Risk of dementia among relatives of Alzheimer's disease patients in the MIRAGE study: What is in store for the oldest old?

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Article abstract—Despite recent advances in the molecular genetics of Alzheimer's disease (AD), several fundamental questions concerning risk of illness are unresolved, namely, if Mendelian factors account for the incidence of the disease, and if AD is an inevitable consequence of the aging process. This study was designed to address these issues and other aspects of familial aggregation of the disorder. A consecutive sample of 1,694 patients who met criteria for a diagnosis of probable or definite AD were ascertained in 13 centers participating in the Multi-Institutional Research in Alzheimer Genetic Epidemiology (MIRAGE) project. Lifetime risk and age at onset of AD among various strata of 12,971 first-degree relatives was estimated using survival analysis procedures. The lifetime risk of AD in first-degree relatives was 39.0% ± 2.1% by age 96 years. Age-specific risk of AD declined after age 90 and the data set included 61 apparently unaffected persons who survived to age 96 without becoming demented. Female relatives had a higher risk of AD than male relatives at all ages. By age 80, children of conjugal AD couples had a cumulative risk of 54%, 1.5 times greater than the sum of the risks to children having affected mothers or fathers, and nearly 5 times greater than the risk to children having normal parents. Children of affected fathers had a cumulative risk that was 1.4 times the corresponding risk to children of affected mothers. Risk assessment in early-onset and late-onset families, using various strategies for determining the age cut-off, yielded contradictory results. These data suggest the following: (1) the lifetime risk among relatives does not support a simple autosomal dominant inheritance pattern of disease; (2) women are innately more susceptible to AD than men; (3) the proportion of hereditary cases may be higher in men than women; (4) distinction between early-onset and late-onset forms of AD has little meaning in the absence of a biological marker; (5) the risk of AD decreases after age 90; and (6) AD therefore may not be an inevitable concomitant of the aging process, a conclusion that has profound implications for basic and applied AD research. The age- and sex-specific lifetime risks derived from this study are sufficiently robust to be a reliable source of information for counseling relatives of AD patients.

NEUROLOGY 1996;46:641–650

Alzheimer's disease (AD) is one of the most common causes of dementia and is the fourth leading cause of death in the United States.[1,2] The prevalence of AD varies across decades, from about 3% of individuals 65 years old to nearly 50% of people 85 years old.[3,4] AD occurring at ages younger than 65 years, often referred to as early-onset AD, is rare but is still one of the most common causes for declining cognitive function in late middle age. The average length of time from onset of symptoms to death is approximately 7 to 8 years.[5,6] At present, there is no cure, and only minor palliative treatment is available.

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Supported in part by NIH grants R01-AG09029 (to L.A.F.), P50-AG05134 (to the Massachusetts Alzheimer Disease Research Center), P30-AG10130 (to the Alzheimer Disease Center at Emory University), R01-AG11503 (to R.C.G.), AG05142 (to the Alzheimer Disease Research Center at the University of Southern California), P30-AG10182 (to the Alzheimer Disease Center at the University of Kansas), AG08031 (to the Alzheimer Disease Center at the Mayo Clinic), and R01-AG07584 and U01-AG06781 (to W.A.K. and E.B.L.), and by an Alzheimer Society of Canada grant (to the University of British Columbia Alzheimer Disease Clinic). N.T.L. was supported by German Academic Exchange Service, Program of Epidemiology. L.V. was supported by the Department of Veterans Affairs.

Received August 31, 1995. Accepted September 13, 1995.

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Family, epidemiologic, and molecular studies have implicated genetic factors in the etiology of AD.[7] Some familial cases with age at onset in the fourth and fifth decades have defects in genes recently identified on chromosomes 1 and 14.[8,9] The frequency of these mutations in the population is not yet known. Manifestation of early-onset AD is also associated with mutations in the β-amyloid precursor protein (APP) gene on chromosome 21, but this is a very rare cause of AD.[10-13] A genomic search localized a gene for familial late-onset AD to chromosome 19,[14] and association studies of loci in this region subsequently implicated the apolipoprotein E (ApoE) gene as a likely susceptibility locus.[15] The ε4 allele of ApoE is several times more frequent in sporadic patients with late-onset disease than in cognitively normal persons in the general population.[16] This finding has been replicated in numerous clinic-based and cross-sectional patient populations including those enriched for early-onset disease[17-22] (for a review see reference 23).

In spite of the remarkable dose-dependent effect of ε4 on risk and age at onset of AD,[24,25] the predictive value of ApoE genotype is relatively modest.[26] Several studies suggest that susceptibility to AD is determined by the interaction of ApoE with other genetic and environmental factors.[17,21,27,28] This idea is supported by results from segregation analysis that indicate that several factors, including at least one major gene and gender, account for transmission of AD in families.[29]

Despite advances in the epidemiology and molecular genetics of AD, several basic questions about risk of disease still remain. First, what is the risk of AD to first-degree relatives? Second, does risk of AD increase unabated with age, i.e., would everyone develop AD if they lived long enough? Third, is the apparent increase in risk to women related only to their greater longevity than men? During the last decade, several investigators addressed these questions by examining incidence of disease in relatives of AD probands using survival analysis methods.[30-33] Although all studies agree that first-degree relatives of a patient have a substantially higher risk of disease than unrelated individuals, they differ by as much as 25% in the estimated lifetime risk to relatives of AD cases. Predictably, authors finding a lifetime risk near 50% conclude that AD is most likely transmitted as an autosomal dominant trait with age-dependent penetrance,[34-39] whereas others observing a lifetime risk below 40% conclude that the genetic mechanism is complex or heterogeneous.[40-43] Variability in lifetime risk estimates in previous studies is due in part to the paucity of data among persons older than 85 years. The reported confidence intervals for risks in this portion of the age spectrum are very large. To overcome problems encountered in previous reports on the genetic epidemiology of AD, we investigated the relationship between risk of disease, age, and sex in 12,971 first-degree relatives of 1,694 rigorously diagnosed probands of the MIRAGE (Multi-Institutional Research in Alzheimer Genetic Epidemiology) study.

Methods. *Subjects.* A total of 1,694 patients (674 men and 1,020 women) were enrolled at 13 centers in the United States, Canada, and Germany participating in the MIRAGE study. The MIRAGE centers include the Alzheimer's Disease Resource and Referral Center at the Boston University Medical Center; the Geriatric Research Education and Clinical Center, Edith Nourse Rogers Memorial Veterans Hospital, Bedford, MA; the Bryan Alzheimer Disease Research Center at Duke University; the Wesley Woods Center at Emory University, Atlanta, GA; the Alzheimer Disease Center at the University of Kansas; the Memory Disorders Unit of the Massachusetts General Hospital; Mayo Clinic Alzheimer's Disease Center and Alzheimer's Disease Patient Registry; the Wien Center at Mount Sinai Medical Center in Miami Beach, FL; the Southern California Alzheimer's Disease Diagnostic and Treatment Center at the Rancho Los Amigos Medical Center, Downey, CA; the Toronto Hospital Alzheimer's Disease and Related Disorders Clinic at Toronto University, Canada; the University of British Columbia Alzheimer's Disease Clinic; the University of Washington Alzheimer Disease Patient Registry; and the Memory Outpatient Clinic at the Technical University of Munich, Germany.

All AD patients who attended these clinics between April 1986 and August 1995 were eligible for this study; all were selected on the basis of clinical diagnosis independent of any family history information. The diagnosis of AD was uniform across our centers[44]; to be eligible for this study, we required a rating of 1 (166 patients) or 2 (1,528 patients) on the A axis of the MIRAGE AD rating scale (ADRS).[44] These ratings correspond to NINCDS/ADRDA criteria for definite or probable AD.[45] Information on family history of dementia among first-degree relatives was collected using standardized questionnaire instruments and verified by multiple informants by direct or telephone interview. Relatives were considered to be affected if they met criteria for ratings 1 to 4 on the ADRS where 3 = possible AD and 4 = "potential possible" AD. Additional details regarding patient sampling and evaluation and the family history protocol are published elsewhere.[44,46]

Selected characteristics of the 1,694 probands and their 12,971 first-degree relatives (parents, siblings, and children) are given in table 1. Probands had a significantly younger mean age at onset than the affected relatives ($p < 0.001$). The 831 affected relatives were members of 626 families indicating that 37.0% of the probands had a positive family history of AD. Of these 626 families, 477 (76.2%) had one affected relative, 110 (17.6%) had two affected relatives, and 39 (6.2%) had three or more affected relatives. Approximately 15% (473 of 3,069) of the parents and 6% (357 of 5,590) of the siblings were affected. Only one of the 4,313 offspring, who ranged in age from 0 to 78 years (mean = 44.0 ± 11.8 years), was reported as having suspected AD at the time of evaluation.

Estimation of lifetime risk and age at onset distribution. Risks of dementia and the age at onset distribution for first-degree relatives of the AD probands were estimated using a maximum likelihood procedure.[33] Like traditional Kaplan-Meier survival analysis,[30] this method allows for the possibilities that a proportion of relatives

Table 1 Characteristics of Alzheimer's disease probands and their first-degree relatives

	Probands			First-degree relatives		
	N (%)	Mean age at onset	Mean education level (years)	No. of affected	No. of unaffected	Mean age at onset
Men	674 (39.8)	68.5 ± 8.9	12.7 ± 3.6	277	6,249	72.8 ± 10.8
Women	1,020 (60.2)	70.7 ± 8.8	11.5 ± 3.3	554	5,891	75.1 ± 9.3
Total	1,694 (100)	69.8 ± 8.9	12.0 ± 3.5	831	12,140	74.3 ± 9.9

asymptomatic at the time of study may be susceptible and express the disease later in life, and that some relatives may have died of causes unrelated to AD although they may have developed symptoms had they survived. This method also considers persons for whom onset age or age at last report is missing. In this study, 4 affected and 368 unaffected individuals (2.9% of all relatives) were lacking these data but were able to be incorporated in the analysis. In order to estimate lifetime risk of AD beyond the oldest observed onset at age 96, age-specific risks obtained from the survival analysis method described above were incorporated into a Taylor polynomial function.[47] Risk of AD was extrapolated to the oldest censoring age of 104 years.

Gender effects were evaluated by stratifying the relatives by sex and sex of the proband. Risk of AD was estimated separately for parents and sibs to investigate generation effects. To test hypotheses about transmission of illness, risk among sibs having no affected parents was compared with the risks among sibs having affected mothers, affected fathers, and two affected parents. Several studies suggest that risk of illness, and consequently the disease mechanism, differs among relatives of early-onset and late-onset patients. We assessed this possibility under various assumptions of the cut-off between early-onset and late-onset. Following the procedure of Rao et al.,[29] four different strategies for determining the cut-off were used. One cut-off was set arbitrarily at the traditionally recognized age 65. The mean onset age among probands of 69.8 years was used as a second cut-off. To guard against biased ascertainment of the onset age pattern within a family on the basis of a single affected individual, a third cut-off was deduced by computing the median of the family mean onset ages, which was 72 years. In all three strategies, families were classified as early-onset or late-onset by comparing the proband's onset age with the cut-off value. Families were also classified by comparing the family mean onset age with the 72-year median.

Parameter estimates and their standard errors for the estimated lifetime risk and mean onset age were compared between various subgroups at the oldest age common to both groups. Since asymptotically these maximum likelihood statistics have normal distributions, a large-sample Z statistic was used for these comparisons.[48] A logrank statistic was used to test homogeneity of onset age distributions.[49]

Results. The lifetime risk for dementia to first-degree relatives of all AD probands was 39.0% ± 2.1% at age 96 years (table 2 and figure, A). Further inspection of the age-specific risks for AD among relatives of probands (table 3) revealed that cumulative risk increased by an average of 1.90% ± 0.79% per year between the ages of 80 and 90. During the 10th decade, the cumulative risk increased by 1.00% ± 0.60% per year. The significantly lower rate among the nonagenarians ($p = 0.034$) and the observation that 61 persons survived to the oldest onset age (96 years) apparently without developing symptoms of AD are consistent with the hypothesis that cumulative risk may be approaching an asymptote. Extrapolation of the cumulative risk curve to the maximum age in the sample of 104 suggests that, at most, the lifetime risk would increase to approximately 42%.

The risk of developing AD was significantly higher in female relatives than male relatives at all ages (figure, B). By age 93, women have a 13% higher risk than men of developing AD (table 2). However, the estimated mean age at onset was not different between men and women. Parents of AD patients had a significantly higher risk than sibs of developing AD at all ages beginning at 68 years (figure, C). At age 94 (the maximum onset age common to both groups), the difference in risk was 9.9% (table 2). At age 80, sibs of 21 probands having two affected parents had a risk of AD that was at least 32.3% greater than the risk among sibs having fewer than two affected parents (table 2 and figure, D). At age 85, sibs of 124 probands having an affected father had twice the risk of developing AD than sibs of 1,129 probands whose parents were normal ($p = 0.0022$) and a 1.4 times greater risk than sibs of 271 probands having an affected mother ($p = 0.13$). Notably, the sex ratio among affected sibs was the same when the father (0.37) or the mother (0.30) was affected ($p = 0.40$). The risk of AD among sibs having an affected mother was not significantly different from the risk among sibs having two normal parents.

Relatives of early-onset probands had a 7.3% higher lifetime risk of developing AD by age 93 than relatives of late-onset probands when the median onset age of 72 was used as the cut-off (figure, E). This significant trend was evident when families were classified according to age 65 or the probands' mean onset age of 69.8, but the differences were less significant (table 2). Regardless of the cut-off, the curves for early-onset and late-onset families were significantly different (for all logrank tests, $p < 0.0001$). Thus, although early-onset and late-onset probands have a similar proportion of affected relatives, age at onset appears to be a familial characteristic. However, classification of families according to the familial pattern of age at onset revealed that at ages below 82 years relatives in early-onset families had higher risks, whereas after this age they had lower risks than relatives in late-onset families. For example, relatives in late-onset families had a 7.9% higher lifetime risk of AD at age 86 (figure, F).

Table 2 Estimated lifetime risk of Alzheimer's disease and the age at onset distribution among first-degree relatives stratified by sex, relationship to the proband, and onset age group

Group	Number of relatives		Oldest onset age	Lifetime risk Risk ± SE	Comparison risk Risk ± SE*	Z, P	Onset age (yr) Mean ± SE
	Affected	Unaffected					
All	831	12,140	96	39.0 ± 2.1	N/A		82.0 ± 0.6
Males	277	6,249	96	30.9 ± 4.2	27.6 ± 2.6†	3.99, 0.000068	82.5 ± 1.6
Females	554	5,891	95	43.9 ± 2.5	40.7 ± 2.0		81.6 ± 0.6
Parents	473	2,596	96	42.8 ± 2.4	41.0 ± 2.1	2.42, 0.016	81.2 ± 0.7
Siblings	357	5,233	94	31.1 ± 3.5	31.1 ± 3.1		81.5 ± 1.2
Siblings Born to:							
Two affected parents	16	59	80	54.1 ± 10.9	54.1 ± 10.9‡		72.8 ± 1.5
Affected fathers	51	427	91	46.5 ± 11.5	21.8 ± 3.5	2.82, 0.0048	80.3 ± 2.5
Affected mothers	60	859	88	26.8 ± 5.3	15.3 ± 2.2	3.49, 0.0004	78.1 ± 1.6
Normal parents	230	3,887	94	29.1 ± 4.0	11.5 ± 0.9	3.90, 0.000096	82.4 ± 1.4
Onset age: 65 years							
Early (<65)	180	3,138	93	39.5 ± 4.1	39.5 ± 4.1	1.08, 0.28	80.5 ± 1.1
Late (≥65)	651	9,002	96	38.7 ± 2.4	34.7 ± 1.7		82.4 ± 0.7
Onset Age: Mean							
Early (<69.8)	337	5,389	95	42.0 ± 3.6	39.8 ± 3.0†	1.77, 0.077	81.4 ± 1.0
Late (≥69.8)	494	6,751	96	37.2 ± 2.6	33.5 ± 1.9		82.4 ± 0.7
Onset Age: Median§							
Early (<72)	439	6,558	96	43.6 ± 3.6	39.6 ± 2.5†	2.24, 0.025	81.8 ± 1.0
Late (≥72)	392	5,582	94	35.3 ± 2.6	32.3 ± 2.1		82.4 ± 0.7
Onset Age: Median**							
Early (<72)	340	5,951	86	19.5 ± 1.2	19.5 ± 1.2	4.46, 0.000008	72.0 ± 0.6
Late (≥72)	491	6,189	96	46.7 ± 2.8	27.4 ± 1.3		84.2 ± 0.5

* Risk at maximum age common to both groups (that is, the smaller of the two oldest onset ages unless otherwise indicated).
† Comparison age = 93 years.
‡ Referent group.
§ Relatives classified according to onset age of proband.
** Relatives classified according to mean onset age for family.

Discussion. In this sample of 1,694 families, the risk of AD by age 96 years among 12,971 first-degree relatives of patients with probable or definite AD was 39%. This risk, which is approximately twice the estimated cumulative incidence of AD in the general population,[50] supports the well-established hypothesis that AD has a strong genetic component, but it is unlikely that autosomal dominant or co-dominant inheritance can fully explain aggregation of disease in these families because the risk, which was adjusted for age-dependent penetrance, is significantly less than 50%. This conclusion confirms our findings from segregation analyses of 400 AD families, which implicated multiple mechanisms for transmission of the disorder.[29] Our data showing that by age 80 sibs of probands born to conjugal AD couples have a risk (54%) that is greater than the sum of the risks to children having affected mothers or fathers (37%) and nearly five times greater than the risk to children having normal parents are consistent with an additive model such as the one proposing a dose effect of the ApoE-ε4 allele on risk of AD[24]; however, multifactorial or polygenic inheritance patterns cannot be ruled based on these data alone. Bird et al.[51] previously showed that children of conjugal AD couples have an increased risk of AD, but meaningful empirical risk estimates could not be gleaned from their sample because the majority of children were younger than 55.

This sample of first-degree relatives, to our knowledge, is by far the largest studied in this manner. In comparison with lifetime risks reported by other investigators, our estimates are relatively precise (i.e., small standard errors) even at ages beyond 90 years. As shown in table 3, there were 294 persons alive after age 90 and 61 persons who survived to the oldest onset age (96 years) were reported to be cognitively intact. Studies reporting lifetime risks approaching 50% before age 90 may be inflated because of a relative paucity of unaffected persons surviving to very late ages, missing information on survival ages of unaffected persons, and ascertainment bias toward cases with a positive family history. In fact, with one exception,[52] studies with fewer than 100

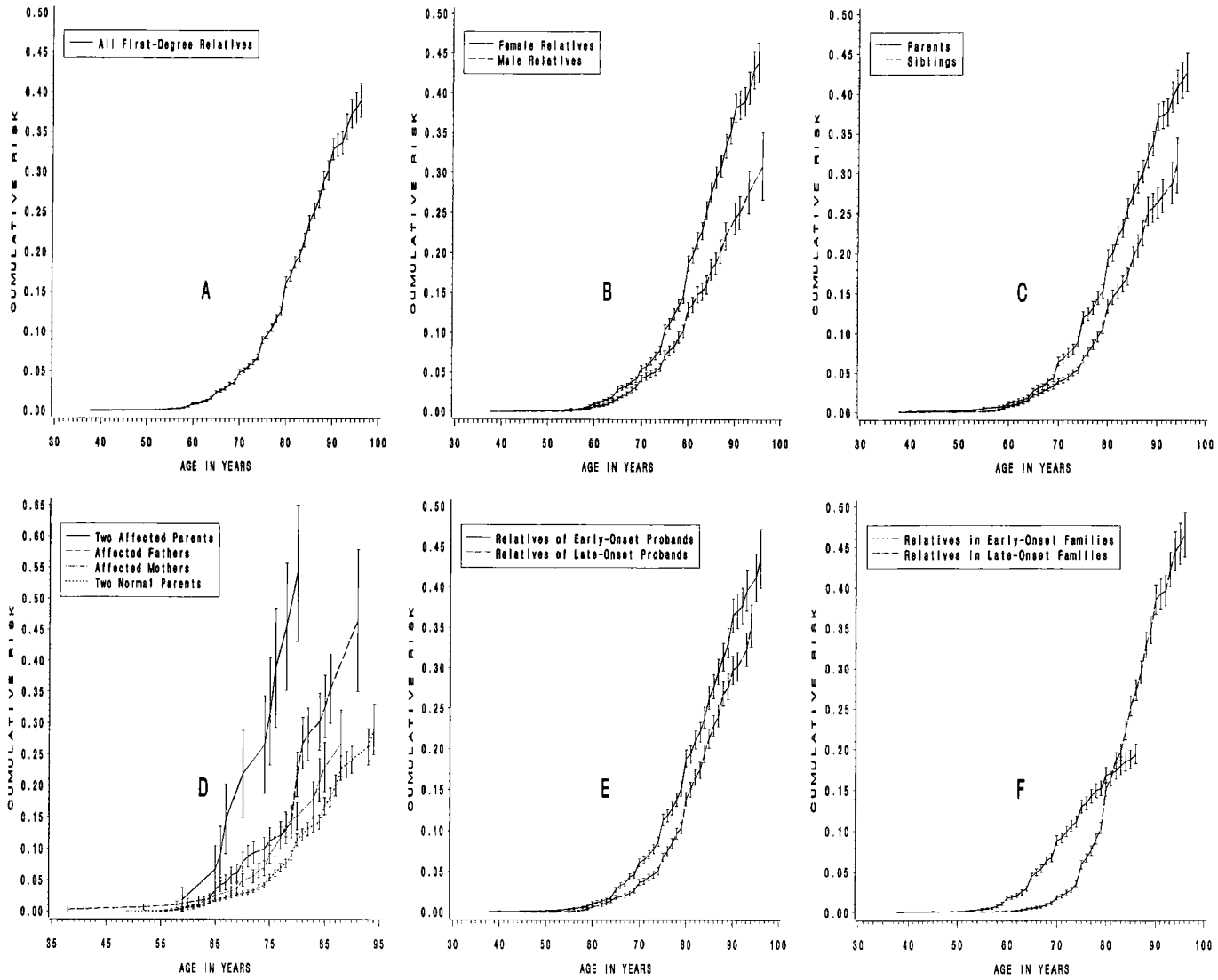

Figure. Estimated lifetime incidence of Alzheimer's disease (AD) in various strata of first-degree relatives of AD probands: (A) All first-degree relatives; (B) Male and female first-degree relatives; (C) Parents and siblings; (D) Siblings of AD probands having two affected parents, an affected mother, an affected father, or cognitively normal parents; (E) First-degree relatives of early-onset and late-onset AD probands (probands were classified as early-onset or late-onset using the median age at onset of 72 years as the cut-off); (F) First-degree relatives in early-onset and late-onset AD families (families were classified as early-onset or late-onset by comparing the family mean age at onset to the median age at onset of 72 years). Vertical lines show standard errors at each onset age in affected relatives and spouses.

probands reported the highest risks to first-degree relatives.[34,36-39,53] Lifetime risks based on data from more than 100 probands were substantially less than 50%.[40-43,54]

Epidemiologic studies indicate that AD affects women more than men.[50,55,56] Some authors explain this observation by increased longevity among women,[40,50] but our data and those from two other survival analyses showing a sex difference in risk are inconsistent with this idea.[36,42] Rao et al.[29] found that women have a higher risk of AD than men at all ages, and that the gender effect is independent of an underlying genetic susceptibility or sex-specific age at onset patterns. Although men and women may have different risks because of their different patterns of exposure to environmental risk factors such as smoking or head trauma, innate factors such as estrogen, exposure to which appears protective in women,[57,58] probably modulates susceptibility.

Additional insights into the gender difference in lifetime risk are suggested by the analyses of families by cognitive status of the parents. The finding of a greater risk of AD among offspring of affected fathers than affected mothers is incompatible with Mendelian and mitochondrial patterns of transmission. However, assuming that the underlying genetic mechanisms are the same in men and women, one explanation for the gender-related effects on risk and transmission of AD is that the proportion of hereditary cases is higher in men than women. Hence, affected men are more likely to transmit the disorder to offspring. On the other hand, the incidence of AD

Table 3 *Cumulative risk for developing Alzheimer's disease in first-degree relatives**

Age	Cum. risk % ± SE	No. of onset	No. of censored		No. of survivors	Increase in risk (%)
			Affected†	Unaffected		
0	0.00 ± 0.00	0	0	1,693‡	10,907	0.00
38	0.03 ± 0.02	2	0	317	10,587	0.03
40	0.05 ± 0.03	1	1	952	9,633	0.02
45	0.07 ± 0.03	1	0	860	8,772	0.02
49	0.09 ± 0.03	1	0	438	8,333	0.01
51	0.10 ± 0.04	1	0	175	8,157	0.02
52	0.12 ± 0.04	1	0	184	7,972	0.02
53	0.14 ± 0.04	1	1	370	7,600	0.03
55	0.24 ± 0.06	5	1	174	7,420	0.10
56	0.28 ± 0.06	2	1	176	7,241	0.04
57	0.31 ± 0.07	2	0	143	7,096	0.03
58	0.42 ± 0.08	6	1	156	6,933	0.11
59	0.57 ± 0.09	8	1	177	6,747	0.15
60	0.90 ± 0.12	18	2	199	6,528	0.33
61	0.95 ± 0.12	3	1	138	6,386	0.05
62	1.14 ± 0.13	10	1	173	6,202	0.19
63	1.34 ± 0.14	11	0	164	6,027	0.20
64	1.61 ± 0.16	14	3	183	5,827	0.27
65	2.30 ± 0.19	36	0	240	5,551	0.69
66	2.57 ± 0.20	13	3	188	5,347	0.27
67	2.81 ± 0.21	12	2	214	5,119	0.24
68	3.34 ± 0.24	25	0	222	4,872	0.53
69	3.63 ± 0.25	13	2	227	4,630	0.29
70	4.87 ± 0.29	53	2	289	4,286	1.24
71	5.12 ± 0.30	10	1	214	4,061	0.25
72	5.67 ± 0.32	21	1	287	3,752	0.55
73	6.16 ± 0.34	17	4	214	3,517	0.49
74	6.81 ± 0.36	22	3	226	3,266	0.65
75	8.95 ± 0.43	67	3	288	2,908	2.14
76	9.61 ± 0.45	19	1	242	2,646	0.66
77	10.50 ± 0.48	23	7	202	2,414	0.89
78	11.66 ± 0.52	28	1	208	2,177	1.16
79	12.61 ± 0.55	21	9	189	1,958	0.95
80	16.23 ± 0.66	74	2	220	1,662	3.62
81	17.06 ± 0.68	15	7	156	1,484	0.83
82	18.71 ± 0.74	27	3	164	1,290	1.65
83	19.60 ± 0.76	13	2	130	1,145	0.89
84	21.53 ± 0.83	25	7	140	967	1.93
85	23.63 ± 0.91	24	4	123	816	2.10
86	25.14 ± 0.97	15	6	107	688	1.51
87	26.63 ± 1.03	13	0	101	574	1.49
88	28.95 ± 1.13	17	3	74	480	2.32
89	30.20 ± 1.12	8	1	80	391	1.25
90	32.88 ± 1.34	14	2	81	294	2.68
91	33.38 ± 1.37	2	3	49	240	0.50
92	33.67 ± 1.40	1	0	60	179	0.29
93	35.67 ± 1.61	5	3	47	124	2.00
94	37.36 ± 1.82	3	3	29	89	1.69
95	38.07 ± 1.93	1	2	22	64	0.71
96	38.99 ± 2.12	1	2§	22	39	0.92

* Data on 372 individuals with missing censoring ages incorporated into risk estimates.
† Age at onset unknown but prior to censoring age.
‡ Includes unaffected persons censored prior to age 38.
§ 2 affected persons with unknown onset ages were censored at age 97.

may be higher in women because they are more susceptible than men to the influence of nonhereditary risk factors. This hypothesis is consistent with results from pedigree studies showing a substantially higher rate of phenocopies (i.e., indistinguishable nongenetic cases of AD) among women than men.[29] However, we could not rule out the possibility that this finding is artifactual due to chance (differences in the cumulative risk estimates were not significant at all ages) or selection bias of families with parents who lived long enough to develop AD (affected fathers had a mean age at onset that was 2.1 years younger than the mean for affected mothers [$p = 0.028$]).

The finding that parents of AD probands have a higher risk for AD than sibs is difficult to interpret. Mendelian models and most environmental models of disease transmission are inconsistent with this pattern. Our retrospectively ascertained sample of families could be biased due a high proportion of sibs not having outlived the period of high risk; the mean censoring age of the unaffected sibs was 6.8 years younger than that for unaffected parents ($p < 0.0001$). Heston et al.[59] previously reported this pattern in a survey of 125 patients who underwent autopsy. Other investigators[37,43] using a life-table approach observed a higher lifetime risk in parents than sibs, but the results were not significant, possibly due to inadequate sample size.

Our study also revealed that when using age 72 as a cut-off between early-onset and late-onset AD, relatives of early-onset probands had a 7.3% higher risk of becoming affected than relatives of late-onset probands. This finding is in agreement with the results of Li et al.,[60] who showed evidence for higher risk of AD among relatives of early-onset probands than late-onset probands when using a cut-off at age 75 years. When early-onset and late-onset AD were defined according to the traditional age cut-off of 65 years or the mean onset age of 70 years for probands in the sample, we observed the same pattern of higher lifetime risk among relatives of early-onset probands, but the difference was not significant. Other investigators reported the same nonsignificant trend using age 65 as a cut-off.[36,38,40] In contrast to these results, adjusting for the onset age pattern within a family suggested that relatives in early-onset families had a lower risk of developing AD after age 82. Although this finding is counterintuitive to the idea that early-onset AD is dominantly transmitted and late-onset AD has a more complex genetic component,[29] it is in agreement with data from a large study of familial AD that showed that relatives in late-onset families had a 30% higher lifetime risk than relatives of early-onset probands.[61]

A difference in risk of AD between relatives of early-onset and late-onset families is unlikely to be related to ApoE because the frequency of the $\epsilon 4$ allele appears to be the same in both early-onset and late-onset cases.[18,62] On the other hand, increased risk of AD to relatives in early-onset families may reflect the presence of mutations in β-APP or disease loci on chromosomes 1 or 14. A similar argument would explain the finding of higher risk of AD to relatives in late-onset families, presuming there exist genetic defects other than ApoE that predispose individuals to late-onset AD. An alternative explanation for the possible higher risk of AD among late-onset families is ascertainment bias. Unaffected sibs in early-onset families are younger, and thus have a greater chance of still developing AD, than sibs in late-onset families. Nonetheless, our results suggest that imposing an arbitrary age cutoff to distinguish subtypes of AD has limited utility for research or clinical purposes.

Previous life table studies were unable to determine whether risk of AD increases indefinitely or reaches a plateau at some age beyond normal human life span. Examination of the cumulative risk estimates in our data set gives an impression that the slope of the curve may decrease after age 90. Although the rate of increase in risk is slower after age 90 (1.0% per year) than between ages 80 and 90 (1.9% per year), a larger sample enriched for persons surviving their ninth decade might be needed to determine whether this is a meaningful plateau. This hypothesis is supported by Silverman et al.[54] who, using an actuarial life table method of estimating lifetime risk, found that age-specific risk of AD decreases after age 80.

Epidemiologic studies focusing on the very old disagree on whether the prevalence of AD increases in persons older than age 90.[63,64] Both of these studies address the *prevalence* of dementia, which is quite different from the *risk* or *incidence*.[65] Although incidence data from the Lundby Study[66] and the Framingham Study[67] support the notion that risk of AD continues to climb with age, precise incidence data have not been reported for the 90-year+ age cohort. Extrapolation of family data showing a dose effect of ApoE-$\epsilon 4$ on risk and age at onset of AD led to the conclusion that everyone would develop AD if they lived to age 140,[68] but this study had relatively few persons older than 90 years, in comparison with our sample containing approximately 400 persons aged 90 or older. In contrast, our findings support the hypothesis that AD is a distinct disease entity and not an inevitable concomitant of the aging process.[69] This question is not only of theoretical interest in terms of disease classification, but it has profound implications for basic and applied AD research. Payami et al.[53] found that risk of AD was significantly lower among relatives of optimally healthy individuals than among relatives of AD patients or population-based controls. These findings are consistent with the idea that genetic factors exist that promote healthy aging, including protection against AD.[70] The fact that 61 first-degree relatives survived to age 96 and were reported to be cognitively intact suggests that the age-specific incidence may decrease in nonagenarians and centenarians. However, this conclusion should be viewed with caution be-

cause there are little data documenting the manifestation and clinical course of AD in persons older than 90 years. Future studies of the genetic and environmental profiles of cognitively normal, very elderly individuals may be equally important to the studies of such profiles of demented persons.

There are several caveats to the interpretation of our results associated with diagnostic uncertainty, study design, and limitations of the statistical methods. First, the majority of relatives were not examined in a manner as rigorous as the probands, and thus there is the possibility of misclassification. Informants may tend to underreport dementia in very old relatives because of preconceptions of the normal aging process. However, our family history method involving the use of multiple informants and careful record review has been shown to be highly reliable in AD.[71] Second, it has been suggested that the definition of onset of disease may have led to an underestimation of the true risk.[72] However, our use of multiple informants and medical records minimized this bias. Moreover, a younger onset age would have little impact on the comparisons between groups. Third, our results are based largely on patients attending specialized AD clinics and may not be representative of AD cases in the general population. However, a population-based study of early-onset AD in the Netherlands reported an identical lifetime risk of 39% among relatives of 198 patients.[42] Fourth, nonparametric life-table methods do not estimate risk of disease for ages in which there are no incident cases beyond the maximum age at onset in the sample. Finally, it is not feasible to discern specific disease transmission mechanisms from our analyses. For example, although the risk curve for a simple, age-dependent, fully penetrant autosomal dominant trait should be a sigmoid curve asymptotic to a final risk of 50%, failure to obtain this pattern does not dismiss dominant inheritance, and presence of this pattern does not prove its existence.

In summary, elderly relatives of patients with AD constitute an important group to study genetic and environmental risk factors for dementia. This study indicates that risk of AD declines among persons older than 90 years, and factors other than greater longevity among women account for the higher incidence of AD in that gender. Heredity may account for a higher proportion of AD in men than women, but additional studies are necessary to verify this hypothesis. The age-specific lifetime risks of AD in table 3 and the figure are a reliable source of information for genetic counseling. Caution should be exercised before employing risks modified for relationship (parents versus sibs) or onset age group (early versus late). Assessment of disease risk based on specific genetic factors such as ApoE would be more desirable,[68] but the positive predictive value of ApoE genotype is relatively modest and needs to be studied further.[22,26,28,73,74]

Acknowledgments

We thank Dina Buzzurro, Annette Karst, Dr. Dagmar Mosch, Mary Severson, Beth Souza, Anita Thibert, Jean Turnbull, and Carol Utley for collecting family history information.

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Are malnutrition and stress risk factors for accelerated cognitive decline? A prisoner of war study

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Article abstract—We set out to test the hypothesis that severe malnutrition and stress experienced by prisoners of war (POWs) are associated with cognitive deficits later in life. We assessed 101 former Australian POWs of the Japanese and 108 veteran control subjects using a battery of neuropsychological tests, a depression scale, a clinical examination for dementia, and CT. We divided the POWs into high weight loss (>35%) and low weight loss groups (<35%). We found no significant differences in cognitive performance between the POWs and control subjects or between high and low weight loss groups on any of the tests or in the prevalence of dementia. Scores on the depression scale showed that the former POWs had more depressive symptoms than the control subjects a decade previously, but the difference had diminished over time. This study does not support the hypothesis that malnutrition is a risk factor for accelerated cognitive decline nor the theory that severe stress can lead to hippocampal neuronal loss and cognitive deficits. Cognitive deficits in earlier studies of former POWs may have been associated with concurrent depression.

NEUROLOGY 1996;46:650–655

Cognitive decline may be an inevitable accompaniment of the aging process, although it is minimal on average until individuals reach the eighth decade.[1] However, for a proportion of older people, cognitive decline is accelerated as a result of exposure to toxins such as alcohol, head injury, and dementing processes, especially Alzheimer's Disease (AD). As the aged population increases, particularly in the developed world, there has been a growing interest in research on possible risk factors for accelerated cognitive decline.

In 1986, Calne et al.[2] advanced the hypothesis that AD, Parkinson's disease (PD), and motor neurone disease are due to environmental damage to specific regions of the CNS. This damage remains subclinical for several decades but makes those affected especially prone to the consequences of age-related neuronal attrition. They based the hypothesis on the association found between environmental factors and certain neurodegenerative diseases, for example, methylphenyltetra-hydropyridine and PD, polio virus infection and postpoliomyelitis syndrome, chickling pea ingestion and lathyrism, dietary factors and amyotrophic lateral sclerosis-PD complex of Guam, and boxing and the punch drunk syndrome (dementia pugilistica). In each case, there is a long latency period between exposure to the environmental factor and development of a disorder.

Calne et al.[2] postulated that although the nervous system has a capacity for compensation, this capacity is finite. Neurons lost while an individual is young may go unnoticed when compensation is possible, but advancing age-related neuronal loss is likely to accentuate this earlier cerebral insult. Broe,[3] however, argued that it is unlikely that progressive loss of specific neuronal populations, as in PD, could be attributed to subclinical damage early in life followed by progression due to intrinsic ageing processes.

Abalan[4] and Abalan et al.[5] advanced the hypothesis that malnutrition is a risk factor for AD, either through an inadequate diet or through malabsorp-

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Supported by a grant from the National Health and Medical Research Council.

Received March 21, 1995. Accepted in final form September 7, 1995.

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Risk of dementia among relatives of Alzheimer's disease patients in the MIRAGE study: What is in store for the oldest old?

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Neurology 1996;46;641-650
DOI 10.1212/WNL.46.3.641