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Review

Targets for the Prevention of Dementia

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Abstract. The prevalence of dementia is expected to increase dramatically over the upcoming decades due to the aging population. Since treatment is still short of a cure, preventative strategies are of the utmost importance. Stimulating activity (cognitive, physical, and social), vascular risk factors, and diet may be important in preventative strategies. Dementia risk may be modified by participation in stimulating activities. One study suggested that the cognitive, physical, and social components of activity were of equal importance to cognitive outcomes. However, while exercise interventions appear to benefit global cognition, the benefits from cognitive training appear to be domain specific. People with vascular risk factors (hypertension, diabetes, dyslipidemia, and obesity) appear to be at higher risk for dementia than those without in observational and clinical trials. Controlled trials suggest that vascular risk management via some pharmaceutical interventions may benefit cognition, though results are inconsistent. Finally, people who adhere to a Mediterranean diet or who have high intake of antioxidants and omega-3 fatty acids have reduced likelihood of dementia in observational studies. However, supplementation in controlled trials has not generally proved successful at improving cognitive outcomes. A single supplement may be insufficient to prevent dementia; it may be that the overall diet is more important. Future large randomized controlled studies should examine whether interventions can reduce the risk of dementia and whether combining cognitive, physical, and social activity, vascular risk reduction, and dietary interventions might have additive or multiplicative effects.

Keywords: Cognitive activity, dementia, diet, physical activity, prevention, social engagement, vascular risk

INTRODUCTION

The prevalence of dementia is expected to rise dramatically over the coming decades due to increasing longevity and the aging of the baby boomer population [1,2]. However, even if cognitive change is likely with aging, dementia is not inevitable. Some people do not develop dementia despite extreme old age and even in the presence of neuropathic features normally associated with dementia [3].

Despite substantial progress, treatment of dementia remains short of a cure [4]. At best, current treatments can slow or delay progression of dementia symptoms [4,5]. As a result, increasing attention is being paid to factors that might prevent or delay the onset of dementia. If preventative strategies can delay dementia onset by 2 years, then up to 25% of dementia cases may be prevented [6].

Understanding how to prevent dementia is critical. By identifying people at risk and implementing preventative interventions, there is potential to reduce the prevalence and costs dramatically. In many cases, the same factors that put people at risk for dementia may be targets for interventions. Here, we will discuss some of

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Table 1
Activity engagement in relation to dementia risk

	Cognitive activity	Physical activity	Social activity
Observational Studies	• Education, occupational attainment, and cognitively stimulating activities are associated with diminished risk of dementia.	• People who are more physically active have lower risk of cognitive decline and dementia.	• People with less social support and low participation in social activities have higher risk dementia
Controlled Trials	• Cognitive interventions appear to improve cognitive function. However, the effects appear to be domain specific.	• Studies generally show that people have improved cognitive performance after exercise interventions.	• No interventions have specifically addressed social engagement or support. However, participation in a volunteer intervention showed a trend towards improved cognitive outcomes.
Future Directions	• Controlled trials should examine cognitive interventions specifically designed to reflect daily life.	• Larger and longer trials examining physical activity in relation to cognition should be performed.	• Controlled trials that investigate social interventions for cognitive outcomes are needed.
	• A large randomized controlled trial combining cognitive, physical, and social activity should be performed to examine its effects on cognitive outcomes relative to single domain interventions.		
Prevention Strategy	• Evidence to date suggests that cognitive and exercise interventions can improve cognitive performance and slow cognitive decline, at least in the short-term. The best potential strategy to prevent dementia might combine all three elements of activity.		

the most promising targets for the prevention of dementia: cognitive, physical, and social activity, vascular risk factors, and diet. We will discuss each factor in two stages: 1) Evidence from observational studies; and 2) Evidence from controlled trials that interventions might reduce risk.

COGNITIVE, PHYSICAL, AND SOCIAL ACTIVITY

In most observational studies, people who engage in higher levels of stimulating activity have lower likelihood of all-cause dementia, Alzheimer's disease (AD), and mild cognitive impairment (MCI) in old age compared to people who engage in lower levels [7–9]. However, there is great variation among activities. The stimulation incurred can include cognitive, physical, and/or social elements. Here, we discuss the benefits of each type of activity. However, if the cognitive, physical, and social components of activity are of equal importance, as suggested by one study [10], then the most successful preventative strategy may incorporate all three elements (Table 1).

Cognitive activity

Observational studies. Aside from age, education is arguably the most established risk factor for dementia. People who are more educated have lower rates of AD and all-cause dementia than those with less education in most studies [11–14]. High levels of education are also associated with slower cognitive decline during normal aging [12,15–17]. In contrast, people who are highly educated may have faster cognitive decline after the onset of AD [12,18–21], though not all studies agree [22]. Some researchers suggest this faster decline occurs because high education causes AD onset to be delayed until the neuropathology is more severe [12]. There is some evidence to support this theory. One study reported that elderly people who were more educated were able to withstand higher degrees of neuropathology without exhibiting the symptoms of dementia compared to those who were less educated [23], a trait referred to by some as "cognitive reserve" [12]. Occupational attainment and leisure activity are also proposed to contribute to cognitive reserve [12].

People who engage in cognitively stimulating activity during leisure time also have reduced risk of dementia. In several prospective, observational studies, people who engaged in mentally challenging activities – such as learning, reading or playing games-both at younger and older ages were less likely to develop dementia compared to those people who did not engage in these activities [24,25].

Controlled trials. Most interventional trials have demonstrated that cognitive training can improve cognitive outcomes in older adults with normal cognition, MCI, or dementia [26–31]. In the ACTIVE trial, a large clinical trial of 2802 elderly people, memory, reasoning, and speed of processing training resulted in cognitive improvements equivalent to a 7- to 14-year reduction of normal aging effects [27]. However, the benefits in this study and others appeared to be domain

specific [26,27]. Several trials concluded that cognitive training improved memory, reasoning, and mental processing speed in older adults, but that the effects did not generalize across domains or improve daily functioning [26].

Future directions. Although the evidence from early trials show that cognitive training may improve specific cognitive outcomes, interventions benefit daily function minimally [26,27]. Future trials should investigate whether adapted, multi-domain interventions designed to mimic daily life might be effective in improving global cognition and daily function. Simple interventions including mental activities such as playing games or learning a new skill, which are associated with reduced rates of dementia and cognitive decline in observational studies [24], might be effective. Trials should also investigate whether cognitive interventions might prevent the onset of dementia in longitudinal studies.

Physical activity

Observational studies. Over the last decade, many studies have examined physical activity in relation to cognition in old age. Though the studies used a variety of age ranges and definitions of exercise, most studies concluded that elderly people who are more physically active had lower risk for dementia [32,33]. The association seems to hold true for both AD and vascular dementia [32,33], though the relationship with AD has been more consistent. Why this is so is unclear but may reflect diagnostic preferences and power to detect difference, where fewer people are diagnosed with vascular dementia than AD in most studies.

In addition to dementia, people who are more physically active have lower rates of cognitive decline and MCI [34–37], though not all studies agree [38]. Since people with MCI have higher risk of dementia [39,40], by preventing MCI, physical activity may also prevent some cases of dementia.

Physical activity appears to be protective both in late-life and in earlier life. Although fewer studies have investigated the association between mid-life physical activity and cognitive impairment, most have found that people who were more active at mid-life had lower incidence of both AD and all-cause dementia in old age [41–43]. However, the protective effect may be more prominent for leisure-time physical activity than work-related physical activity [42,43]. Two studies also suggested that physical activity in early-life can improve cognitive performance in late-life [44,45].

Controlled trials. Physical activity need not be lifelong to be beneficial to cognition. Some exercise interventions with durations of weeks and months have improved cognitive function in people without cognitive impairment, though other studies found no effect [46]. A recent Cochrane review suggested that the strongest effect appeared to be for attention [46]; in contrast, an earlier meta-analysis suggested that the strongest effects were for executive function [47]. Exercise interventions are also associated with slower cognitive decline in people with cognitive impairment [48], indicating physical activity may be useful as a treatment in addition to as a preventative intervention [49,50].

Future directions. Despite the promising results, the controlled trials that have examined exercise interventions in relation to cognition have generally been low to moderate in both size and quality [46]. Larger trials are needed to investigate the role of physical activity in relation to cognitive performance and the incidence of dementia. Such trials are underway – for example, the Lifestyle Interventions and Independence for Elders (LIFE) study will begin in 2010 and will randomize 1600 people to either exercise or control groups and follow them for an average of 2.7 years. The LIFE study includes cognitive function as a secondary outcome [51]. While we wait for results from ongoing trials, physical activity can be carefully recommended, if not for cognitive impairment, then for other health outcomes strongly linked to physical activity such as cardiovascular disease and some types of cancer [52, 53].

Social engagement

Observational studies. Higher social engagement, measured in a variety of manners, appears to be associated with reduced risk of dementia. People who have an extensive social network have lower likelihood of dementia than those with few social connections [54]. Participation in socially engaging leisure activities – such as visits with friends and relatives, going to movies, clubs, centers, and church/synagogues, and volunteering – is also associated with reduced risk of dementia [55]. Some suggest that social activity may increase the ability to handle neuropathological load without showing symptoms of cognitive impairment ("cognitive reserve"), as suggested with cognitive activity, so that people can maintain cognitive performance even with neuropathic features normally associated with dementia [55]. However, another study indicated that the relationship between low social en-

gagement and the risk of dementia may be restricted to those subjects who experienced a decline in social engagement from mid-life to late-life [56]. This suggests that low social engagement may be an early symptom of cognitive impairment rather than a risk factor.

Controlled trials. We are aware of no controlled trials that have examined social engagement on its own in relation to dementia risk or cognitive outcomes. As a result, the importance of social engagement in a successful prevention strategy is still unclear. However, a volunteering intervention that was designed to include social, cognitive, and physical components showed a trend towards improved cognition in the intervention group compared to a control group [57]. The volunteering intervention appeared to be most beneficial for those with baseline cognitive impairment [57]. Larger studies should evaluate whether social and multidomain interventions (cognitive, physical, and social) might be able to improve cognitive outcomes in those at risk for dementia.

VASCULAR RISK FACTORS

Observational studies

People with vascular risk factors are at higher risk not only for vascular dementia but also for AD. Both vascular dementia and AD share many risk factors (hypertension, diabetes, elevated cholesterol) and pathologic features (inflammatory markers, protein misfolding) with cardiovascular disease [58]. Even mild cerebrovascular disease appears to increase the risk of cognitive impairment for any level of AD pathology [59].

Hypertension is arguably the most studied vascular risk factor in relation to dementia, with inconsistent results. Mid-life hypertension was associated with increased likelihood of dementia in late-life in a number of observational studies [60,61]. However, the relationship between late-life hypertension and cognitive impairment is less clear. Both high systolic blood pressure and low systolic blood pressure have been associated with augmented risk for dementia [61,62]. Another study found no association between blood pressure and the incidence of dementia [63]. The reason for these inconsistent results may be that hypertension is a risk factor for dementia but that hypotension is an early-symptom of the disease.

If hypertension in mid-life is a risk factor for dementia, then antihypertensives have the potential to reduce the risk of dementia in people with hypertension. In observational studies, this appears to be the case. People with hypertension who took antihypertensives had lower risk of dementia than those who do not [64–66]. However, the results from controlled trials (discussed below) are less consistent. It may be that older, sicker patients who were likely to develop dementia in observational trials were also less likely to receive treatment for hypertension.

There is general accord that people with diabetes in late-life have higher risk of dementia and MCI compared to those who do not [67–69], though some studies show no association [70]. Similarly, mid-life diabetes is associated with augmented risk of dementia in some but not all studies [70]. The relationship with diabetes seems to be stronger and more consistent for vascular dementia and vascular cognitive impairment-no dementia than for AD or amnestic MCI [70–73]. Counter intuitively, some studies report that people who are treated for diabetes have a greater likelihood of dementia than those who are not [68,74]; however, this relationship is likely confounded by severity, where people who receive treatment have more severe diabetes than those who do not. Diabetics with hypoglycemic episodes, a complication of uncontrolled diabetes, also have a higher risk of dementia [75].

Diabetes is also associated with faster cognitive decline in normal aging [76]. In contrast, diabetics have slower cognitive decline after AD onset [77], perhaps. The slower decline after AD onset may occur because diabetics have less severe AD neuropathic features at AD onset [78]. One study suggested that people with dementia who have type 2 diabetes have a fewer plaques and neurofibrillary tangles than people with dementia only [78], indicating that diabetics may have more severe symptoms of cognitive impairment for a given level of neuropathology.

Other vascular risk factors are also associated with rates of cognitive impairment, though evidence is more limited. Obesity at mid-life, as measured using body mass index (BMI) or waist circumference, is associated with higher likelihood of dementia in late-life [79,80]. However, the relationship is less consistent in later life. In people 76 years and older, is relationship between BMI and dementia may resemble a U-shaped curve, where those with very high or low BMI have higher risk of dementia [81]. It is possible that high body fat is a risk factor for dementia while weight loss is a symptom of dementia pathology prior to diagnosis.

Dyslipidemia is also associated with enhanced risk of cognitive impairment in old age. People with high levels of low-density lipoproteins in late life have in-

creased risk of cognitive impairment and dementia with stroke [82,83]. A number of observational trials have examined whether statin therapy might reduce the risk of cognitive impairment in people with dyslipidemia but the results are not convincing. Most cross-sectional studies found a link between statin use and reduced likelihood of dementia but longitudinal studies did not [84].

Vascular risk factors frequently occur in clusters. A cluster of three or more vascular risk factors (hypertension, hyperglycemia, abdominal obesity, and/or low high density lipoprotein) is referred to as the metabolic syndrome. People with the metabolic syndrome also had augmented risk of cognitive impairment and cognitive decline in a number of studies [85–87]. The effects of each vascular risk appeared to be approximately additive in one study [88]. Interestingly, another study found that metabolic syndrome was associated with slower cognitive decline in the oldest old [89]. Why this is so is unclear but may reflect selective survival in the very old.

Controlled trials

The evidence from controlled trials regarding vascular risk factor management for the prevention of dementia is not conclusive. Results from randomized controlled trials examining antihypertensive medication use in relation to cognition have had inconsistent results [90–92]. However, the results from the Hypertension in the Very Elderly Trial (HYVET) favored treatment of hypertension to improve cognitive outcomes when combined into a meta-analysis with previous results [91]. However, most trials – including HYVET – were designed to examine other primary outcomes [91,92]. The trials did not include detailed cognitive measures and may not be powered sufficiently to detect change in cognitive outcomes.

Despite some promising results from observational studies and smaller trials that suggested that statin use improved cognitive outcomes in people with hypercholesterolemia [90], these results were contradicted by two large, randomized controlled trials. Each trial concluded that statin therapy did not improve cognitive outcomes [93,94]. Consequently, current evidence suggests that statin therapy may not have a role in dementia prevention.

Results from one study favored glycemic control through medical management in type 2 diabetics to improve cognitive outcomes; however the trial was not placebo controlled [95]. Consequently, the results are very preliminary. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) Memory in Diabetes Study (ACCORD-MIND) examined whether intense glycemic control improved cognitive outcomes relative to standard care in type 2 diabetics who are 60 years or older [96]. At baseline, those with better blood sugar control as measured by A1C had higher cognitive performance on a number of tests [97]. Although the longitudinal cognitive results have not yet been released, the main ACCORD trial was terminated early due to an excess of deaths in the intense glycemic control group relative to the standard control group [98]. It is unlikely that any potential cognitive benefits could justify intense glycemic control given these results.

Future directions

There are several areas that still need to be studied with regards to vascular risk management and cognition. Lifestyle management should be examined in relation to cognitive outcomes in people with high vascular risk. In addition, a large, randomized controlled trial of medical management for glycemic control in diabetics is needed to definitely determine whether standard glycemic control improves cognitive outcomes; however, given the cardiovascular benefits of standard glycemic control, a randomized controlled trial to examine the cognitive benefits is unlikely to occur.

Despite the inconsistent or missing results regarding vascular risk management, it is relatively agreed that people with vascular risk factors are at higher risk for dementia than those without vascular risk factors. As a result, clinicians treating people with vascular risk factors should be aware of and screen for symptoms of cognitive impairment. Preventative strategies – which may include lifestyle management and medications targeting dementia pathologic features – may be efficacious in reducing the likelihood of dementia in this high-risk group.

DIET AND SUPPLEMENTATION

Observational studies

Many risk factors (hypertension, diabetes, and obesity) and pathologic features (inflammation) of dementia can be modified by diet so it is reasonable to suggest that diet may alter the risk of dementia. In most studies, adherence to a Mediterranean diet is associated with lower likelihood of AD and dementia, as is greater consumption of fruits and vegetables [99–101]. Adherence

to a Mediterranean diet may also slow cognitive decline [100]. Other studies found that people who consume high amounts of fish have lower risk of dementia and slower cognitive decline in old age [102–105]. The reason for the association between fish, fruit, and vegetable intake and dementia risk has not been definitely identified but may be related to anti-oxidative, anti-inflammatory, or metabolic effects. On a component level, some attribute the relationship between the Mediterranean diet and cognition to antioxidants and/or polyunsaturated fatty acids, where consumption of each is associated with reduced risk of dementia and improved cognition in observational studies [104, 106–109]. However, it may be that overall diet is more important than any one component.

Antioxidant intake, either through diet or supplementation, was proposed to modify dementia risk by combating oxidative stress, which is associated with augmented AD pathology [110]. Some observational studies supported this theory and suggested that people who took vitamin E and C supplements (antioxidants) had slower cognitive decline and a lower risk of AD in old age than those who did not [107]. However, other large, prospective, observational studies found no association between vitamin intake and dementia risk [111, 112]. As discussed below, the results from controlled trials do not support supplementation for dementia prevention.

Controlled trials

Most randomized controlled studies that investigated vitamin E supplementation for cognitive performance found no difference between the intervention and control groups [113–116]. This suggests that the associations in observational studies may be due to uncontrolled confounding or other biases rather than causation. Alternatively, vitamin supplementation may only be beneficial for those who are vitamin deficient.

Studies regarding consumption of long-chain omega-3 fatty acids, one type of essential polyunsaturated fatty acid that is common in many types of fish, have been similarly inconclusive [117,118]. Despite associations in observational studies, randomized controlled trials have not consistently found an association between omega-3 fatty acid supplementation and cognitive outcomes [117]. Omega-3 fatty acid supplementation had no effect on memory and attention in cognitively healthy elderly people [118]. However, most studies have been limited by a short follow up period.

Future directions

The relationship between diet and dementia is likely confounded by numerous variables such as education, physical activity, vascular disease, and socioeconomic status. This may explain the inconsistent results of observational and controlled trials. Alternatively, it may be that one supplement is not sufficient to improve cognition or prevent dementia but that it is the overall diet and lack of deficiencies that optimizes cognitive outcomes. Interventions should examine the association between supplementation and cognitive outcomes in people who are vitamin deficient versus sufficient. In addition, overall dietary education and modification may have more of an effect than individual supplements. However, given that adherence to a Mediterranean diet is associated with reduced risk of mortality and cardiovascular disease [119], people who adopt healthy diets are likely to have positive health outcomes regardless of the effect on cognitive functioning.

Increasing attention has recently been paid to vitamin D as a means to prevent dementia. Although evidence is very preliminary and generally cross-sectional, some studies suggest that higher serum 25-hydroxyvitamin D may be associated with better global cognition [120]. Vitamin D is also associated with a number of risk factors for dementia including diabetes, cerebrovascular disease, and depression [121]. Future prospective observational and controlled trials should examine vitamin D intake in relation to cognition, particularly in institutionalized elderly people who are likely to be deficient in vitamin D.

CONCLUSION

Cognitive, physical, and social activity, vascular risk factors, and diet are associated with the likelihood of dementia in many observational studies. Modification of each presents a potential strategy to prevent dementia (Fig. 1). Randomized controlled trials have supported activity interventions most strongly, followed by vascular risk factor modification. However, the best strategy to prevent dementia is still unclear. Given that the risk factors are largely correlated – people who are more active generally have better diet and lower vascular risk, it may be that living a healthy, engaged life is the best way to prevent dementia and that any one single factor is insufficient to prevent the disease. Future trials should continue to examine the implication of risk factor modification and, in particular, how we might combine interventions for optimal results.

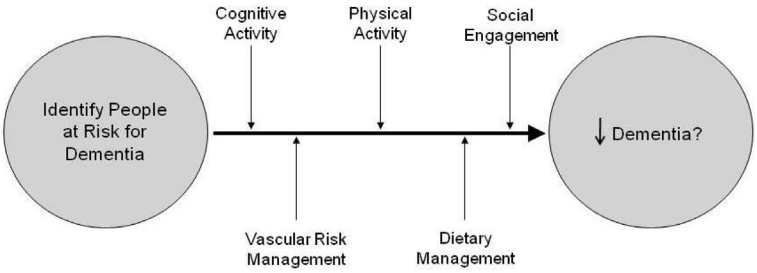

Fig. 1. Potential strategies for preventing dementia.

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