Annu. Rev. Public Health 2004. 25:1–24
doi: 10.1146/annurev.publhealth.25.101802.122951

First published online as a Review in Advance on November 3, 2003

CAN DEMENTIA BE PREVENTED? BRAIN AGING IN A POPULATION-BASED CONTEXT

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Key Words Alzheimer's, vascular dementia, primary prevention, secondary prevention

■ **Abstract** As a consequence of global aging of the human population, the occurrence of cognitive impairment and dementia is rapidly becoming a significant burden for medical care and public health systems. By the year 2020, the WHO predicts there will be nearly 29 million demented people in both developed and developing countries. Primary and secondary prevention of dementia through individual and population-level interventions could reduce this imminent risk. Vascular risk factors such as type 2 diabetes, hypertension, dietary fat intake, high cholesterol, and obesity have emerged as important influences on the risk of both vascular and Alzheimer's dementia. Understanding the reasons for differences between populations in genetic vulnerability and environmental exposures may help to identify modifiable risk factors that may lead to effective prevention of vascular and Alzheimer's dementia.

INTRODUCTION

Dementia is now widely recognized as an important global public health problem. Rapid advances in neuroscience and increased interest in the burden of dementia syndromes on communities and nations have brought the importance of dementia to the forefront. This renewed focus is in no small measure due to aging of the world population and related increases in family, clinical, and social burdens from patients with dementia. Epidemiology and other public health research approaches have incorporated clinical and basic neuroscience into population-based research to begin to delineate the natural history of these syndromes and identify risk factors for dementia development. Identification of preventable or modifiable factors that influence the risk of dementia may lead to evaluation of preventive interventions. An estimated 4 million people in the United States are believed to suffer from Alzheimer's disease (AD) alone; if those with vascular dementia and other common dementias were included, the numbers might double (31). The World

Health Organization (WHO) estimates there are 18 million people with dementia in Europe, Africa, Asia, and Latin America and predicts there will be nearly 29 million by 2020 (39).

Dementia is not one biological condition, but rather is a syndrome defined by measurable cognitive decline to the point where physical, social, and intellectual functions are clearly impaired. Specific criteria for the diagnosis of the dementia syndrome and its components are available from several sources (84, 129). Over 200 types of dementia have been described, most of which are very uncommon, with some related to known genetic abnormalities. The heterogeneity of this syndrome makes estimating its impact more complex.

Population-based clinical and basic research all contribute to the identification of modifiable risk factors and the development of effective interventions. Clinical treatments or rehabilitative interventions that retard or halt the progression of this chronic illness or result in regression of disease have the potential to be applied as preventive interventions. In this review, we emphasize identification of modifiable environmental risk factors. Treatments focused on proximal features of dementia are likely to be part of the pathology of the disease and less appropriate for a review of disease prevention.

THE ECONOMIC AND PUBLIC HEALTH BURDEN OF DEMENTIA

Costs of Care and Treatments

Treating and managing dementia patients include direct medical care costs for acute care hospitals and long-term care. Some authors have recently projected an 83% increase in costs of caring for Alzheimer's dementia (111) by the year 2020. Rice and colleagues estimated that formal care costs for dementia in the United States averaged $27,672 per patient per year. Of these costs, long-term care is the most expensive component and is primarily paid out of pocket by the patients' family. Indirect costs such as lost wages and productivity averaged $10,400 to $34,517 per patient per year, influenced by patient severity, and length of survival with disease. Patients with AD are more likely to live in nursing homes (124) than other elderly individuals. Since most drugs currently available for AD treatment have modest effects at best, these treatments do not substantially impact progression of the disease in the overall population. Other treatments such as statins are in the early stages of evaluation as preventive treatments for AD. Treatments that prevent comorbid diseases, such as stroke or type 2 diabetes, may affect the rate of AD development or progression, and may be more cost-effective as preventive agents than current therapies. However all forms of primary and secondary prevention as well as tertiary treatments need to be explored more fully.

The Population Burden of Dementia

PREVALENCE The prevalence of major dementias, both AD and vascular dementia, has been extensively reviewed elsewhere (74, 75, 106, 113) (Table 1). Briefly, the prevalence of dementia in European studies of people aged 65 and older has ranged between 5% and 10% and doubles every 4 years to reach 30% at age

TABLE 1 Incidence of dementia in population-based studies

Study	Study design	Population	Incidence per 1000 person years
North-American Studies			
Monongahela County, PA (47)	Cohort, rural elderly, U.S.	65+	19.32
Cache County, Utah Study (91)	Cohort, Utah	65+	25.48
Seattle, WA: Adult Change in Thought (76)	Cohort	65+	20.30
	Cohort	65+	
Indiana, USA (58)	African American		32.4
Canada (25)	Cohort	65+	5.4 (m) 7.9 (w)
New York City (AD only) (130)			
White	Cohort	65+	30.8
African American			30.0
Caribbean Hispanics			19.0
European Studies			
Rotterdam, The Netherlands (78)	Cohort	65+	10.5 (m) 17.3 (w)
Denmark (78)	Cohort	65+	15.6 (m) 19.4 (w)
Britain (78)	Cohort	65+	10.7 (m) 18.5 (w)
France (78)	Cohort	65+	11.5 (m) 15.2 (w)
Italy (83)	Cohort	65–84	12.5 (all)
African, Asian-Indian, Chinese, and Japanese Studies			
Africa (58)	Cohort, Yoruba	65+	13.5
Indo-U.S. Cross-National Dementia Epidemiology study (20)	Cohort Rural elderly	65+	3.24
Japan (46)	Cohort	65+	19.2 (m) 20.9 (w)
China (81) (147, 149)	Cohort	65+	9.0
		65+	11.5
		60+	8.9

w = women, m = men.

80 (113). Most European studies suggest a higher risk of dementia in women. Dementia prevalence is consistently lower in most developing countries. In Nigeria, prevalence of dementia in those aged 65+ was slightly over 2% (59); in Ballabgarh, India less than 2% (47); and in Shanghai about 5% (149). Nearly all population-based studies report an increase in both prevalence and incidence of dementia with increasing age.

INCIDENCE In developed countries, dementia incidence is about 1% per year in those aged 65 and older (113). Incidence varies across race/ethnic groups and within race/ethnic groups in different geographic regions. At the time of this review, very few incidence studies have been conducted in developing countries. These include only India (47), Africa (58), and China (149). There has been some published research on dementia in South America and Mexico (64); however, they are not population-based cohort studies that can reliably provide estimates of dementia incidence. One barrier, among many, to doing dementia research in developing countries or across cultural groups is the lack of relatively unbiased screening and assessment instruments that are feasible for use in settings with minimal resources and populations with low literacy levels. A methodology for ascertaining dementia in developing countries, which may make such research more feasible in the future, has been proposed by the 10/66 group (106, 107).

A consistent pattern emerges from comparison of dementia incidence rates across populations: Rates appear to be lower in developing countries compared to developed countries. The majority of all incidence studies have been done in Europe and in the United States in populations of European ancestry. The single published study in Japan reported incidence rates similar to those found in the United States among those of European ancestry (46). Even among developed countries, there is considerable variation. For example, incidence in some European countries (4, 6) is lower than in the United States. Some authors have postulated the existence of a European north-south gradient in dementia risks, with the highest incidence occurring in northern European countries and the lowest in southern European countries (3). If this gradient exists, it may be owing to variations in exposure to lifestyle factors, such as diet, or to lower frequency of APO e4 or other dementia-related genotypes present in southern European populations.

Comparisons of immigrants to those remaining behind in the mother country are useful for distinguishing the effects of environmental exposures from genetic vulnerability. However, there are few studies comparing dementia in immigrants to genetically similar groups in their country of origin. Hendrie has reported incidence rates in African Americans 2.4 times higher than in Africans from Nigeria (58). An earlier report (141) suggested that dementia prevalence in Japanese men living in Hawaii might be higher compared to Japanese men living in Japan; there are differences in diagnostic approaches between the two countries that may confound this finding. Meguro and colleagues (87) reported a similar prevalence of senile dementia in Japanese men living in São Paulo, Brazil compared to those living in Miyagi Prefecture, Japan. Cross-national comparison studies are by nature

complicated by differences in diagnostic methodology and cross-cultural biases in assessment tools. However, they capture differences in environmental and genetic vulnerabilities that can be explored further to identify new approaches to preventing dementia. The lower rates reported in developing countries may point to selective survival differences related to competing risks or to higher exposure to dementia risk factors in the developed countries.

INCIDENCE OF SUBTYPES The major subtypes of dementia are Alzheimer's dementia and vascular dementia. Diagnostic classification of vascular dementia remains controversial and is evolving. Vascular causes of dementia are widely regarded as modifiable through prevention and reduction of risk factors and may offer the most significant hope at this time for primary prevention of dementia. Dementia with Lewy Bodies (DLB) may be a separate syndrome from AD, but the diagnostic classification of DLB is still evolving.

Nearly all studies of dementia that have, to date, addressed incidence of subtypes are in the United States, European countries, Japan, and China. In a cross-national European study of dementia in 7 countries, Alzheimer's accounted for about 70% of all dementia, followed by 15% for vascular dementia. A report from the Italian Longitudinal Study on Aging (ILSA) reported AD incidence rates of 6.55 per 1000 person years (py) and 3.30 per 1000 py for vascular dementia. Lobo (83) and colleagues have reported some variation in the proportion of all dementias attributable to vascular dementia compared to Alzheimer's. Finland and Pamplona had the highest proportion attributable to other dementias, and Sweden had the highest attributable to Alzheimer's. Reports from Japan (46, 63, 145) suggest that vascular dementia accounts for a higher proportion of total dementia cases in that country: Estimates of the proportion of dementias classifiable as vascular range from 32% (46) to 47% (145). Variations in occurrence of disease across population groups, such as global regions, ethnicities, and genders, can be broadly indicative of differences in genetic predisposition and environmental exposures that may influence risk or progression of disease. Further, detection of disease may be affected by socioeconomic circumstances or cultural views and practices. Certainly, differences in the occurrence of dementia in developing and developed countries or between disadvantaged and advantaged populations (for example, African Americans versus European Americans) are necessarily subject to influence by differential selective survival related to disadvantage. Some work (91) has suggested that dementia incidence declines in very old ages. These views have not yet been adequately evaluated in light of competing risks from earlier cardiovascular mortality or other causes of premature death in populations.

Ascertainment of Dementia for Estimating Population Burdens

Studies that are based on community health care diagnosis of dementia may find inconsistent results owing to the variability in extent of patient evaluation and

diagnostic rigor by the health care system. Dementia is often not diagnosed or not treated in typical community health care settings (43). Even when dementia is evaluated in the health care setting, verification of subtype by neuroimaging is often absent and a differential diagnosis of dementia is incomplete. Dementia is challenging to diagnose in older populations, and inter-rater discordance in dementia and AD diagnosis has been documented (61). Some older persons remain incompletely diagnosed because of lack of access to medical care, residence in long-term care institutional settings, decisions made by caregivers or others responsible for dementia patients that prevent a full evaluation, or by the confounding effects of substantial comorbidity.

Mild cognitive impairment (MCI), a possible early precursor of dementia, is variously defined as the absence of dementia meeting Diagnostic Standards Manual IV criteria with the presence of subjective memory complaints, normal general cognitive functioning, objective memory impairment, and autonomy in activities of daily living (53, 77). There are conflicting reports on how strongly current definitions of MCI predict the development of dementia. However, work that can successfully define early predictors of dementia will be of importance for preventing the progression to later, less treatable phases. Despite these limitations, important and potential risk factors for dementia onset have been identified.

RISK FACTORS FOR DEMENTIA

Prevention of Dementia

Prevention may be thought of in three nonexclusive stages: primary, secondary, and tertiary. Primary prevention generally refers to the prevention of disease before its biological onset or to prevention of risk factors for disease (sometimes called primordial prevention). Secondary prevention refers to the early detection of asymptomatic disease, usually through screening that leads to early treatment. Except for people at high risk for dementia, such as those with certain genotypes or high levels of identified environmental exposures, it is very difficult to precisely identify asymptomatic individuals who are likely to acquire dementia at some point in the future. A role for early dementia screening in primary care has been proposed. However, a recent report from the U.S. Preventive Services Task Force suggests there is insufficient evidence to support instituting such a universal screening policy (138). Tertiary prevention generally refers to interventions that retard progression of or rehabilitate overt clinical disease. In addition to existing drug treatments for dementia that modestly retard progression of dementia, tertiary preventive approaches may include behavioral or rehabilitative patient interventions and improvement in the quality of supportive care in the community or the institutional setting for the patient, the family, and other informal caregivers. A previous review in the *Annual Review of Public Health* (104) addresses existing evidence from observational studies on a set of potential lifestyle risk factors for Alzheimer's disease that pointed the way toward potential interventions. The present review

addresses population burdens of the major forms of dementia; variability in risk associated with environmental exposures, lifestyle and behaviors, race/ethnicity, and genetic contributions; and existing evidence on clinical trials and interventions that have the potential for directly preventing or treating dementias.

Genetics and Dementia in a Population-Based Context

Few candidate genes have so far been firmly identified in connection with Alzheimer's disease. The most established of these is the APOE lipoprotein genotype. The e4 allele of this genotype is associated with increased risk of both AD and vascular dementia. Homozygosity for e4 is usually more strongly associated with both dementia and coronary artery disease than heterozygotic combinations with only one e4 allele. The contribution of APOE to dementia risk varies by age, gender, and ethnicity or ancestral background. APOE may account for up to 40% of the genetic risk for sporadic late-onset AD (50). However, the fraction of AD cases that are attributable to APOE e4 is estimated at about 5% (69) in Mexican Americans, whereas in Americans of European ancestry Evans has estimated that AD incidence would be reduced by 13% if the APOE e4 allele did not exist. Slooter has estimated a 20% reduction in dementia (40, 125) with the elimination of e4 in Dutch studies.

Presenilin (PS1 and PS2) genes are also accepted as contributors to early onset AD, but these are probably far less common in populations than APOE e4 and far fewer cases are attributable to these genes (80, 143). Other genetic factors that may be related to lipid metabolism, inflammation, oxidative stress, hypertension, stroke, or type-2 diabetes have implications for the risk of vascular dementia, probably for AD, and might interact with APOE to influence the risk of dementia.

EARLY EFFECTS OF APOE A number of reports have demonstrated higher LDL among children with the e4 allele (10, 51, 109, 127). Important longitudinal work from the Bogalusa Heart Study (128) has reported that presence of the APOE e4 increased LDL more over a 15-year follow up compared to e3; further, those with e2 were more responsive to lifestyle changes such as obesity or dietary fat intake. Taken together, these findings support the notion that APOE e4 could increase coronary heart or artery disease risks from birth onward. Whether this also holds true for cognitive outcomes is not known. In fact, little has been done to examine effects of APOE e4 on changes in cognitive status from youth to older adulthood; the Scottish Mental Survey of 1932 (27) was able to report that APOE e4 predicted change in cognitive ability from age 11 to age 80 but did not influence ability at age 11. It is likely that APOE e4 is associated with cumulative exposure over time to elevated LDL, amyloid deposition, and oxidative processes that affect vascular disease and subsequent dementia risk later in life, rather than manifesting more immediate, direct effects on cognition in childhood. Most research supports the notion that those homozygous for the e4 allele experience greater loss of hippocampal volume, changes in brain metabolism, and increased risk for cognitive decline and dementia. The various APOE allele combinations are associated with varying

rates of atherogenesis, such that the risk of dementia and cognitive impairment is significantly higher among those with the ApoE e4 allele and higher levels of atherosclerosis (126).

CROSS-POPULATION STUDIES OF e4 The e4 allele of the APOE gene has been linked to an increased risk of both AD and vascular dementia in a variety of populations. There is considerable variability in the allele distribution of the APOE genotype by race, ethnicity, and nationality. Available studies are limited in two major ways: (*a*) Data on APOE allele frequencies, often taken from small, clinical samples, can be biased by the high prevalence of demented subjects, the older age of these subjects, and the lack of representativeness of these samples and matched controls for general populations; (*b*) understanding of racial and ethnic diversity in the effects of APOE on dementia is hindered by inappropriate classifications of ethnic groups. For example, classification as "Hispanic" of people of Mexican, Caribbean, Central-American, and South-American ancestry mixes together groups that are diverse from a historic, cultural, and genetic point of view. Similar issues pertain to Asians and other ethnic groups. A 1997 review by Farrer (50) summarized the risk of AD associated with heterozygosity and homozygosity for the APOE e4 allele; a higher risk of AD was consistently present across all ethnic groups associated with homozygosity for e4; heterozygosity was also associated with an increased risk of AD with the exception of African Americans, where e4 heterozygosity was not associated with an increased risk of AD. More recent work (33, 34) has suggested that certain APOD lipoprotein polymorphisms [APOD is a high-density-lipoprotein (HDL)-associated glycoprotein] may modify the association between APOE e4 and AD. Desai's (33) work suggests that the risk of AD associated with APOE e4 positivity was higher in those with the APOD polymorphism Intron 1*2 allele; this allele combination was also higher in those with AD compared to control subjects. A few laboratory and pathology studies have implicated APOD polymorphisms in neurodegenerative and neuroregenerative processes (66, 131). This polymorphism may only occur in individuals of African ancestry compared to individuals of European ancestry in the United States (34); however, no other studies have reported population-level distributions of APOD in non-European ancestry samples.

GENETICS AND PREVENTION OF DEMENTIA Primary and secondary prevention of dementia related to genetic factors logically focuses on modifying environmental and lifestyle exposures that influence risk by interacting with genetic vulnerability. Because none of the known genetic risk factors for dementia is determinative, screening to identify high-risk cases may not be feasible, effective, or desirable, and universal screening is even less so.

Lipids are likely to be an important pathway in amyloid beta-protein deposition, tau phosphorylation, and disruption of synaptic plasticity and neurodegenerative endpoints (29, 30, 89, 90). Since the effects of APOE e4 on lipids are well documented, interventions that prevent exposure to dietary fat or other factors that are

known to increase LDL, or those that may reduce LDL through treatments (i.e., statins), may be effective in reducing dementia risk. The effectiveness of dietary modifications or treatment with drugs that lower LDL has been evaluated in a few studies involving children and adults (19, 140). Work by Pedro-Botet (99) and by Campos (19) have demonstrated that those with APOE e2 may be more responsive to lipid-lowering interventions compared to those who are e4+. Other work (56, 144) has provided some evidence that APOE e4 modifies the effects of hormone treatments on lipids such that e4+ individuals are less responsive to treatment. The contribution of genetic variation to disease differences between populations may be relatively small if a recent report by Rosenberg is supported (117). This report has suggested that "within-population differences among individuals account for 93% to 95% of genetic variation" and between-population differences account for 3% to 5%.

Early Versus Late Exposure

A growing body of evidence points to early life exposures to factors in the childhood socioeconomic environment, such as education, parental occupation, age at menarche, and early nutritional intake, that may affect the risk of dementia in old age. The reserve hypothesis (49) represents the notion that early exposures in utero and in childhood affect brain size, synaptic plasticity, and dendritic density. Although this has been demonstrated in nonhuman primates and in rodents, deprivation in humans in early life is correlated frequently with adverse exposures in adult life, such as occupational toxins and lifelong poverty. Disentangling the contributions of early exposures versus later exposures and their relative consequences for dementia risk is difficult to accomplish in nearly all population-based studies. Moceri (92), for example, has provided evidence that a disadvantaged childhood environment characterized by area of residence in childhood and parental status is associated with a higher risk of AD. Similar work by Kim (71) and Hall (52) has linked markers of early inadequate nutrition (e.g., as suggested by shorter limb length) and rural residence with a higher risk of dementia. De Ronchi (32) reported a nearly fivefold increase in dementia risk associated with low education. Farmer (42) has also reported an inverse association between cognitive change and education in the Epidemiologic Catchment Area CA study. In a study of older Mexican-American women, Haan reported an inverse association between education and dementia risk (69) and a higher risk of cognitive impairment in women who reported a late menarche, an indicator of early nutritional deprivation.

CAN PREVENTION OF VASCULAR DISEASE PREVENT DEMENTIA? Increasing evidence is emerging at the molecular, physiologic, clinical, and social levels that vascular disease and risk factors play important etiologic roles in both vascular dementia and Alzheimer's dementia. De la Torre (28, 29) has reviewed this evidence extensively, pointing out eight evidentiary themes at the population, clinical, and molecular levels that support the role of vascular processes in dementia. The role

played by ApoE and potentially other genetically driven lipoproteins also supports this notion. Further, there is evidence linking traditional vascular risk factors such as obesity, exercise (9), hypertension, stroke (22, 23, 55, 79, 97, 100), and type 2 diabetes (14) to both vascular and Alzheimer's dementia. Inflammatory factors such as homocysteine (13, 14) and c-reactive protein (120) are being investigated; a growing body of evidence supports the notion that oxidative stress (44) is implicated in dementia. Clinical trials using anti-inflammatory drugs, lipid-lowering drugs such as statins (24), and antidiabetic drugs (2) are underway. However, a recent clinical trial of nonsteroidal anti-inflammatory drugs (NSAIDs) (3) did not show any benefit as a tertiary preventive treatment for progression in AD patients.

Chemical and Physical Environmental Exposures and Dementia

Several types of environmental exposures have been explored as possible causes of dementia and AD in particular. Some work has been done to explore the relation of neurodegenerative diseases and cognitive function and prior pesticide exposure. In a study in three regions of Quebec, Canada, the relative risk of developing AD was 2.4 for men in occupations with pesticide exposure (7, 48). Clearly, more work is needed with better exposure information to establish such associations and explore the preventability of these exposures.

Brain accumulation of aluminum in cases of dialysis-associated dementia was demonstrated, raising the issue of whether aluminum exposure was associated with the incidence of primary AD. However, this notion has not been proven (18), and there have not been any recently published investigations on this issue. Brains from AD patients have been reported to have abnormal accumulation of iron in senile plaques, and some but not all studies have suggested that iron may mediate the in vitro neurotoxicity of amyloid-beta peptide (12). Iron may play a role in the aggregation of tau protein, leading to the formation of neurofibrillary tangles (146). Lead, like iron, has been implicated in the genesis of neurofibrillary tangles (54). Zinc has been postulated to have both pathogenic and protective roles in AD (26). The role(s) of elemental metals or their complexes in AD and dementia seems to be worthy of pursuit and may lead to treatments for dementia with metal-binding agents (17). Potential interventions to reduce or eliminate these exposures have no substantial basis yet for preventing neurodegenerative diseases.

HEAD TRAUMA There have been reports of an increased density in Aβ plaque in the brains of individuals who died of head trauma, but Adle-Biassette (1) found that there was no difference in density of Aβ deposits between cases of head trauma and controls. A case-controlled study showed that a history of head trauma was significant for both AD and non-AD dementias, but the effect was limited to males (119). Several epidemiologic studies have reported increased risk of dementia in individuals with head trauma (103, 145). The Multi-Institutional Research in Alzheimer's Genetic Epidemiology (MIRAGE) project showed that the risk of

AD was elevated with a history of head trauma when compared to family and spouse controls, and there was a smaller elevation in risk for those carrying APOE4 alleles (50). However, the Canadian Study on Health and Aging and the Rotterdam Study showed no change in dementia risk for those with a history of head trauma (78, 82).

ALCOHOL The relationship between alcohol consumption and dementia is complex, mediated by dose and type of alcohol. High levels of alcohol intake, usually associated with clinical problem drinking and alcoholism, can lead to cognitive decline, but the neuropathological findings in alcoholic dementia are distinct from Alzheimer's disease. Alcohol-associated cognitive impairment may be confounded by other factors in these patients, such as smoking, dietary deficiencies of vitamins and antioxidants, or head trauma.

Moderate alcohol consumption may be protective (37, 62). For example, the Rotterdam Study (118) and the Cardiovascular Health Study (96) showed light-to-moderate alcohol consumption as significantly protective for all dementia (hazard ratio = 0.58 (95% CI 0.38–0.90). The third Copenhagen City Heart Study showed wine consumption, but not other alcohol types, reduced the risk of dementia (134). Dementia was more common in older alcohol abusers in the Canadian Study of Health and Aging for all diagnosed types except probable AD (132). In a Japanese study of vascular dementia, alcohol consumption was a significant risk factor for vascular dementia but not AD (46).

Neurologic effects of alcohol on the brain may be modified by genetic cofactors. The Epidemiology of Vascular Aging study showed that the association between alcohol consumption and cognitive decline was modified by APOE e4 genotype (36). Noncarriers of APOE4 who drank were at decreased risk of cognitive deterioration, whereas carriers of APOE4 who drank were at increased risk. The Cardiovascular Health Study showed that the risk associated with very high alcohol consumption was more pronounced among those with APOE e4 (96). Although a growing body of epidemiological data from observational studies suggests that moderate alcohol consumption is associated with protection from dementia, abstainers may include individuals too ill to consume alcohol or those with a family history of alcoholism.

DIETARY FACTORS Nutritional factors have been investigated as potential modifiable risk factors for dementia. Much of this work focuses on lipids, oxidation, and inflammation. Modifiable exposures in these realms include dietary fat, antioxidants, and folate-vitamin B12-homocysteine metabolism. A number of studies have reported that high intakes of total fat, saturated fat, and total cholesterol increase risk for incident dementia (37, 38, 67, 68, 85, 86). High fish intake may be protective for incident dementia and AD, with relative risks of 0.4 (95% CI 0.2–0.91) and 0.3 (0.1–0.9) respectively. Morris et al. (93) found that vegetable fat and omega-6 fatty acid intake decreased the risk of AD, whereas saturated or transunsaturated fats increased the risk.

One study of dietary antioxidant vitamins C and E showed that plasma levels of vitamin C were lower in AD patients with poorer cognitive function despite similar dietary intake (114). At least two studies (41, 94) have reported that those with high levels of dietary vitamin C and E are at decreased risk of dementia (37). The Washington Heights-Inwood Columbia Aging Project found no association between vitamins C and E or the carotenes in the development of AD (86). A case-control study of patients with AD found that patients with AD had a lower level of beta-carotene and vitamin A but not alpha-carotene when compared to controls (65). Studies of nutritional factors in AD patients are generally confounded by changes in eating habits and weight common in AD patients. Several studies in humans have reported an inverse association between homocysteine and cognitive impairment or dementia (95, 110, 122, 142). Inflammatory processes are of increasing interest in dementia research for this reason.

EXERCISE Although it is clear that physical exercise offers health benefits for older people, evidence supporting a specific effect of exercise for prevention of dementia is still under investigation. Mechanistically, exercise has been suggested to enhance brain neurotrophic factors (11) and modify apoptosis (101). Exercise may benefit dementia by preserving muscle mass, preventing falls, and consequent head trauma. Evidence that exercise can preserve optimal cardiovascular function, deter stroke and microvascular disease, and improve regional cerebral blood flow has been offered (23, 73). Given the substantial and diverse effects of exercise on biological functions, the potential role of exercise for prevention of dementia should receive further attention.

SMOKING Cigarette smoking has been reported to both promote and deter dementia occurrence. For example, there is a selective loss of $\alpha 4$ subtype of nicotinic receptors in the brains of AD patients, and this loss is related to the presence and density of amyloid-β1-42 plaques (12). The degree of reduction in nicotinic receptor binding is also related to the severity of dementia (12, 21, 102). Nicotine has also been shown to inhibit apoptosis of neurons (60), and the idea of smoking cessation as an intervention to prevent subcortical vascular dementia has been suggested (116). Even if smoking has a protective effect on AD, it could be completely or partially offset by an increased risk of vascular dementia (16, 98). Smokers may have decreased perfusion to both cortical and subcortical regions of the brain, as well as acceleration of cerebral atrophy and ventricular enlargement (88). Reported associations between cigarette smoking and AD have been varied (15, 60). A study of a cohort of British male doctors showed no significant change in risk for dementia according to smoking status (35). A comparison of three Canadian datasets showed inconsistent positive, negative, and neutral findings for smoking and AD (136). Subsequent analysis of these data showed a significant interaction between smoking status and alcohol consumption on the risk of AD in two of the datasets, with the risk of smoking and drinking together having a smaller increase in risk than either main effect alone (135). Others (60) have found a

protective effect of smoking on AD, limited to males and greater among those with a positive family history. A meta-analysis (5) of 21 case-control studies showed a pooled estimated odds ratio of 0.74 (95% CI = 0.66–0.84) for smoking. Another meta-analysis provided a pooled relative risk for AD of 1.11 (CI = 0.93–1.34) associated with cigarette smoking in four cohort studies, although the estimate raised to 1.99 (CI = 1.33–2.98) when only two of the four studies were included that described the number of smokers at baseline who later developed AD (5). As for other exposures (98), Apolipoprotein E genotype may modify the smoking effect on dementia and AD, such that those who are e4 positive are not affected by smoking with respect to AD risk. Four European prospective studies found that among those with a family history of dementia, there was no association between smoking and dementia, whereas those without a family history of dementia had a RR of 2.28 (78). APOE4 carriers have fewer nicotinic receptors, and nicotine may help increase the density of the receptors or assist in the release of neurotransmitters. It is likely that survivor bias due to early smoking-related mortality may affect study outcomes by removing smokers from the population before they can develop later-stage dementia.

Interventions and Treatments for Primary and Secondary Prevention of Dementia

At present, drug treatments for slowing or halting the progression of dementia are few and have limited effectiveness. Recent efforts to identify treatments that might be efficacious for primary or secondary prevention have included NSAIDS, statins, and antihypertensive medication.

NSAIDS Several observational studies have reported an inverse association between the use of NSAIDS and the risk of dementia (70, 112). The operative mechanism may be the anti-inflammatory properties of NSAIDS. Cache County study data (148) suggested that long-term NSAID use reduced the incidence of AD. However, a recent clinical trial of NSAIDS (3) in AD patients did not find a benefit for progression. The reduction in AD risk associated with use of NSAIDs may represent a role for primary prevention related to NSAIDS rather than treatment.

ANTIHYPERTENSIVE TREATMENT A positive association between systolic blood pressure and dementia has been reported in a number of epidemiologic studies. Similarly, stroke appears as a comorbidity or an etiologic factor for both vascular and AD in at least 10 studies. This has given rise to the reasonable notion that hypertension treatment may reduce the risk of dementia. Despite this potential, only two randomized clinical trials have been attempted that directly address this question. The Syst-Eur randomized clinical trial (45), designed to examine primary prevention of stroke as an outcome of antihypertensive drug treatment, reported a 53% reduction in vascular or mixed dementia and a 60% reduction in AD. The PROGRESS (137) clinical trial of prevention of recurrent stroke by treatment with

antihypertensive medications reported a 34% reduction in a composite measure of cognitive impairment and dementia. Whether antihypertension treatment affects dementia by reducing Aβ deposition or other hallmarks of AD is not known. Now underway, the European SCOPE trial (n = 5000) (133) will examine the effects of treatment with an antihypertensive medicine (candesartan cilexetil) versus placebo on dementia outcomes.

HORMONE THERAPY Accumulated evidence suggested that exogenous estrogen therapy in postmenopausal women may be associated with increased risk of dementia (61). Despite varying methods and different types of estrogen therapy, with and without added progestational agents, most observational studies with a significant result showed protection associated with hormone replacement therapy (HRT). Unopposed estrogen was reported to have greater benefits for dementia than opposed treatments. However, the Women's Health Initiative (WHI), a large, randomized clinical primary prevention trial of conjugated equine estrogens and medroxyprogesterone acetate (Prempro®), found that dementia was twice as frequent in the active treatment arm compared to the placebo arm; there was no significant difference in the occurrence of cognitive impairment without dementia (108, 123). Both vascular dementia and AD were more common in the treatment group. The WHI HRT study was not able to evaluate the effects of HRT on dementia subtypes owing to small numbers of AD cases. The WHI trial has also confirmed Prempro® as a cause of stroke (105); it is possible that the increased risk of all-cause dementia is related to the thromboembolic properties of HRT, which may overwhelm any neuroprotective effects. A three-year clinical trial (97) failed to provide any evidence for Prempro® as an effective treatment for Alzheimer's dementia in hysterectomized women with AD.

STATINS Hydroxymethylglutaryl-coenzyme A reductase inhibitors (statins), in addition to impeding large-vessel atherosclerosis and its consequences, have several metabolic effects on the brain that may be related to AD pathogenesis (72). Some epidemiological studies have shown a negative association between statin use and AD risk, and several mechanisms have been postulated (24, 115). Investigators in one epidemiological study searched for indication bias for treatment for cardiovascular disease as an explanation for association but failed to find it (115). A Cochrane review published in 2001 concluded that the evidence for a causal association was not yet present (121) but that this should be a high priority for future research. It seems likely that trials in the treatment of clinical AD and other dementias will appear in the next few years.

VACCINATION FOR PRIMARY OR SECONDARY PREVENTION OF AD A single population-based, observational study (139) has reported a reduced risk of AD (OR = 0.41) associated with vaccination for diphtheria, tetanus, polio, or influenza. Recent work done at Elan Pharmaceuticals (8) using a transgenic mouse model for AD reported that antibodies against amyloid β-peptide (Aβ) injected

intraperitoneally cleared plaques and stopped peptide degradation. A subsequent small trial in humans with AD provided evidence that this treatment increased inflammatory response in the brain and elevated neurotoxicity. Recent work by Nath and colleagues (57) has found that AD patients have a higher immune (antibody) response to aggregated Aβ compared to soluble Aβ. However, aggregated Aβ may be less neurotoxic than the soluble form. It is not yet clear whether the immune response observed in AD patients is secondary to the development of disease or is a proximal cause. It is likely that inflammatory and oxidative factors related to this response are involved in AD and probably in vascular dementia as well. The single observational study may have been biased by residual confounding related to the likelihood that older persons who routinely seek vaccinations differ by socioeconomic status and health behaviors from those who do not. The general issue of infection and immunity in dementia has not been well explored as yet.

EFFECTIVENESS OF INTERVENTIONS IN PREVENTING DEMENTIA A fairly consistent pattern of results from recent trials of the above treatment interventions in AD patients has failed to show significant benefits (and in some cases shows harm). These discouraging oucomes may be, in part, due to the advanced stage of dementia of study participants. Brain imaging studies show that most advanced dementia patients have brain and hippocampal atrophy and white matter hyperintensities; most also have the hallmark pathologies of AD, that is, plaques and tangles. There are no studies at present that have addressed the reversibility of brain atrophy or white matter hyperintensities in response to any intervention, partly owing to the current logistical, technical, and cost limitations of serial imaging studies.

CONCLUSIONS: CAN DEMENTIA BE PREVENTED?

At one time, it was common to think of dementia as an inevitable outcome of aging; it is now clearer that dementia is the result of a set of underlying pathological processes at least some of which may be preventable or modifiable. Certain forms of cognitive decline, such as memory loss, are considered to be predictive of specific dementias, especially Alzheimer's. Despite this improved recognition, we do not yet have approaches to early screening that can predict future dementia with certainty or can differentiate the future risk of one dementia subtype from another. Some of this is due to uncertainty about the etiology of Alzheimer's dementia and the role that vascular disease plays in its causation. Mounting evidence points toward vascular disease as a major culprit for both Alzheimer's and vascular dementia. Although still controversial, this finding would be good news: The past 30 years of public health and medical interventions have shown that we can prevent vascular disease and that clearly identified vascular risk factors exist that are modifiable.

Primary prevention of chronic disease depends on early identification of modifiable risk factors for which effective interventions exist and can be applied.

These may include dietary fat intake, dietary antioxidants, obesity, type 2 diabetes, hypertension, physical exercise, smoking, and alcohol consumption. Genetic vulnerability related to APO e4 modifies many of these risks, and such interactions may increase the contribution of genetic factors in the context of exposure to higher-risk environments. Preventive activities aimed at changing individual behaviors are often expensive and difficult to execute in a population-based context. In a broad sense, public health interventions that restrict access to smoking (for example), increase screening and control of hypertension or diabetes, or stem the rising tide of obesity may also reduce the population burden of dementias. Secondary prevention of dementia depends on effective screening and early detection of dementia. If effective treatments exist, early detection can lead to modification of dementia risk. Indeed, multiple efforts are now underway to differentiate, through cognitive screening and neuroimaging, those who will progress to dementia from those who will not. For those at high risk of progression to dementia, significant modifications in lifestyle and treatment of comorbid conditions, such as hypertension or diabetes, may be effective strategies on the individual level. On the population level, interventions may include public and provider education regarding dementia or practices and policies that support routine dementia screening for people over age 50.

Dementia is a preventable syndrome, and progression to dementia can be prevented or modified. In 20 years, if the WHO is correct, there will be close to 100 million people with dementia in the world. Even in wealthy, developed countries, the cost and burden of caring for these patients now falls on their families; in most developing countries, there is no safety net at all and the future consequences of these policy failures are daunting to imagine.

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Annual Review of Public Health
Volume 25, 2004

CONTENTS