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No Association Between Apoε4 Alleles, HIV Infection, Age, Neuropsychological Outcome or Death

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Abstract

The ε4 allele of the ApoE gene may have important interactions with physical health and cognitive function among individuals with HIV disease. The purpose of this study is to examine the relationships between ε4, HIV disease, age, neuropsychological impairment and death in a large, well-characterized study sample. 2,846 men participating in the Multicenter AIDS Cohort Study had ApoE genotyping and neuropsychological test data available for analysis. We found a significant association between HIV infection and time to death (from any cause), as well as older age, race, and education. But, ApoE status was not significantly associated with time to death.

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Similarly, we found a significant association between HIV infection and time to incident cognitive impairment, as well as age, education, and HIV serostatus; Apoε4 status was not related to incident cognitive impairment. There were no significant interactions between ApoE, HIV infection, and age on cognitive impairment. These data replicate and strengthen prior findings of the lack of association between ApoE ε4 and cognitive outcomes in HIV disease. We conclude that within the specific constraints of an exclusively male study in which the majority of participants were less than 65 years of age (range: 22-87 years), it appears reasonable to conclude that the ε4 allele is not significantly interacting with HIV serostatus.

Keywords

HIV disease; APOE; Cognition; Age

Introduction

Apolipoprotein E (ApoE) is a class of apolipoproteins that mediate cholesterol metabolism (Mahley 1988). In the central nervous system, ApoE is produced primarily by astrocytes and transports cholesterol to neurons via ApoE receptors (Liu, Kanekiyo et al. 2013). The gene, *APOE*, is mapped to chromosome 19, and the ε4 allele of this gene is found in approximately 14 percent of the general population (Wardell, Suckling et al. 1982, Sing and Davignon 1985, Jarvik 1997). The frequency of the ε4 allele is elevated among individuals with atherosclerosis (Menzel, Kladetzky et al. 1983), Alzheimer's disease (AD) (Corder, Saunders et al. 1993, Strittmatter, Saunders et al. 1993), and with impaired cognitive function (Brayne, Harrington et al. 1996). *APOE* is also associated with mortality (Lane, Gao et al. 2003, Drenos and Kirkwood 2010, Beydoun, Beydoun et al. 2013), coronary artery disease and death (Tiret, de Knijff et al. 1994, Guang-da, You-ying et al. 2004).

Because of its links with cholesterol metabolism, heart disease and with increased risk for AD, it is reasonable to conjecture that ε4 might have important interactions with physical health and cognitive function in individuals with HIV disease. Indeed, there are some limited data linking ε4 to mortality in HIV disease (Valcour, Shiramizu et al. 2008). Reports from cross-sectional studies found no association between the presence of an ε4 allele and cognitive impairment in HIV disease (Andres, Feger et al. 2010, Joska, Combrinck et al. 2010, Sun, Abadjian et al. 2010, Morgan, Woods et al. 2013), although this is not a consistent finding (Spector, Singh et al. 2010, Chang, Andres et al. 2011, Hoare, Westgarth-Taylor et al. 2012, Soontornniyomkij, Moore et al. 2012). However, it should be noted that studies that did find an association between HIV disease and ε4 include chronological age in their models (Panos, Hinkin et al. 2013). The purpose of this study is to replicate and extend these previous findings in a larger sample, and specifically to examine *incident* cognitive impairment (i.e. from a state of normal cognition) as well as time to death (Rosvall, Rizzuto et al. 2009).

Methods

This research was reviewed and approved by the Institutional Review Boards at each of the clinical sites of the Multicenter AIDS Cohort Study (MACS). Each participant signed a written statement of informed consent prior to starting any research-related activities.

Subjects

The MACS is an ongoing, prospective cohort study in the United States of the natural and treated history of HIV infection among men who have sex with men. A total of 6,972 men have been enrolled in the study at four study sites since its inception in April, 1984 (4,954 in 1984–1985, 668 in 1987–1991, and 1,350 in 2001–2003). Participants return every 6 months for an interview, physical examination, and collection of blood for laboratory testing. The interview covers physical health, medical treatments, and sexual and substance use behaviors (see: http://www.statepi.jhsph.edu/macs/macs.html). All men complete the Centers for Epidemiological Studies Depression Scale (CES-D) (Radloff 1977).

We refer to the men who enrolled in 1984-1985 or 1987-1991 as Cohort 1 (C1), and those who enrolled between 2001-2003 as Cohort 2 (C2). C1 was the original sample of 4,954 men, and C2 was a “New Recruit Cohort” that focused on enrolling minority and special target groups such as the partners of the men in the original cohort. C2 enrollment also focused on recruiting racial/ethnic minorities as well as a special target group of uninfected men who had been censored from C1 in 1995.

Genomic DNA extraction

Genomic DNA was isolated from lysates of either buffy-coat or B-cell immortalized cell lines from individuals within the MACS. Genomic DNA concentration and quality was assessed using UV spectrophotometry (NanoDrop, Thermo Fisher Scientific, Waltham, MA) and/or by fluorometric quantitation (Quant-IT PicoGreen, Life Technologies, Carlsbad, USA).

Genotyping

End-point genotyping of *APOE* Single Nucleotide Polymorphisms (SNPs) rs429358 [C/T] and rs7412 [C/T] was performed using TaqMan and OpenArray technologies (Life Technologies, Carlsbad, USA). Genomic DNA was introduced to nanoliter reaction wells on a high-density microplate containing validated TaqMan primers and probes. PCR amplification was completed as recommended by the manufacturer. Water non-template and known positive controls were plated on each array for internal quality assurance and quality checks. Arrays were imaged after amplification on one of two OpenArray NT imagers. SNP genotypes were ascribed after clustering VIC and FAM signals (STATA 12.1, College Station, TX), and were then used to determine the ApoE alleles present(Zuo, van Dyck et al. 2006).

Neuropsychological (NP) Evaluation

The neuropsychological component of the MACS, and the recruitment cohort and survivorship difference have been described in detail (Becker, Kingsley et al. 2014). The NP

evaluation includes measures from multiple cognitive domains related to the classification of HIV-Associated Neurocognitive Disorder (HAND) (Miller, Selnes et al. 1990, Miller, Satz et al. 1991, Selnes and Miller 1994, Woods, Rippeth et al. 2004, Antinori, Arendt et al. 2007). Because we did not assess activities of daily living at the earlier study visits, we were unable to assign HAND classifications, but were nevertheless able to provide evidence of existing cognitive deficits.

Classifications of cognitive impairment were operationalized using the criteria outlined by Woods et al (Woods, Rippeth et al. 2004) and Antinori et al. (Antinori, Arendt et al. 2007). Six cognitive domains were defined using measures from the MACS neuropsychological test battery: 1) Executive Function (Trail-Making Part B, Stroop Interference); 2) Speed of Information Processing (Symbol Digit Modalities Test, Stroop Color Naming); 3) Attention and Working Memory (two measures of one-back reaction time using the CalCAP Reaction Time program); 4) Learning (Rey Auditory Verbal Learning Test – Sum of Trials 1 through 5, Rey Complex Figure Immediate Recall); 5) Memory (Rey Auditory Verbal Learning Test Delayed Recall, Rey Complex Figure Delayed Recall); and 6) Motor (most impaired hand on the Grooved Pegboard). We used data from the MACS seronegative men to create the statistical models to derived T-scores for each participant (i.e., both infected and uninfected men) for each test adjusting for age, years of education, ethnicity (Caucasian vs. other), and number of times the test had been administered. For each domain a summary T-score was calculated by averaging the two T-scores or, in the case of the Motor domain, using the lowest T-score on either the dominant or nondominant hand of the Grooved Pegboard. If the T-score for one of the tests was >= 40 and the other one was <40 then the domain was assigned the lowest obtained T-score plus five. If only one test in a domain was completed, the T-score for that test was used. For individuals who had T-scores for at least four of the six cognitive domains, classifications of cognitive functioning were made as follows (Antinori, Arendt et al. 2007): 1) Within Normal Limits if one or fewer domains had T-scores 1 SD or more below the mean (i.e., $T \leq 40$); 2) Mild Impairment if two or more domains had T-scores ≤ 40, and the individual did not meet criteria for the more severe category 3 that follows; and 3) Severe Cognitive Impairment if two or more domains had T-scores ≤ 30, or one domain had a T-score ≤ 25.

It is important to note that the neuropsychological classification was fully automated. The results were not reviewed to determine the probable cause of the impairment. However, we created a binary variable (present/absent) to indicate the presence of a confounding condition *at any time during follow-up* that could, in and of itself, alter cognitive functions. These included serious medical diagnoses (e.g., heart failure), CNS infections, stroke, serious psychiatric disorders (e.g., affective, substance abuse, etc.), among others (See Supplemental Table for list of conditions). 31.9% of the uninfected men, and 34.1% of the infected had at least one confounding condition.

Statistical Analysis

We examined the unadjusted associations between ApoE genotype and other variables using t-tests and contingency tables as appropriate. Time to event in years (i.e., cognitive impairment or death) was tested using Cox proportional hazard models. And we identified

and accounted for any differences in association as a function of recruitment cohort differences (Becker, Kingsley et al. 2014).

Results

Of the 4,275 men who had ApoE genotyping available for this analysis, 2,846 also had neuropsychological test data. The individuals who contributed data to this study were more likely to represent racial minorities, less likely to be HIV-infected, and more likely to be alive and active in the study as of December 31, 2012, relative to those who did not contribute data (See Supplemental E-Tables 1A and 1B). 2,040 men from C1 (59.8% of the cohort), and 806 men from C2 (93.4%) had ApoE genotyping data available. C1 contributed 71.7% of the ApoE data, and C2 contributed 28.3% for this analysis (See Table 1).

There was a significant association between race and ApoE genotype; 23.2% of the men who identified themselves as White had at least one copy of the ε4 allele. By contrast, 31.2% of the men in other races (primarily African-American, but including Hispanics) had at least one ε4 allele [χ^2 = 20.8, df=1, p<.001, Relative Risk = 1.54 (1.27 – 1.85)]. Therefore, all subsequent associations were evaluated in the White and non-White groups separately.

The allele frequencies for ApoE among the White participants were: ε2 .075, ε3 .80, and ε4 . 13. Among the minority participants, the allele frequencies were: ε2 .11, ε3 .72, and ε4 .18. These rates are comparable with population estimates (i.e., both Caucasian and other races) of the allele distributions: ε2 .09, ε3 .77, and ε4 .15 (Sing and Davignon 1985).

There were also differences in the distribution of ε4 as a joint function of cohort and minority status. Among the White participants, the level of ε4 was .23 in C1 and .23 in C2 (χ^2 = 0.002, p>0.05). By contrast, among the minority participants, the level of ε4 differed: from .25 in C1 to .36 in C2 (χ^2 = 11.53, p<.001). In unadjusted models, we found no significant associations between the presence of an ε4 allele and age, as either a continuous variable (Table 1) or a dichotomous variable [≤40 vs. ≥ 50 years, Supplemental Tables E3A and 3B (Valcour, Shiramizu et al. 2008)]. We further found no unadjusted associations between ApoE status and HIV serostatus or death (See Table 1). With regard to the neuropsychological outcomes, there was a borderline association between ε4 and having incident impairment *only* in the minority participants in C2 (χ^2 = 3.45, p>0.06, RR= 1.16 (1.00-1.35)); there were no other associations between ε4 and incident cognitive dysfunction.

We used Cox Proportional Hazard Models to investigate the association between time to death (measured from study entry) and ApoE ε4, HIV serostatus, age at entry, white race, and cohort of entry. We found a significant association between HIV infection and time to death (from any cause), as well as older age, and race. However, ApoE status was not significantly associated with time to death (See Table 3).

Finally, we examined time to incident cognitive impairment (either mild or severe) among the 1,481 individuals classified as cognitively normal at their first neuropsychological evaluation *and* not having identified confounding conditions. There was no association

between ε4 and time to develop cognitive impairment (See Table 4). In none of our analyses did we find significant interactions between ε4, HIV infection, age, and either death or cognitive impairment (See Supplemental Table E4). We repeated these analyses including all 2,204 participants who were cognitively normal at their first evaluation and included "potentially confounding conditions" as a covariate in the models. Again, ApoE was not related to time to cognitive impairment.

We repeated the analyses using data only from the 1,134 White participants without potentially confounding conditions. There was no association between ApoE ε4 and time to impairment (Hazard = .99, 95% Confidence Interval = .78-1.3). When we further restricted the analysis to those men who were older than 49 years at the time of their last evaluation, we again found no effect of ApoE ε4 on time to impairment (HR=1.06, .66-1.7). Among the non-White participants only, we also found no association between ApoE ε4 and time to impairment (HR= 1.48, .97-2.3).

Finally, we repeated the analyses separately for the White and non-White participants coding ApoE ε4 as either absent, one copy or two copies. Among the White participants the presence of either one or two copies of the ε4 allele was not associated with cognitive impairment (one copy= .99(.77-1.3); two copies= 1.04 (.49-2.2). Among the non-Whites, there was a paradoxical effect of one copy [HR= 1.60 (1.0 – 2.5)] compared to carrying two copies of the ε4 allele [HR=.45 (.06-3.02)], which may be due to the difference in sample sizes (no copies: n = 244; 1 copy: 93; 2 copies: 10).

Discussion

The purpose of this study was to replicate and extend previous findings related to the (lack of) association between ApoE ε4 and critical outcomes in the context of HIV disease. We found a significant increase in the rate of ε4 among non-White participants (primarily African-American), and -- once we controlled for race -- we found no significant associations between ApoE genotype and either HIV infection, age, death, or neuropsychological dysfunction. In particular, our analysis of incident neuropsychological impairment among those men who were classified as cognitively normal at their first NP study visit found no association between ApoE genotype and the development of cognitive dysfunction.

There are a variety of factors that can affect time to NP impairment, and these factors are themselves inter-correlated. However, within the constraints of this study, including differences in recruitment cohorts, age, race and potentially confounding medical conditions, we did not find an effect of ApoE genotype on time to cognitive impairment from a state of normal cognition. This does not preclude the possibility that ApoE may have an impact on specific cognitive functions or cognitive domains. However, our findings indicate that the transition from normal to impaired cognition is unaffected by ApoE ε4. These findings are consistent with the report from the Wiulfred Hall Study reporting no effect of ε4 on time to HIV-Associated Dementia (Burt, Agan et al. 2008).

While future, more fine-grained analyses might well find important roles of ApoE in various outcomes in HIV disease (e.g., cardiovascular), it is reassuring that -- at least to the extent that we were able to examine it here in terms of cognition -- ApoE appears to behave the same in HIV-infected individuals as it does in the uninfected men. It is important to note that the men in our study were in their mid-30s at the time of entry, and it is only recently (and in the context of combination antiretroviral therapy) that factors related to cholesterol metabolism and cardiovascular risk may become critical outcome variables (cf. (Kingsley, Cuervo-Rojas et al. 2008). However, it is important to reiterate that the follow-up of these participants averaged of 12.6 years (range: 0.8 – 26.4) between the first and last evaluations, and the average age was 48.1 years (range: 21.7 – 87.05) at the last evaluation.

Our failure to find an association between ApoE genotype, age, and cognitive impairment is at odds with some reports (Spector, Singh et al. 2010, Hoare, Westgarth-Taylor et al. 2012, Soontornniyomkij, Moore et al. 2012, Panos, Hinkin et al. 2013). However, the discrepancy may be, in part, due to the fact that these other reports have detailed cross-sectional analyses which may be affected by selective survival (i.e., the older infected men may be more likely to have had a longer history of uncontrolled HIV replication and thus entered any study with greater degree of CNS involvement). Our longitudinal analysis of time to develop cognitive impairment thus strengthens the conclusions by others (Andres, Feger et al. 2010, Joska, Combrinck et al. 2010, Sun, Abadjian et al. 2010, Morgan, Woods et al.) that within the age band tested (i.e., primarily younger than 65 years), ApoE ε4 genotype does not differentially impact HIV-infected individuals.

Further, some studies have reported finding interactions between HIV disease, age, and ApoE status [cf. (Valcour, Shiramizu et al. 2008, Panos, Hinkin et al. 2013)]; we found no such associations here. Again, this may be due, in part, to the fact that we adjusted our estimates for race as well as for cohort of entry, which adjusts for survivor bias. However, when we analyzed data only from men alive in December, 2012, (i.e., ignoring effects of selective survival), we still found no association with age (See Supplemental Table E3B).

One weakness of the MACS cohort relates to the racial distribution between the two recruitment cohorts (Becker, Kingsley et al. 2014); C1 was primarily White men having sex with men, and C2 had a significantly higher proportion of minority participants, many of whom were injection drug users. We also found that the rate of ε4 was higher among minority participants in C2 than among minority participants in C1; the reason for this is unclear (and may be a sampling artifact). These factors likely play an important role in explaining the small effects of ApoE on incident cognitive function in the minority subjects only, and primarily in C2. It will be important to replicate these analyses in large samples of African-Americans with and without HIV disease to determine whether any of the APOE alleles confer differential risk of impairment or death [cf., (Lee, Tang et al. 2001)].

Another weakness of our study is that we did not complete an *a priori* power analysis, in part because a pilot study (to estimate the effect size) wasn't feasible (however, see (Hoenig and Heisey 2001, Kraemer, Mintz et al. 2006, Moore, Carter et al. 2011). However, if we were to assume that our measured Hazard Ratio of 1.11 is reasonable, and use a raw standard deviation of (log(1.4)-log(1.11))/1.96=0.11, with $\alpha = 0.05$, we would have needed

60,000 men for 80% power to detect an association (http://www.stata.com/manuals13/ststpowercox.pdf). From this we conclude that, based on our data, any effect of ε4 is small.

In conclusion, our results have replicated and strengthened prior findings of the lack of association between ApoE ε4 and cognitive outcomes in HIV disease. This does not suggest that Apoε4 is unimportant among individuals over the age of 65 years or that it will not confer greater risk for non-HIV-associated neurodegenerative conditions. It *does* suggest that the phenomenon of accelerated aging we know applies to HIV infection does not seem to extend to the ApoE ε4 effect. Further, given that the MACS includes only men, there may be sex differences in ApoE ε4 effects that could not be examined here [cf. (Beydoun, Beydoun et al. 2013, Kulminski, Arbeev et al. 2014)]. However, within the specific constraints of the various outcomes examined in the literature, it appears reasonable to conclude that the ApoE ε4 allele is not significantly interacting with HIV serostatus to increase risk of incident cognitive impairment or death.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Descriptive Statistics by Cohort, Race, and ApoE ε4 Status at First NP Visit

Cohort	1				2			
Race	Minority		White		Minority		White	
ε4 Present	No	Yes	No	Yes	No	Yes	No	Yes
N (%)	231 (70.2)	98 (29.8)	2377 (77.1)	705 (22.9)	342 (65.4)	181(34.6)	262 (76.8)	79 (23.2)
Age [4]	32.09 (7.1)	32.14 (7.1)	33.79 (7.5)	33.55 (7.6)	38.29 (8.6)	39.02 (8.6)	36.78 (10)	38.47 (9.8)
Study Status [1]	31.60 (73)	26.53 (26)	33.49 (796)	34.04 (240)	77.19 (264)	74.03 (134)	82.82 (217)	82.82 (65)
HIV Infected [2]	51.08 (118)	50.00 (49)	34.29 (815)	34.33 (242)	57.60 (197)	58.01 (105)	46.95 (123)	50.63 (40)
AIDS [2]	23.38 (54)	22.45 (22)	28.19 (670)	31.21 (220)	6.43 (22)	7.18 (13)	3.44 (9)	2.53 (2)
AIDS Death [5]	81.33 (61)	80.56 (29)	80.42 (649)	84.40 (211)	29.63 (8)	55.56 (5)	28.57 (2)	0.00 (0)
cART [3] (% of HIV+)	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)	65.48 (129??)	70.48 (74)	65.85 (81)	80.00 (32)
Education (Years) [4]	15.54 (2.4)	15.15 (2.5)	15.96 (2.3)	15.93 (2.4)	13.06 (2.3)	12.96 (2.2)	15.53 (2.9)	15.12 (2.7)
CES-D	10.93 (9.5)	9.96 (6.8)	9.57 (8.6)	9.49 (8.4)	14.83 (12)	15.42 (12)	12.78 (11)	11.81 (12)
Ever Classified Cognitively Impaired [2]	30.83 (37)	38.78 (19)	46.71 (674)	48.83 (209)	59.18 (187)	67.65 (115)	43.44 (106)	43.42 (33)

[1] Active as of 12/31/2012 (Percent (N))

[2] Percent (N) Yes or Present

[3] Combination antiretroviral therapy (cART)

[4] Mean (standard deviation)

[5] Death due to AIDS related condition.

Table 2

Unadjusted Associations Between APOE ε4 Genotype, Cognition and Death as Function of Race [1]

	Caucasian			Minority		
	ε4−	ε4+	Effect Size [2]	ε4−	ε4+	Effect Size [2]
N=	1301	380		376	147	
Age	37.7 (8.4)	38.3 (8.9)	.06	42.0 (10.7)	40.5 (10.4)	.13
Education [3]	15.8 (2.4)	15.8 (2.5)	.03	14.1 (2.7)	13.8 (2.5)	.22
HIV Status [4]	39.8 (518)	41.8 (159)	1.09 (.86-1.37)	43.9 (165)	51.7 (76)	1.37 (.93-2.00)
Alive [5]	70.8 (921)	73.7 (280)	1.15 (.89-1.49)	88.8 (334)	87.1 (128)	.85 (.47-1.52)
Cognitive Impairment [5]	33.8 (440)	33.7 (128)	.99 (.78-1.27)	31.4 (118)	35.4 (52)	1.20 (.80-1.79)
Confounding Conditions [4]	32.0 (416)	34.5 (131)	1.12 (.88-1.43)	35.1 (132)	29.9 (44)	.79 (.52-1.19)

[1] Among individual cognitively normal at first evaluation.

[2] Relative Risk for categorical variables; Cohen's *d* for continuous variables.

[3] Mean (standard deviation)

[4] Percent (N) infected.

[5] Percent (N) Yes or Present.

Table 3

Cox Regression Models of Time to Death Hazard Ratios and 95% Confidence Interval

	Model 1	Model 2	Model 3
Age at Entry	.95(.94-.96) *	.95(.94-.96) *	.97(.96-.98) *
Race (Caucasian)	2.48(1.9-3.2) *	2.47(1.9-3.2) *	1.71(1.3-2.2) *
HIV Infected	5.00(4.2-6.0) *	5.00(4.2-6.0) *	5.44(4.6-6.5) *
ApoE ε4 (present)		.99(.82-1.2)	1.01(.84-1.2)
Cohort (C2)			.24(.17-.35) *

p<.05

Table 4

Cox Regression Models of Incident Cognitive Impairment Hazard Ratios and 95% Confidence Interval

	Model 1	Model 2	Model 3
Age	1.04 (1.03-1.06)*	1.04 (1.03-1.06)*	1.04 (1.03-1.05)*
Education (Years)	.98 (.94-1.02)	.98 (.94-1.02)	.99 (.95-1.03)
Race (Caucasian)	.93 (.74-1.2)	.93 (.74-1.2)	1.09 (.86-1.4)
HIV Infected	1.24 (1.0-1.5)*	1.24 (1.0-1.5)*	1.24 (1.0-1.5)*
ApoE ε4 (Present)		1.11 (.89-1.4)	1.11 (.89-1.4)
Cohort (C2)			.98 (.76 – 1.26)

* $p < .05$