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Dementia Risk Reduction: The Evidence

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The Dementia Collaborative Research Centres are an Australian Government funded initiative established to advance Australian research into dementia and the translation of research into clinical practice. The three Centres each focus on a different area of dementia research:

- Assessment and better care outcomes
- Prevention, early intervention and risk reduction
- Consumers, carers and social research

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FOREWORD

The objective of this paper is to provide an updated overview of significant studies on protective and risk factors for dementia in general and Alzheimer's disease in particular. This builds on the research carried out by the authors and published in *Dementia: Can it be prevented?* Alzheimer's Australia's Position Paper 6, August 2005.

This document does not set out to be a comprehensive review of all the available evidence or studies, but does quote major papers where relevant. Nor is there complete agreement between medical experts.

Nonetheless, there is an increasing body of evidence to support a range of lifestyle strategies as a means of reducing the risk of developing dementia. Much of this evidence is derived from population studies that may not necessarily hold true for an individual. There is no guarantee that acting on the best evidence available will help everybody.

We need to establish better evidence on risk factors and on what may prevent or delay the onset of dementia and reduce the number of people affected by dementia, the duration of the illness and the human and economic cost of care. Alzheimer's Australia has partnered with the Dementia Collaborative Research Centres to maximise research effort.

Dementia research is not only a matter for Government. It needs the support of the wider community and the corporate sector. Investment in research needs to be lifted to a level where we have greater confidence that therapeutic interventions can be in place before the first baby boomers reach 75 years of age. The window of opportunity before 2020 is small, so it is important to invest in dementia research now.

On behalf of Alzheimer's Australia I would like to thank Associate Professor Michael Woodward and his colleagues for the very significant commitment they made in preparing this paper.



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INTRODUCTION

It would be a major benefit to society if we could reduce the risk of dementia. It is estimated that Australia in 2007 has over 220,000 people with dementia and it is predicted that by 2050 there will be over 730,000¹. Even delaying the onset by 5 years is predicted, in time, to halve the number of people with dementia. But can we truly prevent or delay dementia, and what can we do to reduce the risk of developing dementia?

This paper, developed by a team of Australian geriatricians and psychogeriatricians, examines the international and local evidence for the prevention and risk reduction of dementia. It identifies factors that we may be able to control in our lives to reduce cognitive decline and delay or prevent the onset of dementia, and it provides a glimpse of possible future breakthroughs.

Can dementia be prevented?

A question of major concern to governments, the baby boomer generation and people with dementia, is whether dementia can be prevented.

At this time, it is not possible to either prevent or cure dementia, although there is extensive research in both areas. It is appropriate, however, to consider ways of reducing the risk of developing dementia with the hope that such approaches may either delay or prevent onset.

Numerous risk and protective factors have been identified and the evidence is presented in this paper. Not all these factors can be modified. The current list of risk and protective factors may be inaccurate and is certainly likely to change as more studies are performed. Also, there is no guarantee that what shows benefit for a population will be beneficial for every individual. In addition, it is important to note that lifestyle changes to reduce the risk of dementia or treatments to delay onset, will not necessarily be the same strategies required to prevent dementia. Conversely, a medication may be ineffective in treating established Alzheimer's disease, but useful in its prevention.

Will risk reduction be specific to one type of dementia?

There are over 100 recognised causes of dementia, of which Alzheimer's disease accounts for about 60%, vascular dementia 20% and dementia with Lewy bodies 10-15%. In younger people (below age 60), frontotemporal dementia may be almost as common as Alzheimer's disease.

Researchers are increasingly recognising the overlap between the various types of dementia and these conditions are called mixed dementias. The more common mixed dementias involve Alzheimer's disease and vascular dementia, and Alzheimer's disease and dementia with Lewy bodies. Indeed, people who have dementia from multiple pathological causes may reflect the fact that these conditions are not entirely unrelated. Thus, in people with Alzheimer's disease we often see evidence of strokes, and in Lewy body dementia amyloid (the brain deposit seen in Alzheimer's disease) is often found, even when a diagnosis of mixed dementia is not clinically appropriate.

Therefore, risk factors for one form of dementia may also be risk factors for other dementias, and prevention may target more than one type of dementia. For instance, mid life high blood pressure is a risk factor for Alzheimer's disease and also for vascular dementia, so treatment of this condition with anti-hypertensives may help to prevent Alzheimer's disease, vascular dementia and mixed Alzheimer's/vascular dementia.

PROTECTIVE AND RISK FACTORS FOR DEMENTIA

Protective factors for Alzheimer's disease

A comprehensive review of international research literature has identified that there are currently several factors that *may* protect a person from developing Alzheimer's disease or delay its onset (Table 1). Whilst there is not universal agreement, the evidence suggests that there are at least eight possible protective factors and a further two factors are cited, although their protective benefits for Alzheimer's disease appear unlikely. Control of risk factors may also be considered protective.

Table 1 Protective factors for Alzheimer's disease

Possible	Unlikely
<ul style="list-style-type: none"> • Physical activity • Ongoing intellectual stimulation • Leisure/social activities • Higher education • Anti-inflammatory drugs ^a • Cholesterol lowering drugs (statins) ^a • Anti-hypertensive (blood pressure lowering) drugs for those with high blood pressure • Moderate alcohol intake ^b 	<ul style="list-style-type: none"> • Drugs used to treat established Alzheimer's • Omega-3 fatty acids

- a. Findings are from epidemiological studies and no prospective randomised trial has yet demonstrated benefit. These drugs can have serious side effects and it is important to take these drugs only with doctor's orders.
- b. This may depend on gene status as some studies have found that moderate alcohol is not protective for those with the apolipoprotein E – epsilon 4 allele.

With all these factors it is important to acknowledge that this paper is concerned with protective factors for Alzheimer's disease and we are not considering the impact of these factors on other diseases or conditions.

Risk factors for Alzheimer's disease

There are four **well established** risk factors for Alzheimer's disease (Table 2):

- old age: the risk of developing dementia increases with age. For people aged 70 to 74 years there is a 1 in 30 chance, compared to a 1 in 3 chance for people aged 90 to 94 years.
- genetic mutations: a very uncommon risk factor for Alzheimer's disease
- genetic factors: nearly all people with Down syndrome develop Alzheimer's disease; a genetic variant, the apolipoprotein E – epsilon 4 allele, is associated with a higher risk of developing Alzheimer's disease
- family history: a person with a parent(s) who has Alzheimer's disease has an increased risk compared with the general population

Other likely factors include:

- head injury (especially more severe)
- small head size
- vascular risk factors, including smoking, hypertension, diabetes and atrial fibrillation
- fatty diet
- hypothyroidism
- low birth weight for gestational age
- low education

There is continuing research into the following factors which may contribute to the risk of developing Alzheimer's disease but these are not yet scientifically established.

These **less likely** factors include:

- depression
- low B₁₂ or folate
- elevated homocysteine (which is a by-product of a wide variety of chemical reactions in the body). It is not known whether the higher level of homocysteine is a direct cause of dementia or simply a factor.
- hormone replacement therapy
- sleep disorders
- female gender
- exposure to very strong electromagnetic fields
- exposure to aluminium (found in the foods we eat, drinking water, many cosmetics, in drugs and in the air)

Table 2 Risk factors for Alzheimer's disease

Well established	Likely	Less likely
Old age Genetic mutations (rare) Other genetic factors: – Down syndrome – Apolipoprotein E status Family history of Alzheimer's disease	Head injury (especially more severe) Head size (smaller) Vascular risk factors including smoking and hypertension Fatty diet	Depression Elevated homocysteine / low B ₁₂ and folate Hormone Replacement Therapy/Oestrogen Sleep disorders Female gender Exposure to very strong electromagnetic radiation Aluminium

Risk factors for vascular dementia

The main identified risk factors for vascular dementia are shown in Table 3. Several of these factors can be seen to relate to midlife lifestyle factors and therefore are amenable to earlier modification.

Vascular dementia protective factors have not been specifically identified, although factors which protect against vascular disease itself are likely to be protective for vascular dementia.

Table 3 Risk factors for vascular dementia

• Old age	• Elevated cholesterol
• Male gender	• Smoking
• Hypertension	• Obesity
• Stroke	• Elevated homocysteine
• Family history of vascular disease	• Cardiac disease and major cardiac surgery
• Diabetes, type 2	• Atrial fibrillation

Risk factors for other forms of dementia

There are no amenable risk or protective factors yet identified for the other two most common forms of dementia – dementia with Lewy bodies and frontotemporal dementia.

DEMENTIA RISK REDUCTION: WHAT WE CAN CONTROL

What can we do to reduce our risk of developing Alzheimer's disease and vascular factors? This section identifies what we can control and what we cannot control.

- We can control what we eat and drink
- We can control what we do
- We can use medications where appropriate
- We can control some vascular factors
- We can consider some **other** related factors

1. What we eat

Fat intake

A high intake of saturated fat is a risk factor for Alzheimer's disease. However, moderate to high intakes of monounsaturated and polyunsaturated fats have been associated with reduced risk for dementia.

In one study, moderate intake of unsaturated fats at midlife reduced the risk of dementia in late life by around 50%, whereas moderate saturated fat intake approximately doubled the risk². However, more scientifically designed intervention studies are needed before recommending modifying fat intake specifically for this purpose.

Finding

Although more studies are needed, reducing excess saturated fat and including moderate amounts of unsaturated fats probably has other health benefits so there is no need to delay this dietary change.

Increasing omega-3 fatty acids (found in fish and some other foods) to reduce dementia risk has received support following some studies suggesting this was protective³. Recent reviews have concluded that the evidence for this is "limited"⁴. There are two randomised trials of omega-3 supplements to prevent dementia proceeding but the findings will not be available until 2008.

Finding

There is currently insufficient evidence to support a high omega-3 diet or use of omega-3 supplements.

Vitamins and antioxidants

Alzheimer's disease is characterised by damage to nerve cells around the amyloid deposits that may be caused, at least in part, through the production of "free radicals" that oxidise tissues. Vitamins that have anti-oxidant effects include vitamins C and E. Studies vary in their findings of potential protective effects.

The Rotterdam study of 5395 people initially free of Alzheimer's disease had subjects with differing levels of vitamin C and E intake (from either foods or supplements) and followed them over a six year period. Those with highest intake of vitamin E had a 45% lower risk of developing Alzheimer's disease compared to those with the lowest intake, and higher intakes of vitamin C also reduced risk⁵. However, in a randomised intervention study, the Heart Protection Study, supplementation with vitamins A, C and E did not protect against cognitive decline⁶. Also, in a trial of treatment of Mild Cognitive Impairment, vitamin E had no effect in reducing the progression of cognitive decline or conversion to Alzheimer's disease⁷.

A large randomised prevention study using vitamin E is currently in progress in the US.

Finding

Current evidence seems more supportive of dietary vitamin E as a possible protective factor, so a diet with adequate food sources of vitamin E is recommended. This includes cruciferous vegetables such as broccoli and cauliflower. If sufficient dietary vitamin E cannot be assured, a moderate dose supplement (not more than 400 mg a day) could be considered. Recently, daily doses of 400mg of vitamin E or above has been associated with increased mortality⁸ and increased heart failure in patients with vascular disease or diabetes⁹, so these higher doses should be avoided. Vitamin E can interact with other medications and conditions (e.g. increased risk of bleeding if on warfarin) so people should always first discuss supplement commencement with their doctor.

There is insufficient evidence at this stage to recommend vitamin C supplements to prevent dementia.

Homocysteine, B₁₂ and folate

Folate and vitamin B₁₂ are necessary for cell function, and deficiencies have been associated with neurological conditions including cognitive impairment and dementia.

In a Swedish study of 370 subjects who did not have dementia initially, when followed for 3 years, Alzheimer's disease developed twice as frequently in those who had initially low B₁₂ and folate levels¹⁰. B₁₂ and folate deficiencies are also associated with elevated homocysteine levels, although such elevation alone (irrespective of B₁₂ and folate levels) is independently associated with the development of dementia. In the Framingham study (of people living in a town near Boston), in 1,092 subjects initially free of dementia, over an average follow-up of 8 years, higher homocysteine levels were associated with double the risk of developing Alzheimer's disease¹¹.

A recent study from the US, where flour products have been fortified with folic acid since 1998, reported that in people over 60 years of age high folate levels protected against cognitive decline, but only in those with normal vitamin B₁₂ levels¹². Those with low vitamin B₁₂ and high folate were 5 times more likely to show cognitive impairment and also anaemia. So folate supplementation should not be started before checking for vitamin B₁₂ deficiency.

Finding

It is as yet unknown whether B₁₂ or folate supplementation reduces the risk of developing dementia. Also, the dose and route (oral or injection) is not defined. Until further evidence arises it seems prudent to check for and treat any deficiencies of these vitamins although routine checking of homocysteine has not yet been evaluated. Low dose oral B₁₂ and folate supplements are one of the safest of the agents that may help reduce the risk of dementia, especially in those at risk of being deficient and should also be considered by those found to have elevated homocysteine levels. People should always first discuss supplement commencement with their doctor.

Alcohol

Several studies have shown that light to moderate alcohol consumption is associated with a lower risk of dementia as a whole, and of Alzheimer's disease and cognitive impairment.

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-drinkers¹³. In a Perth study of 616 men over age 80, consumption of up to 2-4 standard drinks a day was associated with a 50% reduction in the risk of poorer cognition (Mini Mental State Examination score below 24/30)¹⁴. The benefits of alcohol may be produced through its favourable effects on the cardiovascular system, although there may be other mechanisms.

However, excessive alcohol consumption may increase the risk of dementia. 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 years¹⁵.

Finding

There is insufficient evidence to promote alcohol consumption to non-drinkers as a means of reducing dementia risk, especially as such a direction may be associated with a risk of progressing to alcohol excess, which is a health hazard. However, there may be benefits for those currently using alcohol moderately.

Caffeine

One small study in 54 Portuguese people with Alzheimer's disease showed a lower caffeine intake over the last 20 years than in controls (74mg per day compared to 200mg per day)¹⁶. 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. However, no association was found between caffeine consumption and cognitive decline in men, or between caffeine intake and risk of dementia for either gender¹⁷.

Finding

At this stage increasing caffeine intake, which may cause other health problems, cannot be recommended.

2. What we do

Physical and leisure/social activities

While we do not yet have definitive evidence from randomized trials, several observational studies have found that physical activity in mid and late life is associated with a lower risk of cognitive decline and dementia.

In a study of 1,449 people followed up for an average of 21 years, leisure time physical activity at least twice a week at midlife was associated with a 52% reduced risk of all dementia and a 62% reduced risk of Alzheimer's disease¹⁸. Physical exercise at least 3 times per week in people over age 65 was associated with a 38% reduced risk of dementia after 6 years follow up¹⁹.

In another study, participation in high numbers of different activities including walking but also intellectual, leisure and social activities (Table 4) was associated with a 38% lower risk of developing dementia over an average of 3 years in 1,772 people over age 65 initially free of dementia²⁰.

Table 4 Activities found to be protective when included in high levels of leisure activity

• Walking for pleasure or excursion	• Being visited by friends or relatives
• Physical conditioning	• Going to classes
• Going to cinema, restaurants and sporting venues	• Reading magazines, newspapers and books
• Community/volunteer work	• Watching TV or listening to radio
• Going to a club or centres	• Playing cards or bingo
• Going to church/synagogue/temple	• Knitting, music or other hobbies
• Visiting friends and relatives	

Physical activity may improve blood flow to the brain, reduce cardiovascular risk factors and possibly stimulate nerve cell growth and survival. It has numerous health benefits.

Finding

Leisure and social activities may also stimulate nerve growth and survival but this has yet to be proven. Physical, leisure and social activities are recommended prevention activities.

Education and intellectual stimulation

Numerous studies have shown that more years of schooling and further education are associated with a lower risk of developing dementia. There is, however, little evidence for the benefits of formal late-life education.

Encouragingly, cognitively stimulating activities such as listening to radio, reading, doing crosswords and visiting museums were found in a 4½ year prospective study of Catholic clergy to protect against cognitive decline and Alzheimer's disease²¹. The authors developed a composite score of such activities (0-5) and a one-point increase was associated with a 47% lower risk of cognitive decline and a 33% reduced risk of Alzheimer's disease. Perhaps such activities stimulate the production of more brain cell connections giving individuals a greater protective "reserve" against dementia. A recent meta-analysis concluded that higher brain reserve as a result of complex education, occupation and mental activities is associated with a 46% reduced risk of dementia²².

Finding

At this stage, increasing or maintaining social and intellectual activities is recommended as a strategy that may help to prevent dementia.

A study in Stockholm investigated mental, physical and social components of the leisure activities of people aged 75 years and older and found that all 3 components were associated with a reduced risk of dementia after 6 years follow up²³. Combining components offered the greatest benefit, with those whose activities included higher levels of 2 or all 3 components having a 47% reduced risk of dementia.

Occupation

Despite numerous studies seeking a link between previous occupation and dementia, the only potential risk factor that has shown up in several studies is exposure to **strong** electromagnetic radiation^{24,25}. Such radiation can come from exposure to electrical tools, especially if working close to them (e.g. sewing machines, carpentry, electric typewriters, or welding devices).

No study has shown a link between mobile phone or computer usage and dementia.

Finding

It is recommended to use shielded electric motors where possible.

3. Medications

Cholesterol lowering drugs ('statins')

Cholesterol is essential to brain function and the formation of synapses (connections between brain cells). However, there is evidence to suggest that excess cholesterol can contribute to the typical changes of Alzheimer's disease (amyloid deposits) and that cholesterol lowering drugs might reduce this. In humans, some studies have shown a lower risk of dementia in users of statins (cholesterol lowering drugs), irrespective of the baseline cholesterol level.

In a study of 10,000 patients of general practitioners in the United Kingdom, statin use was associated with a 71% reduced risk of all dementia²⁶. As with all the protective factors, we need prospective randomised trials to prove the value of cholesterol lowering. In two recent large trials, the Heart Protection Study²⁷ and the PROSPER²⁸ study, treatment with a statin did NOT reduce the risk of cognitive impairment or dementia. However, relatively crude measurements of cognitive impairment were used.

Finding

More studies are required before statins, which are costly and have a range of side effects, are recommended for dementia prevention.

Anti-inflammatory drugs

It has been recognised that there is inflammation in the brain of those with Alzheimer's disease and it has been shown in some observational studies that people treated for arthritis long term with anti-inflammatory agents (e.g. drugs such as Brufen, Indocid, Naprosyn and Voltaren) were less likely to have Alzheimer's disease.

In the Rotterdam study of 8,000 people initially free of dementia, followed up for an average of 7 years, longer term use of such agents reduced the risk of Alzheimer's disease (but not vascular dementia) by 80%²⁹. In a recent analysis of 9 studies, with over 13,000 people, the risk of Alzheimer's disease amongst users of anti-inflammatories was 28% less than in non-users, and 73% less in those who had used such agents for over 24 months³⁰.

Longer term prospective prevention trials are needed. Unfortunately, such a trial - the Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT)³¹ - was terminated late in 2004 because it was found that the high dose of the anti-inflammatory agent used, celecoxib, may have been harmful in a separate trial using celecoxib for prevention of colon growths. This highlights the need to balance potential risks against benefits for any therapeutic intervention aimed at preventing dementia.

Finding

At this time, anti-inflammatory medications cannot be recommended to reduce the risk of Alzheimer's disease.

Oestrogen/hormone replacement therapy (HRT)

Many studies have shown that the use of HRT (current or previous) is associated with a lower risk of dementia.

The brain has oestrogen receptors, and oestrogen affects brain blood flow and levels of neurotransmitters (chemicals by which nerve cells communicate with each other). Certainly it is known that there is a rise in the incidence of Alzheimer's disease in women after the menopause, but this may be an ageing effect. Oestrogen may improve memory in women without cognitive problems but not all studies have confirmed this³².

In a study of 1,124 elderly women initially free of Alzheimer's disease and followed for 5 years, oestrogen (a component of HRT) use was associated with a 60% reduction in the development of Alzheimer's disease³³. Other observational studies (cohort studies), however, have failed to demonstrate this protective effect.

When this was put to the test in the Womens' Health Initiative Memory Study, a prospective interventional study, the apparently protective effect was seen to be probably a harmful effect³⁴. Some 2,229 cognitively intact women aged 65 and over took HRT, and the control group of 2,303 women were given a placebo. After an average 4 years of follow-up, 40 HRT-treated and 21 placebo-treated women developed dementia, mostly Alzheimer's.

This double chance of dementia development was mirrored in a greater risk of substantial cognitive decline on the Mini Mental State Examination in the HRT-treated group. HRT was also found to increase the risk of breast cancer, cardiovascular events and stroke³⁵, but HRT did reduce the risk of osteoporosis and fractures.

It should be emphasised that short term use of HRT for menopausal symptoms has not been shown to be unsafe. A recent review of studies of HRT and dementia risk concluded that early initiation of HRT at menopause may provide cognitive benefits, while HRT initiated in late life, as in the Womens' Health Initiative Memory Study, may have detrimental effects³⁶.

The movement in and out of favour of hormone replacement therapy exemplifies the dangers of assuming that an apparently protective factor identified in population studies is beneficial for everyone, and shows the importance of conducting prospective trials wherever feasible.

In males with reduced testosterone levels after therapy for prostate cancer, small studies have shown that short term oestrogen use has no beneficial effect on cognition³⁷.

Finding

HRT cannot be recommended for the prevention of dementia.

Alzheimer's disease treatment

Have any of the current drugs used to treat established Alzheimer's disease been shown to prevent dementia? These drugs are memantine (Ebixa) and the cholinesterase inhibitors donepezil (Aricept), galantamine (Reminyl) and rivastigmine (Exelon). There have been claims made in some presentations, but no conclusive evidence of a preventative effect has yet been published.

Perhaps the most interesting studies to date examined the use of donepezil in those with a condition called Mild Cognitive Impairment (MCI). This condition, characterised by subjective and objective memory loss but retention of functional abilities and an absence of dementia, is associated with an increased risk of progression to dementia compared to the general population. In a 24 week trial of donepezil for MCI there was no positive benefit³⁸. In a recently completed 3 year trial of donepezil, vitamin E or placebo in 790 people with MCI, progression to Alzheimer's disease was not different in the three arms at the 3 year trial endpoint³⁹. However, there were fewer people progressing to Alzheimer's disease in the donepezil arm at 6 and 12 months (16 cases at 12 months compared to 38 of those on placebo) with a subsequent greater rate in the donepezil arm. There is insufficient evidence at this time to justify routinely recommending donepezil to those with MCI although the option should be discussed in view of these recent results. Similarly negative results have been reported for galantamine and rivastigmine.

Finding

While cholinesterase inhibitors and memantine are approved for treating established Alzheimer's disease, they are not recommended for the prevention of Alzheimer's, even in those with memory complaints but no dementia. Donepezil may, however, delay progression to dementia in those with MCI for up to 18 months, with a subsequent 'catch up' rate of progression over the ensuing 18 months.

4. Vascular risk factors

Some vascular risk factors are modifiable through medication and lifestyle changes. However, some vascular conditions, such as diabetes, are largely genetic, with limited potential for modification. Most vascular risk factors are risk factors for both Alzheimer's disease and vascular dementia.

High blood pressure

Mid-life hypertension is a risk factor for dementia⁴⁰. Treatment of hypertension in old age has been identified in several studies to reduce the risk of cognitive decline and dementia. In a 4 year European study of 2,400 patients, treatment reduced the risk of dementia by 55%, from 7.4 to 3.3 cases per 1,000 patient treatment years. This effect was seen even after all patients were offered treatment after the first 2 years⁴¹. This means that treatment of 1,000 patients for 5 years could prevent 20 cases of dementia.

Another study that followed hypertensive men from midlife found that for each additional year of treatment there was a further reduction in the risk of dementia⁴². Those treated for more than 12 years had a 60% reduced risk of all dementia and 65% reduced risk of Alzheimer's disease compared to those never treated, and their risk was similar to those with normal blood pressure.

In the PROGRESS collaboration, the use of a blood pressure lowering agent in patients with previous strokes or 'mini strokes' (TIAs), irrespective of blood pressure, was associated with a reduced risk of cognitive impairment or dementia in those who sustained new strokes⁴³. This suggests that reducing the burden of brain damage from strokes may result in a lower future risk of dementia.

Finding

Regular blood pressure checks and assiduous control of elevated blood pressure are recommended throughout mid and later life.

Diabetes

Type 2 diabetes (the type which usually has a later onset and is initially not usually treated with insulin) is a risk factor for Alzheimer's disease⁴⁴.

Whilst there are genetic determinants, there are also environmental influences on the development of type 2 diabetes. Potentially, reduction of obesity, attention to diet and exercise reduce the risk of diabetes. Type 2 diabetes may be operating as a risk factor by specific mechanisms and not just as a vascular risk factor.

Hypoglycaemic episodes associated with poor diabetes control, usually in type 1 diabetes, can cause brain damage which can also be associated with cognitive impairment.

Finding

Prevention and good control of diabetes are important health practices although these have not yet been shown to prevent dementia.

Other vascular risk factors

Previous stroke, cardiac rhythm abnormalities and a history of (other) heart disease have also been shown to be risk factors for dementia. However, it has not yet been shown that modification of these factors prevents dementia.

It nevertheless makes good sense to attend to these factors, as other health benefits, particularly prevention of cardiac disease and stroke, are clear. Similarly, antiplatelet agents such as aspirin may help to prevent dementia but this has not yet been proven. Smoking initially appeared to be a protective factor against Alzheimer's disease in cross-sectional studies, but more accurate longitudinal cohort studies show it is a risk factor for dementia and cognitive decline, as concluded in a recent review of 19 studies⁴⁵.

Cardiac bypass surgery has also been associated with cognitive decline as much as 5 years after the operation⁴⁶, and this risk may be similar for less invasive cardiac surgery⁴⁷. Optimal medical treatment around the time of surgery may reduce this risk. However, the benefits of such surgery may well outweigh the risk of subsequent cognitive problems.

Finding

It clearly is important to stop smoking for a range of health reasons, including that smoking may increase the risk of dementia. Control of cardiovascular risk factors is important to health and is recommended, even though such control has not yet been proven to prevent dementia. Optimal treatment around the time of major cardiac surgery is also important but has not yet been shown to be a preventative factor.

5. Other factors

Head injury

Head injury, particularly more severe injury (such as that causing unconsciousness) has been shown to be a risk factor for the subsequent development of Alzheimer's disease in several studies.

In a USA veteran study, moderate to severe head injury during World War II increased the subsequent risk of developing Alzheimer's disease and dementia in general⁴⁸. For severe head injury, the risk was 4.5 times greater than in those without a head injury. In another study of 2,233 patients with Alzheimer's disease matched with 14,668 family member controls, head injury with loss of consciousness increased the risk of Alzheimer's 10-fold⁴⁹. However, not all studies have shown this increased risk. The Rotterdam study reported no association between head trauma causing loss of consciousness and dementia⁵⁰. Boxing has also been associated with head injury and a form of dementia, but not with Alzheimer's disease.

There are several mechanisms by which head injury may contribute to the development of dementia. For instance, after head injury one of the secretase enzymes is more active, and this may result in amyloid deposits. Obviously it is prudent to avoid head injury as much as possible. This includes use of protective head gear during appropriate sports and activities such as bike-riding and always using seat belts in cars. These actions have other health benefits that justify their use, irrespective of dementia prevention.

Finding

Head injury prevention is recommended.

Sleep disturbances and sleepiness

Daytime sleepiness and sleep disorders have been associated with cognitive impairment.

In the Honolulu-Asia Aging study, in 2,346 men initially free of dementia and followed for 3 years, dementia developed twice as frequently in those initially reporting daytime drowsiness⁵¹. Conditions such as sleep apnoea have been associated with cardiac and other vascular disease, and this may mediate some of the association with dementia.

Finding

Intervention studies are lacking but it seems prudent for people who are sleeping poorly, snoring heavily or excessively sleepy by day, to seek medical attention. Sleeping tablets are not recommended as they have been associated with cognitive impairment. There are other safer ways to improve sleep and some sleep disturbances require specific therapies.

Depression

Depression has been associated with an increased risk of Alzheimer's disease and dementia in several studies.

In a study of 1,953 people with Alzheimer's disease, depressive symptoms before dementia onset were twice as common as in controls⁵². 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 all epidemiological studies also reported an association between depression and Alzheimer's disease even when those episodes of depression had been more than 10 years before the onset of Alzheimer's disease⁵³. Depression has been associated with vascular changes in the brain, and this may mediate the association.

Finding

No study has yet shown that treatment of depression reduces the subsequent risk of dementia but it is clearly important to identify and treat depression.

Aluminium

Excessive aluminium exposure causes cognitive impairment, and some 15 years ago aluminium was number one on the list of potential causes of Alzheimer's disease.

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 subsequently suffered cognitive deficits, but not (yet) an increased rate of development of dementia⁵⁴. Aluminium is the third most common element on earth and we are exposed to it from many environmental sources including in water, from cooking utensils, in polluted air, in deodorants and through medical agents such as some antacids. In reviewing the evidence in 1993, Sir Richard Doll (who first uncovered the link between smoking and lung cancer) stated that the jury was still out on the association between aluminium and dementia⁵⁵.

Finding

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.

Other

Reports of a range of other potentially modifiable risk/protective factors have been inconsistent or insufficiently examined. Some have a plausible role in dementia prevention, including curcumin (turmeric) (in curry powder), green tea and polyphenols (antioxidants found in fruit and vegetable juices). Others do not appear to have a biologically plausible role in dementia, and none has been subject to intervention studies.

DEMENTIA RISK REDUCTION: WHAT WE CANNOT CONTROL

There are significant dementia risk factors that we cannot control.

These include:

- ageing
- the history of dementia in the family
- gender
- head size

We cannot control: Ageing

Ageing has been consistently shown to be the major risk factor for Alzheimer's disease and other dementias^{56,57}. It has been suggested that because of this, control of risk factors (e.g. diet, exercise, vascular factors) that might result in longer life will not be able to reduce the incidence of dementia⁵⁸. However, many others disagree.

We cannot control: Genes

Several genetic mutations and natural gene variations have been associated with a higher risk of developing Alzheimer's disease. These mutations are broadly of three types – some affect the production or clearance of amyloid (e.g. Down syndrome), some affect lipid (fat) metabolism (e.g. apolipoprotein E status) and some affect inflammation⁵⁹. The dementias are sometimes inherited but may occur for the first time in the affected individual (e.g. Down syndrome). These dementias are most commonly Alzheimer's disease but frontotemporal dementia with a movement disorder called Parkinsonism can also be inherited, as can rare other dementias including that associated with Huntington's disease.

We cannot control: Family History

Having a parent with dementia increases the risk of developing dementia but does not automatically mean that the children will develop the condition. Results from a large systematic research study with people with Alzheimer's disease have shown a lifetime risk (to age 96) of Alzheimer's disease of 39% for a first-degree relative (a child or sibling) compared to 36% for those without such a relative. Female relatives tend to have a higher risk than male relatives. If both parents have Alzheimer's disease, the risk to children rises to 54% by age 80, which is 1.5 times higher than the risk if only one parent is affected, and 5 times higher than the risk if neither parent is affected⁶⁰.

We cannot control: Gender

Studies have generally shown that females have a *slightly* higher risk of developing dementia, even when age is taken into account⁶¹.

We cannot control: Head size

Smaller head size is a risk factor for dementia⁶². This has been linked to a theory of brain reserve. Those with larger brains have more reserve to withstand the effects of progression of dementia pathology and of other illnesses which directly or indirectly affect the brain.

PREVENTATIVE FACTORS ON THE HORIZON

Developments in neuroscience, epidemiology, genetics and medical technology have advanced our knowledge of cause and progression of dementia. This knowledge in turn fuels the creation of new treatments⁶³.

The following advances are currently the most promising:

Gene therapy

Gene therapy is very far from being applied clinically. A gene that can break down the amyloid peptide has not yet proceeded beyond animal studies. Recently, skin cells genetically modified to produce nerve growth factor were injected into the brain of 8 people with Alzheimer's disease, with some evidence of positive benefits⁶⁴ - but much more work is needed before this approach can be recommended.

Amyloid processing & deposition

Several related approaches that may be useful in preventing Alzheimer's disease are based on our understanding of how the amyloid precursor protein is reduced to the peptide (a small protein) that builds up as amyloid deposits. This peptide results from the actions of two enzymes called gamma (γ) and beta (β) secretase. Drugs which suppress the activities of these enzymes, or increase the activity of another enzyme which breaks apart this peptide (alpha secretase) are undergoing clinical trials in those with dementia, but no results have yet been published.

Vaccination with the amyloid peptide is also a promising approach. Such vaccination causes antibodies to be produced that seem to remove the amyloid deposits⁶⁵. However, clinical trials were ceased when an unwanted inflammation of the brain and its enveloping membranes was found in 17 people (approximately 5% of the whole group) with Alzheimer's disease treated this way⁶⁶. Other vaccination approaches that may bypass this unwanted effect are being developed.

For both these approaches (gene therapy and modification of amyloid), clinical trials have only been in those with established Alzheimer's disease. Even if such trials were negative, these approaches may have a role in the prevention of dementia.

CONCLUSIONS

There is good evidence to support a range of lifestyle strategies as a means of reducing your risk of developing dementia.

It is **recommended** that you:

- Keep intellectually stimulated, and engage in social/leisure activities
- Keep physically active and sleep well
- Regularly check blood pressure and cholesterol throughout mid and late life and keep elevated blood pressure, cholesterol and other vascular risk factors controlled
- Don't smoke
- Continue light to moderate drinking but there is no need to start if currently a non-drinker
- Eat healthily, avoiding too much saturated fat
- Maintain adequate B₁₂ and folate intake and consider supplements if deficient or homocysteine is found to be elevated, but discuss with your doctor first
- Maintain adequate dietary vitamin E and consider supplements (not more than 400mg a day) if adequate dietary intake cannot be assured, but discuss with your doctor first
- Protect against head injury
- Avoid intense electromagnetic radiation by using shielded electric motors

There are several medications available that may be protective and that are available for other conditions, but they need to be used appropriately. There is insufficient evidence currently to recommend any medications for the prevention of dementia.

The following recommendations are made on the basis that evidence of dementia prevention is currently lacking:

- Do not use cholesterol-lowering statins for dementia prevention
- Do not use anti-inflammatory agents for dementia prevention
- Do not use HRT/oestrogen for dementia prevention
- Do not use cholinesterase inhibitors (galantamine, donepezil, rivastigmine) or memantine to prevent dementia, even if worried about memory

Overall, you should think about your whole body including your brain when assessing health behaviours and disease management. In each case it is wise to discuss issues with your doctor.

As a society we are becoming increasingly aware of the need to maintain a sound diet, exercise, intellectual stimulation and social connectedness. This review reinforces that message and adds the need to 'mind your mind'.

GLOSSARY

Alzheimer's disease

The commonest form of dementia which affects memory and other cognitive functions

Amyloid deposits

Deposits of a protein that characterises Alzheimer's disease

Anti-hypertensives

Drugs to lower blood pressure

Anti-inflammatory agents

Drugs to reduce inflammation and pain

Antiplatelet agents

Drugs that act against a blood component to reduce clotting

Apolipoprotein E

A protein that binds to fat, and transports it around

Cholesterol

A fat that is essential to cell structure, but which in excess can cause blood vessel occlusion

Cholinesterase inhibitors

Drugs to inhibit a brain enzyme and increase levels of a chemical, acetylcholine, that is deficient in some dementias

Cohort study

A study that follows a group of people born in a certain time interval

Dementia with Lewy bodies

A form of dementia characterised by deposition of Lewy bodies in the brain

Familial Alzheimer's disease

Alzheimer's disease that is inherited by one half of the children, on average

Folate

A vitamin essential to brain and blood cell formation

Homocysteine

A marker of folate and vitamin B₁₂ metabolism; elevated levels associated with poor health outcomes

Hormone Replacement Therapy

Use of female hormones in people deficient in these

Hypertension

High blood pressure

Intervention study

A study where an action is taken to try to change outcomes for a group of people

Nerve growth factor

A hormone that stimulates growth of some nerve cells

Oestrogen (Estrogen)

The commonest female hormone

Omega-3 fatty acid

A form of fat that is generally good for health

Progesterone

The other common female hormone

Prospective study

A study which follows a group of people forward into time

Secretase enzymes

Proteins that break down larger proteins

Sleep apnoea

A condition where breathing stops, usually at night, causing a range of health problems

Statin

A drug used to lower cholesterol

Vascular dementia

A form of dementia related to poor blood supply to areas of the brain

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for further information about the people involved and the research activities