Chapter 5

EPIDEMIOLOGY AND CLINICAL GENETICS OF ALZHEIMER'S DISEASE

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Since its recognition as a distinct entity in 1907, Alzheimer's disease (AD) has been a baffling disorder to study for a variety of reasons, including the absence of a diagnostic marker, the difficulty of establishing guidelines for pinpointing the onset of dementia, and lack of definitive features of cognitive decline in a normally aging population. Epidemiologic investigations in the past decade, however, have helped to define our current concepts of AD and dementia in the elderly. For example, descriptive studies have shown the magnitude of the public health problem facing us, as the numbers of elderly (including those with dementia) quadruple by the middle of the next century. For the first time, analytic investigations have confirmed the importance of the apolipoprotein E (Apo E) genotype and family history as major risk factors. Case-control and, more recently, prospective studies have found increased risk in subjects with poor education, head trauma, and perhaps myocardial infarction, thus providing other clues to the pathogenesis and progression of disease. The identification of potential risk (and protective) factors in these studies has encouraged new therapeutic approaches and lines of scientific investigation, including the value of hormone replacement, antioxidant therapies, and anti-inflammatory compounds. In the next decade, clinical trials will grow in importance, not only in AD patients but also in nondemented populations as we develop experimental trials for the prevention of AD.

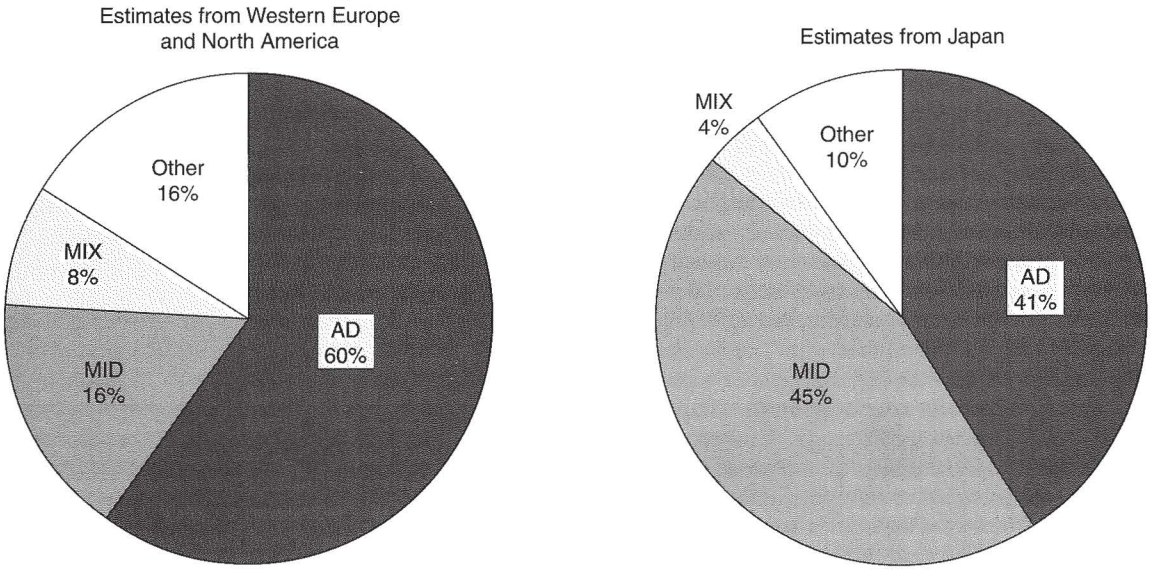
Descriptive Epidemiology

INCIDENCE, PREVALENCE, AND MORTALITY OF ALZHEIMER'S DISEASE

The most consistent and robust finding in the epidemiology of dementia is the exponential rise in prevalence as a function of age in the 65- to 85-year age range throughout the world. Studies in the United States and western Europe invariably report Alzheimer's disease to be the most common cause of dementia in the elderly (50 to 75 percent), followed by vascular or mixed (AD and vascular) disease.[1–6] In contrast, Japanese and Russian studies have often reported higher rates of multi-infarct dementia (Fig. 5-1).[7–9]

Published prevalence rates for AD—that is, the proportion of people with AD at a given time—vary widely even between communities only miles apart (Fig. 5-2).[1,10] It has been estimated that more than 76 percent of the variance in these rates is due to differences in methodology rather than actual differences in prevalence.[11] A particularly pervasive methodologic issue has been the determination of who constitutes a "case" of AD. The absence of a diagnostic biological marker for AD and the insidious onset of symptoms (which defines the disease) make it difficult to distinguish "normal" cognitive changes from the onset of disease. Moreover, different experimental and cultural settings do not lend themselves to the application of uniform criteria. In general, population-based studies and studies that included milder cases of dementia have reported the highest prevalence rates of AD [10,12] and may be more representative of the actual societal burden of AD.

FIGURE 5-1 Estimated relative frequencies of common causes of dementia around the world.



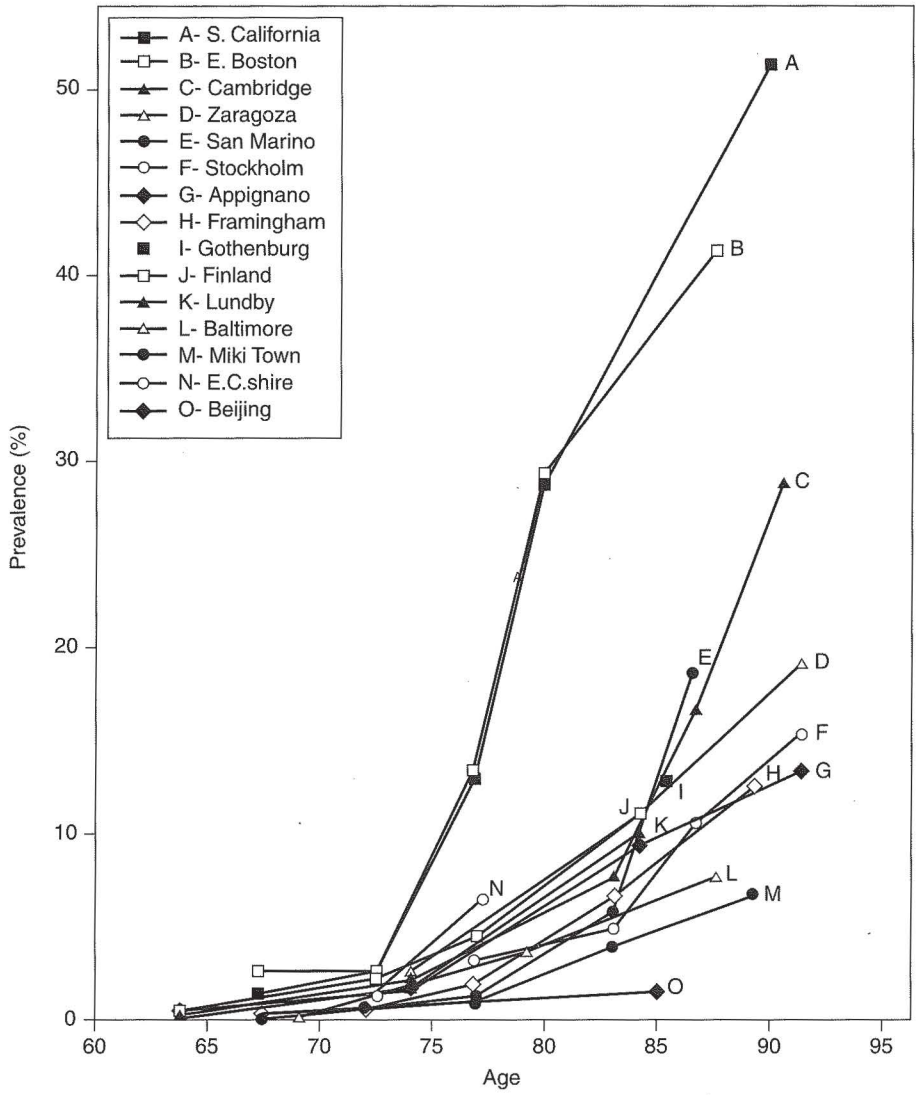


FIGURE 5-2 Alzheimer's disease prevalence rates. Sources of data are as follows: A, Pfeffer, 1987[12]; B, Evans, 1989[10]; C, O'Connor, 1989[2]; D, Lobo, 1990[267]; E, D'Alessandro, 1988[5]; F, Fratiglioni, 1991[3]; G, Rocca, 1990[264]; H, Bachman, 1991[1]; I, Skoog, 1993[261]; J, Sulkava, 1985[6]; K, Rorsman, 1986[265]; L, Folstein, 1991[176]; M, Fukunishi, 1991[262]; N, Brayne, 1989[263]; O, Li, 1989[266].

Incidence rates of AD (Fig. 5-3) also appear to rise in an exponential fashion, at least until the ninth decade. Although a decline in incidence was observed at age 95 in the Lundby study,[13] the majority of studies, with limited numbers of subjects over age 90, have suggested increasing rates with increasing age.[14–17]

Mortality is increased in patients with AD, although the effect is most pronounced in individuals with advanced disease. In one population-based study, overall mortality in AD patients was increased by about 44 percent over less than 5 years. Those with mild or moderate cognitive impairment, however, had approximately the same risk of death as their age- and gender-matched peers, whereas those with cachexia and severe cognitive loss had approximately a 4.6-fold increased risk of dying.[18] Unfortunately, therapeutic strategies that reduce mortality rates in patients with AD are likely to increase the prevalence of this devastating disease, since prevalence equals incidence multiplied by duration, or $P = I \times D$.

Analytic Studies

In epidemiology, case-control studies offer the most cost- and time-effective method of identifying risk factors for a disease. Ideally, when putative risk (or protective) factors are identified in case-control studies, they are followed by prospective studies with more accurate determination of exposure status. These studies, however, are observational and do not establish causality. Ultimately, findings should be confirmed by experimental/clinical trials. In AD, a large number of analytic studies have led to the identification of interesting putative risk factors.

DEMOGRAPHIC FACTORS

EDUCATION AND OCCUPATION

The association of poor education with an increased risk of dementia and AD has been a consistent finding in studies worldwide.[3,19–22] The effect has been particularly notable in

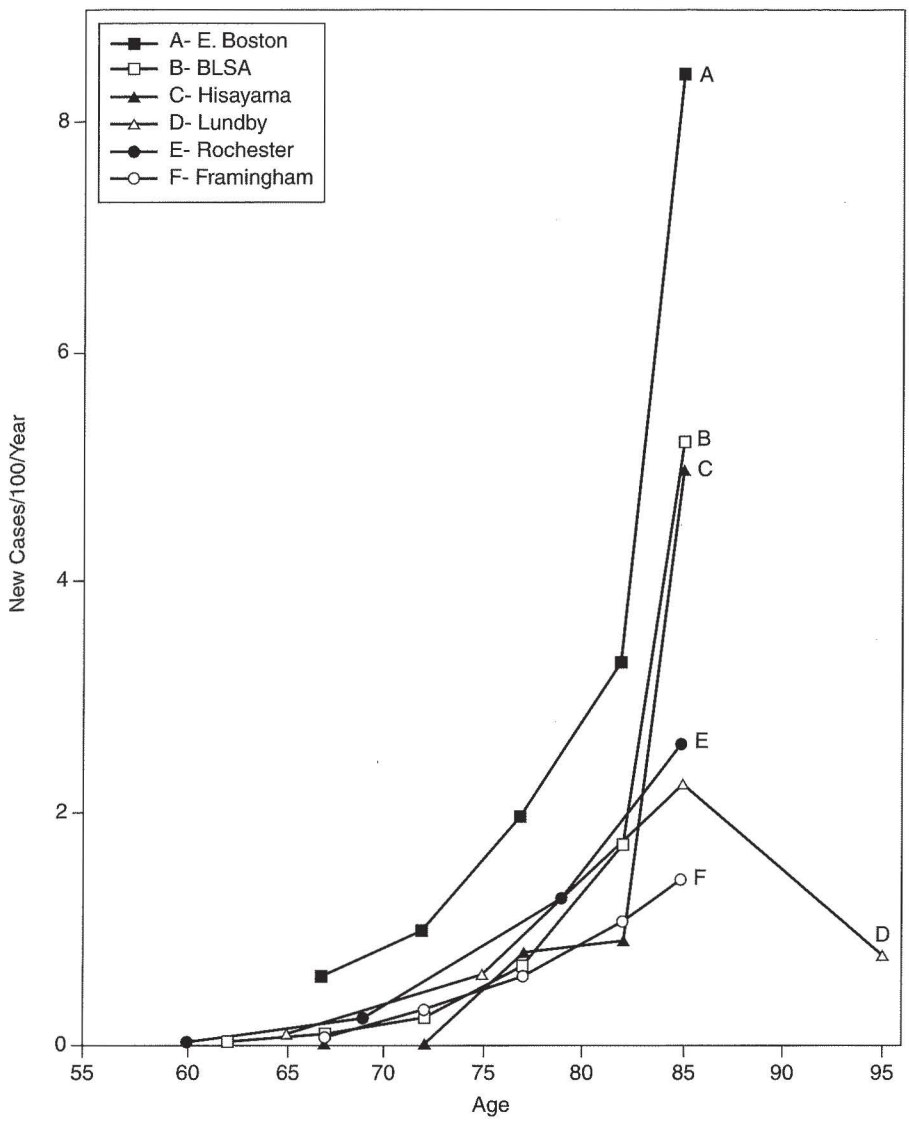


FIGURE 5-3 Alzheimer's disease incidence rates. Sources of data are as follows: A, Hebert, 1995[15]; B, Kawas, 1997[188]; C, Yoshitake, 1995[268]; D, Hagnell, 1991[13]; E, Kokmen, 1993[14]; F, Bachman, 1993[269].

studies with significant numbers of subjects with a grade-school education or less. Similarly, an inverse association of occupation level and AD has been reported in some studies,[23,24] although not in others.[25,26] Several reasons may explain the effects of education and occupation on AD. A cognitive reserve hypothesis suggests that individuals with higher educational and occupational attainment can tolerate more severe degrees of AD pathology before the disease expresses itself clinically. The biological plausibility of this hypothesis is supported by regional cerebral perfusion studies showing differential perfusion deficits in AD patients with different educational and occupational attainment.[24,27] Additionally, in animal studies, rearing in complex environments appears to modify synaptic density and synaptic transmission.[28–31] Although the reserve hypothesis suggests a direct protective effect of education, the education effect may actually be due to test bias. It is well recognized that performance on cognitive tests and differences in clinical diagnosis may be related to educational background.[32–37] Most of the time differences in performance are adequately controlled by adjusting the measures according to educational level. Furthermore, in studies where cognitive measures were not utilized, education was still associated with a greater likelihood of functional independence with advancing age.[38,39] Education may also serve as a surrogate factor for other, unmeasured variables. Other socioeconomic factors, such as poverty and lifestyle, are known to be associated with educational and occupational attainment. The education effect may, therefore, reflect the influence of one or more of these factors. Indeed, education may be a manifestation of genetic and familial factors. Twin studies confirm that genetic influences have a significant impact on educational attainment as well as on performance on cognitive tests.[40–43] The interaction of education with known genetic risk factors for AD is not well established; however, a recent report showed that lower educational level, independent of Apo-E status, was associated with cognitive decline.[44]

GENDER

Gender and the risk of AD remains an inconclusive issue. In prevalence studies, women account for about two-thirds of all cases of AD. The higher proportion of women, however, reflects the higher percentage of women in the older age groups, since women live longer than men. Moreover, women with dementia live longer than men with dementia,[45,46] further contributing to the higher prevalence rates ($P = I \times D$). Although women may carry an increased risk for late-onset familial AD,[47,48] several studies show little or no gender difference in age-specific incidence rates.[49–52]

GENETICS AND FAMILY HISTORY

Many lines of evidence have pointed to a genetic etiology of AD. The earliest descriptions of AD as a familial disorder were reported by Meggendorfer[53] in 1925 and Schottky[54] in 1932. Since then, dozens of kindreds with familial AD have been described.[55–57] More recently, numerous population-based epidemiologic studies have consistently shown family history of dementia, particularly in first-degree relatives, to be an important risk factor for developing AD.[58–64] Comparison of disease concordance in monozygotic and dizygotic twins[65–68] and autopsy studies of other genetic diseases, specifically Down's syndrome (trisomy 21),[69–71] strengthened the association of AD with genetic factors. During the past decade, several different genes have been identified as important mediators of AD pathogenesis. Mutations in three genes, including those encoding for the amyloid precursor protein and for presenilins 1 and 2, are direct causes of the majority of early-onset familial AD cases. Unlike these genes, the Apo E gene does not cause AD but modifies the susceptibility of individuals to late-onset familial and sporadic AD. From an epidemiologic standpoint, the most important factors are family history and the individual's Apo E genotype, as these contribute to the majority of cases in the population.

There are essentially three groups with different patterns of family history of AD. The first group, which consists of so-called sporadic cases, with no clear family history of dementia, accounts for up to 75 percent of cases worldwide. The second group includes affected individuals with a history of affected relatives who appear to develop dementia randomly. An estimated 25 to 35 percent of AD cases have at least one affected relative.[72] The third group consists of cases with prominent family history consistent with a Mendelian inheritance pattern. Typically, AD is inherited as an autosomal dominant trait with nearly complete penetrance in these families.[55–57,73] In other words, multiple family members develop AD in every generation regardless of gender. Even though this group, termed *familial AD* (FAD), represents only 1 to 2 percent of all AD cases,[72,74,75] it provides the most striking evidence for a genetic cause of AD and was the logical target for initial investigations.

THE APP GENE

Investigations into the genetic basis of FAD initially focused on chromosome 21 because of the association of AD pathology and Down's syndrome (DS). Autopsy studies have shown that nearly all DS patients over the age of 40 accumulate senile plaques and neurofibrillary tangles similar to those of patients with AD.[69,70] Moreover, the occurrence of DS in relatives of AD cases may be higher than in controls.[62,76] The determination of dementia in a mentally retarded population is difficult, however, because of limitations of available cognitive measures and diagnostic criteria.[77] Nevertheless, segregation of four early-onset FAD kindreds with two markers on chromosome 21 was reported in an early genetic linkage study.[78] The amyloid precursor protein (APP) gene was mapped to the same chromosomal region by other investigators.[79,80] Furthermore, mixed expression of AD and hereditary cerebral hemorrhage with amyloidosis of the Dutch type, an autosomal dominant disease associated with mutation of the APP gene,[81] was described in different members of one family.[82] In 1991 a missense mutation was found in exon 17 of the APP gene from probands of a British FAD kindred.[83] This region of the APP gene contributes to the formation of the β-amyloid peptide and the mutation was present only in affected individuals. Five additional mutations in the APP gene of other affected families were subsequently described.[84–88] However, fewer than 20 FAD kindreds had APP gene mutations,[74,75] and linkage to the APP gene was not observed in late-onset FAD kindreds.[89] Thus, mutations in the APP gene account for a very small fraction of FAD cases.

PRESENILIN GENES

Linkage to a region on chromosome 14 was reported in 1992.[90] Although several early-onset FAD kindreds that did not have APP gene mutations were linked to this region, a few families, including those of Volga German descent, did not segregate with the others. A suspect gene, S182, or presenilin 1 (PS-1), was cloned in 1995, and five missense mutations were identified in eight early-onset FAD kindreds.[91] A large number of mutations that account for about 50 percent of all FAD cases have now been identified.[86,92]

Also in 1995, a locus on chromosome 1 was linked to affected families of Volga German origin.[93] A gene within this region showed remarkable sequence homology to PS-1,[94] and sequencing of the target gene, termed presenilin 2 (PS-2), revealed a missense mutation in most affected members of Volga German families.[95] The protein products of PS-2 and PS-1 are structurally similar. The function of the presenilins is not known; however, mutations of these genes appear to alter APP processing and amyloid deposition similarly to APP gene mutations.[96,97] They may also influence apoptosis or programmed cell death.[98] Although APP and presenilin gene mutations account for only a small percentage of AD cases, they provide evidence that deposition of β-amyloid may be a primary event in the pathogenesis of AD and are under active study.

THE APOLIPOPROTEIN E GENE

In 1993, Roses and colleagues discovered the association of apolipoprotein E genotype (Apo E) and AD. Apo E has since emerged as a major susceptibility factor for developing AD and is now included in virtually every epidemiologic study of AD. Apo E is a normal component of very low density lipoprotein (VLDL), high-density lipoprotein (HDL), and chylomicrons, and it mediates uptake of lipid particles in var-

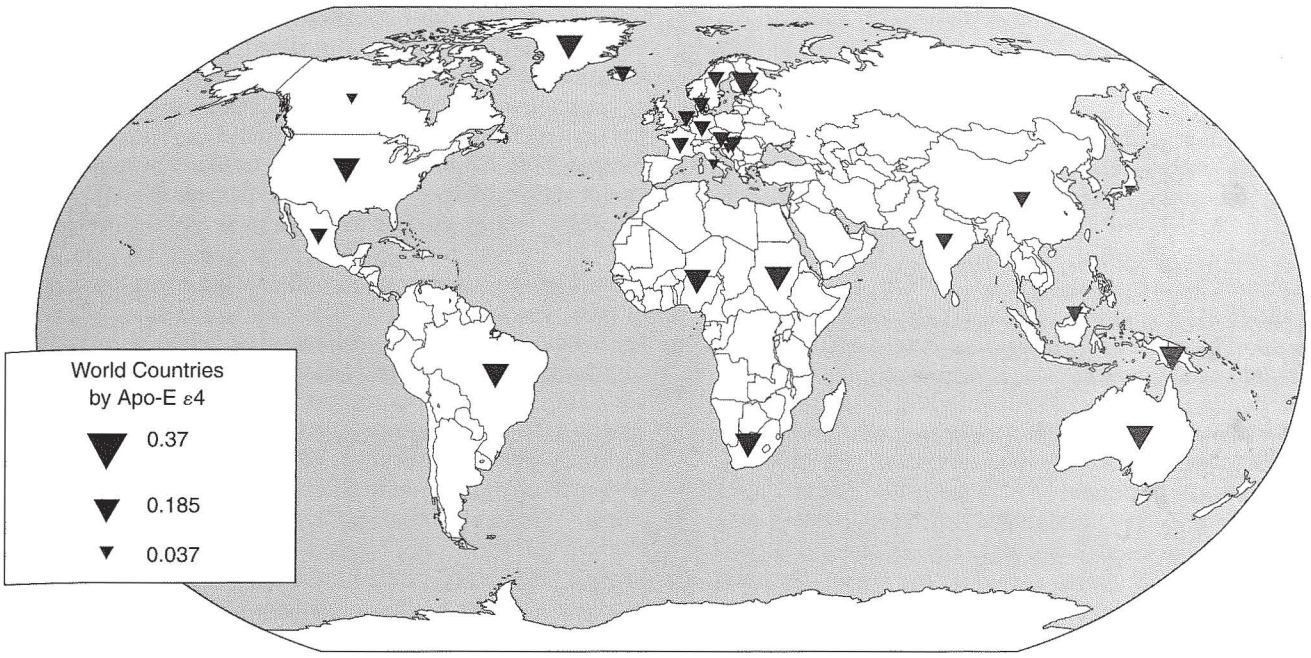


FIGURE 5-4 Geographic distribution of estimated apolipoprotein-E ϵ4 allele frequencies.

ious tissues via binding to the LDL receptor and LDL receptor–associated protein.[99] Since intense study of the Apo E gene was triggered by its association with type III hyperlipoproteinemia, a rare hereditary lipid disorder,[100] allelic variations of the Apo E gene have been well studied in numerous populations.[101–103] Apo E may have a special role in nervous tissue, specifically in the development, maintenance, and repair of myelin and neuronal membranes.[104–106]

The Apo E gene is located on the long arm of chromosome 19 and has at least five different allelic polymorphisms, termed ϵ1, ϵ2, ϵ3, ϵ4, and ϵ5. The polymorphisms ϵ2, ϵ3, and ϵ4 account for over 99 percent of the distribution in the general population. The ϵ3 allele is most common overall (77 percent), followed by ϵ4 (15 percent) and ϵ2 (8 percent). There is wide variation of allele frequencies in different populations, both regionally (Fig. 5-4) and by ethnic group (Table 5-1).

TABLE 5-1 Apolipoprotein E Allele Frequencies in Various Populations

Population Sample	ALLELE FREQUENCIES				Population Sample	ALLELE FREQUENCIES			
	N	ϵ2	ϵ3	ϵ4		*N*	ϵ2	ϵ3	ϵ4
Whites					Blacks				
Finland[248]	615	0.04	0.73	0.23	Nigeria[248]	176	0.03	0.66	0.31
Sweden[101]	407	0.08	0.72	0.20	Sudan[103]	103	0.08	0.62	0.29
Netherlands[248]	2000	0.08	0.75	0.17	United States[248]	194	0.03	0.71	0.26
Iceland[103]	185	0.07	0.77	0.17	Native and isolated groups				
Denmark[249]	477	0.09	0.74	0.17	Khoi San, South Africa[252]	247	0.08	0.55	0.37
Germany[248]	1031	0.08	0.77	0.15	Mowanjum, Australia[253]	64	0.00	0.74	0.26
United States[248]	1209	0.08	0.79	0.14	Orang Asli, Malaysia[254]	203	0.14	0.62	0.24
France[248]	223	0.13	0.74	0.13	Inuit Eskimos, Greenland[255]	133	0.02	0.76	0.23
Hungary[103]	202	0.06	0.81	0.13	Yanomani Indian, Brazil[256]	96	0.00	0.84	0.16
Tyrolean[103]	469	0.09	0.79	0.12	American Indian[257]	4541	0.02	0.85	0.13
Norway[250]	239	0.09	0.80	0.12	Mayan, Mexico[258]	135	0.00	0.91	0.09
Italy[102]	365	0.07	0.83	0.09	Hutterites, Alberta[259]	793	0.00	0.94	0.06
Asians and Pacific Islanders					Amish, United States[165]	106	~	~	0.04
New Guinea[251]	110	0.15	0.49	0.37					
India[103]	142	0.05	0.83	0.13					
Malaysia[103]	118	0.11	0.77	0.12					
Japan[103]	319	0.08	0.85	0.07					
China[103]	190	0.10	0.83	0.07					

SOURCE: Adapted from Kamboh,[260] with permission.

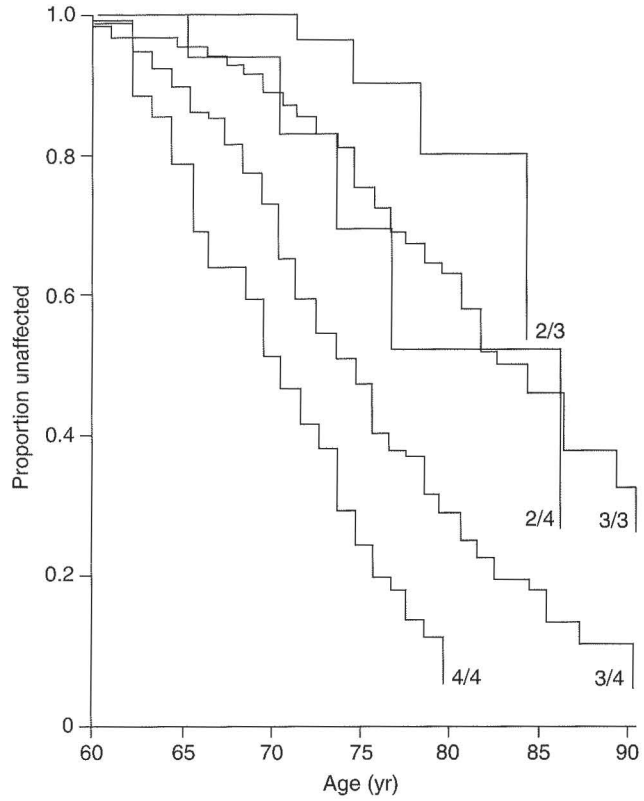


FIGURE 5-5 Risk of remaining unaffected by Alzheimer's disease in relation to Apo E genotype. The proportions of surviving subjects with each of the indicated Apo E genotypes were estimated by Kaplan-Meier product limit distributions for subjects older than 60 years. ***(From Corder and Saunders,[270] with permission.)***

Detection of Apo E within β-amyloid plaques from subjects with AD and Jakob-Creutzfeldt disease (CJD) provided some evidence for an association between amyloidogenesis and Apo E.[107] Additional studies showing high-avidity binding of Apo E to synthetic β-amyloid[108,109] and linkage to chromosome 19[110] further supported this hypothesis. In a case-control study (30 randomly selected individuals from several late-onset FAD kindreds), a significantly higher frequency of the ε4 allele (0.50) was found in cases than in 91 controls (0.16).[108] In an expanded series (234 members of 42 late-onset kindreds), the ε4 allele frequency was 0.80 among 95 affected individuals compared with 0.31 in controls.[111] Moreover, there was a dose-response relationship: individuals with more copies of the ε4 allele were more likely to be affected; those with two ε4 alleles had an eightfold increase in risk over individuals without an ε4 allele.[111] In another case-control study with three control groups ($N = 2224$), early- ($n = 32$) and late-onset ($n = 72$) FAD cases, clinically diagnosed sporadic cases ($n = 138$), and pathologically diagnosed sporadic cases ($n = 352$), the ε4 allele appeared in higher frequencies only in the late-onset FAD and sporadic cases.[112] Numerous studies have shown similar results, including studies of samples from populations with relatively lower ε4 frequency, such as Japan.[113–116] The pattern of risk of AD in relation to Apo-E genotype typical of most case-control studies is illustrated in Fig. 5-5. In studies of incident AD, similar results were found,[117–119] as shown in Fig. 5-6.

An effect of Apo E genotype on risk of amyloid-associated disease was implicated by the detection of Apo E within amyloid plaques from various diseases, including AD. However, Apo E genotype has not been associated with increased risk of CJD, familial amyloidotic polyneuropathy, or DS.[120] In studies of patients with inclusion-body myositis (IBM), the ε4 allele frequency was not elevated above that of controls in three samples but was elevated in one.[121–124] Reliable interpretation of these results is somewhat hindered by the small sample sizes used in all four investigations.

The effect of Apo E genotype on risk of other dementias and neurodegenerative diseases has also been studied. Risk of dementia in subjects with DS may be increased in ε4 carriers.[125]

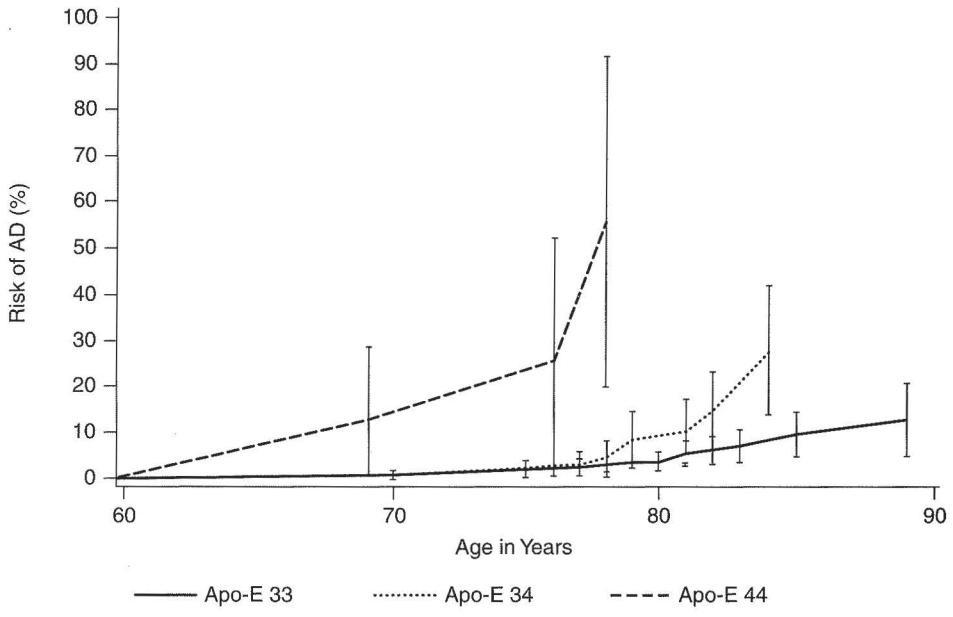


FIGURE 5-6 The cumulative incidence of all Alzheimer's disease among 1030 participants in the Framingham Study Dementia Cohort is significantly increased with the presence of either one or two Apo E ε4 alleles. However, 45 percent of the Apo E ε4 homozygotes have no evidence of dementia up to age 80. Sixteen Apo E ε4 homozygotes, 194 Apo E ε3/ε4 heterozygotes, and 686 ε3 homozygotes are presented. Only one of the 134 Apo E ε2 carriers (ε2/ε2, ε2/ε3, ε2/ε4) had AD, and this group is not presented. The Apo E ε4 homozygotes are represented only to age 80 years. The Apo E ε3/ε4 heterozygotes are represented to age 85 ($n = 22$), and the Apo E ε3 homozygotes are represented to age 90 ($n = 27$). ***(From Myers et al,[271] with permission.)***

Risk of vascular dementia may be affected by Apo E genotype because of associations of Apo E ε4 with atherosclerosis,[126] cardiovascular disease,[127,128] and cerebrovascular disease.[129] However, there is little agreement among studies of Apo E in vascular dementia.[115,130–133] Several reasons may account for the discrepancies between these studies. Diagnostic criteria for vascular dementia have been difficult to establish. Additionally, the coexistence of AD and stroke pathology in many dementia cases further complicates diagnostic accuracy.[75] In one autopsy study, however, an increased frequency of the ε4 allele was found in cases of mixed AD and vascular dementia but not in cases of pure vascular dementia.[132] Risks of Parkinson's disease (PD),[134,135] progressive supranuclear palsy (PSP), and Pick's disease were not associated with the Apo E genotype.[136] Interestingly, the Apo E genotype has been associated with increased risk of the Lewy body variant (LBV) of AD but not with risk of diffuse Lewy body disease (DLBD).[137] Clearly, these findings provide some evidence for a specific association of Apo E ε4 and AD pathology.

Apo E has also been associated with increased deposition of β-amyloid in AD and DS patients and nondemented elderly controls.[136,138,139] Consequently, Apo E has been implicated as a determinant of age at onset and rate of decline in affected individuals. Indeed, age at onset has been shown to decrease by as much as 12 years with increasing doses of the ε4 allele.[111] Because AD and death are competing outcomes in an aging population, any factor that decreases the onset age will be associated with disease more frequently. Moreover, there is an age-related decrease in the frequency of Apo E ε4 in the general population.[127,140,141] Lower frequencies of ε4 in older age groups may be due to Apo E ε4–associated life-threatening conditions, such as atherosclerosis and cardiovascular disease. Interestingly, age-specific risk due to Apo E ε4 status decreases in the oldest subjects.[142,143] Apo E ε4 apparently has its greatest effect on risk of AD during the seventh decade of life, and this decreases with each successive decade.[144] Although population studies of the oldest patients are limited by diminishing sample sizes, Apo E ε4 carriers surviving beyond age 85 may be protected from the Apo E–associated risk of AD.

Protective genetic factors in AD are not well established. Evidence suggests that Apo E ε2 protects against AD,[145] although there is some disagreement between studies.[146] Other, yet undetermined factors in the pathogenesis and clinical expression of AD undoubtedly exist. Interaction of Apo E with other genetic and environmental factors likely determines the true risk of AD in different individuals.

Measurement of the rate of decline in affected individuals stratified by Apo E genotype has also been attempted. Progression of AD has been associated with genetic risk.[147] Hypothetically, the rate of decline could be faster in cases carrying 1 or more ε4 alleles because of greater deposition of β-amyloid. Some studies have supported this hypothesis,[148–150] while others have refuted it.[151–154] However, methodologic problems preclude definitive answers.[155] It is important to consider the assumption that β-amyloid accumulation and clinical progression mirror one another. Clinical severity has been repeatedly associated with the quantity of neurofibrillary tangles but not with the number of senile plaques.[156–158] Clinically normal individuals meeting pathologic diagnostic criteria for AD at autopsy are well described.[159] Moreover, β-amyloid deposition is also greater in nondemented Apo E ε4 carriers than in noncarriers.[139] Thus, the onset and progression of clinical symptoms may vary considerably among individuals with similar degrees of pathologic burden. Although Apo E ε4 may be associated with greater or faster deposition of β-amyloid in the brain, other genetic and/or environmental factors are necessary for the final clinical expression of AD.

Apo E is the first biological marker enabling stratification of large numbers of AD cases for studying interactions with other risk factors. For example, risk of AD due to head injury may be amplified in Apo E ε4 carriers, as both exposures are associated with deposition of β-amyloid in the brain (see "Head Injury," below).[160,161] AD patients who are not ε4 carriers appear to respond better to treatment with tacrine than do ε4 carriers.[162,163] Interactions of Apo E with other genes is implicated in studies of various ethnic groups. Among Cherokee Indians, a lower occurrence of AD was found in subjects with a higher genetic degree of Cherokee ancestry, even when stratified by Apo E genotype.[164] In a sample of Amish subjects from a community in Indiana, a low frequency of dementia was attributed to genetic factors other than the relatively low population frequency of the ε4 allele.[165] Although both African-American and Nigerian blacks have relatively high population frequencies of the ε4 allele of Apo E, only the African-American ε4 carriers are reported to be at higher risk for AD.[166,167] Comparisons of relative risks in Caucasians, African Americans, and Hispanics have also led to the conclusion that other genetic factors may modify Apo E-associated risk in different populations.[168,169]

APO E AND DIAGNOSIS OF ALZHEIMER'S DISEASE

The usefulness of Apo E genotyping in diagnosing AD is limited. Unlike the APP and presenilin genes, Apo E does not cause AD. An estimated 50 percent of AD patients worldwide are not ε4 carriers,[170] and only 30 to 40 percent of all ε4 carriers are estimated to develop AD in their lifetime.[75] Even ε4 homozygotes, who have reported odds ratios ranging from 5.1 to 17.9,[75] have only a 30 percent estimated lifetime risk of AD.[171] Odds ratios for subjects with one ε4 allele have ranged from 2.2 to 4.4,[75] and a 29 percent lifetime risk is estimated for all individuals with at least one ε4 allele.[172] The difference in lifetime risk between ε4 carriers and non-carriers has been estimated at only 14 percent.[172] In preliminary studies, Apo E genotyping was found to have significant predictive value in a referral sample of elderly subjects with mild cognitive impairment,[173] while a low predictive value was found in a cognitively intact elderly population sample.[174] Although Apo E genotyping has virtually no utility for predicting AD in cognitively normal subjects, it may serve as an adjunct to current diagnostic procedures in the hope of extending antemortem diagnostic accuracy.[74,175] Studies quantifying its utility are in progress.

EXPOSURES AND ASSOCIATED CONDITIONS

HEAD INJURY

Head trauma was one of the first risk factors to be reported for AD in a study by Heyman et al. in 1984.[176] Subsequently,

a number of case-control studies have supported the importance of head injury as a risk factor,[177–180] although others have found very little effect.[181,182] In case-control studies, the problem of selective recall remains. Would the informants be more likely to remember head injuries if they were concerned about a patient's progressive dementia? Prospective investigations are needed to answer this question. A preliminary analysis in the Baltimore Longitudinal Study of Aging (NIA) showed no increase in AD risk among subjects who prospectively reported head injury.[183] Recently, data from one population-based study suggest that head trauma may be a risk factor for AD only in subjects with the $\epsilon 4$ allele of Apo E.[160] A postulated biological mechanism evokes the development of diffuse plaques in the brain following head injury; this response may be influenced by Apo E genotype. Supporting this scenario, diffuse amyloid plaques have been detected in one-third of individuals within 2 years of the time of severe head injury.[184]

ESTROGEN EXPOSURE

Several observational studies[185–188] have reported that the risk of AD in women who used estrogen replacement therapy was about half that in nonusers. In addition, some studies showed AD risk to decrease with increasing dose and duration of estrogen use.[185,187] A potential confounder is that estrogen replacement therapy is utilized more frequently by women with higher education levels. Nonetheless, estrogens are known to affect regulation of acetylcholine and nerve growth factor, thus providing some biological plausibility. Moreover, three small clinical trials have reported improvement in cognition and affect in a subgroup of AD patients on estrogens.[189–191] A larger multicenter trial of estrogen replacement in women with AD is currently being conducted by the Alzheimer's Disease Cooperative Study (NIA).

NONSTEROIDAL ANTI-INFLAMMATORY COMPOUNDS AND INFLAMMATORY CONDITIONS

The use of nonsteroidal anti-inflammatory drugs (NSAIDs) has also been associated with a reduced risk of AD in several case-control and prospective studies.[59,192–194] AD has also been reported to occur less frequently in patients with inflammatory conditions such as rheumatoid arthritis[195] and leprosy.[196]

Further research is necessary to determine whether NSAIDs or other anti-inflammatory agents provide direct protection or whether patients with inflammatory conditions are protected by mechanisms other than drug use. Supporting the former hypothesis, NSAIDs have been studied in AD patients with some improvement in cognition, although toxicity limited their use in some patients.[63,197] Moreover, studies in patients with leprosy have suggested a lower incidence of AD in patients who had been taking dapsone (a synthetic sulfone bacteriostatic drug that also has anti-inflammatory activity) compared to those who had not taken the drug within the previous 5 years.[196] Further extending this hypothesis are pathologic studies suggesting that reactive microglia and complement proteins may play an integral role in the development of AD pathology.[198,199]

MATERNAL AND PATERNAL AGE

Because of the relationship between DS and AD, the risk of advanced maternal age was investigated. Whereas some studies noted an increase in risk with parental age,[200–202] other investigations did not.[203–206] Risk of dementia does not appear to be increased in parents with a DS child unless the mother was under the age of 35 when the child was born.[207]

MYOCARDIAL INFARCTION

In the Bronx Aging Study,[208] myocardial infarction was a risk factor for dementia, particularly in elderly women. This isolated report requires replication, but other investigations also suggest links between vascular disease and AD, including studies of Apo E $\epsilon 4$, a risk factor for coronary disease as well as AD. Furthermore, autopsy studies of nondemented subjects with coronary artery disease have shown a marked increase in the number of diffuse plaques in the brain as compared to age-matched individuals without severe coronary disease.[209]

SMOKING

A majority of studies have found no relationship of AD and smoking.[59,60,176,181,210–215] However, a metanalysis of data from seven of these studies showed an inverse relationship of smoking to risk of AD.[216] An inverse relationship was also found in two other studies,[217,218] and a single study found an increased risk of AD in smokers.[219] Smoking has also been found to exert a "protective" effect independently of Apo E status.[220] In a longitudinal study, however, smoking was not related to incidence of AD.[214] Nicotine has been shown to improve cognitive performance in experimental animal studies.[221,222] The findings in several human studies also suggest that nicotine may improve reaction time and short-term memory in AD subjects.[223–227] Because of small sample sizes, however, different routes of administration and dose schedules of nicotine, and different durations of follow-up, these results are difficult to interpret. Nicotine has been shown to enhance hippocampal synaptic transmission[228] and to retard amyloidosis in vitro.[229] In addition, nicotine may upregulate nicotinic receptors, which are known to diminish in AD.[230]

That smoking is protective for any disease seems counterintuitive. Indeed, such a relationship may result from selection bias secondary to differential survival.[231] That is, smokers who survive into later age unaffected by smoking-related diseases likely make up a group of individuals who are genetically protected from smoking-related illnesses. These resilient individuals may be additionally protected from other age-related diseases, including AD. Thus, a significant number of elderly smokers selected for study may be these genetically "protected" individuals, resulting in a "protective" effect of smoking.

ALZHEIMER'S AS A CHRONIC DISEASE

A view of AD as a chronic disease with a long preclinical period has been suggested by Katzman (Fig. 5-7).[232] Considerable data support this model of AD. Perhaps the most intriguing are those from longitudinal studies in which data were collected decades before the development of dementia.

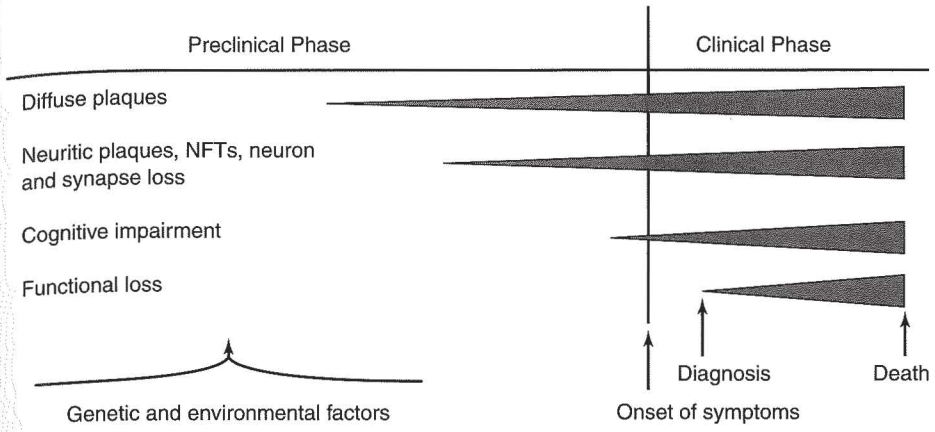


FIGURE 5-7 A chronic disease model of AD. *(Adapted by J. Troncoso from Katzman,[232] with permission.)*

For example, comparison of twins discordant for AD showed significant differences in verbal IQ scores 20 years before development of dementia (i.e., twins who subsequently developed AD had lower scores than their cotwins without AD).[233] More recently, linguistic analyses of autobiographies written by nuns at age 22 were used to predict AD later in life.[234] Using subjects from the Baltimore Longitudinal Study of Aging (BLSA; National Institute on Aging), we examined this issue in a different setting. In preliminary studies of well-educated subjects who had been followed longitudinally for up to 40 years, we were able to detect differences in Benton Visual Retention Test scores 20 years before death in autopsy-confirmed AD subjects[235] and 15 years before diagnosis in clinical cases.[236]

Clinical (Prevention) Trials

A model of AD as a chronic illness over several decades provides the possibility of many years during which intervention would be possible to ameliorate the irreversible decline that is the tragedy of this disease. Essentially all AD clinical trials to date have been conducted in patients already suffering the symptoms of dementia. These studies have supported the cholinergic contribution to the cognitive impairment of AD[237–242] and the potential role in AD for estrogen replacement therapy,[191,243,244] NSAIDs,[197,245,246] and antioxidant therapies.[247] Although there is value in ameliorating symptoms of AD once they become clinically evident, this strategy could actually increase the number of subjects with AD (prevalence) by increasing duration of disease. From a public health perspective, primary prevention and, therefore, primary prevention trials are essential.

Large scale primary prevention trials are costly and generally require several years for completion. Over the next few years, modified strategies that would contain costs and time are appropriate. For example, studies could be designed to target elderly subjects with the $\epsilon 4$ allele of Apo-E or a family history of AD, or subjects who are suffering from memory loss that may represent the early stages of the disease. The selection of high-risk groups with which to examine interventions is likely to become one of the most productive strategies for the near future. Even a modest average delay of 6 months would save several billion dollars currently spent on health care while also improving many lives. This goal is within our grasp.

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NEURODEGENERATIVE DEMENTIAS:

CLINICAL FEATURES AND PATHOLOGICAL MECHANISMS

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