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Nonpharmacologic Treatment and Prevention Strategies for Dementia

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ABSTRACT

Purpose of Review: Epidemiologic studies can provide critical evidence to inform the timing and duration of nonpharmacologic interventions. Although more studies are needed to further determine long-term efficacy, the evidence supporting modifiable risk factors for prevention is compelling, and prevention strategies that incorporate multidomain nonpharmacologic factors may have the most impact.

Recent Findings: Epidemiologic studies have identified a number of promising nonpharmacologic factors that have the potential to lower the risk of developing dementia.

Summary: Potential modifiable strategies for dementia prevention include cardiovascular risk factors; lifestyle risk factors such as physical, cognitive, and social activity as well as nutrition, smoking, and alcohol use; and sleep quality. Results of randomized controlled trials for the treatment of cardiovascular risk factors have not been consistent, while interventions that increase physical, cognitive, and social activity have demonstrated protective effects for dementia risk. Trials of single-nutrient dietary supplementation have also been conflicting, but focus on multinutrient supplementation shows promise. Observational data also indicate that sleep quality may be a modifiable risk factor for dementia prevention.

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INTRODUCTION

Evidence from epidemiologic studies has been crucial in identifying several potential modifiable risk factors for dementia. Although new disease-modifying drugs are currently under investigation, recent pharmacologic trials have not been very successful. It may still be years before an effective drug is available for prevention of Alzheimer disease (AD). Although a consensus report from the NIH determined that the body of proof for modifiable risk factors is not yet conclusive,[1] nonpharmacologic strategies may be promising alternatives, with several already under investigation in randomized controlled trials. In addition, epidemiologic studies of these modifiable risk factors can help facilitate the transition from observational data to effective prevention. This review summarizes the major nonpharmacologic risk factors with potential effects on dementia prevention.

CARDIOVASCULAR RISK FACTORS

A number of cardiovascular risk factors have demonstrated a strong relationship with cognitive decline and dementia, including hyperlipidemia, hypertension, obesity, and diabetes.[2] These findings are strengthened by

studies investigating the association between metabolic syndrome (a constellation of cardiovascular risk factors) and cognitive function.[3] In epidemiologic studies, midlife vascular risk factors have been consistently associated with risk of late-life dementia,[2] but the association of late-life vascular risk factors with dementia is less well established.[4]

Data from observational cohort studies indicate that high cholesterol levels can increase a patient's risk of dementia, and both neuropathologic and observational studies of patients on statin therapies correspond with these findings.[5] High cholesterol may increase the production and aggregation of amyloid-β by increasing enzyme activation in the amyloidogenic pathway and by interfering with the peptide's interactions with the cell membrane, but few studies have distinguished between the effects of specific lipids such as high-density or low-density lipoproteins.[5,6] Efforts to translate these findings into preventive interventions remain unsuccessful, as randomized controlled trials have not shown any benefits from statin therapy; however, the lack of positive results could be related to issues of blood-brain barrier permeability as well as timing of therapy.[6] In addition, although the data are limited, the US Food and Drug Administration has recently modified drug safety labeling to inform health care providers and consumers of reports that some patients may experience memory loss or cognitive impairment while on statin therapies.

As with hypercholesterolemia, high blood pressure in midlife, approximately ages 40 to 60, has also been associated with increased risk of vascular dementia and AD. An increasing number of studies also indicate that hypotension in late life, roughly age 60 and older, may increase dementia risk due to effects on cerebral blood flow.[7] Evidence from blood pressure treatment trials (such as Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation [ADVANCE], Hypertension in the Very Elderly Trial cognitive function assessment [HYVET-COG], and the Study on Cognition and Prognosis in the Elderly [SCOPE]) varies; some trials demonstrate a benefit, and others report no effects, which may be a result of differences between classes of drugs used for hypertension therapy.[8] To further understand the effects of blood pressure treatment, the ongoing Systolic Blood Pressure Intervention Trial (SPRINT) will monitor the course of cognitive decline with intensive blood pressure control.[9]

The association between obesity and increased risk of dementia might be related to obesity's role as a marker of vascular and inflammatory damage, since adipose tissues also secrete inflammatory proteins such as leptin, which may affect neurodegeneration.[10] Similar to hypertension, obesity in late life may not have the same association as midlife obesity with risk of developing dementia.[11] While few studies have focused solely on weight loss for dementia prevention, a meta-analysis of weight loss trials reported benefits for attention and executive function primarily in obese subgroups; however, long-term randomized controlled trials are needed to determine the effectiveness of such interventions.[12]

The commonly observed diabetes-associated increase in the risk of dementia could be the result of several pathways, including disruption of insulin signaling necessary for brain function, increased accumulation of advanced glycation end products, and interference with amyloid-β clearance.[13] The role of glycemic control is still uncertain but may have a U-shaped association with

KEY POINTS

- Cardiovascular risk factors (including hyperlipidemia, hypertension, obesity, and diabetes) are associated with increased risk of dementia.
- Results of previous treatment trials for hyperlipidemia and hypertension have been mixed, but additional randomized controlled trials are needed to understand the potential impact for dementia prevention.

KEY POINT

- Epidemiologic studies indicate that physical activity may delay cognitive decline, and evidence from early randomized controlled trials supports these findings.

cognitive impairment. Studies have demonstrated associations with both hyperglycemia and hypoglycemia.[14] Preliminary treatment trials with intranasal insulin have been encouraging, and studies have reported positive effects for cognition in patients with cognitive impairment.[15]

LIFESTYLE RISK FACTORS

Physical Activity

Observational studies suggest a strong association between physical activity and maintenance of cognitive function. Physical activity may reduce risk of dementia by increasing oxygen saturation and neurogenesis as well as decreasing vascular risk factors, inflammation, and depressive symptoms.[16] A meta-analysis of prospective studies in nondemented older adults found that high, moderate, and low levels of physical activity were all protective against cognitive decline compared to no physical activity.[17] In support of these findings, imaging studies also suggest that physical activity is associated with beneficial effects on brain structure.[18] Generally, higher levels of physical activity have been more protective in cohort studies; however, in one prospective study of older women, sustained strenuous physical activity before menopause was negatively associated with cognitive function in late life.[19]

Evidence from randomized controlled trials indicates that both aerobic exercise and resistance training can delay cognitive decline.[20] Although these findings are still preliminary, physical activity interventions in older adults have reported benefits for executive function, processing speed, delayed memory, and attention; patients with mild cognitive impairment have shown particularly positive effects.[20] In patients with dementia, physical activity interventions have improved depressive symptoms, quality of life, and physical function; however, the benefits for cognitive function are still unclear.[21]

Cognitive and Social Activity

The protective effects of cognitive activity have given rise to the concept of cognitive reserve, in which factors such as education can serve as a buffer against the effects of neuropathologic damage associated with dementia. High levels of education have been consistently associated with decreased risk of dementia, and older adults with dementia who have more education tend to have higher levels of plaque accumulation than older adults with less education but similar progression of symptoms.[22] In a study of older adults, the effect of plasma amyloid-β on cognitive decline was attenuated by cognitive reserve (defined as a high level of education or literacy),[23] and neuropathologic studies indicate that cognitive activity may increase neuronal density and cortical thickness, which modifies or compensates for the effects of cerebrovascular disease.[24] In evaluations of cognitive engagement (ie, participation in activities such as games, puzzles, or reading), increased cognitive activity was also associated with lower risk of cognitive decline and dementia.[25] In addition, a small study of older adults found that cognitive activity in early and midlife was associated with lower levels of amyloid-β deposition,[26] and cohort studies indicate that frequent cognitive activity can compensate for the effects associated with low level of education.[27]

Randomized controlled trials in both healthy and impaired adults indicate that cognitive training can be beneficial, and suggest that interventions targeting multiple domains are better than those focused on a single domain; however, the effects on dementia risk are still not

confirmed.[28] A recent Cochrane review suggests that cognitive interventions, particularly those that involve cognitive stimulation, can benefit cognitive function in dementia patients, although evidence for other outcomes (including improvements in quality of life and well-being) was more uncertain.[29]

As with cognitive activity, higher levels of social engagement and social networks have also been associated with lower cognitive decline and reduced risk of dementia in observational studies.[30] The benefits of social engagement may be linked to the mechanisms of cognitive reserve. Social activities can increase cognitive stimulation as well as enhance social support and influence. However, reverse causality may also be an underlying factor for this association. As dementia progresses, patients may be less able to engage in social activity.[31] Nevertheless, several long-term prospective studies with follow-up times of over a decade have also demonstrated similar protective relationships between social engagement and risk of dementia in both mid- and late-life.[32] Evidence from some trials suggests that increased engagement in social activity can reduce the risk of cognitive decline and dementia. A group-based intervention to increase social engagement in lonely older adults led to improvement in their Alzheimer Disease Assessment Scale—Cognitive Subscale (ADAS-Cog) scores after 3 months.[33] Similarly, a social-interaction intervention improved cognitive function in Chinese elders, although the results were not as significant as those for physical activity.[34] The amount and duration of social engagement required to lower dementia risk is undetermined, but an observational study of social network characteristics in older adults indicates that the quality of social engagement, defined as satisfaction with social engagement and perception of receiving more in relationships than given, was more important for cognitive function than the number of ties and social interactions.[32]

Diet and Nutrition

The biological and epidemiologic evidence to support the role of nutrient intake in dementia risk is robust. Although few studies have investigated the lifelong effects of diet on dementia risk, early-life nutrition has been shown to affect academic and cognitive performance,[35] and studies in late life have investigated the effects of a variety of specific nutrients, including B vitamins (essential for DNA metabolism, including homocysteine methylation), antioxidants (protective against oxidative damage and amyloid-β toxicity), and fatty acids (necessary for neural membrane integrity with possible protective effects against oxidative damage).[36] While many studies have demonstrated strong associations between deficiencies for these nutrients and cognitive function, the findings from most randomized controlled trials of single-nutrient supplements have not been positive. For example, trials of folic acid supplementation in older adults without dementia ranging from 1 month to 3 years did not show significant benefits for cognitive function.[37] A similar line of evidence has emerged for antioxidants, in which supplementation with vitamins E and C has not been consistently protective.[36] Large randomized controlled trials have demonstrated that *Gingko biloba* use is not effective,[38,39] and trials for fatty acids in older adults have shown few benefits[40]; however, a meta-analysis of fatty acid trials by individual cognitive domain outcomes suggests that there may be improvement on specific domains, including immediate recall and processing speed in nondemented patients with cognitive impairment.[41]

KEY POINT

- Interventions that increase a patient's cognitive and social activity may have the potential to serve as a buffer against the neuropathologic damage associated with dementia.

KEY POINTS

- Nutrient deficits have been associated with increased risk of dementia. Single-nutrient supplementation trials have not consistently demonstrated benefits, but results from multinutrient trials are promising.
- Smoking is associated with increased risk of dementia, whereas moderate alcohol use may have a protective effect.

Several factors may contribute to the lack of efficacy in these trials. Most early studies did not assess nutrient deficiencies, and there may be threshold benefits for nutrient supplementation. In addition, a single-nutrient effect at the individual level may be too small to capture with pilot trials. Furthermore, while observational studies often evaluate the effects of individual nutrients, the standard diet includes a wide range of nutrients that could have both synergistic and antagonistic interactions.

Dementia prevention through dietary intervention may be more effective if multinutrient deficiencies are addressed. In a cohort of older adults, the Mediterranean diet (which is high in antioxidants and omega-3 fatty acids) was associated with lower risk of mild cognitive impairment and AD,[42] and analysis of other healthy dietary patterns has shown similar protective associations with cognitive function.[43] This is also supported by preliminary cross-sectional data investigating dietary patterns' relation to total cerebral brain volume and to white matter hyperintensity volumes.[44] To date, a small number of multinutrient trials have been conducted; in healthy older adults, the effects of multivitamin supplementation were mixed,[45] but preliminary multinutrient and medical food interventions that have included vitamins, minerals, and fatty acids for patients with dementia have reported a delay in cognitive decline and improvement in memory.[46] Further optimization of nutrient supplementation could make interventions more effective, and future investigations into changing dietary behaviors across the life span, once confirmed, could have significant public health impact.

Alcohol and Smoking

Both alcohol and smoking are important lifestyle risk factors that significantly affect dementia risk. Although nicotine may have short-term benefits to cognition, cigarette smoking increases inflammation and oxidative stress,[47] and neuroimaging studies indicate that smoking may negatively affect both macrostructures and microstructures of the brain.[48,49] Meta-analysis of prospective studies indicates that, compared to nonsmokers, current smokers had higher rates of cognitive decline as well as increased risk of dementia, while former smokers did not have an increased risk of dementia when compared to nonsmokers (**Case 4-1**).[47] Although few smoking-cessation trials focus on benefits for cognitive function, a recent study of older adults enrolled in a smoking-cessation intervention revealed that participants who were able to quit smoking experienced less cognitive decline than unsuccessful quitters after 2 years; however, the two groups did not differ in brain imaging outcomes.[50]

In contrast to smoking, moderate alcohol consumption may lower dementia risk. Studies have reported that there may be a J-shaped curve in risk, in which moderate alcohol use is protective compared to nondrinking, but higher levels of alcohol consumption are associated with increased risk of dementia. Meta-analysis of epidemiologic studies found that moderate alcohol use was associated with decreased risk of AD and any dementia.[51] Proposed pathways may be related to lowering lipid levels, modifying hormone levels, preconditioning, or in the case of wine, antioxidant effects.[52] The protective effect of different alcohol types is unclear, with some studies reporting benefits for all types and others for wine consumption only.[51]

SLEEP QUALITY

Sleep disturbances are common in patients with dementia,[53] and observational studies indicate that sleep

Case 4-1

A 67-year-old woman presented with concerns about lowering her risk of Alzheimer disease (AD). Her mother had been diagnosed with AD at age 76 and recently died of AD-related complications at 88 years old. The patient's two siblings, aged 74 and 79, were both high-functioning and had not reported any symptoms. Her aunts and uncle had never been diagnosed with AD, and she had no other family history of neurodegenerative disease. The patient reported that she had no cognitive complaints or symptoms.

After neuropsychologic testing, she was diagnosed as being cognitively normal. Her physical and neurologic examinations were also normal. She was mildly obese with a body mass index (BMI) of 33.7 kg/m^2. Four years ago, she was diagnosed with hypertension and had been treated with a low-dose beta-blocker since then; she did not take any other medications. Her job as a lawyer was mostly sedentary, and she had little time for physical activity. She was a former smoker and occasionally drank one to two glasses of alcohol in social settings. Her partner had reported that the patient's snoring had worsened over the course of several years.

Comment. The patient may be at increased risk for AD because of her family history in a first-degree relative; however, currently approved treatment is not clinically indicated, as she has not reported any symptoms and her neuropsychologic testing is normal. In this case, genetic testing (if done at all) would primarily occur in a research setting and is unlikely to be positive for autosomal dominant AD, considering the late age of the mother's disease onset and a less than 50% pattern of inheritance among family members. She is encouraged to make an appointment for additional evaluation if new symptoms emerge, and if possible, to bring an informant in future visits to provide a collateral history.

The patient is counseled to adhere to her current treatment for hypertension and encouraged to maintain her abstinence from smoking. To decrease her cardiovascular and dementia risk, it is recommended that she increase her weekly participation in moderate- to high-intensity physical activity. Regular physical activity may also lower her BMI, which would further reduce her risk profile. Increased social and cognitive activities, such as volunteering, reading, or cognitive exercises, could also be suggested. In addition, she could be referred to a sleep expert to test her for sleep-disordered breathing and provide possible treatment options if needed.

quality is related to cognitive function in both early and late life. In children, poor sleep quality is associated with lower IQ and poor academic performance in school,[54] and in older adults, sleep disturbance and duration have also been linked to poor cognitive outcomes.[55] While most of these studies have assessed sleep quality with subjective questionnaires, a small number have used objective sleep measures, which provides additional support for this association in older adults; however, many prior investigations have only assessed cross-sectional associations, and the temporality of the relationship was uncertain. Recently, a prospective study of older adults found that sleep-disordered breathing was associated with an increased risk of dementia.[56] Altered circadian rhythms, including decreased amplitude and

KEY POINTS

- The evidence for sleep quality as a modifiable risk factor is preliminary, but observational studies support a possible role for treatment of sleep disturbances and sleep-disordered breathing.
- Epidemiologic studies can provide critical evidence to inform the timing and duration of nonpharmacologic interventions.
- Nonpharmacologic interventions could play a major role in reducing dementia prevalence, especially when their effects are considered collectively.

robustness as well as shifted time of peak activity, have also been associated with an elevated risk of developing dementia.[57] Because these findings are recent, prevention trials have not yet begun; however, small trials of continuous positive airway pressure indicate that treatment of sleep-disordered breathing may improve cognitive function in patients with dementia.[58]

CONCLUSION

Despite encouraging progress in identifying nonpharmacologic risk factors, the translation of current observational evidence to effective trials and prevention has significant obstacles, with many questions still unanswered. These issues may be especially difficult to resolve with randomized controlled trials because they would require prolonged maintenance of an intervention study for large, diverse cohorts. Early studies and trials indicate that nonpharmacologic interventions may face just as many challenges as pharmacologic interventions, and because the NIH State of the Science report concluded that the level of evidence for nonpharmacologic interventions is insufficient, the panel of experts also recommended more vigorous standards for measures of exposure and cognitive outcomes, as well as the continued utilization of long-term population-based studies.[1]

While most epidemiologic cohort studies have focused on mid- and late-life risk, and some studies have considered early-life exposures, much less is known about the role of modifiable risk factors across the full life course. Because dementia has a prolonged prodromal phase, understanding effects across the life course can help focus the timing and duration of prevention targets. The evaluation of exposures is complementary to this perspective. Many investigations measure a risk factor at one point in time rather than assess the factor longitudinally, but the effects can vary, and initial epidemiologic findings indicate that there may be ''critical windows'' in the life course during which a risk factor is particularly effective or detrimental.[59] In addition to lifelong evaluation of modifiable risk factors, studies have yet to specify populations that would most benefit from intervention. For example, the possible modifying effects of genetic risk factors for nonpharmacologic risk factors are still undefined.

These remaining questions notwithstanding, nonpharmacologic interventions have the potential for significant public health impact. A recent review of modifiable risk factors for AD estimated that a 25% reduction of cardiovascular risk factors (diabetes, hypertension, and obesity) would decrease the number of AD cases by 770,000 worldwide and 233,000 in the United States, and a 25% reduction of physical inactivity behaviors would decrease the number of cases by 1,000,000 worldwide and 232,000 in the United States. The study also provides support for targeting multiple modifiable factors to significantly reduce disease prevalence. It was estimated that a 25% reduction of a combination of seven modifiable risk factors (ie, diabetes, hypertension, obesity, depression, physical inactivity, smoking, and education/cognitive inactivity) would prevent up to 3 million cases worldwide and 492,000 cases in the United States.[60]

With the goal of targeting multiple modifiable pathways, a small number of randomized controlled trials have started to test the efficacy of multidomain interventions. These include the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) with both physical

and cognitive activity components, dietary intervention, and vascular risk factor management; and the Multidomain Alzheimer Preventive Trial (MAPT), which will test omega-3 supplementation as well as a multidomain intervention with cognitive training, physical training, and nutritional education.[61] The Prevention of Dementia by Intensive Vascular Care (PreDIVA) study will target multiple vascular risk factors, including hypertension and hyperlipidemia, through primary care management and counseling.[62] In the future, the most effective interventions may be those that are tailored for specific subpopulations and combine both pharmacologic and nonpharmacologic strategies.

KEY POINT

- The latest nonpharmacologic randomized controlled trials will test the efficacy of targeting multiple modifiable risk factors, and future interventions may incorporate both pharmacologic and nonpharmacologic methods.

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