

Risk Factors for Dementia

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Dementia is a complex human disease. The incidence of dementia among the elderly population is rising rapidly worldwide. In the United States, Alzheimer's disease (AD) is the leading type of dementia and was the fifth and eighth leading cause of death in women and men aged ≥ 65 years, respectively, in 2003. In Taiwan and many other counties, dementia is a hidden health issue because of its underestimation in the elderly population. In Western countries, the prevalence of AD increases from 1–3% among people aged 60–64 years to 35% among those aged > 85 years. In Taiwan, the prevalence of dementia for people aged ≥ 65 years was 2–4% by 2000. Therefore, it is important to identify protective and risk factors for dementia to prevent this disease at an early stage. Several factors are related to dementia, e.g. age, ethnicity, sex, genetic factors, physical activity, smoking, drug use, education level, alcohol consumption, body mass index, comorbidity, and environmental factors. In this review, we focus on studies that have evaluated the association between these factors and the risk of dementia, especially AD and vascular dementia. We also suggest future research directions for researchers in dementia-related fields. [*J Formos Med Assoc* 2009; 108(10):754–764]

Key Words: Alzheimer's disease, dementia, risk factor, vascular dementia

Alzheimer's disease (AD) is the leading subtype of dementia. In the United States in 2003, it was the fifth and eighth leading cause of death in women and men aged ≥ 65 years, respectively.¹ Taiwan became an aging country in 1993 ($\geq 7\%$ of the population aged ≥ 65 years, as defined by the World Health Organization), and the aged population exceeded 10% at the end of 2006. As medical care advanced over time in Taiwan, life expectancy reached 75 and 81 years for men and women, respectively, in 2007.² This has led to the observation of an increasing number of dementia cases. In Taiwan, dementia affects more than 160,000 people according to data from the Association of Dementia in Taiwan in 2009. This

is twice as many as 15 years ago. There are about 5 million AD patients in the United States and this is estimated to rise to 16 million in 40 years.³ In Western countries, AD affects 1–3% of people aged 60–64 years, and 3–12% of people aged 70–80 years. This proportion increases to 25–35% for people older than 85 years.⁴ In contrast, the prevalence of dementia in Taiwanese people aged ≥ 65 years was estimated to be 2–4% by 2000, which is lower than that in other developed countries.⁵ In addition, the actual number is underestimated because: (1) the aging population in Taiwan is composed mainly of people at a relatively younger age of 65–75 years; (2) the mortality rate is higher among those with

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dementia than those without; (3) diagnosis of dementia is complicated and it is easily overlooked; and (4) genetic differences exist between ethnic groups (e.g. there are fewer *APOEε4* allele carriers in Taiwan).⁵ Therefore, the actual prevalence of dementia in Taiwan is probably greater than has been observed.

Dementia is categorized into a few subtypes according to its causes. AD accounts for about half of the affected population, followed by vascular dementia (VaD) (20–25%), mixed dementia (5–10%), Parkinson's disease, dementia with Lewy bodies, physical brain injury, Huntington's disease, Creutzfeldt–Jacob disease, frontotemporal dementia/Pick's disease, and normal pressure hydrocephalus.^{5,6} AD is also the most common neurodegenerative disorder and affects 20–30 million individuals worldwide.⁷ AD has been further categorized into two forms according to its onset: sporadic cases (>95%) with late-onset disease, and autosomal-dominant mutation cases (<5%) with early onset.

The pathogenesis of AD includes the formation and deposition of amyloid β ($A\beta$), neurofibrillary tangles (assembled by hyperphosphorylated Tau protein), and inflammation.^{8,9} Among these, it is widely accepted that fibrillar $A\beta$ plays an important role in AD pathogenesis through activation of microglia and stimulates the release of inflammatory mediators, which lead to neuronal dysfunction and subsequent cell death.¹⁰ However, recent clinical evidence and animal studies have revealed that astrocyte and microglial activation may be an early event in AD, which occurs before the formation of $A\beta$.^{11–16} The importance of inflammation on the progress of AD has been emphasized. However, it is uncertain whether $A\beta$ and neurofibrillary tangles are causal factors of AD. Current medical treatment for dementia aims to improve cognitive and behavioral symptoms; therefore, it is essential to identify markers for the early stage of dementia to prevent or halt disease progress.

Factors associated with dementia include age, sex, inflammation, genetic factors, comorbidity, environmental factors, and lifestyle. Protective

factors include high education level, moderate alcohol consumption, use of hormone replacement therapy (HRT) for women, use of anti-inflammatory drugs, and diet. Associations between these factors and dementia might vary by disease subtype and are discussed in this review.

Methods

We performed searches of MEDLINE (<http://medline.cos.com>) and PubMed (<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi>) to identify relevant articles published between 1966 and 2009. We also searched EMBASE (<http://www.embase.com>) for articles published between 1991 and 2009.

Genetic Effects

Several studies have used candidate gene approaches to explore the association between genetic variants and the risk of dementia. Among these, the *APOE* gene is of great importance in the majority of people with dementia, which mostly are sporadic cases. The association between *APOE* genotype and the risk of AD was first reported by Corder et al in 1993.¹⁷ A Swedish twin study has reported that 60–80% of AD is attributable to genetic effects.^{18,19} For late-onset AD, genetic variations in the *APOE* gene play an important role. For early-onset cases, *APP*, *preselin (PS)-1*, and *PS-2* genes are of interest.²⁰ As the number of *APOEε4* alleles increases, the risk of late-onset AD increases from 20% to 90%, and the mean age at onset decreases from 84 to 68 years.¹⁷ A meta-analysis has shown that the *APOEε4* allele is a major risk factor for AD in all ethnic groups for men and women aged between 40 and 90 years.²¹ This association is stronger among Japanese than Caucasians but weaker among African-Americans and Hispanics.²¹ Even though the *APOEε4* allele has been related to an elevated risk of AD,²² only 50% of AD cases carry an *APOEε4* allele.²³ This

reflects that genes other than *APOE* may play a role in the pathogenesis of AD.

Inflammation is an important process in the pathogenesis of AD, and recent studies have shown that polymorphisms of one of the inflammatory genes alone or in combination have comparable effects on AD risk to those for the *APOE* ϵ 4 allele. For example, *IL-1* α -889 allele T is associated significantly with the risk of late-onset AD regardless of the genotype of *APOE*.²⁴ Homozygous variant carriers of high-risk alleles, e.g. *IL-1* α -889 and *IL-1* β +3953²⁵⁻²⁷ or the combination of the *APOE* ϵ 4 and high-risk allele of *TNF- α* ,²⁸ could predict people at high risk of AD.²⁹ These findings reflect that the joint effect of inflammatory and *APOE* genes may be better predictors of disease risk than *APOE* genotypes alone. In contrast to the candidate gene approach, recent genome-wide association studies³⁰⁻³² have consistently found that *APOE* is a significant risk factor for dementia among Caucasians.

Age

The effects of aging and parental age at birth have been linked to the risk of dementia. In the United States and Europe, several cohort studies³³⁻³⁹ have shown that the risk of dementia and AD increases with age. This association has been observed in all subtypes of dementia in a Spanish study.³⁹ A meta-analysis that included 17 Chinese studies has also shown that the prevalence of AD and VaD increases with age.⁴⁰ As a whole, the effect of aging is a relatively consistent risk factor for dementia across various ethnic groups.

Relatively few studies have evaluated the association between parental age at birth and the risk of dementia. Some studies have found that advanced parental age at birth is associated with an increased risk of AD, probably because of chromosomal abnormality.⁴¹⁻⁴³ However, other studies have failed to replicate this association.⁴⁴⁻⁴⁶ Parental health status might vary significantly between individuals and populations; therefore, it may not be a reliable predictor for dementia.

Sex

Sex is an important risk factor for AD among elderly people. A Dutch follow-up study has found that the incidence of AD in women is higher than that in men after the age of 85 years.⁴⁷ However, there are no sex differences in rates or risk for VaD. The same team has also reported that the risk of AD declines in men but not in women after the age of 90 years.⁴⁸ The overall incidence of VaD is lower in women than in men.⁴⁸ A meta-analysis that included only Chinese populations has shown a higher prevalence of AD, but not VaD, among women as compared with men aged ≥ 60 years.⁴⁰ The above findings can be explained by a protective effect of estrogen for premenopausal women, and earlier death for men from cardiovascular disease.⁴⁷ In contrast, the association between sex and risk of dementia has been shown to be not significant in Italian and Spanish populations.^{39,49} Several factors might complicate this association, e.g. sex steroid hormones, lifestyle, ethnicity, and genetic polymorphisms of sex-related genes. Therefore, it is important to consider various risk factors while the association between sex and risk of dementia is explored.

Physical Activity

The association between physical activity and risk of dementia has been explored extensively. Some cohort studies have observed that physical activity is associated positively with cognitive function among older people.^{50,51} Other studies have found that physical activity is associated with a reduction of 30–50% in cognitive decline.⁵²⁻⁵⁴ A meta-analysis that included 30 randomized trials has found that exercise training has a positive effect on cognitive function.⁵⁵ A randomized trial in the elderly conducted after the meta-analysis has found that 24 weeks of physical activity intervention may improve cognitive function.⁵⁶ Furthermore, a cross-sectional study in community-dwelling residents aged 70–79 years has shown that high

levels of recreational activity are associated significantly with lower levels of the inflammatory markers interleukin-6 and C-reactive protein.⁵⁷ Such potential benefits of increased physical activity on inflammatory markers will need to be confirmed in clinical trials. The protective effect of physical activity might be a result of reduced vascular risk and obesity, lower levels of inflammatory markers, enhanced fitness, neuronal health, and physical function, as well as positive behavior.^{55,58} In a follow-up study in the United States, individuals who participated in at least four physical activities within 2 weeks before study recruitment had a significantly lower risk of dementia compared with those who engaged in only one or no activity.⁵⁹ This association was significant among *APOEε4* allele non-carriers, but absent from *APOEε4* allele carriers.⁵⁹ As a whole, most previous studies have supported the notion that physical activity can reduce the risk of dementia, probably through improvement of cognitive function and overall health status. Different measurements of cognition, various lengths of study period, and different subject characteristics have been used to evaluate the effect of physical activity on the risk of dementia, and these might explain the inconsistency of previous findings.

Smoking

The effect of smoking on dementia risk is controversial. A recent meta-analysis has shown that current smoking is associated significantly with an increased risk of AD but not with VaD and cognitive decline.⁶⁰ Two follow-up studies^{61,62} in the United States and one in China⁶³ have reported a significant association between current smokers and the risk of dementia. This association was not significant among former smokers.^{61,62} Previous inconsistent findings possibly have resulted from survival bias, some potential issues for case-control studies (e.g. recall bias, under- and overestimation of smoking), and failure to stratify the subjects by smoking status (current and

former smoking) in the analysis. Smoking could be a potential confounder for the association of cerebrovascular diseases with dementia. However, cerebrovascular diseases have not been explored consistently in previous studies. Future studies using a follow-up design will be able to provide more accurate data on cigarette smoking. Stratification by smoking status (current *vs.* former smoking) is warranted to elucidate this association.

Drugs

Several drugs are related to the risk of dementia. This review only discusses some commonly used drugs. A French study has shown that former, but not current use of benzodiazepines, was related to an increased risk of dementia in a nested case-control study.⁶⁴ Conversely, some drugs might be beneficial in lowering dementia risk. Statins (HMG-CoA reductase inhibitors) are used widely to lower the level of cholesterol, especially low-density lipoprotein cholesterol, in patients with cardiovascular disease. In a follow-up study of an elderly population in the United States, statin use was associated inversely with the risk of prevalent dementia, but not for incident dementia or AD.⁶⁵ Similarly, a recent observational study has found that simvastatin significantly reduces the risk of dementia among individuals over 65 years of age.⁶⁶ Statins seem to reduce the risk of dementia effectively through an anti-inflammatory mechanism by lowering the level of cholesterol, and isoprenylation.⁶⁶ More randomized clinical trials are needed to confirm the effect of statins, as well as studies stratified by dementia subtypes (e.g. VaD and mixed type) and age of dementia onset. Four clinical trials have investigated the effects of antihypertensive drugs on the risk of dementia. The Syst-Eur trial⁶⁷ has shown that active treatment with nitrendipine, with the possible addition of enalapril and/or hydrochlorothiazide, could lower the incidence of dementia by 50% as compared with the placebo group. The PROGRESS study has found that active treatment with perindopril with/without indapamide was

associated significantly with a reduction in cognitive decline as compared with the placebo group.⁶⁸ However, the SCOPE study⁶⁹ (candesartan with/without hydrochlorothiazide *vs.* placebo) and the SHEP trial⁷⁰ (chlorthalidone with/without atenolol or reserpine *vs.* placebo) have failed to show a significant reduction in dementia incidence. Other classes of antihypertensive drugs (e.g. angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, diuretics, and calcium channel blockers) might lower the risk of dementia.⁷¹ The findings from antihypertensive drugs are inconclusive, which could be the result of the different etiology of dementia subtypes, as well as different pharmacokinetics and pharmacodynamics. Previous studies mainly have explored overall dementia, and prospective studies and clinical trials stratified by dementia subtypes are needed to explore the effects of various drugs on the risk of dementia.

Several studies have found an association between HRT and lower risk of AD among women.⁷²⁻⁷⁷ The phenomenon can be explained by the protective effect of estrogen.⁴⁷ However, this relationship was not observed in the Women's Health Initiative Memory Study.⁷⁸ In addition, the decreased endogenous estrogen level was related to an increased risk of AD.⁷² However, no association was observed in other studies.^{79,80} Perimenopausal women are at a relatively young age, which has a lower risk of dementia, and experience complicated physiological changes. The heterogeneity of HRT, different study designs, and many other factors could confound the association between HRT and the risk of dementia and explain previous inconsistent findings. A well-defined cohort study would help to elucidate the relationship between HRT and the risk of dementia.

Animal studies have reported that some non-steroidal anti-inflammatory drugs (NSAIDs) can lower the level of A β -42,⁸¹ which is independent of cyclooxygenase activity,⁸² and long-term NSAIDs exposure can lower the risk and slow down progression of AD.^{8,83} A meta-analysis of four prospective studies has found that lifetime NSAID exposure was associated with a 26% reduction in

risk of AD. A meta-analysis of three prospective studies has shown that use of NSAIDs for ≥ 2 years contributed to a 58% reduction in risk of dementia.⁸⁴ However, some randomized clinical trials have failed to demonstrate this association.⁸⁵⁻⁸⁷ A recent cohort study has confirmed the protective effect of NSAIDs on the risk of AD [hazard ratio, 0.63; 95% confidence interval (CI), 0.45-0.88].⁸⁸ Few randomized clinical trials are available to evaluate the effect of NSAIDs on dementia because of their potential cardiovascular side effects.^{89,90} More observational studies are needed to confirm the association between use of NSAIDs and risk of dementia. In addition, drug-drug interactions need to be considered to rule out the confounding effect from other medications. To date, the mechanism of protection against dementia by NSAIDs is not clearly understood.^{91,92}

Education

In a follow-up study, subjects with less education had a higher risk of non-AD dementia [odds ratio (OR), 1.75; 95% CI, 1.03-2.98] as compared with those with a high school diploma.⁹³ However, this association was not observed for AD.⁹³ In addition to childhood education, less post-secondary education (i.e. education beyond high school or 12th-grade level) was significantly associated with an increased risk of dementia after the age of 60 years.⁹⁴ Similarly, a study in the United States has found that Caucasians with low education level (≤ 10 years) had twice the risk of dementia of those with high education level (> 10 years).⁹⁵ A cohort study has reported a significant association between education level and cognitive function, but the association was not significant between education and rate of cognitive decline.⁹⁶ It is possible that individuals with lower education level tend to have lower cognitive function compared with those at the same age but with higher education level. Therefore, the onset of dementia among the former is likely to be earlier than that in the latter. As a

whole, education level is related to socioeconomic status⁹⁷ and sex,⁴⁷ both of which may complicate the association between education level and risk of dementia. The different cutoff points of the education level between studies, and failure to explore the association by dementia subtypes in some studies, could explain previous controversial findings.

Alcohol Consumption

Alcohol intake seems to protect older people from dementia, including AD, in a J-shape association.⁹⁸ A recent meta-analysis, including 20 cohorts and three nested case-control studies, has indicated that alcohol drinking may be protective for AD and dementia, but not for VaD and cognitive decline.⁹⁹ However, some studies have shown that heavy alcohol consumption might be associated with an increased risk of dementia in patients with mild cognitive impairment or in men carrying the *APOEε4* allele.^{100,101} In contrast, the consumption of liquor, beer, and total alcohol is not associated with a decreased risk of AD.¹⁰² Decreased risk of AD is associated with wine consumption of up to three servings daily among individuals aged ≥ 65 years without the *APOEε4* allele.¹⁰² Controversial findings in previous studies could have resulted from different types of alcohol (e.g. liquor, beer or wine), different follow-up time, measurement of alcohol consumption, and other confounding factors. More studies with more accurate measurement are needed to confirm this association.

Body Mass Index (BMI)

Overweight and obesity are risk factors of AD, hyperinsulinemia and diabetes.¹⁰³ A recent meta-analysis,¹⁰⁴ including 10 follow-up studies with subjects aged 40–80 years at baseline, has shown a U-shape relationship between BMI and dementia.¹⁰⁴ However, a recent follow-up study¹⁰⁵ has demonstrated an increased risk of dementia among

obese persons (BMI > 30), as compared with those with normal weight (BMI 20–25) at 50 years of age. Whereas, there was a reverse association between BMI and risk of dementia at ≥ 65 years of age.¹⁰⁵ In contrast, weight gain and increased waist circumference and skinfold thickness are related to increased risk of dementia.¹⁰⁴ Another study has found that steady annual weight loss of 1 kg/m² among old people was related to a 35% increase in AD risk, as compared with individuals without BMI changes.¹⁰⁶ Weight loss can reflect underlying diseases and obesity can be related to subsequent vascular diseases. Old people experience muscle loss, therefore, waist circumference rather than BMI might be a better surrogate of overweight or obesity. This could explain partly the controversial findings from previous studies.

Comorbidity

Dementia risk is related to various diseases. Hypertension is an important risk factor for VaD¹⁰⁷ but not AD.¹⁰⁸ Type 2 diabetes is associated strongly with insulin resistance, which is related to the formation of A β and inflammatory agents in the brain,^{109,110} and the subsequent increased risk of AD.¹⁰⁹ On average, around half of individuals with vascular cognitive impairment might develop dementia within 5 years after a stroke.¹¹¹ In addition, there is an increased risk of dementia among individuals > 84 years old and who have had two or more infections in the 4 years preceding diagnosis of dementia compared to those who have had zero or one infection.¹¹² Human immunodeficiency virus and hepatitis C virus have been reported to be associated with dementia.^{113,114} Moreover, traumatic brain injury can induce the early development of AD.¹¹⁵ A meta-analysis that included 15 case-control studies has found that head injury is associated with an elevated risk of AD among men but not women.¹¹⁶ Men tend to be involved with more dangerous work than women, and therefore have a higher risk of head injury and subsequent increased risk of dementia than do women. Furthermore, two meta-analyses

have shown consistently that a history of depression is a risk factor for AD in later life.^{117,118} As a whole, infections, vascular factors and related diseases, head injury, and psychological conditions can share a common inflammatory pathway that contributes to the etiology of dementia.

Environmental Factors

The role of environmental factors on the progress of dementia is complicated. Aluminum is related to the risk of dementia because it can act as a co-factor in the progression of dementia.^{119,120} It has been speculated that other metals, such as iron, copper and zinc, are related to dementia.^{119,121–123} Several nutrients have also been linked with the risk of dementia. For example, serum vitamin D level is lower among women with mild dementia than among those without.¹²⁴ In addition, a clinical trial has shown that vitamin E is not beneficial to patients with mild cognitive impairment at a stage between normal aging and early stages of dementia.¹²⁵ Some macronutrients, such as glucose, protein (tryptophan and tyrosine) and unsaturated fatty acids, have been linked to age-related changes in cognitive function among people with AD and VaD.¹¹⁹ Dementia can be exacerbated via oxidative stress as a result of higher energy and lower antioxidant intake.¹²⁶ People with AD or VaD have similar dietary patterns, except that the former consume more animal fats than the latter.¹²⁶ In addition, excessive intake of *n*-6 polyunsaturated fatty acids (PUFAs) or deficiency of *n*-3 PUFAs may lead to chronic inflammation, platelet aggregation, or microvascular endothelial dysfunction.¹²⁶ Environmental exposure before the onset of dementia may be influential and many environmental factors are yet to be identified.

Conclusions

Dementia is a complex human disease and many factors contribute to its pathogenesis. As a result

of improved health care and changes in lifestyle, longer life spans have led to an increasing number of people with dementia. In the post-genome era, the advance of high-throughput genotyping technology, e.g. microarrays, and statistical tools have allowed us to extensively assess the association between genetic factors and risk of dementia. Environmental factors, which have not been well identified, might also play an important role in the pathogenesis of dementia. Future research should place an emphasis on identifying new environmental risk factors, perform whole-genome association studies at different levels (DNA, RNA and protein), explore the interaction between genetic and environmental factors, and include non-Caucasian populations, to unravel the etiology of dementia.

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