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Gender Difference in Apolipoprotein E–Associated Risk for Familial Alzheimer Disease: A Possible Clue to the Higher Incidence of Alzheimer Disease in Women

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Summary

Late-onset Alzheimer disease (AD) is associated with the Apolipoprotein E (APOE)–ε4 allele. In late-onset familial AD, women have a significantly higher risk of developing the disease than do men. The aim of this study was to determine whether the gender difference in familial AD is a function of APOE genotype. We studied 58 late-onset familial AD kindreds. Kaplan-Meier survival analysis was used to assess genotype-specific distributions of age at onset. Odds ratios were estimated by logistic regression with adjustment for age and by conditional logistic regression with stratification on families. All methods detected a significant gender difference for the ε4 heterozygous genotype. In women, ε4 heterozygotes had higher risk than those without ε4; there was no significant difference between ε4 heterozygotes and ε4 homozygotes. In men, ε4 heterozygotes had lower risk than ε4 homozygotes; there was no significant difference between ε4 heterozygotes and those without ε4. A direct comparison of ε4 heterozygous men and women revealed a significant twofold increased risk in women. We confirmed these results in 15 autopsy-confirmed AD kindreds from the National Cell Repository at Indiana University Alzheimer Disease Center. These observations are consistent with the increased incidence of familial AD in women and may be a critical clue to the role of gender in the pathogenesis of AD.

Introduction

Late-onset Alzheimer's disease (AD) affects an estimated 3%–10% of individuals over age 65 years (Bachman et al. 1992; Evans et al. 1989), and 25%–50% of all cases are familial (≥2 affected first-degree relatives) (Fitch et al. 1988; Hofman et al. 1989; Edwards et al. 1991; Payami et al. 1994*a*). The established risk factors for AD are age, family history of dementia, and presence of allele ε4 of the Apolipoprotein E (APOE) gene (Katzman 1994). APOE has three major alleles: ε2, ε3, and ε4, with relative frequencies of .08, .77, and .15 in Caucasians (Davignon et al. 1988*b*). Allele ε4 is associated with both sporadic and familial AD, but the association is stronger with familial AD (Corder et al. 1993; Payami et al. 1993; Saunders et al. 1993).

Whether gender is an independent risk factor for AD has been controversial. Prevalence studies have generally shown higher rates in women than in men (Aronson et al. 1990; Rocca et al. 1991; Bachman et al. 1992), but population-incidence studies have been inconsistent, some showing a significantly higher rate in women and others finding no gender difference (Schoenberg et al. 1987; Kokmen et al. 1988; Bachman et al. 1993). The increased prevalence rate in women may in part be due to longer survival of women after onset of dementia but may also be indicative of a gender difference in the risk of AD. The controversy in incidence results may be due to heterogeneity. Studies that have examined the incidence of AD in relatives of random patients have consistently found higher risk or earlier age at onset in women than in men (Breitner et al. 1988; van Duijn et al. 1993; Rao et al. 1994; Silverman et al. 1994), which, in the face of inconsistent population incidence results, suggests that gender may be a risk factor only in familial AD. We recently tested this hypothesis in two independent samples of well-characterized familial AD kindreds and found significantly higher age-specific risk and earlier age at onset for women than for men in both data sets (Payami et al. 1996), supporting the notion that gender is an independent risk factor for familial AD.

The aim of the present study was to determine whether the increased risk to women in familial AD is a function of APOE genotype. In an earlier study of familial AD, we noted a significantly higher risk for ε4

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heterozygous women than for ε4 heterozygous men (Payami et al. 1994*b*). This finding has been controversial because in another study of familial AD the increased risk to ε4 heterozygous women was not statistically significant (Corder et al. 1995*a*). These studies were considered preliminary because the method used in both cases treated family members as unrelated individuals. In this paper, we investigated the effect of gender on the risk of AD in a larger data set than previously reported. We estimated gender-and genotype-specific odds ratios, taking into account family relationship of the subjects and longer survival of women. To confirm the results, we analyzed an independent data set consisting of autopsy-confirmed kindreds from the National Cell Repository (NCR) at the Indiana University Alzheimer Disease Center.

Subjects and Methods

The Oregon/Washington/Minnesota data included 58 late-onset familial AD kindreds, recruited and evaluated by the Oregon and Washington Alzheimer Disease Centers and the University of Minnesota research group. The kindreds were selected for having at least two first-degree relatives with AD and family average age at onset >60 years. The 58 kindreds comprised 29 nuclear families and 29 extended families. All families were Caucasian, from mixed European origin. The NINCDS-ADRDA guidelines (McKhann et al. 1984) were used for clinical diagnosis. Fifty of the 58 families had at least one autopsy-confirmed case of AD. Every participant or legal guardian signed informed consent in the presence of a witness. Age at onset was defined as the age when memory loss was first noticed by relatives. Subjects were tested for all the known AD genes. No evidence was found for the presence of a pathologic mutation in the amyloid precursor protein gene on chromosome 21 (Kamino et al. 1992) or in STM2 on chromosome 1 (Levy-Lahad et al. 1995). When the entire family group was considered, no evidence was found for linkage to S182 (AD gene on chromosome 14); however, there was evidence for linkage in a subgroup of families of intermediate age at onset (60–70 years) (Schellenberg et al. 1994). Thus, some of the families may have a mutation in S182.

APOE genotypes were determined using the method described by Hixson and Vernier (1990). The observed genotype frequencies were compared to the random (Hardy-Weinberg) expectations by a χ^2 test. Allele frequencies were estimated by allele counting. Age-at-onset distributions were plotted using Kaplan-Meier survival analysis, and the difference between the curves was tested by log rank statistics. Logistic regression analysis was used to estimate odds ratios after adjusting for age. Similar analyses were used to analyze subgroups classified by gender and genotype. Unconditional logistic regression can give biased estimates because it does not take family relationship into account. To account for the family unit, conditional logistic analysis was used, stratifying on families. This method gives unbiased estimates when the sampling unit is not the individual, such as matched pairs or families (Kleinbaum 1994). However, it does not distinguish nuclear families from extended families. Thus, although it may be the best method available, it is not ideal. SPSS software (release 5, 1992) was used for Kaplan-Meier survival analysis and for unconditional logistic regression analysis. LogXact-Turbo computer program (CYTEL 1993) was used for conditional logistic regression.

In all analyses, age was specified as age at last contact, or at death for the unaffected individuals, and age at onset for the affected individuals. We used age at onset instead of age at last contact or death for the patients because we wished to evaluate the effect of gender on the onset of AD and to avoid possible confounding by longer survival of women after disease onset.

The NCR data included kindreds that were ascertained by various groups and pooled by the NCR at Indiana University. Because of confidentiality, we are not aware of the sites where or the methods by which these families were originally ascertained. Only the Oregon families that have been placed in the NCR pool were identified and excluded to avoid overlap with the Oregon data. The 47 families that were sent to us were chosen by the NCR staff for being the largest and best-characterized kindreds in the NCR database. To minimize confounding due to missing data, before genotyping, we prioritized the families according to the completeness of data and availability of autopsy documentation. We chose the top 15 kindreds that had autopsy documentation and at least three affected individuals with known ages at onset. The kindreds were Caucasian, and the average age at onset in each kindred was >60 years. The 15 kindreds were composed of 11 nuclear families and 4 extended families. We genotyped every available sample from sibships with affected members by using a method similar to the method described by Hixson and Vernier (1990). The NCR data were analyzed separately using the Kaplan-Meier survival analysis and logistic regression as described above.

Results

Oregon/Washington/Minnesota Data

APOE genotypes were available for 182 women (101 affected and 81 unaffected) and 113 men (60 affected and 53 unaffected). Genotypes were grouped according to the number of the ε4 alleles present: ε4 homozygous (ε4/ε4), ε4 heterozygous (ε4/ε− including ε4/ε3 and ε4/ε2) and no ε4 (ε−/ε− including ε3/ε3, ε3/ε2, and ε2/ε2). The average ages at onset for the ε4/ε4, ε4/ε−, and ε−/ε− subjects were 69.8 ± 5.1, 71.0 ± 6.8, and 73.6

Table 1

Apo E Genotype and Allele Frequencies

	Total	ε4/ε4	ε4/ε3	ε4/ε2	ε3/ε3	ε3/ε2	ε2/ε2
All women	182	.16	.52	.04	.23	.05	0
All men	113	.24	.47	.04	.22	.03	0
Affected women	101	.16	.64	.04	.14	.02	0
Affected men	60	.35	.44	.03	.18	0	0
Unaffected women	81	.16	.37	.04	.34	.09	0
Unaffected men	53	.11	.51	.06	.26	.06	0
		ε4/ε4	ε4/ε−	ε−/ε−			
All women	182	.16	.56	.28			
All men	113	.24	.51	.25			
Affected women	101	.16	.68	.16			
Affected men	60	.35	.47	.18			
Unaffected women	81	.16	.41	.43			
Unaffected men	53	.11	.57	.32			
		ε4	ε3	ε2			
All women	364	.44	.51	.05			
All men	226	.50	.47	.03			
Affected women	202	.50	.47	.03			
Affected men	120	.58	.40	.02			
Unaffected women	162	.36	.58	.06			
Unaffected men	106	.40	.55	.05			

± 8.6 for women and 67.3 ± 8.3, 69.6 ± 8.1, and 68.6 ± 8.2 for men. The average ages of the ε4/ε4, ε4/ε−, and ε−/ε− unaffected subjects were 63.8 ± 13.4, 67.7 ± 15.4, and 59.1 ± 17.4 years for women and 63.5 ± 15.7, 67.0 ± 12.7, and 62.6 ± 22.6 years for men.

The APOE genotype and allele frequencies are shown in table 1. Considering all family members who were sampled (affected and unaffected), men and women had similar APOE genotype frequencies. Considering affected individuals only, men and women had significantly different genotype frequencies ($P = .01$), although the significance level is probably inflated because some of the subjects are related. The difference appeared to be due to an excess of the ε4/ε− genotype in women, because when compared to the Hardy-Weinberg expectations, the observed genotype frequency distribution for affected women was significantly distorted ($P < .001$) with an excess of ε4/ε− and deficiencies of ε4/ε4 and ε−/ε−, while the observed distribution for affected men was in close agreement with the Hardy-Weinberg expectations. Despite the apparent difference in the genotype frequency distributions, allele frequencies were similar in affected men and affected women.

Age-adjusted odds ratios of being affected were estimated with logistic regression (table 2). In women, ε4/ε4 and ε4/ε− had higher risk than ε−/ε−; ε4/ε4 and ε4/ε− were similar. In men, ε4/ε4 had significantly higher risk than ε4/ε− and ε−/ε−; ε4/ε− and ε−/ε− were similar. For men and women with similar genotypes, ε4/ε− women had significantly higher risk than ε4/ε− men; there was no significant difference between ε4/ε4 men and women or between ε−/ε− men and women.

Since these data represent data from families, and

Table 2

Odds Ratio of Developing AD, Using Unconditional Logistic Regression, Adjusting for Age

	Odds Ratio	95% CI	*P*
Women:			
ε4/ε4 (29) vs. ε−/ε− (50)	2.53	.95–6.75	.06
ε4/ε− (103) vs. ε−/ε− (50)	3.71	1.74–7.90	.0007
ε4/ε4 (29) vs. ε4/ε− (103)	.68	.29–1.62	.4
Men:			
ε4/ε4 (27) vs. ε−/ε− (28)	5.43	1.64–17.97	.006
ε4/ε− (58) vs. ε−/ε− (28)	1.36	.54–3.46	.52
ε4/ε4 (27) vs. ε4/ε− (58)	3.98	1.39–11.44	.01
Women versus Men:			
ε4/ε4 women (29) vs. ε4/ε4 men (27)	.32	.09–1.07	.06
ε4/ε− women (103) vs. ε4/ε− men (58)	2.11	1.08–4.10	.03
ε−/ε− women (50) vs. ε−/ε− men (28)	.76	.27–2.10	.60

NOTE.—Numbers in parentheses represent sample size.

family unit might alter the risk status, we fit a conditional logistic model with stratification on families. In this analysis, gender was a significant risk factor for the ε4/ε− genotype (odds ratio for women vs. men = 2.64, P = .02, 95% confidence interval [CI]: [1.19– 5.88]) but not for the ε4/ε4 (P = .10) or the ε−/ε− genotype (P = .31).

The Kaplan-Meier curves (fig. 1) exhibited the same trends as was seen with odds ratios. In women, the curve for ε4/ε− was significantly different from ε−/ε− (P = .02) but not from ε4/ε4. In men, the curve for ε4/ε− was significantly different from ε4/ε4 (P = .01) but not from ε−/ε−. In contrast to Kaplan-Meier curves, the difference in lifetime cumulative risks was not statistically significant.

NCR Data

APOE genotypes were available for 56 women (38 affected and 18 unaffected) and 34 men (18 affected and 16 unaffected). The average ages at onset for the ε4/ε4, ε4/ε−, and ε−/ε− subjects were 69.3 ± 8.1, 72.2 ± 7.4, and 73.1 ± 11.4 years for women and 64.8 ± 6.8, 76.2 ± 4.5, and 72.0 ± 8.2 years for men. The average ages of the ε4/ε4, ε4/ε−, and ε−/ε− unaffected subjects were 72.0 ± 9.0, 66.9 ± 9.6, and 76.1 ± 7.3 years for women and 77.0 ± 0, 72.0 ± 7.8, and 67.7 ± 9.5 years for men.

When all family members who were genotyped were considered, there was no significant difference in the genotype frequencies of men and women (ε4/ε4, ε4/ε−, ε−/ε−: .21, .47, .32 vs. .11, .62, .27). When only the affected individuals were considered, men and women had different genotype frequencies (.33, .50, .17 vs. .08, .74, .18, P = .05). Genotype frequencies differed significantly from the Hardy-Weinberg expectations in both affected men and affected women, but in different directions: in affected women, there was an excess of ε4 heterozygotes, whereas in affected men there was an excess of ε4 homozygotes.

The NCR data showed the same pattern of gender difference as our data. Using logistic regression adjusting for age, ε4/ε− women had significantly higher risk than ε4/ε− men (odds ratio = 6.88, 95% CI [1.52–31.19, P = .01]). There was no significant difference between ε4/ε4 men and women (odds ratio = .26, 95% CI [.01–4.6, P = .36]) or between ε−/ε− men and women (odds ratio = 2.39, 95% CI [.41–13.87, P = .33]). The sample size of the NCR data was too small to allow stratification on families. When Kaplan-Meier survival analysis was used (fig. 2), women showed a significant difference between ε4/ε− and ε−/ε− (P = .02) but not between ε4/ε− and ε4/ε4. Men, on the other hand, showed a significant difference between ε4/ε− and ε4/ε4 (P = .004) but not between ε4/ε− and ε−/ε−.

Discussion

The purpose of this study was to assess the influence of gender on APOE-associated risk in late-onset familial AD. We studied 58 kindreds that were ascertained by us and, for confirmation, an additional 15 autopsy-proven kindreds from the NCR. Currently, there is no ideal method for estimating risk ratios from family data. For this reason, we analyzed the data with the three most commonly used methods: Kaplan-Meier survival analysis, unconditional logistic regression adjusting for age, and conditional logistic regression stratifying on families. The results were qualitatively the same for all analyses; every method gave statistically significant evidence for a gender difference for the ε4 heterozygous genotype.

The present study includes two data sets with familial late-onset AD. In both data sets, ε4 heterozygous women appeared to have significantly higher risk than ε4 heterozygous men. A third data set with familial late-onset AD was analyzed by Corder et al. Although their initial study did not show a significant difference (1995*a*), they recently reported different patterns of risk for men and women in relation to APOE ε4 (Corder et al. 1995*b*).

Our study included large kindreds that were selected for having multiple affected individuals; thus the results cannot be generalized to smaller families or to sporadic AD. A number of studies of sporadic AD have questioned the gender effect on the APOE genotype. Tsai et al. (1994) combined the ε4/ε4 and ε4/ε− genotypes and found no difference between men and women. The two studies that investigated the ε4/ε− genotype separately detected a gender difference. Poirier et al. (1993) studied Caucasian subjects and found a higher frequency of the ε4 heterozygous genotype in women than in men, which is consistent with our results. They also detected a gender difference in the frequency of the ε4 allele, which we did not. Yasuda et al. (1995) studied Japanese subjects and found a higher risk for ε4 heterozygous women than for ε4 heterozygous men. In their study, the ε4 allele frequency was similar in men and women.

Corder et al. (1995*b*) have suggested that the higher prevalence of AD in women may be a result of longer survival in affected women. The gender difference in our studies cannot be attributed to differences in survival after the onset of dementia. When adjusting for the ages of the subjects, we used current age or age at death for the asymptomatic individuals, but for the affected individuals we used their ages at onset. As a result, affected individuals were effectively eliminated from further consideration once they became demented, and disease duration did not enter the analyses. This strategy enabled us to study the effect of gender on the onset of dementia and to avoid confounding by longer survival of women after disease onset.

One possible explanation for our results is that gender plays a role in the pathogenesis of familial AD and influences the risk of developing the disease. The role of gender in AD has been controversial. Community-based incidence studies have been inconsistent, but family

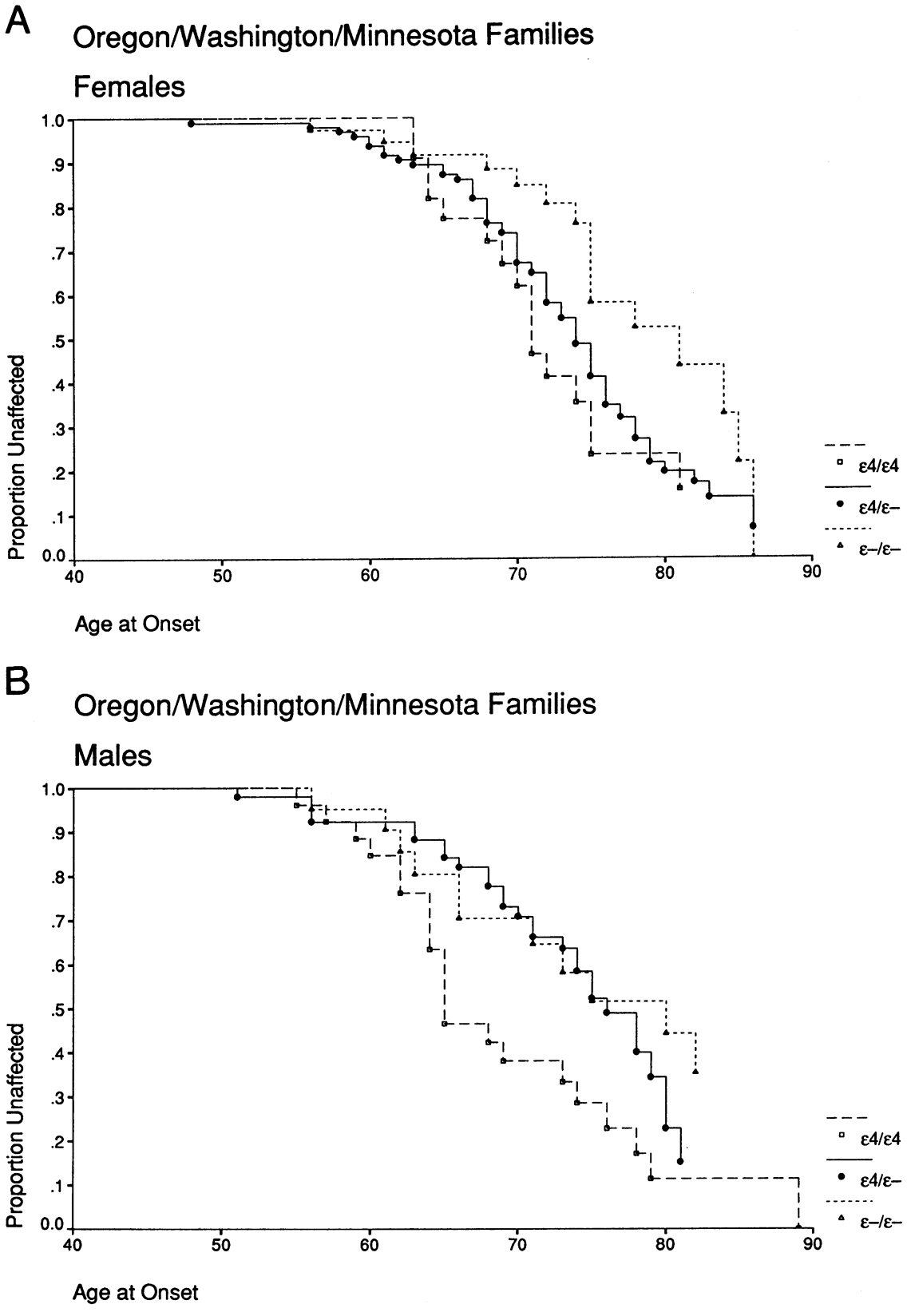

Figure 1 Genotype-specific distribution of age at onset in Oregon/Washington/Minnesota families. *A*, Differences in age-at-onset curves in women: ε4/ε4 (N = 29) vs. ε–/ε– (N = 50), P = .02. ε4/ε4 (N = 29) vs. ε4/ε– (N = 103), P = .53. ε4/ε– (N = 103) vs. ε–/ε– (N = 50), P = .02. *B*, Differences in age-at-onset curves in men: ε4/ε4 (N = 27) vs. ε–/ε– (N = 28), P = .01. ε4/ε4 (N = 27) vs. ε4/ε– (N = 58), P = .01. ε4/ε– (N = 58) vs. ε–/ε– (N = 28), P = .40.

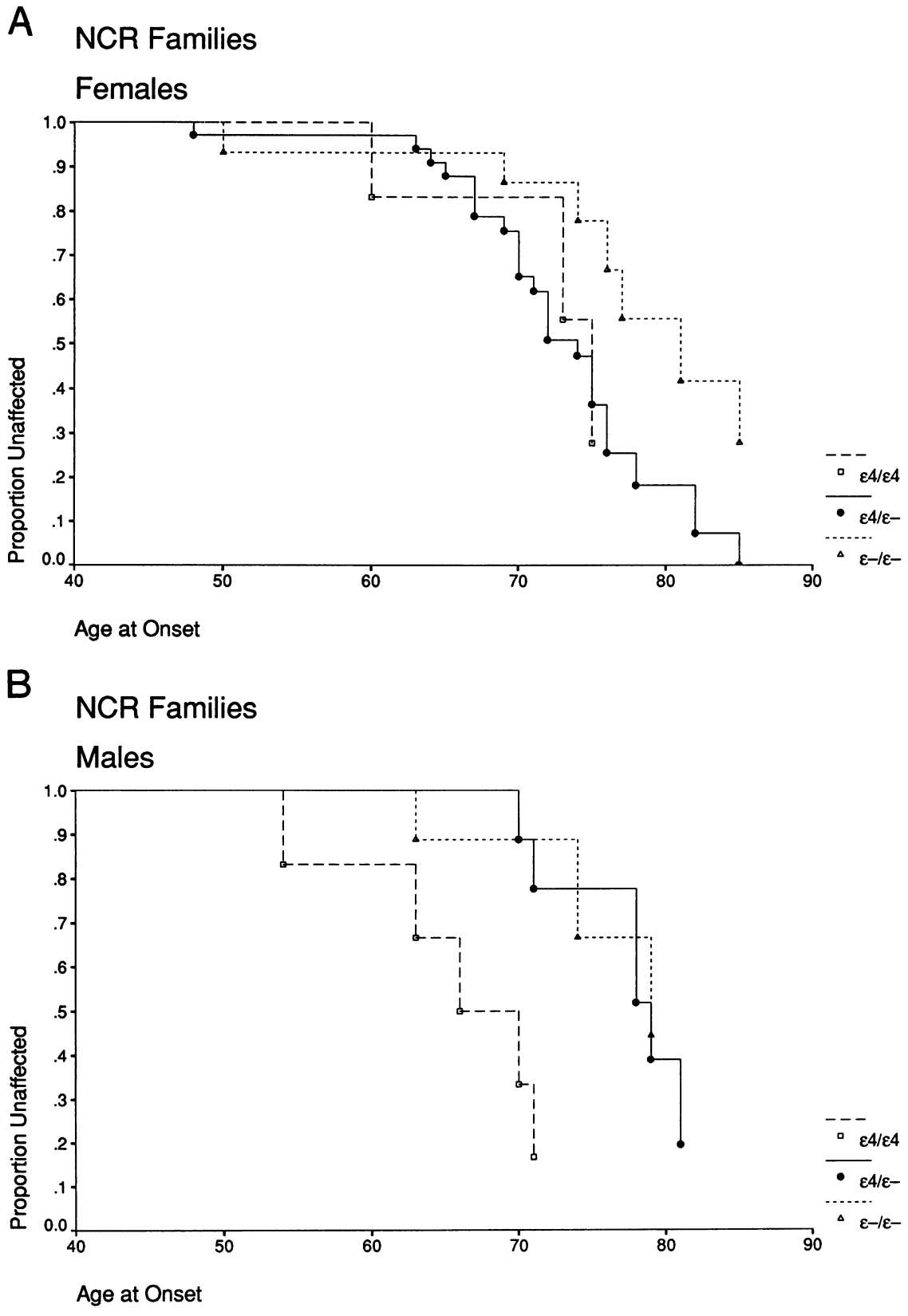

Figure 2 Genotype-specific distribution of age at onset in NCR families. *A*, Differences in age-at-onset curves in women: ε4/ε4 (N = 6) vs. ε–/ε– (N = 15), P = .35. ε4/ε4 (N = 6) vs. ε4/ε– (N = 35), P = .67. ε4/ε– (N = 35) vs. ε–/ε– (N = 15), P = .01. *B*, Differences in age-at-onset curves in men: ε4/ε4 (N = 6) vs. ε–/ε– (N = 11), P = .02. ε4/ε4 (N = 6) vs. ε4/ε– (N = 13), P = .004. ε4/ε– (N = 13) vs. ε–/ε– (N = 11), P = .98.

studies have generally shown higher age-specific risks for female relatives of patients than for male relatives, suggesting that gender is an independent risk factor for familial AD (Breitner et al. 1988; van Duijn et al. 1993; Rao et al. 1994; Silverman et al. 1994; Payami et al. 1996).

A recent study has demonstrated an interaction between APOE genotype, gender, age, and cholesterol levels in AD, suggesting that some aspects of cholesterol transport may be involved in the pathogenesis of this disease (Jarvick et al. 1995). Apo E plays a major role in lipid transport and metabolism. Recently, it has been proposed that the link between AD and Apo E involves a dysfunction of lipid-transport system in hippocampal response to injury (Poirier 1994). Gender is known to affect the influence of Apo E on the distribution of plasma lipids and apolipoproteins (Reilly et al. 1994) and thus may also affect the efficacy of Apo E in redistributing myelin cholesterol during nerve repair.

A number of studies have implicated estrogen in cognitive health and AD. It has been suggested that estrogen has a protective effect against age-related cognitive decline (Honjo et al. 1989; Henderson et al. 1991; Barrett-Conner and Kritz-Silverstein 1993), and estrogen use after menopause may enhance memory function in older women (Kampen and Sherwin 1994; Robinson et al. 1994). Although controversial, estrogen-replacement therapy may reduce the risk of AD in women (Brenner et al. 1994; Paganini-Hill and Henderson 1994). It is possible that the gender difference observed here is related to hormonal changes that women experience at menopause.

ε4 is a major risk factor for AD, but it is neither necessary nor sufficient for the development of the disease (Corder et al. 1993; Payami et al. 1993). It is now clear that factors other than ε4 are involved in the etiology of AD (Corder et al. 1993; Payami et al. 1993; Bennett et al. 1995). It is possible that the added susceptibility due to the other risks (e.g., estrogen depletion) is inconsequential in ε4 homozygotes, who are already highly susceptible, but is relatively substantial in ε4 heterozygotes and can increase their risk to the level of ε4 homozygotes.

Another possible explanation for the results is that the data were skewed by incomplete sampling of the family members. This may seem unlikely, since two independent data sets yielded similar results, but it is conceivable that a similar bias existed in both our data and the NCR data. Despite efforts to sample every affected and unaffected individual in each sibship, a considerable number of family members were deceased, and their genotypes could not be reconstructed. Further, some of the currently unaffected subjects may eventually develop AD; thus follow-up of the younger subjects may alter the results.

In light of the reported association of APOE with longevity (Kervinen et al. 1994; Schachter et al. 1994), stroke (Pedro-Botet et al. 1992; Couderc et al. 1993), and, possibly, heart disease (Payne et al. 1992; van Bockxmeer and Mamotte 1992; Wilson et al. 1994), we questioned whether our results were seriously compromised by competing risks and the missing genotypes of the deceased relatives. First, although the APOE profile of the population changes with age, middle-aged and octogenarian men and women have similar genotype frequencies (Davignon et al. 1988*a*; Wilson et al. 1994). Thus the difference that we see in men and women with AD cannot be attributed to a gender/APOE effect on longevity. In our AD kindreds, there was no difference in genotype frequencies in men and women, except for those who had developed AD, which suggests that the gender difference is specific to AD.

Next, we wondered whether the missing genotypes represented death from heart disease, stroke, or another common cause that might be influenced by an APOE/gender interaction. In the 21 Oregon kindreds that we examined, the missing genotypes were due to death from cancer (8 women and 9 men), heart disease (4 women and 9 men), AD (7 women and 4 men), stroke (3 women and 3 men), other causes combined (4 women and 11 men), and unknown causes (6 women and 2 men). In light of the diverse causes of death, and the infrequency of each, it is difficult to attribute the gender difference in AD to any individual cause. However, nearly 30% of the deaths were due to stroke and heart disease combined. Thus the possibility remains that the data were skewed by the missing genotypes of the deceased individuals.

Finally, we reasoned that if the increased risk to ε4 heterozygous women is real, then, in light of the high frequency of this genotype in AD kindreds, women should exhibit a higher risk than men when APOE genotype is not considered. Alternatively, if the results are due to missing genotypes, there should not be a gender difference when all family members are accounted for. We assessed the gender-specific risk of AD in the Oregon families, regardless of APOE and with virtually no missing data, and for confirmation, in families from the NCR. In both data sets, we found significantly elevated age-specific risk in women than in men (Payami et al. 1996). In short, we found no evidence that our results are caused by selection bias. Nevertheless, we cannot rule out the possibility that the data were skewed by the missing data. Resolution of this issue requires large prospective studies that take gender and family history of AD into account and are well controlled for competing risk factors.

If confirmed, an increased risk to ε4 heterozygous women can have a major public health impact. Although ε4 homozygosity confers the highest risk of AD in both men and women, this genotype is relatively rare. Only 3% of middle-aged Americans (ages 40–77) and 0.4%

of Canadian octogenarians are reportedly ε4 homozygous, as compared with 20% of middle aged and 16% of octogenarians who are ε4 heterozygous (Davignon et al. 1988*a*; Wilson et al. 1994). Therefore, in light of the high prevalence of ε4 heterozygosity, a twofold difference in risk between men and women with this genotype could have a major effect on the gender-specific incidence of the disease in the population.

In summary, we have found evidence for a gender difference in the APOE-associated risk for familial AD and confirmed it in an independent data set. The results may reflect a gender difference in the etiology of AD or in survival, because of competing risks. In conclusion, this study raises some critical questions that have wide implications in basic research, public health, and genetic counseling. The role of gender in AD, and its possible interaction with APOE, warrants further investigation.

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