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Apolipoprotein E ε4 Allele Is Unrelated to Cognitive or Functional Decline in Alzheimer's Disease: Retrospective and Prospective Analysis

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Key Words
Alzheimer's disease · Apolipoprotein E · Cognition · Activities of daily living

Abstract
Objective: The apolipoprotein E (ApoE) ε4 allele is a well-documented genetic risk factor for Alzheimer's disease (AD). Its role, if any, in the progression of cognitive and functional impairment in AD has been the subject of discrepant reports in the literature. This study aimed to determine whether ApoE ε4 dose is related to the progression of cognitive and functional decline in AD patients by combined retrospective and prospective analyses. ***Methods:*** A sample of 366 AD patients was genotyped for ApoE. Subjects received tests of cognition (Mini-Mental State Examination, MMSE; Alzheimer's Disease Assessment Scale-Cognitive subscale, ADAS-Cog) and daily function (Instrumental Activities of Daily Living, IADL; Alzheimer's Disease Cooperative Study-Activities of Daily Living, ADCS-ADL) at baseline and at multiple subsequent time points during their participation in a variety of research protocols. In retrospective analyses, scores on baseline cognitive and functional measures were compared cross-sectionally among genotype groups, controlling for duration of symptoms. In prospective analyses, longitudinal rates of change for each measure were computed by linear regression and compared across genotype groups. ***Results:*** No association was observed between ApoE ε4 dose and any of the retrospective or prospective measures of cognitive or functional decline in this AD patient sample. ***Conclusions:*** Although ApoE ε4 increases the risk for AD and decreases the age of disease onset in population studies, it did not significantly influence the rate of disease progression in cognitive or functional domains in our sample.

Introduction

The apolipoprotein E (ApoE) locus on chromosome 19 is the only well-documented genetic risk factor for the development of sporadic AD [1]. Among the three major isoforms of ApoE, the most common allele is ε3, which occurs with approximately 78% frequency in populations of European ancestry, followed by ε4 at 14%, and ε2 at 8% [2, 3]. In a variety of cross-cultural studies, ApoE ε4 has been reported to increase an individual's risk of developing AD, and decrease an individual's age of onset, in proportion to the number of ε4 alleles present [4, 5]. By contrast, the ApoE ε2 allele has been reported to have a 'pro-

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tective' effect, decreasing the risk of developing AD and delaying the age of onset [6].

Besides increasing AD risk and accelerating AD onset, the ApoE ε4 allele has also been shown to promote the neuropathological features of AD, including β-amyloid (Aβ) deposition [7–10] and neurofibrillary tangle formation [7–10]. Furthermore, the ε4 allele appears to be associated with the clinical manifestations of AD through an association with its pathological hallmarks rather than another mechanism [11]. The role of ApoE in the central nervous system and the mechanism by which the ε4 allele confers an increased risk of AD remain largely unspecified [for a review, see 12]. Proposed mechanisms for the involvement of ApoE in AD pathogenesis include differential properties of ApoE isoforms with respect to cholesterol homeostasis [13], binding to Aβ [14, 15], or binding to the microtubule-associated proteins MAP2c and tau [16].

The links between the ApoE ε4 allele and decreased age of AD onset and increased accumulation of pathological features has prompted the hypothesis that ε4 may play a role in accelerating the clinical manifestations of the disease. However, that hypothesis has thus far not been confirmed by most clinical studies. The majority of studies have shown no effect of ApoE genotype on rate of cognitive decline in AD [8, 17–29]. However, some investigators have reported that the presence of at least one ε4 allele may increase [30–32] or even decrease [33, 34] the rate of cognitive decline.

Despite widespread interest in the potential role of ApoE in modulating the course of cognitive symptoms in AD, comparatively few studies have addressed the possibility that ApoE may influence the rate of functional decline in activities of daily living (ADLs) experienced by AD patients. Loss of performance in ADLs, such as self-care, grooming and common household tasks, is associated with increased patient and caregiver distress, and greater healthcare costs [35, 36]. Although ADL performance is associated with global cognitive status in AD, recent studies have demonstrated a more specific correlation of ADL impairment with executive cognitive dysfunction and frontally mediated behavioral disturbances [37, 38]. This evidence suggests the importance of monitoring ADL performance directly, rather than via broad cognitive tests like the MMSE [37]. The few genetic studies that have used ADL performance as an outcome variable have thus far found no significant effect of ApoE genotype on functional decline in AD [8, 19, 22, 28].

Almost all previous studies of ApoE ε4 effects on AD progression have used prospective longitudinal measurement, although one prior report [33] employed a cross-sectional retrospective analysis, while controlling for disease duration. Prospective analyses permit the empiric measurement of cognitive and functional outcomes in patients followed over time. While retrospective designs introduce the error inherent in estimating duration of symptoms, they allow examination of a longer segment of the disease course, including the earliest stages. Thus, studies that simultaneously utilize both methodologies in the same cohort of patients may provide a unique perspective for this growing literature. The aims of our study were to combine retrospective and prospective analyses: to help resolve the ambiguity of the literature regarding ApoE genotype and cognitive decline, and to provide novel data relating ApoE genotype to widely used measures of ADL performance.

Methods

Subjects

The study sample comprised 366 patients with probable AD [39] who enrolled in a study of the genetics of AD and were initially evaluated in the Yale Alzheimer's Disease Research Unit between July 1992 and August 2003. Most of these patients then participated in a variety of other research protocols permitting the accumulation of longitudinal cognitive and functional data. Thirteen of these patients have subsequently died and had autopsy confirming definite AD [40]. The demographics and clinical characteristics of patients are displayed in table 1. The racial composition of the sample was: European-American (n = 354; 96.7%), African-American (n = 6; 1.6%), Hispanic (n = 5; 1.4%) and Asian-American (n = 1; 0.3%).

All patients underwent a comprehensive evaluation by a research physician and ancillary staff, including cognitive assessment, medical history, physical and neurological examinations, serum chemistries, thyroid function studies, complete blood count, B_{12}, folate, VDRL, urinalysis, electrocardiogram, and brain MRI or CT. Subjects were excluded for any neurological or medical disorder (other than AD) that could produce cognitive deterioration or for significant psychiatric illness, alcohol, or substance abuse. Research protocols in which subjects participated following their initial evaluation included investigational therapeutic trials, neuroimaging studies, and neuropsychological studies. Some investigational and clinically prescribed AD treatments received by subjects – in particular cholinesterase inhibitors, high-dose vitamin E ($\geq$400 IU daily), and psychotropic drugs – may potentially have impacted cognitive and functional variables analyzed in this study. These treatments were assumed to be independently distributed with regard to ApoE genotype; however, this assumption was also tested statistically (see below).

Family history of AD was assessed using the Alzheimer Dementia Risk Questionnaire [41] and the Dementia Questionnaire [42] and was considered to be positive if at least one first-degree relative met criteria for primary degenerative dementia. No cases suggestive of autosomal dominant transmission were identified. Additionally, each subject was evaluated for an approximate date of dis-

Table 1. Subject characteristics (mean ± SD)

	ε4 non-carriers (n = 156)	ε4 heterozygotes (n = 159)	ε4 homozygotes (n = 51)
Demographics			
Age	73.4 ± 9.6	74.4 ± 7.3	71.6 ± 7.0
Sex, female	59.6%	59.1%	70.6%
Education, years	13.1 ± 3.3	13.7 ± 3.5	13.6 ± 2.8
Disease characteristics			
Onset age	69.0 ± 9.5	69.9 ± 7.3	67.0 ± 6.8
Duration, years	4.5 ± 2.0	4.5 ± 2.1	4.6 ± 1.9
Family history, positive	42.9%	52.8%	54.9%
ApoE genotype	$15_{2,3}$ $141_{3,3}$	$5_{2,4}$ $154_{3,4}$	$51_{4,4}$
Concomitant therapies at baseline			
Cholinesterase inhibitors	37.8%	36.5%	29.4%
Antipsychotics	3.2%	4.4%	0.0%
Antidepressants	14.7%	20.1%	19.6%
Vitamin E (400 IU daily)	35.9%	36.5%	39.2%

Family history was positive if primary degenerative dementia was present in a first-degree relative.

ease onset, based on careful review of medical records and detailed interviews with one or more primary caregivers. The date of onset was operationally defined as the date at which the 'earliest definite symptom' appeared. All subjects (or their responsible next of kin) provided written informed consent and were studied under a protocol approved by the Yale Human Investigation Committee.

Cognitive and Functional Evaluation

Subjects were evaluated using a number of cognitive tests and functional rating scales at the time of initial presentation (see table 2). Several of these measures were repeated longitudinally, at varying frequencies, depending on the different requirements of the research protocols in which subjects subsequently participated. Many subjects enrolled in multiple studies spanning several years. The cognitive performance of subjects was measured using the Mini-Mental State Examination (MMSE) [43] and the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-Cog) [44]. The MMSE evaluated memory, praxis and orientation on a scale of 0 (maximal impairment) to 30 (no impairment). The ADAS-Cog provided a broader test of cognition, using eleven subscales: word recall, naming, following commands, constructional praxis, ideational praxis, orientation, word recognition, language ability, comprehension of spoken language, word-finding difficulty and remembering test instructions. The ADAS-Cog is scored from 0 to 70, with lower scores indicating better performance.

The functional capacity of subjects in ADLs was assessed using both the Instrumental Activities of Daily Living (IADL) questionnaire [45] and the Alzheimer's Disease Cooperative Study-Activities of Daily Living inventory (ADCS-ADL) [46]. The IADL was performed only once at baseline (and therefore included in retrospective but not prospective analyses) and evaluated everyday functioning along eight domains: using the telephone, shopping, food preparation, housekeeping, laundry, transportation, handling medications, and finances [45]. A score of 1 for a given domain indicated no impairment, with higher scores denoting greater degrees of impairment. Since not all domains were valid for all subjects (e.g. men who never did laundry before AD onset), the IADL score was calculated as the sum of individual activity scores divided by the total possible valid points for that subject. The range of scores was therefore 0.27 (no impairment) to 1.00 (maximal impairment). The ADCS-ADL provides a comprehensive assessment of ADL performance across 28 functional domains and is scored from 0 (maximal impairment) to 78 (no impairment) [46]. Both the IADL and ADCS-ADL ratings were obtained on the basis of information provided by a caregiver actively involved in the patient's daily life.

Of the four cognitive and functional measures, the MMSE was performed on the entire sample (n = 366), whereas all other measures were available for only certain subsets of the subject population (as detailed in table 2). All subject data were obtained by trained raters who were unaware of the subjects' ApoE genotypes.

Determination of ApoE Genotype

DNA was prepared from whole blood in the laboratory of J.G. by standard salting-out procedures. Genotypes were obtained by the polymerase chain reaction (PCR)-restriction fragment length polymorphism method [47] using a PCR procedure slightly modified from Tsai et al. [48]. The PCR product was digested by HhaI (New England Biolabs) and subjected to electrophoresis in 5% MetaPhor agarose (FMC Corp., Rochland, Me., USA). Gels were stained with ethidium bromide and DNA visualized by UV transillumination. The three alleles were scored as described by Hixson and Vernier [47]. Eight percent of genotypes were repeated as a quality check, with complete concordance.

Statistical Analysis

Subject characteristics (including demographics, disease characteristics, and concomitant therapies) were compared across gene dose groups using analysis of variance (ANOVA) for continuous variables or χ^2 analysis for dichotomous variables.

Table 2. Cognitive and functional data at baseline (mean ± SD)

Variable	ε4 non-carriers	ε4 heterozygotes	ε4 homozygotes
MMSE (n = 366)	n = 156 17.1 ± 5.8	n = 159 17.0 ± 5.5	n = 51 18.2 ± 4.5
ADAS-Cog (n = 300)	n = 128 26.6 ± 11.7	n = 127 27.8 ± 12.5	n = 45 27.3 ± 10.7
IADL (n = 353)	n = 154 0.65 ± 0.19	n = 151 0.65 ± 0.20	n = 48 0.68 ± 0.18
ADCS-ADL (n = 188)	n = 86 55.2 ± 15.5	n = 80 60.3 ± 13.5	n = 22 56.8 ± 12.7

MMSE = Mini-Mental State Examination; ADAS-Cog = Alzheimer's Disease Assessment Scale-Cognitive Subscale; IADL = Instrumental Activities of Daily Living; ADCS-ADL = Alzheimer's Disease Cooperative Study-Activities of Daily Living.

Gene dose groups did not differ significantly in any cognitive or functional variable adjusted for disease duration, as well as age, sex, and education.

The effect of ApoE ε4 dose (0, 1, or 2 copies) on the rate of AD progression was analyzed using both retrospective and prospective techniques. The retrospective analyses examined cross-sectional cognitive (MMSE, ADAS-Cog) and functional (IADL, ADCS-ADL) data obtained at each subject's initial visit, while controlling for the duration of symptoms by analysis of covariance (ANCOVA). Although disease duration was the essential covariate in all retrospective analyses, age, sex, and educational attainment were also included as covariates in the ANCOVA models.

Prospective analyses of disease progression were also conducted for the MMSE, ADAS-Cog (including its word recall and word recognition subtests, in light of the recent report of Hirono et al. [32] that change in these subtests was related to ApoE ε4 dose), and ADCS-ADL for all subjects who had at least three observations spanning at least 6 months of research participation. For these analyses, an annualized rate of change in performance on each scale was calculated by least-squares regression, using all available measurements for each subject. Rates of change were compared across ApoE ε4 dose groups by ANCOVA, controlling for age, sex, and education.

Results

Subject Characteristics

The overall subject sample (n = 366) was comprised of ε4 homozygotes (n = 51), ε4 heterozygotes (n = 159) and non-carriers (n = 156). Table 1 summarizes the characteristics of each ApoE ε4 dose group with regard to demographics, disease characteristics, and baseline concomitant treatments. The ε4 dose groups did not differ significantly in age ($F = 2.37$; $df = 2,363$; $p = 0.10$), sex ($\chi^2 = 2.33$; $df = 2$; $p = 0.31$), education ($F = 1.56$; $df = 2,363$; $p = 0.21$), onset age ($F = 2.40$; $df = 2,363$; $p = 0.09$), duration of symptoms ($F = 0.08$; $df = 2,363$; $p = 0.93$), or family history of AD ($\chi^2 = 3.93$; $df = 2$; $p = 0.14$). Finally, they did not differ in baseline use of cholinesterase inhibitors ($\chi^2 = 1.20$; $df = 2$; $p = 0.55$), antipsychotics ($\chi^2 = 2.36$; $df = 2$; $p = 0.31$), antidepressants ($\chi^2 = 1.70$; $df = 2$; $p = 0.43$), or high-dose vitamin E ($\chi^2 = 0.19$; $df = 2$; $p = 0.91$).

Retrospective Analysis of Cognitive and Functional Progression

Table 2 presents a summary of the retrospective analyses of cognitive and functional progression in AD patients. It specifically contains the baseline cognitive and functional data according to ApoE ε4 dose.

MMSE. MMSE performance was analyzed in the overall sample of 366 subjects. Gene dose groups did not differ significantly in MMSE performance ($F = 1.06$; $df = 2,359$; $p = 0.35$), controlling for disease duration, age, sex, and education.

ADAS-Cog. ADAS-Cog performance was analyzed in a sub-sample of 300 subjects. The demographic profile of this sub-sample and all others analyzed below did not differ from that of the overall sample characterized in table 1. Gene dose groups did not differ significantly in ADAS-Cog performance ($F = 0.43$; $df = 2,293$; $p = 0.65$), controlling for disease duration, age, sex, and education.

IADL. IADL performance was analyzed in a sub-sample of 353 subjects. Gene dose groups did not differ significantly in IADL performance ($F = 1.09$; $df = 2,346$; $p = 0.34$), controlling for disease duration, age, sex, and education.

Table 3. Prospective analysis of cognitive and functional progression (mean ± SD)

Variable	ε4 non-carriers	ε4 heterozygotes	ε4 homozygotes
	n = 101	n = 97	n = 34
MMSE annual change (n = 232)	–3.18 ± 3.90	–3.02 ± 3.20	–3.20 ± 4.14
Number of observations	7.1 ± 3.2	6.4 ± 2.8	6.8 ± 3.8
Duration of observation, years	1.80 ± 1.19	1.81 ± 1.33	1.67 ± 1.34
	n = 88	n = 80	n = 30
ADAS-Cog annual change (n = 198)[1]	6.03 ± 9.92	6.09 ± 8.60	6.33 ± 6.85
Number of observations	9.4 ± 5.2	8.9 ± 4.8	10.4 ± 5.6
Duration of observation, years	1.55 ± 1.11	1.62 ± 1.28	1.80 ± 1.39
	n = 75	n = 75	n = 22
ADCS-ADL annual change (n = 172)	–10.28 ± 11.85	–9.96 ± 8.66	–12.58 ± 14.53
Number of observations	7.6 ± 3.5	6.6 ± 2.8	6.7 ± 2.7
Duration of observation, years	1.54 ± 1.10	1.28 ± 0.89	1.20 ± 0.85

MMSE = Mini-Mental State Examination; ADAS-Cog = Alzheimer's Disease Assessment Scale-Cognitive Subscale; ADCS-ADL = Alzheimer's Disease Cooperative Study-Activities of Daily Living.

Data displayed are longitudinal rates of change per year computed by linear regression.

[1] Rates of ADAS-Cog change are positive because lower scores indicate better performance.

ADCS-ADL. ADCS-ADL performance was analyzed in a sub-sample of 188 subjects. Gene dose groups did not differ significantly in ADCS-ADL performance (F = 2.81; df = 2,181; p = 0.063), controlling for disease duration, education, and age.

Prospective Analysis of Cognitive and Functional Progression

Table 3 presents a summary of the prospective analyses of cognitive and functional progression in AD patients. It specifically contains the annualized rates of change for cognitive and functional measures according to ApoE ε4 dose.

MMSE. Annualized rate of change in MMSE performance was analyzed in a sub-sample of 232 subjects. Subjects received an average of 6.7 assessments (range 3–18) spanning 1.8 years of follow-up (range 0.5–6.4). The rate of MMSE change did not differ significantly across gene dose groups (F = 0.00; df = 2,226; p = 1.00; covariates: age, sex, education).

ADAS-Cog. Annualized rate of change in ADAS-Cog performance was analyzed in a sub-sample of 198 subjects. Subjects received an average of 9.4 assessments (range 3–25) spanning 1.6 years of follow-up (range 0.5–5.8). The rate of ADAS-Cog change did not differ significantly across gene dose groups (F = 0.01; df = 2,192; p = 0.99; covariates: age, sex, education). In light of the recent report of Hirono et al. [32] that change in ADAS-Cog memory subtest scores, in particular, was related to ApoE ε4 dose, we also examined the annualized rate of change on the word recall and word recognition subtests and found no difference across gene dose groups (word recall: F = 0.69; df = 2,190; p = 0.50; word recognition: F = 2.02, df = 2,190; p = 0.14; covariates: age, sex, education).

ADCS-ADL. Annualized rate of change in ADCS-ADL performance was analyzed in a sub-sample of 172 subjects. Subjects received an average of 7.1 assessments (range 3–18) spanning 1.4 years of follow-up (range 0.5–4.9). The rate of ADCS-ADL change did not differ significantly across gene dose groups (F = 0.41; df = 2,166; p = 0.66; covariates: age, sex, education).

Discussion

Although several previous investigators have examined the relationship between ApoE ε4 dose and the rate of progression in AD, the present study is the first to employ concurrent retrospective and prospective analyses in a large cohort of patients. In retrospective analyses we found no effect of ApoE ε4 dose on baseline cross-sectional cogni-

Table 4. Comparison with relevant studies

Study (first author)	Subject sample	Cognitive measures	Functional measures	Analysis (mean duration of follow-up, years)
ApoE ε4 has absent or equivocal effect on cognitive or functional decline				
Basun (1995) [17]	60	MMSE		Prospective (3)
Asada (1996) [18]	70	CDR, HDSR		Prospective (2.2)
Dal Fornoe (1996) [19]	78	MMSE, cognitive battery	PGDRS	Prospective (3.5)[1]
Gomez-Isla (1996) [8]	153	BDRS	RIL	Prospective (2.6)
Growdon (1996) [20]	66	Cognitive battery		Prospective (2)
Holmes (1996) [21]	145	MMSE, BDRS		Prospective (1.3)
Kurz (1996) [22]	61	MMSE, CAMCOG	DS-CAMDEX	Prospective (3.0)
Murphy (1997) [23]	86	MMSE		Prospective (3.6)
Jonker (1998) [24]	34	CAMCOG		Prospective (3)
Lehtovirta (1998) [25]	31	MMSE		Prospective (3)
Farlow (1999) [26]	373	ADAS-Cog		Prospective (0.4)
Slooter (1999) [27]	85	MMSE		Prospective (4.4)
Aerssens (2001) [28]	504	ADAS-Cog	DAD	Prospective (≤ 1)
Mori (2002) [29]	55	MMSE, ADAS-Cog		Prospective (1)
Kleiman, this study	366	MMSE, ADAS-Cog	IADL, ADCS-ADL	Retrospective/ prospective (1.6)
ApoE ε4 accelerates rate of cognitive decline				
Craft (1998) [30]	201	DRS		Prospective (2.5)
Kanai (1999) [31]	33	MMSE		Prospective (1.7)
Hirono (2003) [32]	64	ADAS-Cog		Prospective (1)
ApoE ε4 decelerates rate of cognitive decline				
Frisoni (1995) [33]	62	MMSE, CDR		Retrospective/ prospective (1)
Stern (1997) [34]	99	mMMS		Prospective (3.6)

Subject sample refers to the number of subjects who had at least one follow-up assessment on at least one listed cognitive or functional measure. MMSE = Mini-Mental State Examination; CDR = Clinical Dementia Rating; HDSR = Hasegawa's Dementia Screening-Revised; PGDRS = Psychogeriatric Dependency Rating Scale; BDRS = Blessed Dementia Rating Scale; RIL = Record of Independent Living; CAMCOG = Cambridge Cognitive Examination; DS-CAMDEX = Dementia Scale of Cambridge Mental Disorders of the Elderly Examination; ADAS-Cog = Alzheimer's Disease Assessment Scale-Cognitive Subscale; DAD = Disability Assessment in Dementia; IADL = Instrumental Activities of Daily Living; ADCS-ADL = Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale; DRS = Dementia Rating Scale; mMMS = Modified Mini-Mental State.

[1] 3.5 years for most tests; 5.5 years for PGDRS.

tive or functional measures, while controlling for estimated duration of symptoms. In prospective analyses we observed no effect of ε4 dose on longitudinal rates of change for each measure as computed by linear regression.

The vast majority of ApoE ε4 progression studies have employed prospective longitudinal measurement, although one prior study [33] utilized a cross-sectional retrospective analysis. Retrospective designs have the inherent drawback of requiring an estimation of disease onset by the recollection of an informant. However, they may permit consideration of a longer and earlier segment of the disease course. Prospective analyses are limited by following patients for only a small portion of their disease course (0.5–4 years, see table 4) and neglect the earliest stages of disease. Thus, retrospective and prospective analyses may provide complimentary information. The fact that both types of analysis yielded essentially the same results in the present study lends additional credence to the conclusions.

Our method of retrospective analysis differed somewhat from that of Frisoni et al. [33] who estimated MMSE at onset of symptoms using an education norms-based algorithm derived from cognitively unimpaired elders. We considered a similar algorithm but found that educa-

tional attainment was not a significant predictor of MMSE score (or ADAS-Cog) in a healthy elderly sample with demographics comparable to our AD patient group (data not shown). This difference may be due to the fact that our samples were more highly and homogeneously educated than those of Frisoni et al.

Comparison to Other ApoE ε4 AD Progression Studies

Table 4 situates the present results within the broader literature. Ours is among only a few ApoE ε4 AD progression studies to consider both cognitive and functional outcome measures in the same cohort of subjects.

Cognitive Decline. Our finding that ApoE ε4 dose neither accelerated nor decelerated the rate of cognitive decline in AD accords with the vast majority of published studies on the subject [8, 17–19, 21–28]. However, a smaller number of studies found that ApoE ε4 is associated with either an accelerated [30–32] or decelerated [33, 34] rate of cognitive decline. Discrepancies in the literature may owe to sampling error, particularly in those studies with few ε4 homozygotes. Only two previous studies used samples comparable in size to the present one – Farlow et al. [26] and Aerssens et al. [28]. These studies both analyzed placebo-treated patients from pooled clinical trial data and thus had relatively shorter follow-up periods than the present study. Nonetheless, both shared our finding that ApoE genotype did not influence the rate of cognitive decline.

That the majority of studies have found global cognitive progression to be unrelated to ApoE ε4 genotype in AD does not preclude the possibility of more selective cognitive effects of the ε4 allele. MRI studies have suggested accelerated atrophy of medial temporal lobe structures that subserve memory function in AD patients who carry ε4 [29, 49–52], and ε4 homozygotes have been reported to have more severe memory loss cross-sectionally than other AD patients [53]. In a recent longitudinal study of 64 AD patients, Hirono et al. [32] reported that 1-year changes in memory subtests of the ADAS-Cog – as well as total ADAS-Cog – were significantly correlated with ApoE ε4 dose. However, in our sub-sample of 198 patients who were administered the ADAS-Cog on average 9.4 times over 1.6 years, we were unable to replicate this finding. We observed no difference in the annualized rate of change in word recall and word recognition subtests (or total ADAS-Cog) across gene dose groups.

Functional Decline. Our finding that ApoE ε4 allele dose did not influence the rate of functional decline in AD accords with the few available studies on the subject. Dal Forno et al. [19] found that a small number of ε4 homozygotes (n = 12) declined faster than patients lacking the ε4 allele (n = 25) on the Physical Capacity subscale of Psychogeriatric Dependency Rating Scale (PGDRS), although other pairwise comparisons between gene dose groups were not significant. Gomez-Isla et al. [8] found no effect of ApoE ε4 genotype on the ADL scale of the Record of Independent Living in 141 AD patients followed longitudinally (mean follow-up period 31.8 months). Kurz et al. [22] observed no difference between ε4 carriers and non-carriers in everyday performance rated with the Dementia Scale of the Cambridge Mental Disorders of the Elderly Examination (CAMDEX) in 64 AD patients who were followed for up to 3 years. Aerssens et al. [28] examined rates of change in score on the Disability Assessment for Dementia (DAD) in 504 placebo-treated AD patients enrolled in clinical trials (3–12 months duration) and reported no effect of ε4 dose. These collective findings suggest that ApoE genotype is not a meaningful predictor of the rate of functional decline in AD patients.

Interpretation of a Negative Effect of ApoE ε4 on AD Progression

If a preponderance of studies have found no evidence that the ApoE ε4 allele modulates AD progression after onset, this has been difficult to reconcile with the fact that ε4 accelerates disease onset [4, 5] and promotes the hallmark neuropathology of AD [7–11]. Several writers have commented on the likely dissociation between processes leading to the onset of AD and those that determine its clinical course [54–56]. Plassman and Breitner [55] noted that if the dementia of AD progresses at a rate independent of ApoE genotype, this would imply a shift in pathogenetic mechanisms around the time of clinical onset. Roses [57] has proposed that the disease process becomes 'autocatalytic' at that point. Chapman et al. [56], using evidence from studies of the onset and progression of AD and multiple sclerosis, suggested that ApoE ε4 influences disease pathology by diminishing the efficacy of neuronal maintenance and repair. In the case of AD, which has a long period of biologic deterioration prior to clinical diagnosis, ε4 carriers would be expected to reach the clinical threshold significantly earlier than non-carriers, as they may be less capable of repairing neuronal damage during the subclinical phase of the disease. Among patients who have already reached the clinical threshold, however, different rates of neuronal deterioration would not necessarily create observable differences in cognitive or functional performance.

We would further propose that the apparent absence of an ApoE ε4 effect in modulating AD progression may relate to the presence in ε4-negative subjects of diseases other than AD, and especially, of genetically different forms of AD, influenced by loci other than ApoE. First, the majority of progression studies utilize subjects without autopsy confirmation of diagnosis. The ε4-negative samples in these studies are likely to contain a higher percentage of subjects with etiologies of dementia for which ε4 is a weaker risk factor, e.g., frontotemporal dementia [58, 59]. If the rate of progression is indeed more rapid in frontotemporal dementia compared to AD [60], this phenomenon might offset a small effect of ε4 in accelerating clinical deterioration in AD patients. Second, comparison of ApoE ε4-positive and -negative AD samples has generally assumed that these populations differ only by the presence or absence of the ε4 allele, whereas they are likely to differ systematically by other genetic or environmental factors as well. Family history of AD has been shown to be a risk factor for AD beyond the effect of ε4 alone [55], which is one reflection of the existence of additional genetic or environmental risk factors for AD. Samples of ε4-negative AD patients are likely enriched for these factors [61], which may in turn be associated with a form of AD conferring a later age of onset but equal or increased rates of clinical progression. Thus, the growing body of research examining phenotypic associations of ApoE ε4 in AD samples is almost certainly confounded by an effective disequilibrium with other factors.

This study certainly has a number of potential limitations that warrant comment. First, our subjects were drawn from participants in research protocols in an academic medical center and may differ demographically from a population sample [62]. In particular, our subject observations were performed largely during the course of trials of investigational drugs whose effects on the course of AD progression might obscure that of genotype alone. However, most of the experimental treatments in question were ultimately found not to influence the progression of AD symptoms, and any small effect was likely distributed randomly with respect to ApoE genotype, as borne out for several specific concomitant therapies. A second potential selection bias is signaled by the fact that our ApoE ε4 dose groups did not quite differ ($p = 0.09$) in age of disease onset, thus diverging from most epidemiologic samples [5]. Conceivably, ε4 would only influence the rate of disease progression insofar as it was also associated with earlier onset. Furthermore, our retrospective analysis of disease progression was potentially limited by recall bias, as disease onset was estimated by the recollection of relatives. However, relatives' prospective and retrospective ratings have been found to be in reasonably close agreement, particularly when the AD patient still resides in the community [63]. Moreover, inaccuracies in retrospective onset determination are unlikely to show systematic biases with respect to ApoE genotype. Finally, our statistical model for prospective analyses (comparison of linear regression slopes across ApoE groups) was potentially limited by considerable variability between subjects in numbers of observations, intervals between observations, and duration of follow-up. However, this method is probably reasonable and unbiased insofar as these sources of variation are randomly distributed with respect to ApoE genotype.

In conclusion, we observed no association between ApoE ε4 dose and any of the retrospective or prospective measures of cognitive or functional decline in this AD patient sample. Although ApoE ε4 increases the risk for AD and decreases the age of disease onset in population studies, it did not significantly influence the rate of disease progression in cognitive or functional domains in our sample.

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