

Neuropathology-Independent Association Between *APOE* Genotype and Cognitive Decline Rate in the Normal Aging-Early Alzheimer Continuum

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Neurol Genet 2023;9:e200055. doi:10.1212/NXG.0000000000200055

Abstract

Background and Objectives

We previously found that the *APOE* genotype affects the rate of cognitive decline in mild-to-moderate Alzheimer disease (AD) dementia independently of its effects on AD neuropathologic changes (ADNC) and copathologies. In this study, we tested the hypothesis that the *APOE* alleles differentially affect the rate of cognitive decline at the normal aging-early AD continuum and that this association is independent of their effects on classical ADNC and copathologies.

Methods

We analyzed *APOE* associations with the cognitive trajectories (Clinical Dementia Rating scale Sum of Boxes [CDR-SOB] and Mini-Mental State Examination [MMSE]) of more than 1,000 individuals from a national clinicopathologic sample who had either no, mild (sparse neuritic plaques and the Braak neurofibrillary tangle [NFT] stage I/II), or intermediate (moderate neuritic plaques and the Braak NFT stage III/IV) ADNC levels at autopsy via 2 latent classes reverse-time longitudinal modeling.

Results

Carrying the *APOE* ϵ 4 allele was associated with a faster rate of cognitive decline by both CDR-SOB and MMSE relative to *APOE* ϵ 3 homozygotes. This association remained statistically significant after adjusting for ADNC severity, comorbid pathologies, and the effects of ADNC on the slope of cognitive decline. Our modeling strategy identified 2 latent classes in which *APOE* ϵ 4 carriers declined faster than *APOE* ϵ 3 homozygotes, with latent class 1 members representing slow decliners (CDR-SOB: 76.7% of individuals, 0.195 vs 0.146 points/y in *APOE* ϵ 4 vs *APOE* ϵ 3/ ϵ 3; MMSE: 88.6% of individuals, -0.303 vs -0.153 points/y in *APOE* ϵ 4 vs *APOE* ϵ 3/ ϵ 3), whereas latent class 2 members were fast decliners (CDR-SOB: 23.3% of participants, 1.536 vs 1.487 points/y in *APOE* ϵ 4 vs *APOE* ϵ 3/ ϵ 3; MMSE: 11.4% of participants, -2.538 vs -2.387 points/y in *APOE* ϵ 4 vs *APOE* ϵ 3/ ϵ 3). Compared with slow decliners, fast decliners were more likely to carry the *APOE* ϵ 4 allele, younger at initial visit and death, more impaired at initial and last visits, and more likely to have intermediate (vs none or mild) ADNC levels, as well as concurrent Lewy bodies and hippocampal sclerosis at autopsy.

Discussion

In a large national sample selected to represent the normal aging-early AD continuum, the *APOE* ϵ 4 allele is associated with a modest but statistically significant acceleration of the cognitive decline rate even after controlling for its effects on ADNC and comorbid pathologies.

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Funding information and disclosures are provided at the end of the article. Full disclosure form information provided by the authors is available with the full text of this article at [Neurology.org/NG](https://www.neurology.org/NG).

The Article Processing Charge was funded by the authors.

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Glossary

AD = Alzheimer disease; ADNC = AD neuropathologic changes; CAA = cerebral amyloid angiopathy; CDR-SOB = Clinical Dementia Rating scale Sum Of Boxes; HScl = hippocampal sclerosis; MMSE = Mini-Mental State Examination; NACC = National Alzheimer Coordinating Center; NFTs = neurofibrillary tangles; NP = neuritic plaque; TDP-43 = transactive response DNA-binding protein of 43 kDa; UDS = Uniform Data Set.

Alzheimer disease (AD) is increasingly recognized as a heterogeneous clinicopathologic construct with frequently disparate syndromic presentations, rates of clinical progression, and/or severity and mixture of underlying pathologic findings. This heterogeneity is a major challenge for the success of clinical trials pursuing a disease-modifying effect and therefore represents a research area of the highest priority.¹ Clinical and pathologic heterogeneity are linked because individuals with 1 or more comorbid pathologies in the brain have a faster progression of their cognitive decline.² While the driver(s) of this heterogeneity remains largely unknown, both acquired environmental and genetic factors could conceivably cooperate and account for it. Among the latter, the *APOE* genotype is a primary suspect given its known effects on clinical and pathologic phenotypes. Regarding *APOE* clinical correlates, besides a differential impact on age at symptom onset, we and others^{3,4} have found that, in individuals with dementia due to AD, the *APOE*ε4 allele accelerates and the *APOE*ε2 allele slows down the rate of cognitive decline relative to the *APOE*ε3 reference allele and that they do so independently of their effects on the presence and severity of AD neuropathologic changes (ADNC) and comorbid pathologies. Moreover, the *APOE*ε4 allele has been associated with an amnesic presentation of AD,⁵⁻⁷ whereas the attention/dysexecutive,⁶⁻⁸ the primary progressive aphasia,⁹ and the posterior cortical atrophy¹⁰ presentations of AD appear to have a weaker association with the *APOE*ε4 allele, suggesting an *APOE*ε4-mediated selective vulnerability of temporolimbic networks. Regarding *APOE* pathologic correlates, it is well-established that the *APOE*ε4 allele is associated with more severe Aβ plaque deposition and cerebral amyloid angiopathy (CAA), and there is growing evidence of similar *APOE* allele-specific independent effects on the extent of neurofibrillary tangles (NFTs)¹¹ and the co-occurrence and severity of transactive response DNA-binding protein of 43 kDa (TDP-43) proteinopathy,^{12,13} Lewy body pathology,¹⁴⁻¹⁶ and cerebrovascular diseases.^{17,18}

In this study, we tested the hypothesis that the *APOE* alleles differentially affect the rate of decline of both global cognition and specific cognitive domains (representing distinct neural networks) independently of their effects on ADNC and concurrent pathologies at the normal aging-early AD transition. To this end, we built reverse-time longitudinal models to analyze the cognitive trajectories of a national clinicopathologic sample with either no, mild, or intermediate ADNC levels at autopsy.

Methods

Standard Protocol Approvals, Registrations, and Participant Consents

As determined by the University of Washington Human Subjects Division, the National Alzheimer Coordinating Center (NACC) database itself is exempt from Institutional Review Board review and approval because it does not involve human subjects, as defined by federal and state regulations. However, all contributing AD Centers are required to obtain informed consent from their participants and maintain their own separate Institutional Review Board review and approval from their institution prior to submitting data to NACC.

Eligibility Criteria and Data Collection

The NACC study is a National Institute on Aging-funded longitudinal cohort study of cognitive aging conducted by more than 30 Alzheimer Disease Centers across the United States. Participants undergo baseline and annual follow-up visits in which a Uniform Data Set (UDS)¹⁹ is collected that includes demographics, medical history, medication list, and standardized motor, behavioral, functional, and neuropsychological questionnaires and tests.^{20,21} Participants are also offered to join fluid (plasma/serum and CSF) and imaging biomarkers (MRI and PET) studies and to donate their brain for diagnostic and research purposes following a standardized neuropathologic evaluation protocol.²² The NACC data set was interrogated between September 2005 and March 2021 data freezes. Inclusion criteria included the following: (1) autopsy available; (2) death within 2 years from the last visit; (3) age at death at 50 years or older; and (4) *APOE* genotype available. Exclusion criteria were as follows: (1) primary neuropathologic diagnosis other than ADNC; (2) *APOE* genotype not available or ε2/ε4 (due to a possible cancellation of their presumed opposing effects); (3) cognitive impairment due to medical illness, medication adverse side effects, or alcohol; and (4) CERAD neuritic plaque (NP) score frequent or the Braak NFT stage V/VI. The clinical constructs of “normal cognition,” “impaired not mild cognitive impairment,” “mild cognitive impairment,” and “dementia” were deliberately ignored as eligibility criteria to better understand the correlations between *APOE* genotype, semiquantitative measures of neuropathology, and cognitive trajectories. Data collected included age at first and last visit and death, sex, education (number of years), race and ethnicity, *APOE* genotype, scores from longitudinal neuropsychological evaluations, and autopsy neuropathologic variables.

Cognitive Outcome Measures

Cognitive outcome measures included the Clinical Dementia Rating scale Sum Of Boxes (CDR-SOB) score of the CDR Dementia Staging Instrument, the Mini-Mental State Examination (MMSE) score, and cognitive domain-specific z scores for memory, attention, executive functions, and language. The latter were derived from the individual neuropsychological tests of the UDS neuropsychological battery following the factor structure reported by Hayden et al.,¹⁴ as explained elsewhere.² In brief, z scores for these tests were obtained for the mean and SD of the group of participants with intact cognition (i.e., CDR-SOB = 0) at first visit. The logical memory immediate and delayed recall were combined to obtain a memory z score; the digits forward and backward and their length to obtain an attention z score; the Trail Making Tests A and B and the Digit Symbol Test to obtain an executive z score; and the semantic verbal fluency (number of animals and vegetables in 1 minute) and the Boston Naming Test to obtain a language z score.

Statistical Analyses

To ascertain the cross-sectional neuropathologic correlates of *APOE* genotype in this autopsy cohort, we applied logistic regression models with the neuropathologic dependent variable categorized into 2 levels (the CERAD NP score moderate vs none/sparse; the Braak NFT stage III/IV vs 0/I/II; Lewy bodies present vs absent; hippocampal sclerosis [HSc] present vs absent), *APOE* genotype as an independent variable (i.e., the presence of the *APOE*ε4 or *APOE*ε2 alleles with *APOE*ε3

homozygotes as reference group), and age, sex, and education as covariates. For each neuropathologic variable with multiple ordered categories (CAA mild vs none, moderate vs mild, and severe vs moderate; and arteriolosclerosis mild vs none, moderate vs mild, and severe vs moderate), we applied adjacent categories logit models with *APOE* genotype as an independent variable and the same covariates as in the logistic regression models, allowing potentially different effects for different adjacent categories.²³ Models for the Braak NFT stage and CAA severity were also controlled for the CERAD NP score.

Next, to test whether the *APOE*ε4 (*APOE*ε3/ε4 and *APOE*ε4/ε4) and *APOE*ε2 (*APOE*ε2/ε2 and *APOE*ε2/ε3) participants significantly differed from the *APOE*ε3 (*APOE*ε3/ε3) reference group regarding the rate of cognitive decline (CDR-SOB, MMSE, and cognitive domain-specific composite measures) and whether these effects are independent of *APOE* allele associations with ADNC and comorbid pathologies, we applied a reverse-time longitudinal modeling strategy as described elsewhere.^{2,15} In brief, to link the cognitive trajectories to the neuropathologic autopsy findings, the last clinic visit within 2 years from death was treated as the first visit and cognitive score trajectories were modeled in the reverse time toward the first clinic visit, so that the neuropathologic autopsy variables could be appropriately treated as baseline covariates. This approach makes the assumptions that, in a given individual's brain, NPs increase from none/sparse to moderate, whereas NFTs spread from the entorhinal cortex (the Braak NFT stage I/II) to limbic regions (the Braak NFT stage III/IV) in a sequential manner

Figure 1 Flowchart of Study Participants

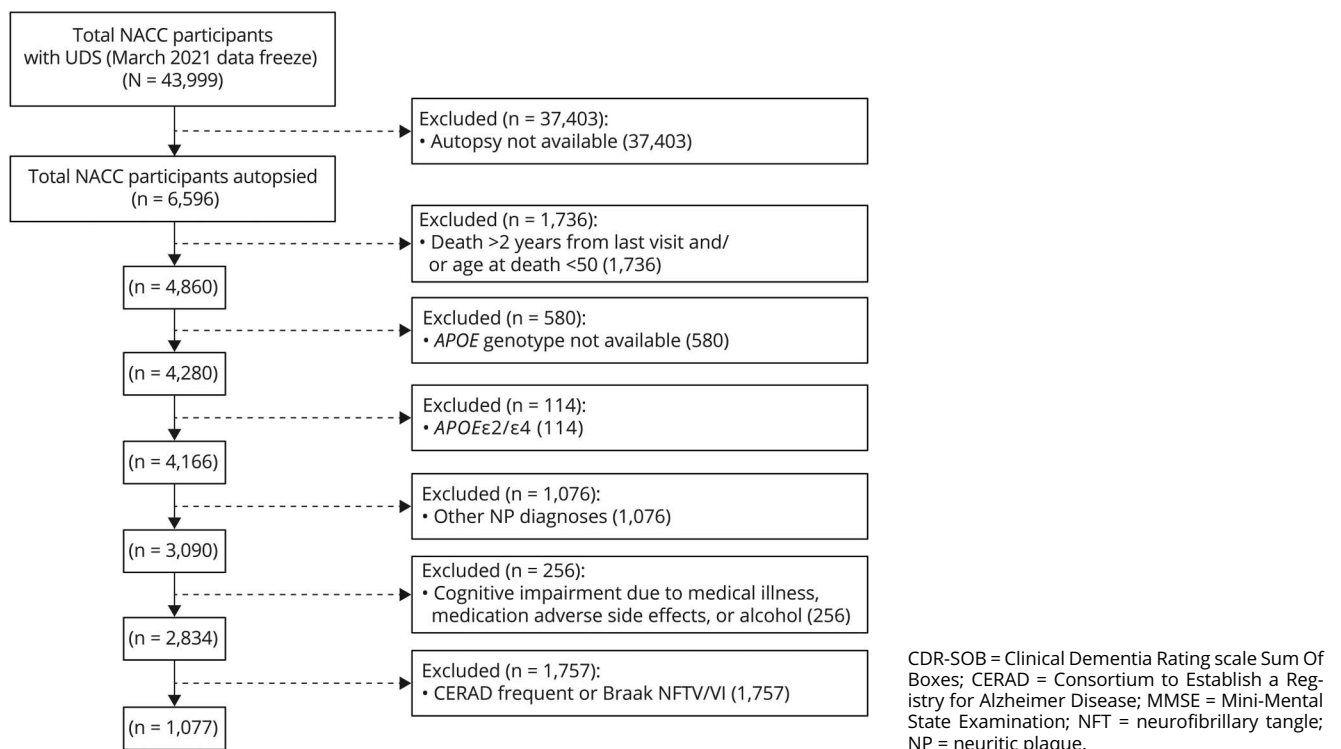


Table 1 Demographic, Clinical, and Neuropathologic Characteristics of Study Participants by *APOE* Group

	Total	<i>APOE</i> ε2	<i>APOE</i> ε3	<i>APOE</i> ε4	<i>p</i> Value
N (%)	1,077 (100.0)	153 (14.2)	651 (60.4)	273 (25.4)	—
Sex, female, n (%)	509 (47.3)	88 (57.5)	302 (46.4)	119 (43.6)	0.017
Race, White, n (%)	1,016 (94.3)	143 (93.5)	614 (94.3)	259 (94.9)	0.833
Age at first visit, y	80.9 (8.8)	82.7 (9.1)	81.5 (8.5)	78.4 (8.9)	<0.001
Age at death, y	86.0 (9.3)	87.9 (9.0)	86.8 (9.0)	83.2 (9.5)	<0.001
Education, y	15.4 (3.2)	15.5 (3.0)	15.4 (3.2)	15.5 (3.4)	0.764
Follow-up, no. of visits	4 (2–7)	4 (2–7)	4 (2–7)	4 (2–6)	0.095
Follow-up, y	4.67 (2.33–7.42)	5 (2.42–7.25)	4.83 (2.42–7.67)	4.08 (2.17–6.83)	0.075
First–last visit interval, y	3.9 (1.43–6.77)	3.89 (1.26–6.31)	4.05 (1.95–6.97)	3.22 (1.18–6.31)	0.091
Last visit–death interval, y	0.75 (0.42–1.08)	0.75 (0.42–1.17)	0.75 (0.42–1.08)	0.75 (0.33–1.08)	0.733
CDR-SOB first visit	2.4 (4.0)	1.7 (3.2)	2.1 (3.8)	3.5 (4.6)	<0.001
CDR-SOB last visit	5.2 (5.9)	3.9 (5.1)	4.7 (5.8)	6.9 (6.3)	<0.001
MMSE first visit	26.5 (4.9)	27.3 (4.1)	26.8 (4.7)	25.3 (5.8)	<0.001
MMSE last visit	23.9 (6.7)	25.6 (5.8)	24.6 (6.1)	21.5 (7.7)	<0.001
Memory z score first visit	–0.71 (1.30)	–0.38 (1.30)	–0.61 (1.27)	–1.13 (1.28)	<0.001
Memory z score last visit	–0.89 (1.42)	–0.60 (1.29)	–0.74 (1.39)	–1.43 (1.46)	<0.001
Attention z score first visit	–0.30 (1.01)	–0.27 (1.01)	–0.23 (1.00)	–0.50 (1.00)	0.002
Attention z score last visit	–0.63 (1.04)	–0.52 (1.06)	–0.57 (1.00)	–0.85 (1.09)	0.01
Executive z score first visit	–0.39 (1.14)	–0.36 (1.16)	–0.34 (1.08)	–0.56 (1.26)	0.078
Executive, z score last visit	–0.84 (1.27)	–0.88 (1.37)	–0.69 (1.16)	–1.19 (1.39)	0.004
Language z score first visit	–0.59 (1.20)	–0.41 (1.21)	–0.53 (1.15)	–0.81 (1.30)	0.002
Language z score last visit	–1.09 (1.34)	–0.88 (1.31)	–1.02 (1.31)	–1.38 (1.38)	0.005
CERAD score					<0.001
CERAD NP none	433 (40.2)	86 (56.2)	285 (43.8)	62 (22.7)	
CERAD NP sparse	314 (29.2)	36 (23.5)	186 (28.6)	92 (33.7)	
CERAD NP moderate	330 (30.6)	31 (20.3)	180 (27.6)	119 (43.6)	
The Braak NFT stage					<0.001
Braak NFT 0	55 (5.1)	9 (5.9)	37 (5.7)	9 (3.3)	
Braak NFT I	172 (16.0)	28 (18.3)	113 (17.4)	31 (11.4)	
Braak NFT II	284 (26.4)	42 (27.5)	193 (29.6)	49 (17.9)	
Braak NFT III	246 (22.8)	41 (26.8)	129 (19.8)	76 (27.8)	
Braak NFT IV	320 (29.7)	33 (21.6)	179 (27.5)	108 (39.6)	
Lewy bodies present	313 (29.1)	37 (24.2)	160 (24.6)	116 (42.5)	<0.001
HScI present	90 (8.4)	13 (8.5)	54 (8.3)	23 (8.4)	0.996
Arteriolosclerosis					0.390
Arteriolosclerosis none	180 (16.7)	21 (13.7)	110 (16.9)	49 (17.9)	
Arteriolosclerosis mild	372 (34.5)	59 (38.6)	221 (33.9)	92 (33.7)	

Continued

Table 1 Demographic, Clinical, and Neuropathologic Characteristics of Study Participants by *APOE* Group (continued)

	Total	<i>APOE</i> ε2	<i>APOE</i> ε3	<i>APOE</i> ε4	<i>p</i> Value
Arteriolosclerosis moderate	295 (27.4)	43 (28.1)	178 (27.3)	74 (27.1)	
Arteriolosclerosis severe	116 (10.8)	17 (11.1)	78 (12.0)	21 (7.7)	
CAA					<0.001
CAA none	610 (56.6)	97 (63.4)	406 (62.4)	107 (39.2)	
CAA mild	264 (24.5)	33 (21.6)	153 (23.5)	78 (28.6)	
CAA moderate	139 (12.9)	15 (9.8)	63 (9.7)	61 (22.3)	
CAA severe	43 (4.0)	6 (3.9)	14 (2.2)	23 (8.4)	

Abbreviations: CAA = cerebral amyloid angiopathy; CDR-SOB = Clinical Dementia Rating Scale Sum Of Boxes; CERAD = Consortium to Establish a Registry for Alzheimer Disease; HScl = hippocampal sclerosis; MMSE = Mini-Mental State Examination; NFT = neurofibrillary tangle; NP = neuritic plaque.

along the follow-up period; indeed, PET imaging studies support these assumptions.^{24,25} We did not include the Thal amyloid phases in these models because these do not affect antemortem cognition.²⁶ Moreover, to adjust for the right truncation of cognitive trajectory by time to death, we built a joint latent class model²⁷ for the longitudinal cognitive outcome (mixed-effects submodel) and the time-to-event analyses (i.e., last visit to first visit in reverse time, Cox proportional hazards submodel), with a logistic submodel for latent class membership. We used the Bayes Information Criterion to determine the optimal number of latent classes best supported by the data. Because different cognitive outcomes could potentially have different unobserved participant characteristics associated with them and with the *APOE* genotype, we allowed the latent classes to vary across longitudinal models, although we found a large membership overlap between latent classes from the CDR-SOB and MMSE models (733/866 [84.6%] after excluding individuals with missing values in covariates). We also implemented a right truncation adjustment for time to last visit by time to death to avoid potential bias due to the oversampling of shorter times to death. We evaluated 3 models in a stepwise fashion: model 1 was adjusted by sex, age, and education; model 2 was further adjusted by the CERAD NP score and Braak NFT stage; and model 3 was further adjusted by the effects of the CERAD NP score and Braak NFT stage on the slope of the cognitive outcome and by comorbid pathologies. The selection of comorbid pathologies for model 3 was based on univariate models in which 1 comorbid pathology variable was added at a time. Because the CERAD NP score frequent and Braak NFT stage V/VI were exclusion criteria, no ceiling or floor effects were detected in either CDR-SOB or MMSE scores or in any of the cognitive domain-specific *z* scores (not shown), therefore no change point was implemented.²

Data Availability

The NACC database is a publicly available resource available to researchers, and data requests can be submitted online at the following NACC website: nacc.redcap.rit.uw.edu/surveys/?s=KHNPKLJW8TKAD4DA.

Results

Sample Description

A total of 1,077 participants met all our eligibility inclusion criteria and none of the exclusion criteria (Figure 1), of whom 153 (14.2%) were *APOE*ε2 carriers, 651 (60.4%) were *APOE*ε3 homozygotes, and 273 (25.4%) were *APOE*ε4 carriers. Demographic, clinical, and neuropathologic characteristics of study subjects split by *APOE* genotype are summarized in Table 1. *APOE*ε4 carriers were more likely to be male, were younger, and had higher CDR-SOB and lower MMSE scores as well as lower memory-, attention-, executive-, and language-specific *z* scores than *APOE*ε3 homozygotes at first and last visits, whereas opposite trends were observed for *APOE*ε2 carriers. There were no statistically significant differences in education, follow-up duration, or lapse between last visit and death/autopsy. All downstream statistical analyses were adjusted by age at death, sex, and education.

Neuropathologic Correlates of the *APOE* Genotype in This Autopsy Sample

Table 1, links.lww.com/NXG/A574, summarizes the associations between ADNC and comorbid pathologies and *APOE* genotype in this sample. Relative to *APOE*ε3 homozygotes, carrying the *APOE*ε4 allele was associated with a higher CERAD NP score (moderate vs none/sparse) and Braak NFT stage (III/IV vs 0/I/II), a higher severity of CAA, and the presence of Lewy bodies, but not with the presence of HScl or the severity of arteriolosclerosis. A dose-dependent effect was observed whereby *APOE*ε4 homozygotes were more likely to have a higher CERAD NP score, Braak NFT stage, and CAA severity than *APOE*ε3 homozygotes compared with *APOE*ε3/ε4 participants; however, only *APOE*ε3/ε4 carriers were more likely to have Lewy bodies than *APOE*ε3 homozygotes.

*APOE*ε4 Is Independently Associated With a Faster Cognitive Decline in the Normal Aging-Early AD Continuum

To determine any independent association between the *APOE* alleles and the rate of cognitive decline, we applied reverse-time

Table 2 Associations of *APOE* Alleles With Global and Domain-Specific Cognitive Outcomes

Outcome Contrast	N	Model 1				Model 2				Model 3			
		Estimate	SE	95% CI		Estimate	SE	95% CI		Estimate	SE	95% CI	
CDR-SOB	1,067												
CERAD NP moderate vs none/sparse		N.A.	N.A.	N.A.	N.A.	0.169	0.025	0.119	0.218	0.184	0.027	0.131	0.236
Braak NFT III/IV vs 0/I/II		N.A.	N.A.	N.A.	N.A.	-0.011	0.023	-0.056	0.034	-0.027	0.023	-0.072	0.018
<i>APOE</i> genotype													
ε2 vs ε3/ε3		-0.004	0.028	-0.060	0.051	-0.026	0.030	-0.085	0.034	0.007	0.033	-0.058	0.071
ε4 vs ε3/ε3		0.095	0.027	0.042	0.147	0.058	0.025	0.008	0.108	0.049	0.026	-0.001	0.099
ε2 vs ε4		-0.099	0.035	-0.167	-0.031	-0.084	0.035	-0.152	-0.016	-0.042	0.038	-0.117	0.032
MMSE	992												
CERAD NP moderate vs none/sparse		N.A.	N.A.	N.A.	N.A.	-0.133	0.044	-0.220	-0.047	-0.166	0.040	-0.245	-0.087
Braak NFT III/IV vs 0/I/II		N.A.	N.A.	N.A.	N.A.	-0.003	0.033	-0.068	0.063	0.022	0.032	-0.041	0.086
<i>APOE</i> genotype													
ε2 vs ε3/ε3		0.003	0.045	-0.085	0.091	0.004	0.043	-0.079	0.088	-0.037	0.045	-0.125	0.051
ε4 vs ε3/ε3		-0.180	0.038	-0.254	-0.106	-0.159	0.041	-0.239	-0.080	-0.150	0.040	-0.228	-0.072
ε2 vs ε4		0.183	0.052	0.082	0.285	0.164	0.052	0.062	0.265	0.113	0.054	0.006	0.220
Memory	967												
CERAD NP moderate vs none/sparse		N.A.	N.A.	N.A.	N.A.	0.003	0.012	-0.021	0.027	0.001	0.012	-0.023	0.025
Braak NFT III/IV vs 0/I/II		N.A.	N.A.	N.A.	N.A.	-0.032	0.010	-0.051	-0.012	-0.030	0.010	-0.050	-0.010
<i>APOE</i> genotype													
ε2 vs ε3/ε3		-0.001	0.013	-0.026	0.023	-0.003	0.013	-0.029	0.022	-0.001	0.014	-0.028	0.025
ε4 vs ε3/ε3		-0.006	0.013	-0.031	0.019	-0.001	0.013	-0.026	0.023	-0.003	0.013	-0.028	0.021
ε2 vs ε4		0.005	0.016	-0.027	0.036	-0.002	0.016	-0.033	0.030	0.002	0.016	-0.030	0.034
Attention	970												
CERAD NP moderate vs none/sparse		N.A.	N.A.	N.A.	N.A.	0.001	0.012	-0.022	0.025	0.000	0.013	-0.026	0.025
Braak NFT III/IV vs 0/I/II		N.A.	N.A.	N.A.	N.A.	-0.024	0.010	-0.044	-0.005	-0.024	0.010	-0.043	-0.004
<i>APOE</i> genotype													
ε2 vs ε3/ε3		0.022	0.016	-0.010	0.054	0.022	0.015	-0.006	0.051	0.020	0.016	-0.010	0.051
ε4 vs ε3/ε3		-0.030	0.012	-0.053	-0.008	-0.025	0.012	-0.048	-0.002	-0.025	0.012	-0.049	-0.002
ε2 vs ε4		0.052	0.019	0.016	0.089	0.047	0.017	0.014	0.081	0.046	0.018	0.010	0.081
Executive	849												
CERAD NP moderate vs none/sparse		N.A.	N.A.	N.A.	N.A.	-0.022	0.010	-0.042	-0.001	-0.023	0.011	-0.045	-0.001
Braak NFT III/IV vs 0/I/II		N.A.	N.A.	N.A.	N.A.	0.005	0.009	-0.012	0.022	0.007	0.009	-0.011	0.025
<i>APOE</i> genotype													
ε2 vs ε3/ε3		-0.006	0.012	-0.029	0.017	-0.005	0.012	-0.029	0.018	-0.004	0.013	-0.029	0.022
ε4 vs ε3/ε3		-0.023	0.011	-0.044	-0.003	-0.020	0.011	-0.041	0.002	-0.018	0.012	-0.041	0.006
ε2 vs ε4		0.017	0.014	-0.011	0.044	0.014	0.015	-0.014	0.043	0.014	0.016	-0.018	0.046

Continued

Table 2 Associations of *APOE* Alleles With Global and Domain-Specific Cognitive Outcomes (continued)

Outcome Contrast	N	Model 1				Model 2				Model 3			
		Estimate	SE	95% CI		Estimate	SE	95% CI		Estimate	SE	95% CI	
Language	965												
CERAD NP moderate vs none/sparse		N.A.	N.A.	N.A.	N.A.	-0.024	0.009	-0.041	-0.007	-0.027	0.010	-0.046	-0.008
Braak NFT III/IV vs 0/I/II		N.A.	N.A.	N.A.	N.A.	-0.022	0.007	-0.036	-0.008	-0.019	0.008	-0.034	-0.004
<i>APOE</i> genotype													
ε2 vs ε3/ε3		0.011	0.010	-0.007	0.030	0.010	0.010	-0.009	0.029	0.007	0.010	-0.014	0.027
ε4 vs ε3/ε3		-0.002	0.009	-0.018	0.015	0.007	0.009	-0.010	0.025	0.006	0.009	-0.012	0.024
ε2 vs ε4		0.013	0.011	-0.009	0.035	0.003	0.012	-0.020	0.026	0.000	0.013	-0.024	0.025

Model 1 is adjusted by age, sex, and education. Model 2 is further adjusted by the CERAD NP score (moderate vs none/sparse) and Braak NFT stage (III/IV vs 0/I/II). Model 3 is further adjusted by the presence and severity of comorbid pathologies and the interaction between the CERAD NP score and Braak NFT stage and the slope of cognitive trajectory. Estimates are in the forward time scale. Statistically significant results at a significance level of 0.05 are depicted in boldface.

longitudinal models, which link the individuals' autopsy findings with their CDR-SOB and MMSE trajectories in reverse time scale by considering the last visit proximate (≤ 2 years) to death/autopsy as baseline. These models revealed that carrying the *APOE*ε4 allele is associated with a faster rate of cognitive decline by both CDR-SOB and MMSE relative to *APOE*ε3 homozygotes. This association remained statistically significant whether adjusting only for age, sex, and education (model 1); further adjusting for the severity of ADNC (i.e., CERAD NP score and Braak NFT stage) (model 2); or additionally adjusting for comorbid pathologies and the effects of ADNC on the slope (model 3) (Table 2 and Figure 2). By contrast, no significant difference was observed between *APOE*ε2 carriers and *APOE*ε3 homozygotes in any of the models. Noteworthy, our modeling strategy identified 2 latent classes in which the differences between *APOE*ε4 carriers and *APOE*ε3 homozygotes were statistically significant. The slope of these 2 latent classes differed markedly, with latent class 1 members representing slow decliners (CDR-SOB: 76.7% of individuals, 0.195 vs 0.146 points/y in *APOE*ε4 vs *APOE*ε3/ε3; MMSE: 88.6% of individuals, -0.303 vs -0.153 points/y in *APOE*ε4 vs *APOE*ε3/ε3), whereas latent class 2 members were fast decliners (CDR-SOB: 23.3% of individuals, 1.536 vs 1.487 points/y in *APOE*ε4 vs *APOE*ε3/ε3; MMSE: 11.4% of individuals, -2.538 vs -2.387 points/y in *APOE*ε4 vs *APOE*ε3/ε3) (Table 3). Compared with slow decliners, fast decliners were not only more likely to carry the *APOE*ε4 allele but also younger and more impaired at initial and last visits and more likely to have intermediate (vs none or mild) ADNC levels as well as concurrent Lewy bodies and HScl at autopsy (Table 4).

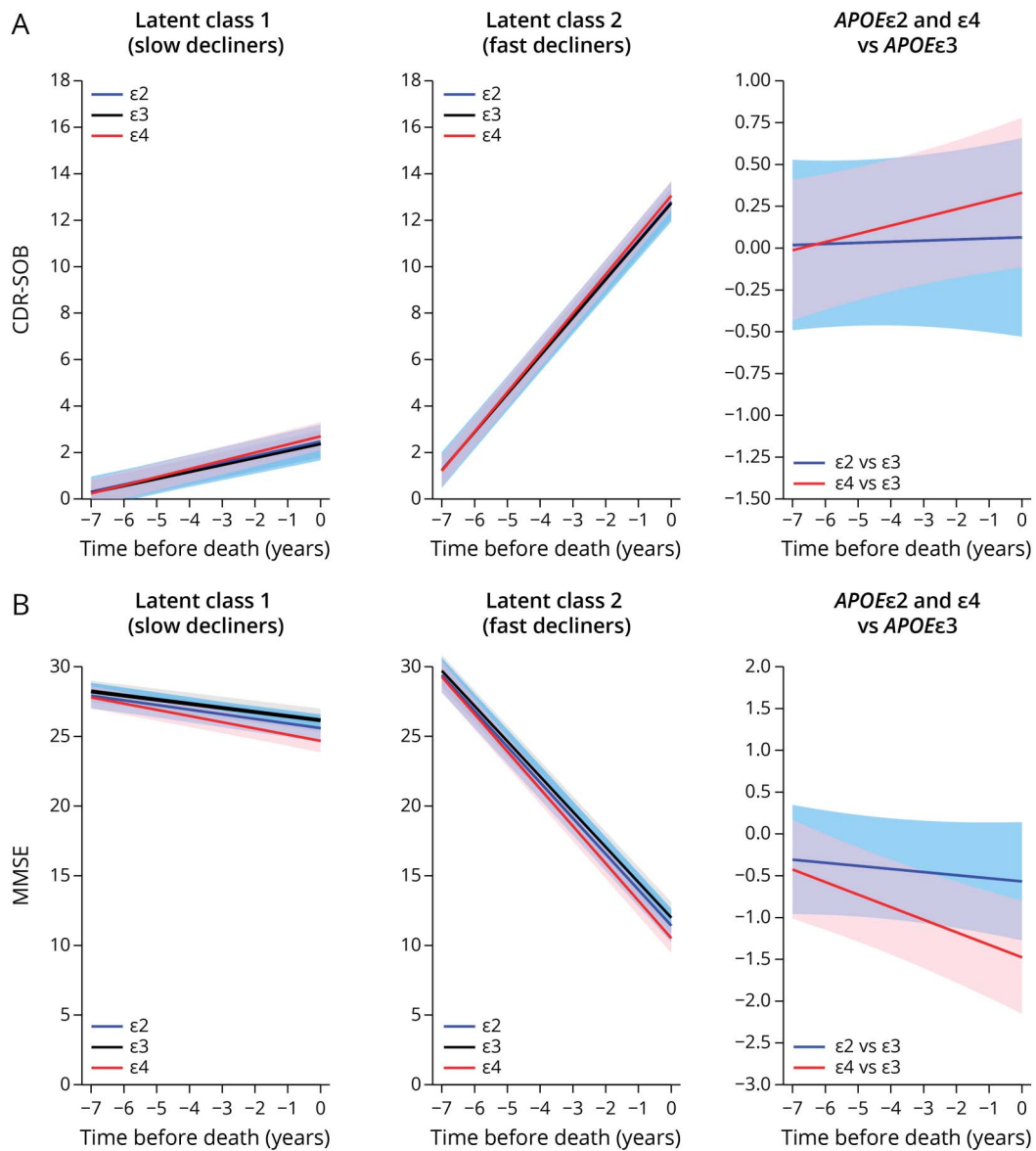
***APOE*ε4 Is Independently Associated With a Faster Decline in Attention and Executive Function, but Not Memory or Language**

Next, to investigate possible differential associations between *APOE* alleles and specific cognitive domains corresponding to different brain networks, we applied similar models with

memory-, attention-, executive-, and language-specific composites as cognitive outcome measures (Table 2 and Figure 3). Unexpectedly, *APOE*ε4 carriers did not significantly differ from *APOE*ε3 homozygotes in the trajectory of the memory domain in any of the models. Of note, *APOE*ε4 carriers had poorer memory *z* scores than *APOE*ε2 carriers and *APOE*ε3 homozygotes at both initial and last visits (Table 1 and Figure 2), suggesting a potential floor effect; however, 2 subsequent sensitivity analyses restricting the sample to individuals with a CDR-SOB score of ≤ 0.5 either at their first visit or at their last visit (within 2 years from death) did not change these results. Because of our prespecified CERAD NP score frequent and Braak NFT stage V/VI exclusion criteria, only 29 of the 273 *APOE*ε4 carriers in this sample were *APOE*ε4 homozygotes, therefore precluding a conclusive *APOE*ε4 allele dose-response analysis.

Similarly, no differences were found in the language domain in any of the models. By contrast, *APOE*ε4 carriers declined significantly faster than *APOE*ε3 homozygotes in the attention domain, but this difference reached statistical significance only in latent class 2 (fast decliners). Last, the executive domain declined significantly faster in *APOE*ε4 carriers than *APOE*ε3 homozygotes when adjusting for age, sex, and education (model 1, $p = 0.028$); however, this difference was only marginally significant when further adjusting by the CERAD NP score and Braak NFT stage (model 2, $p = 0.077$, 95% CI [-0.041 to 0.002]) and lost statistical significance when further adjusting by comorbid pathologies and the effect of ADNC on the slope (model 3, $p = 0.135$, 95% CI [-0.041 to 0.006]) likely due to insufficient power and the compounding effect of comorbid pathologies on executive function. Indeed, model 3 revealed that Lewy bodies are independently associated with a faster decline in all 4 cognitive domains; moderate and severe (vs none) arteriosclerosis with faster executive dysfunction; HScl with faster memory decline; and severe (vs none) CAA with faster language impairment. Model 3 also revealed seemingly neuropathology-specific

Figure 2 Effects of *APOE* Genotype on CDR-SOB and MMSE Trajectories



Model 3-based trajectories for CDR-SOB (A) and MMSE (B) scores with the intercept at the time of death calculated for an 86-year-old woman with 15 years of education and autopsy findings of CERAD NP score moderate and Braak NFT stage III/IV. Graphs depict the 3 *APOE* groups in latent class 1 (slow decliners) and latent class 2 (fast decliners) as well as the differences *APOE*ε4 vs *APOE*ε3 and *APOE*ε2 vs *APOE*ε3. Shaded areas correspond to the 95% CIs. CDR-SOB = Clinical Dementia Rating scale Sum Of Boxes; CERAD = Consortium to Establish a Registry for Alzheimer Disease; MMSE = Mini-Mental State Examination; NFT = neurofibrillary tangle; NP = neuritic plaque.

associations between ADNC and cognitive domains, with the Braak NFT stage (III/IV vs 0/I/II) independently correlating with a faster decline in memory and attention, whereas the CERAD NP score (moderate vs none/sparse) was independently correlated with a faster executive dysfunction, and both ADNC were associated with a faster decline in language.

Consistent with the aforementioned results relative to CDR-SOB and MMSE trajectories, examination of the cognitive domain-specific composite outcome measures revealed no significant differences in the trajectory of any of these cognitive domains between *APOE*ε2 carriers and *APOE*ε3 homozygotes in any of these models (Table 2). Last, we performed a sensitivity analysis

removing the 29 *APOE*ε4 homozygotes to determine whether they were driving the *APOE*ε4 vs *APOE*ε3 differences described earlier, and the results remained largely unchanged (eTable 2, links.lww.com/NXG/A575); although some of the contrasts lost statistical significance, this was due to the loss of statistical power, as indicated by their 95% CI boundary close to zero.

Discussion

While it is well-established that the *APOE* genotype dramatically affects the risk of developing AD and the conversion rate from mild cognitive impairment to dementia, these effects are

Table 3 Cognitive Decline Slopes of the 2 Latent Classes

<i>APOE</i> genotype	CDR-SOB (points/y)	MMSE (points/y)	Memory (z score)	Attention (z score)	Executive (z score)	Language (z score)
Latent class 1 (slow decliners)						
$\epsilon 4$	0.195 (0.141 to 0.249)	-0.303 (-0.385 to -0.222)	0.043 (0.017 to 0.070)	-0.007 (-0.037 to 0.023)	-0.074 (-0.098 to -0.051)	-0.046 (-0.065 to -0.027)
$\epsilon 3/\epsilon 3$	0.146 (0.112 to 0.179)	-0.153 (-0.201 to -0.105)	0.047 (0.030 to 0.064)	0.018 (-0.007 to 0.044)	-0.057 (-0.070 to -0.043)	-0.052 (-0.064 to -0.040)
$\epsilon 2$	0.152 (0.092 to 0.213)	-0.190 (-0.275 to -0.106)	0.046 (0.020 to 0.072)	0.039 (-0.002 to 0.080)	-0.060 (-0.085 to -0.036)	-0.046 (-0.065 to -0.026)
Latent class 2 (fast decliners)						
$\epsilon 4$	1.536 (1.469 to 1.603)	-2.538 (-2.694 to -2.382)	-0.158 (-0.189 to -0.126)	-0.144 (-0.175 to -0.113)	-0.377 (-0.413 to -0.341)	-0.330 (-0.358 to -0.301)
$\epsilon 3/\epsilon 3$	1.487 (1.424 to 1.549)	-2.387 (-2.530 to -2.245)	-0.154 (-0.178 to -0.130)	-0.119 (-0.146 to -0.092)	-0.359 (-0.389 to -0.330)	-0.336 (-0.362 to -0.310)
$\epsilon 2$	1.494 (1.411 to 1.576)	-2.425 (-2.588 to -2.262)	-0.155 (-0.186 to -0.125)	-0.098 (-0.137 to -0.059)	-0.363 (-0.402 to -0.324)	-0.329 (-0.361 to -0.298)

Abbreviations: CDR-SOB = Clinical Dementia Rating scale Sum Of Boxes; MMSE = Mini-Mental State Examination. The numbers in the parentheses are 95% CIs.

generally attributed to its effects on the accrual of ADNC, especially A β plaques. In this study, we investigated the independent contribution of the *APOE* genotype to the heterogeneity of the rate of clinical progression at the earliest stages of the normal aging-AD continuum in a national clinicopathologic sample with no, mild, or moderate ADNC at autopsy. We found that the *APOE* $\epsilon 4$ allele is associated with an acceleration of the rate of global (CDR-SOB and MMSE) and attention function decline independently of its effects on ADNC and comorbid pathologies.

This longitudinal study extends our similar previous analysis of an NACC sample selected to represent the other end of the AD spectrum, i.e., individuals who end up having moderate or frequent NPs and the Braak NFT stage III/IV or V/VI at autopsy examination.⁴ By focusing here on the normal aging-early AD continuum (i.e., excluding participants with frequent NPs and Braak NFT stage V/VI), we circumvented the ceiling and floor effects typical of these cognitive measures in advanced AD dementia and, consequently, the need for a change point in our longitudinal models. While both analyses concluded that, relative to *APOE* $\epsilon 3$ homozygosity, carrying the *APOE* $\epsilon 4$ allele is associated with a statistically significant faster cognitive decline independently of ADNC and comorbid pathologies, the differences in this normal aging-early AD sample are quantitatively smaller and clinically less relevant compared with those found in the autopsy sample with moderate/high ADNC⁴ (0.04 CDR-SOB points/y and -0.15 MMSE points/y here vs 0.68 CDR-SOB points/y and -0.42 MMSE points/y in our prior study). These observations support a nonlinear association of *APOE* genotype with the rate of cognitive decline along the course of ADNC accrual and the use of nonlinear²⁸ or segmented linear²⁹ models to investigate this relationship. Of note, the 2-latent class modeling enabled us to recognize 2 subgroups of individuals with distinct slopes of clinical progression, with fast decliners being more likely to be *APOE* $\epsilon 4$ carriers, younger at first visit and death, more impaired at first and last visits, and more likely to have intermediate ADNC (the Braak NFT stage III/IV and

moderate NPs), Lewy bodies, and HScl at autopsy, but not more severe vascular pathologies (CAA or arteriolosclerosis). We speculate that this variance in the rate of progression may be explained by other factors, both intrinsic (i.e., polygenic risk score,³⁰ microglia immune responses,³¹ and the interaction between diverse tau species and genetic background^{32,33}) and modifiable (i.e., cognitive reserve, environmental exposures, and vascular) risk factors.³⁴

It has been reported that the *APOE* $\epsilon 4$ allele favors an amnesic over executive/attentional, aphasic, or visuospatial/perceptive presentations of AD, suggesting that *APOE* $\epsilon 4$ confers a selective vulnerability of the temporolimbic network to ADNC.^{5-10,35,36} Others have shown that the *APOE* $\epsilon 4$ allele has some beneficial effects on a visual working memory task even in the presence of A β plaques.³⁷ Although *APOE* $\epsilon 4$ carriers had worse memory z scores at first and last visits than *APOE* $\epsilon 3$ homozygotes and *APOE* $\epsilon 2$ carriers, we did not observe a significant association between the *APOE* $\epsilon 4$ allele and the rate of memory decline in this sample. Our sensitivity analyses argue against the possibility that a floor effect in the memory composite underlies this lack of association. The small number of *APOE* $\epsilon 4$ homozygotes (n = 29) precluded a meaningful allele dose-response analysis. The language trajectory did not differ between *APOE* $\epsilon 4$ carriers and *APOE* $\epsilon 3$ homozygotes, whereas the association between the *APOE* $\epsilon 4$ allele and faster executive dysfunction was not independent of *APOE* $\epsilon 4$ effects on ADNC and comorbid pathologies. Conversely, we did observe a selective association between the *APOE* $\epsilon 4$ allele and a faster rate of decline in the attention domain (as assessed with the digits forward and backward test), which was independent of ADNC and comorbid pathologies. The neuropathology-independent nature of this association raises the question whether the *APOE* $\epsilon 4$ allele may have a deleterious effect on attention already in mid-adulthood. However, prior longitudinal studies investigating *APOE* allele associations with performance in attentional/executive processes in middle-age adults have yielded

Table 4 Demographic, Genetic, Clinical, and Neuropathologic Differences Between Latent Class 1 and 2 Members

	Total	Latent class 1 (slow decliners)	Latent class 2 (fast decliners)	1 vs 2 <i>p</i> value
N (%)	936 (100.0)	697 (74.5)	239 (25.5)	NA
Sex, female, n (%)	509 (54.4)	345 (49.5)	104 (43.5)	0.128
Race, White, n (%)	882 (94.2)	656 (94.1)	226 (94.6)	0.950
APOE genotype				<0.001
APOEε2	153 (16.3)	108 (15.5)	29 (12.1)	
APOEε3	651 (69.6)	441 (63.3)	129 (54.0)	
APOEε4	273 (29.2)	148 (21.2)	81 (33.9)	
Age at first visit, y	80.9 (8.8)	81.5 (8.5)	79.6 (9.4)	0.006
Age at death, y	86.0 (9.3)	87.2 (8.8)	84.0 (10.0)	<0.001
Education, y	15.4 (3.2)	15.5 (3.1)	15.7 (3.7)	0.486
Follow-up, no. visits	4 (2–7)	5 (3–8)	3 (2–6)	<0.001
Follow-up, y	4.67 (2.33–7.42)	5.33 (2.67–8.17)	3.83 (1.87–6)	<0.001
First–last visit interval, y	3.9 (1.43–6.77)	4.53 (2.04–7.22)	3.06 (1.06–5.37)	<0.001
Last visit–death interval, y	0.75 (0.42–1.08)	0.75 (0.42–1.17)	0.58 (0.33–1)	<0.001
CDR-SOB first visit	2.4 (4.0)	0.9 (1.7)	6.0 (5.1)	<0.001
CDR-SOB last visit	5.2 (5.9)	2.1 (2.8)	13.3 (3.6)	<0.001
MMSE first visit	26.5 (4.9)	27.9 (2.6)	22.9 (6.7)	<0.001
MMSE last visit	23.9 (6.7)	26.2 (3.9)	15.4 (6.9)	<0.001
Memory z score first visit	–0.71 (1.30)	–0.39 (1.13)	–1.63 (1.32)	<0.001
Memory z score last visit	–0.89 (1.42)	–0.60 (1.27)	–2.61 (0.73)	<0.001
Attention z score first visit	–0.30 (1.01)	–0.16 (0.92)	–0.75 (1.09)	<0.001
Attention z score last visit	–0.63 (1.04)	–0.45 (0.93)	–1.49 (1.08)	<0.001
Executive z score first visit	–0.39 (1.14)	–0.19 (1.03)	–1.06 (1.19)	<0.001
Executive, z score last visit	–0.84 (1.27)	–0.75 (1.20)	–2.52 (1.06)	<0.001
Language z score first visit	–0.59 (1.20)	–0.26 (0.95)	–1.50 (1.36)	<0.001
Language z score last visit	–1.09 (1.34)	–0.77 (1.10)	–2.73 (1.18)	<0.001
CERAD score				<0.001
CERAD NP none	433 (46.3)	313 (44.9)	71 (29.7)	
CERAD NP sparse	314 (33.5)	213 (30.6)	70 (29.3)	
CERAD NP moderate	330 (35.3)	171 (24.5)	98 (41.0)	
The Braak NFT stage				0.008
Braak NFT 0	55 (5.9)	35 (5.0)	13 (5.4)	
Braak NFT I	172 (18.4)	109 (15.6)	35 (14.6)	
Braak NFT II	284 (30.3)	204 (29.3)	45 (18.8)	
Braak NFT III	246 (26.3)	160 (23.0)	57 (23.8)	
Braak NFT IV	320 (34.2)	189 (27.1)	89 (37.2)	
Lewy bodies present	313 (33.4)	160 (23.0)	101 (42.3)	<0.001
HScl present	90 (9.6)	46 (6.6)	31 (13.0)	0.003

Continued

Table 4 Demographic, Genetic, Clinical, and Neuropathologic Differences Between Latent Class 1 and 2 Members (*continued*)

	Total	Latent class 1 (slow decliners)	Latent class 2 (fast decliners)	1 vs 2 <i>p</i> value
Arteriosclerosis				0.108
Arteriosclerosis none	180 (19.2)	124 (17.8)	52 (21.8)	
Arteriosclerosis mild	372 (39.7)	281 (40.3)	76 (31.8)	
Arteriosclerosis moderate	295 (31.5)	211 (30.3)	77 (32.2)	
Arteriosclerosis severe	116 (12.4)	81 (11.6)	34 (14.2)	
CAA				0.322
CAA none	610 (65.2)	415 (59.5)	130 (54.4)	
CAA mild	264 (28.2)	175 (25.1)	61 (25.5)	
CAA moderate	139 (14.9)	84 (12.1)	36 (15.1)	
CAA severe	43 (4.6)	23 (3.3)	12 (5.0)	

Abbreviations: CAA = cerebral amyloid angiopathy; CDR-SOB = Clinical Dementia Rating scale Sum Of Boxes; CERAD = Consortium to Establish a Registry for Alzheimer Disease; HScl = hippocampal sclerosis; MMSE = Mini-Mental State Examination; NFT = neurofibrillary tangle; NP = neuritic plaque.

conflicting results, with some reporting a disadvantage of *APOE*ε4 carriers³⁸⁻⁴⁰ and others, no difference⁴¹ or even an advantage^{42,43} (reviewed in reference 44).

Unlike our prior analysis of a NACC sample with moderate/high ADNC, in this normal aging-early AD sample, we did not detect a statistically significant protective effect of the *APOE*ε2 allele over the *APOE*ε3 allele for any of the cognitive outcome measures, whereas the *APOE*ε2 vs *APOE*ε4 contrast did yield a protective effect of *APOE*ε2 based on MMSE, CDR-SOB (except in model 3), and attention domain trajectories. Only 7 of the 153 *APOE*ε2 participants in our sample were homozygotes—a rare genotype associated with an extremely low likelihood of developing AD⁴⁵ and a slower rate of cognitive decline⁴⁶—precluding any dose-response analysis.

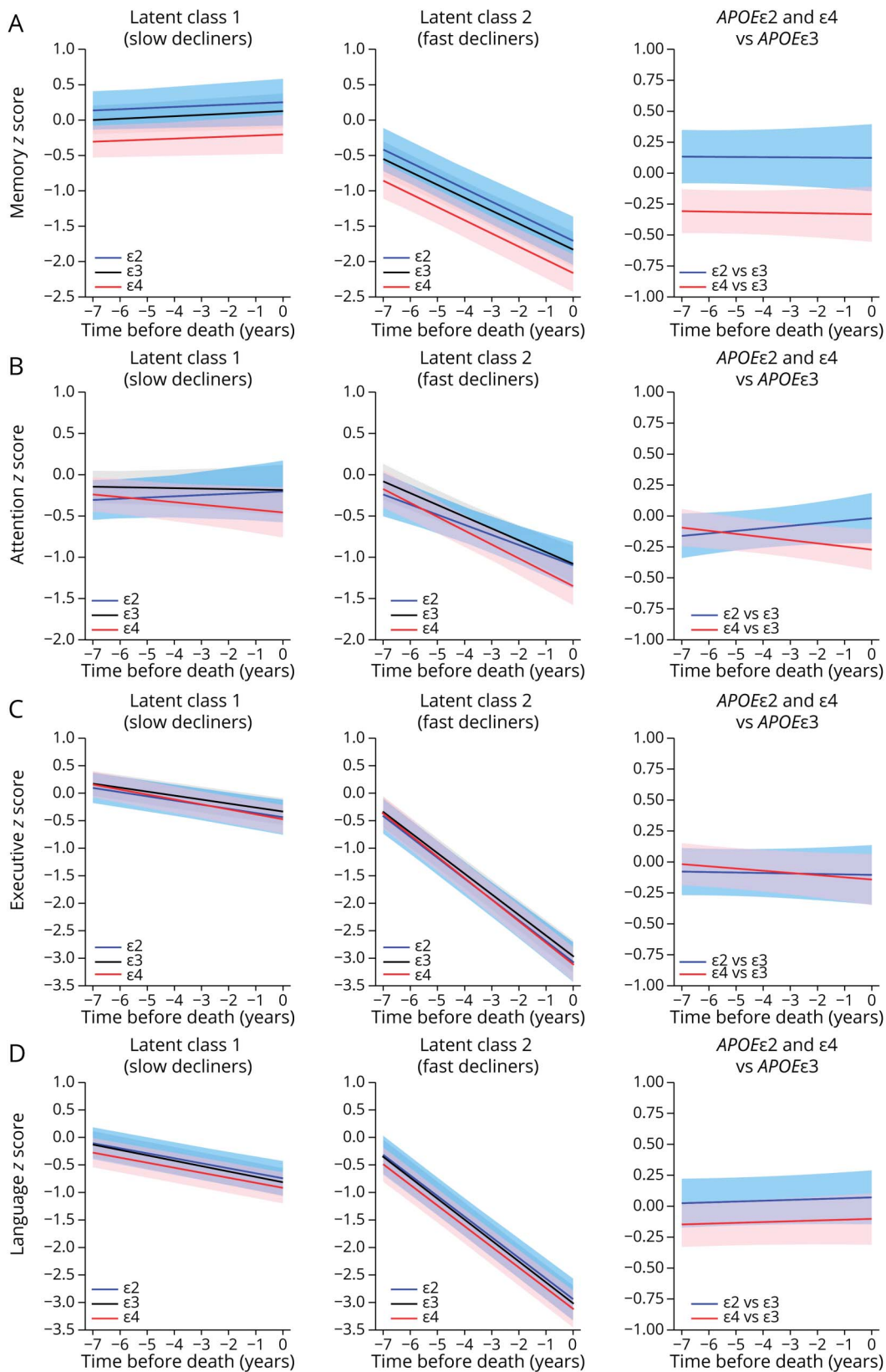
The findings reported in this study have potentially important pathophysiologic implications. Applying the resistance vs resilience framework⁴⁷ to this study and our prior analyses of the NACC autopsy cohort,^{4,11,23} it appears that the *APOE*ε4 allele not only promotes ADNC (including CAA) but also lowers the brain ability to cope with them (i.e., resilience), with an effect size augmenting as ADNC severity increases. Conversely, the *APOE*ε2 allele clearly provides resistance against the accumulation of ADNC^{11,45} but would only confer detectable resilience against cognitive impairment as substantial ADNC (i.e., moderate and frequent NPs and the Braak NFT stage ≥ III) accumulate in the brain.^{4,11} Furthermore, the demonstration of *APOE*ε4-linked neuropathology-independent effects on cognitive decline raises the question of what the unmeasured mediator(s) of such deleterious effects might be. Microglial and blood-brain barrier dysfunction are primary suspects because recent studies have reported that *APOE*ε4 exacerbates microglial phagocytic and proinflammatory transcriptional programs⁴⁸⁻⁵⁰ and disrupts the blood-brain barrier integrity and function.^{18,51} But neuronal and

synaptic mechanisms have also been proposed, and a multitarget scenario is plausible.⁵² Additionally, these results have relevant implications for the design and interpretation of preventative and therapeutic clinical trials targeting early AD. Specifically, they are in agreement with simulation trials indicating that a strategy of enrichment in *APOE*ε4 carriers may enhance the power to detect significant effect differences between the treatment and placebo groups within the duration of the trial, provided that the intervention tested has an equal response in *APOE*ε4 carriers and noncarriers^{53,54} (but see also references 55 and 56). Moreover, they reinforce the goal of developing *APOE*ε4-directed therapies regardless of their downstream effects on ADNC levels.⁵⁷

Some limitations of our methodology should be acknowledged. First, the ethnic/racial composition of this sample limits the generalizability of our findings to other racial/ethnic groups. The *APOE*ε4 allele is known to have a weaker association with AD risk in Blacks and Hispanics,⁵⁷ but its impact on rate of cognitive decline needs to be investigated. Second, we could not perform an ε4 allele dose-response analysis because of the low number of *APOE*ε4 homozygotes. Third, we did not include interaction terms such as the interaction between *APOE* genotype and comorbid pathologies and between these and the slope of cognitive decline to avoid overfitting of the models. Fourth, we could not evaluate the impact of *APOE* alleles on the visuospatial domain because the appropriate tests for this domain (e.g., Benson figure copy) were only available in the version 3 of the UDS (data freeze March 2014).²¹ Last, TDP-43 data were not available for a large proportion of subjects because this was incorporated to the NACC neuropathology protocol in 2014²²; therefore, HScl was used instead as an imperfect proxy of TDP-43 proteinopathy.⁵⁸

In summary, in a sample selected to represent the normal aging-early AD continuum, the *APOE*ε4 allele is associated

Figure 3 Effects of *APOE* Genotype on Cognitive Domain-Specific Trajectories



Model 3-based trajectories for memory- (A), attention- (B), executive- (C), and language-specific (D) composite z scores with the intercept at the time of death calculated for an 86-year-old woman with 15 years of education and autopsy findings of CERAD NP score moderate and Braak NFT stage III/IV. Graphs depict the 3 *APOE* groups in latent class 1 (slow decliners) and latent class 2 (fast decliners) as well as the differences *APOE*ε4 vs *APOE*ε3 and *APOE*ε2 vs *APOE*ε3. Shaded areas correspond to the 95% CIs. CERAD = Consortium to Establish a Registry for Alzheimer Disease; NFT = neurofibrillary tangle; NP = neuritic plaque.

with a modest but statistically significant acceleration of the cognitive decline rate even after controlling for its effects on ADNC and comorbid pathologies. Further studies to identify the mechanism(s) of these differential effects of *APOE* alleles on cognition in the normal aging-AD continuum are warranted.

Acknowledgment

The NACC database is funded by the NIA/NIH Grant U24 AG072122. NACC data are contributed by the NIA-funded ADCRCs: P30 AG062429 (PI James Brewer, MD, PhD), P30 AG066468 (PI Oscar Lopez, MD), P30 AG062421 (PI Bradley Hyman, MD, PhD), P30 AG066509 (PI Thomas Grabowski, MD), P30 AG066514 (PI Mary Sano, PhD), P30 AG066530 (PI Helena Chui, MD), P30 AG066507 (PI Marilyn Albert, PhD), P30 AG066444 (PI John Morris, MD), P30 AG066518 (PI Jeffrey Kaye, MD), P30 AG066512 (PI Thomas Wisniewski, MD), P30 AG066462 (PI Scott Small, MD), P30 AG072979 (PI David Wolk, MD), P30 AG072972 (PI Charles DeCarli, MD), P30 AG072976 (PI Andrew Saykin, PsyD), P30 AG072975 (PI David Bennett, MD), P30 AG072978 (PI Neil Kowall, MD), P30 AG072977 (PI Robert Vassar, PhD), P30 AG066519 (PI Frank LaFerla, PhD), P30 AG062677 (PI Ronald Petersen, MD, PhD), P30 AG079280 (PI Eric Reiman, MD), P30 AG062422 (PI Gil Rabinovici, MD), P30 AG066511 (PI Allan Levey, MD, PhD), P30 AG072946 (PI Linda Van Eldik, PhD), P30 AG062715 (PI Sanjay Asthana, MD, FRCP), P30 AG072973 (PI Russell Swerdlow, MD), P30 AG066506 (PI Todd Golde, MD, PhD), P30 AG066508 (PI Stephen Strittmatter, MD, PhD), P30 AG066515 (PI Victor Henderson, MD, MS), P30 AG072947 (PI Suzanne Craft, PhD), P30 AG072931 (PI Henry Paulson, MD, PhD), P30 AG066546 (PI Sudha Seshadri, MD), P20 AG068024 (PI Erik Roberson, MD, PhD), P20 AG068053 (PI Justin Miller, PhD), P20 AG068077 (PI Gary Rosenberg, MD), P20 AG068082 (PI Angela Jefferson, PhD), P30 AG072958 (PI Heather Whitson, MD), and P30 AG072959 (PI James Leverenz, MD).

Study Funding

This study was supported by the NIH (NIA K08AG064039 to A. Serrano-Pozo, NINDS R01NS094610 to J. Qian and R.A. Betensky, the Massachusetts Alzheimer's Disease Research Center NIA P30 AG062421 to A. Serrano-Pozo and B.T. Hyman, and the New York University Alzheimer's Disease Research Center NIA P30 AG066512 to R.A. Betensky) and The Jack Satter Foundation, Inc. (A. Serrano-Pozo).

Disclosure

J. Qian reports no disclosures; Y. Zhang currently works for Sanofi Genzyme; R.A. Betensky serves on the data safety monitoring boards of Biogen, Reata, and PTC Therapeutics, serves as a consultant for Cowen Inc., Pfizer, and Amgen, and has served as an expert witness for Amarin, Actavis, Amazon, Teva, Padagis, and Apotex; B.T. Hyman has a family member who works at Novartis and owns stock in Novartis, serves on the scientific advisory board of Dewpoint and owns stock,

serves on a scientific advisory board or is a consultant for Abbvie, Arvinas, Biogen, Novartis, Cell Signaling Technologies, Sangamo, Sanofi, Takeda, US Department of Justice, and Vigil, and his laboratory is supported by sponsored research agreements with Abbvie, F Prime, and Spark as well as research grants from the NIH (PI), the Cure Alzheimer's Fund (PI), the Tau Consortium (PI), The JPB Foundation (PI), the Alzheimer's Association (mentor), and BrightFocus (mentor); A. Serrano-Pozo's laboratory is funded by the NIH/NIA, the Alzheimer's Association, The Jack Satter Foundation Inc., and The Karen Toffler Charitable Trust, and he has a material transfer agreement with Ionis Pharmaceuticals, Inc. Full disclosure form information provided by the authors is available with the full text of this article at Neurology.org/NG.

Publication History

Received by *Neurology: Genetics* August 22, 2022. Accepted in final form November 16, 2022. Submitted and externally peer reviewed. The handling editor was Associate Editor Suman Jayadev, MD.

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Neurol Genet 2023;9;

DOI 10.1212/NXG.0000000000200055

This information is current as of January 20, 2023

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