

Prevention of Dementia and Cognitive Decline: *Notes from the NIH-State-of-the-Science Conference*

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The National Institutes of Health (NIH)-State-of-the-Science Conference on “Preventing Alzheimer’s Disease and Cognitive Decline” sought to review the available evidence and provide carefully reasoned recommendations. The preliminary draft statement of the conference panel found insufficient evidence to support any definitive recommendations to prevent Alzheimer’s disease or the cognitive impairment related to advancing age. Equally disappointing was the conclusion that present diagnostic criteria for both Alzheimer’s disease and cognitive decline lack the consensus necessary for uniform application and risk identification. Nonetheless, a number of promising predictors of both increased and decreased risk emerged. In addition, they overlap substantially with recommendations for the prevention of heart disease and stroke. As a result, the tentative prevention recommendations put forth by the Alzheimer’s Association remain not only the best available but the most promising as well.

BACKGROUND

The first NIH-State-of-the-Science Conference on “Preventing Alzheimer’s Disease and Cognitive Decline” was held April 26–28, 2010, at the William H. Natcher Conference Center on the NIH campus.¹ It was sponsored by the National Institute on Aging, Office of Medical Applications of Research and sought to address the following questions.

- What factors are associated with a reduction in the risk of cognitive decline among older adults and of the risk of Alzheimer’s disease?
- What are the risks and benefits of interventions to delay Alzheimer’s disease and do they vary among identifiable population subgroups?
- What are the risks and benefits of interventions to improve or maintain cognitive performance and are there differences among subgroups?
- Are factors related to the risk of Alzheimer’s disease

the same or different from those involved in cognitive decline?

- If recommendations to protect against cognitive decline or Alzheimer’s disease are not justified by the strength of current evidence, what studies need to be performed to do so?

The conference was planned by a committee originally led by Nancy Andreasen, MD, PhD, professor and chair of Psychiatry at the University of Iowa, and subsequently by Neil Buckholtz, PhD, chief of the Dementias of Aging Branch at the National Institute on Aging. The planning committee consisted of representatives from the NIH, the Centers for Disease Control and Prevention, the Agency for Healthcare Research and Quality, and academia. A group of seven educational planners was also employed to coordinate the effort.

BIAS CONTROL

The conference structure included three elements. First, there was a systematic review by Duke University’s Evidence-

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based Practice Center which was presented by three speakers. The goal was to assess the available evidence or the lack thereof based on a priori quality criteria rather than the personal perspective of any individual no matter how well informed. Second, there were presentations by 18 invited speakers chosen on the basis of their published scientific research and diversity of opinion. Individual perspectives in addition to published research were welcome. Third, there were 15 panelists from an array of clinical, health, and advocacy backgrounds but with general rather than expert opinions on the topic. They were also chosen on the basis of freedom from potential conflicts of interest as a result of affiliations with the pharmaceutical industry, other commercial interests, or dementia-related research support. Speakers and panelists were kept separate except for conference presentations to prevent any appearance of private influence. Panelists were invited to publicly query speakers following their presentations. Others in attendance could pose questions in person if time permitted or later via the Internet.

These arrangements conveyed a commitment to ensure that the final opinions would reflect the most objective perspective possible on the state of the science as well as to ensure that the public's health interest, rather than that of any advocacy group or individual scientist, remained uppermost. The draft recommendations of the panel appear in Table 1.¹ Their conclusions are conservative, suggesting that if any bias was present it was bias against finding protective factors. Difficulties inherent in risk identification as well as promising predictors discussed by presenters are examined below.

TABLE 1
CONSENSUS CONFERENCE CONCLUSIONS¹

- Cognitive decline and dementia are major sources of morbidity and mortality world wide, placing substantial burdens on individuals, their families, and society.
- Firm conclusions about modifiable risk factors for Alzheimer's disease and cognitive decline cannot be drawn.
- Consensus for diagnostic criteria for Alzheimer's disease and cognitive decline is lacking. Existing criteria have not been applied uniformly.
- Evidence to support the use of medications or dietary supplements to prevent Alzheimer's disease and cognitive decline is lacking.
 - The use of antihypertensive medications, the use of omega-3 fatty acids, physical activity, and cognitive engagement is promising but unproven.
- Both randomized controlled trials and population-based studies are needed to investigate the following:
 - Strategies to sustain cognitive performance among people at risk for decline
 - Factors that might delay the onset of dementia
 - Factors that might slow the progression of dementia

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OBSTACLES AND AVENUES TO THE DETECTION OF RISK PREDICTORS

The identification of predictors of late-life disease is confounded not only by the aging process itself. Concurrent illnesses and the breadth of exposure through potential critical periods of life offer an array of obstacles as well as avenues to risk identification. The problem is compounded by substantial inter-individual variation on measures of inborn and acquired intellectual capacity, the latter altered by both educational and occupation attainments. However, the challenge of risk identification is not unique to late-onset neurodegenerative illness.

Originally published in 1998, the Framingham risk score for the onset of coronary heart disease is one of the most thoroughly validated and widely used predictive tools in medical practice today.² Its development paralleled the marked decline in cardiovascular mortality. However, as originally constructed, the risk calculator began counting at 35 years of age.² Subsequent refinements have reduced the contribution of age to risk.³ One of the best known contributors to the Framingham score, total cholesterol with the high and low density components, is both predictive and modifiable. Modifiability was proven by a variety of interventions examined with the gold standard of randomized controlled trials. Nonetheless randomized controlled trials are not the only means of establishing risk and the potential of risk reduction.

Ganguli and Kukull⁴ distinguish between two subcategories of predictors that should be identified: "(1) early markers or manifestations of the disease itself, indicating that preclinical disease has begun, and (2) independent risk factors that increase or decrease the likelihood that the pathological disease process will begin." For example, smoking is a risk factor for lung cancer; still, once concern has begun, it cannot be reversed by smoking cessation. Yet, because the association of smoking with lung cancer is so substantial in epidemiologic studies, it is considered causative. Thus, although randomized controlled trials of interventions to reduce Alzheimer's disease and cognitive impairment have been disappointing, a number of potential predictive factors remain promising.

PROMISING PREDICTORS

Peterson⁵ reviewed biomarkers that might be useful predictors from a pre-symptomatic state to the earliest signs of mild cognitive impairment. These included spinal fluid assays of amyloid components and tau, imaging procedures

for amyloid plaques, functional and structural brain changes, and measures of cognitive performance. Many of these are incorporated in the Alzheimer's Disease Neuroimaging Initiative, which is designed to assess the value of biomarkers and imaging in predicting progression of mild cognitive impairment to Alzheimer's disease.⁵

Unfortunately, the biomarker with the strongest association for development of Alzheimer's disease, the presence of the apolipoprotein E ϵ 4 allele, is a risk factor that cannot be modified.⁶ However, other risk factors with evidence supporting low to moderate associations with development of cognitive decline or Alzheimer's disease might be decreased with adequate screening and treatment. Conditions such as hypercholesterolemia, diabetes mellitus, and current smoking are risk factors associated with dementia⁶ and are simultaneous risk factors for cerebrovascular disease. Presence of three or more vascular risk factor poses a three-fold risk of developing dementia.⁷ The results of studies regarding the treatment of vascular risk factors to reduce cognitive decline and dementia are inconclusive but suggest that earlier rather

than later treatment is more effective due to the relative long period of time an individual may be exposed to vascular risk factors. It follows that adequate mid-life screening of vascular risk factors could play a role in preventing cognitive decline. A comparison of proven predictors of heart disease and stroke and putative predictors of Alzheimer's disease and cognitive decline appears in Table 2.⁸⁻¹⁰ When compared to established predictors of heart disease and stroke there is substantial overlap.

Depressive disorders have been associated with increased risk of development of both Alzheimer's disease and cognitive decline.⁶ Depression is associated with incident myocardial infarction and subsequent cardiovascular mortality in late life as well.¹¹ Late-life depression, as opposed to depression with onset at an earlier age, is associated with higher rates of dementia. Nonetheless, the link between depression and development of dementia is unclear and further studies need to be performed to decipher the cause and effect roles of the underlying pathology of both depression and dementia.¹² Current evidence supports an improvement but not complete remission of cognitive symptoms with treatment of geriatric depression. With depressive symptoms affecting over 15% of older Americans,¹² clarifying the relationship of screening and treatment of late-life depression and its role in prevention of dementia would be a valuable determination.

The role of modifiable lifestyle factors, such as diet and exercise, in the prevention of dementia is also promising. The disease process in Alzheimer's disease is thought to involve oxidative stress and inflammation; diets rich in antioxidant nutrients, such as vitamin E, vitamin C, carotenoids, and flavonoids, can reduce the amount of oxidative damage to brain tissue. Docosahexaenoic acid (DHA), a fatty acid found in fish, is found in metabolically active areas of the brain, suggesting that adequate levels of this compound are needed for optimal cognitive functioning. Studies¹³ have shown that diets including fish high in DHA eaten once per week have protective effects against Alzheimer's disease. The evidence supporting Vitamin B₁₂ and folic acid supplementation in the role of preventing dementia is inconclusive, though it has been widely accepted for some time that Vitamin B₁₂ deficiency causes a neurologic disorder involving cognitive decline as a symptom.

Physical activity and exercise is thought to reduce the risk of dementia by reducing the risk of comorbid illness (eg, diabetes mellitus and cerebrovascular disease) and through the direct effects on cognition via increased neurogenesis and neurotrophins (eg, brain-derived neurotrophic factor, insulin-like growth factor 1, and vascular endothelial growth

TABLE 2

PROVEN PREDICTORS OF HEART DISEASE AND STROKE COMPARED TO PUTATIVE PREDICTORS OF ALZHEIMER'S DISEASE AND COGNITIVE DECLINE⁸⁻¹⁰

<i>Heart Disease^a</i>	<i>Stroke^a</i>	<i>Alzheimer's Disease, Cognitive Decline Prior to Dementia¹⁰</i>
Age, family history	Age	Age, family history
Hypertension	Systolic blood pressure	Hypertension
Smoking	Smoking	Physical frailty
Diabetes	Diabetes	Insulin elevation
Male gender	Prior heart disease	Physical strength*
High total cholesterol, low HDL, high LDL, triglycerides	Atrial fibrillation	Apolipoprotein E
Belly fat, "apple shaped body"	Left ventricular hypertrophy	Impaired odor identification
Obesity	Use of antihypertensive medication	Mediterranean diet*
Lack of physical activity		Leisure activity* Cognitive activity* Conscientiousness* Sense of purpose* Chronic distress

*Associated with reduced risk

HDL=high-density lipoprotein; LDL=low-density lipoprotein.

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factor) in areas of the brain associated with enhanced learning and memory.¹⁴ Further studies need to be performed on the type, intensity, duration, and frequency of physical activity in order to suggest any clear guidelines in the prevention of dementia.

Post-mortem research has shown that brain pathology occurs years earlier than the clinical symptoms of dementia. The concept of cognitive reserve may account for the discordance in amount of pathology and the expression of that pathology in the form of cognitive decline.¹⁵ Cognitive engagement, leisure activity, and social interactions have been implicated in increasing the amount of reserve, thus slowing the onset of dementia symptoms. Educational level and occupational level have unclear correlations with dementia risk, but recent studies¹⁶ have shown that lower levels of literacy lead to a more rapid decline in memory, suggesting that literacy level, an indicator of quality of education, is a better predictor of cognitive decline than level of education.

CONCLUSION

The preliminary draft statement of the conference panel found insufficient evidence to support definitive recommendations to prevent Alzheimer's disease or the cognitive impairment related to advancing age. More troubling was

TABLE 3

ESTABLISHED RECOMMENDATIONS FOR THE PREVENTION OF HEART DISEASE COMPARED TO PRELIMINARY RECOMMENDATIONS TO PREVENT ALZHEIMER'S DISEASE^{8,17}

<i>Heart Disease⁸</i>	<i>Alzheimer's Disease¹⁷</i>
Stop smoking	Stop smoking, avoid excess alcohol
Exercise for 30 minutes most days if not everyday	Exercise both the mind and body; stay socially engaged
If hypertensive get treated; If diabetic lower your blood sugar through diet, exercise, medications if needed	Minimize any risks of heart disease and stroke
Use diet and exercise to achieve and maintain a healthy body weight	Keep body weight within healthy guidelines
Use diet, exercise and medications if needed to lower your cholesterol	If elevated, lower your cholesterol
Limit consumption of animal fats, trans fats, starches, and sugar	Take steps to avoid falls and head injury
Eat lots of whole grains and whole grain products, high fiber fruits and vegetables ("if it's white, don't bite")	

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the conclusion that existing diagnostic criteria for both Alzheimer's disease and cognitive decline lack the degree of consensus necessary for uniform application and risk identification. Nonetheless, a number of promising predictors of both increased and decreased risk emerged. The current evidence supports a heart-healthy lifestyle including a diet low in saturated fats and high in fish and antioxidants, plenty of physical activity, and rich in social and cognitive engagement as protective against development of dementia. Certain dementia risk factors cannot be modified, but improved recognition and treatment of comorbid illness, including cardiovascular risk factors and major depressive disorder, may prevent onset or slow progression of cognitive decline among older adults. Moreover, there are lifestyle factors that could prevent or delay the onset of cognitive decline due to diseases such as Alzheimer's disease.

There is substantial overlap when these tentative predictors of cognitive decline and Alzheimer's disease are compared to established predictors of heart disease and stroke. This is not to say that vascular risk factors cause Alzheimer's disease; rather, they often occur in the same individual and once present may accelerate decline. As a result, the prevention recommendations put forth by the Alzheimer's Association in Table 3 remain not only the best available but the most promising as well.^{8,17} Finally, interventions which prevent or delay the disability of a disease may be highly beneficial without ever preventing the illness. Stated differently, we need not cure Alzheimer's disease if we can push the associated disability to the very end of the life span. **PP**

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