Apolipoprotein E and Cognition in Community-Based Samples of African Americans and Caucasians

Amy R. Borenstein, PhD; James A. Mortimer, PhD; Yougui Wu, PhD;
Fern M. Jureidini-Webb, PhD; M. Daniele Fallin, PhD;
Brent J. Small, PhD; Michael Mullan, MD, PhD;
Fiona C. Crawford, PhD

To compare relative frequencies of apolipoprotein E (APOE) alleles in African-American and Caucasian populations and test associations with cognition, we studied two community-based samples: one of 253 African Americans and another of 466 Caucasians age 60–84 years. Logistic regression, adjusting for age, sex, education, and history of hypertension and diabetes was used to associate APOE with five cognitive measures. The APOE-ε4 allele frequency was 29.5% in African Americans and 12.1% in Caucasians. In the African Americans, no association was found between the presence of the APOE-ε4 allele and any of the cognitive measures. Among Caucasians, APOE-ε4 carriers performed more poorly on three of the five tests. We also report a considerably higher frequency of the APOE-ε4 allele in our African-American sample compared to other US-based studies. (*Ethn Dis*. 2006;16:9–15)

From the Department of Epidemiology and Biostatistics (ARB, JAM, YW), Department of Gerontology (BJS), University of South Florida, Tampa, Department of Community Health and Family Medicine, University of Florida, Jacksonville (FMJW), Roskamp Institute, Sarasota (MM, FCC), Florida, Department of Epidemiology, Johns Hopkins University, Baltimore, Maryland (MDF).

Address correspondence and reprint requests to Amy R. Borenstein, PhD, Department of Epidemiology and Biostatistics, College of Public Health, MDC-56, University of South Florida, 13201 Bruce B. Downs Boulevard, Tampa, FL 33612-3805, 813-974-6670, 813-974-4719 (fax), aborenst@hsc.usf.edu

INTRODUCTION

Recent studies of dementia and Alzheimer disease (AD) have reported higher prevalence and incidence rates among African-American compared with Caucasian populations.[1,2] By contrast, lower rates have been reported among older African Blacks.[3]

The apolipoprotein E-ε4 (APOE-ε4) allele is a robust risk factor for AD among Caucasians.[4,5] However, among African Americans and African Blacks, the evidence for this association is controversial. In a large prospective study of African Americans in Indianapolis, the ε4 allele was positively associated with the presence of AD,[6] while in a methodologically standardized study of Africans in Nigeria, no association was present.[7] In a multicenter case-control study, the APOE-ε4 allele was reported to confer increased risk among both African Americans and Caucasians.[8] Different findings were reported in a prospective study in North Manhattan, where the relative risk for AD among African Americans associated with one or two ε4 alleles was 1.0 (95% CI 0.6–1.6), compared with 2.5 for Caucasians (95% CI 1.1–6.4).[1] In that study, African Americans without an ε4 allele had cumulative risks of AD to age 90 that were four-fold higher than Caucasians, even when adjusted for education and sex. In addition, a large prospective study of community-dwelling African-American and Caucasian residents in Chicago reported no association between the ε4 allele and incident AD among African Americans.[9]

Some of the differences between studies may be due to differential associations between individuals who are homozygous vs heterozygous for the ε4 allele. In the Indianapolis cohort, for example, the risk for AD associated with the heterozygous form of APOE (specifically ε3/ε4) was 1.2 (95% CI 0.6–2.5), while that associated with the homozygous form was 4.8 (95% CI 1.7–13.6).[6] This finding is consistent with a meta-analysis that showed that homozygosity for APOE-ε4 increased the risk for AD five-fold but that heterozygosity was not associated with the disease in African Americans.[5]

The association between APOE-ε4 and cognition has been studied cross-sectionally in 202 individuals in the United Kingdom of African Caribbean descent.[10] In that study, ε4 increased the risk for cognitive impairment (OR=1.60, 95% CI 0.84–3.05), especially for those aged 70–75 (OR=6.2, 95% CI 1.3–29.8). In the Cardiovascular Health Study, Blacks with the ε4 allele were at a 50% higher risk (95% CI 0.9–2.5) for scoring low (<80/100) on the Modified Mini Mental State Examination (3MS) compared with those who did not carry an ε4 allele; among Whites, the magnitude of the association was similar but attained statistical significance.[11] However, the risk of declining by five or more points on the 3MS over a two-year period was not elevated for Blacks with an ε4 allele.

In the present study, we report the frequencies of APOE genotypes in two methodologically standardized cross-sectional studies: the Hillsborough Elder African-American Life Study (HEALS), in which all of the participants were African-American, and the

In the Cardiovascular Health Study, Blacks with the ε4 allele were at a 50% higher risk (95% CI 0.9–2.5) for scoring low (<80/100) on the Modified Mini Mental State Examination (3MS) compared with those who did not carry an ε4 allele . . .

Charlotte County Healthy Aging Study (CCHAS), in which >99% of the participants were Caucasian. We compared the associations between the APOE-ε4 allele and cognitive performance on five neuropsychological measures in these two studies. By design, this study did not diagnose individuals in the community as to whether they had dementia or not, the study aimed to examine associations between the APOE-ε4 allele and neuropsychological performance. However, since the association was hypothesized to exist within groups with impending dementia, we used a dichotomous approach to classify outcomes.

METHODS

Study Samples

Two separate studies were conducted, which were methodologically standardized to one another: one in Hillsborough County (HEALS) and the other in Charlotte County (CCHAS). In each county, we identified, from the 1990 US Census, two census tracts with high proportions of individuals aged ≥65 years. Charlotte County, the location of the study of the Caucasian sample, was reported in 1990 to have the highest proportion of persons age 65 and over in Florida.[12] In HEALS, we

surveyed two US Census tracts that reported a high proportion of older African Americans. Details of the CCHAS sample can be found in Small.[13]

In HEALS, 2394 households were surveyed, and we obtained census data from 2205 (92%). Of these, 424 were deemed eligible and were invited, with 253 participating (59.7%, 131 of 207 from tract 1 and 122 of 147 from tract 2). In CCHAS, 4107 households were surveyed, we obtained census data for 2164 (53%). A total of 1392 letters of invitation were sent, 584 of these could not be contacted, and 808 were determined to be eligible. The final CCHAS sample consisted of 466 individuals (57.5%, 244 of 393 from tract 1 and 222 of 415 from tract 2). In CCHAS, we administered a questionnaire on 328 of 338 refusers/noncompleters. Refusers did not differ by age, but more women refused (P<.05), and refusers had less education (12.3 vs 13.9 for completers, P<.001).[13] Refusal data were not collected in HEALS, since it was not logistically possible to do so.

Procedures

In both studies, each participant received three visits over a one-week period. At the first visit, a trained interviewer administered an in-person interview at the participant's home or at a neutral location (eg, church), depending on the participant's preference. During this visit, extensive risk factor, quality of life, dietary, and medical and family history questionnaires were administered. Approximately one week later, a second interviewer returned and administered sensory, cognitive, and other performance-based tests. During the week, a certified phlebotomist came in the morning to collect 30 mL of blood: 20 mL were sent for analysis at SmithKline Laboratories (total cholesterol, triglycerides, HDL, hemoglobin A_{1c}, and folate) and the remainder was sent to the Roskamp Laboratories (FCC and MM) for APOE genotyping.

Both studies were approved by the University of South Florida Institutional Review Board, and written informed consent was obtained from all participants after a detailed explanation of the purposes and procedures of the study. In CCHAS, participants did not receive monetary compensation for participation but received feedback regarding their blood findings, dietary health, and personality inventory. Participants in HEALS received $75, $25 for completing the interview and $50 for the blood donation, as well as the same study results as the CCHAS sample. Incentive plans were determined for each community on the basis of focus groups conducted before study implementation.

DNA Extraction and APOE Genotyping

DNA extraction and genotyping for APOE was conducted by using standard PCR amplification and digestion techniques.[14] Genotype and allele frequencies were calculated as well as ε4 carrier status (presence or absence of an APOE-ε4 allele).

Cognitive Measures

Five cognitive measures were used for the present analysis. General cognitive ability was measured with the modified Mini-Mental State Examination (3MS),[15] which was administered according to standardized protocol. Four measures were derived from the modified Hopkins Verbal Learning Test (HVLT).[16,17] In the HVLT, 12 words were read three times to the participant. At the end of each trial, the participant was asked to recall as many words as possible. An intrusion task lasting five minutes was given after the three learning trials (Stroop test[18]). This was followed by a request to the participant to spontaneously recall the 12 words learned earlier ("delayed free recall"). The participant was then told that the 12 words could be grouped into three categories of four words each: four-legged animals, precious stones, and

Table 1. Means and standard deviations of sample demographic characteristics, Apolipoprotein E-ε4 frequency, and outcomes in HEALS and CCHAS

Variable	HEALS (African Americans)			CCHAS (Caucasians)		
	n	Mean	SD	*n*	Mean	SD
Age	253	71.63	6.97	466	72.50	6.22
Sex (% female)	253	0.56	0.50	466	0.51	0.50
Education (years)	252	9.70	2.90	463	13.90	3.03
APOE-ε4 (% positive)	207	0.53	0.50	462	0.22	0.41
3MS total	241	84.68	9.78	465	91.59	7.61
Delayed free recall	253	6.17	1.91	465	7.47	2.85
Gain from cued recall	253	0.68	1.21	465	0.95	1.55
Recognition discrimination	253	8.91	2.42	465	9.51	2.04
Savings score	252	0.91	0.16	464	0.93	0.45

places to live. Using these cues, participants attempted to recall as many words as possible. The number of words recalled after cueing minus the number recalled freely constituted "gain from cued recall." The participant was then read a list that contained the same 12 words as before and 12 new words and asked to identify the words they had heard before. The number of words (out of 12) recognized correctly minus the number of words recognized incorrectly composed the measure of "recognition discrimination." Finally, we calculated a "savings score" by dividing the number of words freely recalled after the delay by the number recalled after the third learning trial. Normative data have been published from both tests in both of our samples.[19–22]

Statistical Analysis

For univariate comparisons between studies, student *t* test and chi-square tests were used. The 3MS and HVLT measures were dichotomized into low and high performance. For each mea-

sure, people scoring in the lowest 20th percentile were deemed poor performers. Since no participant had frank dementia, using quintiles of performance best approximated poor cognitive performance. Cut-points for the lowest 20%, for HEALS and CCHAS respectively, were: 3MS: <80, <90, delayed free recall: <5, <6, cued recall: <5, <6, recognition discrimination: <7, <8, and savings score: <0.83, <0.80. Fit to Hardy-Weinberg proportions (HWP) was examined in each study separately via chi-square tests with one degree of freedom, comparing observed genotype counts to those expected under HWP. For analysis with the cognitive variables, APOE genotypes were coded according to the number of copies of the ε4 allele. A dominant model was then assumed such that APOE status was collapsed into ε4 carriers (1 or 2 copies) vs noncarriers (0 copies). Multiple logistic regression was employed to assess the associations between APOE-ε4 carrier status and poor cognitive performance controlling

for age, education, sex, and self-reported history of diagnosed diabetes and hypertension.[23]

RESULTS

Table 1 compares the samples by their demographic characteristics, the frequency of the APOE-ε4 allele, and the outcome measures. Individuals in the HEALS sample were approximately one year younger than in the CCHAS sample. No difference was seen by sex. The HEALS sample had on average four years of education less than the CCHAS sample. Crude performance on all five cognitive measures was better in the CCHAS sample, but the difference was minimal for savings score.

We compared APOE genotype frequencies and ε4 allele frequencies between the two samples (Table 2). The frequency of the ε4 allele in the African-American sample (HEALS) was 29.5% compared with 12.1% in the Caucasian sample (CCHAS). In HEALS, 43.3% were ε3/ε4 compared with 17.0% in CCHAS, and the ε4/ε4 genotype was 2.6 times more common in HEALS.

In Table 3, associations between ε4 (1 or 2 alleles) and poor performance on cognitive tests are shown, adjusted for age, education, sex, and history of diabetes and hypertension. In HEALS, no associations or trends were apparent. In CCHAS, recognition discrimination was associated with the presence of an ε4 allele, and a strong trend existed for an association with delayed free recall and savings score.

In Table 4, the results from Table 3 are stratified by age of the participant. In CCHAS, all of the associations between the presence of an ε4 allele and cognitive outcomes were stronger in the group aged ≥75 years, except for gain from cued recall. Participants with an ε4 allele were 3.42 times more likely (95% CI 1.46–8.00) to perform poorly on recognition discrimination compared to those

Table 2. Apolipoprotein E isoform genotypes in HEALS (African Americans) and CCHAS (Caucasians)

Sample	No.	ApoE Genotype Frequency, %						ApoE Allele Frequency, %		
		ε2ε2	ε2ε3	ε2ε4	ε3ε3	ε3ε4	ε4ε4	ε2	ε3	ε4
HEALS (African Americans)	208	0	9.6	4.3	37.0	43.3	5.8	7.0	63.5	29.5
CCHAS (Caucasians)	458	0	14.6	3.1	64.0	17.0	2.2	8.8	79.1	12.1

Table 3. Associations between APOE-ε4 and dichotomized cognitive outcome measures, adjusted for age, education, sex, and history of diagnosed diabetes and hypertension for HEALS (African Americans) and CCHAS (Caucasians)

Outcome	HEALS (African Americans) OR	HEALS (African Americans) 95% CI	CCHAS (Caucasians) OR	CCHAS (Caucasians) 95% CI
3MS total	0.63	0.27–1.48	1.08	0.61–1.90
Delayed free recall	0.90	0.40–2.06	1.67	0.97–2.90
Gain from cued recall	0.61	0.24–1.57	1.86	0.84–4.11
Recognition discrimination	0.64	0.28–1.49	1.93	1.05–3.56
Savings score	1.65	0.80–3.43	1.54	0.92–2.57

The ε4 allele was associated with cognitive impairment (OR= 1.6, 95% CI 0.8–3.1), but was stronger and statistically significant in the older age group (OR= 6.19, 95% CI 1.3–29.8).

with no ε4 allele. In HEALS, the ε4 allele was not associated with any cognitive outcome in either age group, in fact, in the older age group, a trend toward inverse relations existed.

DISCUSSION

Using methodologically standardized studies of two ethnically diverse community-dwelling populations, we found that the presence of the APOE-ε4 allele was associated with measures of delayed recall and recognition discrimination in older Caucasians but not with the same measures in older African Americans. Our findings in African Americans are best compared with those of a study of 202 African Caribbeans aged 55 to 75 years who were living in

South London, United Kingdom.[10] In that study, 11 cognitive measures, including four measures of memory, were used to dichotomize participants into those with and without cognitive impairment. The ε4 allele was associated with cognitive impairment (OR=1.6, 95% CI 0.8–3.1), but was stronger and statistically significant in the older age group (OR=6.19, 95% CI 1.3–29.8). We observed the same trend for increased associations with higher age in Caucasians (CCHAS), but did not find any association with cognitive outcomes among African Americans (HEALS).

Previous studies of the association between the ε4 allele and AD in different ethnic populations have yielded varying results. The Indianapolis-Ibadan Dementia Project, which compared older African Americans with

older Nigerians, was the first to report disparate findings for the association between ε4 and prevalent AD. In Indianapolis, the homozygous form of ε4 increased risk for AD (OR=4.83, 95% CI 1.7–13.6), but the heterozygous form did not (OR=1.2, 95% CI 0.6–2.5).[6] In contrast, no association was found in a methodologically standardized study of Nigerians in Ibadan (ε4 present in 16.7% of AD patients and 20.5% of controls).[7] Similar results to those found in Indianapolis were reported for prevalent cases of AD among African Americans in the North Manhattan Study;[24] ε4 homozygotes showed a significantly increased risk (3.0, 95% CI 1.5–5.9), and ε4 heterozygotes showed a reduced risk (0.6, 95% CI 0.4–0.9). The finding of an elevated risk for ε4 homozygotes was confirmed in a meta-analysis of 235 African-American cases and 240 controls from 40 studies. The OR for ε4 homozygosity in this meta-analysis was 5.7 (95% CI 2.3–14.1), but no association was found for ε4 heterozygosity.[5]

Other cross-sectional studies have reported positive associations for both ε4 homozygotes and heterozygotes. In a clinic-based case-control study in Alabama of AD among African-American patients,[25] ε4 homozygotes and ε4 heterozygotes were at higher risk for AD (OR=5.6, 95% CI 1.5–21.0 and OR=2.5, 95% CI 1.3–5.0, respectively) compared with individuals with two ε3 alleles. Another case-control analysis of African Americans

Table 4. Associations between APOE-ε4 and dichotomized cognitive outcome measures, stratified by age, adjusted for education, sex, and history of diabetes and hypertension for HEALS (African Americans) and CCHAS (Caucasians)

Outcome	HEALS (African Americans) OR	HEALS (African Americans) 95% CI	CCHAS (Caucasians) OR	CCHAS (Caucasians) 95% CI
Younger (<75)				
3MS total	1.45	0.36–5.79	0.59	0.23–1.51
Delayed free recall	0.76	0.15–3.77	1.23	0.53–2.83
Gain from cued recall	0.19	0.03–1.09	2.33	0.83–6.60
Recognition discrimination	1.13	0.25–5.07	1.22	0.46–3.45
Savings score	1.65	0.53–5.18	1.32	0.63–2.73
Older (≥75)				
3MS total	0.25	0.06–1.97	1.65	0.78–3.52
Delayed free recall	0.40	0.12–1.27	2.27	1.06–4.86
Gain from cued recall	0.96	0.26–3.53	1.31	0.34–5.13
Recognition discrimination	0.38	0.12–1.21	3.42	1.46–8.00
Savings score	1.37	0.44–4.27	1.81	0.86–3.83

also found significant effects for both ε4 homozygotes (OR=10.5, 95% CI 5.1–21.8) and heterozygotes (OR=2.6, 95% CI 1.8–3.7).[26]

Incidence studies have not shown the increased risk of AD among African Americans to be associated with the presence of ε4 alleles. In the northern Manhattan study, African Americans were 4.4 times more likely (95% CI 2.3–8.6) to develop incident AD by age 90 than Caucasians, but the presence of one or two copies of the ε4 allele did not influence this risk (RR=1.0, 95% CI 0.6–1.6).[1] This disparity in risk of AD between African Americans and Caucasians remained after adjusting for clinically overt cardiovascular and cerebrovascular disease.[2] Similarly, in a recently published study conducted in Chicago, no association was found between the presence of the ε4 allele and incident AD (OR=1.02, 95% CI 0.39–2.48) among African Americans.[9]

Studies in which cognitive decline was the outcome of interest have generally shown relatively weak associations with the presence of ε4 alleles. In the Cardiovascular Health Study, the relative risk of a decline of five or more points on the 3MS over a two-year period associated with one or more ε4 alleles was 1.3 (95% CI 0.8–2.2) among African Americans compared with 1.7 (95% CI 1.3–2.1) among Caucasian participants.[11] In the Duke EPESE, models predicting an increase of two or more errors on the Short Portable Mental Status Questionnaire over a four-year follow-up period showed no interaction between the ε4 allele and race (OR for Caucasians was 1.6, for African Americans 1.45).[27]

The APOE genotypes in our studies did not fit HWP (*P*=.02 and *P*=.004 for HEALS and CCHAS, respectively). This finding appears to be due to a lack of ε2ε2 homozygotes in our samples and should not greatly affect our results, as we have focused on genotypes, rather that allele frequencies, in our analyses

and thus did not rely on the HWP assumption.[28]

The results reported here are consistent with those of community-based studies showing associations between the presence of one or more ε4 alleles and incident AD among Caucasians but not among African Americans.[2,9] Differences between our results and those of studies showing associations between ε4, cognition, and dementia among individuals of African descent may be due to the more advanced age of our sample,[10] its community-based vs clinical origin,[25,26] the type of assessment, or the fact that ε4 heterozygotes were combined with homozygotes in our analyses.[5,6,24] Because we are studying a genetic risk factor, the cross-sectional nature of our study does not affect our ability to interpret a temporal sequence between exposure and outcome.

In the present study, 12 African Americans were homozygous for ε4. While this number does not permit formal comparisons, when analyses were conducted with dummy variables for ε4 homozygosity vs heterozygosity comparing to the reference group (no ε4 alleles), no increased risk was observed for any of the cognitive outcomes in association with homozygosity in this sample, in fact, the ORs for heterozygosity and homozygosity were extremely similar, and we pooled the data by the presence of an ε4 allele. In CCHAS, the usual allele dose-response was observed (data not shown).

We also conducted analyses in which the neuropsychological measures were treated as continuous variables. These analyses showed similar, though more modest, associations with the presence of ε4 alleles in CCHAS. This finding is consistent with most of the effect being restricted to the lowest quintile of performance, as might be expected if pre-clinical AD were detected. In a previous publication, when we focused our analyses on individuals in CCHAS whose 3MS scores were >82, we did not observe an association

between the same cognitive measures (analyzed as continuous measures) and ε4 status,[13] which suggests that the contribution of ε4 to cognitive deficit is likely an indicator of impending dementia.

Among Caucasians, we found a stronger effect in individuals >75 years of age. A number of studies have reported that the association between ε4 and AD decreases with age.[5,29] The interaction between ε4 and age on cognitive performance in Caucasians may alternatively be explained if older individuals with an ε4 allele are closer to the threshold of cognitive or brain reserve capacity.[30]

Our African-American participants had a considerably higher allele frequency for ε4 (29.5%) compared with most other estimates, which are around 20%.[1,5,25,26,31] Only those in Sudanese and Nigerian populations were similar.[32] The reason for this finding is unclear, although it may be related to regional variation in APOE-ε4 frequency, which is particularly evident among African populations.

In summary, we report a higher frequency of the APOE-ε4 variant in a community-based, older African-American population than was found in most other US studies. Despite the high ε4 frequency, no association was observed between the presence of an ε4 allele and any cognitive outcome. In a methodologically standardized study of Caucasians, we observed the same associations between ε4 and cognition as has been reported in numerous studies. A number of biologic mechanisms have been proposed to explain why APOE-ε4 increases the risk of AD.[33] The ε4 allele has, in many studies, been shown to modestly increase the risk for coronary artery disease, but the effect of the ε4 allele on the risk of AD is stronger.[33] In some studies, APOE-ε4-positive individuals with AD show an increased Aβ plaque burden and also have smaller hippocampal volumes.[34] The ε4 allele may promote Aβ deposition and aggregation or inhibit Aβ

clearance from the brain. APOE variants may have differential direct effects on neurons or glial cells, including tau and survival of neurons.[33] Lastly, whether the vascular effects exerted by APOE are independent of the AD pathologic process is unknown. In African-American populations, perhaps other mechanisms are relevant, of specific interest will be the direct vascular contribution to AD and genetic influences other than APOE.

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AUTHOR CONTRIBUTIONS

Design and concept of study: Borenstein, Mortimer, Wu, Jureidini-Webb

Acquisition of data: Borenstein, Jureidini-Webb, Mullan, Crawford

Data analysis and interpretation: Borenstein, Mortimer, Wu, Fallin, Small, Mullan, Crawford
Manuscript draft: Borenstein, Fallin, Small

Statistical expertise: Borenstein, Mortimer, Wu, Fallin, Small
Acquisition of funding: Borenstein, Mullan, Crawford

Administrative, technical, or material assistance: Borenstein, Jureidini-Webb, Mullan, Crawford
Supervision: Borenstein