

Review

Prospects for the prevention of dementia

Anthony F. Jorm

Centre for Mental Health Research,
Australian National University

Abstract

Prevention of diseases can involve either: (a) their elimination from the lifespan of the individual, or (b) their postponement until later in the lifespan. The elimination of Alzheimer's disease or vascular dementia is not likely in the near future, although on-going trials of vaccination against Alzheimer's pathology offer some prospects. Postponement of dementia remains a more likely scenario. Possible ways of postponing Alzheimer's disease include medications such as anti-inflammatory drugs, oestrogen and antioxidants; and possibly the reduction of occupational risk factors like electromagnetic fields and medical risk factors like head trauma. For vascular dementia, there are lifestyle changes and medications like antihypertensives, antiplatelet drugs, folate and cholesterol lowering drugs. Prevention of dementia is sometimes justified on the basis that it will save government money. However, the situation is complex and in some circumstances, prevention may actually lead to an increase in costs to government.

Correspondence to: Professor. A. F. Jorm, Centre for Mental Health Research, Australian National University

E-mail: Anthony.Jorm@anu.edu.au

Introduction

There are many different diseases causing dementia, including Alzheimer's disease, cerebrovascular disease and Lewy body disease. This article focuses on the two most prevalent types: Alzheimer's disease and vascular dementia. Although these two types of dementia were formerly viewed as quite separate, there is now increasing evidence that Alzheimer's disease might also involve a vascular component [1]. For this reason, the potential approaches for preventing these two types of dementia sometimes overlap.

Prevention by Elimination and by Postponement

What does it mean to prevent a disease? When considering the topic of disease prevention, the examples that typically come to mind are infectious diseases. With infectious diseases, it is possible to totally eliminate the disease from the population, as has happened with smallpox and may happen soon with polio. However, with chronic diseases of ageing, prevention generally means the postponement of the disease until later in the life span. For example, if people develop a dementing disease at a later age than they normally would, they will have more healthy years of life and we can say that the disease has been prevented for a period of time.

The effect of delaying disease onset can be seen from some calculations carried out for Alzheimer's disease in the United States [2]. It is estimated that if the current situation prevails, there will be 2,890,000 Alzheimer's cases by the year 2007. However, if the onset of Alzheimer's disease could be delayed by 2 years, there would be a saving of around 600,000 cases. If these figures were translated to the Australian situation, postponing Alzheimer's disease might reduce the prevalence by tens of thousands of cases.

Prospects for Disease Elimination

Given that no chronic disease has yet been eliminated, the elimination of Alzheimer's disease or vascular dementia is not likely to occur in the foreseeable future. However, disease elimination is not impossible. The best hope for the elimination of a dementing disease comes from work on vaccination against Alzheimer's disease. Schenk and colleagues in the United States have astounded the research community with their work on vaccination against beta-amyloid, one of the major brain changes found in Alzheimer's disease [3]. These researchers have worked with mice that have had a human Alzheimer's disease gene added to their genome. If these mice were vaccinated with beta-amyloid peptide when they were young, they developed very few or no beta-amyloid plaques as they got older. Even if they were vaccinated when older, after they had begun to develop beta-amyloid plaques, the vaccination still had an effect. Further accumulation of beta-amyloid was stopped and even reversed. However, it must be remembered that these mice have had a *rare* human Alzheimer's gene added. Even if the vaccine works for Alzheimer's disease due to this gene, it may not work for the vast majority of cases, which are due to complex genetic and environmental causes. Nevertheless, the vaccine is now being tested for safety on humans with Alzheimer's disease. If it proves to be safe, it will be tested as a treatment, and perhaps, eventually, as a preventive intervention.

Levels of Evidence for Disease Postponement

There are various levels of evidence, which might show that dementia can be postponed, some of which are stronger than others. The best type of evidence is a randomized controlled trial in which one group receives a preventive intervention and a control group does not. Both

groups are then followed up over a period of time to see whether fewer people in the intervention group develop dementia compared to the control group. Randomized controlled trials of prevention must be very large and take many years, so they are inevitably very expensive, and for this reason very few have been carried out.

The next best type of evidence is the prospective study. This type of study does not actually involve a preventive intervention. Rather, a large sample of people is assessed and classified as having the preventive factor or not having it. The sample is then followed up over time to see how many of each group develop dementia. There are now quite a lot of prospective studies, which provide evidence relevant to prevention.

The weakest type of evidence comes from case-control studies. In a case-control study, a group of people with dementia is compared to a control group. The two groups are assessed to see whether or not the demented group has more or less of the factor thought to be preventive. Case-control studies are the easiest and cheapest to carry out and are therefore the most common type of evidence available.

Prospects for the Postponement of Alzheimer's Disease

There are three areas where current research suggests preventive possibilities:

- Using medications, which might have preventive effects, in particular anti-inflammatory drugs, oestrogen replacement, and anti-oxidants.
- Reducing occupational risk factors. The particular occupational factor discussed here is electromagnetic fields.
- Reducing medical risk factors. The particular one discussed here is head trauma.

Anti-inflammatory drugs

It has been proposed that Alzheimer's disease involves inflammatory processes, which lead to damage to nerve cells [4]. This theory predicts that anti-inflammatory drugs should have a preventive effect. Anti-inflammatory drugs are often used long term to treat diseases like arthritis, so it is possible to see if users are less likely to develop Alzheimer's disease. A pooling of data from many case-control studies has found that people who used the main class of anti-inflammatory drugs, the non-steroidal anti-inflammatory drugs (NSAIDs) had around half the risk of Alzheimer's disease [4]. A similar protective effect was found for the other class of anti-inflammatory drugs, the steroids. Prospective studies have found more mixed results, but some have found a protective effect. Anti-inflammatory drugs would seem to be a good prospect for randomized controlled trials. However, these drugs can have side effects, which make preventive trials difficult. A prevention trial is currently underway in the United States. This trial involves people, who are at high risk of developing dementia, rather than with the general population, because for high-risk individuals the benefits may outweigh the risk of side effects.

Oestrogen replacement

Oestrogen is thought to protect the brain from deterioration in several ways and it has been suggested that oestrogen replacement therapy for post-menopausal women might be protective against Alzheimer's disease. A pooling together of data from several case-control and prospective studies has found oestrogen replacement gives 30% lower risk [5]. However, women who use oestrogen replacement therapy tend to be better educated and have

different lifestyles, so it could be these other factors, rather than the oestrogen, that are having the protective effect. Again, randomized controlled trials are needed. Fortunately, there is a large trial underway in the USA, the Women's Health Initiative Memory Study [6]. There have also been two recent trials on the use of oestrogen in the treatment of Alzheimer's disease [7, 8]. Neither of these found any benefit to women who already have Alzheimer's disease. However, it is still possible that oestrogen postpones the onset of Alzheimer's disease.

Antioxidants

A third type of medication which might have a preventive effect is antioxidants. Antioxidants mop up destructive molecules in the body called free radicals. It has been proposed that the destructive effect of free radicals is one of the causes of brain cell death in Alzheimer's disease. There have been prospective studies looking at whether Vitamin C and Vitamin E, both of which are antioxidants, protect against Alzheimer's disease or against cognitive impairment in general. Some studies show that vitamin C might be protective [9-11], but the evidence on vitamin E is largely negative [9, 11, 12]. Again, large randomized controlled trials are needed to find out for sure whether or not vitamin C or other antioxidants might prevent dementia.

Reducing Exposure to Electromagnetic Fields

Reducing occupational risk factors is another possible path to prevention. Although considerable research has been carried out looking for occupational factors that increase risk for Alzheimer's disease, the only potential risk factor that has emerged from this research is exposure to electromagnetic fields. A number of studies have been carried out showing that occupations that involve use of electric motors close to the body have around 3 times greater risk of developing Alzheimer's disease [13]. These occupations include carpenter, electrician, machinist, seamstress, sheet metal worker, tool maker, typist and welder. However, to complicate matters, other studies have not found this association, so it is certainly not an established risk factor [14, 15]. If the association were to be confirmed, then we could implement preventive measures like better shielding of electric motors or moving them further from the body.

Reducing Head Trauma

A final area of where prevention might be possible is in reducing head trauma. Many studies have found that people who have been knocked unconscious are more likely to develop Alzheimer's disease [16, 17], although there are also some very good studies that do not find that head trauma is a risk factor [18, 19]. However, prevention of head trauma is already an important public health goal, with compulsory seat belts, helmets and restrictions on boxing. Nevertheless, if Alzheimer's disease is a possible long-term outcome of head trauma, it gives even more justification for these preventive efforts.

Prospects for the Postponement of Vascular Dementia

There is much less research on risk factors for vascular dementia than on risk factors for Alzheimer's disease. However, many cases of vascular dementia are due to strokes, so risk factors for stroke can also be presumed to be risk factors for vascular dementia. In general, we might expect that simple lifestyle changes such as reducing salt in the diet, not smoking and increasing exercise would help postpone vascular dementia. However, there is no research directly examining the preventive potential of such lifestyle changes. There are also

a number of medications, which have the potential to delay the onset of vascular dementia. These are antihypertensive drugs, antiplatelet drugs, folate and cholesterol lowering drugs. The evidence on each of these is briefly reviewed below.

Treatment of Hypertension

Hypertension is by far the most important risk factor for vascular dementia, and there is even some evidence that it may be a risk factor for Alzheimer's disease as well. Reducing hypertension might therefore have a major preventive effect. In the hypertension area, there are some large randomized controlled trials on the prevention of stroke, and some of these studies have evaluated the effects on dementia as well. The most interesting of these studies is the Syst-Eur trial [20]. In this study, people aged 60 or over with systolic hypertension were randomly assigned to receive either antihypertensive medication or placebo. Over two years, treatment decreased the incidence of stroke, but more importantly, it also decreased the incidence of dementia by around 50%, which was just statistically significant at the .05 level. What is particularly interesting, is that most of the cases were of Alzheimer's disease rather than vascular dementia. So it may be that treatment of hypertension does help the prevention of Alzheimer's disease. We need more evidence on this. Fortunately there is another large trial underway, called the PROGRESS trial [21]. This involves giving an antihypertensive drug or placebo to 6000 patients who have had a stroke or a transient ischemic attack. One of the goals of this study is to find out whether treatment prevents dementia. The final results are expected soon.

Anti-Platelet Treatment

A second possible drug treatment that may prevent vascular dementia is anti-platelet treatment. Aspirin is the best known example of an anti-platelet drug. These drugs reduce the risk that blood will clot and produce a stroke. There have been many studies on the use of aspirin and other antiplatelet drugs to prevent strokes. These studies clearly show that use of antiplatelet drugs prevents strokes in people who already have some evidence of vascular disease, for example they have already had a heart attack, angina or a stroke [22]. By contrast, in people who do not already have some vascular disease, antiplatelet treatment does not produce a net benefit, because although it reduces strokes due to clotting, it increases those due to bleeding in the brain. Surprisingly, no one has studied the effect of antiplatelet treatment on the prevention of vascular dementia, even though any treatment that prevents stroke is a good candidate for the prevention of vascular dementia as well. However, aspirin has been used to slow progression of vascular dementia [23], which also supports the possibility of a preventive effect.

Reducing Homocysteine

Another preventive possibility is the use of folate to lower the level of homocysteine in the blood. Homocysteine is a by-product of a wide variety of chemical reactions in the body. There is some evidence that it may be a risk factor for stroke [24]. More importantly, there are a small number of case-control studies showing that homocysteine is associated with both vascular dementia and Alzheimer's disease [25, 26]. However, there are no prospective studies as yet, so it is not known whether the higher level of homocysteine is a cause of dementia or an effect. If homocysteine is a cause of dementia, there is a simple way to reduce it through an increased intake of folate in the diet. Again, randomized controlled trials are needed to find out if increased folate might help prevent vascular dementia.

Lowering Cholesterol

Cholesterol lowering drugs might also have a preventive role. A meta-analysis of 16 randomized controlled trials of statin drugs to reduce cholesterol found that they reduced stroke risk by 29% [27]. Two recent case-control studies have also indicated that statin drugs may lower risk of dementia [28, 29]. Randomized controlled trials are needed to properly evaluate the effect of these drugs on the prevention of both vascular dementia and Alzheimer's disease.

Points Where Prevention Can be Applied

The various possibilities discussed so far are all examples of either universal prevention or selective prevention. In *universal prevention* the preventive intervention is applied to the whole population, even though many people may have a low risk of developing a disease. An example of universal prevention would be adding more folate to the Australian diet to lower homocysteine and possibly prevent vascular dementia

The second approach is *selective prevention*. In selective prevention, the preventive intervention is applied only to people who are at high risk. This approach is used instead of universal prevention when the intervention is costly or there is some risk, so we would not want to expose the whole population to it. Examples are giving antihypertensive medication to people with high blood pressure or antiplatelet drugs to people who have evidence of vascular disease.

The third approach, not covered so far in this article, is *indicated prevention*. This is applied to people with minimal symptoms foreshadowing disease. Indicated prevention is one step before early intervention, which occurs once the disease is clearly present.

Prospects for Indicated Prevention

Researchers have proposed the existence of various states of cognitive impairment, which are not sufficiently severe to be called dementia. An example is the concept of Mild Cognitive Impairment (MCI) which has been proposed as an indicator of high risk for developing dementia [30]. People with MCI have a memory impairment beyond that expected for their age and education, yet are not demented. According to the researchers who proposed the concept of MCI, about 10-12% of cases develop into dementia per year [30].

Given that people with MCI are at high risk for developing dementia, there are on-going efforts to develop treatments for the indicated prevention of dementia [31]. Current drug treatments for Alzheimer's disease only provide symptomatic relief and do not slow the progression of the disease. But it is only a matter of time before some drug is developed which actually slows progression. If such a drug were very cheap, and had no side effects, we might want to give it to everybody above a certain age as a preventive measure. However, if it were expensive and had side effects, as is more likely to be the case, it could be reserved for people with minimal symptoms, for example with MCI.

Indicated prevention seems a good idea on the surface, but the issues involved are not simple. To illustrate, imagine a scenario in which a drug is given to people with MCI to slow down Alzheimer brain changes. If this drug meant that they spent more time in the milder stages of Alzheimer's disease, but it did not extend the total time spent living with the disease, it would clearly be a useful intervention. Imagine, however, that the drug meant that people

lived longer and the disease process was stretched out in time. In this case, the people who received indicated prevention would have spent more years of their life living with the disabilities caused by cognitive impairment. It is less clear that indicated prevention would be useful in this circumstance.

Cost Implications of Prevention

Prevention is often justified in terms of saving government expenditure, but this is not necessarily the case. Certainly, if dementia could be eliminated entirely, there would be a saving of money. A group of Dutch researchers has examined the effects on life-time health care costs of eliminating various diseases [32]. For dementia, they found a 3% saving for men and an 8% saving for women.

Surprisingly, eliminating most diseases, such as cancer and heart disease, was actually estimated to increase health care costs. The reason for this paradoxical result is that everyone has to die from some cause, and the major health care cost comes in the final years of life. If a person does not die from a particular disease, then they will die from something else later on, which might actually cost more. For example, a sudden fatal heart attack will obviously cost much less than a final 10 years lived with dementia. The big savings in prevention only come from eliminating diseases, which cause major disability, and dementia is one of these.

With prevention by postponement of disease, the issue of cost savings is simpler: the costs are not eliminated, only postponed until later in the lifespan. With indicated prevention, as pointed out above, prevention may actually cost more money. So why should we bother with prevention? The primary factor to consider is whether people have more satisfying years of life, which are free from disability, rather than saving the government money.

Conclusion

The elimination of dementing diseases remains a tantalizing possibility, but is not likely in the near future. However, the postponement of dementia is certainly realistic. There are a lot of promising areas for preventive action and large randomized controlled trials are needed to evaluate their effectiveness. The prevention of dementia is certainly one of the big frontiers for gerontological research and may have profound effects on how we see older age, how we prepare ourselves for ageing and the types of health care and aged care services that may be required in the future.

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