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PROMISING STRATEGIES FOR THE PREVENTION OF DEMENTIA

Laura Middleton, Ph.D.¹ and Kristine Yaffe, M.D.^{1,2,3}

¹ Department of Psychiatry, School of Medicine, University of California, San Francisco and the San Francisco Veterans Affairs Medical Center, San Francisco, CA

² Department of Neurology, School of Medicine, University of California, San Francisco and the San Francisco Veterans Affairs Medical Center, San Francisco, CA

³ Department of Epidemiology and Biostatistics, School of Medicine, University of California, San Francisco and the San Francisco Veterans Affairs Medical Center, San Francisco, CA

Abstract

The incidence and prevalence of dementia is expected to increase several fold in the coming decades. Given that the current pharmaceutical treatment of dementia can only modestly improve symptoms, risk factor modification remains the cornerstone for dementia prevention. Some of the most promising strategies for the prevention of dementia include vascular risk factor control, cognitive activity, physical activity, social engagement, diet, and recognition of depression. In observational studies, vascular risk factors - including diabetes, hypertension, dyslipidemia, and obesity - are fairly consistently associated with increased risk of dementia. In addition, people with depression are at high risk of cognitive impairment. Other studies have reported that intake of anti-oxidants or polyunsaturated fats may be associated with reduced incidence of dementia in population studies and that people who are cognitively, socially, and physically active have reduced risk of cognitive impairment. However, randomized trials of risk factor modification have been mixed. Most promisingly, interventions of cognitive and physical activity improve cognitive performance and slow cognitive decline. Future studies should continue to examine the implication of risk factor modification in controlled trials, with particular focus on whether several simultaneous interventions may have additive or multiplicative effects.

INTRODUCTION

By 2050, the number of people with Alzheimer's disease (AD) and other forms of dementia in the US is expected to almost triple. The predicted rise in dementia prevalence can largely be attributed to increasing longevity and the aging of the "baby boomer generation." This shift toward an aging population is important because the incidence of all-cause dementia nearly doubles with every five years of age.

The cost of caring for people with dementia will, not surprisingly, rise along with the prevalence. In 2008, the US medicare costs for AD alone was approximately \$91 billion.¹ It is estimated that the cost of caring for people with dementia will grow to \$189 billion by 2015.¹ Furthermore, the indirect cost of dementia to society extends beyond the direct costs and includes lost productivity, increased absenteeism, and replacement expenses of caregivers.

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Corresponding Author: Kristine Yaffe, 4150 Clement Street – 181, San Francisco, CA 94121, (t) (415) 221-4810 x3985, (f) (415) 750-6641, Kristine.Yaffe@ucsf.edu.

CONTRIBUTIONS

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Given the expected dramatic increase in the incidence and the prevalence of dementia, the identification of successful prevention and treatment strategies is critical. However, the current pharmaceutical treatment of dementia can only modestly improve symptoms and cannot cure or prevent dementia. As a result, prevention of dementia through risk factor identification and modification is of the utmost importance until disease modifying agents prove efficacious. If the onset of AD can be delayed by five years, the expected prevalence would decrease by more than 1 million cases after 10 years and more than 4 million cases after 50 years.² In this article, we discuss some of the most promising strategies for the prevention of dementia, including vascular risk factor control, cognitive activity, physical activity, social engagement, diet and treatment of depression.

PREVENTION STRATEGIES

Vascular Risk Factor Reduction

Although AD and vascular dementia have traditionally been viewed as distinct disorders, it is now generally agreed that the two rarely occur in isolation. Both types of dementia share many risk factors and pathologic features with atherosclerosis.³ In addition, the presence and severity of cerebrovascular pathology appears to increase the risk and stage of AD for any given level of AD neuropathology.³ Thus, the modification of vascular risk might reduce the risk of dementia regardless of type.

Traditional cardiovascular risk factors such as hypertension, dyslipidemia and diabetes appear to increase the risk of developing the dementia in old age, with several possible mechanisms (Figure 1). In over 20 observational studies, older adults with diabetes have approximately double the risk of developing dementia and mild cognitive impairment compared to those who do not have diabetes.^{4,5} Initial observations indicated that diabetes was most strongly associated with the risk of vascular dementia but more recent research has confirmed that people with diabetes also have a high risk of developing AD.⁶

People with hypertension in midlife consistently have increased risk of AD and all-cause dementia in several observational studies.^{7,8} In contrast, the association between late-life hypertension and dementia is more controversial. Both very high systolic blood pressure and very low diastolic blood pressure in late life have been associated with increased risk of dementia and AD.⁹ However, other studies have found no relationship between late life hypertension and the risk of dementia.¹⁰ Some suggest that while hypertension is a risk factor for dementia, blood pressure may decrease with the onset of AD.¹¹

Other vascular risk factors also seem to increase the risk of dementia. People with high serum levels of total cholesterol and low-density lipoproteins in late life have increased risk of cognitive impairment and dementia with stroke.⁷ This relationship has, however, been less consistent than the relationship between hypertension or diabetes and dementia. In addition, several studies have found that people who are obese in mid-life and possibly later in life have an increased risk of developing dementia.^{6,7} Despite this relationship, people with dementia are more likely to have low body mass than be obese.⁶ Low body mass may, however, be a sign of frailty, which predisposes the person to AD, or may be an early symptom of AD itself.⁶

Given the individual relationship of vascular risk factors with dementia and the frequency of their co-existence, it is not surprising that studies evaluating the effect of multiple or composite vascular risk factors on the risk of dementia have found that subjects who had diabetes, hypertension, high cholesterol, or were smokers at mid-life were more likely to develop dementia later in life. The effects of each vascular risk factor were approximately additive.¹² Similarly, the 'metabolic syndrome', which is a clustering of disorders that include abdominal

obesity, hypertriglyceridemia, low high density lipoprotein, hypertension and/or hyperglycemia, has been associated with increased risk of cognitive impairment and cognitive decline, especially in subjects with high levels of inflammation.¹²

Since people are more likely to have multiple vascular risk factors than just one, it is difficult to establish mechanistic links between individual risk factors and dementia. The mechanisms linking vascular risk factors to cognitive impairment are likely numerous and complex (Figure 1). The direct relationship between hypertension, cerebrovascular disease (in its most severe case, stroke), and subsequent dementia is well-established,¹¹ and cerebrovascular disease is also likely to link obesity, diabetes, dyslipidemia to cognitive impairment. The degenerative changes in the cerebrovascular vessels may also cause the dysfunction of both the endothelium and blood-brain barrier.¹¹ Consequently, endothelial cells may produce an excess of free radicals and cause subsequent oxidative stress with increased blood-brain barrier permeability to proteins leading to β -amyloid accumulation.¹¹

There is also a growing body of work that suggests a direct link between insulin and AD pathology. Specifically, *in vitro* studies indicate that insulin causes a significant increase in extracellular β -amyloid levels.⁶ Consequently, people with insulin resistance, such as type II diabetics or those with precursor hyperinsulemia, may have insulin caused increases in β -amyloid levels. Furthermore, cholesterol is a key regulator of neuronal function that may regulate β -amyloid plaque deposition in the brain.⁷

In addition, adipose tissue secretes both metabolic and inflammatory factors.⁸ In particular, the secretion of inflammatory adipocytokines may be involved in neurodegenerative pathways.⁸ It is unclear, however, whether adipose tissue is directly linked to cognitive impairment or whether the adipose tissue is a marker of insulin resistance and hyperinsulinemia.⁸

Recognition of vascular risk factors may help to identify those people who are most at risk (and should be regularly screened) for dementia and who are most likely to benefit from preventative interventions. Interventions could include the behavioral (as discussed below) as well as medical treatment of vascular risk factors. Several studies indicate that people who receive treatment for hypertension, both in midlife and later life, have reduced risk of developing cognitive impairment compared to those with untreated hypertension;⁷ however, other studies have not confirmed this.⁷ Similarly, statin therapy in observational studies is associated with reduced risk of dementia and AD.⁷ Randomized controlled trials of both antihypertensive medications and statins have not, however, consistently shown that treatment results in improved cognitive performance or less cognitive decline compared to a placebo.^{7,13,14} Preliminary trials of diabetes medications including rosiglitazone and insulin have indicated that these drugs may be beneficial to cognition in patients with AD^{6,15,16} and mild cognitive impairment.¹⁵

Cognitive Activity

From initial reports that elders with more education have lower incidence of dementia, research has emerged to suggest that cognitive activity, more generally, is associated with a reduced risk of developing cognitive decline and dementia.¹⁷ Several prospective observational studies have reported that people who engage in mentally stimulating activities—such as learning, reading or playing games—at younger ages¹⁸ and older ages¹⁹ are less likely to develop dementia compared to those people who do not engage in these activities.

Elders who are cognitively active may have higher degrees of neuropathology without exhibiting the symptoms of dementia compared to those who do not engage in cognitively stimulating activity.¹⁷ This phenomenon is referred to as “cognitive reserve”, a concept that arose from the initial observation that people with higher levels of education had greater

cognitive performance for equal loads of AD pathology.¹⁷ The expanded construct now includes occupation and leisure activity among cognitive activities that maximize cognitive reserve.¹⁷

Recent trials have demonstrated that cognitive interventions may reduce the risk of cognitive impairment and slow cognitive decline.²⁰ The benefit of cognitive training, however, seems to be domain specific. Several trials found that while cognitive training can improve memory, reasoning, and mental processing speed in older adults,²⁰ cognitive training did not generalize across domains and did not affect everyday functioning.²¹ In addition, elders with memory impairment may be less able to make gains from memory training than those without impairment.²² Consequently, the impact of cognitive training in elders on the risk of dementia is unclear but several trials are underway.

Physical Activity

Recent attention is being paid to the role of physical activity as a potentially protective factor against the risk of dementia. In observational studies, people who are physically active often demonstrate less cognitive decline and a lower risk of dementia than people who are sedentary.²³ In addition, physically active people may have a lower incidence of AD, though the association is less consistent for vascular dementia^{23,24} (Table 1). Although fewer studies have investigated the association between mid-life physical activity and cognitive impairment, most have found that mid-life activity is associated with a lower incidence of both AD and all-cause dementia.²³

Interventional studies have confirmed that even short durations of exercise training can improve cognitive performance. A meta-analysis concluded that people who were not previously physically active can show improved cognitive functioning after exercising for as little as four months.²⁵ Furthermore, exercise interventions may also reduce the rate of cognitive decline in people with cognitive impairment.²⁶

The mechanisms by which physical activity affects cognition are also complex and likely multifactorial. People who exercise have higher levels of brain neurotrophic factors,²⁷ which are implicated in neurological repair. Physical activity also modifies vascular risk²⁷ and vascular risk factors are, as discussed above, associated not only with increased risk of vascular dementia but also of AD.⁴ In addition, rats with high levels of voluntary physical activity also have less β -amyloid plaque formation.²⁷

Social Engagement

People with limited social networks and low social engagement may be more likely to develop dementia compared to those with socially rich lives.¹⁹ Social engagement through visits with friends and relatives, going to movies, clubs, centers, church/synagogues, and volunteering may be protective against developing cognitive impairment.¹⁹ Some have proposed that social activity, similar to cognitive and physical activity, might reduce the risk of dementia by increasing cognitive reserve so that people can better maintain their cognitive performance even with neuropathology.¹⁹

Another study, however, found that the relationship between low social engagement and the risk of dementia was restricted to those subjects who experienced a decline in social engagement from mid-life to late-life.²⁸ This suggests that low social engagement, rather than a risk factor, may be an early symptom of cognitive impairment. Further studies are needed to determine whether social interventions might curb cognitive decline.

The interaction between social activity, cognitive activity, and physical activity is also difficult to disentangle. Many leisure activities contain all three components. By evaluating each leisure

activity for cognitive, social, and physical components, one study concluded that each component is equally important in the protection against dementia.²⁹ As a result, interventions that include cognitive, social, and physical components might be the best strategy to reduce the risk of cognitive impairment and research should investigate this possibility.

Diet

Many of the risk factors for dementia, such as hypertension, diabetes, and obesity, may be modified by diet. In addition, a diet high in anti-oxidants may reduce inflammation, which is associated with the risk of dementia. Thus, it is reasonable to suggest that the risk of dementia itself could be modified by diet. Several observational studies support this hypothesis. For example, elders consuming a Mediterranean diet and higher fruit and vegetable intake may have a lower risk of developing dementia.³⁰ Other studies found that people with high consumption of fish have a lower risk of dementia and cognitive decline.³⁰

The association between high fish, fruit, and vegetable diets and a lower risk of dementia has largely been attributed to antioxidants and polyunsaturated fatty acids. The interest in antioxidants in relation to dementia stemmed from the observation that oxidative stress may contribute to AD pathology. This led to the hypothesis that a high dietary intake of antioxidants might slow cognitive decline and lower the risk of dementia. Indeed, in some studies, people with higher intakes of vitamin E and C (both antioxidants), either through diet or supplements, have a slower cognitive decline and a lower risk of AD in old age.³⁰ However, the relationship has not been consistent and other large, prospective observational studies found no association between vitamin intake and dementia risk.³⁰ Furthermore, randomized controlled trial evidence has, at best, been inconsistent with most studies finding no relationship between vitamin E supplementation and cognitive performance.^{30,31,32} Therefore, it remains unclear whether the observed association between antioxidant use and dementia are causal or are due to uncontrolled confounding or other biases.

The investigations regarding polyunsaturated fatty acid consumption in relation to cognitive outcomes have been similarly inconclusive.³³ While several observational studies, though not all, reported that people with high polyunsaturated fatty acid consumption had a lower risk of dementia and AD, randomized controlled trials have not confirmed the results.³³ Furthermore, polyunsaturated fatty acid supplementation had no effect on memory and attention in cognitively healthy elders.³³ As a result of these trials, the relationship between polyunsaturated fatty acids and cognition has come under question, although further study is still warranted. Moreover, given that adherence to a Mediterranean diet and high consumption of anti-oxidants and polyunsaturated fatty acids are associated with a reduced risk of cardiovascular disease, people who adopt healthy diets are likely to have positive health outcomes regardless of the effect on cognitive functioning and without any adverse effects.

Depression

It is well known that people, especially older adults, with depression have reduced cognitive performance.²⁷ In addition, many people with dementia also have depression.³⁴ It is unclear, however, whether depression is a risk factor for dementia or whether it is a prodromal symptom.

Some observational studies found that older people with depressive symptoms were more likely to have dementia at follow up compared to those without these symptoms.^{35,36} Some studies, however, found that depressive symptoms coincided with or followed dementia onset rather than preceded it.³⁴ There are several hypotheses that have been proposed to explain the relationships between depression and dementia: 1) depression may sometimes be an early symptom or prodrome of dementia; 2) the clinical examination required for the diagnosis of depression may make dementia more likely to be detected, especially at an earlier stage; 3)

those with early cognitive deficits may be more likely to become depressed because of the earliest cognitive symptoms.³⁵ Mechanistically, depression is associated with elevated cortisol levels, which may directly damage the hippocampus and increase the risk of dementia.³⁴ Furthermore, recent studies have suggested that people with depression have enhanced deposition of β -amyloid plaques.³⁴

The treatment of depression also seems to improve cognitive function in people who are depressed,³⁷ but may not return cognition to normal levels. In addition, whether the treatment of depression decreases the risk of dementia among people with depressive symptoms has not yet been studied. Additional research is needed to clarify whether depressive symptoms are a true risk factor for dementia and whether the treatment of depressive symptoms might reduce the risk of dementia.

CONCLUSION

Understanding which lifestyle and biological factors might alter the risk of dementia is crucial to the prevention of the disease. Population studies have identified many factors that could be important in reducing the risk of dementia, including factors that identify people at risk for dementia (vascular risk factors, depressive symptoms) and factors that may reduce the risk of dementia (cognitive, physician, and social activity, diet rich in anti-oxidants and polyunsaturated fatty acids, vascular risk factor control). While early interventional studies have been less conclusive (Table 1), future trials should continue to examine the impact of risk factor modification on cognitive outcomes. In particular, interventions that combine a number of factors, such as healthy nutrition along with cognitive, social, and physical activity, should be investigated. In the most optimistic view, dementia could be delayed or even prevented by these interventions. At worst, people will improve their overall health, especially their cardiovascular health, and enjoy a more cognitively and socially engaging life.

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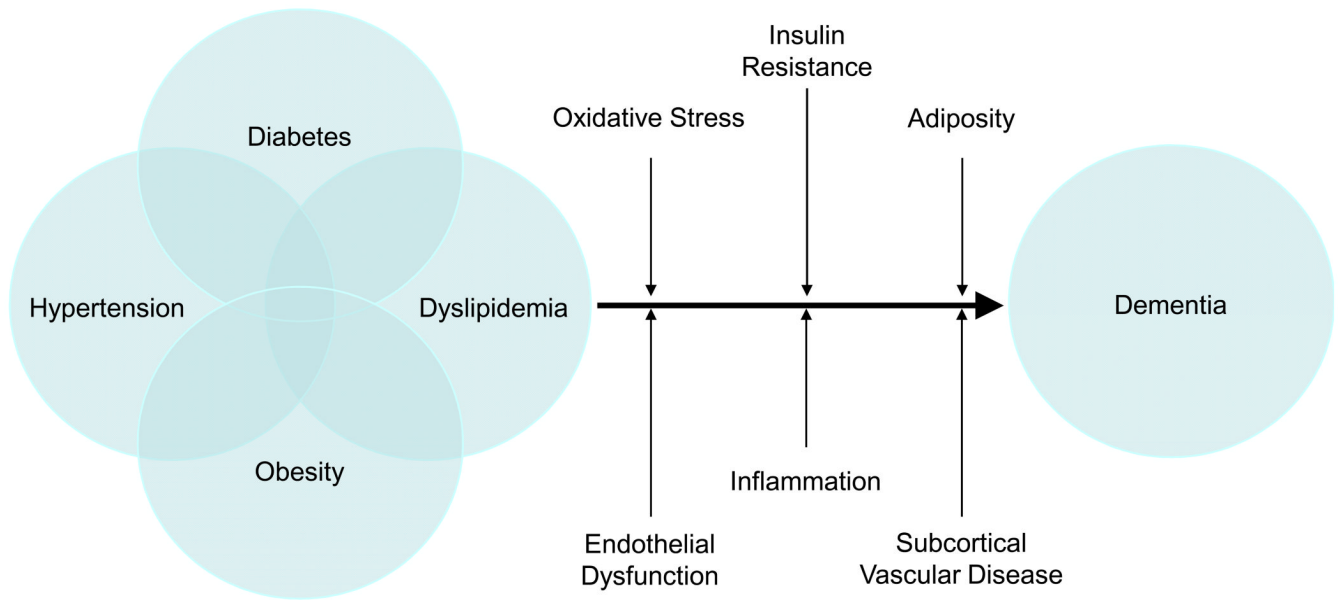


Figure 1. Possible mechanisms that may explain the association between vascular risk factors and increased risk of developing dementia.

Table 1
Summary of evidence and suggestions for future directions on risk factors for dementia.

Risk Factor	Observational Studies	Controlled Trials	Future Directions for Research
Vascular Risk Factors	<ul style="list-style-type: none"> Older adults with diabetes, hypertension, dyslipidemia, obesity, and metabolic syndrome have a higher risk of dementia and cognitive decline in most studies These risk factors at mid-life are also associated with increase risk of dementia Mid-life hypertension is associated with increased risk of dementia in late-life. The association between late-life hypertension and dementia is less consistent. 	<ul style="list-style-type: none"> Anti-hypertensives have not consistently reduced the risk of dementia/cognitive impairment among people with hypertension. Statins have not consistently reduced the risk of dementia among people with dyslipidemia. Initial trials with diabetes medications show improved cognitive performance in some domains 	<ul style="list-style-type: none"> Trials examining the effect of interventions for diabetes and obesity (in progress) Trials identifying mechanistic link between vascular risk factors and dementia and determining whether modification is possible through behavior or treatment
Cognitive Activity	<ul style="list-style-type: none"> Greater education or participation in cognitively engaging activities at younger or older ages is associated with a lower risk of dementia. 	<ul style="list-style-type: none"> Several trials demonstrate better cognitive function and less decline with cognitive interventions The effects of training appear to be domain specific 	<ul style="list-style-type: none"> Further trials examining cognitive interventions (in progress) Controlled trial investigating whether a multi-faceted intervention involving cognitive, physical, and social components leads to improved cognitive function
Physical Activity	<ul style="list-style-type: none"> People who engage in high levels of physical activity in mid- or late-life have a lower risk of dementia 	<ul style="list-style-type: none"> Improved cognitive performance in people with and without cognitive impairment after exercise interventions 	<ul style="list-style-type: none"> Further trials examining physical activity interventions (in progress)
Social Engagement	<ul style="list-style-type: none"> Most studies suggest that people with limited social networks and low social engagement have higher risk dementia 	<ul style="list-style-type: none"> No interventions specifically addressing social engagement 	<ul style="list-style-type: none"> Trials examining social interventions (in progress)
Diet	<ul style="list-style-type: none"> Higher intake of anti-oxidants and polyunsaturated fatty acids is generally associated with a lower risk of dementia 	<ul style="list-style-type: none"> Interventions with anti-oxidants and polyunsaturated fatty acids have benefited cognitive performance and the risk of dementia 	<ul style="list-style-type: none"> Additional controlled trials investigating whether nutritional education and diet modification are beneficial to cognitive function
Depression	<ul style="list-style-type: none"> People with depression or high depressive symptoms have a higher risk of developing dementia 	<ul style="list-style-type: none"> Initial evidence suggests treatment improves cognition in people with depression. 	<ul style="list-style-type: none"> Randomized controlled trial investigating whether treatment of depression benefits cognitive function and reduces the risk of dementia