

Primary Prevention of Alzheimer's Disease: Is It an Attainable Goal?

Jee-Young Han¹ and Seol-Heui Han^{2,3}

¹Department of Neurology, Seoul National University Hospital, Seoul; ²Department of Neurology, Konkuk University School of Medicine; ³Center for Geriatric Neuroscience Research, Institute of Biomedical Science and Technology, Konkuk University, Seoul, Korea

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Address for Correspondence:

Seol-Heui Han, MD

Department of Neurology, Konkuk University School of Medicine and Konkuk University Medical Center, 120-1 Neungdong-ro, Gwangjin-gu, Seoul 143-729, Korea

Tel: +82.2-2030-7561, Fax: +82.2-2030-7018

E-mail: alzdcc@kuh.ac.kr

Alzheimer's disease (AD) is the leading cause of dementia, and the most prevalent neurodegenerative disease in the elderly. The prevalence of AD is predicted to rise as life expectancy grows across populations. The exact cause of this devastating disease is still unknown; however, it is an aging-related multi-factorial disorder, and growing evidence supports the contribution of modifiable environmental factors to unmodifiable factors such as gene and ageing itself. The recent advancement of methodologies and techniques for early diagnosis of AD facilitates the investigation of strategies to reduce the risk for AD progression in the earliest stages of the disease. Pharmacological attempts at curing, halting or modifying it have, by and large, been unsuccessful, and no breakthrough is seen in the near future. However, a lot of elements that seem to contribute to the disease such as risk factors have been identified, mainly from epidemiological and basic research studies. Many of these are amenable to lifestyle modification. Therefore, prevention in the preclinical stage is likely the most effective way to decrease the incidence of this age-associated dreadful neurodegenerative condition, and its associated burden for individuals and society. We provide an overview of modifiable risk factors for AD along with the supporting evidence.

Keywords: Alzheimer's Disease; Primary Prevention; Lifestyle Modification; Nutrition

INTRODUCTION

Astonishing advancement in medical knowledge and everlasting improvements in healthcare services in recent years have contributed to an increased longevity in the worldwide population (1), which is projected to continue to increase. While it is evident that expansion of life expectancy might be indicative of a healthier population, it is also true that a growing number of population are living to an older age with risk factors for age-related neurodegenerative disorders, most typically Alzheimer's disease (AD), which will ultimately result in dramatic increase in the number of people suffering from dementia and related cognitive decline (2). This age-related cognitive decline is a burgeoning public health concern domestically, as well as internationally. Current pharmacological agents available for AD target the neurotransmitter deficits of the disorder, but provide only symptomatic relief for a brief duration. Furthermore, these compounds are unable to halt the degenerative process, and may lead to an unfavorable risk/benefit position and tolerance (3). Over the past decade, research efforts have concentrated largely on therapeutic strategies that aim to prevent the formation and deposition of β -amyloid and tau, or accelerate their clearance, but there has been limited success (4). Therefore, there is an urgent and unmet need to develop novel strategies

that will be able to delay onset of dementia, or halt the progression of disease course. Until then, it would be a reasonable option to adopt any measures known to mitigate dementia risk. It is estimated that about half of AD cases worldwide might be attributable to known risk factors. Taking immediate action on the known risk factors could perhaps prevent up to one-fifth of predicted new cases by 2025 (5). We tried to describe here the most pertinent findings from literature reviews, together with some more speculative ideas and hypotheses for further scrutiny.

STATUS OF AD

How big is the problem?

AD is the most common cause of dementia in persons aged 60 yr and older, representing 60%-80% of cases (6). The second most common cause is vascular dementia or dementia due to the occurrence of multiple strokes. However, increasing evidence from population-based neuropathological and neuroimaging studies shows that mixed neuropathologies (characteristic of AD, cerebral infarctions and Lewy bodies) account for most dementia cases, particularly in very old people (7, 8). AD is a fairly common condition in older age. The overall prevalence among individuals aged 65 yr and older has been estimated to be 10%-13%, and the rate increases exponentially with older

age: from 3% among 65-74-yr-olds to 19% among 75-84-yr-olds, and nearly half (47%) of those aged 85 yr and older (6).

Where are we now?

Given the expected dramatic increase in the incidence and prevalence of dementia, the development of successful prevention and treatment strategies is critical. However, the current pharmaceutical treatment of AD can only modestly improve symptoms, and cannot cure or halt clinical progression. As a result, prevention of dementia through risk factor identification and modification is of the utmost importance until truly efficacious disease-modifying agents are available.

Is Alzheimer's disease preventable?

Prevention is traditionally divided into three levels: primary, secondary, and tertiary prevention. Primary prevention refers to reducing the incidence of the disease by eliminating or treating specific risk factors, which may decrease or delay the development of a specific disease. In the case of AD, people currently without any signs or symptoms of AD could remain without AD through the primary prevention strategy. Secondary prevention aims to detect the disease at an early stage, before any symptom has emerged, when treatment could halt or limit its progression. Tertiary prevention ameliorates the impact of complications and disability of long-term diseases, thus it allows patient to maintain an acceptable quality of life.

In this review, the discussion will be largely focused on primary prevention of AD. Evidence surrounding the prevention of AD will be discussed, where available.

RISK FACTORS AND PREVENTION

Although the exact etiology of AD largely remains unknown, researchers in this field currently agree that it is multifactorial, being the result of complex interactions among ageing, genetic, lifestyle and environmental factors. The primary risk factors for late-onset AD include older age, the APOE ϵ 4 genotype, head injury, family history, low education and low participation in cognitively stimulating activities (9). Among them, advanced age is the strongest risk factor for AD such that the risk doubles every 5 yr after the age of 65. Dysfunctional vascular conditions and related vascular risk factors are the primary focus of the current research in AD aside from vascular dementia (10). Among these factors, physical activity (11), diet (12), hypertension (13), obesity (14), hypercholesterolemia (13), diabetes (15), heart disease (16), cerebrovascular disease (CVD) (7), and metabolic syndrome (17), are the most actively investigated areas. The strong relationship between CVD and diet, as well as between CVD and dementia support the idea that diet also plays a role in dementia at the very least through its effect on cardiovascular-related conditions (18). Genetic causes of AD are restricted

to early-onset cases in persons less than 60 yr of age, and account for only 1% of all cases (19).

There is also increasing evidence suggesting that many risk factors that contribute to the development of late-life dementias are modifiable (13). The same factors that forced people to be at risk for dementia may be targets for interventions (Identifying strategies to delay the onset of dementia is, thus, of great importance for alleviating the rising pressures of this disease on health-care systems and societies (20). Even a very small reduction in the rate of development of AD pathology would have enormous public health benefits.

Cognitive activity (Cognitive training)

Several observational studies demonstrate that education is 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. Engaging in highly complex mental activities conferred protection against the subsequent development of dementia. The term "cognitive reserve (CR)" has been applied to describe this condition that the greater number of neurons or advance neuropsychological competence can protect individuals from developing clinically overt cognitive decline or dementia (21). High CR individuals seem to have a repertoire of strategies to resolve complex tasks, as well as redundant neuronal networks to carry out the same activities (22). Although several randomized controlled trials of cognitive intervention have yielded mixed and inconclusive results, the domain of global cognitive functioning, as measured by Mini-Mental State Examination, showed consistent and significant intervention effects (23). Recently the ACTIVE study group demonstrated the effects of cognitive training on cognitive abilities and everyday function over 10 yr. They randomized 2,832 patients into four groups and three intervention arms: 10 training sessions for memory (verbal episodic memory), reasoning (ability to solve problems that follow a serial pattern), or speed of processing (visual search and identification); four sessions of booster training 11 and 35 months after initial training. The results revealed that compared to the control group, cognitive-trained subjects showed less decline in self-reported instrumental activities of daily living (IADL). Reasoning and speed, but not memory, training resulted in improved targeted cognitive abilities for 10 yr (24). Based on these results, it seems advisable to engage in cognitive training programs as part of a formal multimodal therapeutic approach. At least, these nonpharmacological interventions should be considered as a complementary option of intervention.

Physical activity

The most thoroughly and well-researched behavioral intervention for cognitive functioning is physical activity (PA). PA may also mitigate associated risk factors for cognitive decline such

as cardiovascular disease. One recent meta-analytic study argued that high and moderate intensity PA decreased the risk of cognitive decline in healthy individuals by up to 38% and 35% respectively (25).

Lautenschlager et al. (26) reported that PA has been shown to improve cognitive outcomes in patients with mild cognitive impairment. One recent prospective study on PA suggests that cognitively normal older adults who report higher levels of physical activity may have slightly better cognitive performance, but the potential cognitive benefits of higher levels of physical activity over time may be most evident in individuals at genetic risk for AD (27).

It is believed that BDNF plays a central role on the effects of exercise on synaptic plasticity. It has recently been reported that an exercise regimen known for its capacity to enhance learning and memory through a BDNF-related mechanism, promotes remodeling of chromatin containing the BDNF gene (28). Multiple genes analysis using microarray technology has been instrumental in determining the pathways stimulated by exercise in the brain. These studies have shown that voluntary exercise elevated the expression of a subgroup of genes that are associated with the actions of BDNF and insulin-like growth factor (IGF) systems on synaptic plasticity (29).

Aerobic exercise reduced the risk of cognitive impairment and dementia which can be explained by either a direct neurotrophic effect of exercise or by an improvement in the cerebrovascular and cardiovascular risk profiles. The authors argue that aerobic exercise attenuates progression of neurodegenerative processes and age-related loss of synapses and neuropil via facilitation of neurotrophic factors and neuroplasticity (30). These findings are in line with animal experiments in which aerobic exercise enhances hippocampal dendritic length and dendritic spine complexity (31). In a long-term, prospective cohort study, the usual weekly walking distances reported by healthy adults at baseline were positively associated with neocortical and hippocampal MRI volumes 9 yr later (32). Recently, Rovio et al. (33) reported that leisure-time PA at midlife (on average 21 yr before the diagnosis of dementia) is related to a decreased risk of dementia and AD. Individuals participating at least twice a week in a leisure-time PA had 50% lower odds of dementia compared with sedentary persons. The association was somewhat stronger for AD than for overall dementia; those in the active group had 60% lower odds of AD compared with those in the sedentary group, even after adjusting for potential confounding factors. The APOE $\epsilon 4$ allele status appeared to modify the associations between PA and dementia or AD as PA had more pronounced effects against dementia or AD among the APOE $\epsilon 4$ carriers; dementia may have affected the individuals' observed PA (33). Thus, ongoing, moderate-intensity physical exercise should be considered as a prescription for lowering cognitive risks and slowing cognitive decline across the age spectrum.

Vascular risk factor controls

Mounting evidence indicates that vascular disease and risk factors not only elevate the risk of vascular dementia (VaD) but also AD (34). Moreover, the neuropathology of cognitive impairment in later life is often a mixture of Alzheimer disease and microvascular brain damage, which may overlap and synergize to heighten the risk of cognitive impairment (35). It is recently reported that midlife cardiovascular risk factors are related to impairments in executive functions as ascertained by novel errors and traditional measures (36). An association of elevated blood pressure in midlife with an increased risk of dementia and AD later in life has been reported in several population-based studies (37, 38) while follow-up studies of late-life blood pressure and risk of dementia yield mixed results, largely depending on the length of follow-up. The short-term follow-up studies (e.g., less than 3 yr) often found no association or even an inverse association between blood pressure and risk of dementia and AD. However, studies of very old people (i.e., 75 + yr) with a longer follow-up period (i.e., more than 6 yr) also revealed an increased risk of dementia associated with low blood pressure, suggesting that low blood pressure is a significant risk factor for dementia in very old people (39).

The association of diabetes and pre-diabetes with AD may reflect the direct effects of chronic hyperglycemia, hyperinsulinemia, or insulin resistance on brain neurodegenerative changes (40). Multiple mechanisms related to diabetes-related glucose and insulin dysregulation can lead to vascular and neuronal damage (41). Studies suggest that the longer the duration of diabetes, the poorer the cognitive function (42).

Dyslipidemia has been suggested as a risk factor for AD (2). Some reports, mostly retrospective epidemiological studies, have observed a decreased prevalence of AD in patients taking the cholesterol lowering drugs, statins. People with high levels of low-density lipoproteins in late life have increased risk of cognitive impairment and dementia with stroke (43). The production of amyloid- β ($A\beta$) is modulated by cholesterol, and studies on animal models have consistently demonstrated that hypercholesterolemia is associated with an increased deposition of cerebral $A\beta$ peptides (44). Several mechanisms contribute to AD development and progression, and increasing epidemiological and molecular evidence suggests a key role of cholesterol in its initiation and progression. Altered cholesterol metabolism and hypercholesterolemia appear to play fundamental roles in amyloid plaque formation and tau hyperphosphorylation (45).

Since the above-mentioned vascular risk factors are convincingly associated with an increased risk of incident dementia, treatments targeting vascular risk factors in mid-life seem to be safe and fruitful.

Nutritional approaches

Among other factors, ample evidence suggests that cognitive function is influenced by nutrition (46). The role of nutrition in cardiovascular disease is well documented particularly regarding the protective effect of poly-unsaturated fatty acids of the omega 3 series (n-3 PUFA) (18). We could therefore expect a protective effect of the same nutrients against vascular dementia, but also against the vascular component of AD. A healthy diet could then contribute to simultaneously decrease the risk of several conditions whose incidence sharply increases with ageing. Consequently, the potential of nutritional intervention to prevent or delay cognitive impairment and the development of AD is a subject of growing scientific interest. Elevated saturated fatty acids could have negative effects on age-related cognitive decline and mild cognitive impairment (MCI). Furthermore, at present, epidemiological evidence suggests a possible association between fish consumption, monounsaturated fatty acids and polyunsaturated fatty acids (PUFA; in particular, n-3 PUFA) and a reduced risk of cognitive decline and dementia. Poorer cognitive function and an increased risk of vascular dementia (VaD) were found to be associated with a lower consumption of milk or dairy products. Among different dietary patterns, recent prospective studies provided evidence that a higher adherence to a Mediterranean-type diet (MedDiet) could be associated with slower cognitive decline, reduced risk of progression from MCI to AD, reduced risk of AD, and decreased all-cause mortality in AD patients (47-49). One recent intervention study with MedDiet was associated with better global cognitive performance after 6.5 yr of follow-up compared with a control group who received advice on a lower-fat diet (50). Epidemiological studies have recently reported an association between wine consumption and the incidence of AD. Red wine in particular, another component of the MedDiet, was investigated in the Personnes Agees Quid (PAQUID) study, in which the relative risk for dementia and AD among 318 subjects who drank three or four glasses of wine each day in comparison with 971 total abstainers were 0.21 and 0.25, respectively. Among the 922 older subjects who drank no more than one or two glasses of wine each day with regard to the abstainers the relative risk for AD was significantly reduced (0.55) (51). A possible mechanism for the protective effect of wine is provided by the antioxidant and anti-inflammatory properties of resveratrol and melatonin, which are most prominent in red wine (52-54). Studies suggest that dietary polyphenolics may benefit AD by modulating multiple disease-modifying modalities, both β -amyloid-dependent and independent mechanisms, and provide impetus for the development of polyphenolic compounds for AD prevention (55). They also show antioxidant, cardioprotective, anticancer, antidiabetic, neuroprotective and anti-aging activities (54).

A recent review article emphasized the potential role of nu-

tritional supplementation to prevent cognitive decline by counteracting deleterious neurodegenerative and pathological process. The literature reinforces the need for early intervention in AD and suggests that multi-nutritional intervention, targeting multiple aspects of the neurodegenerative process during the earliest possible phase in the development of the disease, is likely to have the greatest therapeutic potential (56). Therefore effective, nutrition-based approaches would be of great benefit due to a relatively low risk of side effects in a presymptomatic or prodromal stage, and benefit a relatively healthy population allied to the necessarily long exposure time (57).

Stress management

High levels of perceived stress are associated with a higher risk of developing AD (58). Increasing evidence has been accumulating about the role of stress as an important challenge to the onset and progression of AD. The hippocampus, a main structure of the brain damaged during AD, is the first brain region, besides the hypothalamus, to be recognized as a target of stress hormones, including cortisol, sympathetic and parasympathetic neurotransmitters, cytokines and metabolic hormones (59). Neuroinflammatory mechanisms induced by stress is likely to cause neuronal dysfunction and impaired neurogenesis which eventually develop AD (60).

Sleep is a very important physiologic phenomenon to reduce mental and physical tensions alike. Several studies suggest that sleep may influence AD pathogenesis. Sleep-wake abnormalities are associated with the presence of amyloid deposition in the preclinical stage of AD. Moreover, sleep abnormalities may increase soluble $A\beta$ levels over the long term, leading to an increased chance of amyloid plaque accumulation, further sleep disruption, and, subsequently, symptomatic AD (61). In a couple of cross-sectional studies, insufficient or decreased sleep quality was associated with poor cognitive function (62, 63).

The attenuating effect of meditation on stress reduction, the prevention of psychosomatic disorders, blood pressure, and other cardiovascular diseases has been well recognized (64). Meditation techniques are considered to be specific cognitively stimulating activities. Newberg et al. suggests that the application of meditation techniques in patients with neurodegenerative diseases has a positive impact on memory, and attention (65). One recent pilot study demonstrated that in adults most susceptible to the development of dementia, meditation may reduce hippocampal atrophy and improve functional connectivity in the same areas of the brain most affected by the disease process (66). Thus meditation can be a potentially suitable non-pharmacological intervention aimed at the prevention of cognitive decline in the elderly (67).

Social engagement

Social relationships are hypothesized to prevent or slow down

cognitive decline. It has been well documented that individuals with reduced social networks are more susceptible to develop cognitive decline compared with those who have more extensive social interactions (68). Brenowitz et al. (69) reported that compared with living with a spouse/partner, risk of MCI was significantly higher for those living with others (hazard ratio: 1.35; 95% confidence interval: 1.03, 1.77), but not for living alone. Risk of MCI was not associated with having children or having siblings. Participation in socially engaging leisure activities-such as visits with friends and relatives, going to the movies, clubs, centers, and church/synagogues, and volunteering was also associated with reduced risk of dementia. It is possible that aspects of cognitive processing that allow people to develop and maintain large social networks might also provide a reserve against the development of cognitive impairment despite the accumulation of AD pathology, or otherwise compensate for the effects of degeneration of non-social cognitive systems (70, 71).

Multimodal interventions

Recent reviews suggest that multimodal interventions that include more than one behavioral or lifestyle intervention may have a greater likelihood of influencing neurobiological mechanisms underlying cognitive decline than any one activity alone (72). Tai Chi is a good example of multimodal interventional strategy. Tai Chi is an increasingly popular multimodal mind-body exercise that incorporates physical, cognitive, social, and meditative components in the same activity. Tai Chi shows potential to enhance cognitive function in older adults, particularly in the realm of executive functioning and in individuals without significant impairment (73). Recent prospective study suggests that individuals who participated in the 4-month exercise and frontal cognitive stimulation intervention program had better performance on dual-task activities, better postural balance on the force platform, and greater functional capacity than control participants. Therefore, their results confirmed the hypothesis that a combination of physical exercise and frontal cognitive stimulation has a favorable effect on frontal cognition relative to postural control and functional capacity components in individuals with AD (74). According to recent studies, the combination of diet and exercise can deliver more beneficial effects than intervention alone (75, 76).

CONCLUSION

AD is now considered as epidemic in the 21st century; however, in spite of enormous intellectual, financial and time investments, the exact pathomechanism of AD is still far from being fully elucidated. Current treatment options for AD are limited to couple of classes of symptomatic medications targeting cholinergic and glutaminergic neurotransmitter derangements respectively. Moreover, neither class of medication is thought to signifi-

cantly alter the causal pathways in AD, i.e., none can stop or slow the progress of the disease. In recent years, many drug candidates aimed at disease modification have advanced into large, randomized controlled trials, but none has demonstrated efficacy in slowing down the relentless progression of AD. It is, therefore, critical to address the current lack of effective treatments to target the underlying pathology and disease process in AD.

Epidemiological studies have identified many risk factors for AD, some genetic but most environmental and therefore modifiable. In this context, a concerted action to fight the AD epidemic must be taken by aggressive risk factor management through the above-mentioned lifestyle modification strategies until effective disease modifying drugs are available.

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ORCID

Seol-Heui Han <http://orcid.org/0000-0003-3608-2514>

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