APOE $\epsilon 4$ modifies the relationship between infectious burden and poor cognition

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Abstract

Objective

We investigated whether *APOE* $\epsilon 4$ is an effect modifier of the association between infectious burden (IB) and poor cognition in a multiethnic cohort, the Northern Manhattan Study.

Methods

IB was assessed by a quantitative weighted index of exposure to common pathogens associated with vascular risk, infectious burden index (IBI), and by serology for individual infections. Cognition was assessed by completion of the Mini-Mental State Examination at baseline and a full neuropsychological test battery after a median follow-up of approximately 6 years. Adjusted linear and logistic regressions estimated the association between IBI and cognition, with a term included for the interaction between *APOE* $\epsilon 4$ and IBI.

Results

Among those with full neuropsychological test results ($n = 569$), there were interactions between IBI and *APOE* $\epsilon 4$ ($p = 0.07$) and herpes simplex virus 1 (HSV-1) and *APOE* $\epsilon 4$ ($p = 0.02$) for processing speed. IBI was associated with slower processing speed among non- $\epsilon 4$ carriers ($\beta = -0.08$ per SD change in IBI, 95% confidence interval [CI] -0.16 to -0.01), but not among *APOE* $\epsilon 4$ carriers ($\beta = 0.06$ per SD change in IBI, 95% CI -0.08 to 0.19). HSV-1 positivity was associated with slower processing speed among non- $\epsilon 4$ carriers ($\beta = -0.24$, 95% CI -0.45 to -0.03), but not among *APOE* $\epsilon 4$ carriers ($\beta = 0.27$, 95% CI -0.09 to 0.64).

Conclusions

Potential effect modification by the *APOE* $\epsilon 4$ allele on the relationship of infection, and particularly viral infection, to cognitive processing speed warrants further investigation.

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Glossary

AD = Alzheimer disease; CI = confidence interval; HSV = herpes simplex virus; IB = infectious burden; IBI = infectious burden index; MMSE = Mini-Mental State Examination; NOMAS = Northern Manhattan Study.

Chronic infection has been linked to poor cognition or dementia in previous studies,^{1–9} including the Northern Manhattan Study (NOMAS). We previously found an association between an infectious burden index (IBI), a composite serologic measure of exposure to common pathogens linked to stroke risk, and poor cognitive performance on global cognitive measures.² In a subsequent study in the NOMAS, which used detailed full neuropsychological testing, we found an association between infectious burden (IB) and the executive function domain and also decline in memory over time.³ There is accumulating evidence of a link, in particular, between Herpesviridae and Alzheimer disease (AD),^{5,7,8} which has led to 2 clinical trials of antiviral therapy in patients with AD.^{10,11}

Another independent risk factor for poor cognition is *APOE* $\epsilon 4$, 1 of 3 common allelic variants of the *APOE* gene ($\epsilon 2$, $\epsilon 3$, and $\epsilon 4$) located on chromosome 19q13.2. *APOE* functions in regulating lipid metabolism and has wide-ranging effects on multiple organ systems.¹² One copy of the *APOE* $\epsilon 4$ allele increases AD risk approximately 2-fold, whereas 2 *APOE* $\epsilon 4$ alleles increase AD risk approximately 5-fold.¹³ There is evidence that the strength of this association may be modified by race/ethnicity,^{13–15} with greater variability of results among African Americans.¹³

We might expect that *APOE* $\epsilon 4$ carrier status and evidence of chronic infection confer additive, increased risk for worse cognitive outcomes. Of interest, there is epidemiologic evidence of an unexpected interaction between IB and *APOE* $\epsilon 4$ carrier status, suggesting a possible protective effect of *APOE* $\epsilon 4$ against infection and its chronic cognitive sequelae. One study of an Amazonian cohort of forager-horticulturalists found that amongst those with high parasitic burden, *APOE* $\epsilon 4$ carriers had better cognitive performance than non- $\epsilon 4$ carriers.¹⁶ Another study in a large rural Ghanaian population found that *APOE* $\epsilon 4$ appeared to protect against infection and promote fertility among women exposed to high pathogen levels.¹⁷ These results are consistent with observations from multiple studies of patients with chronic hepatitis showing that those with the *APOE* $\epsilon 4$ genotype appeared to have slower progression of disease and better outcomes.^{18–22}

Few studies in a Western population have explicitly examined the possible interaction between IB and *APOE* $\epsilon 4$ carrier status on overall risk for poor cognition. A protective effect of *APOE* $\epsilon 4$ against infection is plausible as there is evidence that beta-amyloid acts as an innate immune protein in response to infection.²³ The primary objective of our study is to examine whether *APOE* $\epsilon 4$ modifies the association between IB and cognitive outcome in a multiethnic US cohort. Specifically, we hypothesize that the association between IB and poor

cognition is weaker in *APOE* $\epsilon 4$ carriers than in *APOE* $\epsilon 4$ noncarriers. Furthermore, in an exploratory secondary analysis, we hypothesize that the interaction between IB and *APOE* $\epsilon 4$ on cognitive outcomes varies by race/ethnic group, with a stronger modifying association among whites.

Methods

Standard protocol approvals, registrations, and patient consents

The institutional review boards at Columbia University Medical Center and the University of Miami both approved this study. All participants gave informed consent to participate.

Description of the study population and baseline data collection

NOMAS is a prospective cohort study consisting of 3,298 stroke-free participants enrolled between 1993 and 2001, as previously described.²⁴ Briefly, participants were recruited from individuals residing in northern Manhattan, NY, for at least 3 months in a household with a telephone, who were aged ≥ 40 years at the time of enrollment, and had no previous diagnosis of stroke.

Data collection at baseline included basic demographic information, medical history including vascular risk factors, and blood samples. Interviews were conducted by trained bilingual research assistants in English or Spanish. Blood samples were later analyzed for infectious serologies, as below. From a subset of 984 participants with both serologic data and *APOE* $\epsilon 4$ data, 977 participants had all covariates of interest and were included in the present study.

Assessment of IB

Blood samples collected at enrollment were centrifuged and frozen at -70°C in 1 mL aliquots until the time of analysis. Serologies were measured using ELISA for *Chlamydia pneumoniae* (Savyon Diagnostics, Ashdod, Israel), *Helicobacter pylori*, cytomegalovirus (CMV, Wampole Laboratories, Princeton, NJ), and herpes simplex virus 1 and 2 (HSV-1 and -2, Focus Diagnostics, Cypress), as previously described.²⁴ Immunoglobulin G titers were used for all pathogens except *C. pneumoniae*, for which immunoglobulin A titers were used based on results of previous studies.^{25,26} Testing was performed in batches, with laboratory technicians blinded to clinical status. Not all participants had blood available for the measurement of all 5 serologies. Therefore, a subsample of 1,625 participants was included in the calculations of the IBI.

The IBI, a quantitative weighted index associated with vascular risk, was created, as previously described.^{3,24} Briefly, multivariable-

adjusted Cox models were used to estimate regression coefficients and 95% confidence intervals (CIs) for the association between each serologic result (positive vs negative) and risk of stroke, with all other serologies included as covariates. Each parameter estimate represents the strength of the association between the individual serologic result and risk of stroke. These parameter estimates were then used to construct the weighted IBI. The IBI has been found to be associated with cognitive outcomes in previous NOMAS studies.^{2,3}

Cognitive assessment

Cognitive function was ascertained using the Mini-Mental State Examination (MMSE)²⁷ at the baseline visit and a full neuropsychological test battery on a follow-up visit at a median of 6 years 3 months after baseline.³ Testing was performed by bilingual trained research assistants in English or Spanish, depending on the native language spoken in the home environment. The neuropsychological test battery assessed cognitive domains of memory, processing speed, language, and executive function, and domain-specific *z* scores were calculated. Higher *z* scores in memory, processing speed, language, and executive function indicate better performance in those domains. Tests used for each domain were selected based on an exploratory factor analysis and previous findings.²⁸ Specific tests selected for each domain have been previously described in detail.³ Briefly, memory was assessed using scores on a 12-word 5-trial list-learning task.²⁸ Executive function was assessed using subscores on the Color Trails Test²⁹ and the Odd-Man-Out Test.³⁰ Processing speed was assessed by the Grooved Pegboard task (nondominant hand),³¹ the Color Trails Test Form 1,²⁹ and the Visual-Motor Integration Test.³² Language was assessed using 3 tests: a test of naming (modified Boston Naming Test),³³ a test of category fluency (Animal Naming),³⁴ and a test of phonemic fluency (C, F, L in English speakers and F, A, S in Spanish speakers).³⁴

APOE ε4 assessment

APOE ε4 allele carrier status was assessed by *Hha*I digestion of PCR products amplified from genomic DNA. APOE ε4 was entered into regression models as a dichotomous variable (presence of 1 or 2 copies of the APOE ε4 allele vs absence of the APOE ε4 allele).

Covariates

Race/ethnicity was ascertained by self-report based on questions modeled after the U.S. Census and conforming to standard definitions outlined by Directive 15.³⁵ Educational attainment was assessed by self-report at baseline and at the time of neuropsychological testing. Health insurance status (Medicaid or no insurance vs Medicare without Medicaid or private insurance) was obtained by self-report at baseline. Physical activity was evaluated by an in-person questionnaire, which was adapted from the National Health Interview Survey of the National Center for Health Statistics.³⁶ Physical activity was defined as a dichotomous variable: activity vs no activity in a typical 2-week period. Standardized questions adapted from the Behavioral Risk Factor Surveillance System by the Centers

for Disease Control and Prevention were used to assess for the presence of hypertension, hypercholesterolemia, and diabetes mellitus. Hypertension was defined either as participant self-report of hypertension, blood pressure measurement of 140/90 mm Hg or greater, or use of antihypertensive medication. Hypercholesterolemia was defined either as participant self-report of hypercholesterolemia, total cholesterol level greater than 200 mg/dL, or cholesterol-lowering medication use. Diabetes mellitus was defined as participant self-report of diabetes mellitus, fasting glucose of 126 mg/dL or greater, or use of insulin or oral antidiabetic medications.

Statistical analyses

The IBI and individual infectious serologies were the exposures of interest, and cognitive function was the outcome of interest. MMSE scores were analyzed as both continuous and a binary outcome (MMSE ≤ 24 vs > 24), based on previously defined thresholds to facilitate clinical interpretation.^{2,37} Cognitive domain *z* scores were analyzed as continuous outcomes. Multivariate linear regression models were constructed to examine the association between infection and both MMSE score and each cognitive domain. Logistic regression was conducted to examine the association between infection and a binary MMSE score. Model 1 assessed the unadjusted association between infection and cognition. Model 2 adjusted for age, sex, race/ethnicity, education, and health insurance status (a proxy measure of socioeconomic status). Models of neuropsychological testing used the education self-reported by participants at this visit. Model 3 additionally adjusted for physical activity, hypertension, diabetes mellitus, and hypercholesterolemia. The rationale for selection of covariates was based on the literature, biological plausibility, and previous experience with the cohort. Interaction between IB and APOE ε4 was assessed by entering the interaction term for IB × APOE ε4 into regression models. In an exploratory secondary analysis, the interaction between IB and APOE ε4 was examined, stratified by race/ethnicity. All hypothesis testing was 2 sided, and *p* values less than 0.05 (less than 0.10 for interaction terms) were considered to be significant.³⁸ All analyses were performed using SAS version 9.1.3 (SAS Institute, Cary, NC).

Data availability

Anonymized data will be made available to qualified investigators on request for purposes of replicating procedures and result. Further information regarding data from the NOMAS cohort and contact information can be found at northernmanhattanstudy.org.

Results

Population characteristics

There were 977 participants in the primary analysis with MMSE as the cognitive outcome. Of those, 26% were APOE ε4 carriers. The distribution of IBI and most individual infections did not vary by APOE status. APOE ε4 carriers had slightly higher prevalence of *C. pneumoniae* than noncarriers.

The proportions of *APOE* $\epsilon 4$ and non- $\epsilon 4$ carriers differed by race/ethnicity. Blacks were more likely than whites to be *APOE* $\epsilon 4$ carriers, whereas a greater proportion of whites were found among non- $\epsilon 4$ carriers. *APOE* $\epsilon 4$ and non- $\epsilon 4$ carriers did not differ significantly by age, sex, education, health care insurance status, or by the presence of vascular risk factors (physical activity, hypertension, diabetes, and hypercholesterolemia). *APOE* $\epsilon 4$ carriers had lower memory scores and worse performance on the MMSE (mean 25.75) at baseline compared with non- $\epsilon 4$ carriers (mean MMSE 26.35) (table 1). Of 977 participants, 569 participants underwent neuropsychological testing at the follow-up examination. Baseline characteristics of participants who underwent neuropsychological testing are described in table e-1 (links.lww.com/NXG/A278). Participants who had neuropsychological testing ($n = 569$) did not differ significantly from participants who did not have neuropsychological testing ($n = 408$) in terms of IB, but were on average younger and more likely to be Hispanic (table e-2, links.lww.com/NXG/A278).

***APOE* $\epsilon 4$ as a modifier of the association between IB and cognition**

There was an interaction between IB and *APOE* $\epsilon 4$ for processing speed ($p = 0.07$). IB was associated with slower processing speed among non- $\epsilon 4$ carriers ($\beta = -0.08$ per SD change in IB, 95% CI -0.16 to -0.01 , $p = 0.03$), but not among *APOE* $\epsilon 4$ carriers ($\beta = 0.06$ per SD change in IB, 95% CI -0.08 to 0.19 , $p = 0.42$), after adjusting for sociodemographic and vascular risk factors. No interaction was found between IB and *APOE* $\epsilon 4$ for MMSE or for neuropsychological test results in the memory, language, or executive function domains (table 2). In an exploratory analysis of specific infections and cognition, positive HSV-1 serology was also associated with a slower processing speed among non- $\epsilon 4$ carriers ($\beta = -0.24$, 95% CI -0.45 to -0.03), but not among *APOE* $\epsilon 4$ carriers ($\beta = 0.27$, 95% CI -0.09 to 0.64). *C. pneumoniae* infection and HSV-2 infection were both associated with worse memory among *APOE* $\epsilon 4$ carriers, but not among non- $\epsilon 4$ carriers (table 3).

Exploratory analysis of *APOE* $\epsilon 4$ as a modifier stratified by race/ethnicity

The modification effects of *APOE* $\epsilon 4$ for the association between infection and cognition do not differ by race-ethnicity (p for difference >0.10 with 2 d.f.). However, there was a trend toward the effect of modification being more apparent among whites than other race/ethnicity groups. Among whites ($n = 76$), there was an interaction between IB and *APOE* $\epsilon 4$ for processing speed ($p = 0.01$). IB was associated with slower processing speed among non- $\epsilon 4$ carriers ($\beta = -0.24$ per SD change in IB, 95% CI -0.39 to -0.08), but not among *APOE* $\epsilon 4$ carriers ($\beta = 0.28$ per SD change in IB, 95% CI -0.09 to 0.64), after adjusting for sociodemographic and vascular risk factors. Similarly, for whites, HSV-1-positive participants who were non- $\epsilon 4$ carriers were more likely to have slower processing speed ($\beta = -0.34$, 95% CI -0.76 to 0.07) than *APOE* $\epsilon 4$ carriers ($\beta = 1.26$, 95% CI 0.19 to 2.32), after adjusting for sociodemographic and vascular

risk factors (interaction $p = 0.01$). Among blacks and Hispanics, no interaction between IB and *APOE* $\epsilon 4$ was found for any cognitive domains, except for the memory domain among Hispanics ($\epsilon 4$ carriers: $\beta = -0.19$, 95% CI -0.38 to 0.00 ; non- $\epsilon 4$ carriers: $\beta = 0.00$, 95% CI -0.11 to 0.11 ; $p = 0.09$).

Discussion

We found limited evidence of effect modification by *APOE* status for the effect of IB, and specifically HSV-1, on cognition. Although *APOE* $\epsilon 4$ did not modify the association between IB and most domains of cognition in our multiethnic cohort, it did modify the association of IB and HSV-1 on the domain of processing speed. Specifically, IB and HSV-1 were associated with slower processing speed among non- $\epsilon 4$ carriers, but not among *APOE* $\epsilon 4$ carriers. The effect modification was more apparent among whites, although we did not find a statistically significant difference across the 3 race/ethnicity groups due to the relatively small sample size. We also found an interaction between *C. pneumoniae* infection, HSV-2 infection, and *APOE* $\epsilon 4$ on the memory domain. The interaction between *APOE* $\epsilon 4$ and infection likely depends on both IB and specific type of infection. Further research is needed to clarify the modification effect of *APOE* $\epsilon 4$ on different types of infections.

Although there is suggestive evidence of a link between HSV^{5,7} (more broadly Herpesviridae^{23,39}) and dementia, fewer studies have explicitly evaluated the interaction between HSV and *APOE* $\epsilon 4$ on risk for dementia or poor cognition. One study found an interaction between *APOE* $\epsilon 4$, Herpesviridae seropositivity, low education, and the development of cognitive impairment.⁴⁰ There is also evidence that *APOE* $\epsilon 4$ allele frequency is higher in patients with AD positive for HSV-1 than for patients with AD negative for HSV-1.⁴¹ We conjecture that the co-occurrence of *APOE* $\epsilon 4$ and herpes infection can be understood as either *APOE* $\epsilon 4$ leading to increased susceptibility to infection or survivor bias. One study of elderly French participants without dementia, however, found no effect modification of *APOE* $\epsilon 4$ with HSV on risk for AD. The same study found an association between anti-HSV IgM (but not IgG) and higher risk of AD.⁴² These findings are in contrast to evidence from animal studies, which suggest that *APOE* $\epsilon 4$ facilitates the invasiveness of HSV-1 into the brain.⁴³ There is evidence that beta-amyloid functions as an innate immune protein and is capable of exerting antimicrobial effects by entrapping herpes virus in a transgenic AD mouse model and in human neuronal cell culture.²³ Additional studies are necessary to clarify the potential interaction between Herpesviridae infection and *APOE* $\epsilon 4$ on cognition. Given our limited sample size, the possibility that these isolated positive findings are due to chance cannot be fully excluded. Our findings were, however, consistent with previous studies that have found a protective effect of *APOE* $\epsilon 4$ against infection^{18–22} as well as previous studies that suggest beneficial effects of *APOE* $\epsilon 4$ during childhood development (when infections are particularly common).^{44,45}

Table 1 Characteristics^a of participants

N	APOE ε4 carrier status				p Value ^d
	ε4 carriers		Non-ε4 carriers		
	Participants (n = 253)	Median IBI (IQR)	Participants (n = 724)	Median IBI (IQR)	
Infectious burden (IBI)	0.97 ± 0.34	NA	0.99 ± 0.34	NA	0.580
Sociodemographic risk factors					
Age, y	68.04 ± 9.45	NA	67.71 ± 9.85	NA	0.640
Age <70 y	153 (60%)	1.04 (0.66–1.26)	437 (60%)	1.08 (0.91–1.26)	
Age ≥70 y	100 (40%)	1.08 (0.88–1.26)	287 (40%)	1.08 (0.91–1.26)	
Female sex	153 (60%)	1.08 (0.82–1.26)	480 (66%)	1.08 (0.91–1.26)	0.095
Male sex	100 (40%)	1.08 (0.82–1.26)	244 (34%)	1.08 (0.67–1.26)	
Non-Hispanic white	37 (15%)	0.91 (0.44–1.08)	154 (21%)	0.88 (0.40–1.08)	0.001
Non-Hispanic black	72 (28%)	1.13 (1.00–1.26)	135 (19%)	1.08 (0.91–1.26)	
Hispanic	133 (53%)	1.08 (0.82–1.26)	417 (58%)	1.08 (1.00–1.26)	
Other	11 (4%)	NA	18 (2%)	NA	
Education (≥high school)	119 (47%)	1.00 (0.58–1.17)	335 (46%)	1.00 (0.66–1.17)	0.834
Education (<high school)	134 (53%)	1.08 (0.91–1.26)	389 (54%)	1.13 (1.00–1.26)	
Medicaid or no insurance	115 (45%)	1.08 (0.82–1.26)	341 (47%)	1.08 (1.00–1.26)	0.652
Medicare or private insurance	138 (55%)	1.08 (0.82–1.26)	383 (53%)	1.04 (0.82–1.17)	
Vascular risk factors					
No physical activity	116 (46%)	1.08 (0.82–1.26)	324 (45%)	1.08 (0.91–1.26)	0.762
Physical activity	137 (54%)	1.08 (0.82–1.26)	400 (55%)	1.08 (0.82–1.26)	
No hypertension	77 (30%)	1.04 (0.82–1.17)	206 (28%)	1.08 (0.91–1.26)	0.550
Hypertension	176 (70%)	1.08 (0.82–1.26)	518 (72%)	1.08 (0.86–1.26)	
No diabetes mellitus	205 (81%)	1.08 (0.82–1.26)	587 (81%)	1.08 (0.86–1.26)	0.986
Diabetes mellitus	48 (19%)	1.11 (0.91–1.26)	137 (19%)	1.08 (0.91–1.26)	
No hypercholesterolemia	89 (35%)	1.08 (0.82–1.17)	262 (36%)	1.08 (0.91–1.26)	0.773
Hypercholesterolemia	164 (65%)	1.08 (0.82–1.26)	462 (64%)	1.08 (0.86–1.26)	
MMSE ^b					
MMSE score	25.75 ± 4.18	NA	26.35 ± 3.45	NA	0.026
MMSE <24	58 (23%)	1.08 (1.00–1.26)	146 (20%)	1.17 (1.00–1.26)	
MMSE ≥24	195 (77%)	1.08 (0.82–1.26)	578 (80%)	1.08 (0.82–1.26)	
Neuropsychological test domain z scores ^c	ε4 carriers		Non-ε4 carriers		p Value
	Participants (n = 134)	Median IBI (IQR)	Participants (n = 435)	Median IBI (IQR)	
Memory	−0.21 ± 1.01	NA	0.00 ± 0.84	NA	0.022
Language	−0.10 ± 0.92	NA	−0.08 ± 0.81	NA	0.845
Processing speed	−0.09 ± 0.92	NA	−0.06 ± 0.90	NA	0.716
Executive function	−0.13 ± 0.89	NA	−0.06 ± 0.87	NA	0.426

Abbreviations: IB = infectious burden; IBI = infectious burden index; IQR = interquartile range; MMSE = Mini-Mental State Examination.

^a Values are mean ± SD, n (%), or median (IQR).^b MMSE at baseline visit.^c Neuropsychological testing at follow-up visit, at a median of 6 years 3 months after baseline.^d χ^2 test/Student *t* test.

Table 2 Association of infectious burden index with cognitive function, stratified by *APOE* $\epsilon 4$ carrier status^a

	Model 1 (unadjusted)			Model 2 ^d (adjusted for sociodemographic risk factors)			Model 3 ^e (adjusted for sociodemographic and vascular risk factors)		
	$\epsilon 4$ carriers	Non- $\epsilon 4$ carriers	Interaction <i>p</i> value	$\epsilon 4$ carriers	Non- $\epsilon 4$ carriers	Interaction <i>p</i> value	$\epsilon 4$ carriers	Non- $\epsilon 4$ carriers	Interaction <i>p</i> value
Mean difference in baseline MMSE^b per SD in IBI									
MMSE	-0.71 (-1.15 to -0.26)	-0.74 (-1.00 to -0.48)	0.90	-0.25 (-0.66 to 0.15)	-0.17 (-0.42 to 0.09)	0.73	-0.26 (-0.66 to 0.15)	-0.17 (-0.42 to 0.09)	0.71
MMSE ≥ 24	0.72 (0.51 to 1.01)	0.56 (0.44 to 0.72)	0.24	0.86 (0.59 to 1.26)	0.75 (0.57 to 0.99)	0.55	0.87 (0.60 to 1.27)	0.76 (0.57 to 1.00)	0.56
Mean difference in neuropsychological test domains^c per SD in IBI									
Memory	-0.28 (-0.43 to -0.13)	-0.14 (-0.22 to -0.05)	0.11	-0.12 (-0.25 to 0.01)	-0.03 (-0.10 to 0.05)	0.23	-0.10 (-0.23 to 0.03)	-0.03 (-0.11 to 0.05)	0.35
Language	-0.27 (-0.41 to -0.12)	-0.22 (-0.30 to -0.15)	0.62	-0.10 (-0.21 to 0.02)	-0.03 (-0.10 to 0.03)	0.32	-0.09 (-0.20 to 0.02)	-0.04 (-0.10 to 0.03)	0.42
Processing speed	-0.17 (-0.34 to -0.01)	-0.17 (-0.25 to -0.08)	0.97	0.02 (-0.15 to 0.19)	-0.08 (-0.15 to 0.00)	0.21	0.06 (-0.08 to 0.19)	-0.08 (-0.16 to -0.01)	0.07
Executive function	-0.29 (-0.44 to -0.14)	-0.28 (-0.36 to -0.20)	0.85	-0.15 (-0.28 to -0.02)	-0.10 (-0.17 to -0.02)	0.45	-0.14 (-0.27 to -0.01)	-0.10 (-0.17 to -0.02)	0.57

Abbreviations: IBI = infectious burden index; MMSE = Mini-Mental State Examination.

^a Values are odds ratios (MMSE ≥ 24) or β -coefficients (all other outcomes) with corresponding 95% CIs and interaction term *p* values.

^b MMSE at baseline visit.

^c Neuropsychological testing at follow-up visit, at a median of 6 years 3 months after baseline.

^d Model 2 adjusted for age, sex, race/ethnicity, education, and health insurance status.

^e Model 3 additionally adjusted for physical activity, hypertension, diabetes mellitus status, and hypercholesterolemia status.

Of interest, in an exploratory secondary analysis, the strength of the interaction between *APOE* $\epsilon 4$ and infection and the magnitude of the effect of infection on cognition appeared to vary by race/ethnicity, although the difference across race/ethnicity groups was not statistically significant. Specifically, the modifying effect of *APOE* $\epsilon 4$ appeared to be the strongest among whites, also present among Hispanics, and absent among blacks. The presence of a differential effect by race/ethnicity despite the limited power of our exploratory analysis is striking and warrants further investigation in future studies.

It is possible that the overall lack of positive findings in our study may be related to the relatively smaller proportion of whites in the NOMAS cohort (21%), vs blacks (24%) and Hispanics (52%). Our findings of a difference by race/ethnicity are consistent with previous studies, which have found a stronger association between *APOE* $\epsilon 4$ and poor cognitive outcomes among whites than among blacks.¹³ Studies in blacks have yielded mixed results, with some family aggregation or clinic-based studies finding an association between *APOE* $\epsilon 4$ and poor cognitive outcomes, and other population-based studies finding little to no association.¹³

The precise mechanism for the potential protective effect of *APOE* $\epsilon 4$ on infection and its relation to cognition remains uncertain, although there is evidence of an antimicrobial effect of beta-amyloid fibrils/deposits.²³ The thrifty gene hypothesis⁴⁶ posits that certain apparently detrimental genotypes (such as *APOE* $\epsilon 4$) in high-income populations may have previously conferred a selective survival advantage in preindustrial populations. Specifically, *APOE* $\epsilon 4$'s potential protective effects against infection and in favor of fertility may have caused it to be selected for in a preindustrial population exposed to higher burden of infections and at greater risk for early demise due to childhood infections. With the rise of industrialization and changing lifestyles (cleaner environments with lower pathogen burden), individuals are living longer, but also at greater risk for dementia, due to the unwanted detrimental effects of *APOE* $\epsilon 4$ at older ages (e.g., poor cognition and dementia).

The major strength of our study is our study design. Few studies in a Western population have directly examined the possible interaction between IB and *APOE* $\epsilon 4$ carrier status on overall risk for poor cognition. The 2 previous studies that had explicitly examined a potential benefit of *APOE* $\epsilon 4$

Table 3 Association of specific infections with neuropsychological test domains, stratified by APOE $\epsilon 4$ carrier status^{a,b}

	Model 1 (unadjusted)		Model 2 ^c (adjusted for sociodemographic risk factors)		Model 3 ^d (adjusted for sociodemographic and vascular risk factors)	
	$\epsilon 4$ carriers	Non- $\epsilon 4$ carriers	$\epsilon 4$ carriers	Non- $\epsilon 4$ carriers	$\epsilon 4$ carriers	Non- $\epsilon 4$ carriers
HSV-1						
Memory	-0.19 (-0.63 to 0.25)	-0.23 (-0.48 to 0.02)	0.17 (-0.19 to 0.54)	0.02 (-0.19 to 0.24)	0.18 (-0.18 to 0.55)	0.01 (-0.20 to 0.22)
Language	-0.46 (-0.87 to -0.05)	-0.41 (-0.64 to -0.18)	-0.02 (-0.34 to 0.30)	-0.01 (-0.20 to 0.17)	-0.02 (-0.34 to 0.30)	-0.03 (-0.22 to 0.16)
Processing speed	-0.06 (-0.52 to 0.40)	-0.37 (-0.62 to -0.12)	0.25 (-0.12 to 0.63)	-0.21 (-0.42 to 0.00)	0.27 (-0.09 to 0.64)	-0.24 (-0.45 to -0.03)
Executive function	-0.29 (-0.73 to 0.15)	-0.48 (-0.73 to -0.24)	0.16 (-0.22 to 0.53)	-0.07 (-0.29 to 0.14)	0.16 (-0.21 to 0.52)	-0.10 (-0.31 to 0.11)
HSV-2						
Memory	-0.24 (-0.56 to 0.07)	-0.09 (-0.26 to 0.08)	-0.31 (-0.57 to -0.05)	0.07 (-0.08 to 0.22)	-0.29 (-0.55 to -0.04)	0.06 (-0.08 to 0.21)
Language	-0.06 (-0.36 to 0.23)	-0.20 (-0.36 to -0.04)	-0.04 (-0.26 to 0.18)	0.10 (-0.03 to 0.23)	-0.04 (-0.26 to 0.19)	0.09 (-0.04 to 0.22)
Processing speed	0.02 (-0.31 to 0.35)	-0.18 (-0.35 to 0.00)	0.09 (-0.18 to 0.35)	-0.03 (-0.18 to 0.11)	0.11 (-0.16 to 0.37)	-0.04 (-0.19 to 0.10)
Executive function	-0.26 (-0.56 to 0.05)	-0.31 (-0.48 to -0.14)	-0.25 (-0.51 to 0.01)	-0.03 (-0.17 to 0.12)	-0.24 (-0.50 to 0.01)	-0.03 (-0.18 to 0.11)
<i>H. pylori</i>						
Memory	-0.05 (-0.35 to 0.26)	-0.16 (-0.33 to 0.01)	0.15 (-0.11 to 0.40)	-0.03 (-0.17 to 0.11)	0.16 (-0.09 to 0.41)	-0.02 (-0.16 to 0.12)
Language	-0.27 (-0.55 to 0.02)	-0.16 (-0.32 to 0.00)	-0.10 (-0.32 to 0.12)	0.00 (-0.12 to 0.13)	-0.10 (-0.32 to 0.12)	0.01 (-0.12 to 0.13)
Processing speed	-0.22 (-0.54 to 0.09)	-0.05 (-0.22 to 0.12)	-0.10 (-0.35 to 0.16)	0.00 (-0.14 to 0.14)	-0.09 (-0.34 to 0.16)	0.01 (-0.12 to 0.15)
Executive function	-0.02 (-0.32 to 0.29)	-0.12 (-0.28 to 0.05)	0.17 (-0.08 to 0.42)	0.06 (-0.08 to 0.20)	0.17 (-0.08 to 0.43)	0.07 (-0.07 to 0.21)
<i>C. pneumoniae</i>						
Memory	-0.34 (-0.66 to -0.02)	-0.07 (-0.24 to 0.10)	-0.30 (-0.57 to -0.04)	0.00 (-0.14 to 0.14)	-0.28 (-0.55 to -0.02)	0.00 (-0.15 to 0.14)
Language	-0.25 (-0.55 to 0.05)	-0.18 (-0.34 to -0.02)	-0.27 (-0.50 to -0.04)	-0.10 (-0.23 to 0.02)	-0.26 (-0.49 to -0.03)	-0.11 (-0.23 to 0.02)
Processing speed	-0.13 (-0.47 to 0.21)	-0.05 (-0.22 to 0.13)	-0.12 (-0.40 to 0.15)	-0.03 (-0.17 to 0.11)	-0.09 (-0.36 to 0.18)	-0.04 (-0.18 to 0.10)
Executive function	-0.29 (-0.61 to 0.03)	-0.03 (-0.20 to 0.15)	-0.33 (-0.59 to -0.06)	0.02 (-0.12 to 0.16)	-0.30 (-0.56 to -0.04)	0.01 (-0.13 to 0.15)

Continued

Table 3 Association of specific infections with neuropsychological test domains, stratified by APOE ε4 carrier status^{a,b} (continued)

	Model 1 (unadjusted)		Model 2 ^c (adjusted for sociodemographic risk factors)		Model 3 ^d (adjusted for sociodemographic and vascular risk factors)	
	ε4 carriers	Non-ε4 carriers	ε4 carriers	Non-ε4 carriers	ε4 carriers	Non-ε4 carriers
Cytomegalovirus						
Memory	−0.54 (−0.92 to −0.16)	−0.39 (−0.62 to −0.17)	−0.08 (−0.39 to 0.23)	−0.14 (−0.35 to 0.06)	−0.04 (−0.37 to 0.28)	−0.14 (−0.34 to 0.07)
Language	−0.59 (−0.95 to −0.24)	−0.55 (−0.76 to −0.34)	−0.14 (−0.43 to 0.14)	−0.07 (−0.25 to 0.11)	−0.12 (−0.41 to 0.16)	−0.08 (−0.26 to 0.11)
Processing speed	−0.49 (−0.90 to −0.08)	−0.44 (−0.67 to −0.21)	0.02 (−0.32 to 0.36)	−0.18 (−0.39 to 0.03)	0.09 (−0.24 to 0.43)	−0.17 (−0.38 to 0.03)
Executive function	−0.57 (−0.94 to −0.19)	−0.77 (−0.99 to −0.55)	−0.18 (−0.51 to 0.14)	−0.31 (−0.51 to −0.10)	−0.16 (−0.49 to 0.17)	−0.29 (−0.50 to −0.09)

Abbreviations: *C. pneumoniae* = *Chlamydia pneumoniae*; HSV-1 = herpes simplex virus 1; HSV-2 = herpes simplex virus 2; *H. pylori* = *Helicobacter pylori*.^a Values are β-coefficients with corresponding 95% CIs and *p* values.^b Neuropsychological testing at follow-up visit, at a median of 6 years 3 months after baseline.^c Model 2 adjusted for age, sex, race/ethnicity, education, and health insurance status.^d Model 3 additionally adjusted for physical activity, hypertension, diabetes mellitus status, and hypercholesterolemia status.

with infection on health outcomes were conducted in more homogenous populations (Amazonian forager-horticulturalists¹⁶ and rural Ghanaian¹⁷), and the generalizability of those results to a Western population was unclear. Another strength of our study is the use of a multiethnic population-based cohort. The NOMAS cohort includes a large proportion of Hispanic participants, who are often underrepresented in studies on cognition. Last, we were able to adjust for numerous demographic as well as vascular covariates (potential confounders) in our models.

One limitation of our study is the small proportion of whites in the cohort, considering that the association between APOE ε4 and cognition was most robust among whites. Future studies, which replicate these procedures in multiple cohorts, are needed to clarify race/ethnic differences for the modification effect of APOE ε4 between infection and cognitive outcomes. Another key limitation is that data on parasitic infection (or proxies for parasitic burden such as eosinophil count) were not available. Of note, the 2 previous studies^{16,17} that found a protective benefit of APOE ε4 for infection both used proxy markers (eosinophil count and open well as water source) to assess parasitic burden. It is possible that APOE ε4 may exert an even stronger protective benefit against certain infections or certain types of infections (parasitic) than other types of infections; however, we lacked the data on parasitic infections necessary to evaluate this possibility. To further examine the thrifty gene hypothesis as it relates to APOE ε4's effect on infection, future studies should seek to include a more comprehensive array of infectious measures, including measures of parasitic infections. Last, the possibility of residual unmeasured confounding exists, although we have accounted for a number of confounders, including education and health insurance status (proxies for socioeconomic status), as well as vascular risk factors. Future studies should ideally also include a measure of allostatic load, as stress has a significant influence on susceptibility to infection and reactivation of infection.

We found limited evidence that APOE ε4 modifies the association between IB and a measure of processing speed in a multiethnic cohort. The results of our hypothesis-generating study suggest that an antimicrobial role of the ε4 allele is possible. The effect of infection on risk for poor cognition among ε4 carriers warrants further investigation in other cohorts.

Disclosure

The authors report no disclosures. Go to [Neurology.org/NG](https://www.neurology.org/NG) for full disclosures.

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Kevin Strobino, MPH	Columbia University, New York City	Statistical analysis; data interpretation; and revision of the manuscript
Yeseon P. Moon, MS	Columbia University, New York City	Statistical analysis; data interpretation; and revision of the manuscript
Ying Kuen Cheung, PhD	Columbia University, New York City	Statistical analysis; data interpretation; and revision of the manuscript
Ralph L. Sacco, MD, MS	University of Miami, Florida	Data interpretation and revision of the manuscript
Yaakov Stern, PhD	Columbia University, New York City	Data interpretation and revision of the manuscript
Mitchell S.V. Elkind, MD, MS	Columbia University, New York City	Study idea, design, and planning of statistical analysis; data interpretation; and revision of the manuscript

References

- Strandberg TE, Pitkala KH, Linnavuori KH, Tilvis RS. Impact of viral and bacterial burden on cognitive impairment in elderly persons with cardiovascular diseases. *Stroke* 2003;34:2126–2131.
- Katan M, Moon YP, Paik MC, Sacco RL, Wright CB, Elkind MSV. Infectious burden and cognitive function: the Northern Manhattan Study. *Neurology* 2013;80:1209–1215.
- Wright CB, Gardener H, Dong C, et al. Infectious burden and cognitive decline in the Northern Manhattan Study. *J Am Geriatr Soc* 2015;63:1540–1545.
- Honjo K, van Reekum R, Verhoeff NPLG. Alzheimer's disease and infection: do infectious agents contribute to progression of Alzheimer's disease? *Alzheimers Dement* 2009;5:348–360.
- Qin Q, Li Y. Herpesviral infections and antimicrobial protection for Alzheimer's disease: implications for prevention and treatment. *J Med Virol* 2019;91:1368–1377.
- Ashraf GM, Tarasov VV, Makhmutov A, et al. The possibility of an infectious etiology of Alzheimer disease. *Mol Neurobiol* 2019;56:4479–4491.
- De Chiara G, Piacentini R, Fabiani M, et al. Recurrent herpes simplex virus-1 infection induces hallmarks of neurodegeneration and cognitive deficits in mice. *PLoS Pathog* 2019;15:e1007617.
- Haas JG, Lathe R. Microbes and Alzheimer's disease: New findings call for a paradigm change. *Trends Neurosci* 2018;41:570–573.
- Itzhaki RF, Lathe R, Balin BJ, et al. Microbes and Alzheimer's disease. *J Alzheimers Dis* 2016;51:979–984.
- Devanand D, Wisniewski T. Anti-viral therapy in Alzheimer's disease. 2017. Available at: clinicaltrials.gov/ct2/show/NCT03282916. Accessed August 26, 2019.
- Lovheim H. Feasibility and Effects of Valaciclovir Treatment in Persons With Early Alzheimer's Disease (VALZ-Pilot). 2016. Available at: clinicaltrials.gov/ct2/show/NCT02997982. Accessed August 26, 2019.
- Ewbank D. Demography in the age of genomics: a first look at the prospects. In: *Cells and Surveys: Should Biological Measures be Included in Social Science Research?* National Academies Press (US); 2001. Available at: [ncbi.nlm.nih.gov/books/NBK110049/](https://www.ncbi.nlm.nih.gov/books/NBK110049/). Accessed November 18, 2018.
- Mayeux R. Apolipoprotein E, Alzheimer disease, and African Americans. *Arch Neurol* 2003;60:161.
- Hendrie HC, Murrell J, Baiyewu O, et al. APOE ε4 and the risk for Alzheimer disease and cognitive decline in African Americans and Yoruba. *Int Psychogeriatr* 2014;26:977–985.
- Hall K, Murrell J, Ogunniyi A, et al. Cholesterol, APOE genotype, and Alzheimer disease: an epidemiologic study of Nigerian Yoruba. *Neurology* 2006;66:223–227.
- Trumble BC, Stieglitz J, Blackwell AD, et al. Apolipoprotein E4 is associated with improved cognitive function in Amazonian forager-horticulturalists with a high parasite burden. *FASEB J* 2017;31:1508–1515.
- van Exel E, Koopman JJE, van Bodegom D, et al. Effect of APOE ε4 allele on survival and fertility in an adverse environment. *PLoS One* 2017;12:e0179497.
- Ahn SJ, Kim DK, Kim SS, et al. Association between apolipoprotein E genotype, chronic liver disease, and hepatitis B virus. *Clin Mol Hepatol* 2012;18:295–301.
- Mueller T, Fischer J, Gessner R, et al. Apolipoprotein E allele frequencies in chronic and self-limited hepatitis C suggest a protective effect of APOE4 in the course of hepatitis C virus infection. *Liver Int* 2016;36:1267–1274.
- Fabris C, Vandelli C, Toniutto P, et al. Apolipoprotein E genotypes modulate fibrosis progression in patients with chronic hepatitis C and persistently normal transaminases. *J Gastroenterol Hepatol* 2011;26:328–333.
- Wozniak MA, Itzhaki RF, Faragher EB, et al. Apolipoprotein E-epsilon 4 protects against severe liver disease caused by hepatitis C virus. *Hepatology* 2002;36:456–463.
- Wozniak MA, Lugo Iparraguirre LM, Dirks M, et al. Apolipoprotein E-ε4 deficiency and cognitive function in hepatitis C virus-infected patients. *J Viral Hepat* 2016;23:39–46.
- Eimer WA, Vijaya Kumar DK, Navalpur Shanmugam NK, et al. Alzheimer's disease-associated β-amyloid is rapidly seeded by herpesviridae to protect against brain infection. *Neuron* 2018;100:1527–1532.
- Elkind MSV, Ramakrishnan P, Moon YP, et al. Infectious burden and risk of stroke: the Northern Manhattan Study. *Arch Neurol* 2010;67:33–38.
- Elkind MS, Lin IF, Grayston JT, Sacco RL. Chlamydia pneumoniae and the risk of first ischemic stroke: the Northern Manhattan Stroke Study. *Stroke* 2000;31:1521–1525.
- Elkind MSV, Tondella MLC, Feikin DR, Fields BS, Homma S, Di Tullio MR. Seropositivity to Chlamydia pneumoniae is associated with risk of first ischemic stroke. *Stroke* 2006;37:790–795.
- Folstein MF, Folstein SE, McHugh PR. "Mini-Mental State." A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;12:189–198.
- Siedlecki KL, Rundek T, Elkind MSV, Sacco RL, Stern Y, Wright CB. Using contextual analyses to examine the meaning of neuropsychological variables across samples of English-speaking and Spanish-speaking older adults. *J Int Neuropsychol Soc* 2012;18:223–233.
- D'Elia LF, Satz P, Uchiyama C, White T. Color Trails Test Professional Manual. Odessa: Psychological Assessment Resources; 1996.
- Flowers KA, Robertson C. The effect of Parkinson's disease on the ability to maintain a mental set. *J Neurol Neurosurg Psychiatry* 1985;48:517–529.
- Matthews C, Klove H. Instruction Manual for the Adult Neuropsychology Test Battery. Madison: University of Madison Medical School; 1964.
- Beery KE. Developmental Test of Visual-Motor Integration (VMI) Manual. Chicago: Follett; 1967.
- Flanagan JL, Jackson ST. Test-retest reliability of three aphasia tests: performance of non-brain-damaged older adults. *J Commun Disord* 1997;30:33–42; quiz 42–43.
- Harrison JE, Buxton P, Husain M, Wise R. Short test of semantic and phonological fluency: normal performance, validity and test-retest reliability. *Br J Clin Psychol* 2000;39:181–191.
- Wallman KK, Hodgdon J. Race and ethnic standards for Federal statistics and administrative reporting. *Stat Rep* 1977:450–454.
- Moss AJ, Parsons VL. Current estimates from the National Health Interview Survey. United States, 1985. *Vital Health Stat* 10 1986;160:i-iv; 1–182.
- Black SA, Espino DV, Mahurin R, et al. The influence of noncognitive factors on the Mini-Mental State Examination in older Mexican-Americans: findings from the Hispanic EPESE. Established population for the Epidemiologic Study of the Elderly. *J Clin Epidemiol* 1999;52:1095–1102.
- VanderWeele TJ, Knol MJ. A tutorial on interaction. *Epidemiologic Methods* 2014;3:33–72.
- Readhead B, Haure-Mirande JV, Funk CC, et al. Multiscale analysis of independent Alzheimer's cohorts finds disruption of molecular, genetic, and clinical networks by human herpesvirus. *Neuron* 2018;99:64–82.e7.
- Strandberg TE, Pitkala K, Eerola J, Tilvis R, Tienari PJ. Interaction of herpesviridae, APOE gene, and education in cognitive impairment. *Neurobiol Aging* 2005;26:1001–1004.
- Itzhaki RF, Lin WR, Shang D, Wilcock GK, Faragher B, Jamieson GA. Herpes simplex virus type 1 in brain and risk of Alzheimer's disease. *Lancet* 1997;349:241–244.
- Letenneur L, Pérès K, Fleury H, et al. Seropositivity to herpes simplex virus antibodies and risk of Alzheimer's disease: a population-based cohort study. *PLoS One* 2008;3:e3637.
- Burgos JS, Ramirez C, Sastre I, Bullido MJ, Valdivieso F. ApoE4 is more efficient than E3 in brain access by herpes simplex virus type 1. *Neuroreport* 2003;14:1825–1827.
- Mitter SS, Oriá RB, Kvalsund MP, et al. Apolipoprotein E4 influences growth and cognitive responses to micronutrient supplementation in shantytown children from northeast Brazil. *Clinics (Sao Paulo)* 2012;67:11–18.
- Wright RO, Hu H, Silverman EK, et al. Apolipoprotein E genotype predicts 24-month bayley scales infant development score. *Pediatr Res* 2003;54:819–825.
- Corbo RM, Scacchi R. Apolipoprotein E (APOE) allele distribution in the world. Is APOE * 4 a 'thrifty' allele? *Ann Hum Genet* 1999;63:301–310.

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