

Prevention of late-life dementia: what works and what does not

Philip W. Tipton, Neill R. Graff-Radford

Department of Neurology, Mayo Clinic, Jacksonville, Florida, United States

KEY WORDS

Alzheimer disease, dementia, dementia prevention, lifestyle modification

ABSTRACT

Advances in the treatment and prevention of disease have contributed to an aging global population. Subsequently, there is an increasing prevalence of age-related conditions, such as dementia. There are currently no disease-modifying therapies commercially available, and there is a growing emphasis on strategies to prevent dementia. We have reviewed the relevant literature pertaining to dementia risk and putative prevention factors. We present our findings by summarizing the pertinent items that may play a role in prevention and conclude our recommendations at this time.

Introduction Life expectancy has increased over the past 100 years. This has been attributed to advances in areas such as nutrition, education, sanitation, and medicine.¹ Developments in medical science have been critically important to these advancements as the world has progressed through mortality milestones. Exactly 100 years ago, the globe was shaken by the 1918 influenza pandemic, illustrating the impact of infectious diseases at the time. With the advent of antibiotics and vaccinations, the era of infectious diseases gave way to a time where mortality became dominated by heart diseases and cancer. Improved strategies to manage cardiovascular risk factors, as well as treat cardiac disease and cancer, have lessened their grip upon the global society. From 2000 to 2014, the United States saw a decrease in the percentage of deaths due to heart disease (by 14%), stroke (by 21%), breast cancer (by 1%), prostate cancer (by 9%), and HIV (by 54%).²

Neurodegenerative diseases are age-related, meaning that their prevalence increases as more persons live into the risk period. Many of these diseases result in dementia, of which Alzheimer disease (AD) is the most common, accounting for 60% to 80% of all cases of dementia.³ From 2000 to 2014, the percentage of deaths attributed to AD increased by 89%.^{2,4} Unfortunately, no treatment has been discovered to delay or prevent the disease so there has been a substantial increase in AD prevalence. In 2016, the estimated number of 47 million individuals with dementia worldwide was projected to triple by 2050.

The 2016 estimate of \$818 billion for dementia-related expenses is expected to surpass 1 trillion dollars by the end of 2018.⁵ With these figures in mind, it is paramount that we try to prevent these diseases.

The purpose of this review is to summarize the pertinent factors that may play a role in prevention and to conclude the most reasonable recommendations at this time.

Associations and risk factors for dementia As in all diseases, risk factors can be divided into modifiable and nonmodifiable ones. The nonmodifiable risk factors include sex, genetics, and age. Our understanding of genetic associations has substantially increased with advances in genetic techniques. While early studies identified a small proportion of patients with causative mutations (eg, *APP*, *PSEN1*, and *PSEN2*), other genetic modifications, such as the presence of the APOEε4 allele, have been demonstrated to pose an increased risk of developing AD. Many risk gene variants that are more prevalent in the population but impose a relatively low risk of AD have been identified; however, this risk begins to increase when multiple risk gene variants are combined.⁶

To address the topic of prevention, a more thorough discussion of modifiable risk factors is warranted. In 2015, numerous modifiable risk factors were identified in the National Institute of Health and Care Excellence and National Institutes of Health guidelines.^{7,8} Livingston et al⁹ have recently assigned a percentage attributable fraction

Correspondence to:
Philip W. Tipton, MD,
Department of Neurology, Mayo Clinic,
4500 San Pablo Rd, Jacksonville,
Florida 32224, United States,
phone: +1 904 953 2623,
email: tipton.philip@mayo.edu
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to each of these risk factors to quantify their relative contribution to the overall risk pool. Lower education level was the sole early-life risk factor, while hearing loss, hypertension, and obesity were identified as midlife risk factors. Late-life modifiable risk factors included smoking, depression, physical inactivity, social isolation, and diabetes mellitus. Below we address each of these risk factors and others in more detail.

Education Factors such as the level of education have been investigated as potential risk modifiers. A reduction in risk of dementia among individuals with an education level of high school graduate or higher was reported (hazard ratio [HR], 0.77; 95% confidence interval [CI], 0.67–0.88).¹⁰ It is unclear if education beyond high school provides an additional protective effect. One theory to explain these findings is called cognitive reserve, which has received a substantial amount of attention within the scientific literature ever since the Katzman's observation that some patients with postmortem AD pathology were asymptomatic.¹¹ These patients were found to have an increased number of large pyramidal neurons. It is currently unclear whether this resilience is the result of a more favorable brain parenchyma substrate or more effective utilization of brain networks resulting in a higher symptomatic threshold to cognition-related pathology.¹²

Another factor that is intertwined with education is innate cognitive ability. For example, the Scottish Mental Survey of 1932 gathered IQ scores for all children born in 1921 and attending school in Scotland.¹³ A subsequent study found that children who had higher IQs at the age of 11 years had less chance of developing dementia in their 70s.¹⁴ Many hypotheses have been put forward on the basis of these data. For example, researchers investigated if intellectually gifted children go on to have more education and perform cognitively challenging jobs or if the factors that make children intellectually more talented also decrease the chance of dementia.

Sensory impairment Studies indicated, through retrospective analysis, that hearing loss is a risk factor for cognitive decline.^{15–20} There is now a substantial amount of supportive evidence from prospective studies.^{21–24} Hearing loss is associated with an increased incidence of dementia and also a faster rate of cognitive decline even when controlling for other potential confounders such as age, APOEε4 allele status, and education.²⁵ Cognitive decline appears greatest in individuals with severe hearing loss who do not use hearing aids.²⁶ Even self-reported hearing impairment has been associated with accelerated cognitive decline that is attenuated with the use of hearing aids.²⁷ Some studies have failed to show an association between hearing loss and cognitive decline.^{28,29} A large retrospective longitudinal study showed no association in unilateral hearing loss, while bilateral and side-unspecified

hearing loss cohorts were associated with higher risk of dementia incidence.³⁰ A recent meta-analysis demonstrated that cognitively normal individuals with hearing loss were at greater risk of developing dementia (relative risk [RR], 1.94; 95% CI, 1.38–2.73).⁹

Visual impairment has also been implicated as a risk factor for cognitive dysfunction. Best corrected vision worse than 20/40 was associated with accelerated cognitive and functional decline.^{16,17} However, a recent longitudinal study showed no association between the incidence of dementia and visual impairment defined as best corrected vision of worse than 6/12 in the more impaired eye.²⁹

Cerebrovascular risk factors Cerebrovascular risk factors of hypertension, hyperlipidemia, obesity, and diabetes mellitus are associated with an increased risk of dementia. Among the cerebrovascular risk factors, hypertension has the greatest attributable risk during midlife while diabetes has the greatest risk in late life.^{9,31} A recent meta-analysis found hypertension, heart disease, dyslipidemia, and diabetes to be associated with an increased risk of vascular dementia but not AD.³² Suri et al³³ recently reported an association between asymptomatic intracranial atherosclerosis, measured by 3-Tesla magnetic resonance angiography, and cognitive impairment/dementia in white males. Hughes et al³⁴ demonstrated that arterial stiffness, measured by pulse wave velocity, was associated with lower brain volumes in AD-susceptible regions.

Smoking Smoking is associated with dementia, with a global percentage attributable risk for AD of 19.1%, based on data from 2010.³⁵ A meta-analysis revealed a population attributable fraction for all-cause dementia of 5.5%.⁹ The mechanisms for this effect are incompletely understood but the suspects include oxidative stress, inflammation, and atherosclerotic processes.³⁶ A recent meta-analysis demonstrated an increased risk of all-cause dementia (RR, 1.30; 95% CI, 1.15–1.66), AD (RR, 1.40; 95% CI, 1.13–1.73), and vascular dementia (RR, 1.38; 95% CI, 1.15–1.66).³⁷ Moreover, the authors also found that smoking cessation decreases this risk to that of never smokers.

Depression and anxiety The relationship between dementia and depression is complex given the challenge in determining if depression is a part of the dementia syndrome or a risk factor. The latter is strengthened by findings from the Baltimore Longitudinal Study of Aging, which demonstrated a correlation between the number of depressive episodes and the risk of dementia.³⁸ A meta-analysis of several studies demonstrated that individuals with depression have an increased odds of developing all-cause dementia (odds ratio [OR], 1.64; 95% CI, 1.49–1.81), AD (OR, 1.40; 95% CI, 1.29–1.53), and vascular dementia (OR, 1.64; 95% CI, 1.42–1.89).³² The same

meta-analysis included 2 studies showing an increased OR of developing all-cause dementia among individuals with anxiety (OR, 2.05; 95% CI, 1.29–3.28).

Physical activity Physical activity helps reduce the risk of cerebrovascular diseases, diabetes, obesity, and hypertension.³⁹ This may explain, in part, the inverse relationship between physical activity and the risk of cognitive decline.^{40,41} A previous meta-analysis of 16 prospective studies found that higher levels of physical activity were associated with a lower risk of dementia (RR, 0.72; 95% CI, 0.60–0.86) and AD (RR, 0.55; 95% CI, 0.36–0.84).⁴² However, this study excluded cases of dementia without a diagnosis of neurodegenerative disease. Sofi et al⁴³ aimed to determine the effect of physical activity on cognitive decline among individuals without dementia. Their meta-analysis of 15 prospective studies demonstrated that subjects who performed a high level of physical activity were significantly protected against cognitive decline at follow-up (HR, 0.621; 95% CI, 0.54–0.70).⁴³ In the Dominantly Inherited Alzheimer Network study,⁴⁴ individuals carrying an autosomal dominant AD gene mutation who did more aerobic exercise accumulated less amyloid in the brain measured on positron emission tomography scan. A recent study of Swedish women found that high cardiovascular fitness in midlife, as measured by maximal ergometer cycling testing, was associated with a decreased risk of incident dementia over a 44-year follow-up (HR, 0.12; 95% CI, 0.03–0.54).⁴⁵

One of the most compelling studies is a randomized single-blind prospective trial on 120 cognitively normal individuals who were randomized to either toning, stretching, and balancing or aerobics.⁴⁶ After 1 year, those in the aerobics group showed an increase in anterior hippocampal volume and improvements in spatial memory. Hippocampal volume correlated with fitness and greater serum levels of brain-derived neurotrophic factor. A recent literature review looked at the evidence supporting several forms of physical activity as a preventative measure against cognitive decline and Alzheimer-type dementia but was not conclusive.⁴⁷

Social isolation There is a growing body of evidence suggesting that social isolation is a risk factor for hypertension,⁴⁸ coronary heart disease,⁴⁹ and depression,⁵⁰ all of which have been established as risk factors for cognitive decline.³² A European study found that both men and women from Finland and Denmark with less social contact had greater functional decline at 5-year follow-up.⁵¹ A large meta-analysis including 308 849 individuals found an association between survival and complex measures of social integration (OR, 1.91; 95% CI, 1.63–2.23).⁵² A recent meta-analysis by Kuiper et al⁵³ assessed 19 prospective studies to find a relationship between several social relationship factors and the risk of

incident dementia.⁵³ Specifically, low social participation (RR, 1.41; 95% CI, 1.13–1.75), less frequent social contact (RR, 1.57; 95% CI, 1.32–1.85), and more loneliness (RR, 1.58; 95% CI, 1.19–2.09) were associated with incident dementia. These findings underscore the importance of social relationships and a strong support network.

Alcohol use The complex effect of alcohol on neurological function has led some authors to suggest a U-shaped relationship between alcohol consumption and negative brain outcomes.⁵⁴ Light-to-moderate drinking has been associated with a lower risk of dementia,^{55,56} whereas chronic heavy alcohol use is associated with well-established entities, such as Korsakoff syndrome. Moderate alcohol use has been less clearly defined with regard to the risk of adverse cognitive outcomes. A recent study in the United Kingdom demonstrated a dose-dependent relationship between alcohol consumption and hippocampal atrophy, with a faster decline in lexical fluency among those with higher alcohol use.⁵⁴ This study, consisting of 30 years of recurrent cognitive testing, failed to demonstrate a protective effect of light drinking, raising concerns regarding previous claims of a protective effect of light alcohol intake.

Diet There appears to be an association between dietary nutrients and cognitive performance.^{57,58} Oxidative stress and vascular impairments are thought to contribute to cognitive decline. This has led many investigators to focus efforts on the role of antioxidants in disease prevention. The Mediterranean diet contains many antioxidant-rich foods, such as nuts, berries, and red wine. The Prevención con Dieta Mediterránea (PREDIMED) was a multicenter trial of 7447 people with high cardiovascular risk that were randomized to a Mediterranean diet supplemented with extra-virgin olive oil, a Mediterranean diet supplemented with mixed nuts, or a control diet (low-fat).⁵⁹ Those in the treatment groups experienced a reduced incidence of major cardiovascular events. Valls-Pedret et al⁶⁰ followed 447 cognitively healthy persons enrolled in PREDIMED.⁶⁰ They found that the Mediterranean diet supplemented with olive oil or nuts is associated with improved cognitive function measured by changes in memory and frontal cognition scores. A separate study of 552 PREDIMED participants showed cognitive improvements measured by the Mini-Mental Status Examination and clock-drawing test.⁶¹ The Dietary Approaches to Stop Hypertension (DASH) diet is also associated with neurocognitive improvements in executive function, memory, and learning.⁶²

Morris et al⁶³ proposed a hybrid of the Mediterranean and DASH diets called the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND), which emphasizes the components of each diet thought to provide neuroprotection.⁶³ They found that the MIND diet was associated with a slower rate of cognitive decline.

A subsequent study compared the Mediterranean, DASH, and MIND diets to determine their effect on the incidence of AD in 923 individuals.⁶⁴ They found that high adherence to all 3 diets was associated with a reduced risk of AD, while moderate adherence to the MIND diet still resulted in a decreased, although to a lesser degree, risk of AD.

Medications Several classes of medications have been implicated in the development of cognitive dysfunction. However, with improved study measures, many of these assumptions have been disproven. Such is the case of statin use, which was reported with memory loss and confusion that resolved after medication usage was stopped.⁶⁵ Since that time, studies have not substantiated this claim. A meta-analysis encompassing 23 443 patients demonstrated no significant differences in cognitive measures among those with statin therapy compared with placebo.⁶⁶ More recently, Zissimopoulos et al⁶⁷ analyzed the association between statin use and AD incidence for men and women of different races / ethnicities, using the 4 most commonly prescribed statins (simvastatin, atorvastatin, pravastatin, and rosuvastatin). They found a decrease in AD incidence among all statin users, which was statistically significant in all groups except for black men.⁶⁷

Research in animal models has demonstrated that lansoprazole promoted higher A β 40 levels in the brain⁶⁸ by increased amyloid production. Proton pump inhibitors (PPIs) are associated with vitamin B₁₂ deficiency, which, in turn, can lead to neurologic symptoms such as dementia.⁶⁹ In recent years, several large prospective trials have been conducted to assess the risk of dementia with the use of PPIs. Data from 3076 patients in the German Study on Aging, Cognition and Dementia in Primary Care Patients found that patients receiving PPIs had an increased risk of all-cause dementia (HR, 1.38; 95% CI, 1.04–1.83).⁷⁰ In the following year, Gomm et al⁷¹ found similar results in their prospective study of 73 679 participants derived from the largest German statutory health insurer. They found that those receiving regular PPI medication had increased risk of incident dementia compared with those not receiving PPI medication (HR, 1.44; 95% CI, 1.36–1.52).⁷¹ Conversely, a prospective study of 13 864 middle-aged and older women in the Nurses' Health Study II found no convincing association between PPI use and cognitive function.⁷² In the same year, Taipale et al⁷³ looked at all 70 718 community-dwelling individuals diagnosed with AD during the years 2005 to 2011 in Finland and found no association with PPI use. More recently, Gray et al⁷⁴ performed cognitive screening on 3484 individuals every 2 years for a mean follow-up of 7.5 years. They found that the use of PPIs, even at high cumulative exposure, was not associated with the risk of dementia or AD.

Anticholinergic medications are widely used for conditions ranging from overactive bladder to seasonal allergies. While many of these agents

require a prescription, many others are available as over-the-counter purchases. It has been well-demonstrated that acute effects of anticholinergics on the central nervous system may include a variety of psychiatric and cognitive disturbances, such as deficits in memory, attention, agitation, hallucinations, and overt delirium.⁷⁵ Elderly patients are more susceptible to these effects than younger individuals.⁷⁶ This is thought due to an age-related decrease in cholinergic neurons and/or receptors, less efficient hepatic metabolism and renal excretion of medications, and increased blood-brain barrier permeability.⁷⁷ Despite a lack of compelling evidence, these effects have generally been thought to be transient and reversible. Gray et al⁷⁸ followed 3434 cognitively normal individuals with cognitive evaluation biennially for a mean follow-up time of 7.3 years. They found higher cumulative anticholinergic use to be associated with increased risk for dementia.⁷⁸

Vitamin deficiency Several vitamin deficiencies have been associated with an increased risk of developing cognitive impairment. Travica et al⁷⁹ conducted a systematic review, which demonstrated higher mean vitamin C concentrations in cognitively intact individuals compared with those who were cognitively impaired.⁷⁹ Moreover, there appears to be a potential association between plasma vitamin C concentrations and cognition; however, optimal vitamin C levels have not been established. Littlejohns et al⁸⁰ identified an association of vitamin D deficiency with an increased risk of all-cause dementia and AD. High vitamin E levels have been associated with a reduced risk of developing AD.⁸¹ The proposed mechanism behind the potentially protective effect of vitamin E is rooted in its antioxidant properties, given the growing body of evidence suggesting that free radical formation may play a role in the pathophysiological mechanism underlying AD. However, supplementation should be reserved for use only when vitamin E levels are low and then used with caution. A meta-analysis by Miller et al⁸² concluded that high-dosage (≥ 400 IU/d) vitamin E supplements may increase all-cause mortality.

Plasma levels of total homocysteine reflect the functional status of 3 B vitamins (folate, vitamin B₁₂, and vitamin B₆), and elevated homocysteine level is a risk factor for the development of cognitive decline, white matter changes, brain atrophy, neurofibrillary tangles, and dementia.^{83,84} In 2002, Seshadri et al⁸⁵ demonstrated a concentration-related effect of baseline total homocysteine levels with the risk of incident dementia (RR, 1.4; 95% CI, 1.1–1.9) in 1092 cognitively normal individuals from the Framingham cohort.

Sleep apnea Obstructive sleep apnea (OSA) has been associated with neurocognitive and cardiovascular morbidities.⁸⁶ Neuropsychological deficits of attention / vigilance, delayed long-term visual and verbal memory, visuospatial / constructional abilities, and executive functioning appear

TABLE 1 Multidomain strategy for dementia prevention

Diet and supplementation
Mediterranean diet
MIND diet ^a
Vitamin B complex if deficient
Vitamin C if deficient
Vitamin D if deficient
Vitamin E in food such as nuts
Exercise
Regular aerobic exercise (at least 150 min/wk)
Cognitive training
Learn new skills, participate in cognitively challenging activities, eg, cross word puzzles
Socialization
Stay socially active with an active support network
Cerebrovascular risk reduction
Practice good sleep hygiene
Good control of hypertension, hyperlipidemia, diabetes mellitus
Avoid the use of tobacco products
Manage weight to an age-appropriate body mass index
Miscellaneous
Treat sleep apnea
Practice good oral hygiene
Avoid exposure to loud noises and treat hearing impairment appropriately
Minimize the use of anticholinergic medications
Avoid heavy alcohol use
Adequately treat depression and anxiety

a See the Diet section and Morris et al.⁶³

most often associated with OSA.⁸⁷ Canessa et al⁸⁸ demonstrated improvements in cognitive function and increased volumes of hippocampal and frontal structures after only 3 months of treatment for OSA.⁸⁸ Other studies have demonstrated that continuous positive airway pressure treatment of OSA improves executive dysfunction, delayed long-term verbal and visual memory, attention/vigilance, and global cognitive functioning.⁸⁷

Dental hygiene Oral health problems, such as periodontitis, are more prevalent with increasing age and have been associated with cognitive dysfunction. Noble et al⁸⁹ used a serological marker of periodontitis, immunoglobulin G (IgG) for *Porphyromonas gingivalis*, to demonstrate an association with impaired delayed memory and calculation. IgG levels of other periodontal microbiota (*Actinomyces naeslundii* and *Eubacterium nodatum*) have been associated with an increased incidence of AD.⁹⁰

Preventative strategies Prescription medications While many studies have demonstrated risk factors for cognitive decline, incident dementia, and AD, there are far fewer studies that have converted this information into effective preventive measures. Various pharmacological interventions have been assessed, including dementia medications, antihypertensives, diabetes

medications, nonsteroidal anti-inflammatory drugs, aspirin, and lipid-lowering agents. Butler et al⁹¹ reviewed 51 unique trials and found multiple limitations including high attrition, short follow-up, inconsistent cognitive outcomes, and possible selective reporting.⁹¹ For these reasons, they conclude that evidence does not support the use of any of these pharmacological treatments for cognitive protection.

Over-the-counter medications In a similar review, Butler et al⁹² reviewed 56 unique studies that assessed the efficacy of over-the-counter supplements as cognitive protection. Represented studies assessed ω -3 fatty acids, soy, ginkgo biloba, B vitamins, vitamin D plus calcium, vitamin C or β -carotene, and multi-ingredient supplements. Due to high attrition, short follow-up, and the use of a highly variable set of cognitive outcome measures, the authors concluded that evidence is currently insufficient to recommend any over-the-counter supplement for cognitive protection.

Cognitive training Cognitive training has been studied as a means for preventing cognitive decline. Butler et al⁹³ conducted a systematic review representing 6 trials looking at populations with normal cognitive function. The authors concluded that in older adults with normal cognition, training improves cognitive performance in the domain trained, while evidence regarding prevention/delay of cognitive decline or dementia was insufficient due to heterogeneous interventions and outcome measure, outcomes that mostly assessed test performance rather than global function or dementia diagnosis, and potential publication bias. The ACTIVE study⁹⁴ was a randomized, controlled single-blind trial with 3 intervention groups that participated in 10 training sessions for memory, reasoning, or speed-of-processing, with 4-session booster training at 11 and 35 months after training. Ten-year follow-up data revealed that each intervention group experienced less decline in self-reported instrumental activities of daily living compared with controls.⁹⁵ Furthermore, reasoning and speed-of-processing training resulted in improved scores in the area of training.

Exercise While there is compelling evidence that exercise is healthy for the brain (see the Physical activity section), this has not been translated into effective prevention or treatment after the onset of dementia symptoms. A systematic review of various physical activity interventions by Brasure et al⁹⁶ included 32 trials with several limitations including heterogeneous interventions and cognitive testing measures, small and underpowered studies, and inability to assess the clinical significance of cognitive test outcomes.⁹⁶

Multidomain intervention The multidomain intervention was conducted by Ngandu et al⁹⁷ in the FINGER trial and consisted of 1260 individuals

who were randomized to the intervention (nutritional intervention, a physical exercise training program, cognitive training, and vascular risk monitoring) or control groups. At 2-year follow-up, the intervention group demonstrated 25% greater improvements on neuropsychological testing in specific cognitive domains of executive function, attention, and processing speed.

Conclusions Despite the lack of level 1 evidence for most strategies, some activities associated with good brain health are reasonable to recommend. Evidence does suggest that the multidomain approach will likely provide the greatest degree of protection; however, the details of this approach remain incompletely studied. Based on the findings in this review, we recommend several interventions that are generally associated with overall wellness (TABLE 1). The rise in prevalence of cognitive impairment increases the urgency to find better means of prevention. We expect that the results of ongoing and future studies will lead to improved strategies for the prevention of cognitive decline and dementia.

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