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Authors
Dal Forno, G
Carson, KA
Brookmeyer, R
et al.

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APOE genotype and survival in men and women with Alzheimer's disease

G. Dal Forno, MD; K.A. Carson, ScM; R. Brookmeyer, PhD; J. Troncoso, MD; C.H. Kawas, MD; and J. Brandt, PhD

Abstract—*Background:* The ϵ4 allele of the *APOE* gene (*APOE*) is more frequent in patients with AD than in the general population, but studies are inconclusive as to whether it affects rate of progression or survival. Because survival in AD is generally longer in women than in men, the authors investigated whether *APOE* affects 10-year survival equally in men and women. *Methods: APOE* testing was performed on 125 patients with probable AD enrolled in the Johns Hopkins AD Research Center between November 1984 and March 1987. The 39 men and 86 women were followed at 6-month intervals until censoring (by death or withdrawal from the study) or March 1997. Patients were dichotomized into those with and those without at least one ϵ4 allele. For each sex, a Cox proportional hazards regression, allowing for delayed entry and covarying for age at onset, was used to examine the effect of ϵ4 on survival. *Results:* All patients who died during the study period and had autopsy (n = 92) were found to have definite AD. Average survival from disease onset did not differ by sex (12.1 years in men; 12.3 years in women). In neither sex were differences found between ϵ4-positive and ϵ4-negative subgroups in education, duration of AD at entry, or severity of dementia. However, in both sexes the ϵ4-positive subgroup was approximately 3 years older at onset of AD and at entry to the study than the ϵ4-negative subgroup. Adjusting for age at onset, the presence of an ϵ4 allele significantly increased the relative risk of death only for men (RR = 2.69; 95% CI = 1.23 to 5.87). *Conclusions:* In this sample of mostly white, well-educated research participants with AD, the *APOE* ϵ4 allele was associated with shorter survival in men but not in women.

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The ϵ4 allele of *APOE* is more prevalent among persons with AD than among the general population.[1-6] In addition, having an ϵ4 allele has been associated with earlier disease onset in typical, late-onset AD.[3,7-9] Furthermore, there appears to be a gene-dose effect, such that individuals homozygous for ϵ4 have earlier onset than heterozygous individuals.[4]

Although the precise mechanism by which the *APOE* polymorphism affects risk and onset of AD remains unknown, a more rapid deposition or accumulation in the brain of β-amyloid protein[1,2] and/or an accelerated formation of paired helical filaments have been proposed.[10] If either hypothesis is true, one would expect to observe faster progression and shorter survival in patients with the ϵ4 allele. However, the studies to date on progression and survival have been inconclusive. Some have suggested that *APOE* has no effect on rate of clinical decline,[11-17] others have suggested that the ϵ4 allele is associated with more rapid decline,[18-20] and still others find an association of ϵ4 with more gradual decline.[21-22] In a large cohort of patients with AD followed prospectively, we found a small but significant effect of ϵ4 on rate of decline in some cognitive and functional measures (having at least one ϵ4 allele being associated with more rapid decline), but a clear gene-dose effect was not observed.[23]

Some studies[22,24] report longer survival among patients with AD with the ϵ4 genotype, but two large, population-based studies[12,25] found no such effect. Although survival is reduced in patients with AD compared with healthy elderly, it may be particularly reduced in men who have AD or other cognitive disorders.[25-27] A recent Finnish study suggests that *APOE* genotype and sex may interact to influence survival.[25] In that study of 16 men and 32 women with AD followed for 3 years, mortality was significantly higher in men without the ϵ4 allele compared with women without the ϵ4 allele. However, the small sample (n = 48), small number of deaths (n = 22), and short follow-up period limits interpretation of these results. Therefore, the current study investigated whether the ϵ4 allele affects survival of men and women differently in a significantly larger cohort of patients with AD followed for up to 12 years.

Methods. *Subjects.* Between November 1984 and March 1987, the Johns Hopkins AD Research Center

From the Departments of Neurology (Drs. Dal Forno, Carson, Troncoso, and Kawas) and Psychiatry and Behavioral Sciences (Dr. Brandt), the Neuropathology Laboratory, and the Department of Pathology (Dr. Troncoso), and the Alzheimer's Disease Research Center (Drs. Dal Forno, Carson, Brookmeyer, Troncoso, Kawas, and Brandt), The Johns Hopkins University School of Medicine; and the Department of Biostatistics (Dr. Brookmeyer), The Johns Hopkins University School of Public Health, Baltimore, MD.

G.D.F. is now affiliated with the University Campus BioMedico of Rome. C.H.K. is now affiliated with the University of California at Irvine.

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Address correspondence and reprint requests to Dr. Jason Brandt, Department of Psychiatry and Behavioral Sciences, The Johns Hopkins University School of Medicine, 600 N. Wolfe Street, Meyer 218, Baltimore, MD 21287-7218; e-mail: jbrandt@jhmi.edu

(ADRC) enrolled 209 patients who met the National Institute of Neurologic Disorders and Stroke–AD and Related Disorders Association criteria for possible or probable AD.[28] At entry to the ADRC, a thorough medical history was taken from each patient with the help of a caregiver. Neurologic and psychiatric examinations and a neuropsychological evaluation were performed, and appropriate laboratory studies were reviewed or performed to rule out other causes of dementia. Exclusion criteria were a current or past history of major mental illness, current alcohol or drug abuse, or a CNS disorder other than AD. Extrapyramidal signs insufficient to diagnose PD or marked behavioral disturbance did not preclude participation in the study. All procedures were fully explained to patients and their surrogate decision-makers, and informed consent was obtained before enrollment.

At each semiannual visit to the ADRC, interim histories were taken and neurologic, psychiatric, and neuropsychological evaluations were repeated. This information was used to monitor the course of the patient's illness to determine whether the clinical diagnosis should be reconsidered. Patients were included in the current analyses if they were diagnosed with probable AD at study entry and at each subsequent visit. Patients who died and had brain autopsy were required additionally to meet the neuropathologic criteria for definite AD of the Consortium to Establish a Registry for AD.[29] Of the 188 patients meeting these criteria, 125 had DNA available for genotyping.

Procedures. Patients were followed with semiannual visits until March 1997 or until death or withdrawal from the study. *APOE* analysis was performed by PCR amplification and restriction enzyme isotyping of DNA from all patients who consented to genetic testing and from whom nucleated cells were available.[30]

Data analysis. For simple group comparisons, *t*-tests or χ^2 tests were used, as appropriate. The 63 patients without DNA available were compared with the study sample on demographic characteristics and severity of disease at study entry. The 86 genotyped women were compared with the 39 genotyped men on these same variables. *APOE* genotype was dichotomized by presence or absence of an ϵ4 allele. Comparisons of the ϵ4-positive and ϵ4-negative groups on demographic characteristics, disease severity, and survival were performed. Because survival rates are different for men and women,[26-27] the effect of ϵ4 on survival was analyzed separately for each sex. Because we were interested in disease course, the abscissa in the survival analyses was time since disease onset (i.e., duration of illness) rather than time since study entry, as in other studies.[22] Because patients with known disease onset may die before they enter the study, patients were considered at risk of death only at time points that exceeded their own duration of illness at entry,[31] an adjustment known as "delayed entry" or "left truncation."[32] Kaplan–Meier analysis, allowing for delayed entry, was used to graph and to compare the survival functions of those with and without an ϵ4 allele, in men and in women. Cox proportional hazards regression, also allowing for delayed entry, was used to estimate the risk associated with the presence of ϵ4, after covarying for age at disease onset. The SAS (SAS Institute, Cary, NC) procedure *Phreg* was used for this analysis.[33]

Table 1 *Demographic and baseline clinical characteristics and median survival time for genotyped and nongenotyped samples*

Characteristics	Genotyped	Nongenotyped
n	125	63
Sex, % F	68.8*	55.6
Race, % African-American	10.4*	20.6
Education, highest grade	12.8 (0.34)	12.5 (0.42)
Age at onset, y	65.6 (0.76)	66.2 (1.07)
Age at entry, y	69.8 (0.76)	70.3 (0.97)
Duration at entry, y	4.2 (0.21)	4.2 (0.35)
Mini-Mental State Examination score	14.6 (0.52)	13.3 (0.75)
Physical Dependency Scale of PGDRS score	4.7 (0.45)	5.6 (0.96)
Median survival from onset, y (CI)	12.2† (11.0–13.1)	10.7 (8.5–11.8)

Values are means (SEM) unless otherwise noted.

* $p < 0.10$ by continuity-adjusted χ^2.
† $p < 0.01$ by log-rank χ^2.

PGDRS = Psychogeriatric Dependency Rating Scales.

Results. Demographic characteristics and baseline disease severity measures for the genotyped study group and the nongenotyped patients are shown in table 1. There was a trend ($p < 0.10$) for a greater proportion of women and a smaller proportion of African-Americans in the genotyped sample. In addition, survival was longer in the patients from whom DNA was available ($p < 0.01$). However, there were no other significant differences between the study group and the nongenotyped patients.

For the 125 genotyped patients, descriptive statistics on demographics and baseline severity measures, stratified by sex, are presented in table 2. The men were significantly younger at disease onset and study entry than the women, although duration of disease at entry was similar. Also, the men were more highly educated, performed better on the Mini-Mental State Examination, and had lower scores (indicating greater competence in self-care) on the physical functioning scale of the Psychogeriatric Dependency Rating Scales.[34] The survival of male and female patients was equivalent.

Demographic characteristics, baseline severity measures, and endpoint data for each sex, stratified by the presence or absence of an ϵ4 allele, appear in table 3. There were no significant differences between ϵ4-positive and ϵ4-negative subgroups for either sex on any variable. However, in both sexes the ϵ4-positive subgroup was approximately 3 years older at onset and study entry than the ϵ4-negative subgroup. All the patients who came to autopsy had neuropathologically confirmed AD.

Kaplan–Meier curves for men and women are shown in the figure. For men, the median survival from onset for the ϵ4-positive subgroup was 11.0 years (95% CI = 8.9 to 12.8). For the ϵ4-negative subgroup, median survival was 14.5 years (CI = 12.2 to 16.5). The log-rank χ^2 comparing survival in men with and without an ϵ4 allele was significant ($p < 0.01$). For women, the median survival for the ϵ4-positive subgroup was 8.3 years (CI = 1.6 to 17.1); for the ϵ4-negative subgroup it was 9.2 years (CI = 7.1 to 15.9).

Table 2 *Demographic and baseline clinical characteristics and survival of men and women in the genotyped sample*

Characteristics	Men	Women	*p* Value
n	39	86	–
Race, % African-American	0	15.1	0.009
Education, highest grade	14.0 (0.61)	12.2 (0.39)	0.01
Age at onset, y	62.0 (1.41)	67.3 (0.84)	0.001
Age at entry, y	66.4 (1.47)	71.4 (0.83)	0.002
Duration at entry, y	4.4 (0.40)	4.1 (0.25)	0.55
Mini-Mental State Examination score	16.2 (0.84)	14.0 (0.64)	0.05
Physical Dependency Scale of PGDRS score	3.6 (0.72)	5.2 (0.56)	0.09
Deaths, n (%)	35 (89.7)	63 (73.3)	0.07
Median survival from onset, y (CI)	12.1 (10.0–13.1)	12.3 (10.5–14.2)	0.23

Values are means (SEM) unless otherwise noted.

PGDRS = Psychogeriatric Dependency Rating Scales.

The log-rank χ^2 comparing survival in women with and without an ϵ4 allele was not significant ($p = 0.79$). (These survival estimates for women are notably shorter than those in table 2. This is because of the deaths of a few women at short durations, when the risk set was small.)

Risk ratios (RR) for death as a function of ϵ4, adjusted for age at onset, were computed using Cox proportional hazards regression. For men, RR = 2.69 (CI = 1.23 to 5.87; Wald χ^2, $p = 0.01$). For women, RR = 1.03 (CI = 0.59 to 1.82; not significant). Therefore, after adjusting for age at onset of AD, the presence of an ϵ4 allele significantly increased the relative risk of death for men but not for women.

Because there were 13 African-American women and no African-American men in the study sample, the apparent lack of an *APOE* effect in women might be confounded by race. Therefore, we repeated the Cox regression analysis, limiting the sample to white women only (n = 73). The increased risk attributed to *APOE* remained nonsignificant (RR = 1.25, CI = 0.65 to 2.41).

The Kaplan–Meier and Cox proportional hazards regression models allowed for left truncation, thereby taking into account the risk set limitation. In addition to performing these left truncation models, we analyzed the data calculating survival time from entry into the study, adjusting for both age at onset and duration of symptoms. The resulting risk ratios for ϵ4 were very similar to our initial results. (For women, RR = 1.08 [CI = 0.62 to 1.89]; for men, RR = 2.72 [CI = 1.28 to 5.80].) Likewise, when modeling the data with age at study entry on the abscissa, adjusting only for age at onset, risk ratios for ϵ4 did not substantially change. (For women, RR = 1.15 [CI = 0.63 to 2.10]; for men, RR = 2.35 [CI = 1.03 to 5.38].)

When causes of death for both men and women were examined, there was not a preponderance of cardiovascular or cerebrovascular deaths in either group. Because of the small number of related causes of death, statistical analysis of these data was not possible, even if we combined cerebrovascular and cardiovascular causes.

Table 3 *Demographic and baseline clinical characteristics and survival by sex and APOE genotype*

	Men		Women	
Characteristics	ϵ4-Negative	ϵ4-Positive	ϵ4-Negative	ϵ4-Positive
n	14	25	26	60
Race, n (%) African-American	0 (0.0)	0 (0.0)	6 (23.1)	7 (11.7)
Education, highest grade	13.4 (1.19)	14.3 (0.69)	12.1 (0.67)	12.2 (0.48)
Age at onset, y	59.9 (1.54)	63.2 (2.00)	65.3 (1.78)	68.2 (0.91)
Range	50–73	46–79	48–79	52–83
Age at entry, y	64.6 (1.97)	67.3 (2.01)	69.4 (1.74)	72.2 (0.90)
Duration at entry, y	4.8 (0.75)	4.1 (0.46)	4.2 (0.49)	4.1 (0.30)
Mini-Mental State Examination score	18.0 (1.23)	15.1 (1.07)	13.5 (1.14)	14.2 (0.78)
Physical Dependency Scale of PGDRS score	3.9 (1.43)	3.3 (0.75)	5.8 (1.36)	5.0 (0.59)
Deaths, no. (%)	12 (85.7)	23 (92.0)	17 (65.4)	46 (76.7)
Neuropathology				
Autopsied, n	12	22	16	42
AD*	12	22	16	42

There were no significant differences between either men or women with and without the ϵ4 allele. Values are means (SEM) unless otherwise noted.

* Primary neuropathologic diagnosis of definite AD.

PGDRS = Psychogeriatric Dependency Rating Scales.

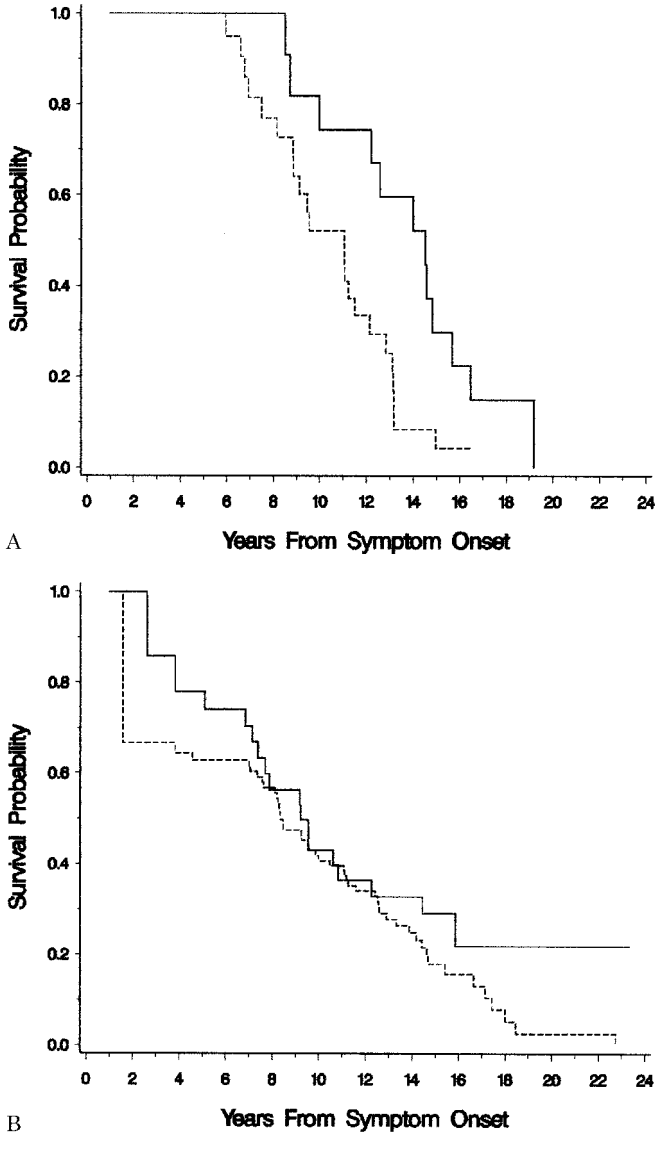

Figure. Kaplan–Meier survival estimates from time of onset of symptoms, allowing for delayed entry, for male (A) and female (B) patients with AD with (broken line) and without (solid line) an APOE *ϵ4 allele.*

Discussion. In the current cohort of patients with mostly autopsy-confirmed AD, men had shorter survival if they were carriers of the *APOE* ϵ4 allele, whereas women did not. This finding may help explain the disparate results of previous studies on survival as a function of *APOE*, most of which did not stratify by sex.[11-25] In addition, our finding suggests that one potential reason for the sex difference in prevalence of AD is the particularly rapid demise of male patients with ϵ4. Although it is relatively well established that women with AD live longer than men with AD,[26-27] previous studies on sex differences in survival have not assessed the influence of *APOE* genotype.

Because our sample was composed of already-affected patients who then enrolled in the ADRC, persons who developed AD and died before enrollment never entered our "risk set." Failure to account for this "left censoring" as we did is a significant limitation of many previous studies of this kind.[35-36] In addition, the size of our sample was larger and our follow-up period was longer than in most previous studies. Although we see these as major strengths of this study, the demographic characteristics of our sample may limit the generalizability of our results. Our patients were research volunteers, recruited through university specialty clinics. Most were highly educated white persons who had dedicated caregivers, all factors known to influence survival. In addition, our subjects—particularly our male subjects—-had earlier onset, on average, than in most previous studies. This may in part be the result of our detailed querying of knowledgeable family members for the earliest sign of memory or functional decline that subsequently worsened, and our use of the date this sign appeared (rather than the date of diagnosis) to mark disease onset.

The patients in our sample with the ϵ4 allele were slightly (although not significantly) older at disease onset and study entry than those without ϵ4. Our not finding an earlier onset associated with this genotype, as some others have,[4,7-9,15] may be related to the younger age of our subjects overall. Our sample is otherwise typical of many published AD cohorts, including frequency of the ϵ4 allele and family history of dementia. Lack of an ϵ4 effect on age at onset is therefore unlikely to be caused by our inclusion of early-onset, familial cases of AD, which are known to have other genetic etiologies.

When comparing genotyped and nongenotyped patients, there was a significant difference in median survival time from onset ($p < 0.01$) but no difference in demographic or baseline severity measures. A shorter survival in the nongenotyped group is probably artifactual of the recent introduction of *APOE* genotyping and hence the unavailability of blood samples for genetic analysis from patients who died shortly after entering the ADRC. Approximately 45% of the nongenotyped patients were men, compared with only 31% of the genotyped patients, further supporting the shorter survival of men with AD.

Although all genetic risk factors for AD identified to date localize on autosomal chromosomes, sex differences clearly exist in the prevalence of AD and probably in its incidence as well.[37-48] In addition, the role of sex hormones in risk for AD is being recognized increasingly.[49-52] The pathogenesis of AD might involve complex interactions among *APOE* genotype, sex, age, and total cholesterol levels,[53] possibly through the abnormal distribution of plasma lipids and apolipoproteins.[54] Differential survival by sex may also be related to differences in morbidity caused by cerebrovascular disease, known to be influenced by estrogens or other sex-related factors. In our cohort, there was no excess of cerebrovascular or cardiovascular deaths among men with or without

the ε4 allele, although the small number of subjects in each cell precluded meaningful statistical analysis. Larger samples would be needed to determine whether the effect of ε4 on survival in men is mediated by vascular pathology.

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Randomized pilot study of nimesulide treatment in Alzheimer's disease

P.S. Aisen, MD; J. Schmeidler, PhD; and G.M. Pasinetti, MD, PhD

Abstract—*Background:* Nonsteroidal anti-inflammatory drugs (NSAID) may be useful in the treatment of AD. Clinical and laboratory experience with nimesulide, an NSAID with preferential cyclooxygenase-2 inhibition, suggests that it may be a good candidate for AD therapy. *Methods:* This pilot study investigated the clinical feasibility of nimesulide treatment in AD. Forty persons with probable AD, most of whom were taking cholinesterase inhibitors, were enrolled in a randomized, controlled, parallel-group trial designed to assess tolerability and short-term cognitive/behavioral effects of nimesulide. In the initial 12-week double-blind phase, participants were treated with nimesulide 100 mg by mouth twice daily or matching placebo; during the second 12-week phase all participants received active drug. Participants who tolerated the drug well and perceived benefit were invited to continue open-label nimesulide treatment. *Results:* Short-term therapy with nimesulide, compared with placebo, had no significant effect on total assessment scores of measures of cognition, clinical status, activities of daily living, affect, and behavior. Long-term therapy was well tolerated for periods exceeding 2 years. *Conclusion:* These findings support the feasibility of nimesulide therapy in AD; assessment of efficacy will require a larger, long-term treatment study.

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Results of epidemiologic studies suggest that use of nonsteroidal anti-inflammatory drugs (NSAID) confers some protection against AD and may slow the rate of cognitive decline in patients with the disease.[1,2] This apparent therapeutic benefit may be explained by suppression of inflammatory activity in the AD brain[3]; many studies indicate that destructive inflammation contributes to the neurodegenerative process.[4] More specifically, cyclooxygenase (COX), the inflammatory enzyme targeted by NSAID, may be involved in the pathophysiology of AD.[5]

COX catalyzes the conversion of membrane-derived arachidonate to prostaglandin H_2, which is subsequently converted to prostaglandins with wide-ranging activity. Prostaglandins are important in inflammatory processes but are also involved in vascular regulation, platelet function, renal function, and protection of gastrointestinal mucosa. As a result, COX inhibitors are

From the Department of Neurology (Dr. Aisen), Georgetown University Medical Center, Washington, DC; and the Department of Psychiatry (Drs. Aisen, Schmeidler, and Pasinetti) and the Neuroinflammation Research Laboratories (Dr. Pasinetti), Department of Psychiatry, Mount Sinai Medical Center, New York, NY.

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Address correspondence and reprint requests to Dr. Paul S. Aisen, Department of Neurology, Georgetown University Medical Center, 1 Bles Building, 3800 Reservoir Road, NW, Washington, DC 20007; e-mail: psa@georgetown.edu

