

Education and APOE-e4 in Longitudinal Cognitive Decline: MacArthur Studies of Successful Aging

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Longitudinal data from the MacArthur Study of Successful Aging were used to test for interactions between education and apolipoprotein E (APOE) genotype with respect to time trends in cognitive performance. Interactions between education, APOE-e4 status, and time were found for overall cognitive function, and for subscales measuring memory and naming: The presence of the e4 allele was associated with steeper declines in cognition for those with a greater than eighth-grade education. For those with an eighth-grade education or less, time trends did not differ by APOE genotype. A measure of cognitive impairment (i.e., scores of ≤ 7 on the Short Portable Mental Status Questionnaire) yielded parallel though weaker evidence for a similar interaction with respect to risk of cognitive impairment. These findings suggest that the presence of at least one e4 allele appears to reduce the protective effects of education for those with at least a ninth-grade education or more, resulting in steeper cognitive declines with age.

THE RAPIDLY growing size of our older population, with their elevated risks for cognitive decline, if not frank cognitive impairment, underscores the importance of efforts to understand factors that influence risks for declines in cognitive functioning. Factors ranging from genetic polymorphisms such as the apolipoprotein E (APOE) genotype to potentially more modifiable factors such as educational attainment have been a focus of research. More recently, the possibility of interactions between genetic characteristics and other, potentially modifiable, characteristics of the individual or environment has gained attention. One such possible interaction is that of APOE genotype with educational attainment in relation to risk for cognitive decline.

Consistent evidence documents the link between greater educational attainment, better cognitive function, and lower risk for cognitive decline (Albert et al., 1995b; Cagney & Lauderdale, 2002; Lee, Kawachi, Berkman, & Grodstein, 2003), as well as lower risks for dementia and Alzheimer's disease (Evans et al., 1997; Gilleard, 1997; Letenneur et al., 2000). Precise mechanisms for this effect of education remain unclear. Proposed mechanisms have included possible confounding with general socioeconomic conditions such that education serves largely as a marker for other education-related factors, including general health status and health behaviors, which are also known to influence cognition. Education, however, has been shown to remain a significant predictor of cognitive aging, independent of factors such as health status and health behaviors (e.g., Albert et al., 1995b; Lee et al., 2003). Other hypothesized mechanisms have included more direct effects of education on the brain; these theories focus on the possibility that education promotes brain development, resulting, for example, in greater dendritic branching, which may in turn result in greater "brain reserve." With aging, such a reserve allows the individual to maintain higher levels of cognitive functioning in the face of declines in underlying brain structure

or function (Katzman, 1993; Stern, 2002). Such arguments are consistent with evidence from both animal and human studies showing that exposure to enriched environments results in a greater number of synapses (Diamond, 1988; Jacobs, Schall & Scheibel, 1993). Other hypotheses regarding the education-cognition relationship have posited that educational attainment may be a marker for (or consequence of) greater initial, genetically mediated brain reserve (Pedersen, Reynolds, & Gatz, 1996). A third hypothesis posits that the protective effects of educational attainment are the result of education-related differences in activities that entail greater ongoing mental or cognitive stimulation throughout the life course, including participation in occupations or leisure activities that entail more mental demands and stimulation (Richards, Hardy, & Wadsworth, 2003; Schooler, Mulatu, & Oates, 1999; Stern et al., 1995; Wilson et al., 1999, 2002).

APOE-e4 represents another, more recently identified, risk factor for cognitive aging. Initially identified as a risk factor for both familial (Corder et al., 1993; Poirier et al., 1993) and sporadic (Myers et al., 1996; Saunders et al., 1993) cases of Alzheimer's disease (AD), the APOE-e4 genotype has also been shown to be associated with increased risks for poorer functional status (Albert et al., 1995a) and lower cognitive performance (Bretsky, Guralnik, Launer, Albert, & Seeman, 2003; Dik et al., 2001; Fillenbaum et al., 2001). Though the precise mechanisms through which the APOE-e4 allele confers risk for AD, and for cognitive decline more generally, are not clearly known, the presumption is that it contributes to the accumulation of the cortical atrophy and senile plaques that underlies AD and possibly other types of brain dysfunction that result in decline in cognitive function with aging. APOE plays a central role in both the metabolism and transportation of the lipids that are key to the maintenance of synaptic plasticity as well as in synaptogenesis (Dallongeville, Lussier-Cacan, & Davignon, 1992; Soininen

& Riekkinen, 1996). Thus, individuals differing in their APOE genotype likely also differ in their ability to initiate neuronal repair as well as in their susceptibility to degeneration.

Despite the fact that risks for cognitive decline linked to APOE genotype, and to educational attainment, have each been linked in turn to their postulated effects on brain structure or function, there has been little research on the possibility of an interaction between these two significant risk factors. If education, as has been hypothesized, is associated with more complex brain development, including development of greater synaptic density, then this relatively greater richness in synapses and in neural networks provided by educational experience might well serve as a counterweight to cognitive deterioration induced by APOE-e4. Such a finding would be consistent with related recent findings that education modifies the relation between extent of neuritic and diffuse plaques (measured at autopsy) and the level of cognitive function, with better education resulting in a reduction in the deleterious effects of senile plaques on cognitive function (Bennett et al., 2003). In a parallel vein, one might hypothesize that more highly educated individuals enjoy greater, or at least longer, protection against risks incurred by the presence of the APOE-e4 allele(s).

In the following analyses, we seek to test this hypothesized interaction between education and APOE genotype. There is, to our knowledge, only one prior study (Kalmijn, Feskens, Launer, & Kromhout, 1997) that has tested this hypothesis, and it used a sample composed only of elderly men. Though the actual test for interaction was not significant (possibly because of the small sample of poorly educated men, $n = 43$ vs 313 for better educated), the pattern of the findings in that study suggested that presence of the e4 allele may attenuate the benefits of education, as education did not appear to be associated with differences in cognitive decline in the presence of the e4 allele whereas it was associated with such risks among those without the e4 allele.

Using longitudinal data from the MacArthur Study of Successful Aging, we seek to extend these earlier results, examining the joint effects of educational attainment and APOE genotype on cognitive decline in a larger cohort of older men and women. The strengths of the MacArthur study include the following: first, there are extensive longitudinal data on cognitive changes based on the Short Portable Mental Status Questionnaire (SPMSQ), along with more detailed assessments of cognitive functioning in multiple major domains; second, there is a community-based sample of both men and women, with ethnic and sociodemographic diversity.

METHODS

Study Population

Subjects were participants in the MacArthur Successful Aging Study, a population-based prospective investigation focusing on a cohort of initially relatively high-functioning men and women, aged 70–79 years (Berkman et al., 1993). Briefly, participants were subsampled on the basis of age and both physical and cognitive functioning from three community-based cohorts located in Durham, NC, East Boston, MA, and New Haven, CT (Cornoni-Huntley, Brock, Ostfeld, Taylor, & Wallace, 1986) with the goal of identifying those in the top third of the population. Baseline data were collected between

May 1988 and December 1989 and included a 90-min, face-to-face interview assessing (a) physical and cognitive performance; (b) health status; (c) demographic, social, and psychological characteristics, including educational attainment; and (d) other lifestyle characteristics.

Age-eligible men and women ($n = 4,030$) were screened on the basis of physical and cognitive criteria with the intention of identifying high-functioning individuals (i.e., those in the top third of the age group). Physical selection criteria were developed from pilot data and included the following: (a) no reported disability on the seven-item Activities of Daily Living (ADL) scale (Katz, Ford, Moskowitz, Jackson & Jaffe, 1963); (b) no more than one reported mild functional limitation on eight items assessing gross mobility and range of motion (Nagi, 1976; Rosow, Breslau, & Guttman, 1966); (c) ability to hold a semi-tandem balance for at least 10 s; and (d) ability to stand from a seated position five times within 20 s. The cognitive criteria included (a) scoring six or more correct on the nine-item SPMSQ (Pfeiffer, 1975) and (b) remembering three or more of six elements on a delayed recall of a short story. Of relevance to the current analyses, these cognitive screening tools were relatively simple and so excluded only those with frank impairments.

Of the 4,030 eligible men and women, a cohort of 1,313 met all screening criteria; 1,189 (90.6%) agreed to participate and provided informed consent. After baseline data collection, the cohort was subsequently reevaluated in 1991 ($n = 1,118$) and 1995 ($n = 916$).

APOE Genotype

APOE genotyping was performed by use of genetic material isolated from peripheral lymphocytes (Saunders et al., 1993). Frequency of the e4 allele was 0.13, and the relative frequency of the e4/e4 homozygote was quite low, only 1.7% ($n = 17$). Because both neuronal activity–functional studies and epidemiological studies suggest that the presence of either one or two APOE-e4 alleles influences risk (Corder et al., 1993; Dubelaar et al., 2004), we used a dichotomous classification of individuals as either e4 carriers or noncarriers for our analyses—an approach consistent with previous research examining APOE and cognition (Tang et al., 1998; Wilson et al. 1999).

Education

Analyses reported here examined educational attainment in terms of four categories reflecting major stages of educational attainment within the cohort: grade school only (0–8 years), some high school (9–11 years), completed high school (12 years), and some college or more (13+ years). Three dichotomous variables indicating each of the three higher categories were used in the analyses to allow for assessment of potential nonlinearities in the association of different stages of educational attainment with patterns of cognitive aging; the least educated group serves as the reference in all cases.

Cognitive Function

Detailed, performance-based assessments of cognitive function were obtained at each interview, permitting examination of longitudinal patterns of change in domains such as these: (a) abstraction (based on 4 items from the Similarities subtest of the Wechsler Adult Intelligence Scale–Revised, or WAIS-R; range = 0–16; see Wechsler, 1981), (b) language (confrontation

naming that uses a modified, 18-item version of the Boston Naming Test, or BNT; range = 0–18; see Kaplan, Goodglass, & Weintraub, 1983), (c) delayed incidental recall (delayed recall of confrontation-naming items); (d) delayed spatial recognition (range = 0–17; see Moss, Albert, Butters, & Payne, 1986), and (e) spatial ability (figures; range = 0–20; see Rosen, Mohs, & Davis, 1984). Two summary scores were created based on these various subscales. One summary (global) cognition score was created to measure overall cognitive performance (sum of scores on each of the five standard tests listed above; range 0–89; see Inouye, Albert, Mohs, Sun, & Berkman, 1993). A second “memory” subscale score (range = 0–35) was created by summing scores from the two delayed recall tasks (i.e., delayed incidental recall and delayed spatial recognition). These instruments were administered at baseline and at each of the two subsequent follow-ups. Distributions were approximately normally distributed at all time points for all of these more detailed assessments.

The SPMSQ (Pfeiffer, 1975) was used at baseline to screen for study eligibility (scores of 6–9 correct were required for inclusion in the initial cohort). This questionnaire was also repeated at the 1991 and 1995 interviews. Although all cohort members had scores of 6 or more at baseline, declines in cognitive function over time result in considerably wider ranges of scores in 1991 and 1995 (range = 0–9). Because the distribution of SPMSQ scores was highly skewed toward better performance even at the 1991 and 1995 follow-ups, a dichotomization indicating presence or absence of “cognitive impairment” was developed for analysis. Fillenbaum, Heyman, Williams, Prosnitz, and Burchett (1990) have shown that 90% of individuals with scores of 6 or less meet criteria for at least moderate cognitive impairment. Because of the initial selection criteria for a high-functioning cohort, however, less than 10% of participants had scores of 6 or less as of 1991 and fewer than 25% of participants met criteria by 1995. As a result, models testing the desired three-way interactions between education, APOE genotype, and time would not converge. Models using a somewhat more liberal definition of impairment based on the criterion of scores of 7 or less did converge and are reported here.

Covariates

Variables considered for inclusion in the multivariable analyses as potential confounders included demographic characteristics, prevalent and incident comorbidities, health status factors, and health behavior characteristics that have previously been shown to influence patterns of cognitive performance. Demographic variables included age (measured in years as of the baseline interview), gender, and ethnicity (coded White vs African American). Comorbidities included self-reported prevalent and incident myocardial infarction, stroke, diabetes, and hypertension. Additional health status factors that were evaluated included body mass index (based on self-reported height and weight) and self-rated health. Health behavior characteristics of interest included smoking status (current, past, or never smoker), alcohol consumption (measured in terms of average monthly alcohol; see Armor, Polich, & Stambul, 1975), and physical activity (reported strenuous and moderate recreational activities, as well as strenuous and moderate work activities; see Paffenbarger, Hyde, Wing, & Hsieh, 1986; Taylor et al., 1978).

Analysis

We used mixed models for analyses in order to take advantage of all three waves of data. We used SAS Proc GENMOD to implement the generalized estimating equations (GEE) approach (Zeger & Liang, 1986) for analyses of the dichotomous longitudinal data for the SPMSQ. The GEE approach is particularly suited to the analysis of such dichotomous, non-Gaussian longitudinal data as it avoids the need for multivariate distributions by assuming a functional form for the marginal distribution at each time point. Using this approach, one need only specify the relationship between the mean and variance and hypothesized correlation structure. The “link” function used in the GEE analysis is determined by the specified relationship between the mean and variance; in our case, we used a logit link for the dichotomous outcome. We modeled the working correlation structure among the 1988, 1991, and 1995 outcome measures as exchangeable. For the more normally distributed, continuous outcomes, we used SAS Proc Mixed to model patterns of change in cognitive performance over the three assessments (1988, 1991, 1995; see Byrk & Raudenbush, 1992). We modeled effects of education category, time–follow-up, genotype, and ethnicity as fixed effects. We specified an unstructured covariance structure for the random intercept models. For both the GEE and Proc Mixed models, we tested for main and two-way interactive effects of education and APOE genotype (i.e., differences at baseline), as well as three-way interactions with time (i.e., differences in slope over time). For both the GEE and Proc Mixed models, we modeled time as two intervals, comparing each of the two follow-ups (i.e., 1991 and 1995) to the 1988 baseline to allow for evaluation of possible nonlinearities in the patterns of change over time.

We retained demographic characteristics (i.e., age, gender, and ethnicity) in all models regardless of level of statistical significance. For other covariates considered as potential confounders, we used a criterion of $p < .05$ to determine whether they should be included in the multivariable models for the various cognitive outcomes. For the SPMSQ, we retained physical activity, smoking status, and presence of diabetes or stroke in the final models. For all other cognitive outcomes, none of the potential confounders met criteria for inclusion, so those multivariable models include our primary predictors of interest (education and APOE) along with only age, gender, and ethnicity.

Analyses reported here include 895 participants with complete data for predictors as well as at least one wave of follow-up data (i.e., 1991, 1995, or both). As shown in Table 1, comparisons of these individuals with those excluded because of missing data ($n = 289$ because of missing APOE data, and 5 because of missing ethnicity information) indicated that the latter were generally similar to those included in the analyses, differing only in terms of their lower percentage of Blacks and greater preponderance of individuals with 12 years of education. With the exception of one cognitive subscale (spatial recognition), there were no significant differences in terms of baseline cognitive performance (see Table 1). We used SAS version 8.0 for all analyses (SAS Institute, 1999).

RESULTS

Table 1 presents demographic and other characteristics of participants included in the current analyses ($n = 895$). The

Table 1. Descriptive Statistics for the MacArthur Successful Aging Study Cohort

Descriptor	Analysis Sample (N = 895)	Excluded From Analyses (n = 294) ^a	p ^b
Demographic characteristics			
Age (years)	74.3 (2.73)	74.2 (2.69)	.48
Sex (% female)	55.2	56.1	.79
Ethnicity (% Black)	22.6	7.6	< .001
Education (years)	10.64 (3.43)	10.60 (2.93)	.85
Less than HS: 0–8 (%)	29.1	23.9	
Some HS: 9–11 (%)	25.5	27.0	
HS: 12 (%)	24.0	34.8	
College or more (%)	21.5	14.3	.0005
APOE genotype (%)			
e4 positive	23.4	0.0	
e2e2	0.45	0.0	
e2e3	12.9	0.0	
e3e3	63.4	100.0 (n = 5) ^c	
e4e2	2.2	0.0	
e4e3	19.4	0.0	
e4e4	1.7	0.0	
Cognitive function			
1. SPMSQ—baseline	8.2 (0.9) [8]	8.1 (0.9) [8]	.13
% impaired 1991 (≤ 7)	25.9	22.1	.25
% impaired 1995 (≤ 7)	43.7	38.2	.25
2. Total cognition—baseline	53.1 (9.8) [53]	52.4 (10.5) [52]	.26
a. Memory—baseline	14.8 (4.4) [15]	14.5 (4.5) [14]	.39
b. Recognition—baseline	9.4 (3.4) [10]	8.7 (3.7) [8]	.004
c. Naming—baseline	16.7 (1.6) [17]	16.8 (1.6) [17]	.19
d. Copying or figures—baseline	14.9 (3.1) [15]	14.8 (3.1) [15]	.57
e. Similarities—baseline	7.1 (4.8) [6]	6.2 (4.5) [6]	.08

Notes: For the analysis sample and excluded from analyses columns, figures show percent of mean, with standard deviations given in parentheses; medians are given in brackets. HS = high school; APOE = apolipoprotein E; SPMSQ = Short Portable Mental Status Questionnaire.

^aExcluded = 289 no APOE information, and 5 no data on ethnicity.

^bThe p value is for the comparison of the analysis sample to the excluded from analyses group.

^cOnly 5 of those excluded had APOE data (i.e., excluded because of missing ethnicity data); all had the e3e3 genotype.

sample was 55.2% female and 22.6% Black, with an average age of 74.3 years. Average educational attainment was 10.64 years, with 45.5% having completed high school or more education. The APOE-e4 allele was similarly distributed among the different educational groups (23%, 25.4%, 20%, and 24%, respectively, for those reporting no high school, some high school, high school, and more than high school; $p = .57$).

Table 2 presents results of analyses testing for main and interaction effects of education, APOE, and time, for the global cognitive performance measure as well as its component measures of memory, naming, spatial recognition, similarities–abstraction and figures–copying. Significant main effects for education were found for each of the measures of cognitive performance, with increasingly better performance as educational attainment increases. In addition to these main effects for education, however, analyses also yielded evidence for the hypothesized interaction between education and APOE status. Specifically, the analyses revealed significant three-way interactions between education, APOE genotype, and time for

Table 2. Main and Interaction Effects from Mixed Modeling of Time Trends in Cognitive Performance by Education and APOE Genotype

Variable	F	Df	p
Total cognition			
Time	72.95	2, 1408	< .0001
Ed	94.47	3, 1408	< .0001
APOE-e4 (yes or no)	4.52	1, 1408	.03
Ed × Time	1.18	6, 1408	.31
APOE × Time	1.82	2, 1408	.16
APOE × Ed	0.73	3, 1408	.54
Ed × APOE × Time	2.67	6, 1408	.01
Memory subscale			
Time	65.58	2, 1413	< .0001
Ed	15.30	3, 1413	< .0001
APOE	3.46	1, 1413	.06
Ed × Time	0.92	6, 1413	.48
APOE × Time	2.03	2, 1413	.13
APOE × Ed	0.84	3, 1413	.47
Ed × APOE × Time	2.75	6, 1413	.01
Naming			
Time	27.71	2, 1425	< .0001
Ed	35.00	3, 1425	< .0001
APOE	1.49	1, 1425	.22
Ed × Time	0.58	6, 1425	.75
APOE × Time	0.29	2, 1425	.75
APOE × Ed	0.32	3, 1425	.81
Ed × APOE × Time	3.65	6, 1425	.001
Spatial recognition			
Time	39.12	2, 1423	< .0001
Ed	17.69	3, 1423	< .0001
APOE	0.36	1, 1423	.55
Ed × Time	0.55	6, 1423	.77
APOE × Time	2.31	2, 1423	.10
APOE × Ed	0.56	3, 1423	.64
Ed × APOE × Time	1.40	6, 1423	.21
Figures/copying			
Time	25.26	2, 1421	< .0001
Ed	40.57	3, 1421	< .0001
APOE	0.14	1, 1421	.70
Ed × Time	1.10	6, 1421	.36
APOE × Time	0.46	2, 1421	.63
APOE × Ed	1.10	3, 1421	.35
Ed × APOE × Time	0.92	6, 1421	.48
Similarities			
Time	5.77	2, 1457	.003
Ed	116.57	3, 1457	< .001
APOE	3.08	1, 1457	.08
Ed × Time	0.81	6, 1457	.56
APOE × Time	0.56	2, 1457	.57
APOE × Ed	0.53	3, 1457	.66
Ed × APOE × Time	1.07	6, 1457	.38

Notes: Effects are adjusted for age, gender, and ethnicity. Ed = education; APOE = apolipoprotein E.

the global measure of total cognition as well as the memory and naming subscales, indicating that time trends (1988–1991 and 1988–1995) for the education groups differed by e4 status (see Table 2). Figures 1 and 2 provide graphical illustrations of these interactions, showing time trends for the total cognitive score (Figure 1) and the memory score (Figure 2) for each of the e4–education groupings. In both figures, scores are shown separately for those with and without the e4 allele in each

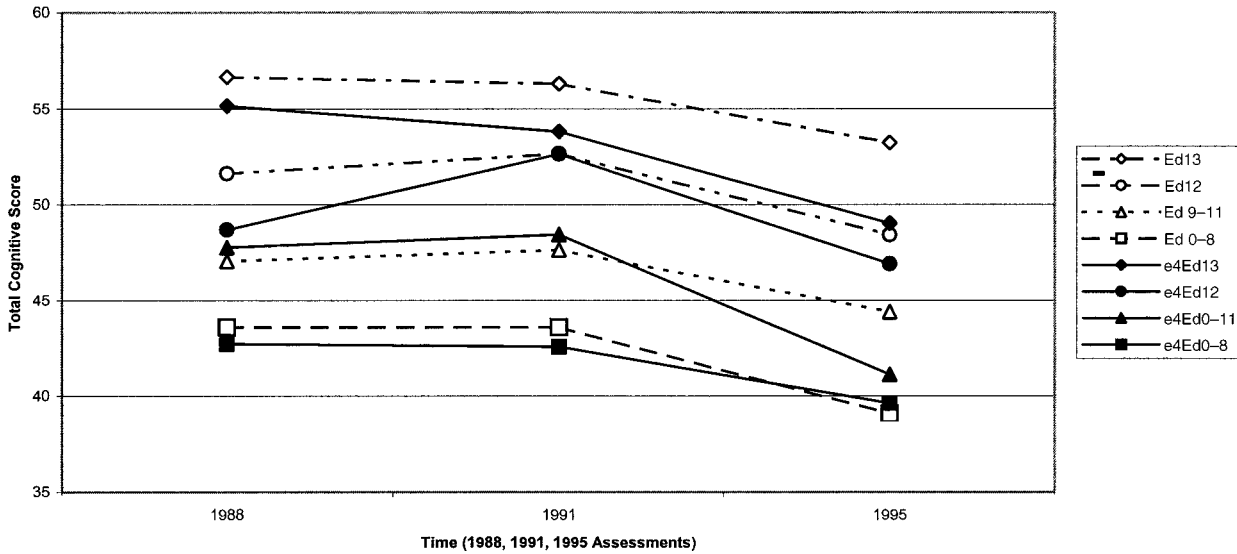


Figure 1. Time trends for total cognitive performance: Education \times APOE genotype interactions. (Legend: Ed13+ = no e4 allele, 13+ years education; Ed12 = no e4 allele, completed high school; Ed9-11 = no e4 allele, some school; Ed0-8 = no e4 allele, no high school; e4/Ed13+ = as at least one e4 allele, 13+ years education; e4/Ed12 = has at least one e4 allele, completed high school; e4/Ed9-11 = has at least one e4 allele, some high school; e4/Ed0-8 = has at least one e4 allele, no high school.)

education group; symbols for a given education group are the same for those with and without the e4 allele, but for those without the e4 allele, the symbol is open whereas a closed symbol is used to delineate their counterparts who have the e4 allele. As shown in Figure 1, total cognitive scores for those with the least education (i.e., 0-8 years) showed no difference between those with and without the e4 allele, and these two groups exhibited the poorest performance at all times. By contrast, for those with the most education (13+ years), presence of the e4 allele was associated with significantly

greater decline over time, resulting in a greater disparity in overall cognitive performance by the final 1995 assessment ($p < .05$). This same pattern was seen for those with 9-11 years of education ($p < .01$). Among those who completed high school (i.e., 12 years education), a comparison of participants with and without the e4 allele revealed a somewhat surprising convergence of scores at the 1991 assessment (those with the e4 allele showing a surprising increase in performance from 1988 to 1991; $p < .10$). These two groups, however, appeared to be diverging again by 1995, with the e4 group

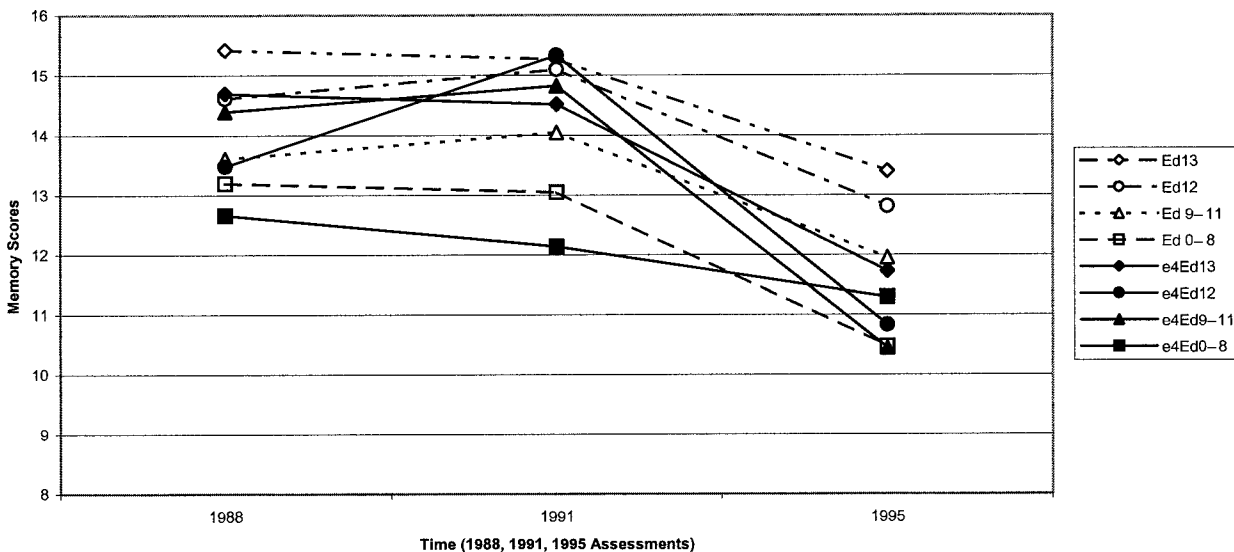


Figure 2. Time trends for memory performance: Education \times APOE genotype interactions. (Legend: Ed13+ = no e4 allele, 13+ years education; Ed12 = no e4 allele, completed high school; Ed9-11 = no e4 allele, some high school; Ed0-8 = no e4 allele, no high school; e4/Ed13+ = has at least one e4 allele, 13+ years education; e4/Ed12 = has at least one e4 allele, completed high school; e4/Ed9-11 = has at least one e4 allele, some high school; e4/Ed0-8 = has at least one e4 allele, no high school.)

Table 3. Main and Interaction Effects of Education and APOE Genotype With Respect to Risks for Cognitive Impairment (Scores of ≤ 7 on the SPMSQ)

Variable	Odds Ratios for SPMSQ $\leq 7^a$			SPMSQ ≤ 7	
	1988	1991	1995	Z	Pr > Z
Estimated Odds Ratios					
Education					
> HS (13+ years)	0.33	0.30	0.23		
Completed HS (12 years)	0.39	0.39	0.43		
Some HS (9–11 years)	0.73	0.55	0.53		
< HS (0–8 years)	Reference	Reference	Reference		
APOE-e4 allele (yes/no)					
	1.06	1.44	1.72		
Main effects					
Time					
'91 vs '88				2.02	0.04
'95 vs '88				6.74	< 0.0001
Education					
13+ years				-4.08	< 0.0001
12 years				-3.76	0.0002
9–11 years				-1.50	0.13
0–8 years					
e4 allele (yes/no)				0.27	0.78
Two-way interactions					
Education \times Time					
13+ years					
'91 vs '88				-0.34	0.73
'95 vs '88				-1.10	0.27
12 years					
'91 vs '88				0.03	0.98
'95 vs '88				0.34	0.73
9–11 years					
'91 vs '88				-1.04	0.30
'95 vs '88				-1.10	0.27
0–8 years (reference group)					
e4 Allele \times Time					
'91 vs '88				1.27	0.20
'95 vs '88				1.85	0.06

Notes: APOE = apolipoprotein E; SPMSQ = Short Portable Mental Status Questionnaire; GEE = generalized estimating equations; HS = high school.

^aGEE models include education and APOE main effects as well as adjustments for age, gender, and ethnicity, smoking status, level of physical activity, and presence of diabetes or stroke.

declining somewhat more than those without the e4 allele, though this difference was not statistically significant. For this same education group, the evidence for divergence by 1995 between those with and without the e4 allele was greater for the memory subscale (see Figure 2) and achieved marginal statistical significance ($p < .10$). Though not shown graphically, the pattern for the naming scores paralleled that shown in Figure 1 for the total cognitive score. For the remaining cognitive outcomes (spatial recognition, figures–copying, similarities–abstraction), the only significant effects were for education (as already noted) and time, indicating parallel declines across the different educational groups (see Table 2). APOE genotype was unrelated to changes in performance on all tests except the similarities where a marginal association with

poorer performance was seen for those with the e4 allele ($p = .08$; Table 2).

GEE analyses of cognitive impairment based on SPMSQ scores of 7 or less revealed significant main effects of education (i.e., baseline differences in cognitive performance). The top portion of Table 3 presents these baseline differences in the column labeled “1988,” showing the relative odds of “impairment” for each of the three higher education groups compared with the least educated (i.e., those having completed eighth grade or less). As one can see, with increasing education, there was a stepwise decline in the odds ratios (ORs), indicating greater and greater reductions in the relative odds of impairment relative to those with the least education. These differences were statistically significant for the top two education groups ($p = .0002$ for those completing high school and $p < .0001$ for those completing 13+ years; see lower portion of Table 3 under main effects for education). Time also exhibited the expected association with increasing likelihood of cognitive impairment ($p = .04$ for the 1988–1991 interval and $p < .0001$ for the longer 1988–1995 interval). There was, however, no evidence of differential effects of education over time (see bottom portion of Table 3 for p values associated with the two-way interaction between education and time). For APOE genotype, there was no evidence for baseline (main effect) differences in cognitive impairment ($p = .78$, lower portion Table 3). However, there was a marginally significant interaction with time ($p = .06$ for the 1988–1995 time interval): The odds of impairment for those with at least one e4 allele increased from 1.05 in 1988 to 1.72 as of 1995 (see upper portion of Table 3).

Tests for a possible two-way interaction between education and APOE (i.e., modification of education effects at baseline by presence of the e4 allele) were not significant (see Table 4). Tests for a possible three-way interaction with time, however, yielded evidence suggesting possible differences in time trends by APOE status for two of the education groups. For those who completed high school (i.e., 12 years of education), there were marginally significant interactions between education and APOE at each follow-up (see Table 4). The pattern of these time trends is illustrated graphically in Figure 3, where ORs are presented separately for those with and without the e4 allele within each of the education groups. As in previous analyses, those with only 0–8 years of education serve as the reference group in all cases. As shown in Figure 3, for subjects with 12 years of education, those without the e4 allele showed little or no change in their relative odds of cognitive impairment over time whereas for those with the e4 allele the relative odds shifted toward 1 (i.e., their odds of impairment moved closer to the higher odds seen in the reference group). As indicated by the nonsignificant two-way interaction between education and APOE status, none of the baseline differences between those with and without the e4 allele were significant for any of the education groups. For those who completed 9–11 years of education (i.e., some high school), the differences in relative odds for those with and without the e4 allele were significant in 1991 ($p = .03$) and marginally significant in 1995 ($p = .09$). As indicated in Figure 3, those with the e4 allele showed a surprisingly greater reduction in their relative odds of impairment than those without the e4 allele in 1991 (i.e., OR = 0.14 vs OR = 0.83 for those without the e4 allele).

However, by 1995, the pattern was more consistent with the expectation that those with the e4 allele would experience greater risk for impairment (i.e., those with the e4 allele in the "9–11 years education" group exhibit odds of impairment that were comparable with the least educated, OR = 1.07, whereas those without the e4 allele continued to experience relatively lower odds, OR = 0.43).

DISCUSSION

Analyses presented here examined longitudinal data from a group of 865 men and women, aged 70–79, participating in the MacArthur Successful Aging Study, to test the possibility of an interaction between education and APOE genotype with respect to risks for cognitive impairment or cognitive decline (as measured by performance assessments across multiple domains of cognitive function). We found significant three-way interactions between APOE, education, and time for a global measure of cognitive performance as well as for subscales measuring memory and naming abilities. The general pattern of these interactions pointed to greater declines in cognitive performance for those with the e4 allele as compared with those without the e4 allele in each education group. The only exception was the group with 0–8 years of education, in which performance was uniformly the poorest, and we saw no differences between those with and without the e4 allele for any of the cognitive outcomes.

Analyses of risk for cognitive impairment (defined as scoring 7 or less on the SPMSQ) revealed significant main effects of education, the more highly educated groups being significantly less likely to exhibit cognitive impairment at baseline. The absence of any interaction with time also indicated that these differences persist through the 1991 and 1995 follow-ups. By contrast, for APOE, there was no significant difference in the likelihood of cognitive impairment at baseline, but a marginally significant interaction with time suggested the possibility of a growing difference over time such that those with at least one e4 allele were marginally more likely to exhibit cognitive impairment by the final 1995 assessment. Tests for a possible three-way interaction between APOE, education, and time also yielded only marginal statistical evidence, suggesting that presence of the e4 allele may reduce the protection afforded by a given level of education. These latter analyses bear replication; the relatively high functioning status of the entire cohort at baseline may have reduced the power of our current analyses to detect interactions with respect to cognitive impairment, as relatively few members of the cohort met criteria for impairment even at the final assessment in 1995. Testing for these same interactions in a more broadly representative cohort of older adults might provide stronger evidence for possible difference in time trends for cognitive impairment by APOE and education status.

An evaluation of these findings requires acknowledgment of some limitations of the study. One such limitation relates to the lack of comprehensive neurological evaluations at baseline that might have revealed evidence for preclinical dementia in some cohort members. Mitigating against this, however, eligibility criteria for the study did require a baseline score of 6 or above on the SPMSQ for entry, placing participants in what is usually considered the normal range. Further, all participants were

Table 4. Testing for Interactions Between Education and APOE Genotype in Relation to Risks for Cognitive Impairment

Variable	SPSMQ ≤ 7	
	Z	Pr > Z
Main effects		
Time		
1991 vs 1988	1.50	0.13
1995 vs 1988	6.73	< .0001
Education		
13+ years	-3.96	< .0001
12 years	-2.78	0.006
9–11 years	-1.00	0.32
0–8 years (reference group)		
e4 allele (yes–no)	0.39	0.70
Two-way interactions		
Education \times Time		
13+ years		
'91 vs '88	-0.04	0.97
'95 vs '88	-0.58	0.56
12 years		
'91 vs '88	-0.68	0.50
'95 vs '88	-0.40	0.69
9–11 years		
'91 vs '88	0.22	0.82
'95 vs '88	-1.77	0.08
0–8 years (reference group)		
e4 Allele \times Time		
'91 vs '88	1.58	0.11
'95 vs '88	-0.07	0.95
e4 \times Education		
E4 \times 13+ years	1.38	0.17
E4 \times 12 years	-1.41	0.16
E4 \times 9–11 years	-0.51	0.61
Three-way interactions		
e4 \times Education \times Time		
e4 \times 13+ years \times 1991		
	-0.54	0.59
e4 \times 13+ years \times 1995		
	-0.30	0.76
e4 \times 12 years \times 1991		
	1.69	0.09
e4 \times 12 years \times 1995		
	1.65	0.09
e4 \times 12 years \times 1995		
	-2.23	0.03
e4 \times 9–11 years \times 1991		
	1.71	0.09
e4 \times 9–11 years \times 1995		
	-0.54	0.59

Notes: APOE = apolipoprotein E; SPMSQ = Short Portable Mental Status Questionnaire.

required to score 3 or above on delayed recall of a story at baseline, and those included in the current analyses (i.e., who remained alive and had complete follow-up data on cognitive performance) were among the cohort members with better baseline cognitive scores. All of these factors reduce the likelihood that the cohort examined here included cases of preclinical dementia, although the lack of complete neurologic screening for the cohort does not rule out the possibility that otherwise undetected preclinical dementia cases were included and were possibly differentially represented among the educational categories. Another potential limitation is the initial restriction of this cohort to those with no evident physical or

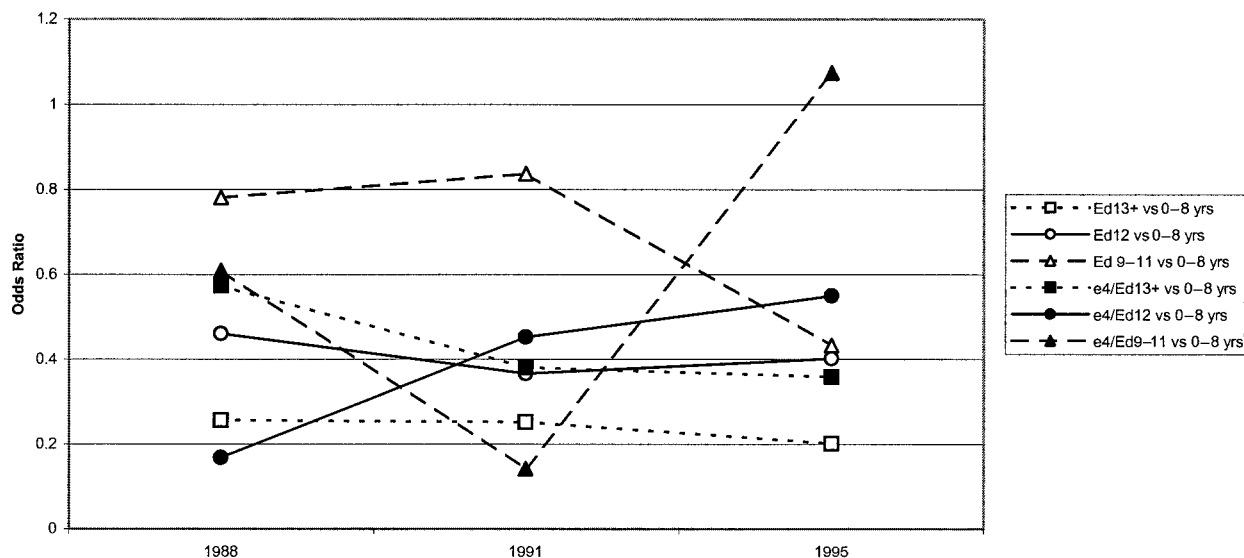


Figure 3. Joint effects of education and APOE on the odds of cognitive impairment over time. (Legend: Ed13+ = no e4 allele, 13+ years education; Ed12 = no e4 allele, completed high school; Ed9-11 = no e4 allele, some high school; Ed0-8 = no e4 allele, no high school; e4/Ed13+ = has at least one e4 allele, 13+ years education; e4/Ed12 = has at least one e4 allele, completed high school; e4/Ed 9-11 = has at least one e4 allele, some high school; e4/Ed 0-8 = has at least one e4 allele, no high school.)

cognitive impairments at study inception. As a result, the degree to which findings from this cohort may (or may not) generalize beyond such relatively high-functioning subgroups of older adults remains to be determined. Further, the initial selection of a relatively high-functioning cohort may have reduced the statistical power of the current analyses, because the range of cognitive performance at baseline was restricted to relatively higher levels of performance and, although declines were certainly evident over time, considerably greater declines would probably have been seen with a more broadly representative cohort of older adults. Indeed, as noted, analyses of the SPMSQ, which measures more severe forms of impairment, yielded the weakest evidence for the hypothesized interaction of education and APOE, and this may have been due, at least in part, to the fact that we could not model impairment based on the usual criterion of scoring 6 or less because of the relative dearth of participants who met this criterion even by the final follow-up in 1995. One might postulate that similar assessments over time in a more broadly representative cohort could yield stronger evidence for the hypothesized interaction with respect to cognitive impairment.

Despite these limitations, there are some major strengths of the study. They relate primarily to the range of cognitive measures and the length of follow-up. Evaluating cognition in older individuals is enhanced by the availability of tests reflecting a spectrum of functional domains. When one is evaluating changes in functioning, a particular concern is reliability in assessing change over time, where delineation of signal versus noise in such tests can be problematic. One study has shown that measurement of signal (vs. noise) is enhanced by the length of time over which an individual has been evaluated as well as the number of repetitions of the test (Van Belle, Uhlmann, Hughes, & Larson, 1990). The current study included a variety of cognitive tests, assessed performance at

three points in time, and included a 7-year follow-up period for a cohort moving from their 70s into their 80s.

This study shows that, over a 7-year follow-up period, educational attainment remains a primary predictor of patterns of cognitive aging, with greater educational attainment generally associated with better performance on all measured outcomes. However, the current findings also suggest the potential importance of the APOE genotype in modifying patterns of cognitive decline over time, particularly for those with greater than an eighth-grade education. For these latter groups (i.e., those with at least some high school, if not more), results of the current analyses suggested that the presence of the e4 allele may be associated with steeper declines in cognitive performance relative to their education-matched counterparts without the e4 allele. These results, pointing as they do to the potential that there are differential protective effects of greater education for those with and without the e4 allele, underscore the importance of further research to clarify the underlying biologic (and other) mechanisms through which genetic factors as well as educational attainment serve to protect against decline in cognitive functioning as people grow older. The importance of understanding these various mechanisms is highlighted by the fact that our ability to develop more effective strategies to prevent or retard cognitive declines in the rapidly growing population of older adults depends on our ability to gain a more complete understanding of the multiple and likely interactive factors that have an impact on patterns of cognitive aging.

ACKNOWLEDGMENTS

Work on this article was supported by the MacArthur Research Network on Successful Aging and the MacArthur Research Network on SES and Health through grants from the John D. and Catherine T. MacArthur Foundation, the Epidemiology, Demography and Biometry Office, and grants AG-17056, AG-17055, and AG-17265 from the Behavioral and Social Research Program of the National Institute on Aging.

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Received January 27, 2004

Accepted September 22, 2004

Decision Editor: Thomas M. Hess, PhD