Prevention of Alzheimer's Disease and Other Dementias

Michael C Woodward

ABSTRACT

Alzheimer's disease (AD) affects 150 000 Australians and prevention is a high priority. Approaches to reduce the risk of AD and other dementias can be based on the risk factors that have been suggested from case-control and longitudinal studies. There is some evidence of benefit from vitamin E supplements (and possibly also vitamin C), a well-balanced diet including adequate folate and vitamin B_{12}, keeping physically and mentally alert, avoiding head injury, continuing moderate alcohol intake, avoiding excess aluminium exposure, avoiding smoking, and keeping elevated blood pressure, diabetes and other vascular risk factors under control. There are currently insufficient data to support the use of cholesterol-lowering agents, anti-inflammatory agents, oestrogen, caffeine, or ginkgo biloba to prevent dementia, but large prospective randomised placebo-controlled prevention trials are in progress for some of these agents and may alter these recommendations. Approaches in the future which look very promising are anti-amyloid vaccination and gene therapy. Targeting high risk groups, such as those with mild cognitive impairment, may increase the benefit of preventative approaches.

J Pharm Pract Res 2003; 33: 138-43.

INTRODUCTION

Alzheimer's disease (AD) affects around 150 000 Australians,[1] and currently there is no cure. It would greatly reduce suffering, carer burden and cost to the community if we could prevent AD and related conditions. But is this possible?

WHAT IS PREVENTION?

Primary prevention refers to preventing a disease from occurring—so people currently without AD, remain without AD. Included in this concept would be delaying the onset of AD—a delay of only five years would halve the number of Australians with the illness.

Secondary prevention limits progression of disease by early detection, diagnosis and treatment. Tertiary prevention ameliorates the consequences of disease by containing disability and dependency, and maintaining an acceptable quality of life.

In this article, the discussion will be largely about primary prevention, although each strategy could be useful in both secondary and tertiary prevention. Evidence around secondary prevention will be discussed, where available.

Michael C Woodward, MBBS, FRACP, Director, Aged and Residential Care Services, Austin Health, Heidelberg Heights, Victoria
Address for correspondence: Michael Woodward, Director, Aged and Residential Care Services, Austin Health, PO Box 5444, Heidelberg Heights Vic. 3081
E-mail: michael.woodward@austin.org.au

RISK FACTORS AND PREVENTION

Numerous risk factors and potential preventative strategies have been identified in studies of people with dementia. Most studies have been cross-sectional or retrospective case-control studies in which a population of people with dementia is characterised (e.g. Do or did they smoke? Have they had a head injury? Have they taken hormone replacement therapy?) and compared with a matched population without dementia. These studies are open to numerous biases and may not lead to identifying true risk factors—they are best seen as generating a list of possible factors rather than a final, definitive list.

A more powerful approach is to characterise a population without any existing dementia then follow them up prospectively for a considerable period of time (at least five years). The characteristics of those who develop dementia over this follow-up period can then be compared with those who do not, and this produces a more accurate list of risk factors. This approach is still subject to cohort effects (different risk factors may apply to different generations) so is best repeated over time, or carried out on several different initial age groups.

Even when risk factors are identified, it cannot be assumed that modifying or preventing them will definitely prevent or delay AD and other dementias—this needs to be proven in large, prospective preventative studies, generally over several years. To date, very few such studies have been completed, so we do not yet have a substantial body of evidence about preventative approaches. However, more such studies are in progress and some risk factors are both strongly associated with AD and are modifiable, so more proven preventative approaches are probably not far away. Unless otherwise stated, all of the studies presented in this paper used retrospective case-control methodology. This article will concentrate on the most promising ways of preventing AD and other dementias in the general population or, where stated, in a certain population group. Risk factors and other strategies that could prevent AD are summarised in Tables 1 and 2.

Cholesterol Lowering

At least two large studies (over 10 000 participants in one, 2305 in the other) have shown that people treated with HMG-CoA reductase inhibitors (statins) have a 70–75% lower risk of developing AD, independent of the initial cholesterol level.[2,3] Another larger study (57 000 people) showed a 50% reduction.[4] Patients in these studies were generally treated for an elevated cholesterol, but it was statin use rather than the cholesterol level that led to inclusion in the study. The duration of statin use

Table 1. Possible risk factors and preventative strategies for Alzheimer's disease*

Risk factor	Possible preventative strategy
Low B_{12} or folate	B_{12}, folate (diet or supplements)
Elevated homocysteine	B_{12} or folate (diet or supplements)
Cardiovascular risk factors	Treat hypertension
	Cease smoking
	Control diabetes
	Use of antiplatelet agents
Head Injury	Protect head
Occupational hazards	Shield from electromagnetic radiation
Aluminium	Avoid excess exposure
Genetic risk	Embryo selection
	Other gene therapies
Depression	Treat depression

* Evidence discussed in more detail in text.

Table 2. Possible protective factors and preventative strategies for Alzheimer's disease*

Protective factor	Possible preventative strategy
HMG-CoA reductase inhibitor	Use of these agents (independent of cholesterol level)
Anti-inflammatory agents	Use of these agents
HRT	Use of HRT
Vitamins/Antioxidants	Use of vitamin E, C
Alcohol	Moderate consumption
Caffeine	Drink coffee
Physical activity	Regular exercise
Ginkgo biloba	Use of ginkgo biloba
Education	At least 7 years of education
Leisure activities/cognitive stimulation	Engage in such activities
Vaccination	(Safe) anti-amyloid vaccination

* Evidence discussed in more detail in text, HRT = hormone replacement therapy

was not stated. Cholesterol is essential for brain function, but overfeeding rabbits cholesterol causes them to develop the pathological changes of AD. The way in which cholesterol-lowering drugs may prevent AD is not yet clear, but they may affect the processing of the amyloid precursor protein (Prof. Colin Masters, Professor of Pathology, University of Melbourne, personal communication, April 2002). A large study using a statin in those with an increased risk of death from heart disease, but initially no cognitive impairment, has recently been reported and did not show less cognitive impairment in the treatment group compared to the placebo group.[5] Another large prevention trial in the general population is in progress and will be completed next year. Until then, there is insufficient evidence to recommend the routine use of these expensive drugs solely to prevent AD, although a number of clinicians have been prescribing them for this purpose.

Anti-Inflammatory Agents

People treated with anti-inflammatory agents (e.g. for rheumatoid arthritis) have been shown, in several studies, to have a lower risk of developing AD. In a recent large study involving 8000 patients, long-term use (two years or more) of non-steroidal anti-inflammatory agents reduced the risk of AD by 80%, but did not reduce the risk of vascular dementia.[6] There are inflammatory changes around the amyloid plaques of AD,[7] which may be the site of action for anti-inflammatory drugs—but we need prevention trials before we recommend these agents, especially as they have a range of side effects. One large trial in people at higher risk of developing AD is in progress in the USA. Three large trials (one published) of prednisone, rofecoxib, naproxen and celecoxib in the *treatment* of established AD have been negative—showing that a (possible) preventative role does not imply an additional treatment effect.[8]

Hormone Replacement Therapy (HRT)

In case-control studies, females treated with HRT (currently or previously) have a lower risk of developing AD; for example, one large study followed 1124 elderly women for up to five years and found the oestrogen users had a 40% lower risk of developing AD.[9] A meta-analysis of 12 studies (2 cohort studies and 10 case-control studies) showed a relative risk of 0.66 (95% CI, 0.53–0.82) for AD in oestrogen users versus non-users.[10] This, however, is an excellent example of where randomised controlled intervention studies are needed to confirm or disprove a suggested effect. The Women's Health Initiative Memory Study, a randomised controlled trial of oestrogen plus progestogen versus placebo, enrolled 4532 postmenopausal women aged 65 years or older who were initially free of probable dementia. Over a mean of 4.05 years, 40 women in the HRT arm and only 21 in the placebo arm developed probable dementia (mainly AD)—the hazard ratio for probable dementia was 2.05 ($p = 0.01$).[11] Whether these results would be true for other HRT combinations, or for oestrogen alone, is unclear, but at this stage combined oestrogen (0.625 mg of conjugated equine oestrogens) and progestogen (2.5 mg of medroxyprogesterone acetate) cannot be recommended for the prevention of dementia. Also, again, oestrogen has been shown to be ineffective in the treatment of established AD.[12,13] There are feasible mechanisms by which oestrogen may exert a protective effect; for example, the brain cells have oestrogen receptors, and oestrogen increases brain synapses in animal models and improves blood flow to the brain.[14] We also now know from the same study that despite theoretical benefits on the cardiovascular system, long-term oestrogen use actually increases cardiovascular events in women, so any preventative role for dementia needs to be balanced against other potential risks.

Vitamins/Antioxidants

Several studies have shown that a higher intake of antioxidants, including vitamin E, is associated with a lower risk of AD. For example, the Chicago Health and Ageing Project showed that those with a higher intake of vitamin E from food had a 70% lower risk of developing AD, over a four-year follow-up[15] (relative risk 0.30, 95% CI 0.10–0.82). Interestingly, vitamin E from supplements (and vitamin C from any source) was not associated with

any protective effect. In the Rotterdam Study of 5395 people initially free of AD, over a six-year follow-up, higher intake of vitamin C and vitamin E from any source was associated with a lower risk of developing AD,[16] with a relative risk of 0.82 (95% CI 0.68–0.99) and 0.82 (0.67–1.00) respectively for high intake of vitamin C and vitamin E. It is proposed that free radicals damage neurones in AD, and that these vitamins counteract the effects of free radicals. Also, the Honolulu-Asia Aging Study of over 3300 men showed that over an 11-year period, taking both vitamin E and vitamin C supplements reduced the risk of vascular dementia by 88%[17] (odds ratio 0.12, 95% CI 0.02–0.88). However, another recent study of 2309 men followed up for three years showed that vitamin C and vitamin E supplements did not reduce the risk of developing dementia.[18] So what should we do? Both vitamins are relatively non-toxic, so if one felt pressured to adopt *any* preventative measure, a diet rich in vitamin E, with or without vitamin E supplements (1000 mg daily is the dose suggested by these and other trials), could be considered—at least until prospective prevention trials prove otherwise. The evidence for vitamin C supplements (250 mg daily is the dose suggested by these and other trials) is a little less robust, but again, this vitamin is fairly non-toxic.

Alcohol

Initial studies (from the University of Bordeaux!) have strongly suggested that a modest intake of wine protects against AD.[19] More recent work has also supported the protective affect of alcohol. For example, the Rotterdam Study has shown a 42% less risk of any dementia (hazard ratio 0.58, 95% CI 0.38–0.90) in those who consume one to three alcoholic drinks in a day.[20] However, there is not enough evidence yet to support non-drinkers starting to drink alcohol, (or increasing intake, if drinking only a very little), but there is no need for modest imbibers to cease (in the absence of other reasons to cease).

Caffeine

One tiny Portugese study of 54 cases and 54 controls has suggested a protective effect of an average of two to three cups of coffee a day[21]—but much more data are needed before non-consumers rush out and subject themselves to insomnia and headaches!

Head Injury

There are fairly robust data that show that head injury (especially if it causes loss of consciousness) is a risk factor for AD. For instance, in the MIRAGE Study of 2233 AD patients and 14 668 family controls, head injury with loss of consciousness increased the risk of AD tenfold.[22] At this stage, sound advice is to avoid high-risk occupational or leisure activities and to protect one's head (e.g. with a helmet or use of a seat belt) where appropriate.

Folate, Vitamin B_{12} and Homocysteine

This is one of the current glamour areas of dementia research, and numerous studies have shown that low folate, low B_{12} or elevated homocysteine levels are risk factors for dementia. For instance, in the (Swedish) Kungsholmen Project, 370 initially non-demented elderly people were followed for three years. New AD was twice as likely (relative risk 2.1, 95% CI 1.2–3.5) when initially both B_{12} and folate levels were low.[23] In a large cohort of 1092 subjects from the Framingham Study, higher initial homocysteine levels (above 14 mmol per litre) increased the risk of subsequent AD (and other dementias) twofold, over the eight-year follow-up. We need prospective treatment trials. Small doses of folate are added to bread and flour in the USA to prevent neural tube defects in newborns, but such interventions are not yet agreed on in Australia. B vitamins and foods fortified with folate can also reduce homocysteine levels, although there is no evidence for a specific benefit of these approaches, or for vitamin B_6 or thiamine supplements. At this stage, the routine use of (non-toxic) oral B_{12} and folate supplements (together) seems defensible but it may be ineffective. A good diet could achieve as much potential protection. It is unclear whether a high homocysteine level is an independent risk factor—B_{12} and folate deficiencies do cause higher homocysteine levels, but homocysteine is an independent risk factor for vascular disease.[24] The mechanism by which these factors increase the risk of dementia is also not yet clear. Folate and B_{12} deficiencies may impair neuronal repair. Intriguingly, a community study of 156 people without memory problems found that higher homocysteine levels were associated with smaller hippocampal size.[25]

Aluminium

Aluminium is neurotoxic,[26] but there is no convincing evidence that it causes AD. Our major exposure is through drinking water, and water supplies vary greatly in their aluminium concentration. Most Australian water supplies have only low levels of aluminium. Some overseas studies have suggested that exposure to higher levels of aluminium in drinking water is associated with a higher prevalence of AD. For instance, in a survey of 88 county districts in England and Wales, the prevalence of AD was 1.5 times higher in districts where the ten-year mean aluminium concentration in drinking water exceeded 0.11 mg/l than in districts where concentrations were less than 0.01 mg/l.[27] However, case ascertainment was by computerised tomography (CT) scanning records, so many cases of AD may not have been included in the study. At Camelford in Cornwall, town drinking water was contaminated with 20 tonnes of aluminium sulphate in July 1988. Follow-up over ten years showed impaired cognitive performance, but not dementia, in those exposed, compared to family controls.[28] Fluoride levels may modify any effects of aluminium, and other heavy metals (e.g. copper and zinc) may also play a role. Sir Richard Doll, who first uncovered the link between smoking and lung cancer, has concluded that the jury is still out.[29] Proposed Australian epidemiological research has not yet occurred.[30] The pathological processes by which aluminium could cause AD were reviewed by Storey and Masters, who concluded that aluminium exposure is unproven as a cause of AD.[31] It may be prudent at this stage to avoid extensive aluminium exposure (e.g. certain cities' water supplies, spray-on deodorants, aluminium cooking pots and some antacids).

Cardiovascular Risk Factors

Most cardiovascular risk factors, including hypertension and diabetes, increase the risk of AD, vascular dementia and cognitive impairment in general.[32,33] Also, vascular disease increases the severity of dementia; for

example, in an autopsy study of nuns who developed AD, co-existent brain infarcts increased the severity of cognitive impairment.[34] Hypertension in mid-life (age 40), and particularly systolic hypertension, seems to be more a risk factor than later-life hypertension.[31] Treatment of isolated systolic hypertension in one large study of 2400 patients followed for two years reduced the incidence of (all) dementia by 50%[35]—one of the few prospective preventative studies we have. However, the methodology was not robust, and other similar studies (using different antihypertensive drugs) have not shown the same outcome.[36] More recently the results of the PROGRESS Trial of over 6000 patients with a previous stroke or transient ischaemic attack, randomised to placebo or perindopril/indapamide have been presented—there were modest reductions in incident dementia (34%, $p = 0.03$) in those with recurrent stroke but not in the whole actively treated trial population.[37]

Coronary bypass is also associated with cognitive decline—in a prospective study of 261 patients having bypass surgery, 53% showed cognitive impairment at discharge, reducing to 24% at six months and rising to 42% at five years.[38] Cognitive decline at discharge predicted long-term cognitive decline. The mechanism for this is unclear, but may be related to blood pressure and cerebral perfusion fluctuations. Anaesthesia itself probably does not increase the risk of AD.[39]

At this stage, it seems prudent to treat cardiovascular risk factors—not only may this prevent dementia, but it will certainly prevent other problems such as heart attacks and (further) strokes. Also, lowering homocysteine levels (see above) probably also reduces cardiovascular risk.

Diabetes may also be a risk factor for dementia, in particular vascular dementia. For instance, in a study of 702 people over age 80, 187 of whom developed dementia, diabetes mellitus was associated with a hazard ratio of 2.54 (95% CI 1.35–4.78) for the development of dementia, but was not associated with an increased risk of AD.[40] While no study has yet shown that tight diabetic control reduces the risk of dementia, it is at least possible that this would be so (e.g. by reducing strokes), and there are many other reasons for achieving good control of diabetes.

Antiplatelet therapy protects against stroke and could theoretically reduce the risk of vascular and other dementia. However, to date there have been no trials of these agents in the prevention of dementia. Aspirin has, however, been shown to slow progression of vascular dementia in one small treatment trial[41] which surprisingly has not been replicated. At this stage there is no evidence that antiplatelet agents prevent dementia.

Smoking

Early cross-sectional studies suggested smoking protected against AD,[42] but more recent longitudinal studies have shown that smoking is not protective against dementia, including AD. For instance, in a study of 34 434 male British doctors, the relative risk of AD in continuing smokers was 0.99 (50% CI 0.78–1.25).[43]

Occupational Hazards

Of all the occupational exposures examined, only exposure to electromagnetic radiation may increase the risk of AD. For instance, in one study the use of electric motors close to the body increased the risk of AD threefold.[44] Workers potentially at risk include carpenters, electricians, machinists, seamstresses, sheet metal workers, tool makers, typists (electric!) and welders. Other studies have not confirmed this association.[45,46] At this stage, it is recommended that such workers use shielded electric motors where possible. There is no evidence that mobile phone or computer usage increases AD risk.

Physical Activity

Some studies have shown that greater physical activity preserves cognitive function. For example, in the Women Who Walk project, in 5925 women over the age of 65, new development of cognitive impairment over the next six to eight years occurred in 24% of those who were least active, and only 17% of the most active.[47] While we await better studies to provide evidence that physical activity prevents dementia, there are many other good reasons for increasing physical activity (e.g. brisk walking for at least three hours a week).

Cognitive Stimulation, Education and Leisure Activity

Some studies have shown a protective effect of remaining mentally stimulated and of a more prolonged education. For instance, in a recent study of 801 older nuns, higher scores for cognitive activity were associated with a lower risk of developing AD.[48] The composite cognitive activity score ranged from 1.57 to 4.71 and a one-point increase was associated with a 33% reduction in risk of developing AD (hazard ratio 0.67, 95% CI 0.49–0.92) over a five-year prospective follow-up. A similar study of 1772 subjects followed prospectively for up to seven years showed a protective effect of leisure activities such as knitting, going to the cinema, dining with friends, attending sports events, attending clubs, going to church, listening to music, reading papers and books, watching TV, listening to the radio and going to adult education classes.[49] The risk of incident dementia was 38% lower (relative risk 0.62, 95% CI 0.46–0.83) in those with high levels of leisure activity. It would appear that enjoying retirement actively may reduce the risk of developing dementia. Repeated studies have also shown a relationship between less education and the risk of developing dementia. For instance, a recent study showed that less than seven years of education in a rural location increased the risk of AD more than sixfold.[50]

Ginkgo Biloba

While there is evidence that this herb has a modest benefit in established dementia, a recent prospective six-week study in 230 healthy elderly volunteers showed no efficacy in enhancing memory[51] and there is no evidence that it prevents dementia.

Vaccination

One of the most exciting new developments in AD prevention has been the development of a vaccination approach.[52,53] Mice bred to over-express amyloid protein are protected by vaccination with a component of that protein—the amyloid-beta (Aβ) peptide. Early vaccination is more effective than later. Trials in over 370 humans with AD have unfortunately been halted because 18 subjects developed inflammation of the brain and surrounding membranes. However, other approaches

could avoid this; for instance, injecting the antibody itself rather than the Aβ peptide to induce antibody production. It is possible that, as in mice, using this approach may prevent as well as treat established AD, but there is still a long way to go.

Genetic Counselling and Gene Therapy

While a number of genetic conditions/mutations that cause or predispose towards AD have been discovered,[54] it is unlikely that this knowledge will lead to significant prevention of AD in the near future. Most sufferers have already had their children—but there has been one conference report of testing embryos and successfully selecting one which did not bear the genetic mutation. Genetic counselling before having children may be appropriate in some cases of early onset AD. Gene therapy offers additional hope but is a long way from extensive practical application—although some medications may stimulate genes and are probably closer to practical application. For instance, probuchol turns on the apolipoprotein E gene, and one small study has shown beneficial effects in those with established AD (Prof. Konrad Beyreuther, Professor of Neurology, University of Heidelberg, personal communication, April 2002).

Depression

Several studies have found an association between a history of depression and an increased risk of developing AD.[55-58] In a pooled analysis of case control studies of AD, Jorm and colleagues found depression was a risk factor for AD.[59] More recently, Schweitzer and colleagues found that late onset depression was not a prodrome for dementia.[60] At this time, no study has shown that treatment of depression reduces the risk of subsequent dementia.

TARGETING PREVENTION

The above approaches could be used in the general population or in high-risk groups; for example, those with elevated blood pressure or previous strokes. A further type of prevention, called indicated prevention, is appropriate for people with early or minimal symptoms of cognitive decline.[61] In this respect, mild cognitive impairment (MCI) is characterised by mild cognitive loss and is a major risk factor for AD, with about 15% converting to AD each year.[62] Many of the above approaches could potentially be more effective if used in this high-risk group. Additionally, medications used to treat established AD may slow or reduce progression from MCI to AD, and as such be preventative. All three currently marketed cholinesterase inhibitors (galantamine, donepezil and rivastigmine) are currently being trialled in those with MCI[63] and new treatments for AD, as they are developed, will probably also be trialled in those with MCI.

CONCLUSION

Can we prevent AD? At this time we can possibly prevent some cases. There is little potential harm and considerable potential benefit in taking vitamin E supplements (and possibly also vitamin C), eating a well-balanced diet, including adequate folate and B_{12}, keeping physically and mentally alert, avoiding head injury, continuing moderate alcohol intake, avoiding excess aluminium exposure, avoiding smoking and keeping blood pressure and other vascular risk factors controlled. However, we need data from longer and larger prospective prevention trials, and probably also new agents/approaches, to effectively prevent AD and the other dementias in the coming years.

KEY POINTS

1. At this stage, no intervention has been conclusively prospectively demonstrated to prevent Alzheimer's disease.

2. Case-control studies suggest statins, anti-inflammatory drugs, vitamin E (and possibly vitamin C), avoiding elevated homocysteine levels (possibly through folate supplementation), avoiding head injury, maintaining physical and leisure activities, and controlling cardiovascular risk factors, may reduce the risk of Alzheimer's disease.

3. In the future, anti-amyloid approaches such as vaccination may offer greater prospects for the true prevention of Alzheimer's disease.

Competing interests: None declared

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Submitted: January 2003
Accepted after external peer review: March 2003