REVIEW ARTICLE

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 (≥ 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 (Aβ), neurofibrillary tangles (assembled by hyperphosphorylated Tau protein), and inflammation.[8,9] Among these, it is widely accepted that fibrillar Aβ 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 Aβ.[11–16] The importance of inflammation on the progress of AD has been emphasized. However, it is uncertain whether Aβ 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 *APOEε4* allele. For example, *IL-1α-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-1α-889 and IL-1β+3953[25–27] or the combination of the *APOEε4* 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 studies[30–32] 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 studies[33–39] 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 pre-menopausal 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 China[63] 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 trial[67] 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 study[69] (candesartan with/without hydrochlorothiazide *vs.* placebo) and the SHEP trial[70] (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 nonsteroidal anti-inflammatory drugs (NSAIDs) can lower the level of Aβ-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 status[97] 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 study[105] 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/m^2 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 VaD[107] but not AD.[108] Type 2 diabetes is associated strongly with insulin resistance, which is related to the formation of Aβ 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.

References

1. Hoyert DL, Kung HC, Smith BL. Deaths: preliminary data for 2003. *Natl Vital Stat Rep* 2005;53:1–48.
2. *The World Factbook*. Washington, DC: Central Intelligence Agency, 2007.
3. Albert MS. Changing the trajectory of cognitive decline? *N Engl J Med* 2007;357:502–3.
4. Walsh DM, Selkoe DJ. Deciphering the molecular basis of memory failure in Alzheimer's disease. *Neuron* 2004;44: 181–93.
5. Liu CK, Tai CT, Lin RT, et al. Epidemiology of dementia in Taiwan. *Appl Psychol Res* 2000;7:157–69.
6. *Basics of Alzheimer's Disease: What It Is and What You Can Do*. Chicago, IL: Alzheimer's Association, 2005: 8–9.
7. Selkoe DJ. Defining molecular targets to prevent Alzheimer disease. *Arch Neurol* 2005;62:192–5.
8. Heneka MT, O'Banion MK. Inflammatory processes in Alzheimer's disease. *J Neuroimmunol* 2007;184:69–91.
9. Wong PC, Cai H, Borchelt DR, et al. Genetically engineered mouse models of neurodegenerative diseases. *Nat Neurosci* 2002;5:633–9.
10. Walsh DM, Klyubin I, Fadeeva JV, et al. Naturally secreted oligomers of amyloid beta protein potently inhibit hippocampal long-term potentiation *in vivo*. *Nature* 2002; 416:535–9.
11. Cagnin A, Brooks DJ, Kennedy AM, et al. *In-vivo* measurement of activated microglia in dementia. *Lancet* 2001; 358:461–7.
12. Heneka MT, Sastre M, Dumitrescu-Ozimek L, et al. Focal glial activation coincides with increased BACE1 activation

and precedes amyloid plaque deposition in APP[V717I] transgenic mice. *J Neuroinflammation* 2005;2:22.
13. Moechars D, Dewachter I, Lorent K, et al. Early phenotypic changes in transgenic mice that overexpress different mutants of amyloid precursor protein in brain. *J Biol Chem* 1999;274:6483–92.
14. Hu J, Akama KT, Krafft GA, et al. Amyloid-beta peptide activates cultured astrocytes: morphological alterations, cytokine induction and nitric oxide release. *Brain Res* 1998;785:195–206.
15. Lindberg C, Selenica ML, Westlind-Danielsson A, et al. Beta-amyloid protein structure determines the nature of cytokine release from rat microglia. *J Mol Neurosci* 2005; 27:1–12.
16. White JA, Manelli AM, Holmberg KH, et al. Differential effects of oligomeric and fibrillar amyloid-beta 1-42 on astrocyte-mediated inflammation. *Neurobiol Dis* 2005;18: 459–65.
17. Corder EH, Saunders AM, Strittmatter WJ, et al. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science* 1993; 261:921–3.
18. Gatz M, Fratiglioni L, Johansson B, et al. Complete ascertainment of dementia in the Swedish Twin Registry: the HARMONY study. *Neurobiol Aging* 2005;26:439–47.
19. Pedersen NL, Gatz M, Berg S, et al. How heritable is Alzheimer's disease late in life? Findings from Swedish twins. *Ann Neurol* 2004;55:180–5.
20. Richard F, Amouyel P. Genetic susceptibility factors for Alzheimer's disease. *Eur J Pharmacol* 2001;412:1–12.
21. Farrer LA, Cupples LA, Haines JL, et al. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium. *JAMA* 1997;278:1349–56.
22. Strittmatter WJ, Saunders AM, Schmechel D, et al. Apolipoprotein E: high-avidity binding to beta-amyloid and increased frequency of type 4 allele in late-onset familial Alzheimer disease. *Proc Natl Acad Sci USA* 1993;90: 1977–81.
23. Pastor P, Goate AM. Molecular genetics of Alzheimer's disease. *Curr Psychiatry Rep* 2004;6:125–33.
24. Du Y, Dodel RC, Eastwood BJ, et al. Association of an interleukin 1 alpha polymorphism with Alzheimer's disease. *Neurology* 2000;55:480–3.
25. Hedley R, Hallmayer J, Groth DM, et al. Association of interleukin-1 polymorphisms with Alzheimer's disease in Australia. *Ann Neurol* 2002;51:795–7.
26. Griffin WS, Mrak RE. Interleukin-1 in the genesis and progression of and risk for development of neuronal degeneration in Alzheimer's disease. *J Leukoc Biol* 2002;72:233–8.
27. Nicoll JA, Mrak RE, Graham DI, et al. Association of interleukin-1 gene polymorphisms with Alzheimer's disease. *Ann Neurol* 2000;47:365–8.
28. McCusker SM, Curran MD, Dynan KB, et al. Association between polymorphism in regulatory region of gene encoding tumour necrosis factor alpha and risk of Alzheimer's disease and vascular dementia: a case–control study. *Lancet* 2001;357:436–9.
29. McGeer PL, McGeer EG. Polymorphisms in inflammatory genes and the risk of Alzheimer disease. *Arch Neurol* 2001;58:1790–2.
30. Abraham R, Moskvina V, Sims R, et al. A genome-wide association study for late-onset Alzheimer's disease using DNA pooling. *BMC Med Genomics* 2008;1:44.
31. Bertram L, Lange C, Mullin K, et al. Genome-wide association analysis reveals putative Alzheimer's disease susceptibility loci in addition to APOE. *Am J Hum Genet* 2008; 83:623–32.
32. Carrasquillo MM, Zou F, Pankratz VS, et al. Genetic variation in PCDH11X is associated with susceptibility to late-onset Alzheimer's disease. *Nat Genet* 2009;41:192–8.
33. Kukull WA, Higdon R, Bowen JD, et al. Dementia and Alzheimer disease incidence: a prospective cohort study. *Arch Neurol* 2002;59:1737–46.
34. Launer LJ, Andersen K, Dewey ME, et al. Rates and risk factors for dementia and Alzheimer's disease: results from EURODEM pooled analyses. EURODEM Incidence Research Group and Work Groups. European Studies of Dementia. *Neurology* 1999;52:78–84.
35. Ganguli M, Dodge HH, Chen P, et al. Ten-year incidence of dementia in a rural elderly US community population: the MoVIES Project. *Neurology* 2000;54:1109–16.
36. Rocca WA, Cha RH, Waring SC, et al. Incidence of dementia and Alzheimer's disease: a reanalysis of data from Rochester, Minnesota, 1975–1984. *Am J Epidemiol* 1998; 148:51–62.
37. Bachman DL, Wolf PA, Linn RT, et al. Incidence of dementia and probable Alzheimer's disease in a general population: the Framingham Study. *Neurology* 1993;43:515–9.
38. Kawas C, Gray S, Brookmeyer R, et al. Age-specific incidence rates of Alzheimer's disease: the Baltimore Longitudinal Study of Aging. *Neurology* 2000;54:2072–7.
39. Lopez-Pousa S, Vilalta-Franch J, Llinas-Regla J, et al. Incidence of dementia in a rural community in Spain: the Girona cohort study. *Neuroepidemiology* 2004;23:170–7.
40. Liu L, Guo XE, Zhou YQ, et al. Prevalence of dementia in China. *Dement Geriatr Cogn Disord* 2003;15:226–30.
41. Urakami K, Adachi Y, Takahashi K. A community-based study of parental age at the birth of patients with dementia of the Alzheimer type. *Arch Neurol* 1989;46:38–9.
42. Corkin S, Growdon JH, Rasmussen SL. Parental age as a risk factor in Alzheimer's disease. *Ann Neurol* 1983;13:674–6.
43. Bertram L, Busch R, Spiegl M, et al. Paternal age is a risk factor for Alzheimer disease in the absence of a major gene. *Neurogenetics* 1998;1:277–80.
44. Corkin S, Growdon JH, Rasmussen SL. Parental age as a risk factor in Alzheimer's disease. *Ann Neurol* 1983;13:674–6.
45. Jouan-Flahault C, Seroussi MC, Colvez A. Absence of a relationship between senile dementia and parental age. A case report survey in Upper Normandy. *Rev Epidemiol Sante Publique* 1989;37:73–5. [In French]

46. Ptok U, Papassotiropoulos A, Maier W, et al. Advanced parental age: a risk factor for Alzheimer's disease or depression in the elderly? *Int Psychogeriatr* 2000;12:445–51.
47. Andersen K, Launer LJ, Dewey ME, et al. Gender differences in the incidence of AD and vascular dementia: the EURODEM Studies. EURODEM Incidence Research Group. *Neurology* 1999;53:1992–7.
48. Ruitenberg A, Ott A, van Swieten JC, et al. Incidence of dementia: does gender make a difference? *Neurobiol Aging* 2001;22:575–80.
49. Ravaglia G, Forti P, Maioli F, et al. Incidence and etiology of dementia in a large elderly Italian population. *Neurology* 2005;64:1525–30.
50. Yaffe K, Barnes D, Nevitt M, et al. A prospective study of physical activity and cognitive decline in elderly women: women who walk. *Arch Intern Med* 2001;161:1703–8.
51. Barnes DE, Yaffe K, Satariano WA, et al. A longitudinal study of cardiorespiratory fitness and cognitive function in healthy older adults. *J Am Geriatr Soc* 2003;51:459–65.
52. Karp A, Paillard-Borg S, Wang HX, et al. Mental, physical and social components in leisure activities equally contribute to decrease dementia risk. *Dement Geriatr Cogn Disord* 2006;21:65–73.
53. Laurin D, Verreault R, Lindsay J, et al. Physical activity and risk of cognitive impairment and dementia in elderly persons. *Arch Neurol* 2001;58:498–504.
54. Abbott RD, White LR, Ross GW, et al. Walking and dementia in physically capable elderly men. *JAMA* 2004;292: 1447–53.
55. Heyn P, Abreu BC, Ottenbacher KJ. The effects of exercise training on elderly persons with cognitive impairment and dementia: a meta-analysis. *Arch Phys Med Rehabil* 2004;85:1694–704.
56. Lautenschlager NT, Cox KL, Flicker L, et al. Effect of physical activity on cognitive function in older adults at risk for Alzheimer disease: a randomized trial. *JAMA* 2008;300: 1027–37.
57. Reuben DB, Judd-Hamilton L, Harris TB, et al. The associations between physical activity and inflammatory markers in high-functioning older persons: MacArthur Studies of Successful Aging. *J Am Geriatr Soc* 2003;51:1125–30.
58. Barnes DE, Whitmer RA, Yaffe K. Physical activity and dementia: the need for prevention trials. *Exerc Sport Sci Rev* 2007;35:24–9.
59. Podewils LJ, Guallar E, Kuller LH, et al. Physical activity, APOE genotype, and dementia risk: findings from the Cardiovascular Health Cognition Study. *Am J Epidemiol* 2005;161:639–51.
60. Peters R, Poulter R, Warner J, et al. Smoking, dementia and cognitive decline in the elderly, a systematic review. *BMC Geriatr* 2008;8:36.
61. Aggarwal NT, Bienias JL, Bennett DA, et al. The relation of cigarette smoking to incident Alzheimer's disease in a biracial urban community population. *Neuroepidemiology* 2006;26:140–6.
62. Merchant C, Tang MX, Albert S, et al. The influence of smoking on the risk of Alzheimer's disease. *Neurology* 1999;52:1408–12.
63. Juan D, Zhou DH, Li J, et al. A 2-year follow-up study of cigarette smoking and risk of dementia. *Eur J Neurol* 2004;11:277–82.
64. Lagnaoui R, Begaud B, Moore N, et al. Benzodiazepine use and risk of dementia: a nested case–control study. *J Clin Epidemiol* 2002;55:314–8.
65. Zandi PP, Sparks DL, Khachaturian AS, et al. Do statins reduce risk of incident dementia and Alzheimer disease? The Cache County Study. *Arch Gen Psychiatry* 2005;62:217–24.
66. Wolozin B, Wang SW, Li NC, et al. Simvastatin is associated with a reduced incidence of dementia and Parkinson's disease. *BMC Med* 2007;5:20.
67. Forette F, Seux ML, Staessen JA, et al. Prevention of dementia in randomised double-blind placebo-controlled Systolic Hypertension in Europe (Syst-Eur) trial. *Lancet* 1998;352:1347–51.
68. Tzourio C, Anderson C, Chapman N, et al. Effects of blood pressure lowering with perindopril and indapamide therapy on dementia and cognitive decline in patients with cerebrovascular disease. *Arch Intern Med* 2003;163: 1069–75.
69. Lithell H, Hansson L, Skoog I, et al. The Study on Cognition and Prognosis in the Elderly (SCOPE): principal results of a randomized double-blind intervention trial. *J Hypertens* 2003;21:875–86.
70. Applegate WB, Pressel S, Wittes J, et al. Impact of the treatment of isolated systolic hypertension on behavioral variables. Results from the systolic hypertension in the elderly program. *Arch Intern Med* 1994;154:2154–60.
71. Forette F, Seux ML, Staessen JA, et al. The prevention of dementia with antihypertensive treatment: new evidence from the Systolic Hypertension in Europe (Syst-Eur) study. *Arch Intern Med* 2002;162:2046–2.
72. Paganini-Hill A, Henderson VW. Estrogen deficiency and risk of Alzheimer's disease in women. *Am J Epidemiol* 1994;140:256–61.
73. Tang MX, Jacobs D, Stern Y, et al. Effect of oestrogen during menopause on risk and age at onset of Alzheimer's disease. *Lancet* 1996;348:429–32.
74. Kawas C, Resnick S, Morrison A, et al. A prospective study of estrogen replacement therapy and the risk of developing Alzheimer's disease: the Baltimore Longitudinal Study of Aging. *Neurology* 1997;48: 1517–21.
75. Yaffe K, Sawaya G, Lieberburg I, et al. Estrogen therapy in postmenopausal women: effects on cognitive function and dementia. *JAMA* 1998;279:688–95.
76. Waring SC, Rocca WA, Petersen RC, et al. Postmenopausal estrogen replacement therapy and risk of AD: a population-based study. *Neurology* 1999;52: 965–70.
77. Zandi PP, Carlson MC, Plassman BL, et al. Hormone replacement therapy and incidence of Alzheimer disease in

older women: the Cache County Study. *JAMA* 2002;288: 2123–9.
78. Shumaker SA, Legault C, Rapp SR, et al. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. *JAMA* 2003;289:2651–62.
79. Barrett-Connor E, Kritz-Silverstein D. Estrogen replacement therapy and cognitive function in older women. *JAMA* 1993;269:2637–41.
80. Matthews K, Cauley J, Yaffe K, et al. Estrogen replacement therapy and cognitive decline in older community women. *J Am Geriatr Soc* 1999;47:518–23.
81. Eriksen JL, Sagi SA, Smith TE, et al. NSAIDs and enantiomers of flurbiprofen target gamma-secretase and lower Abeta 42 *in vivo*. *J Clin Invest* 2003;112:440–9.
82. Weggen S, Eriksen JL, Das P, et al. A subset of NSAIDs lower amyloidogenic Abeta42 independently of cyclooxygenase activity. *Nature* 2001;414:212–6.
83. Rich JB, Rasmusson DX, Folstein MF, et al. Nonsteroidal anti-inflammatory drugs in Alzheimer's disease. *Neurology* 1995;45:51–5.
84. Szekely CA, Thorne JE, Zandi PP, et al. Nonsteroidal anti-inflammatory drugs for the prevention of Alzheimer's disease: a systematic review. *Neuroepidemiology* 2004; 23:159–69.
85. Wyss-Coray T. Inflammation in Alzheimer disease: driving force, bystander or beneficial response? *Nat Med* 2006;12:1005–15.
86. Aisen PS, Schafer KA, Grundman M, et al. Effects of rofecoxib or naproxen *vs* placebo on Alzheimer disease progression: a randomized controlled trial. *JAMA* 2003; 289:2819–26.
87. Thal LJ, Ferris SH, Kirby L, et al. A randomized, double-blind, study of rofecoxib in patients with mild cognitive impairment. *Neuropsychopharmacology* 2005;30: 1204–15.
88. Szekely CA, Breitner JC, Fitzpatrick AL, et al. NSAID use and dementia risk in the Cardiovascular Health Study: role of APOE and NSAID type. *Neurology* 2008;70:17–24.
89. Scharf JM, Daffner KR. NSAIDs in the prevention of dementia: a Cache-22? *Neurology* 2007;69:235–6.
90. ADAPT Research Group. Cardiovascular and cerebrovascular events in the randomized, controlled Alzheimer's Disease Anti-Inflammatory Prevention Trial (ADAPT). *PLoS Clin Trials* 2006;1:e33.
91. Yan Q, Zhang J, Liu H, et al. Anti-inflammatory drug therapy alters beta-amyloid processing and deposition in an animal model of Alzheimer's disease. *J Neurosci* 2003;23:7504–9.
92. Zilka N, Ferencik M, Hulin I. Neuroinflammation in Alzheimer's disease: protector or promoter? *Bratisl Lek Listy* 2006;107:374–83.
93. Cobb JL, Wolf PA, Au R, et al. The effect of education on the incidence of dementia and Alzheimer's disease in the Framingham Study. *Neurology* 1995;45:1707–12.
94. Chibnall JT, Eastwood R. Postsecondary education and dementia risk in older Jesuit priests. *Int Psychogeriatr* 1998;10:359–68.
95. Shadlen MF, Siscovick D, Fitzpatrick AL, et al. Education, cognitive test scores, and black-white differences in dementia risk. *J Am Geriatr Soc* 2006;54:898–905.
96. Wilson RS, Hebert LE, Scherr PA, et al. Educational attainment and cognitive decline in old age. *Neurology* 2009;72:460–5.
97. Karp A, Kareholt I, Qiu C, et al. Relation of education and occupation-based socioeconomic status to incident Alzheimer's disease. *Am J Epidemiol* 2004;159:175–83.
98. O'Keefe JH, Bybee KA, Lavie CJ. Alcohol and cardiovascular health: the razor-sharp double-edged sword. *J Am Coll Cardiol* 2007;50:1009–14.
99. Peters R, Peters J, Warner J, et al. Alcohol, dementia and cognitive decline in the elderly: a systematic review. *Age Ageing* 2008;37:505–12.
100. Mukamal KJ, Kuller LH, Fitzpatrick AL, et al. Prospective study of alcohol consumption and risk of dementia in older adults. *JAMA* 2003;289:1405–13.
101. Xu G, Liu X, Yin Q, et al. Alcohol consumption and transition of mild cognitive impairment to dementia. *Psychiatry Clin Neurosci* 2009;63:43–9.
102. Luchsinger JA, Tang MX, Siddiqui M, et al. Alcohol intake and risk of dementia. *J Am Geriatr Soc* 2004;52:540–6.
103. Luchsinger JA, Mayeux R. Adiposity and Alzheimer's disease. *Curr Alzheimer Res* 2007;4:127–34.
104. Beydoun MA, Beydoun HA, Wang Y. Obesity and central obesity as risk factors for incident dementia and its subtypes: a systematic review and meta-analysis. *Obes Rev* 2008;9:204–18.
105. Fitzpatrick AL, Kuller LH, Lopez OL, et al. Midlife and late-life obesity and the risk of dementia: cardiovascular health study. *Arch Neurol* 2009;66:336–42.
106. Buchman AS, Wilson RS, Bienias JL, et al. Change in body mass index and risk of incident Alzheimer disease. *Neurology* 2005;65:892–7.
107. Forette F, Boller F. Hypertension and the risk of dementia in the elderly. *Am J Med* 1991;90:14S–9S.
108. Posner HB, Tang MX, Luchsinger J, et al. The relationship of hypertension in the elderly to AD, vascular dementia, and cognitive function. *Neurology* 2002;58:1175–81.
109. Craft S. Insulin resistance and Alzheimer's disease pathogenesis: potential mechanisms and implications for treatment. *Curr Alzheimer Res* 2007;4:147–52.
110. Sun MK, Alkon DL. Links between Alzheimer's disease and diabetes. *Drugs Today (Barc)* 2006;42:481–9.
111. Starkstein SE, Almeida OP. Understanding cognitive impairment and dementia: stroke study. *Curr Opin Psychiatry* 2003;16:615–20.
112. Dunn N, Mullee M, Perry VH, et al. Association between dementia and infectious disease: evidence from a case– control study. *Alzheimer Dis Assoc Disord* 2005;19:91–4.

113. Corder EH, Robertson K, Lannfelt L, et al. HIV-infected subjects with the E4 allele for APOE have excess dementia and peripheral neuropathy. *Nat Med* 1998;4:1182–4.
114. Forton DM, Thomas HC, Murphy CA, et al. Hepatitis C and cognitive impairment in a cohort of patients with mild liver disease. *Hepatology* 2002;35:433–9.
115. Lye TC, Shores EA. Traumatic brain injury as a risk factor for Alzheimer's disease: a review. *Neuropsychol Rev* 2000;10:115–29.
116. Fleminger S, Oliver DL, Lovestone S, et al. Head injury as a risk factor for Alzheimer's disease: the evidence 10 years on; a partial replication. *J Neurol Neurosurg Psychiatry* 2003;74:857–62.
117. Ownby RL, Crocco E, Acevedo A, et al. Depression and risk for Alzheimer disease: systematic review, meta-analysis, and metaregression analysis. *Arch Gen Psychiatry* 2006;63:530–8.
118. Jorm AF. History of depression as a risk factor for dementia: an updated review. *Aust N Z J Psychiatry* 2001;35:776–81.
119. Solfrizzi V, Colacicco AM, D'Introno A, et al. Macronutrients, aluminium from drinking water and foods, and other metals in cognitive decline and dementia. *J Alzheimers Dis* 2006;10:303–30.
120. Rondeau V, Commenges D, Jacqmin-Gadda H, et al. Relation between aluminum concentrations in drinking water and Alzheimer's disease: an 8-year follow-up study. *Am J Epidemiol* 2000;152:59–66.
121. Yonekawa M, Okabe T, Asamoto Y, et al. A case of hereditary ceruloplasmin deficiency with iron deposition in the brain associated with chorea, dementia, diabetes mellitus and retinal pigmentation: administration of fresh-frozen human plasma. *Eur Neurol* 1999;42:157–62.
122. Danscher G, Jensen KB, Frederickson CJ, et al. Increased amount of zinc in the hippocampus and amygdala of Alzheimer's diseased brains: a proton-induced X-ray emission spectroscopic analysis of cryostat sections from autopsy material. *J Neurosci Methods* 1997;76:53–9.
123. Shore D, Henkin RI, Nelson NR, et al. Hair and serum copper, zinc, calcium, and magnesium concentrations in Alzheimer-type dementia. *J Am Geriatr Soc* 1984;32:892–5.
124. Kipen E, Helme RD, Wark JD, et al. Bone density, vitamin D nutrition, and parathyroid hormone levels in women with dementia. *J Am Geriatr Soc* 1995;43:1088–91.
125. Petersen RC, Thomas RG, Grundman M, et al. Vitamin E and donepezil for the treatment of mild cognitive impairment. *N Engl J Med* 2005;352:2379–88.
126. Otsuka M, Yamaguchi K, Ueki A. Similarities and differences between Alzheimer's disease and vascular dementia from the viewpoint of nutrition. *Ann NY Acad Sci* 2002;977:155–61.