Apolipoprotein E and Change in Episodic Memory in Blacks and Whites

L.L. Barnes^{a–c} Z. Arvanitakis^{a, b} L. Yu^{a, b} J. Kelly^d P.L. De Jager^{e–g}
D.A. Bennett^{a, b}

^aRush Alzheimer's Disease Center, and Departments of ^bNeurological Sciences and ^cBehavioral Sciences, Rush University Medical Center, Chicago, Ill., ^dDepartment of Internal Medicine, University of New Mexico School of Medicine, Albuquerque, N. Mex., ^eBrigham and Women's Hospital, and ^fDepartment of Genetics, Harvard Medical School, Boston, Mass., and ^gBroad Institute, Massachusetts Institute of Technology, Cambridge, Mass., USA

Key Words

Apolipoprotein E • Episodic memory • Cognitive decline

Abstract

Background: Apolipoprotein E (APOE) ϵ 4 is related to faster decline in episodic memory in Whites, but the relation is unknown in Blacks. The purpose of this study was to determine whether ϵ 4 has a selective effect on decline in episodic memory in Blacks. **Methods:** Data are from two cohort studies with similar design. The sample consisted of 1,211 participants [28.4% Blacks, mean age = 78.6 years (SD = 7.4), education = 14.7 years (SD = 3.1)] without dementia at baseline, who underwent annual clinical evaluations for up to 6 years. Summary measures of 5 cognitive abilities were derived from 18 neuropsychological tests. **Results:** In mixed models that controlled for age, sex, education, and race, possession of ϵ 4 (present in 32.9% of Blacks and 21.0% of Whites, $p < 0.001$) was related to faster decline in episodic memory and 4 other cognitive abilities (all p values < 0.01). In separate models that examined the interaction of race and ϵ 4 on decline, there was no significant difference between Blacks and Whites in the effect of ϵ 4 on decline in episodic memory, perceptual speed, or visuospatial ability. By contrast, the effect of ϵ 4 differed for semantic memory and working memory. Results were similar after adjusting for vascular

conditions. **Conclusions:** The results suggest that APOE ϵ 4 is related to a faster rate of decline in episodic memory in Blacks similar to Whites. In addition, there were racial differences in the effect of ϵ 4 in other cognitive abilities such that the ϵ 4 allele was related to faster decline in semantic memory and working memory for Whites but not for Blacks.

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Introduction

Apolipoprotein E (APOE) is a cholesterol transport plasma protein that has 3 different alleles (ϵ 2, ϵ 3, and ϵ 4) on chromosome 19. The 3 alleles code for 3 different APOE isoforms (apoE2, apoE3, and apoE4), which results in 6 potential genotypes (ϵ 2/2, ϵ 2/3, ϵ 2/4, ϵ 3/3, ϵ 3/4, and ϵ 4/4). The ϵ 4 allele has been shown to be associated with many adverse health outcomes [1, 2], including Alzheimer's disease (AD) and cognitive decline [3–5].

There is considerable ethnic/racial variation in the APOE genotype frequency with Blacks having a higher frequency of ϵ 4 compared with Whites [6]. Despite the higher frequency among Blacks, however, little is known about its relationship to cognition. Most studies that include Blacks have focused on ϵ 4 as a risk factor for AD, and the findings have been mixed. Of 13 studies that in-

cluded Blacks in their sample and evaluated the effect of *APOE* $\epsilon 4$ on AD, 6 showed an increased risk of AD for Blacks with the $\epsilon 4$ allele, including a recent genome-wide association study [5, 7–11]. Five studies indicated that the $\epsilon 4$ allele was not related to an increased risk of AD in Blacks [6, 12–15]. There were 2 studies that showed risk of AD among $\epsilon 4$ carriers depended on the variant of $\epsilon 4$ status [16, 17]. That is, homozygotes ($\epsilon 4/\epsilon 4$) had an increased risk but not heterozygotes ($\epsilon 3/\epsilon 4$). Findings with cognition as the outcome demonstrate a similar pattern, although a slightly larger proportion of studies report a positive association between *APOE* $\epsilon 4$ and cognition or cognitive decline among Blacks. There were 4 studies that showed that the $\epsilon 4$ allele was related to a faster rate of cognitive decline among Blacks in longitudinal studies [18–20] and lower performance on cognitive tests in cross-sectional studies [21]. In contrast, 2 studies showed that the $\epsilon 4$ allele was not associated with cognitive decline in middle-aged Blacks [22] in a longitudinal study or with performance on cognitive tests in a cross-sectional study [23]. One study [24] had mixed results for cross-sectional and longitudinal findings. They found that Blacks and Whites with $\epsilon 4$ had lower cognition scores in cross-sectional analyses, but in longitudinal analyses, only Whites with $\epsilon 4$ had a faster rate of cognitive decline. Compared to the well-established literature on *APOE* $\epsilon 4$ in Whites, it appears that the effect of $\epsilon 4$ on cognition in Blacks is much more variable. Further, most of these studies did not explicitly test for racial differences in the effect of $\epsilon 4$ on AD or cognition. In fact, we are aware of only 3 studies that have specifically examined the effect of $\epsilon 4$ and cognitive decline in Blacks, and these results were also mixed as noted, with 1 study finding an association in Whites but not Blacks [24], and 2 other studies from the same cohort reporting that the $\epsilon 4$ allele is related to decline in both Blacks and Whites [19, 20].

There is emerging evidence in Whites that the $\epsilon 4$ allele has a relatively selective effect on episodic memory [25–27]. It is possible that the *APOE* findings in Blacks have been mixed because studies have relied only on brief screening measures of cognition [19, 20, 24], potentially obscuring any relatively specific effect of *APOE* on episodic memory. Given that Blacks may have an increased risk of AD [28], of which impairment in episodic memory is an early defining feature, and they have a higher frequency of the $\epsilon 4$ allele, we hypothesized that the $\epsilon 4$ allele would have a selective effect on decline in episodic memory in Blacks similar to Whites. We also examined its relation to decline in 4 other cognitive abilities and the extent to which the association of allele status with cogni-

tive decline varied by race. We used data from the Minority Aging Research Study [29] and the Rush Memory and Aging Project [30], 2 community-based cohort studies of risk factors for cognitive decline. Participants were 65 years and older and free of known dementia at the time of enrollment. They underwent uniform annual clinical evaluations, including detailed cognitive function testing and ascertainment of *APOE* status at baseline. Composite measures of episodic memory, semantic memory, working memory, perceptual speed, and visuospatial ability were the main outcomes.

Methods

Subjects

Participants were from the Minority Aging Research Study and the Rush Memory and Aging Project. The Minority Aging Research Study is a longitudinal study of risk factors for cognitive decline in older Blacks [29]. The Rush Memory and Aging Project is a longitudinal, clinical-pathologic study of risk factors for common chronic conditions of old age [30]. Participants from both cohorts are recruited using identical recruitment strategies from similar geographical regions. Further, the studies have very similar data collection and operational methods, which facilitates analyses of data from the combined cohorts [31]. Both studies were approved by the Institutional Review Board of Rush University Medical Center.

Minority Aging Research Study

The participants were older community-dwelling Blacks. Eligibility required age of 65 years or older, absence of known dementia, self-report of Black race, and consent to annual clinical evaluations and neuropsychological testing. Subjects were recruited from various community-based organizations, churches, and senior subsidized housing facilities in and around the Chicago metropolitan area. The study has a rolling admission, and more than 400 persons have completed a uniform structured baseline clinical evaluation between August 2004 and July 2011.

Rush Memory and Aging Project

Participants were older persons without known dementia who agreed to annual clinical evaluations and signed an informed consent and an Anatomical Gift Act donating his/her brain, spinal cord, and selected nerve and muscle to Rush investigators at the time of death. Participants were mainly recruited from about 40 retirement communities and senior housing facilities across counties in northeastern Illinois. The study involves detailed annual clinical evaluations and organ donation at death. More than 1,400 persons have completed a uniform structured baseline clinical evaluation between October 1997 and July 2011.

Clinical Evaluation

Eligibility for inclusion in the current analyses required that dementia be absent at baseline. Clinical classification of dementia was based on a uniform, structured clinical evaluation that included a medical history, neurological examination, and assess-

ment of cognitive function (see below). On the basis of this evaluation, a clinician classified persons with respect to dementia using the criteria of the joint working group of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association [32]. These criteria require a history of cognitive decline and impairment in at least 2 domains of cognitive function. Of 1,848 persons from the 2 cohorts who were eligible for this study, 74 were excluded because of dementia at baseline, and 101 were excluded who reported Hispanic ethnicity (86 persons) or a racial background other than Black or White (15 persons). Of the remaining 1,673, 377 did not have a valid genotype and 85 did not have at least 2 valid global cognition scores to measure change over time. Of the remaining, 1,211 (345 Black, 866 White) persons are included in the analytic sample.

Assessment of Cognitive Function

A battery of 19 cognitive function tests was administered in a 1-hour session. One test, the Mini-Mental State Examination (MMSE), was used to describe the overall cognitive functioning of the cohorts, but not in analyses. The remaining 18 performance-based tests assessed the level of and change in episodic memory, semantic memory, working memory, perceptual speed, and visuospatial abilities. Details of the cognitive function tests have been reported previously [33]. There were 7 tests of episodic memory (immediate and delayed story recall of story A from the Logical Memory subtest of the WMS-R [34] and of the East Boston Story [35, 36] and Word List Memory, Word List Recall, and Word List Recognition from the procedures established by CERAD [37]); 2 tests of semantic memory (a 15-item version [37] of the Boston Naming Test [37, 38] and Semantic Verbal Fluency from CERAD [36, 37]); 3 tests of working memory (Digit Span Forward and Digit Span Backward from the Wechsler Memory Scale-Revised [34] and Digit Ordering [36, 39]); 4 measures of perceptual speed (Symbol Digit Modalities Test [40], Number Comparison [41], and 2 indices from a modified version of the Stroop Neuropsychological Screening Test, i.e. the number of color names correctly read aloud in 30 s minus the number of errors, and the number of colors correctly named in 30 s minus the number of errors [42]), and 2 tests of visuospatial ability (a 15-item version of Judgment of Line Orientation [43] and a 16-item version of Standard Progressive Matrices [44]).

Composites of two or more cognitive tests, based in part on the results of a previous factor analysis of these tests [33], were used in analyses. For each composite measure, raw scores on individual tests were converted to Z scores using the mean and SD at baseline for the entire sample. The Z scores on the component tests were then averaged to yield the composite score, as previously described [33, 36].

Assessment of Other Covariates

Other covariates included in the statistical models were age at baseline, sex and education. Educational attainment was expressed as years of formal schooling completed, as reported by the participant. Because vascular conditions have been associated with cognitive function and the APOE polymorphism is an important modulator of plasma lipoprotein, premature atherosclerosis, and a higher incidence of clinical coronary heart disease [45, 46], participants were asked about vascular risk factors and conditions in the medical history and clinical evaluation. Com-

posite measures of vascular risk factor burden (i.e., the number of 3 risk factors present – hypertension, smoking, and diabetes mellitus) and vascular disease burden (i.e., the number of 4 conditions present – claudication, stroke, congestive heart failure, and heart attack) were computed on the basis of self-report questions and medication inspection, as previously described [47].

APOE Genotyping

Blood was collected with acid citrate dextrose anticoagulant, stored at room temperature, and underwent lymphocyte separation within 24 h of collection. DNA was extracted from approximately 2–3 million cells, and genotyping was done by Agencourt Bioscience Corporation (Beverly, Mass., USA) utilizing high-throughput sequencing of codon 112 (position 3937) and codon 158 (position 4075) of exon 4 of the APOE gene on chromosome 19, blinded to all clinical data, as previously described [48].

Data Analysis

For all analyses, participants with an $\epsilon 2/4$ allele were excluded from analyses and the remaining participants were divided into three groups: those with an $\epsilon 4$ allele (i.e., $\epsilon 3/4$ and $\epsilon 4/4$), those with an $\epsilon 2$ allele (i.e., $\epsilon 2/2$ and $\epsilon 2/3$), and those with $\epsilon 3/3$ (used as the reference). We first used t tests and χ^2 tests to analyze racial differences in demographic characteristics, overall cognition, and allele status. For the main analysis, we examined the association of allele status with change in 5 cognitive systems. We used linear mixed models to characterize individual paths of change in specific measures of cognitive function and to examine the relationship of allele status to initial level of cognitive function and annual rate of change [49]. The models characterize each person's individual intercept and slope with random effects. Each individual is assumed to follow the mean path of the group except for random effects, which cause the initial level of cognition to be higher or lower and the rate of change to be slower or faster. The primary model included: time from the baseline interview (in years), $\epsilon 4$, $\epsilon 4 \times \text{time}$, $\epsilon 2$, $\epsilon 2 \times \text{time}$, race, and race $\times$ time. All models also controlled for the potentially confounding effects of age, sex, and education. The term for time indicates the mean change in cognition per year in the reference group ($\epsilon 3/\epsilon 3$). The terms for $\epsilon 4$ and its interaction with time test the relation of $\epsilon 4$ to baseline level of cognitive function and annual rate of cognitive change in $\epsilon 4$ carriers. Likewise, the terms for $\epsilon 2$ and its interaction with time test the relation of $\epsilon 2$ to baseline level of cognitive function and annual rate of cognitive change in $\epsilon 2$ carriers. Because of the low frequency of persons with any $\epsilon 2$, we only focus on the results for any $\epsilon 4$ in the current analysis. The terms for race and its interactions with time and $\epsilon 4$ status test racial differences in the effect of $\epsilon 4$ on cognitive decline. Models stratified by race were subsequently conducted to confirm significant race interactions from the primary full models. These models were similar to the primary models except there were no terms for race included. We then conducted a series of secondary data analyses. First, we added control variables for vascular risk factor burden and vascular disease burden to the primary models to determine whether the effect of APOE on decline was independent of these health-related variables. Then, since the Memory and Aging Project began data collection in 1997 and has a longer follow-up time than the Minority Aging Research Study, we examined the association of allele status and cognitive decline in models restricted to a subsample of Memory and Aging Project participants matched on

Fig. 1. Percentage of Blacks and Whites in the Minority Aging Research Study and the Memory and Aging Project with the different combinations of allele genotypes.

Table 1. Sample characteristics of 1,211 participants in the Minority Aging Research Study and the Memory and Aging Project

Characteristic	Blacks (n = 345)	Whites (n = 866)	p value
Age, years	72.8 ± 6.0	80.9 ± 6.7	<0.001
Education, years	14.7 ± 3.5	14.7 ± 2.9	0.94
Number of women ^a	253 (73.3)	638 (73.7)	0.90
MMSE score	27.8 ± 2.5	27.9 ± 2.1	0.71
Number with any ε4 allele ^a	127 ± 36.8	196 ± 22.6	<0.001
Vascular risk factor score	1.48 ± 0.88	1.08 ± 0.79	<0.001
Vascular disease score	0.27 ± 0.56	0.33 ± 0.61	0.14

Figures are means ± SD or numbers with percentages in parentheses.

^a χ^2 test.

follow-up time. To do so, we first determined the longest follow-up time for participants in the Minority Aging Research Study (6.7 years) and included all of the Memory and Aging Project participants who fell within the same calendar window starting from their earliest enrollment date, resulting in a sample size of 557 Memory and Aging Project participants. All models were validated graphically and analytically. Programming was done in SAS [50].

Results

Table 1 compares the characteristics of participants from the two samples (Minority Aging Research Study and Memory and Aging Project) that were merged for the current study. The mean age of the merged sample was 78.6 years (SD = 7.4), mean education was 14.7 years (SD = 3.1), and the mean MMSE score was 27.9 (SD = 2.0).

On average, Blacks were younger than Whites and had a higher number of vascular risk factors. Blacks were more likely to possess at least one ε4 allele (table 1), consistent with other published reports [6, 20, 24]. However, they were comparable to Whites in terms of educational attainment, vascular disease burden, sex composition, and overall cognitive functioning as measured by the MMSE, likely the result of similar recruitment strategies in overlapping catchment areas for the two studies.

The most frequent *APOE* pair of genotypes in both Blacks and Whites was *APOE* ε3/3, and ε2/2 was the least frequent. The distribution of *APOE* genotypes in study participants was as follows: Blacks: ε2/2 = 3; ε2/3 = 51; ε2/4 = 20; ε3/3 = 164; ε3/4 = 94, and ε4/4 = 13; Whites: ε2/2 = 7; ε2/3 = 130; ε2/4 = 18; ε3/3 = 533; ε3/4 = 166, and ε4/4 = 12 (fig. 1).

APOE ε4 and Cognitive Decline

The relation of the *APOE* ε4 allele to cognitive decline in 5 cognitive abilities is summarized in table 2. To test the hypothesis of a selective effect of ε4 on decline in episodic memory in Blacks, we conducted a mixed effects model in the merged sample (including participants from both the Minority Aging Research Study and the Memory and Aging Project) with episodic memory as the outcome measure. Subsequent models examined the effect of ε4 on the other cognitive abilities in 4 other models. In these analyses, possession of at least one ε4 allele was associated with faster decline in all 5 cognitive abilities. The 3-way interaction of ε4, race, and time on study for episodic memory was not significant (estimate = 0.028, SE = 0.021, p = 0.19), suggesting that the effect of ε4 on decline in episodic memory did not differ for Blacks and Whites. By contrast, there were significant 3-way interactions for decline in semantic memory and working memory, which indicated that ε4 is related to a faster rate of decline in Whites, but not in Blacks. To illustrate this finding, results for episodic memory and working memory are shown in figure 2. *APOE* ε4 is related to a faster rate of decline in episodic memory in both Blacks and Whites compared with persons without the ε4 allele, and there is no difference in this effect for Blacks and Whites. By comparison, the results for working memory show a different pattern. The ε4 allele is associated with a faster rate of decline in working memory for Whites compared to Whites without the ε4 allele, but Blacks with and without ε4 have the same rate of cognitive decline in working memory. The same pattern was observed for semantic memory – the ε4 was related to a faster rate of decline in Whites but not in Blacks. These results were largely con-

Fig. 2. Relation of APOE $\epsilon 4$ to decline in episodic memory (**a**) and working memory (**b**) in Blacks and Whites. Blacks without $\epsilon 4$ = dotted line; Whites without $\epsilon 4$ = solid line; Blacks with $\epsilon 4$ = dotted-dashed line; Whites with $\epsilon 4$ = dashed line.

Table 2. Relation of APOE $\epsilon 4$ to level of and change in separate cognitive abilities

	Model 1			Model 2		
	estimate	SE	p value	estimate	SE	p value
Episodic memory						
$\epsilon 4$	-0.156	0.042	<0.001	-0.200	0.051	<0.001
$\epsilon 4 \times \text{time}$	-0.055	0.010	<0.001	-0.064	0.012	<0.001
$\epsilon 4 \times \text{time} \times \text{Black}$				0.028	0.021	0.19
Semantic memory						
$\epsilon 4$	-0.034	0.044	0.44	-0.059	0.054	0.27
$\epsilon 4 \times \text{time}$	-0.058	0.011	<0.001	-0.072	0.013	<0.001
$\epsilon 4 \times \text{time} \times \text{Black}$				0.048	0.024	<0.05
Working memory						
$\epsilon 4$	-0.004	0.046	0.94	-0.016	0.056	0.77
$\epsilon 4 \times \text{time}$	-0.037	0.008	<0.001	-0.047	0.010	<0.001
$\epsilon 4 \times \text{time} \times \text{Black}$				0.039	0.020	<0.05
Perceptual speed						
$\epsilon 4$	-0.065	0.050	0.19	-0.021	0.061	0.73
$\epsilon 4 \times \text{time}$	-0.044	0.009	<0.001	-0.049	0.010	<0.001
$\epsilon 4 \times \text{time} \times \text{Black}$				0.019	0.020	0.34
Visuospatial ability						
$\epsilon 4$	0.015	0.044	0.73	0.024	0.054	0.65
$\epsilon 4 \times \text{time}$	-0.024	0.009	<0.01	-0.032	0.010	<0.01
$\epsilon 4 \times \text{time} \times \text{Black}$				0.032	0.021	0.13

Model 1 includes the main effect of $\epsilon 4$ on each cognitive ability and the interaction of $\epsilon 4$ with time (in years since baseline), controlling for age, sex, education, and race. Model 2 includes the same terms as model 1 plus the 3-way interaction of $\epsilon 4$, time, and Black race. All models excluded persons with $\epsilon 2/\epsilon 4$.

Table 3. Relation of *APOE* $\epsilon 4$ to cognitive decline in 5 cognitive abilities, stratified by race

Outcome measure	Blacks estimate (SE)	p value	Whites estimate (SE)	p value
Episodic memory				
$\epsilon 4$	-0.072 (0.016)	0.23	-0.202 (0.055)	<0.001
$\epsilon 4 \times \text{time}$	-0.038 (0.016)	0.02	-0.065 (0.012)	<0.001
Semantic memory				
$\epsilon 4$	0.012 (0.079)	0.88	-0.055 (0.053)	0.31
$\epsilon 4 \times \text{time}$	-0.022 (0.017)	0.19	-0.073 (0.013)	<0.001
Working memory				
$\epsilon 4$	0.017 (0.086)	0.84	-0.016 (0.056)	<0.77
$\epsilon 4 \times \text{time}$	-0.006 (0.014)	0.67	-0.049 (0.010)	<0.001
Perceptual speed				
$\epsilon 4$	-0.167 (0.078)	0.03	-0.015 (0.063)	0.81
$\epsilon 4 \times \text{time}$	-0.027 (0.014)	0.04	-0.050 (0.011)	<0.001
Visuospatial ability				
$\epsilon 4$	-0.009 (0.086)	0.92	0.026 (0.052)	0.61
$\epsilon 4 \times \text{time}$	-0.002 (0.018)	0.92	-0.033 (0.012)	0.002

All models exclude persons with $\epsilon 2/\epsilon 4$ and control for age, sex, and education.

firmed in models stratified by race for most cognitive abilities with one exception (table 3). The full model indicated no racial difference in the effect of $\epsilon 4$ on rate of decline in visuospatial ability, but in the stratified models, the $\epsilon 4$ allele was only related to a faster rate of decline in Whites. In sum, the $\epsilon 4$ allele was related to a faster rate of decline in all cognitive abilities for Whites, but was only related to a faster rate of decline in episodic memory and perceptual speed in Blacks. Interestingly, the estimates associated with the effect of $\epsilon 4$ on rate of decline in these 2 abilities were only half as large in Blacks as in Whites.

Secondary Data Analyses

Because vascular conditions have been associated with *APOE* and cognitive function, and there are well-documented racial differences in vascular conditions, we repeated the original models controlling for summary indices of vascular risk factors and vascular disease. Results were essentially unchanged (data not shown). Next, we examined whether the results might be influenced by the longer follow-up times, on average, for the Rush Memory and Aging Project participants. The results were very similar to those in the full sample (data not shown).

Discussion

In two prospective cohorts of more than 1,200 community-based older Blacks and Whites free of dementia at baseline, we found in analyses that controlled for age, education, sex, and race, that the *APOE* $\epsilon 4$ allele was related to a faster rate of decline in episodic memory and 4 other cognitive abilities during a mean of about 6 years of observation. Importantly, the negative effect of $\epsilon 4$ on decline in episodic memory was similar for Blacks and Whites, although the magnitude of the relationships appeared to be a bit weaker in Blacks. Adjustment for vascular risk factors and conditions associated with cognitive impairment and typically found to be more prevalent in Blacks did not change any of the results. The results were unaffected by the longer follow-up time for the Memory and Aging Project.

APOE $\epsilon 4$ has been consistently shown in previous studies to be related to cognitive decline in Whites [18, 51], particularly episodic memory [25–27, 52]. Fewer studies have examined racial differences in the relation of *APOE* $\epsilon 4$ and cognitive decline [19, 20, 24]. One study found that a 5-point or greater decline in scores on the 3MSE over about 3 years was related to the *APOE* $\epsilon 4$ genotype in Whites only [24]. By contrast, another study used the Short Portable Mental Status Questionnaire, a brief screen of cognitive function, and found that *APOE* $\epsilon 4$ significantly increased the odds of cognitive decline by 59%, and the effect was similar in Blacks and Whites [19]. Finally, one other study attempted a replication of a previous study [19] using a longer follow-up period and found a similar effect of $\epsilon 4$ in Blacks and Whites [20]. Because all 3 studies used brief global measures that tend to represent fewer cognitive abilities, there is a possibility that a relatively specific effect of *APOE* on episodic memory has been obscured. Because the $\epsilon 4$ allele has been shown to have a relatively selective effect on episodic memory in Whites, and some studies suggest that Blacks may have a higher risk of AD of which episodic memory is the hallmark feature, we hypothesized that there might be selective effects of the $\epsilon 4$ allele on memory in Blacks. Consistent with our hypothesis, we found that the $\epsilon 4$ allele was related to decline in episodic memory among Blacks and the effect was similar to that of Whites.

Examination of other specific cognitive abilities revealed interactions between race and $\epsilon 4$ status only for semantic memory and working memory. These findings were confirmed in models stratified by race: there was no effect of $\epsilon 4$ on semantic memory or working memory among Blacks, but $\epsilon 4$ was related to a faster rate of decline

in these 2 abilities among Whites. The negative effect of $\epsilon 4$ on semantic and working memory among Whites is consistent with other studies [53, 54], but to our knowledge no study has reported findings for specific cognitive abilities among Blacks. Why the $\epsilon 4$ allele would not have a negative effect on semantic and working memory among Blacks is uncertain. One possible explanation could be differences between participants in the two cohorts. For example, Blacks in our study tended to be younger, had a higher number of vascular risk factors than Whites, and were followed for a shorter period of time, but we adjusted for these factors in statistical models and none accounted for the difference. It is possible that other factors not examined here could differentially influence the association of $\epsilon 4$ and cognition within the two racial groups. For example, it has been demonstrated that both lipid levels and cortisol moderate the influence of *APOE* on cognition [55, 56], and Blacks are less likely than Whites to have elevated triglycerides or low high-density lipoprotein [57]. There is also evidence that minority populations, particularly older Blacks, experience, on average, more adverse social-environmental conditions than older Whites, including lower quality of education [58] and limited socioeconomic resources [59]. Such factors not only place older Blacks at a heightened risk for ill health, but could potentially obscure or weaken any association of the $\epsilon 4$ allele with cognition. In fact, one recent paper using data from a population-based sample of older Blacks and Whites found that the effect of $\epsilon 4$ on cognition was stronger in those persons living in neighborhoods with the lowest level of social disorder [60], which in this study were neighborhoods of predominantly White residents.

Finally, it is possible that the genetic architecture of Blacks and Whites differs resulting in a differential association of the $\epsilon 4$ allele with cognition in Blacks. Given that Blacks represent an admixed population with significant genetic contributions from both African and European ancestors [61], it is possible that genetic susceptibility related to the *APOE* $\epsilon 4$ allele is inconsistently expressed because there are other protective genetic factors in West African genomes that contributed to the genomes of modern Blacks. For example, a recent study reported a trend for the association between *APOE* genotype and dementia to be weaker in those with greater degrees of African admixture [62]. Additional longitudinal studies with diverse populations are needed to test these and other hypotheses.

The study has limitations. First, both studies are volunteer cohorts and so the full spectrum of cognitive

function may not be represented in our cohorts. Second, we had fewer Blacks than Whites, potentially limiting our power to detect an effect of *APOE* on cognitive decline in Blacks. Third, the mean follow-up time was shorter for the black participants. Although sensitivity analyses were conducted to equate follow-up time for Blacks and Whites, and results were essentially the same, it is possible that a longer follow-up period would have yielded stronger racial differences.

Confidence in these findings is strengthened by several factors. First, composites of 2 or more individual cognitive function tests were used as outcomes, reducing the opportunity for floor and ceiling effects on single measures, and allowing us to specifically examine episodic memory and 4 other cognitive abilities rather than relying on brief global screens as in previous studies. Second, data come from 2 large, well-characterized epidemiologic cohorts with essentially identical operational methods, allowing for examination of racial differences in the association of *APOE* and cognitive decline. Third, all participants underwent structured annual clinical evaluations allowing for exclusion of persons with baseline dementia and robust modeling of change in cognition over the course of the study.

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