiable lifestyle and medical risk factors for dementia are often conceptualised as delaying factors that postpone the onset of dementia [13,14]. A brain healthy lifestyle can build brain reserve, so that cognitive function remains intact for longer in the face of age-related changes or brain disease.

2.2 GENETICS

The genetics of dementia is not fully understood, but genes are another non-modifiable risk factor. Only a small proportion of dementia cases are thought to be directly inherited and caused by identified individual gene mutations. The majority of dementia cases are sporadic and likely to result from a combination of genetic and environmental influences.

In the rare familial form of Alzheimer's disease, mutations in the amyloid precursor protein, the presenilin 1 and the presenilin 2 genes cause autosomal dominant transmission of the disease [15]. These genes account for perhaps 1% of Alzheimer's cases. The onset of symptoms in familial Alzheimer's is typically before age 60.

In non-familial or sporadic Alzheimer's, the apolipoprotein E (APOE) gene has been identified as a major risk factor [14]. The APOE ϵ 4 allele increases risk while the ϵ 2 allele appears to be protective. APOE ϵ 4 may also increase the risk of cognitive impairment, vascular dementia and Lewy body disease.

Familial frontotemporal dementia accounts for around 10-15% of all cases [16]. The majority of cases are sporadic. Of the familial forms, the MAPT (microtubule associated protein tau) and progranulin genes account for around 50% of cases. Mutations of the C9ORF72 gene have recently been implicated as a fairly common cause of frontotemporal dementia [17]. There are also rare genetic forms of Lewy body disease, cerebrovascular disease and other causes of dementia.

Genes obviously play an important role in the development of cognitive decline and dementia. However, only in a few cases can the cause be attributed solely to a genetic mutation. More research is needed to clarify the interactions between age, genes and environmental risk factors for dementia.

3. MODIFIABLE FACTORS – BRAIN

3.1 MENTAL ACTIVITY

Higher participation in mentally stimulating activities is associated with better cognitive function and reduced risk of cognitive decline and dementia. Those with a history of higher education, mentally demanding occupations or participation in mentally challenging leisure activities are consistently found to have a lower risk of developing dementia.

3.1.1 Mental activity and dementia risk

Reduced risk of cognitive decline and dementia appear to be associated with:

- Higher levels of education
- Mentally demanding occupations
- More cognitively stimulating leisure activities
- Higher intelligence

Meta-analyses suggest reduced risk of dementia for those with high educational attainment compared to low, those with high occupational status compared to low, and those participating in more cognitively stimulating leisure activities compared to those participating in few such activities [18,19]. A dose-response relationship is also evident, such that dementia risk increases with decreasing levels of education for instance [19].

Importantly for older or retired people, increased complex mental activity in late life is associated with lower dementia risk independent of other predictors such as education [18].

A recent French study found 18% of cases of mild cognitive impairment or dementia could be attributed to low crystallised intelligence [20], and a review found 19% of cases of Alzheimer's disease could be attributed to low education [5].

In both cases, these markers of lower levels of mental activity during life accounted for more cases of cognitive impairment or dementia than any other risk factor, including the major genetic risk factor for Alzheimer's disease.

Brain training games and computer programs have not as yet been shown to reduce the risk of dementia [21].

3.1.2 Mental activity and the brain

It is hypothesised that complex mental activity across the lifespan may reduce the risk or delay the onset of dementia by improving brain reserve [18,19]. Mental activity, challenge and learning stimulate the growth of new neurons and synapses [19]. High levels of complex mental activity across the lifespan were found to be correlated with a reduced rate of hippocampal atrophy [22]. Complex cognitive activity contributes to neurological brain reserve (increased synapses, neural numbers and brain volume) and behavioural brain reserve (flexible cognitive strategies). This reserve may allow normal cognitive function to continue for longer in the face of underlying degeneration such as in Alzheimer's disease [19,23].

Recent findings that greater participation in cognitively stimulating activities in early and midlife is associated with reduced beta amyloid in the brain at late-life, as measured by positron emission tomography (PET) scans, suggest that higher levels of mental activity may also prevent or slow the onset and progression of Alzheimer's disease [24]. Neural activity appears to regulate the secretion of beta amyloid, and individuals who participate in a variety of cognitively stimulating activities during the lifespan may develop more efficient neural processing that result in less beta amyloid deposition [24].

3.2 SOCIAL ACTIVITY

Being more socially active is associated with reduced risk of cognitive decline and dementia. This has been shown in several studies measuring social engagement in different ways. Combining social activity with mental and/or physical activity may provide even greater benefit in reducing the risk of developing dementia.

3.2.1 Social activity and dementia risk

A history of being more socially active is associated with reduced cognitive decline and risk of developing dementia, for levels of social activity measured in a number of different ways [14,25].

The association between social engagement and dementia risk has been shown by several studies, for example:

- Participation in high numbers of different leisure activities was associated with a 38% lower risk of developing dementia in 1,772 people over age 65 [26]. Activities included going to clubs, visiting friends or being visited, playing cards and community or volunteer work.
- Larger social networks were associated with a 36% lower risk of dementia in 2,249 elderly women [27].
- Loneliness (perceived isolation) was associated with more than double the risk of developing dementia in 823 older persons [28]. Loneliness was also associated with worse cognition at baseline and more rapid cognitive decline during follow-up.

Midlife social activity may also be related to lower dementia risk, and increasing social engagement in old age appears to be beneficial for cognition [25].

Research suggests that social activities that also involve mental stimulation and/or physical activity can provide even greater benefit. A study in Stockholm investigated mental, physical and social components of the leisure activities of people aged 75 years and older [29]. All three components were associated with a reduced risk of dementia after 6 years follow up. Combining components offered the greatest benefit, with those whose activities included higher levels of two or all three components having a 47% reduced risk of dementia.

There remains the question of reverse causation because most studies in this area commence in old age, with participants who may already be developing dementia, which may lead to social withdrawal [14]. However, overall the evidence points in the direction of social engagement being protective for cognitive function.

3.2.2 Social activity and the brain

Social activity may benefit brain health and cognitive function through a number of mechanisms [14]. Social engagement has been found to have benefits for other health factors that are also related to cognitive functioning, such as vascular conditions and depression, and it may improve health behaviours such as maintaining physical exercise. Social activity may also contribute to brain reserve. Interacting with other people involves many cognitive functions. As with other mentally stimulating activity, this is believed to help build up a reserve of healthy neurons and synapses that may protect against cognitive decline and dementia.

4. MODIFIABLE FACTORS – BODY

4.1 ALCOHOL

Consumption of moderate amounts of alcohol has been associated with better cognitive function and reduced risk of dementia. However, excessive amounts over time may increase the risk. National guidelines recommend consuming no more than 2 standard drinks a day.

4.1.1 Alcohol and dementia risk

Several studies have found that moderate alcohol consumption, compared to abstaining, is associated with a lower risk of cognitive decline, mild cognitive impairment, any dementia and Alzheimer's disease [30]. There is insufficient evidence to promote alcohol consumption to non-drinkers as a means of reducing dementia risk. However, there may be benefits for those currently using alcohol moderately.

In a large study of 8,000 people in Rotterdam, followed up for an average of 7 years, there was a 45% lower risk of dementia in those who consumed 1-3 alcoholic drinks per day, compared to non-drinkers [31].

Three meta-analyses found reduced risks of around 30 to 40% for those drinking moderate levels of alcohol [32-34]. All found significant effects for any dementia and Alzheimer's disease. Two also found a significant effect for vascular dementia [32,34].

However, excessive alcohol consumption can cause cognitive impairment and may increase the risk of dementia [30]. Very heavy drinking over time can cause alcohol-related dementia [35]. While meta-analyses failed to detect a significant association between heavy drinking and dementia risk [32,34], several observational studies have shown this association. For example, in a study of 554 twins in Finland, followed for 25 years, binge drinking at least monthly in midlife was associated with a more

than 3-fold increase in the risk of dementia after the age of 65 years [36].

The upper limit of alcohol consumption that is safe for maintaining cognitive function has not been determined. Alcohol's potential harmful effects for other medical conditions also need to be taken into consideration. The National Health and Medical Research Council's Australian Guidelines to Reduce Health Risks from Drinking Alcohol recommend limiting alcohol intake to no more than 2 standard drinks on any day to reduce the risk of long term harm [37].

4.1.2 Alcohol and the brain

The benefits of alcohol may be produced through its favourable effects on the cardiovascular system, although there may be other mechanisms. Moderate alcohol consumption may protect against cerebrovascular disease, which has been shown to contribute to cognitive impairment and clinical dementia. Alcohol appears to reduce inflammation, increase HDL ('good') cholesterol and inhibit blood clotting, all of which are thought to protect against vascular disease in the body and brain [30,35]. Increasing brain blood flow, increasing insulin sensitivity and antioxidant properties have also been implicated as contributing to alcohol's protective effect [32,33].

Many alcoholic drinks contain antioxidants, which may help reduce oxidative damage in the ageing brain. Red wine is particularly rich in the antioxidant resveratrol, so many studies of alcohol's effects on dementia risk have focused on wine consumption. However, the evidence to date does not support any one type of alcoholic drink being more protective than any other [30].

In contrast to the potential benefits of moderate alcohol consumption, there is evidence that heavy alcohol consumption can have neurotoxic effects and lead to brain damage [35]. Many chronic alcoholics demonstrate significant brain atrophy [35].

4.3 DIET

Diets low in saturated fat and high in fruits and vegetables have been associated with better brain function and reduced risk of dementia. While the benefits of specific nutrients are not yet clear, what is good for the heart seems to be also good for the brain. A healthy diet is likely to contribute to brain health and may reduce the risk of developing dementia.

4.3.1 Diet, brain health and dementia risk

Many individual nutrients have been studied for their potential benefits on cognitive health. More recently, dietary patterns most associated with reduced risk of dementia have been investigated. Dietary choices affect risk for cardiovascular disease, high blood pressure, diabetes, high cholesterol and obesity, all of which in turn are associated with increased risk of cognitive impairment and dementia.

Several prospective studies have found that high intakes of saturated and transunsaturated (hydrogenated) fats are associated with increased risk of dementia, while higher intake of polyunsaturated and monounsaturated fats is associated with reduced risk of dementia [41].

The omega 3 fatty acids contained in fish oils are thought to reduce inflammation in the brain and promote the growth of new neurons. Results are conflicting as to whether omega 3 protects against dementia [42], but some studies have shown an association between higher fish consumption and lower dementia risk.

Nutrients with antioxidant properties may help protect against oxidative damage, considered part of the pathology of Alzheimer's disease and other forms of dementia. Prospective studies provide some evidence of lower dementia risk for higher intake of specific antioxidants, but results are conflicting [43]. A review of studies found no effect for vitamin C, and a potential beneficial effect for dietary vitamin E but not for vitamin E supplements [44]. Clinical trials of antioxidant supplements have failed to demonstrate benefits in terms of reducing risk of cognitive decline or dementia in the elderly, but this doesn't rule out potential benefits of antioxidant strategies begun at earlier ages [43,44].

Deficiencies of B vitamins (folate, vitamin B6 and vitamin B12) and elevated homocysteine levels have been associated with increased risk of cognitive impairment, Alzheimer's disease and vascular dementia [45]. Homocysteine is an amino acid, elevated levels of which are associated with increased risk of cardiovascular and cerebrovascular disease, and increased hippocampal atrophy [46].

Elevated homocysteine may also increase oxidative stress and the production of beta amyloid plaques in the brain [46]. Clinical trials in older adults have not shown that increasing B vitamin intake or using supplements reduces the risk of cognitive decline or dementia, however some trials demonstrated slowing of brain atrophy and improvement in some domains of cognitive function [45]. It is possible that if such supplements were begun in midlife, when chronic elevations in homocysteine could be prevented, they would be more beneficial, but further research is required to determine this [46].

Dietary patterns characterised by higher intake of fruits, vegetables, fish, nuts and legumes, and lower intake of meats, high fat dairy and sweets seem to be associated with lower risk of cognitive impairment and dementia [47]. Several studies have found a lower risk of dementia is associated with higher intake of fruit and vegetables and higher adherence to the Mediterranean diet [43]. One study of 1433 older people determined that 6.5% of cases of mild cognitive impairment or dementia may be attributable to low fruit and vegetable consumption [20]. Another recent study found an 88% lower risk of any dementia and 92% lower risk of Alzheimer's disease in those with an overall healthy diet at midlife, compared to those with an unhealthy diet [48].

There is insufficient evidence to promote specific foods for reducing dementia risk, although fish and fruits and vegetables show promising benefits. The Australian Dietary Guidelines recommend avoiding saturated fat and eating plenty of fruits and vegetables [49]. This general healthy diet is likely to help reduce the risk of cognitive decline and dementia, in addition to cardiovascular disease and other conditions.

4.4 PHYSICAL ACTIVITY

Regular physical exercise is associated with better brain function and reduced risk of cognitive decline and dementia. This has been shown in many studies for exercise undertaken in midlife and in late-life. Even simple exercise like walking has been shown to be beneficial.

4.4.1 Physical activity, cognitive decline and dementia risk

There is growing evidence that regular physical activity throughout life may protect against cognitive decline and dementia in old age. However, there is wide variability in the way studies measure physical activity and cognitive function, and recent reviews have concluded that the quality of evidence is low and further research is needed to determine the optimal type, frequency, duration and intensity of exercise to preserve cognitive function [50,51]. Nevertheless, it was recently estimated that 13% of cases of Alzheimer's disease are potentially attributable to physical inactivity [5].

Several studies have found that older people who exercise regularly are less likely to experience cognitive decline or develop dementia. A meta-analysis of prospective studies found that high levels of physical activity were associated with 38% lower risk of cognitive decline in older people without dementia [51]. Even low to moderate levels of physical activity were associated with 35% lower risk of cognitive decline, compared to those who were sedentary. A meta-analysis investigating dementia as the outcome found a 28% reduced risk of any dementia and 45% reduced risk of Alzheimer's disease for those in the highest physical activity category compared to the lowest [52].

Trials of exercise interventions are also providing promising results. In a randomised controlled trial of people aged 50 and over with subjective memory impairment, a 6 month program of physical activity resulted in improved cognition at the end of the trial and after 18 months follow up [53].

Regular exercise during midlife may also protect against later developing dementia. In one study, exercising at least twice a week at midlife was associated with a 52% reduced risk of dementia at age 65-79 [54].

4.4.2 Physical activity and the brain

Several mechanisms have been proposed to explain the association between physical inactivity and cognitive decline [51,55,56].

- Physical activity helps maintain blood flow to the brain and the necessary supply of oxygen and nutrients.
- Physical activity reduces the risk of cardiovascular disease, obesity, diabetes, high blood pressure high cholesterol and cerebrovascular disease. These conditions are all associated with increased risk and severity of cognitive decline and dementia.
- Inactivity is associated with higher levels of inflammatory markers including C-reactive protein. Inflammation in the brain is associated with the pathological changes that cause cognitive decline and dementia.
- Physical activity appears to stimulate the growth of new neurons and synapses.

Neuroimaging studies have revealed that higher levels of physical activity and related better cognitive function are associated with larger brain volume, including hippocampal volume, and increased connectivity between brain regions [50]. Physical activity is also associated with increased levels of brain-derived neurotrophic factor (BDNF) [50], which is involved in supporting the survival of existing neurons, the growth of new neurons and synapses, and learning and memory.

Regular physical exercise provides a range of health benefits. The evidence supporting the beneficial effects of physical activity on brain health provides yet more reasons to encourage regular physical activity among people of all ages. The National Physical Activity Guidelines outline the minimum levels of physical activity required to gain a health benefit and ways to incorporate physical activity into everyday life [57].

5. MODIFIABLE FACTORS – HEART

5.1 BLOOD PRESSURE

High blood pressure (hypertension), especially at midlife, is associated with an increased risk of developing dementia. Treatment of hypertension has been found to reduce the risk of cognitive decline and dementia in several studies, but this may be age dependent.

5.1.1 Blood pressure and dementia risk

Hypertension is a risk factor for cerebrovascular disease, stroke, cognitive impairment and vascular dementia. Hypertension in midlife may also be associated with an increased risk of Alzheimer's disease, however, hypertension in old age is not [58-60]. A recent review determined that 5% of cases of Alzheimer's disease may be attributable to midlife hypertension [5].

Blood pressure may decline in the preclinical stage of Alzheimer's such that low blood pressure in late-life may be associated with increased incidence [58-60]. Although, low blood pressure may also result in inadequate brain blood flow and contribute to cognitive impairment. While hypertension in old age does not seem to be associated with increased risk of Alzheimer's disease, it has been associated with increased risk of cognitive impairment [61].

The results of clinical trials investigating whether treatment with antihypertensive medications reduces dementia risk in the elderly have been mixed [62]. However, treatment of hypertension in early old age has been identified in some studies to reduce the risk of cognitive decline and dementia. In a 4 year study of 2,400 patients, treatment reduced the risk of dementia by 55% [63].

Studies assessing long term use of antihypertensives from midlife show a cumulative reduction in risk of dementia for each year of treatment [58,64]. A study that followed hypertensive men from midlife found that for each additional year of treatment there was a further reduction in the risk of dementia [64]. Those treated for more than 12 years had a 60% reduced risk of any dementia and 65% reduced risk of Alzheimer's disease compared to those never treated. The risk after 12 years of treatment was similar to those with normal blood pressure [64].

5.1.2 High blood pressure and the brain

Hypertension may contribute to both cerebrovascular pathology and Alzheimer's disease pathology [65]. Hypertension may lead to dysfunction of the blood vessel lining, mini-strokes and major stroke. Blood vessel changes could also affect the vascular clearance of beta amyloid and exacerbate Alzheimer's disease pathology [60,65].

Cerebrovascular pathology is common in older adults, is itself associated with cognitive impairment, and often coexists with Alzheimer's disease pathology. Also, for a given level of Alzheimer's pathology, the probability of manifesting Alzheimer's dementia is increased by the coexistence of cerebrovascular pathology [60,65].

Hypertension is correlated with higher levels of neurofibrillary tangles and amyloid plaques in the brain (the pathological hallmarks of Alzheimer's disease). This may be related to findings that damage due to restricted blood flow may increase beta amyloid production or reduce its clearance from the brain [60,65]. Hypertension and cerebrovascular disease have also been associated with greater hippocampal and cortical atrophy, which may be related to loss of neurons caused by vascular disease [60,65].

5.2 BODY WEIGHT

Obesity at midlife is associated with an increased risk of developing dementia, including Alzheimer's disease. Weight reduction has not as yet been shown to reduce the risk of dementia. In old age, those who are underweight or are losing weight are found to be at increased risk of dementia.

5.2.1 Body weight and dementia risk

Obesity, particularly central obesity, at midlife is associated with increased risk of later developing dementia [38,39]. Midlife obesity has been estimated to account for 2% of cases of Alzheimer's disease [5]. Whether midlife weight loss for those who are obese can reduce the risk of late life dementia has not yet been determined. Although, there is clinical trial evidence that weight loss lowers blood pressure, improves blood lipids and insulin resistance, and positively affects other factors associated with cardiovascular and dementia risk.

Reviews of observational studies found that in midlife [39] and early old age (65 to 75 years) [38], there is a U-shaped relationship between BMI and dementia risk, with increased risk found for those who are underweight (BMI < 18.5) as well as those who are obese (BMI > 30). A meta-analysis found that compared to healthy BMI (18.5 – 25), obese and underweight BMI in midlife are associated with approximately double the risk of late life dementia, while overweight BMI (25 – 30) increases risk by around one-third [39].

In late life (after 75 years), lower BMI and weight loss have been associated with an increased risk of dementia [38]. Weight loss may precede dementia onset by more than 10 years. A recent study of older Australian men found a reduced risk of dementia for those in the overweight BMI range and no increase in dementia risk for those in the obese range [40].

A recent review summarised the findings of the complex relationship between weight and dementia across the lifespan as follows [38]:

- central obesity in middle age predicts dementia in old age
- the relation between obesity and dementia is attenuated with older age
- lower BMI predicts dementia in the elderly
- weight loss may precede dementia diagnosis by decades

5.2.2 Body weight and the brain

There are a number of potential mechanisms by which obesity may affect the brain and increase dementia risk [38]. Insulin resistance and excess insulin can result from obesity and may play a role in reducing beta amyloid clearance from the brain, increasing the risk of Alzheimer's disease. Adipose tissue produces proteins and hormones that are related to excess insulin and inflammation that in turn have effects on the brain. Obesity is also associated with increased risk for high blood pressure, diabetes, cardiovascular disease and cerebrovascular disease, which affect brain health and increase the risk of dementia.

5.3 CHOLESTEROL

High blood total cholesterol, especially at midlife, is associated with an increased risk of developing dementia, especially Alzheimer's disease. Treatment with statins has been found to be associated with reduced risk of dementia in several studies, but there are some conflicting findings.

5.3.1 Cholesterol and dementia risk

Reviews of studies in this area have concluded that high midlife total serum cholesterol is associated with an increased risk of any dementia and of Alzheimer's disease [66,67]. While there are some studies that have not found this association, the majority of studies and meta-analyses show that high midlife cholesterol increases the risk of later developing dementia by around 2 times.

A meta-analysis of studies measuring cholesterol at late-life and following participants over a few years found no association between late life cholesterol and dementia risk [67]. Another study found that a decrease in cholesterol level from midlife to late life was associated with an increased risk of Alzheimer's disease [68]. Cholesterol levels may decline in the preclinical stages of Alzheimer's [66,67].

Several studies have shown reduced risk of dementia in those treated with statins [69], but a meta-analysis found only a small non-significant benefit [70]. It may be that treatment of midlife high cholesterol with statins is most beneficial, but this has not been examined.

5.3.2 Cholesterol and the brain

Cholesterol plays an essential role in healthy brain function [69]. However, some studies suggest increased total cholesterol levels are involved in the development of Alzheimer's disease [70]. High cholesterol levels may accelerate the production of beta amyloid [69,70]. Autopsy findings indicate that lower midlife total cholesterol is associated with a lower number of plaques and tangles [66]. Higher levels of HDL ('good') cholesterol are associated with larger hippocampal volume and reduced risk of cognitive impairment and Alzheimer's disease [69].

Impacts of high total cholesterol levels on oxidative stress and on the vascular system may also contribute to dementia [69,70]. Untreated high total cholesterol can lead to atherosclerosis and cerebrovascular disease.

5.4 DIABETES

Diabetes is associated with an increased risk of developing mild cognitive impairment and dementia, including Alzheimer's disease and vascular dementia. The ability of treatment of diabetes to reduce dementia risk has not been established.

5.4.1 Diabetes and dementia risk

Diabetes, especially type 2, and pre-diabetes syndromes appear to be risk factors for cognitive impairment and dementia. A recent review concluded that type 2 diabetes is associated with increased risk of Alzheimer's disease and vascular dementia [71]. Another review reported meta-analyses that found diabetes was associated with a 47% increased risk of any dementia, a 39% increased risk of Alzheimer's disease, and a 138% increased risk of vascular dementia [72].

Diabetes has also been associated with greater risk for poorer cognitive function and cognitive decline in several studies [14,72]. Global cognitive function and executive function have been shown to be affected by diabetes.

Few studies have examined the effect of treatment of diabetes on dementia risk and the results are mixed [72,73]. The effect of the duration of diabetes on dementia risk has also not been established, however longer duration and greater severity have been associated with increased risk of cognitive decline [14,72]. Prevention of diabetes, through early screening for glucose tolerance and insulin resistance and lifestyle modifications for those at risk, could reduce the incidence of mild cognitive impairment and dementia by 5% according to one study [20]. Another recent review determined that 2% of cases of Alzheimer's disease could be attributed to diabetes [5].

5.4.2 Diabetes and the brain

Diabetes is a disorder characterised by deficiencies in insulin production, response to insulin, or both. Insulin resistance, impaired insulin secretion, excess insulin and glucose intolerance have also been associated with increased risk of cognitive impairment and dementia [14]. The mechanisms underpinning the association between diabetes and dementia risk are unclear. Multiple processes may be involved, such as the effects of insulin resistance, vascular disease, oxidative stress and inflammation [71-73].

Insulin-degrading enzyme is involved in the clearance of beta amyloid from the brain, which may be reduced by excess insulin thus

increasing the formation of plaques and the risk of Alzheimer's disease [72,73]. Diabetes and pre-diabetes syndromes can lead to cerebrovascular disease and are associated with inflammation and oxidative stress, thereby increasing the risk of dementia [14,72,73].

5.5 SMOKING

Smoking is associated with an increased risk of dementia, including Alzheimer's disease.

5.5.1 Smoking and dementia risk

Smoking has been demonstrated to be a risk factor for dementia. Two recent meta-analyses concluded that current smokers have an increased risk of any dementia, Alzheimer's disease, vascular dementia and cognitive decline compared to non-smokers [74,75]. Another review found that 14% of Alzheimer's disease cases may be attributed to smoking [5].

Former smokers were not found to be at increased risk compared to never-smokers, suggesting quitting smoking may be beneficial for dementia risk [74,75].

Smoking at midlife has also been associated with an increased risk of dementia decades later. A prospective study involving over 21,000 people found those smoking more than 2 packs a day at midlife had more than 2.5 the risk of Alzheimer's disease and vascular dementia compared to non-smokers [76].

A recent study examined the association between a history of heavy alcohol use and smoking and age of disease onset in 685 people with Alzheimer's disease. Heavy smoking (defined as one pack per day or more) was associated with a 2-3 year earlier onset of Alzheimer's disease [77].

The adverse health effects of exposure to secondhand smoke are similar to those of active smoking. There is some evidence that passive smoking may also be associated with increased risk of cognitive impairment and dementia [78].

5.5.2 Smoking and the brain

Smoking is associated with increased risk for cardiovascular and cerebrovascular disease and stroke, and with increased oxidative stress, atherosclerosis and inflammation. Smoking may affect dementia risk via its negative effects on the cardiovascular system, increasing risk for both Alzheimer's disease and vascular dementia. Smoking may also interact with other cardiovascular risk factors in an additive manner [74,75].

6. OTHER POTENTIALLY MODIFIABLE FACTORS

6.1 DEPRESSION

People with a history of depression or high depressive symptoms appear to have, on average, a higher risk of developing dementia. Evidence suggests that treatment with antidepressants improves cognition in people with depression, but it is not known if treatment prevents dementia.

6.1.1 Depression and dementia

A history of depression has been associated with an increased risk of Alzheimer's disease and any dementia in several studies [14,79]. Some studies, however, have failed to replicate this finding.

In a study of 1,953 people with Alzheimer's disease, depressive symptoms before dementia onset were twice as common as in controls [80]. It may be that early awareness of cognitive decline contributes to depression, but it seems that this does not fully explain the association. A review of epidemiological studies reported a history of depression was associated with around double the risk of Alzheimer's disease [81].

A recent French study of 1433 older people found that elimination of depression from the elderly population would lead to a 10.3% reduction in cases of mild cognitive impairment and dementia [20]. Another study likewise concluded that around 10% of cases of Alzheimer's disease may be attributable to depression [5].

It is well known that people with depression, especially older adults, have reduced cognitive performance and that many people with dementia also have depression. It is therefore difficult to determine whether depression is a risk factor for dementia or whether it is a prodromal symptom or both [14,79]. A review of studies found that the interval between diagnoses of depression

and Alzheimer's disease was positively related to increased risk of developing Alzheimer's, suggesting that depression is likely a risk factor [81].

Other mental disorders may also be associated with increased dementia risk. In a recent study of predominantly male war veterans, those diagnosed with post-traumatic stress disorder (PTSD) were at nearly twice the risk of developing dementia compared with those without PTSD [82].

6.1.2 Depression and the brain

Depression is associated with elevated cortisol production, which may directly damage the hippocampus and increase the risk of dementia [20,79]. Conversely, depression may arise secondary to dementia due to frontostriatal damage from cerebrovascular or Alzheimer's pathology [14,79]. Recent studies have also suggested that people with depression have enhanced deposition of beta amyloid plaques [79]. Depression has been associated with inflammation and vascular changes in the brain, which may also contribute to cognitive impairment and dementia [5,14].

The treatment of depression seems to improve cognitive function, but it may not return cognition to normal levels even when the depression is in remission [14,79]. Whether the treatment of depression decreases the risk of dementia among people with depressive symptoms has not yet been studied, but it is clearly important to identify and treat depression. Treating depression may slow functional loss in those with cognitive impairment and preventing new episodes of depression may be a useful preventative approach to dementia [20,83].

6.2 HEAD INJURY

Serious head injury, with loss of consciousness, is associated with an increased risk of subsequent cognitive decline and dementia.

6.2.1 Head injury and dementia

Several studies have examined the association between head injury and risk of dementia in late-life. Head injury has been shown to increase the risk of cognitive decline, dementia and Alzheimer's disease [14]. The association may be mediated by the severity of head injury, whether loss of consciousness occurs, the time between head injury and dementia onset and genetic factors [14].

Long term follow up of US World War II veterans who were admitted to hospital during service showed that those who had suffered a head injury with loss of consciousness had an increased risk of subsequently developing Alzheimer's disease compared to those admitted for other reasons [84]. Those with moderate head injuries had 2.3 times the risk and those with severe head injuries had 4.5 times the risk.

A meta-analysis of studies found a 58% increased risk of Alzheimer's disease for those with a history of serious head injury [85]. The association was found to be significant only in males (possibly because they make up the majority of study participants). A more recent review concluded that moderate and severe head injuries increase the risk of dementia by 2 to 4 times [86].

Multiple mild head traumas as experienced by boxers are associated with a high risk of chronic traumatic encephalopathy (CTE), a type of dementia with distinct clinical and pathological features [86]. Recent research suggests that CTE may also be common in football players and military personnel. However, it is less clear whether repeated mild injuries such as brief concussions result in increased risk of the more common forms of dementia including Alzheimer's disease [86].

Several mechanisms have been proposed to explain the association between head injury and increased dementia risk. Damage to the blood brain barrier, increased oxidative stress, neuronal loss, increased enzyme activity leading to increased beta-amyloid deposition and increased tau pathology have all been implicated [14].

7. MYTHS, CONTROVERSIES AND POSSIBILITIES

7.1 ALUMINIUM

Excessive aluminium exposure is neurotoxic and may cause cognitive impairment. In the Camelford water incident, which occurred in 1988 in the UK, 20 tonnes of aluminium sulphate contaminated a town's drinking supply and exposed people were reported to have subsequently suffered cognitive deficits, but not increased rates of dementia [87]. However, the methodology of this study was criticised, and a 2005 inquiry concluded it is unlikely the incident caused any long term health effects [88].

Aluminium is the third most common element on earth and we are exposed to it from many environmental sources including in water, cooking utensils, polluted air and deodorants. Some studies have found higher levels of aluminium in drinking water, or measured in blood samples, are associated with an increased incidence of dementia, but many studies have failed to show any association. A recent review concluded there is only weak evidence that a higher risk of Alzheimer's disease is associated with high aluminium intake through drinking water [89]. It is likely only abnormally high levels pose any risk and there is no danger from the typical levels of aluminium in the environment, cooking utensils or deodorants.

No trials have yet looked at whether there are potential benefits of reducing aluminium intake, and at this stage there is no evidence to support avoidance of aluminium to prevent dementia.

7.2 CAFFEINE

Some studies of coffee and tea consumption suggest a possible protective effect for caffeine. A small study in Portugal found those with Alzheimer's disease had a lower average caffeine intake over the previous 20 years compared to healthy controls (74mg per day compared to 200mg per day) [90]. A more recent study in 7017 French people over 65 found that women who drank 3 or more cups of coffee per day showed less cognitive decline over 4 years than those consuming 1 cup or less [91]. However, no association was found between caffeine consumption and cognitive decline in men, or between caffeine intake and risk of dementia for either gender.

Another study however did find an association between higher caffeine consumption and lower dementia risk [92].

The potential beneficial effects of caffeine may be through mechanisms that reduce beta amyloid production or increase the level of brain proteins important for learning and memory such as brain derived neurotrophic factor (BDNF) [14].

At this stage increasing caffeine intake, which may cause other health problems, with the aim of reducing dementia risk cannot be recommended.

7.3 GENERAL ANAESTHESIA

Long-term cognitive problems have been reported in older adults following surgery with general anaesthesia, suggesting that exposure to anaesthesia may increase the risk of cognitive impairment and dementia [14]. Some animal and laboratory studies suggest that anaesthetic agents can increase the production and aggregation of beta amyloid, increasing the risk of Alzheimer's disease [93]. However, findings from human studies do not support an association [14,93]. A few studies suggest a possible increased risk of dementia after surgery with general anaesthetic, while others show no association, and some suggest a reduced risk of dementia with a history of exposure to anaesthesia. Studies also show that the type of surgery (major or minor) and type of anaesthesia (general or regional) make no difference to the long-term cognitive outcomes for older patients [93].

A meeting of international experts in 2009 concluded that there is not enough evidence to avoid the use of anaesthesia on the basis that it might lead to Alzheimer's disease [93].

Postoperative cognitive dysfunction (POCD) is the term used to describe cognitive problems following surgery. We now know that POCD occurs in the elderly not only after major surgery, but even after minor procedures with sedation [93]. This may represent an unmasking of cognitive impairment that was developing anyway, due to underlying brain disease such as Alzheimer's, rather than any causal link with the anaesthetic or surgery.

At present, there is scarce information on whether anaesthesia and surgery can exacerbate existing Alzheimer's disease, dementia or mild cognitive impairment [93]. This possibility though suggests that non-urgent surgery should be carefully considered for people with these conditions.

More research is needed to determine the long-term impacts of anaesthetic agents on the brain and cognitive function.

7.4 GINKGO BILOBA

Ginkgo biloba is a tree, native to China. Extracts of ginkgo leaves are believed to have antioxidant properties and effects on neurotransmitters, and to increase brain blood flow, and are marketed as enhancers of memory and concentration. However, clinical trials of ginkgo's efficacy as a cognitive enhancer have produced inconsistent findings.

Several clinical trials have investigated ginkgo as a potential treatment for cognitive impairment, dementia or Alzheimer's disease, but most have been small studies of short duration. A recent review found nine trials of six months duration including 2016 participants [94]. These trials showed inconsistent results for cognition, activities of daily living, mood, depression and carer burden. The reviewers concluded that there is no convincing evidence that ginkgo is effective as a treatment for cognitive impairment or dementia [94]. However, some studies have demonstrated beneficial effects, so further research is warranted.

Fewer clinical trials have investigated ginkgo's potential to prevent dementia. The largest study reported to date was a randomised clinical trial in 3069 adults aged 75 and older, with normal cognitive function or mild cognitive impairment, followed up over 6 years. This study found ginkgo showed no benefit for reducing incidence of any dementia or Alzheimer's disease [95].

In June 2011 an expert meeting "The Ageing Brain" took place in Amsterdam, The Netherlands. The aim was to discuss the available evidence on ginkgo and cognitive decline and Alzheimer's disease. The participants concluded that there is enough promising data, both preclinical and clinical, to undertake further research with ginkgo to target cognitive impairment in old age [96].

Adverse effects of ginkgo can include headache, gastrointestinal symptoms and allergic skin reactions. It can also increase bleeding, especially when used in combination with other

agents that may increase bleeding, such as aspirin or warfarin.

Based on the evidence to date, ginkgo biloba cannot be recommended for preventing or treating cognitive impairment or dementia, but research is continuing.

7.5 INFLAMMATION AND ANTI-INFLAMMATORY MEDICATIONS

Inflammation is known to play a role in the pathological brain changes and brain cell death that cause dementia [14,97]. Therefore, studies have investigated whether inflammatory biomarkers are associated with increased risk of dementia, and the potential for anti-inflammatory drugs to reduce the risk.

Levels of indicators of inflammation (including C-reactive protein) can be measured in the blood. Findings from studies of whether elevated blood levels of inflammatory markers are associated with increased risk of cognitive decline or dementia have been inconsistent. A review concluded that these studies do not provide consistent support for an association between elevated inflammatory markers and risk for Alzheimer's disease, but associations between higher levels of inflammatory markers and risk for any dementia are more suggestive, consistent with a reported link between inflammation and vascular dementia [97]. Part of the reason for the lack of a convincing association may be that inflammatory markers measured in blood may not accurately reflect inflammation in the brain. Future research may provide more clarity by measuring brain-specific markers of inflammation [97].

Observational studies have demonstrated support for a protective effect of non-steroidal anti-inflammatory drugs (NSAIDs), finding a history of use is associated with reduced risk of dementia [14,98]. In a meta-analysis of 9 studies, with over 13,000 people, the risk of Alzheimer's disease amongst users of NSAIDs was 28% less than in non-users, and 73% less in those who had used such drugs for over 24 months [99]. However, randomised controlled trials have not found similar protective effects [14]. Possible reasons for the discrepancy include differences in the timing, type and dose of NSAID treatment [100]. One observational study reported a slower rate of cognitive decline when NSAID use began in midlife compared to late-life [101].

NSAIDs can have significant side effects and there is insufficient evidence to recommend their use for reducing dementia risk.

7.6 OESTROGEN AND HORMONE REPLACEMENT THERAPY

Observational studies of postmenopausal hormone replacement therapy (HRT) suggest that it may reduce risk of cognitive decline and dementia [102,103]. The association appears strongest for Alzheimer's disease [103]. However, results from a randomised controlled trial as part of the Women's Health Initiative Memory Study reported no benefit to cognitive function or risk of mild cognitive impairment, and an increased risk of dementia [104]. The important difference in this study was that it involved women aged 65 years or older, whereas the observational studies investigated HRT use at middle age. HRT may still benefit cognitive health if started in women at and soon after menopause. A review concluded that early initiation of HRT at menopause may provide cognitive benefits, while HRT initiated in late life may have detrimental effects [105]. More conclusive evidence is needed before HRT can be recommended as a strategy to reduce the risk of cognitive impairment or dementia [14].

The brain has oestrogen receptors, and oestrogen affects brain blood flow and levels of neurotransmitters important for memory. Oestrogen has also been shown to have neuroprotective effects including stimulating the growth of new neurons and supporting neurons involved in learning and memory, and reducing the production of beta amyloid and protecting against its toxic effects [103]. Oestrogen may improve memory in women without cognitive problems but not all studies have confirmed this [106].

HRT should not be taken specifically to reduce the risk of dementia, but if it is needed to alleviate postmenopausal symptoms during midlife, it is unlikely to have any detrimental effects on women's late life cognitive health.

7.7 STRESS

Studies of rats showed that extreme chronic stress may damage the hippocampus, a brain structure crucial for memory and learning [107]. This gave rise to a hypothesis that chronic stress and raised cortisol levels in humans may increase the risk of Alzheimer's disease. However, this has not been supported by subsequent research. Smaller hippocampal volumes have been associated with poor cognitive function and increased risk of dementia [108]. But recent post-mortem studies have failed to find a relationship between chronic stress or cortisol levels and Alzheimer's disease pathology in the brain or hippocampal atrophy [107,109,110]. In addition, recent animal studies

have failed to find substantial neuronal loss in the hippocampus following exposure to chronic stress. A recent review concluded that there are no convincing arguments to presume a causal role for cortisol in the development of Alzheimer's disease pathology [107].

Several studies have investigated the potential relationship between stress and risk for dementia, by assessing personality traits that make people more prone to psychological distress. Higher proneness to stress has been associated with increased risk of mild cognitive impairment [111], increased risk of dementia and Alzheimer's disease [109,110,112], and more rapid cognitive decline [110]. A study in Swedish twins found that measures of work-related stress at midlife were not associated with later dementia risk, but greater reactivity to stress was associated with an increased dementia risk [113]. It appears that exposure to stress *per se* may not be associated with dementia, and is not associated with the pathology of Alzheimer's disease, but personality characteristics that make people more vulnerable to stress may be associated with increased dementia risk.

7.8 TESTOSTERONE

The brain has testosterone receptors, including in regions important for memory and learning such as the hippocampus. Testosterone has also been shown to have beneficial actions supporting neurons and synapses [114]. Testosterone levels in men and women reduce with ageing, but more markedly in men.

Several studies have reported that compared to healthy older men, men with Alzheimer's disease and other dementias have lower serum testosterone levels [115]. Lower testosterone levels have also been associated with greater risk of Alzheimer's disease, mild cognitive impairment and cognitive decline [116,117], and increased levels of beta amyloid in the brain [118]. Animal studies have shown that testosterone depletion results in increased levels of beta amyloid and hyperphosphorylated tau, the pathological hallmarks of Alzheimer's disease [117]. Some studies suggest that testosterone supplementation may improve cognitive performance and reduce beta amyloid levels [115,119].

Taken together, these findings suggest that the reduction in testosterone during ageing could contribute to the development of Alzheimer's disease, and that testosterone supplementation could assist in the prevention or treatment of cognitive decline and dementia.

However, more research is needed to determine the factors that influence the optimal level of testosterone for maintaining cognitive function with ageing, and whether long term testosterone therapy is safe and effective.

Alzheimer's researchers in Perth are investigating the role of testosterone in beta amyloid production and assessing testosterone replacement therapy in animal and human studies as a potential treatment for Alzheimer's disease [120]. A long term study will assess the efficacy of testosterone at lowering beta amyloid and improving memory.

7.9 VITAMIN D

It is well known that vitamin D deficiency can affect bone health, and it may also be linked with heart disease, some cancers and diabetes. Blood levels of vitamin D reflect synthesis from exposure to sunlight as well as intake from the diet. Most adults are unlikely to obtain more than 5-10% of their vitamin D requirement from dietary sources, with the main source being exposure to sunlight [121]. Vitamin D deficiency affects 31%

of adult Australians and increases significantly with age [122]. The groups at greatest risk of vitamin D deficiency include housebound older or disabled people, those in residential care, dark-skinned people, and others who regularly avoid sun exposure or work indoors [121]. Of course, adequate sun exposure to maintain healthy vitamin D levels has to be weighed against the risk of skin cancer.

Vitamin D deficiency may also be associated with increased risk of cognitive impairment or dementia. A recent meta-analysis of 7 studies comprising 7,688 participants showed a 2.4 times increased risk of cognitive impairment in those with low vitamin D compared with normal vitamin D [123]. In a study of 318 people aged 65 and over, vitamin D deficiency was associated with increased risk of dementia, stroke and cerebrovascular disease [124]. However, there are some conflicting findings and methodological issues between studies including different ways of measuring vitamin D deficiency and cognitive function, so more research is needed. It is also not known whether vitamin D supplementation can reduce the risk of cognitive decline or dementia.

8. PREVENTATIVE STRATEGIES FOR THOSE DIAGNOSED WITH DEMENTIA

Many of the preventative strategies addressed in Alzheimer's Australia's *Your Brain Matters* program are also likely to benefit people diagnosed with dementia. Remaining active and socially engaged, treating depression and managing cardiovascular risk factors may help slow the progression of cognitive decline in those with dementia.

Management of dementia should include preventative approaches to maintain health and wellbeing as much as possible. The management of comorbid conditions may have to be modified in the presence of dementia according to the person's declining ability to self-manage their healthcare.

Drugs with anticholinergic effects can worsen cognition in those with Alzheimer's disease and may blunt the effects of cholinesterase inhibitors [125]. Their use should be minimised in people with Alzheimer's disease and other dementias.

8.1 DEPRESSION

Depression is a common comorbidity in dementia and is itself associated with cognitive impairment. Continuous antidepressant use has been associated with a reduced rate of cognitive decline in people with depression and Alzheimer's disease, compared to non-depressed and untreated depressed people with Alzheimer's [126]. Depression has also been identified as a risk factor for early transition to residential care in people with dementia, with antidepressant treatment seeming to protect against this outcome [127].

Depression has consequences detrimental to people with dementia and should be managed with appropriate behavioural and/or pharmacological treatments, with careful monitoring to determine effectiveness and any adverse effects [8].

8.2 VASCULAR RISK FACTORS

Careful treatment of hypertension (while avoiding episodes of low blood pressure), high cholesterol and diabetes (particularly avoidance of hypoglycemia) is recommended for those with vascular dementia [8]. It is likely to also be important for people with other forms of dementia including Alzheimer's disease.

Treating hypertension, high cholesterol and diabetes has been associated with slower progression of dementia. For people with Alzheimer's disease without cardiovascular disease, vascular risk factor treatment was associated with significantly less cognitive decline over an average follow up time of 2.3 years [128]. In this study, only 7% of the Alzheimer's disease patients had no vascular risk factors, suggesting they are common in the dementia population. Neuroimaging studies have also demonstrated benefits of vascular risk factor treatment in people with dementia, such as slowed progression of white matter lesions [129].

8.3 MENTAL STIMULATION

There is ongoing research to determine whether cognitive training can improve, maintain or slow decline of cognitive function in dementia. A meta-analysis of the literature on cognitive training for people with Alzheimer's disease concluded that it may improve cognitive and functional abilities, or at least slow the rate of decline [130].

Cognitive rehabilitation programs that focus on real life activities and provide education to improve self-management, rather than training specific cognitive skills, may be more beneficial [25].

There is also evidence that cognitive and functional decline in dementia may be delayed by continued participation in mentally stimulating activities [8,131]. People with dementia should be encouraged, as far as possible, to maintain their usual hobbies and activities. While adjustments may be needed as dementia progresses, keeping socially involved and mentally active may be important for the person's cognitive and functional status and mental wellbeing.

8.4 PHYSICAL ACTIVITY

There is good evidence to recommend an individualised exercise program for people with mild to moderate dementia [131]. Benefits include increased strength, fitness, and improvements in cognitive and functional performance [132]. A randomised controlled trial of nursing home residents with Alzheimer's disease reported that a simple exercise program (1 hour twice a week), compared with routine medical care, was associated with slower functional decline [133].

An Australian randomised controlled trial of older people with subjective memory complaints found that a six month physical activity intervention improved cognition over 18 months follow up [53]. This trial is currently being repeated in patients with Alzheimer's disease.

Physical exercise should be continued for as long as possible for people with dementia as it can help prevent muscle weakness, mobility problems, falls and other health complications. It may also help promote a normal day-night routine, improve mood, increase social participation and reduce stress and depression.

8.5 DIET

Eating a well balanced diet can be beneficial for those with dementia, giving the person more energy and helping to avoid health problems. Eating or drinking too little or missing out on essential nutrients can increase confusion. Special attention needs to be paid to avoid or deal with obesity or loss of weight, to ensure an

adequate dietary intake of vitamins and minerals, and to avoid dehydration [8].

Higher adherence to the Mediterranean diet has been associated with lower mortality in people with Alzheimer's disease [134]. For each additional point on an adherence scale of 0 to 9, patients had a 24% lower risk of dying over 4.4 years of follow up, suggesting a dose-response effect. A balanced diet low in saturated fat and high in vegetables and fruit may increase survival in patients with dementia.

Souvenaid is a medical food, taken as a daily drink, which contains a patented combination of nutrients and aims to improve synapse formation and function. Recent clinical trial results suggest that it improves memory performance and brain functional connectivity in people with mild Alzheimer's disease [135]. It is currently being tested in people with prodromal Alzheimer's disease. Souvenaid is not yet approved or available for use as a therapy for Alzheimer's disease.

9. STATE OF THE SCIENCE

9.1 THE NATIONAL INSTITUTES OF HEALTH EVIDENCE REPORT

The American National Institutes of Health (NIH) commissioned a panel of experts to review published literature on the factors associated with the reduction of risk of Alzheimer's disease and determine whether recommendations for interventions could be made. The panel concluded that "firm conclusions simply cannot be drawn about the association of any modifiable risk factor with Alzheimer's disease" [136], noting further research efforts need to be increased [136-138].

At first glance, the panel's report may seem to contradict the substantial research that has been carried out to date on the risk and protective factors of Alzheimer's disease and other forms of dementia. However, this is not necessarily the case. The panel based their conclusions partly on a lack of randomised controlled trials (RCTs) – the most rigorous, highest quality evidence. Undertaking RCTs for dementia prevention and risk reduction research is problematic, from an ethical and pragmatic perspective. For example, to prove that treating midlife high cholesterol reduces Alzheimer's disease risk, researchers could not ethically apply treatment over an extended period of time, to one group and not another, because high cholesterol is a known risk factor for other conditions and needs to be treated.

Further, Qiu and colleagues [139], in their response to the NIH report, argued that the evidence was not evaluated from a life-course perspective. That is, the effect of certain risk factors on the risk for Alzheimer's disease largely depends on age. For example, elevated blood pressure in young and middle age is associated with a greater risk of Alzheimer's disease, while low blood pressure (rather than elevated blood pressure) in later life is associated with an increase in the risk of Alzheimer's disease. Qiu and colleagues point out that the evidence supporting these age-dependent risk factors is usually found in population-based long-term follow-up studies, rather than RCTs, which tend to be conducted only with elderly participants [139].

The NIH report was also criticised for focusing on Alzheimer's disease, when the growing numbers of people of advanced age underlie the looming increase in the number of people with dementia, and many of these people will have a mixed pathology [140]. Flicker and colleagues also criticised the report for not including a broader

range of studies in their review and for being far too negative about the available evidence for modification of lifestyle factors to have an impact on reducing dementia incidence [140].

Additionally, the NIH report acknowledged that there are a number of modifiable factors that have an association with risk for Alzheimer's disease and/or cognitive decline. These include diabetes, high cholesterol in midlife, depression, dietary factors, educational attainment, cognitive engagement, smoking and participation in physical activities [136-139].

In summary, whilst the evidence for dementia prevention is as yet inconclusive, there is a growing body of evidence that shows great promise. The NIH report noted the need for long term population-based studies that follow individuals from midlife into old age to determine how biological, lifestyle, dietary, clinical and socioeconomic factors may influence Alzheimer's disease [136-139].

In the meantime, the community must be informed of existing evidence-based strategies, such as those presented in Alzheimer's Australia's Your Brain Matters program, to increase awareness and promote a 'brain healthy' lifestyle that will also be of benefit in addressing a number of other chronic diseases.

9.2 OTHER EVIDENCE REVIEWS

There have been a number of comprehensive review papers published in the last few years, detailing not only the evidence obtained from RCTs, but also from observational research. There is a positive consensus from these reviews that we can and should continue to examine these modifiable risk factors and promote their potential to reduce the risk of dementia.

Middleton and Yaffe [79,141] proposed that population-based studies have identified a number of modifiable lifestyle factors that may increase the risk of dementia. These include vascular risk factors (diabetes, high blood pressure, high cholesterol and obesity), lack of cognitive stimulation, physical inactivity, social isolation, poor diet and depression. However, they concede that RCTs have been less conclusive and more work is required. Particularly, Middleton and Yaffe advocate the importance of examining multiple risk factors concurrently in future RCTs, in order to determine how we might combine interventions to best reduce dementia risk [79,141].

Hughes and Ganguli [14] also reviewed the evidence for modifiable risk factors for dementia and again highlighted that most of the supporting evidence comes from cross-sectional or observational studies. They proposed that in addition to RCTs, observational studies designed with the life-course perspective in mind are also required, as the majority of studies to date have relatively short follow-up periods [14].

Barnes and Yaffe [5] projected the effect of seven modifiable risk factors (diabetes, elevated blood pressure in midlife, midlife obesity, smoking, depression, cognitive stimulation and physical activity) on the prevalence of Alzheimer's disease. They concluded that up to half of Alzheimer's disease cases worldwide may be attributable to these risk factors, and that if risk factor prevalence were 25% lower, there would be three million fewer cases of Alzheimer's disease throughout the world. This presents a compelling argument for continuing to strengthen the research evidence in this field.

Reviewers in the cardiovascular field are also discussing the contribution of modifiable vascular risk factors to the development of Alzheimer's disease, cognitive impairment and dementia [142-145]. They conclude that cardiovascular conditions are associated with increased risk for Alzheimer's disease and offer opportunities for preventative intervention [143,145]. They recommend that the best time to intervene is in midlife and early old age, and that studies addressing multiple risk factors are required [142,143,145]. They also suggest capitalising on people's concerns about developing dementia to improve adherence to long term lifestyle changes and medications to treat their cardiovascular risk factors [144].

In sum, the evidence base for a number of modifiable dementia risk factors is growing, and more research is required. In particular, studies examining multiple risk factors, and studies considering both midlife and late-life risk factors, are most urgently needed.

10. CURRENT AND FUTURE RESEARCH

10.1 LIFESTYLE STUDIES

The research projects listed below are just some of the studies currently underway, which over the next few years will provide improved knowledge about lifestyle interventions that may influence cognitive health and dementia risk.

10.1.1 Australian studies

The **Study of Mental Activity and Resistance Training (SMART Trial)** aims to determine whether increased mental and physical activity can prevent cognitive impairment or dementia. It is being conducted by ageing and exercise researchers in Sydney. The SMART Trial involves older individuals with borderline cognitive abilities who are therefore at risk of developing dementia. Participants complete supervised cognitive and/or physical training for six months and undergo longitudinal outcome assessments 12 months later. The study will test whether any benefits to mental function are a result of changes in brain structure and function, body metabolism, biochemistry and immune function. For more information, visit the SMART Trial website at http://www.med.unsw.edu.au/PSYCHWeb.nsf/page/brainage_SMART.

The **Australian Imaging Biomarkers and Lifestyle Flagship Study of Ageing (AIBL)** aims to improve our understanding of the causes of Alzheimer's disease, and help develop improved diagnostic methods and preventative strategies. It is a longitudinal study of ageing involving over 1000 volunteers with Alzheimer's disease, mild cognitive impairment, and healthy older people. The study is being conducted by Alzheimer's researchers in Melbourne and Perth. The study involves cognitive testing, blood tests, brain imaging and measures of lifestyle such as diet and levels of physical activity. It will help researchers develop and confirm diagnostic markers of Alzheimer's disease that can be used to diagnose dementia early and monitor disease progression. The researchers will also develop hypotheses about diet and lifestyle factors that might delay the onset of dementia. This will enable studies that may lead to clinically proven preventative strategies for Alzheimer's disease to be designed and conducted. This includes a

current trial to establish whether physical activity can delay progression of cerebrovascular disease in older adults with memory complaints or mild cognitive impairment and at least one cardiovascular risk factor. For further information, visit the AIBL website at <http://www.aibl.csiro.au>.

The **Personality and Total Health (PATH) Through Life** project aims to track and define the lifespan course of depression, anxiety, substance use and cognitive ability, to identify environmental risk and protective factors influencing these characteristics, and to examine the relationships over time between depression, anxiety and substance use with cognitive ability and dementia. PATH is a 20 year longitudinal study involving 7,485 young (aged 20–24 at baseline), middle aged (aged 40–44 at baseline) and older (aged 60–64 at baseline) adults. It is being conducted by ageing researchers at the Australian National University in Canberra. The fourth wave of data collection is currently underway. Findings to date include that cerebrovascular disease is present in midlife and associated with cognitive deficits, suggesting that preventative strategies should, therefore, begin early in life [146]. For further information, visit the Centre for Research on Ageing, Health and Wellbeing website at <http://crahw.anu.edu.au/research/projects/personality-total-health-path-through-life>.

The **Body, Brain, Life (BBL)** project is investigating a novel online intervention to assist middle aged individuals at risk of dementia achieve and sustain changes in several lifestyle areas. It is being conducted by ageing researchers at the Australian National University in Canberra. A risk assessment tool has been developed based on the evidence for the impact of different risk factors for Alzheimer's disease. The efficacy of the BBL program is being evaluated via a randomised controlled trial. If shown to be successful, it has the potential to be implemented as an accessible online intervention in the Australian community, and to contribute to the reduction of the prevalence of dementia risk factors in the wider community. For further information, visit the Centre for Research on Ageing, Health and Wellbeing website at <http://crahw.anu.edu.au/research/projects/body-brain-life>.

The Fitness for the Ageing Brain Study II (FABS II) aims to establish whether physical activity can decrease the rate of cognitive decline among people with mild to moderate Alzheimer's disease. The project is being led by researchers at the National Ageing Research Institute in Melbourne. Previously, the researchers successfully developed an exercise program for people with mild cognitive impairment (FABS). The intervention provided a modest improvement in cognition compared to usual care [53]. The program has also been tested in a pilot study with people with mild to moderate Alzheimer's, which found less cognitive decline in the intervention group. Should this be confirmed in the larger study, a program of physical activity would have the potential benefit of providing an affordable and relatively simple intervention. Delaying deterioration in people with Alzheimer's disease may postpone disability, prolong independent living and potentially reduce the costs associated with care. For further information, visit the National Ageing Research Institute website at <http://www.mednwh.unimelb.edu.au/research/dementia.htm>.

10.1.2 International intervention trials

The Prevention of Dementia by Intensive Vascular Care (preDIVA) trial aims to determine whether treatment of cardiovascular risk factors in elderly people reduces the risk of dementia. It is a large, multi-centre Dutch trial, with 3,700 participants aged between 70 and 78 years of age. The preDIVA intervention includes the treatment of hypertension, high cholesterol and diabetes, as well as focusing on reducing overweight, smoking cessation and stimulating physical exercise. The study duration is six years, and it will test whether the intervention leads to a decrease in dementia. For more information on the preDIVA trial, visit <http://www.controlled-trials.com/ISRCTN29711771/prediva>.

The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) is a multi-domain intervention that aims to prevent cognitive impairment and dementia. It is a large, multi-centre trial, located at six sites across Finland, and involves 1,200 participants from 60 to 77 years of age. Over two years, participants will be given lifestyle interventions including nutritional guidance, exercise, cognitive training, increased social activity, and monitoring and management of metabolic and vascular risk factors such as hypertension, high cholesterol, obesity and impaired glucose tolerance. The participants will be followed up over seven years to determine whether the intervention reduces the risk of cognitive impairment and dementia. For more information on the FINGER trial, visit <http://www.clinicaltrials.gov/ct2/show/NCT01041989?id=NCT01041989&rank=1>.

The Multidomain Alzheimer Preventive Trial (MAPT) aims to evaluate the efficacy of three interventions over a three year period. The French trial includes 1680 participants aged 70 years and over. The first intervention involves supplementation with omega-3 fatty acids; the second involves a multi-domain intervention which focuses on nutrition, physical exercise, cognitive stimulation and social activities. The third intervention is a combination of the first two interventions. The participants will be followed up over five years, and the study aims to measure any changes in cognitive function over this time. For more information on the MAPT trial, visit <http://www.clinicaltrials.gov/ct2/show/NCT00672685?term=MAPT+toulouse&rank=1>.

The Impact of Nutritional Lipids on Neuronal and Cognitive Performance in Aging, Alzheimer's Disease and Vascular Dementia (LipiDiDiet) trial aims to develop a lipid-based diet that can delay or prevent the onset of dementia. Lipids are a group of molecules such as fats, sterols and fat-soluble vitamins, and are often consumed in far less than the recommended amounts in the human diet. The trial is being conducted by researchers at Saarland University in Germany, and involves the dietary management of nutrient deficiencies, as well as providing diet and lifestyle-based health care advice for the elderly. For more information, visit the LipiDiDiet website at <http://www.lipididiet.eu>.

10.2 DRUG TRIALS

Current pharmacological treatment options for Alzheimer's disease (cholinesterase inhibitors donepezil, rivastigmine and galantamine and the NMDA receptor antagonist memantine) provide primarily short-term symptomatic relief, without affecting the progression of the disease. There are no drugs currently approved in Australia specifically for treatment of other forms of dementia. There is an urgent need to develop and validate disease modifying drugs.

There are enormous challenges for this research and despite considerable investment and effort in recent years, no such drugs have as yet been shown to be effective in phase 3 clinical trials. As the pathology associated with Alzheimer's disease begins many years before symptom onset, it may be important to identify Alzheimer's disease much earlier in the disease process, and find drugs that can modify the progression of the disease. There are currently many disease modifying drug trials currently underway throughout the world.

The primary strategies for stopping or delaying the progression of Alzheimer's disease are based on the pathological processes involved in development of the disease. They include the development of drugs to [147-149]:

- reduce beta amyloid production
- prevent beta amyloid aggregation
- promote beta amyloid clearance
- inhibit tau phosphorylation or aggregation

Drugs to reduce beta amyloid production are designed to block the amount of beta amyloid formed in the brain, by inhibiting β -secretase or γ -secretase (the enzymes involved in cleaving beta amyloid from the amyloid precursor protein). Despite promising early results, the few drugs tested to date in this category were not effective in clinical trials, but research is ongoing [147-149].

Recently, problems with beta amyloid clearance rather than an overproduction have been suggested to be more important in the development of Alzheimer's disease.

Immunisation strategies are being developed to prevent beta amyloid aggregation and plaque formation, or to promote beta amyloid clearance from the brain. An early active immunisation trial was stopped due to adverse effects, but new strategies are in development [147-149]. Passive immunotherapies based on antibodies against beta amyloid are currently in phase 3 clinical trials, although, concerningly, one to date has produced negative results for people with mild to moderate Alzheimer's disease [150].

Zinc and copper are involved in beta amyloid aggregation and stabilisation of plaques. PBT2 is a drug developed and being tested in Melbourne that targets copper and zinc to prevent beta amyloid aggregation and dissolve plaques [147,148]. Animal and early human studies suggest PBT2 may improve cognition, but larger clinical trials are required. Other inhibitors of beta amyloid aggregation are also under investigation [149].

Drugs targeting tau are designed to prevent tau from forming neurofibrillary tangles. Lithium has shown some promise as an agent that may reduce tau phosphorylation and cognitive decline but it can have side effects [147]. Other drugs targeting tau are currently in phase 3 clinical trials. Anti-tau therapies could have widespread benefits as tau pathology also occurs in dementias other than Alzheimer's disease [149].

Other approaches include drugs to limit mitochondrial dysfunction (phase 3 trials however have not shown benefit), targeted stem cell strategies that are still at the proof-of-concept stage, and strategies to boost growth of new neurons by introducing nerve growth factor into the brain that are still in development [148,149].

Factors that might explain the failure of drug trials to date include suboptimal study design (inadequate biomarkers and outcome measurements) and importantly, the timing of treatment in relation to the development of disease. Available data from failed phase 3 studies suggest that people with mild to moderate Alzheimer's disease may be too late in the disease process to substantially benefit from disease modifying drug treatment [147,149]. Recent trials are beginning to address this, enrolling participants with prodromal Alzheimer's disease or mild cognitive impairment. Ethical issues will need to be addressed for clinical trials that involve those with preclinical Alzheimer's disease (defined earlier in this document), as this will mean giving unproven drugs to essentially healthy people. Researchers announced at the Alzheimer's Association International Conference 2012 that planning has commenced for three such trials [151].

Even if current phase 3 trials are successful, disease modifying treatments are unlikely to come onto the market before 2020 [148]. And they will not eradicate dementia. The majority of dementia cases arise in people aged 80 and over, who frequently have mixed Alzheimer's, Lewy body and cerebrovascular pathologies. This may limit the effect that therapies targeting individual pathologies have on the majority of cases of dementia [148].

These drug trials are a promising area of research that we hope may result in new treatments and interventions for dementia within the next ten years. However, to date, none of these drugs have been approved for use.

10.3 INCREASED RESEARCH FUNDING IS NEEDED

Whilst scientific research, particularly over the last decade, has shed new hope into the area of dementia prevention, much more is needed. Additional investment in research to consider the prevention, early intervention and treatment of dementia, is pivotal in addressing the looming epidemic. Dementia research in Australia is significantly underfunded compared with other chronic diseases that place equally large (or less) demand on the health system.

In 2009, the National Health and Medical Research Council (NHMRC) spent about \$22 million on dementia research. In comparison, cancer attracted nearly \$160 million, cardiovascular disease around \$110 million and diabetes over \$60 million [152]. A recent analysis of NHMRC funding from 2002 to 2011 showed that dementia research funding was significantly

below that for other chronic diseases each year, and has not shown the same rate of increase in funding over that time as for the other conditions [153]. This has meant that since 2002, the shortfall in funding for dementia compared to diabetes, cancer, cardiovascular disease and mental health, has grown significantly. NHMRC Fellowships for dementia researchers also received far less funding than for other conditions, suggesting a major problem of research capacity that requires strategies to increase the attractiveness of dementia research to young scientists [153].

With dementia being the fourth projected leading specific cause of burden of disease and injury in Australia in 2010 [154], there is an overwhelming need for greater investment in dementia prevention and early intervention research. In 2008, the formal care costs of dementia were estimated to be between \$3.9 billion and \$5.4 billion, with the cost of replacing family carers with paid carers estimated to be \$5.5 billion per year [155]. Research investment should aim to be 1% of the cost of dementia (not including informal care costs), or about \$50 million per annum [155]. This investment is vital to continuing Australia's dementia research effort.

II. CONCLUSIONS AND FUTURE DIRECTIONS

Australia faces a rapid increase in the number of people living with cognitive impairment and dementia and in the social and economic costs of caring for those people. While there is hope for a medical breakthrough and ultimately a cure for dementia, we cannot afford to wait for this. Without a cure, identifying and addressing risk factors in the population remains the most viable strategy for preventing cases of cognitive decline and dementia and reducing the associated financial, societal and individual costs.

The evidence for associations between risk for cognitive decline and dementia and several modifiable medical and lifestyle factors is well established. Proof that modifying these can prevent cognitive decline or dementia for either individuals or groups does not yet exist, but can we afford to wait for this before acting? More research is most certainly needed and is ongoing around the world. Promisingly, many experts suggest we can do much to reduce dementia incidence by implementing preventative health strategies now, based on current evidence.

Preventative health is becoming a focus of Australian health policy. Maintaining cognitive health to date has received little attention with the focus very much on physical health. But people are concerned about losing cognitive function as they age, and public education about potentially modifiable risk factors is seen as important. Dementia related organisations around the world, including Alzheimer's Australia, are promoting risk reduction strategies.

Alzheimer's Australia will continue to develop and evaluate tools and resources which aim to help Australians understand the risk and protective factors for cognitive decline and dementia, and what they can do to reduce their risk. Information is provided via printed and online resources, community presentations and media campaigns. Interactive web-based tools and mobile applications are being evaluated for their effectiveness in improving knowledge about brain health and dementia risk reduction, increasing

motivation to change unhealthy behaviours to address risk factors, and encouraging sustainable adoption of strategies to maintain brain and heart health.

So what is recommended? There is good evidence to support a range of lifestyle and health strategies as a means of reducing your risk of cognitive decline or developing dementia.

- Keeping your brain active matters
 - Keep mentally stimulated
 - Engage in social activities
- Being fit and healthy matters
 - Keep physically active
 - Eat healthily, avoiding too much saturated fat and including plenty of vegetables and fruit
 - Do not be concerned about continuing light to moderate drinking, but there is no need to start if currently a non-drinker
- Looking after your heart matters
 - Regularly check blood pressure, blood glucose and cholesterol throughout mid and late life and keep high blood pressure, diabetes and high cholesterol and other vascular risk factors well controlled
 - Maintain a healthy body weight
 - Don't smoke

As a society we are becoming increasingly aware of the need to maintain a sound diet, exercise, intellectual stimulation and social connectedness. This review of the evidence reinforces that message and adds a further important impact of doing so – maintaining cognitive health and reducing dementia risk. It also highlights that what is good for the heart is good for the brain. We encourage all Australians to look after your brain, body and heart because *Your Brain Matters*.

GLOSSARY

Term	Definition
Adipose tissue	Body fat.
Amyloid plaques	Amyloid plaques between nerve cells in the brain is a hallmark of Alzheimer's disease. They are sticky clumps that are formed from deposits of beta amyloid protein.
Antihypertensives	Drugs to lower blood pressure.
Anti-inflammatory agents	Drugs to reduce inflammation and pain.
Antioxidants	Antioxidants are naturally occurring substances found in food that help to prevent cell damage due to oxidation by free radicals. Free radicals are formed during normal metabolism and are by-products of the complex chemical processes that take place in the cells of our bodies.
Apolipoprotein E	A protein that binds to fat, and transports it around.
Beta amyloid	A protein fragment formed in the breaking down of the amyloid precursor protein. In Alzheimer's disease, these fragments stick together to form amyloid plaques.
Biomarkers	Biological indicators of a disease.
Brain reserve	Brain reserve refers to a reserve of healthy brain cells and connections between cells and efficient cognitive skills that are built up over your lifetime. This reserve can help the brain keep functioning well and delay the onset of dementia.
Brain training	Brain training games or programs are structured programs, usually computerised, designed to train particular cognitive functions by repeated practice. There is no evidence yet that brain training can reduce dementia risk.
Cerebrospinal fluid	A liquid that surrounds the brain and spinal cord, protecting them from injury.
Cerebrovascular disease	Disease of the blood vessels that damages the blood vessels in the brain.
Cholinesterase inhibitors	Drugs to inhibit a brain enzyme and increase levels of a chemical (acetylcholine) that is deficient in some dementias.
Cognitive decline	Cognitive decline is a gradual decrease in cognitive abilities over time. This is what happens in dementia.
Cognitive function	The cognitive functions of the brain are the higher level thinking functions, including memory, learning, attention, language, decision making, reasoning, judgement, comprehension, spatial skills and planning.
Crystallised intelligence	The ability to use knowledge, experience and skills.
Dementia with Lewy bodies	Dementia with Lewy bodies is a form of dementia characterised by the presence of Lewy bodies in the cortex of the brain. Lewy bodies damage nerve cells resulting in cognitive problems.
Enzyme	Enzymes are proteins that increase the rates of chemical reactions in cells. They help convert molecules into different molecules.

Term	Definition
Folate	Folate, or folic acid, is vitamin B9 and is essential for brain and blood cell formation and health. It is found in leafy vegetables such as spinach and lettuces, dried or fresh beans and peas, sunflower seeds, fruits such as oranges, cantaloupe, honeydew melon, banana, raspberry, grapefruit and strawberry, and vegetables such as asparagus, beets, broccoli, corn, brussels sprouts and bok choy.
Frontotemporal dementia	Frontotemporal dementia is a form of dementia that involves damage to the frontal and/or temporal lobes of the brain. Behaviour, language and other cognitive skills are affected.
Hippocampal atrophy	A shrinking of the hippocampus, a brain region involved in memory and learning.
Homocysteine	Homocysteine is an amino acid in the blood. Amino acids are the basic structural units of proteins. At high levels, homocysteine can damage blood vessel walls and the blood clotting mechanism.
Hormone Replacement Therapy	Use of female hormones in people deficient in these; usually a treatment for symptoms of menopause.
Intervention study	A study where an action is taken to try to change outcomes for a group of people, e.g. an exercise intervention to improve cognitive function in people with Alzheimer's disease.
Late-life or old age	Late life, or old age, is a normal developmental life stage and usually refers to those aged 65 and older.
Mediterranean diet	A diet which places particular emphasis on fruits, vegetables, fish and healthy fats.
Meta-analysis	A meta-analysis takes the data from all similar studies and combines them, providing an overall result from all the relevant research. This is a higher level of evidence that is more convincing than a finding from any single study.
Midlife	Midlife, or middle age, is a normal developmental life stage and usually refers to those aged between 40 and 65.
Mind your Mind	The Mind your Mind program was the predecessor to the Your Brain Matters program, developed by Alzheimer's Australia.
Monounsaturated fats	Monounsaturated fats, also known as monounsaturated fatty acids, can assist with lowering blood cholesterol. Monounsaturated fats can be found in olive oil, canola oil, macadamia oil, avocado, nuts, and margarines that are labelled "monounsaturated".
Nerve growth factor	A hormone that stimulates growth of some nerve cells.
Neurocognitive disorder	The fifth version of the Diagnostic and Statistical Manual of Mental Disorders, scheduled for release in 2013, will replace the term dementia with major neurocognitive disorder, to reflect the severity of cognitive impairment at this stage of disease. Similarly, the term mild cognitive impairment will be replaced with minor neurocognitive disorder.
Neuroimaging	Includes the use of various techniques to provide images of the structure or function of the brain.
Neurofibrillary tangles	Neurofibrillary tangles are twisted fibres inside brain cells made up of tau protein. They occur in some forms of dementia and cause a breakdown in the brain cell's ability to communicate with other brain cells.

Term	Definition
Observational study	Observational studies collect real-life information about exposure to a risk or protective factor and subsequent development of disease. For example, an observational study might measure how much exercise people do, then follow them up a number of years later to see who has developed dementia, and how that is related to their earlier exercise habits.
Omega-3 fatty acids	Omega-3 fatty acids are a group of unsaturated fats that have a role in regulating blood pressure and blood clotting, in helping to maintain a healthy immune system, and assisting brain and spinal cord function. Omega-3 fatty acids can be found in cold water fish (salmon, tuna and sardines), flax (linseeds and cold pressed linseed oil), soya beans, walnuts, and dark green leaves (spinach and silverbeet).
Polyunsaturated fats	Polyunsaturated fats are an essential part of the diet. Two important types are omega-6 fatty acids and omega-3 fatty acids. Omega-6 fats are found in vegetable oils such as canola and sunflower and are essential for growth, cell structure and maintaining a healthy immune system.
Prodromal Alzheimer's disease	The presence of early symptoms indicating the onset of Alzheimer's disease. Also called mild cognitive impairment.
Prospective study	A study which follows a group of people forward in time.
Randomised controlled trial	Randomised controlled trials (RCTs) are considered the gold standard in determining whether disease risk can be reduced by intervening to alter a risk factor. They involve randomising individuals to a treatment (e.g. drug or behavioural intervention) or a no-treatment (placebo) condition.
Saturated fats	Saturated fats are those that tend to be solid at room temperature and can be found in whole milk, cream, butter, cheese, meats, coconut oil, palm oil, chicken skin, biscuits and pastries. Many 'fast food' products, processed meats and deep fried food also contain saturated fats. Saturated fats contribute to the risk of heart and brain disease by raising blood cholesterol levels.
Secretase enzymes	Proteins that break down larger proteins
Statins	Statins are a class of drugs that lower blood cholesterol levels and may be prescribed to people with high cholesterol or with heart disease.
Stroke	A stroke is rapid loss of brain function(s) due to disturbance in the blood supply to the brain, caused by a blocked or burst blood vessel.
Vascular	Vascular means 'related to blood vessels'. Vascular risk factors are those that can affect the health and function of our blood vessels, including high blood pressure and high cholesterol.
Vascular dementia	Vascular dementia is a form of dementia associated with problems of circulation of blood to the brain. It can sometimes result from a stroke or many mini-strokes.
Vitamin B12	Vitamin B12, or cobalamin, has a key role in the normal functioning of the brain and nervous system, and the formation of blood. It is involved in DNA synthesis and regulation. It is found in fish, meat, poultry, eggs and dairy products.

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These documents and others available at fightdementia.org.au

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- For comprehensive information about
- Dementia and care
 - Education and training
 - Other services offered by member organisations

visit the [Alzheimer's Australia website](https://www.fightdementia.org.au)
FIGHTDEMENTIA.ORG.AU

For information and advice contact the
NATIONAL DEMENTIA HELPLINE 1800 100 500
This is an initiative of the Australian Government

For information about brain health and dementia risk reduction visit the
[Your Brain Matters website](https://www.yourbrainmatters.org.au)
YOURBRAINMATTERS.ORG.AU

For information about Australian dementia research activities visit the
[Dementia Collaborative Research Centres website](https://www.dementiaresearch.org.au)
DEMENTIARESEARCH.ORG.AU