Apolipoprotein E ε2 and Functional Decline in Amnestic Mild Cognitive Impairment and Alzheimer Disease

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Background: *Recent work has demonstrated the potentially protective effects of the apolipoprotein E (APOE) ε2 allele on cognitive functioning in individuals at risk for developing Alzheimer disease. However, little is known regarding the effect of ε2 genotype on rate of change in daily functioning over time. The aim of the current study was to examine the relationship between APOE genotype and change over time in ability to perform daily activities.* **Methods:** *We examined the relationship between APOE genotype and change in the ability to perform activities of daily living at 12- and 24-month intervals in 225 healthy comparison subjects, 381 individuals with amnestic mild cognitive impairment, and 189 individuals with Alzheimer disease who were enrolled in the Alzheimer's Disease Neuroimaging Initiative study. Neuropsychological measures were also collected at each follow-up.* **Results:** *Overall, individuals with at least one APOE-ε2 allele showed less functional decline over time and better performance on neuropsychological measures than those without an ε2 allele, even after controlling for potential confounders. When diagnostic groups were examined individually, presence of the ε2 allele continued to be associated with slower functional decline, although the relationship was no longer statistically*

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significant in most cases, likely due to reduced statistical power. **Conclusions:** *Our findings suggest that the APOE-ε2 allele provides a buffer against significant changes in daily functioning over time and is associated with better neuropsychological performance across a number of measures.* (Am J Geriatr Psychiatry 2011; 00:1–10)

Key Words: Alzheimer disease, *APOE*, functional decline, mild cognitive impairment, neuropsychology

The likelihood of developing Alzheimer disease (AD) has been linked to the presence of one or more copies of the ε4 allele on the apolipoprotein E (*APOE*) gene, such that individuals with the ε4 allele have been shown to be at higher risk for developing AD.[1] There is also evidence of a link between the presence of the *APOE*-ε4 allele and cognitive impairment,[2–5] including impairments in episodic memory and executive functioning.[3] Higher rates of functional decline have also been found among ε4 individuals,[6] and functional deficits have been identified in ε4 carriers who were cognitively intact at the time of evaluation,[7] although alternative findings have also been published.[8]

In contrast, the *APOE*-ε2 allele appears to confer cognitive benefits.[1–3,9–14] For example, presence of the *APOE*-ε2 allele has been associated with improvement in episodic memory over time[12] and reduced risk of cognitive decline[4] among older adults. Individuals with *APOE*-ε2 genotype have also been reported to be cognitively intact despite the presence of significant AD neuropathology,[14,15] suggesting a protective mechanism. Although the link between ε2 and cognition is well-established, we are not aware of research examining the longitudinal relationship between *APOE*-ε2 genotype and change in daily functioning over time. Specifically, it is unknown whether the possession of one or more *APOE*-ε2 alleles is associated with a slower rate of functional decline in older adults, which may have clinical significance in terms of likely course of the disease and treatment planning. Research into this question may also indicate factors that predict maintenance of daily living skills and independence in older adults.

The current study investigated the association between *APOE*-ε2 genotype and functional outcome at 12- and 24-month follow-ups in a sample of individuals with normal cognition, amnestic mild cognitive impairment (MCI), and probable AD. We compared rate of functional decline in individuals with at least one ε2 allele to those without an ε2 allele. We also examined between-group differences in neuropsychological performance as a function of *APOE* genotype. We hypothesized that individuals with an *APOE*-ε2 allele would show a slower rate of functional decline over time than individuals without an ε2 allele. Consistent with previous findings, we also predicted that the presence of one or more ε2 alleles would be associated with relatively better cognitive functioning.

METHODS

The Alzheimer's Disease Neuroimaging Initiative

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (www.loni.ucla.edu\ADNI). The ADNI was launched in 2003 by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, the Food and Drug Administration, private pharmaceutical companies and non-profit organizations, as a $60 million, 5-year public-private partnership. The primary goal of ADNI has been to test whether serial magnetic resonance imaging, positron emission tomography, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. Determination of sensitive and specific markers of very early AD progression is intended to aid researchers and clinicians to develop new treatments and monitor their effectiveness, as well as lessen the time and cost of clinical trials.

The principal investigator of this initiative is Michael W. Weiner, M.D., VA Medical Center and University of California–-San Francisco. ADNI is the result of efforts of many coinvestigators from a broad

range of academic institutions and private corporations, and subjects have been recruited from more than 50 sites across the United States and Canada. The initial goal of ADNI was to recruit 800 adults, ages 55–90 years, to participate in the research-–approximately 200 cognitively normal older individuals to be followed for 3 years, 400 people with MCI to be followed for 3 years, and 200 people with early AD to be followed for 2 years. For additional information, see www.adni-info.org.

Participants

Participants were enrolled in ADNI and consisted of 228 healthy comparison participants, 391 individuals diagnosed with amnestic MCI, and 193 individuals diagnosed with AD, for a total sample size of 812. Seventeen participants were excluded from data analysis (see later), bringing the total to 795.

Full participant inclusion and exclusion criteria are available at http://www.adni-info.org. All enrolled participants were required to be between the ages of 55–90 years (inclusive), have a study partner capable of providing an independent assessment of functioning, and willing to undergo all procedures. Comparison participants were required to have a Mini-Mental State Exam (MMSE) score between 24–30 (inclusive), a Clinical Dementia Rating Scale (CDR) score of 0, and be nondepressed, non-MCI, and nondemented. Participants with MCI were required to have a MMSE score between 24–30 (inclusive), a memory complaint, objective memory loss as measured by education-adjusted scores on the Logical Memory II subtest of the Wechsler Memory Scale-Revised, a CDR score of 0.5, absence of significant levels of impairment in other cognitive domains, essentially intact activities of daily living, and no dementia. Participants with AD were required to have MMSE scores between 20–26 (inclusive), CDR of 0.5 or 1, and were required to meet NINCDS/ADRDA criteria for probable AD.

Participants underwent serial evaluations of functional and clinical status at various intervals. Neuropsychological data were collected at each evaluation as well, although only neuropsychological data from the baseline evaluation were used in this study. The current study used data collected at the baseline, 12-month, and 24-month evaluations.

Apolipoprotein Genotyping

APOE genotyping was conducted for all ADNI study candidates using blood samples collected at the screening visit. Lumbar puncture was performed with a 20- or 24-guage spinal needle as described in the ADNI procedures manual (http://www.adni-info.org/). Cerebrospinal fluid was collected into collection tubes provided to each site, then transferred into polypropylene transfer tubes followed by freezing on dry ice within 1 hour after collection, and shipped overnight to the ADNI Biomarker Core laboratory at the University of Pennsylvania Medical Center on dry ice. TaqMan quantitative polymerase chain reaction assays were used for genotyping *APOE* nucleotides 334 T/C and 472 CT with an ABI 7900 real-time thermocycler (Applied Biosystems, Foster City, CA) using DNA freshly prepared from whole blood.

Functional and Clinical Measures

Ability to perform activities of daily living was assessed using the Functional Activities Questionnaire (FAQ).[16] The FAQ is an informant-based measure of instrumental activities of daily living (IADLs) that inquires into an older adult's ability to independently carry out various activities, including manage finances, prepare a balanced meal, and remember appointments. Ratings range from normal (0) to dependent (3) on 10 subscales for a total of 30 points, with higher scores indicating worse functional status. The Clinical Dementia Rating (CDR) scale[17] was used to rate the severity of dementia symptoms in all patients.

Neuropsychological Measures

Neuropsychological data used in the current study were collected from each participant at the baseline evaluation. We selected the following measures from the ADNI cognitive battery: MMSE[18]; American National Adult Reading Test (ANART[19]); Delayed Recall measure from the Logical Memory subtest of the Wechsler Memory Scale, 3rd Edition (WMS-III[20]); Delayed Recall measure from Rey's Auditory Verbal Learning Test[21]; Digit Span subtest of the WMS-III; Clock Drawing Test; Verbal Fluency Test (animals,

vegetables); and Trail Making Test, Parts A and B (total time).

An executive functioning composite variable was calculated using the following measures: Clock Drawing (total score), Trail Making Test (Part B; time to completion in seconds), Digit Span Backwards (total score), and Verbal Fluency (animals and vegetables; total correct words produced). Performance on these measures was standardized by calculating z-scores for performance on each test, which were then summed to create a composite score. Scores were standardized across the entire sample as well as within each diagnostic group, and the appropriate standardized variables were used in each analysis. A long-term memory composite variable was calculated using the Logical Memory (Delayed Recall) and Rey's Auditory Verbal Learning Test (RAVLT) (Delayed Recall) measures, and procedures for creating the standardized scores and composite variable were similar to those described earlier.

Data Analysis

We compared ε2 patients to non-ε2 patients on measures of daily functioning and neuropsychological performance. Individuals with at least one *APOE*-ε2 allele (ε2/ε2 or ε2/ε3) were included in the ε2 group. Individuals without an ε2 allele (ε3/ε3, ε3/ε4, and ε4/ε4) were included in the non-ε2 group. Individuals possessing both an ε2 and ε4 allele (N = 17) were excluded from the analyses, consistent with data analysis practices in the literature in this area,[12,14] to examine the independent contribution of ε2 allele to functional change over time. This exclusion left us with an effective sample size of 795 (225 healthy subjects, 381 MCI, and 189 AD cases) for the analyses described later. Of these participants, 33 comparison subjects, 15 individuals with MCI, and 5 AD participants possessed at least one ε2 allele.

An a priori decision was made to analyze both the entire (pooled) sample and each diagnostic group separately. Change scores on the FAQ were calculated from baseline to 12 and 24 months to indicate 12- and 24-month functional change, respectively. Mixed design analysis of variance (ANOVA) was conducted to compare ε2 and non-ε2 individuals on 12- and 24-month functional change. Independent samples *t*-tests were used to compare ε2 and non-ε2 individuals on baseline neuropsychological performance. Due to subject attrition, analyses were based on different sample sizes, depending on how many participants were studied at a particular follow-up. Only participants with complete datasets at a given time point were used in analyses at that time point, while participants with missing data were excluded, and missing data were not imputed.

RESULTS

Demographic and Clinical Data

Demographic and clinical data for participants in each diagnostic group are presented in Table 1. A total of 132 MCI participants (34.6%) converted to AD and 9 comparison participants converted to MCI over 24 months. In addition, 12 MCI participants reverted to a healthy comparison diagnosis, and 2 AD participants reverted to MCI. Of the individuals who converted from MCI to AD, 88 had a ε3/ε4 or ε4/ε4 genotype, 43 had a ε3/ε3 genotype, and 1 had a ε2/ε3 genotype. Of the individuals who converted from comparison to MCI, 6 had a ε3/ε4 or ε4/ε4 genotype and 3 had a ε3/ε3 genotype. Of the individuals who reverted from MCI to comparison, 3 had a ε3/ε4 or ε4/ε4 genotype, 8 had a ε3/ε3 genotype, and 1 had a ε2/ε3 genotype. Both the individuals who reverted from AD to MCI had a ε3/ε4 genotype.

We then compared *APOE*-ε2 patients to non-ε2 patients on demographic and clinical variables (Table 1). Chi-square analysis revealed significant between-group differences in gender ($\chi^2 = 6.54$, $p < 0.02$), such that the ε2 group had a higher percentage of female participants (58.5%), whereas the non-ε2 group had a higher percentage of male participants (59.4%). We also found significant differences in *APOE*-ε2 distribution among diagnostic groups. Overall, the highest percentage of ε2 subjects was found in the comparison group (14.7%), while MCI patients (3.9%) and AD patients (2.6%) had significantly fewer individuals with an ε2 allele. The groups did not differ in age ($t_{[793]} = 0.98$, $p = 0.33$), years of education ($t_{[793]} = 0.09$, $p = 0.93$), or racial distribution ($\chi^2 = 7.07$, $p = 0.13$).

Longitudinal Changes in Daily Functioning

Using the pooled sample, we compared *APOE*-ε2 individuals to non-ε2 individuals on change in

TABLE 1. Demographic and Clinical Data

	Control (N = 225)	MCI (N = 381)	AD (N = 189)	p[a] for ANOVA/x^2
Age (years)	75.9 (5.0)	74.8 (7.4)	75.3 (7.5)	0.13[b]
Education (years)	16.0 (2.9)	15.7 (3.0)	14.7 (3.1)	<0.001[b]
Gender (% male/female)	51.8/48.2	64.7/35.3	52.8/47.2	0.002[c]
Race (% Caucasian)	91.7	93.4	93.8	0.33[d]
APOE genotype (% ε2)	14.7	3.9	2.6	<0.001[c]

Notes: Standard deviations are presented in parentheses.

	ε2	non-ε2	p[a]
Age (years)	76.1 (6.2)	75.2 (6.9)	0.33[e]
Education (years)	15.6 (3.2)	15.5 (3.1)	0.93[e]
Gender (% male/female)	41.5/58.5	59.4/40.6	<0.02[f]
Race (% Caucasian)	84.9	93.5	0.13[g]

[a] Represents p-value for statistical comparison of the groups on the variable.
[b]Results of ANOVA (between group $df = 2$, within group $df = 809$).
[c]Results of χ^2 ($df = 2$).
[d]Results of χ^2 ($df = 8$).
[e]Results of *t*-test ($df = 793$).
[f]Results of χ^2 ($df = 1$).
[g]Results of χ^2 ($df = 4$).

total FAQ score from baseline to 12 months using repeated-measures ANOVA, with genotype (ε2, non-ε2) as the between-subjects variable and time (baseline, 12 months) as the within-subjects variable. To adjust for possible effects of gender on functional decline, gender was also included as a between-subjects variable. The main effects of time ($F_{[1,700]} = 26.94$, $p < 0.001$) and genotype ($F_{[1,700]} = 7.80$, $p < 0.01$) remained significant, while the main effect of gender was not significant ($F_{[1,700]} = 0.20$, $p > 0.65$). In addition, the 3-way interaction (time × genotype × gender) was significant ($F_{[1,700]} = 4.24$, $p < 0.05$), such that ε2 females showed the least change over 12 months (mean change = 0.10 points) relative to ε2 males (mean change = 2.0 points), non-ε2 males (mean change = 1.83 points), and non-ε2 females (mean change = 2.48 points). The time × gender ($F_{[1,700]} = 1.02$, $p > 0.31$) and genotype × gender ($F_{[1,700]} = 0.05$, $p > 0.82$) interactions were not significant. Lastly, we compared changes in individual subscales of the FAQ over time in each group. Subscales included ability to play games of skill, prepare a balanced meal, and travel outside of one's neighborhood. To do this, we compared ε2 to non-ε2 individuals on 12-month change on each subscale using independent samples *t*-tests. None of the comparisons was reached significance.

We next examined change in FAQ over 24 months using the analytic strategy described above. We found significant main effects of genotype ($F_{[1,590]} = 7.82$, $p < 0.01$) and time ($F_{[1,590]} = 20.11$, $p < 0.001$), indicating lower FAQ scores among ε2 individuals than non-ε2 individuals and higher FAQ scores at the 24-month follow-up than at baseline, respectively. We also found a significant genotype × time interaction ($F_{[1,590]} = 16.24$, $p < 0.001$), such that ε2 individuals (mean change = 0.46 points) showed a significantly slower change in FAQ over 24 months than did non-ε2 individuals (mean change = 3.53 points; see Table 2). The main effect of gender was nonsignificant ($F_{[1,590]} = 0.50$, $p = 0.48$), as were the time × gender ($F_{[1,590]} = 1.27$, $p = 0.26$), genotype × gender ($F_{[1,590]} = 0.34$, $p = 0.56$), and time × genotype × gender ($F_{[1,590]} = 1.88$, $p = 0.17$) interactions. We also compared changes in individual subscales of the FAQ

TABLE 2. FAQ Values for ε2 and Non-ε2 Groups at Baseline, 12-Month, and 24-Month Evaluations

	ε2, M (SD)	Non-ε2, M (SD)
Baseline	2.83 (6.4)	5.13 (6.6)
12 Months[a,b]	3.53 (6.7)	6.90 (8.2)
24 Months[c,d,e]	3.29 (6.8)	8.66 (9.5)

Note: Higher scores reflect poorer functioning.
[a]Main effect of time, $F_{[1,702]} = 24.13$, $p < 0.001$.
[b]Main effect of genotype, $F_{[1,702]} = 7.60$, $p < 0.01$.
[c]Main effect of time, $F_{[1,592]} = 19.96$, $p < 0.001$.
[d]Main effect of genotype, $F_{[1,592]} = 7.80$, $p < 0.01$.
[e]Time × genotype, $F_{[1,702]} = 16.11$, $p < 0.001$.

TABLE 3. Mean FAQ Values for ε2 and Non-ε2 Individuals Within Each Diagnostic Group at Baseline, 12-Month, and 24-Month Evaluations

	Control[a]		MCI[b,c]		AD[d,e]	
	ε2	Non-ε2	ε2	Non-ε2	ε2	Non-ε2
Baseline	0.03 (0.2)	0.16 (0.6)	4.3 (6.2)	3.9 (4.5)	16.8 (8.9)	12.9 (6.8)
12 Months	0.09 (0.4)	0.29 (1.1)	6.6 (6.9)	5.6 (5.9)	19.5 (2.4)	17.2 (7.1)
24 Months	0.00 (0.0)	0.46 (1.3)	8.4 (7.0)	8.3 (7.6)	19.3 (7.0)	20.0 (7.3)

Notes: Standard deviations are presented in parentheses.
[a]Controls: No significant effects at 12 or 24 months.
[b]MCI: Main effect of time (12 months), $F_{[1,337]} = 15.01$, $p < 0.001$.
[c]MCI: Main effect of time (24 months), $F_{[1,269]} = 8.41$, $p < 0.005$.
[d]AD: Main effect of time (12 months), $F_{[1,156]} = 7.08$, $p < 0.001$.
[e]AD: Time × genotype (24 months), $F_{[1,129]} = 6.42$, $p < 0.02$.

over 24 months in each group. Results indicated significant between-group differences on the following subscales: shopping alone for necessities ($t_{[552]} = 2.46$, $p < 0.02$), playing games of skill/working on a hobby ($t_{[552]} = 2.76$, $p < 0.01$), preparing a balanced meal ($t_{[552]} = 2.41$, $p < 0.02$), keeping track of current events ($t_{[552]} = 2.17$, $p < 0.05$), paying attention to and understanding a television program/book/magazine ($t_{[552]} = 2.40$ $p < 0.02$), and traveling outside of the neighborhood ($t_{[552]} = 3.60$, $p < 0.001$). In all cases, ε2 participants showed significantly slower rates of decline in these areas than non-ε2 participants.

Next, using the pooled sample, we examined changes in FAQ across time as a function of diagnostic group and genotype. To do this, we used a repeated-measures ANOVA, with Diagnosis (control, MCI, AD) and genotype (ε2, non-ε2) as the between-subjects variables and time (Baseline, 12 months, 24 months) as the within-subjects variable. Results indicated significant main effects of time ($F_{[2,1158]} = 9.35$, $p < 0.001$) and diagnosis ($F_{[2,579]} = 84.52$, $p < 0.001$), while the main effect of genotype did not reach significance ($F_{[1,579]} = 2.19$, $p = 0.14$). The time × diagnosis ($F_{[4,1158]} = 4.03$, $p < 0.005$) and time × genotype ($F_{[2,1158]} = 8.46$, $p < 0.001$) interactions were also significant, while the genotype × Diagnosis interaction did not reach significance ($F_{[2,579]} = 1.21$, $p = 0.30$). Lastly, the 3-way interaction (time × diagnosis × genotype) was significant ($F_{[4,1158]} = 3.93$, $p < 0.005$).

Given the significant 3-way interaction, we next examined changes in FAQ within each diagnostic group as a function of *APOE* genotype, using a similar analytic strategy as described earlier. Results are presented in Table 3. We first examined changes over 12 months. For comparison participants, none of the effects (genotype, time, genotype × time) reached significance (all p's > 0.19). Among the amnestic MCI patients, we found a significant main effect of time, such that FAQ scores were worse at the 12-month follow-up than at baseline. However, neither the main effect of genotype ($F_{[1,337]} = 0.44$, $p = 0.51$) nor the genotype × time interaction ($F_{[1,337]} = 1.06$, $p = 0.72$) reached significance. For the AD group, we again found a significant main effect of time, indicating that FAQ scores were worse at the 12-month follow-up than at baseline. Neither the main effect of genotype ($F_{[1,156]} = 1.04$, $p = 0.31$) nor the genotype × time interaction ($F_{[1,156]} = 0.51$, $p = 0.48$) reached significance.

We next examined change in FAQ within each diagnostic group over 24 months (see Table 3). Among comparison subjects, neither the main effect of time ($F_{[1,190]} = 0.85$, $p = 0.36$) nor the genotype × time interaction ($F_{[1,190]} = 0.46$, $p = 0.23$) was significant. The main effect of genotype was somewhat stronger but did not reach statistical significance ($F_{[1,190]} = 3.72$, $p = 0.055$). For the amnestic MCI group, we found a significant main effect of time, such that FAQ scores were lower at baseline than at 24 months. Neither the main effect of genotype ($F_{[1,269]} = 0.57$, $p = 0.45$) nor the genotype × time interaction ($F_{[1,269]} = 1.85$, $p = 0.17$) reached significance. Among AD patients, neither the main effect of time ($F_{[1,129]} = 3.12$, $p = 0.08$) nor the main effect of genotype reached statistical significance ($F_{[1,129]} = 1.02$, $p = 0.31$). The genotype × time interaction was significant, indicating significantly slower FAQ change among ε2 individuals (mean change = 2.5 points) relative to non-ε2 individuals (mean change = 7.1 points; see Table 3).

TABLE 4. Mean Values on Neuropsychological Measures for ε2 and non-ε2 Individuals

	APOE Genotype				
	ε2, M (SD)	**Non-ε2, M (SD)**	***t***	***df***	**p**
Global/Premorbid					
MMSE	27.7 (2.4)	26.7 (2.7)	2.75	793	0.006
ANART[a]	11.8 (9.9)	13.2 (10.0)	1.00	789	0.32
Memory					
Composite	1.56	−0.11	6.59	792	<0.001
LM—Delay	9.6 (5.8)	5.5 (5.3)			
RAVLT—Delay	7.0 (4.3)	3.4 (3.9)			
Attention					
Digit Span—Forward	8.2 (2.3)	8.2 (2.0)	0.05	793	0.96
TMT A (secs)	44.1 (22.7)	48.2 (27.7)	1.07	791	0.29
Executive Function					
Composite	1.21	0.003	2.38	776	0.02
Clock Drawing	4.4 (0.9)	4.1 (1.1)			
VF—Vegetables	12.8 (4.4)	11.0 (4.4)			
VF—Animals	17.3 (6.0)	16.1 (5.8)			
Digit Span—Backward	6.7 (2.2)	6.1 (2.2)			
TMT B (secs)	120.1 (70)	135.8 (80.7)			

Notes: LM: logical memory; MMSE: Mini-Mental State Exam; RAVLT: Rey's Auditory Verbal Learning Test; TMT A: Trail Making Test, Part A; TMT B: Trail Making Test, Part B; VF: verbal fluency.
[a] total number of errors.

Neuropsychological Performance

In the pooled sample, we compared *APOE*-ε2 individuals with non-ε2 individuals on neuropsychological measures. For memory and executive functioning, only composite measures were analyzed. Results are displayed in Table 4. Overall, the ε2 group had higher scores than the non-ε2 group on the MMSE, executive composite, and memory composite. The groups' performance did not differ on ANART, Digit Span-Forward, or Trail Making Test Part A (see Table 4).

We next examined neuropsychological performance in each diagnostic group as a function of *APOE* genotype. Among comparison participants, non-ε2 individuals (mean = 29.2) had higher MMSE scores than ε2 individuals (mean = 28.8; $t_{[223]} = 2.42$, $p < 0.02$), while ε2 individuals (mean = 8.7) performed better than non-ε2 individuals (mean = 7.2) on RAVLT—Delayed Recall ($t_{[222]} = 2.19$, $p < 0.05$). No other differences in neuropsychological performance were found. In the amnestic MCI group, no significant group differences were found in the primary analyses (global cognition, attention, memory composite, executive composite). However, when performance on individual memory and executive functioning measures was examined, ε2 patients (mean = 5.6) showed significantly better performance relative to non-ε2 patients (mean = 3.7) on Logical Memory—Delayed Recall ($t_{[379]} = 2.71$, $p < 0.01$). The ε2 patients (mean = 5.5) also performed better than the non-ε2 patients (mean = 2.7) in the MCI group on RAVLT—Delayed Recall ($t_{[379]} = 3.26$, $p < 0.005$). Among AD patients, no differences were found.

Lastly, given the documented relationship between MCI-amnestic type and development of AD, we selected MCI patients who were greater than 1.5 SDs *below* the MCI group mean on the memory composite score (N = 88) and MCI patients who were greater than 1.5 SDs *above* the MCI group mean on the memory composite score (N = 71), and we compared frequency of ε2 alleles across groups. Results are displayed in Table 5. We found that MCI patients with relatively poorer memory performance were less likely to have an ε2 allele (1.1%) relative to MCI patients with relatively better memory performance (9.9%). Furthermore, a higher percentage of MCI patients with relatively poorer memory performance (70.5%) had at least one ε4 allele, relative to MCI patients with relatively better memory performance (36.6%). We also compared these groups on rate of functional decline over time. As expected, MCI patients with poorer memory performance showed significantly more decline over 12 and 24 months than those with better memory performance (see Table 5).

TABLE 5. Frequency of ε2 and ε4 Alleles and Rate of Functional Decline Among MCI Patients as a Function of Memory Performance

	MCI Memory Subgroup				
	>1.5 SDs	<1.5 SDs	X^2/t	*df*	p
Genotype					
% ε2 allele	9.9	1.1	6.3	1	0.01
% ε4 allele	36.6	70.5	18.2	1	<0.001
Functional decline					
12 months	0.70 (3.5)	2.83 (4.7)	3.1	142	0.003
24 months	1.26 (4.7)	6.46 (6.2)	4.9	112	<0.001

Notes: Subgroups were composed of MCI patients who were greater than 1.5 SDs *below* the MCI group mean on the memory composite score (N = 88) and MCI patients who were greater than 1.5 SDs *above* the MCI group mean on the memory composite score (N = 71). % ε2 allele = percentage of individuals with at least one ε2 allele. % ε4 allele = percentage of individuals with at least one ε4 allele. Standard deviations are presented in parentheses.

CONCLUSIONS

In the present study, we found that individuals with at least one copy of the *APOE*-ε2 allele showed significantly less functional decline over time and performed significantly better on many neuropsychological measures, relative to individuals without an ε2 allele. When the data were examined within each diagnostic group, results were similar and largely in the same direction. However, most findings in the individual groups did not reach statistical significance. We further discuss each of these points in more detail.

Longitudinal Changes in Daily Functioning—Pooled Sample

Of primary interest in the present study was the relationship between *APOE* genotype and rate of functional change over time. Overall, we found significantly less functional decline over 24 months among individuals with at least one *APOE*-ε2 allele, regardless of diagnosis, including significant group differences on 6 out of 10 FAQ subscales. Although the link between *APOE*-ε2 genotype and preserved cognition has been well-established,[3,11–14] to our knowledge ours is the first study to demonstrate that the *APOE*-ε2 allele is associated with a slower rate of decline in IADLs. Furthermore, the differences in rate of functional decline are not attributable to between-group differences in education or estimated premorbid IQ, as the groups were similar on these factors. These findings provide additional evidence to suggest that possession of an *APOE*-ε2 allele may be related to slower decline, in contrast to *APOE*-ε4, which has been associated with elevated rates of functional decline.[6] The presence of one or more *APOE*-ε2 alleles may potentially contribute to one's cognitive reserve,[22] allowing individuals to function independently for a longer period.

Additional analyses also identified a significant time × genotype × gender interaction at 12 months, such that the least decline was found for women with at least one ε2 allele, relative to ε2 males or non-ε2 individuals. This result indicates that gender influences the relationship between *APOE* genotype and functional decline to some degree at 12 months. However, the effect is no longer significant at 24 months. The mechanisms underlying this finding are unclear. Further research is needed to better address the interaction between gender, *APOE* status, and functional decline.

Longitudinal Changes in Daily Functioning—Individual Diagnostic Groups

When the diagnostic groups were examined individually, results remained similar to those found in the pooled sample, although they did not always reach statistical significance. Within the AD group, ε2 individuals showed significantly slower functional decline over 24 months than non-ε2 AD patients. This finding further suggests a role for ε2 in longitudinal maintenance of IADLs, even among individuals who have already converted to mild AD. In addition, the largest percentage of ε2 individuals by far was found in the healthy comparison group (14.7%), with far less in amnestic MCI (3.9%) and the least in AD (2.6%).

Thus, the ε2 variant is most common among individuals who have remained functionally and cognitively intact to this point, which is in line with research demonstrating a decreased risk for dementia among ε2 carriers.[7]

Despite these significant findings, however, the majority of analyses conducted within individual diagnostic groups did not yield statistically significant results. One potential explanation is that lower statistical power contributed to the null findings in this case. Certainly, sample sizes were significantly reduced when participants were divided into diagnostic groups and further split into genotype groups, which may have resulted in analyses that were underpowered. Future research endeavors should aim to address this question using larger sample sizes to achieve better statistical power.

Potential Clinical Applications

In light of the known relationship between amnestic MCI and likelihood of conversion to AD,[10,23] we conducted post-hoc analyses comparing MCI patients with better versus worse memory performance on rate of functional change. We found that MCI patients with relatively poorer memory showed significantly more functional decline over 12 and 24 months than MCI patients with relatively better memory, further supporting the hypothesis that memory performance among MCI patients is highly predictive of conversion to AD.[24] We also found a greater representation of ε4 alleles and a reduced representation of ε2 alleles among MCI patients with poorer memory performance, relative to those with better memory performance, consistent with previous research[7] and suggesting that *APOE* genotypes confer varying effects on cognition and everyday function in individuals with MCI.

Neuropsychological Performance

APOE-ε2 patients showed significantly better performance than non-ε2 patients on a number of neuropsychological measures in the pooled sample, including significantly higher scores on the memory and executive functioning composite measures. Our data support previous findings that have found a positive effect of ε2 on cognition,[13] including longitudinal studies in which patients are followed over a number of years.[4,12] Not surprisingly, performance on measures of executive functioning[25,26] and memory[27] is highly related to degree of functional impairment among older adults. Future research may further address the relationship between genotype, cognition, and longitudinal changes in daily functioning.

In the individual diagnostic groups, we found that amnestic MCI patients with at least one *APOE*-ε2 allele performed significantly better than non-ε2 amnestic MCI patients on episodic memory measures, with fewer differences seen in comparison participants and no differences in AD participants. This finding raises the possibility that the buffer effect of ε2 on cognition is most optimal at the MCI stage, prior to the onset of AD. Notably, these differences were also found without associated differences in functional decline between ε2 and non-ε2 MCI participants. It is possible that declines in cognition (i.e., memory) represent a precursor to declines in daily functioning among individuals with MCI, and ε2 provides a buffer against such declines at the MCI level. The opposite pattern was found in AD participants: ε2 individuals showed less decline over 24 months than non-ε2 participants but did not show differences on any neuropsychological measures. In this case, the presence of ε2 may continue to provide some degree of protection against functional decline, despite cognitive functioning that is nondistinguishable from that of non-ε2 individuals. Overall, however, and in contrast to the pooled sample findings, the association between ε2 and neuropsychological functioning in the individual diagnostic groups was much less robust.

LIMITATIONS

Limitations of the current study include reduced statistical power for analyses within individual diagnostic groups. As described previously, many of the analyses within individual groups were conducted using smaller sample sizes. A more sufficiently powered study may have yielded more significant findings in each of the diagnostic groups. Secondly, the sample was largely Caucasian and highly educated, reducing demographic variance and potentially limiting the generalizability of our findings to other settings and populations. Lastly, only individuals with amnestic MCI were used in the current study. While

this population is of interest due to the relationship between amnestic MCI and risk for development of AD, findings may not generalize to individuals with nonamnestic MCI.

Summary

The current study examined the longitudinal association between *APOE*-ε2 genotype and functional changes and performance on neuropsychological measures among individuals with amnestic MCI, probable AD, and comparison participants. Overall, we found that individuals with at least one *APOE*-ε2 allele showed significantly less functional decline over 24 months than individuals without an ε2 allele. Possession of an ε2 allele was also associated with better neuropsychological performance across a number of cognitive measures. To our knowledge, we provide the first demonstration of a slower rate of functional decline among individuals with an *APOE*-ε2 allele. Our findings also support the positive influence of ε2 on neurocognition.

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