

Association of *APOE* Genotype With Heterogeneity of Cognitive Decline Rate in Alzheimer Disease

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Abstract

Objective

To test the hypothesis that the *APOE* genotype is a significant driver of heterogeneity in Alzheimer disease (AD) clinical progression, which could have important implications for clinical trial design and interpretation.

Methods

We applied novel reverse-time longitudinal models to analyze the trajectories of Clinical Dementia Rating Sum of Boxes (CDR-SOB) and Mini-Mental State Examination (MMSE) scores—2 common outcome measures in AD clinical trials—in 1,102 autopsy-proven AD cases (moderate/frequent neuritic plaques and Braak tangle stage III or greater) from the National Alzheimer's Coordinating Center Neuropathology database resembling participants with mild to moderate AD in therapeutic clinical trials.

Results

APOE $\epsilon 4$ carriers exhibited ≈ 1.5 times faster CDR-SOB increase than *APOE* $\epsilon 3/\epsilon 3$ carriers (2.12 points per year vs 1.44 points per year) and ≈ 1.3 times faster increase than *APOE* $\epsilon 2$ carriers (1.65 points per year), whereas *APOE* $\epsilon 2$ vs *APOE* $\epsilon 3/\epsilon 3$ difference was not statistically significant. *APOE* $\epsilon 4$ carriers had ≈ 1.1 times faster MMSE decline than *APOE* $\epsilon 3/\epsilon 3$ carriers (-3.45 vs -3.03 points per year) and ≈ 1.4 times faster decline than *APOE* $\epsilon 2$ carriers (-2.43 points per year), whereas *APOE* $\epsilon 2$ carriers had ≈ 1.2 times slower decline than *APOE* $\epsilon 3/\epsilon 3$ carriers (-2.43 vs -3.03 points per year). These findings remained largely unchanged after controlling for the effect of AD neuropathologic changes on the rate of cognitive decline and for the presence and severity of comorbid pathologies.

Conclusion

Compared to the *APOE* $\epsilon 3/\epsilon 3$ reference genotype, the *APOE* $\epsilon 2$ and $\epsilon 4$ alleles have opposite (slowing and accelerating, respectively) effects on the rate of cognitive decline, which are clinically relevant and largely independent of the differential *APOE* allele effects on AD and comorbid pathologies. Thus, *APOE* genotype contributes to the heterogeneity in rate of clinical progression in AD.

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Glossary

A β = β -amyloid; **AD** = Alzheimer disease; **ADC** = Alzheimer Disease Center; **ADNC** = Alzheimer disease neuropathological changes; **BIC** = Bayesian information criterion; **CAA** = cerebral amyloid angiopathy; **CDR-SOB** = Clinical Dementia Rating Sum of Boxes; **CERAD** = Consortium to Establish a Registry of Alzheimer's Disease; **CI** = confidence interval; **HScl** = hippocampal sclerosis; **LB** = Lewy bodies; **MMSE** = Mini-Mental State Examination; **NACC** = National Alzheimer's Coordinating Center; **NFT** = neurofibrillary tangle; **NP** = neuritic plaque; **ROSMAP** = Religious Orders Study and Rush Memory and Aging Project; **TDP-43** = transactive response DNA-binding protein 43kDa; **UDS** = Uniform Data Set.

One milestone in Alzheimer disease (AD) clinical trials has been the incorporation of PET imaging and CSF biomarkers to exclude AD mimics and even design secondary prevention trials for participants with preclinical AD.¹ However, trial success still depends on detecting a treatment vs placebo change in cognitive decline rate, and this is hampered by the substantial variability in rate of clinical progression among participants. One potential contributor to this heterogeneity is the *APOE* genotype, given the opposing effects of the *APOE* ϵ 4 and ϵ 2 alleles on AD risk, age at symptom onset, and AD neuropathologic changes (ADNC).²⁻⁵ However, prior longitudinal clinical studies after symptom onset have reported conflicting results—accelerating,⁶⁻⁹ neutral,¹⁰⁻¹² and slowing effects¹³⁻¹⁵ for *APOE* ϵ 4 vs slowing effects for *APOE* ϵ 2¹⁶⁻¹⁸—likely due, at least in part, to the suboptimal accuracy of a clinically based AD diagnosis.^{19,20} Another proposed driver is the co-occurrence of ≥ 2 brain pathologies,²¹ each of which could independently contribute to cognitive impairment and could be influenced by the *APOE* genotype.²²⁻²⁴

We tested the hypothesis that the *APOE* alleles differentially affect the cognitive decline rate in an autopsy-proven clinical trial—eligible AD sample. We circumvented the limitations of prior clinical studies by (1) selecting a National Alzheimer's Coordinating Center (NACC) sample with sufficient ADNC to warrant enrollment in current biomarker-based therapeutic clinical trials, (2) applying novel reverse-time longitudinal models to link autopsy findings with cognitive trajectories during life, and (3) controlling for the effects of ADNC on cognitive decline rate and for comorbid pathologies.

Methods

Standard Protocol Approvals, Registrations, and Patient Consents

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

Inclusion and Exclusion Criteria

The NACC study is a multicenter longitudinal cohort study conducted in the ≥ 30 ADCs across the United States. Briefly,

participants undergo baseline and annual follow-up visits with demographics and standard motor, behavioral, functional, and neuropsychological evaluations collected in a Uniform Data Set (UDS).^{25,26} Participants can donate their brain on death for research purposes, including a standardized neuropathologic evaluation.²⁷ The NACC Neuropathology database was interrogated for UDS visits conducted between September 2005 and November 2018. Inclusion criteria included age at death ≥ 50 years and last visit < 2 years from the time of death. Exclusion criteria were unknown *APOE* genotype, *APOE* ϵ 2/ ϵ 4 genotype (due to the small number of cases and presumed cancellation of *APOE* ϵ 2 and *APOE* ϵ 4 opposite effects), a primary neuropathologic diagnosis other than ADNC, and cognitive impairment attributed to medical illness, medications, or alcohol. To mimic the scenario of a clinical trial with biomarker-based enrollment of participants, we excluded those with none/sparse neuritic plaques (NP) at postmortem examination because they would have had a negative baseline amyloid PET scan before enrollment.²⁸ Similarly, to resemble a therapeutic rather than preventive design, we included only those with a Braak neurofibrillary tangle (NFT) stage III or higher because individuals with limbic (III/IV) or isocortical (V/VI) Braak NFT stages would have had tau PET scans demonstrating limbic and cortical tau deposits.²⁹ Our prior inverse probability–weighting analyses on the NACC Neuropathology database demonstrated little impact of potential autopsy-related selection bias in clinicopathologic correlations.³⁰

Data Collection

Data collected included (1) demographic variables (age at each visit and at death, sex, years of education, and length of follow-up), (2) *APOE* genotype, (3) neuropsychological scores at each visit (Clinical Dementia Rating Sum of Boxes [CDR-SOB; CDR Dementia Staging Instrument], Mini-Mental State Examination [MMSE], digit span forward and backward, Trail Making Tests A and B, Wechsler Adult Intelligence Scale Digit-Symbol Substitution Test, logical memory immediate and delayed recall, semantic fluency [animals and vegetables in 1 minute], and Boston Naming Test), and (4) autopsy neuropathologic findings (Consortium to Establish a Registry of Alzheimer's Disease [CERAD] NP score, Braak NFT stage, presence of hippocampal sclerosis [HScl] and Lewy bodies [LB], and presence and severity of both arteriosclerosis and cerebral amyloid angiopathy [CAA; none, mild, moderate, severe]), all of which are associated with antemortem CDR-SOB score within the AD continuum.³⁰

Table 1 Characteristics of This NACC Autopsy Cohort

Characteristic	Total (n = 1,109)	APOE ε2	APOE ε3/ε3	APOE ε4
APOE genotype, n (%)^a	NA	45 (4.0)	442 (39.9)	622 (56.1)
Female, n (%)	474 (42.7)	22 (48.9)	206 (46.6)	246 (39.5)
Age at first visit, mean (SD), y	77.94 (9.48)	79.82 (10.68)	79.45 (9.51)	76.73 (9.20)
Age at death, mean (SD), y	82.1 (9.5)	84.9 (11.3)	83.7 (9.6)	80.8 (9.2)
Education, mean (SD), y^b	15.3 (3.2)	15.6 (3.6)	15.3 (3.3)	15.2 (3.1)
Visits, median (IQR), n	3 (2–6)	4 (3–7)	3.5 (2–6)	3 (2–6)
Total length of follow-up from initial visit to death, median (IQR), y	3.80 (1.83–6.09)	5.00 (3.10–6.55)	3.80 (1.80–6.04)	3.74 (1.77–6.05)
Length of follow-up from initial visit to last clinical visit, median (IQR), y	2.99 (1.03–5.36)	4.45 (2.24–5.94)	2.99 (1.03–5.38)	2.95 (1.02–5.24)
Length of follow-up from last clinical visit to death, median (IQR), y	0.68 (0.32–1.05)	0.95 (0.57–1.39)	0.61 (0.29–1.06)	0.68 (0.33–1.02)
CDR-SOB score, mean (SD)				
First visit	7.5 (6.0)	3.8 (4.8)	6.9 (5.9)	8.2 (6.0)
Final visit	12.9 (5.8)	8.7 (6.4)	12.0 (6.2)	13.8 (5.2)
MMSE score, mean (SD)				
First visit	19.2 (8.6)	23.3 (7.5)	20.0 (8.5)	18.3 (8.7)
Final visit	13.8 (9.4)	19.5 (8.4)	15.3 (9.4)	12.3 (9.2)
Memory z score, mean (SD)				
First visit	-1.99 (1.09)	-1.31 (1.36)	-1.82 (1.20)	-2.17 (0.93)
Final visit	-2.19 (1.09)	-1.52 (1.36)	-2.05 (1.20)	-2.39 (0.91)
Attention z score, mean (SD)				
First visit	-0.76 (1.08)	-0.50 (1.18)	-0.69 (1.05)	-0.84 (1.08)
Final visit	-1.24 (1.25)	-0.82 (0.82)	-1.14 (1.18)	-1.38 (1.33)
Executive z score, mean (SD)				
First visit	-1.15 (1.44)	-0.63 (1.30)	-1.15 (1.47)	-1.19 (1.42)
Final visit	-1.76 (1.60)	-1.65 (1.71)	-1.82 (1.55)	-1.72 (1.64)
Language z score, mean (SD)				
First visit	-1.69 (1.47)	-1.14 (1.58)	-1.69 (1.48)	-1.74 (1.44)
Final visit	-2.55 (1.59)	-2.03 (1.72)	-2.51 (1.55)	-2.67 (1.59)
CERAD NP score, N (%)				
Moderate	289 (26.1)	17 (37.8)	152 (34.4)	120 (26.1)
Frequent	820 (73.9)	28 (62.2)	290 (65.6)	502 (73.9)
Braak NFT stage, N (%)				
Limbic (III/IV)	215 (19.4)	19 (42.2)	111 (25.1)	85 (13.7)
Isocortical (V/VI)	894 (80.6)	26 (57.8)	331 (74.9)	537 (86.3)
LB present, N (%)	390 (35.4)	19 (42.2)	137 (31.2)	234 (37.8)
HScl, present, n (%)	128 (11.8)	7 (15.6)	47 (11.0)	74 (12.1)
Arteriolosclerosis, n (%)				
None	165 (17.4)	6 (16.2)	70 (18.9)	89 (16.5)
Mild	336 (35.4)	11 (29.7)	137 (36.9)	188 (34.8)

Continued

Table 1 Characteristics of This NACC Autopsy Cohort (continued)

Characteristic	Total (n = 1,109)	APOE ε2	APOE ε3/ε3	APOE ε4
Moderate	325 (34.2)	15 (40.5)	123 (33.2)	187 (34.6)
Severe	123 (13.0)	5 (13.5)	41 (11.1)	77 (14.2)
CAA, n (%)				
None	244 (22.4)	12 (27.3)	147 (33.7)	85 (13.9)
Mild	342 (31.3)	10 (22.7)	142 (32.6)	190 (31.1)
Moderate	299 (27.4)	11 (25.0)	90 (20.6)	198 (32.4)
Severe	206 (18.9)	11 (25.0)	57 (13.1)	138 (22.6)

Abbreviations: CAA = cerebral amyloid angiopathy; CDR-SOB = Clinical Dementia Rating scale Sum of Boxes; CERAD = Consortium to Establish a Registry of Alzheimer's Disease; HScI = hippocampal sclerosis; IQR = interquartile range; LB = Lewy bodies; MMSE = Mini-Mental State Examination; NA = not applicable; NACC = National Alzheimer's Coordinating Center; NFT = neurofibrillary tangle; NP = neuritic plaque.

^a APOE ε2/ε4 carriers were excluded.

^b Not available for 7 individuals.

Statistics

Statistical analyses were run in R software version 3.6 using R package lamm (R Foundation for Statistical Computing).³¹ Outcome variables included CDR-SOB score, MMSE score, and cognitive domain-specific scores. For the last ones, the scores of the neuropsychological outcome variables at each visit were converted into *z* scores. Briefly, tests were grouped in 4 cognitive domains based on a validated factor structure³² as follows: *z* scores for logical memory immediate and delayed recall were averaged into a memory composite score; *z* scores for Trail Making Tests A and B and Digit-Symbol Substitution Test were averaged into an executive composite score; *z* scores for digits forward trials and length, and digits backward trials and length were averaged into an attention composite score; and *z* scores for animals and vegetables in 1 minute and Boston Naming Test were averaged into a language composite score.

To evaluate the association between APOE genotype and rate of cognitive decline as reflected in longitudinal global functional and cognitive measures (CDR-SOB and MMSE scores), we used statistical methods previously described in detail elsewhere.³³ Briefly, the main specifications and advantages of this methodology are as follows:

1. Reverse time. Traditional forward time analysis precludes linking the neuropathologic measures with individual cognitive trajectories during life because neuropathologic measures are time varying and measurable only at postmortem examination. Therefore, we treated the neuropathologic variables as baseline covariates and modeled the longitudinal cognitive trajectories in reverse time, that is, beginning with neuropsychological scores at the visit closest to death (<2 years prior per inclusion criteria) and moving backward toward the scores obtained at the initial visit.

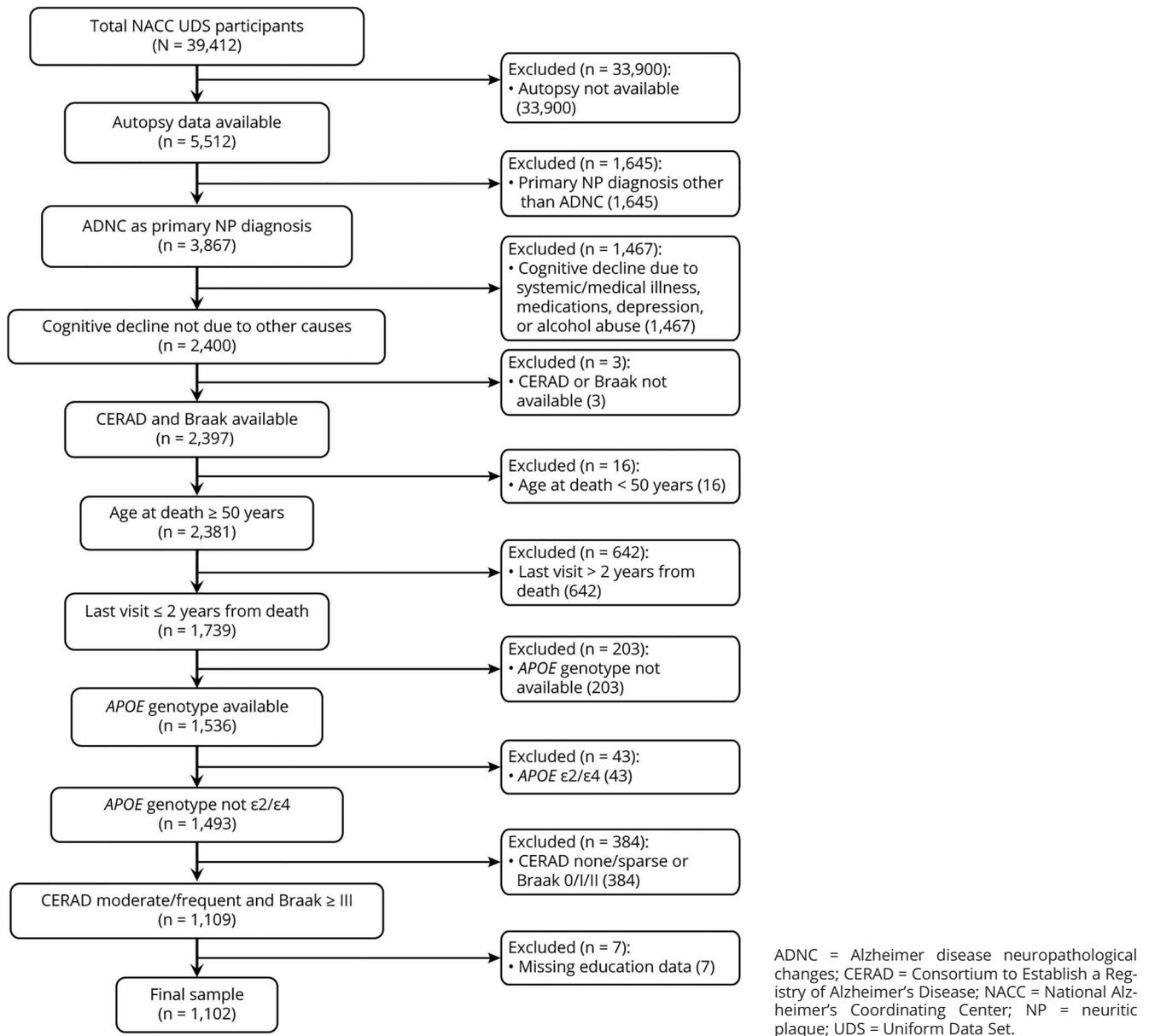
2. Shared latent classes. Longitudinal cognitive trajectories are truncated by events such as last visit or death, and the neuropathologic variables are ascertained at death. Therefore, any potential association between the longitudinal cognitive trajectories and these time-to-events must be accounted for. To achieve this and to control for any unmeasured (latent) features that may be associated with both, we implemented a joint latent class model for the longitudinal cognitive trajectories (mixed-effects submodel), the time-to-event analyses (death to first NACC visit, Cox proportional hazards submodel), and class membership (logistic submodel) and evaluated the number of latent classes best supported by the data with the Bayesian information criterion (BIC).

3. Change point. Longitudinal neuropsychological testing is often affected by floor or ceiling effects as the dementia advances and individuals become untestable. To account for these possible floor/ceiling effects of cognitive outcomes and to capture any change in the slope of cognitive trajectories in advanced AD, we used a piecewise linear model with 2 different linear slopes before and after a change point and determined the change point best supported by the data (2, 2.5, or 3 years before death) with the BIC. We decided not to use change point as a random variable due to the complexity of the model.

4. Right truncation adjustment by time to death. Because this is a clinicopathologic autopsy sample, time to last NACC visit is right truncated by time to death. To avoid potential bias derived from the oversampling of shorter times to death, we adjusted for right truncation of time to last visit by time to death. For a more detailed discussion of the statistical methodology, we refer the reader to our previous article.³²

The covariates used in the mixed-effects submodel for the longitudinal cognitive trajectory analyses and in Cox

Figure 1 Flowchart of Study Participants



proportional hazards submodel for the time-to-event analyses included sex, education, age at death, *APOE* genotype (presence vs absence of $\epsilon 2$ allele, and presence vs absence of $\epsilon 4$ allele, with $\epsilon 3/\epsilon 3$ carriers as reference group), CERAD NP score (frequent vs moderate), and Braak NFT stages (V/VI vs III/IV). After selection of the most suitable number of latent classes and change point for each cognitive variable, CERAD NP score, Braak NFT stage, and the neuropathologic comorbid pathologies (i.e., presence of HScl and LB, presence and severity of both arteriosclerosis and CAA [none, mild, moderate, severe]) with a significant association with the antemortem cognitive variable were added to the models. To assess the differential effects of *APOE* genotype, CERAD NP score, and Braak NFT stage on cognitive trajectory, we allowed interaction terms between each of these 3 variables

and the slope before or after the change point in the modeling. We started with simpler models with *APOE* genotype as predictor and each cognitive measure as outcome variable, adjusted by age, sex, education, CERAD NP score, and Braak NFT stage (model 1). To investigate whether *APOE* genotype effects on the rate of cognitive decline are independent from ADNC and comorbid pathologies, we then built more complex models by further adjusting for interaction terms between CERAD NP score or Braak NFT stage and the slope before or after the change point and for concurrent pathologies (model 2). To use the autopsy variables in the forward-time translation of the analyses, we assumed that amyloid plaque burden does not substantially change over the clinical course of AD and that the sequence of Braak NFT stages is preserved over the extent of longitudinal follow-up. These

Table 2 Associations of *APOE* Alleles With Neuropathologic Findings at Autopsy

	Neuropathologic outcome measure							
	Braak NFT stage (V/VI vs III/IV)	CERAD NP score (frequent vs moderate)	CAA			LB (present vs none)	HScl (present vs none)	Arteriosclerosis (mild vs none, moderate vs mild, or severe vs moderate)
			Mild vs none	Moderate vs mild	Severe vs moderate			
Log OR (95% CI)	Log OR (95% CI)	Log OR (95% CI)	Log OR (95% CI)	Log OR (95% CI)	Log OR (95% CI)	Log OR (95% CI)	Log OR (95% CI)	
Presence of <i>APOE</i> ε2 allele	-0.19 (-0.29 to -0.08)	-0.10 (-0.22 to 0.03)	0.06 (-0.24 to 0.36)	0.06 (-0.24 to 0.36)	0.06 (-0.24 to 0.36)	0.07 (-0.08 to 0.21)	0.03 (-0.07 to 0.13)	0.03 (-0.34 to 0.39)
Presence of <i>APOE</i> ε4 allele	0.06 (0.02 to 0.11)	0.12 (0.07 to 0.17)	0.80 (0.46 to 1.14)	0.48 (0.15 to 0.81)	-0.01 (-0.40 to 0.37)	0.05 (-0.01 to 0.11)	0.02 (-0.02 to 0.06)	0.16 (0.01 to 0.30)
Presence of 1 <i>APOE</i> ε4 allele	0.05 (0.01 to 0.10)	0.13 (0.07 to 0.18)	0.90 (0.55 to 1.26)	0.25 (-0.07 to 0.57)	-0.18 (-0.55 to 0.21)	0.04 (-0.02 to 0.10)	0.02 (-0.02 to 0.06)	0.14 (-0.02 to 0.29)
Presence of 2 <i>APOE</i> ε4 alleles	0.10 (0.03 to 0.17)	0.11 (0.03 to 0.18)	0.75 (0.56 to 0.95)	0.75 (0.56 to 0.95)	0.75 (0.56 to 0.95)	0.07 (-0.02 to 0.16)	0.01 (-0.05 to 0.07)	0.22 (0.002 to 0.44)

Abbreviations: CAA = cerebral amyloid angiopathy; CERAD = Consortium to Establish a Registry of Alzheimer's Disease; CI = confidence interval; HScl = hippocampal sclerosis; LB = Lewy bodies; NFT = neurofibrillary tangle; NP = neuritic plaque; OR = odds ratio. All analyses were adjusted by age at death, sex, and education. Braak NFT stage and CAA analyses were also adjusted by CERAD NP score. Numbers of individuals with *APOE* ε2, *APOE* ε3/ε3, and *APOE* ε4 used are 44, 440, and 618, respectively. Numbers of individuals with 1 and 2 *APOE* ε4 alleles are 468 and 150, respectively.

assumptions are well supported by prior β-amyloid (Aβ) and tau PET imaging studies.^{34,35}

Data Availability

The NACC database is a public resource available to researchers. Data requests can be submitted online at the following NACC website: alz.washington.edu/NON-MEMBER/QUERY/datareqnew.html.

Results

Characteristics of Study Participants

Table 1 summarizes the demographic characteristics, neuropathologic autopsy findings, and cognitive measures of the study participants at baseline and last clinical visit. The flowchart in figure 1 shows that 1,109 individuals met the inclusion criteria and none of the exclusion criteria, but 7 individuals had to be excluded due to missing education data, hence the final sample of 1,102.

Selection of Neuropathologic Covariates for Longitudinal Modeling

To select the neuropathologic covariates for the longitudinal models, we first investigated the effects of *APOE* alleles on ADNC and comorbid pathologies in this convenience sample using multivariate regression models controlling for age at death, sex, and education (table 2). The *APOE* ε4 allele was associated with a higher CERAD NP score (frequent vs moderate), a higher Braak stage (V/VI vs III/IV), more severe CAA (moderate vs mild and mild vs none), and more severe

arteriosclerosis than the *APOE* ε3/ε3 reference group. An *APOE* ε4 dose-dependent effect was observed for most of these associations. In contrast, the *APOE* ε2 allele was associated with a lower Braak stage (III/IV vs V/VI) compared to the *APOE* ε3/ε3 group but not with a lower CERAD NP score (log odds ratio -0.10, 95% confidence interval [CI] -0.22 to 0.03, $p = 0.141$). No significant effect was observed for either *APOE* allele on the presence of LB or HScl. These results largely agree with those from a NACC sample of cognitively impaired (CDR-SOB score >0) selected to represent the AD clinicopathologic continuum.⁵

To further refine the selection of neuropathologic covariates, we examined the effects of concurrent pathologies (CAA, LB, HScl, and arteriosclerosis) on antemortem global cognitive measures (CDR-SOB and MMSE scores) and domain-specific composites. With age at death, sex, education, CERAD NP score, Braak NFT stage, and *APOE* genotype held constant, presence vs absence of HScl was associated with worse memory (-0.294 ± 0.063 , $p < 0.001$) and language (-0.666 ± 0.149 , $p < 0.001$), higher CDR-SOB (2.694 ± 0.436 , $p < 0.001$) and lower MMSE (-3.801 ± 0.752 , $p < 0.001$) scores, presence vs absence of LB with worse executive function (-0.286 ± 0.118 , $p = 0.015$), severe arteriosclerosis vs none with worse attention (-0.376 ± 0.140 , $p = 0.007$), and moderate and severe CAA vs none with higher CDR-SOB (moderate vs none 1.400 ± 0.410 , $p < 0.001$; severe vs none 0.977 ± 0.453 , $p = 0.031$) and lower MMSE (moderate vs none -2.478 ± 0.700 , $p = 0.002$; severe vs none -1.665 ± 0.792 , $p = 0.035$) scores.

Table 3 Effects of *APOE* Alleles on Cognitive Trajectories in Forward Time Scale >3 Years From Death

Outcome contrast	No.	Model 1			Model 2		
		Estimate	SE	95% CI	Estimate	SE	95% CI
CDR-SOB score	1,102						
CERAD NP FREQ vs MOD		NA	NA	NA	0.185	0.072	0.044 to 0.326
Braak NFT V/VI vs III/IV		NA	NA	NA	0.308	0.078	0.154 to 0.461
<i>APOE</i> genotype							
ε2 vs ε3/ε3		0.214	0.141	-0.063 to 0.492	0.204	0.130	-0.050 to 0.458
ε4 vs ε3/ε3		0.686	0.082	0.525 to 0.846	0.660	0.073	0.517 to 0.803
ε2 vs ε4		-0.471	0.129	-0.724 to -0.218	-0.456	0.136	-0.724 to -0.189
MMSE score	988						
CERAD NP FREQ vs MOD		NA	NA	NA	-0.402	0.101	-0.600 to -0.205
Braak NFT V/VI vs III/IV		NA	NA	NA	-0.234	0.113	-0.457 to -0.012
<i>APOE</i> genotype							
ε2 vs ε3/ε3		0.596	0.194	0.215 to 0.977	0.383	0.197	-0.003 to 0.769
ε4 vs ε3/ε3		-0.427	0.098	-0.619 to -0.235	-0.475	0.107	-0.684 to -0.266
ε2 vs ε4		1.023	0.195	0.640 to 1.405	0.858	0.207	0.453 to 1.263
Memory	814						
CERAD NP FREQ vs MOD		NA	NA	NA	-0.027	0.015	-0.056 to 0.003
Braak NFT V/VI vs III/IV		NA	NA	NA	-0.081	0.017	-0.114 to -0.047
<i>APOE</i> genotype							
ε2 vs ε3/ε3		0.033	0.031	-0.027 to 0.093	0.013	0.031	-0.047 to 0.073
ε4 vs ε3/ε3		-0.055	0.014	-0.083 to -0.027	-0.042	0.014	-0.070 to -0.014
ε2 vs ε4		0.088	0.031	0.027 to 0.148	0.055	0.031	-0.006 to 0.117
Attention	826						
CERAD NP FREQ vs MOD		NA	NA	NA	-0.026	0.020	-0.065 to 0.013
Braak NFT V/VI vs III/IV		NA	NA	NA	-0.079	0.024	-0.125 to -0.032
<i>APOE</i> genotype							
ε2 vs ε3/ε3		-0.010	0.035	-0.079 to 0.058	0.008	0.049	-0.088 to 0.104
ε4 vs ε3/ε3		-0.059	0.019	-0.097 to -0.022	-0.034	0.019	-0.070 to 0.002
ε2 vs ε4		0.049	0.036	-0.022 to 0.120	0.042	0.049	-0.055 to 0.138
Executive	611						
CERAD NP FREQ vs MOD		NA	NA	NA	-0.097	0.025	-0.146 to -0.049
Braak NFT V/VI vs III/IV		NA	NA	NA	-0.081	0.026	-0.132 to -0.030
<i>APOE</i> genotype							
ε2 vs ε3/ε3		-0.001	0.048	-0.095 to 0.093	0.099	0.045	0.010 to 0.187
ε4 vs ε3/ε3		-0.064	0.026	-0.115 to -0.014	-0.063	0.025	-0.112 to -0.014
ε2 vs ε4		0.063	0.048	-0.031 to 0.158	0.162	0.047	0.069 to 0.254
Language	826						
CERAD NP FREQ vs MOD		NA	NA	NA	-0.051	0.018	-0.086 to -0.016

Continued

Table 3 Effects of *APOE* Alleles on Cognitive Trajectories in Forward Time Scale >3 Years From Death (continued)

Outcome contrast	No.	Model 1			Model 2		
		Estimate	SE	95% CI	Estimate	SE	95% CI
Braak NFT V/VI vs III/IV		NA	NA	NA	-0.112	0.019	-0.151 to -0.074
<i>APOE</i> genotype							
$\epsilon 2$ vs $\epsilon 3/\epsilon 3$		0.119	0.039	0.043 to 0.194	0.210	0.037	0.137 to 0.283
$\epsilon 4$ vs $\epsilon 3/\epsilon 3$		-0.053	0.021	-0.094 to -0.011	-0.034	0.018	-0.069 to 0.001
$\epsilon 2$ vs $\epsilon 4$		0.171	0.037	0.099 to 0.243	0.245	0.038	0.170 to 0.319

Abbreviations: CERAD = Consortium to Establish a Registry of Alzheimer's Disease; CI = confidence interval; FREQ = frequent; MOD = moderate; NA = not applicable; NFT = neurofibrillary tangle; NP = neuritic plaque.

Estimates represent the unstandardized effect sizes (i.e., differences in trajectory slopes for each cognitive outcome and for each *APOE* genotype contrast). Model 1 is adjusted by age at death, sex, education, and Alzheimer disease neuropathological changes (CERAD NP score FREQ vs MOD and Braak NFT stage V/VI vs III/IV). Model 2 is further adjusted by the interactions between Alzheimer disease neuropathological changes and the slope of cognitive trajectories and by concurrent pathologies.

Longitudinal Modeling Reveals Opposing Effects of *APOE* Alleles on Global Cognitive Trajectory

Overall, on the basis of the BIC, longitudinal models with a change point at 3 years before death were preferred to those with a 2- or 2.5-year change point; with a change point at 3 years, the 2-latent-class model was preferred over the 1-latent-class model for all the cognitive outcomes.

Table 3 shows the results of these models controlled for age at death, sex, education, and ADNC severity (model 1) and with additional adjustments for the effect of ADNC on rate of cognitive decline and for presence and severity of concurrent pathologies (model 2) >3 years before death. Figure 2 illustrates these results. With only demographic and ADNC variables (model 1) held constant, *APOE* $\epsilon 4$ carriers exhibited ≈ 1.5 times faster progression by CDR-SOB score than *APOE* $\epsilon 3/\epsilon 3$ carriers (2.12 vs 1.44 points per year, 95% CI for the difference 0.53–0.85) and ≈ 1.3 times faster than *APOE* $\epsilon 2$ carriers (2.12 vs 1.65 points per year, 95% CI 0.22–0.72), but *APOE* $\epsilon 2$ carriers did not significantly differ from *APOE* $\epsilon 3/\epsilon 3$ carriers (1.65 vs 1.44 points per year, 95% CI -0.06 to 0.49) (figure 2, A and B). By MMSE score, *APOE* $\epsilon 4$ carriers had ≈ 1.1 times faster decline than *APOE* $\epsilon 3/\epsilon 3$ carriers (-3.45 vs -3.03 points per year, 95% CI -0.62 to -0.24) and ≈ 1.4 times faster decline than *APOE* $\epsilon 2$ carriers (-3.45 vs -2.43 points per year, 95% CI -1.41 to -0.64), whereas *APOE* $\epsilon 2$ carriers had ≈ 1.2 times slower decline than *APOE* $\epsilon 3/\epsilon 3$ carriers (-2.43 vs -3.03 points per year, 95% CI 0.22–0.98) (figure 2, E and F).

Holding all demographic, ADNC, and comorbid neuropathologic covariates constant and controlling for the effect of ADNC on the slope of cognitive decline (model 2), we found that *APOE* $\epsilon 4$ carriers exhibited ≈ 1.6 times faster clinical progression by CDR-SOB score than *APOE* $\epsilon 3/\epsilon 3$ carriers (1.80 vs 1.14 points per year, 95% CI for the difference 0.52–0.80) and ≈ 1.3 times faster clinical progression than *APOE* $\epsilon 2$ carriers (1.80 vs 1.34 points per year, 95% CI 0.19–0.72). In contrast, *APOE* $\epsilon 2$

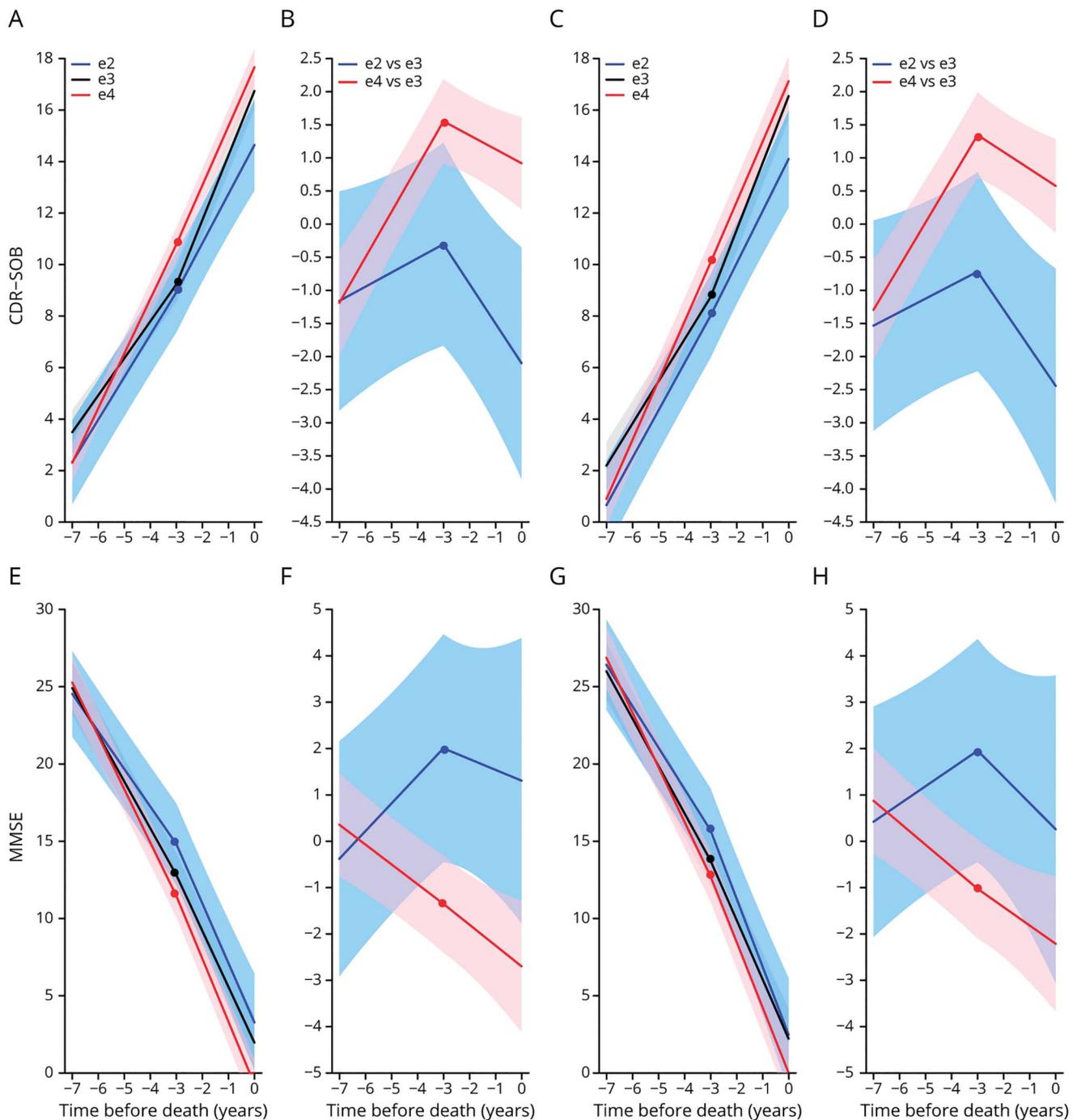
carriers did not significantly differ from *APOE* $\epsilon 3/\epsilon 3$ carriers (1.34 vs 1.14 points per year, 95% CI -0.05 to 0.46) (figure 2, C and D). By MMSE score, *APOE* $\epsilon 4$ carriers had ≈ 1.2 times faster decline than *APOE* $\epsilon 3/\epsilon 3$ carriers (-2.90 vs -2.43 points per year, 95% CI -0.68 to -0.27) and ≈ 1.4 times faster decline than *APOE* $\epsilon 2$ carriers (-2.90 vs -2.04 points per year, 95% CI -1.26 to -0.45), whereas *APOE* $\epsilon 2$ carriers had ≈ 1.2 times slower decline than *APOE* $\epsilon 3/\epsilon 3$ carriers (-2.04 vs -2.43 points per year, 95% CI 0.00–0.77) (figure 2, G and H).

As expected, the 3-year change point revealed and isolated ceiling effects of CDR-SOB score and floor effects of MMSE score within 3 years before death (table 4 and figure 2). In this time frame, the *APOE* $\epsilon 2$ carriers exhibited a significantly slower increase in CDR-SOB score compared to the *APOE* $\epsilon 3/\epsilon 3$ group (1.70 vs 2.28 points per year, 95% CI -1.07 to -0.08), but a ceiling effect of the CDR-SOB score in the *APOE* $\epsilon 4$ group is apparent, with a slower decline relative to the *APOE* $\epsilon 3/\epsilon 3$ group (2.02 vs 2.28 points per year, 95% CI -0.06 to -0.45). Indeed, 29% *APOE* $\epsilon 4$ carriers had already reached the maximum CDR-SOB score of 18 at the 3-year change time point compared to 19% of *APOE* $\epsilon 3/\epsilon 3$ carriers. Similarly, the *APOE* $\epsilon 4$ carriers showed a significantly faster decline in MMSE score than the *APOE* $\epsilon 3/\epsilon 3$ group (-3.37 vs -2.97 points per year, 95% CI [-0.79 to -0.01]), but a floor effect of the MMSE score became apparent in the *APOE* $\epsilon 3/\epsilon 3$ group, causing *APOE* $\epsilon 2$ carriers to show a nonsignificant trend toward an apparent faster decline (-3.54 vs -2.97 points per year, 95% CI -1.47 to 0.34). As an example, 8.2% of *APOE* $\epsilon 3/\epsilon 3$ carriers had reached an MMSE score ≤ 3 at the 3-year change time point vs none of the *APOE* $\epsilon 2$ carriers.

Longitudinal Modeling Reveals Opposing Effects of *APOE* Alleles on Specific Cognitive Domains

Without controlling for the effect of ADNC on rate of cognitive decline or for concurrent pathologies, *APOE* $\epsilon 4$ carriers had a significantly faster decline in all 4 domains analyzed

Figure 2 Effect of *APOE* Alleles on Global Functional and Cognitive Outcome Measures (CDR-SOB and MMSE) Scores



(A and E) Model-based cognitive trajectories of Clinical Dementia Rating Sum of Boxes (CDR-SOB) (A) and Mini-Mental State Examination MMSE (E) scores by *APOE* allele groups (*APOE* $\epsilon 3/\epsilon 3$, *APOE* $\epsilon 2$, and *APOE* $\epsilon 4$ carriers) with the intercept at the time of death calculated for an 82-year-old woman with 15 years of education and autopsy findings of frequent Consortium to Establish a Registry of Alzheimer's Disease (CERAD) neuritic plaque (NP) score and Braak neurofibrillary tangle (NFT) stage V/VI, but without adjustments for the effect of these neuropathologic variables on the rate of cognitive decline or for comorbid pathologies (model 1). (C and G) Model-based cognitive trajectories of CDR-SOB (C) and MMSE (G) scores by *APOE* group with the intercept at the time of death calculated for an 82-year-old woman with 15 years of education and autopsy findings of frequent CERAD NP score and Braak NFT stage V/VI and no comorbid pathologies and with adjustments for the effect of AD neuropathologic variables (CERAD and Braak) on the rate of cognitive decline and for comorbid pathologies (model 2). Note the nearly identical trajectories with and without controlling for neuropathology. (B, D, F, and H) Difference of model-based cognitive trajectories of CDR-SOB (B and D) and MMSE (F and H) scores between *APOE* allele groups (*APOE* $\epsilon 2$ and *APOE* $\epsilon 4$ vs *APOE* $\epsilon 3/\epsilon 3$ carriers) under models 1 (B and F) and 2 (D and H). Shaded areas represent the corresponding 95% confidence intervals.

(memory, executive, attention, language) compared to *APOE* $\epsilon 3/\epsilon 3$ carriers, whereas *APOE* $\epsilon 2$ carriers had a significantly slower decline in language compared to *APOE* $\epsilon 3/\epsilon 3$ carriers

and in both memory and language compared to *APOE* $\epsilon 4$ carriers (table 3, figure 3, and figure e-1 available from Dryad: doi.org/10.5061/dryad.w0vt4b8qk). The models controlling

Table 4 Floor and Ceiling Effects of *APOE* Alleles on Cognitive Trajectories in Forward Time Scale Within 3 Years From Death

Outcome contrast	No.	Model 1			Model 2		
		Estimate	SE	95% CI	Estimate	SE	95% CI
CDR-SOB score	1,102						
CERAD NP FREQ vs MOD		NA	NA	NA	0.081	0.117	-0.149 to 0.311
Braak NFT V/VI vs III/IV		NA	NA	NA	0.246	0.138	-0.024 to 0.517
<i>APOE</i> genotype							
ε2 vs ε3/ε3		-0.599	0.246	-1.082 to -0.116	-0.575	0.252	-1.070 to -0.080
ε4 vs ε3/ε3		-0.212	0.098	-0.403 to -0.020	-0.256	0.099	-0.451 to -0.062
ε2 vs ε4		-0.388	0.244	-0.866 to 0.091	-0.319	0.251	-0.811 to 0.173
MMSE score	988						
CERAD NP FREQ vs MOD		NA	NA	NA	-0.450	0.219	-0.878 to -0.021
Braak NFT V/VI vs III/IV		NA	NA	NA	-0.417	0.242	-0.892 to 0.058
<i>APOE</i> genotype							
ε2 vs ε3/ε3		-0.233	0.411	-1.039 to 0.574	-0.565	0.463	-1.472 to 0.341
ε4 vs ε3/ε3		-0.449	0.184	-0.810 to -0.088	-0.396	0.201	-0.789 to -0.002
ε2 vs ε4		0.216	0.408	-0.583 to 1.016	-0.170	0.466	-1.083 to 0.743
Memory	814						
CERAD NP FREQ vs MOD		NA	NA	NA	0.019	0.034	-0.047 to 0.086
Braak NFT V/VI vs III/IV		NA	NA	NA	0.013	0.036	-0.058 to 0.084
<i>APOE</i> genotype							
ε2 vs ε3/ε3		-0.279	0.073	-0.421 to -0.137	-0.255	0.073	-0.398 to -0.111
ε4 vs ε3/ε3		0.064	0.031	0.004 to 0.124	0.060	0.031	-0.001 to 0.120
ε2 vs ε4		-0.343	0.072	-0.485 to -0.202	-0.314	0.073	-0.458 to -0.171
Attention	826						
CERAD NP FREQ vs MOD		NA	NA	NA	-0.104	0.045	-0.191 to -0.016
Braak NFT V/VI vs III/IV		NA	NA	NA	-0.029	0.048	-0.123 to 0.064
<i>APOE</i> genotype							
ε2 vs ε3/ε3		0.049	0.076	-0.100 to 0.198	0.003	0.090	-0.173 to 0.179
ε4 vs ε3/ε3		0.012	0.036	-0.059 to 0.083	0.028	0.074	-0.118 to 0.174
ε2 vs ε4		0.037	0.076	-0.112 to 0.187	-0.025	0.099	-0.219 to 0.169
Executive	611						
CERAD NP FREQ vs MOD		NA	NA	NA	0.060	0.061	-0.060 to 0.179
Braak NFT V/VI vs III/IV		NA	NA	NA	-0.142	0.062	-0.263 to -0.020
<i>APOE</i> genotype							
ε2 vs ε3/ε3		0.018	0.111	-0.201 to 0.236	0.051	0.117	-0.179 to 0.281
ε4 vs ε3/ε3		0.029	0.061	-0.090 to 0.149	0.057	0.064	-0.069 to 0.182
ε2 vs ε4		-0.012	0.112	-0.232 to 0.208	-0.005	0.116	-0.232 to 0.221
Language	826						

Continued

Table 4 Floor and Ceiling Effects of *APOE* Alleles on Cognitive Trajectories in Forward Time Scale Within 3 Years From Death
(continued)

Outcome contrast	No.	Model 1			Model 2		
		Estimate	SE	95% CI	Estimate	SE	95% CI
CERAD NP FREQ vs MOD		NA	NA	NA	-0.123	0.041	-0.204 to -0.042
Braak NFT V/VI vs III/IV		NA	NA	NA	-0.128	0.043	-0.213 to 0.043
<i>APOE</i> genotype							
$\epsilon 2$ vs $\epsilon 3/\epsilon 3$		0.089	0.081	-0.069 to 0.248	0.124	0.080	-0.032 to 0.280
$\epsilon 4$ vs $\epsilon 3/\epsilon 3$		-0.068	0.039	-0.145 to 0.009	0.013	0.040	-0.066 to 0.091
$\epsilon 2$ vs $\epsilon 4$		0.157	0.080	0.001 to 0.313	0.111	0.080	-0.045 to 0.267

Abbreviations: CDR-SOB = Clinical Dementia Rating scale Sum of Boxes; CERAD = Consortium to Establish a Registry of Alzheimer's Disease; CI = confidence interval; FREQ = frequent; MMSE = Mini-Mental State Examination; MOD = moderate; NA = not applicable; NFT = neurofibrillary tangle; NP = neuritic plaque. Estimates represent the unstandardized effect sizes (i.e., differences in trajectory slopes for each cognitive outcome and for each *APOE* genotype contrast). Model 1 is adjusted for age at death, sex, education, and Alzheimer disease neuropathological changes (CERAD NP score FREQ vs MOD and Braak NFT stage V/VI vs III/IV). Model 2 is further adjusted for interaction terms between CERAD NP score or Braak NFT stage and the slope of cognitive trajectories and for concurrent pathologies.

for ADNC effects on rate of cognitive decline and these comorbid pathologies rendered somewhat different results, likely due to the confounding effects of the latter on different cognitive domains. Possession of an *APOE* $\epsilon 4$ allele was associated with a significantly faster decline compared to the *APOE* $\epsilon 3/\epsilon 3$ reference group in only the memory and executive domains, whereas *APOE* $\epsilon 2$ carriers had a slower decline in language and executive functions than both *APOE* $\epsilon 3/\epsilon 3$ carriers and *APOE* $\epsilon 4$ carriers (table 3, figure 3, and figure e-1 available from Dryad). On the other hand, within 3 years before death, the *APOE* $\epsilon 2$ carriers declined significantly faster than the *APOE* $\epsilon 4$ and *APOE* $\epsilon 3/\epsilon 3$ carriers in the memory domain (table 4, figure 3, and figure e-1 available from Dryad), likely reflecting a floor effect of the memory composite z score in the last 2 groups at advanced dementia stages.

The goodness of fit of the proposed models for global cognitive measures (CDR-SOB and MMSE scores) and domain-specific composites was checked with the use of goodness-of-fit diagnostic graphs. Overall, we found that (1) the participant-specific residuals were approximately symmetric around zero; (2) the normal QQ plots of participant-specific residuals suggested that the residuals are normally distributed in most of their quantile range, and (3) in comparisons of the weighted predicted transformed cognitive outcome values averaged by time intervals along with the weighted average transformed observations,³¹ the individual predictions were close enough to the observations in the mixed-effects submodel (data not shown).

Discussion

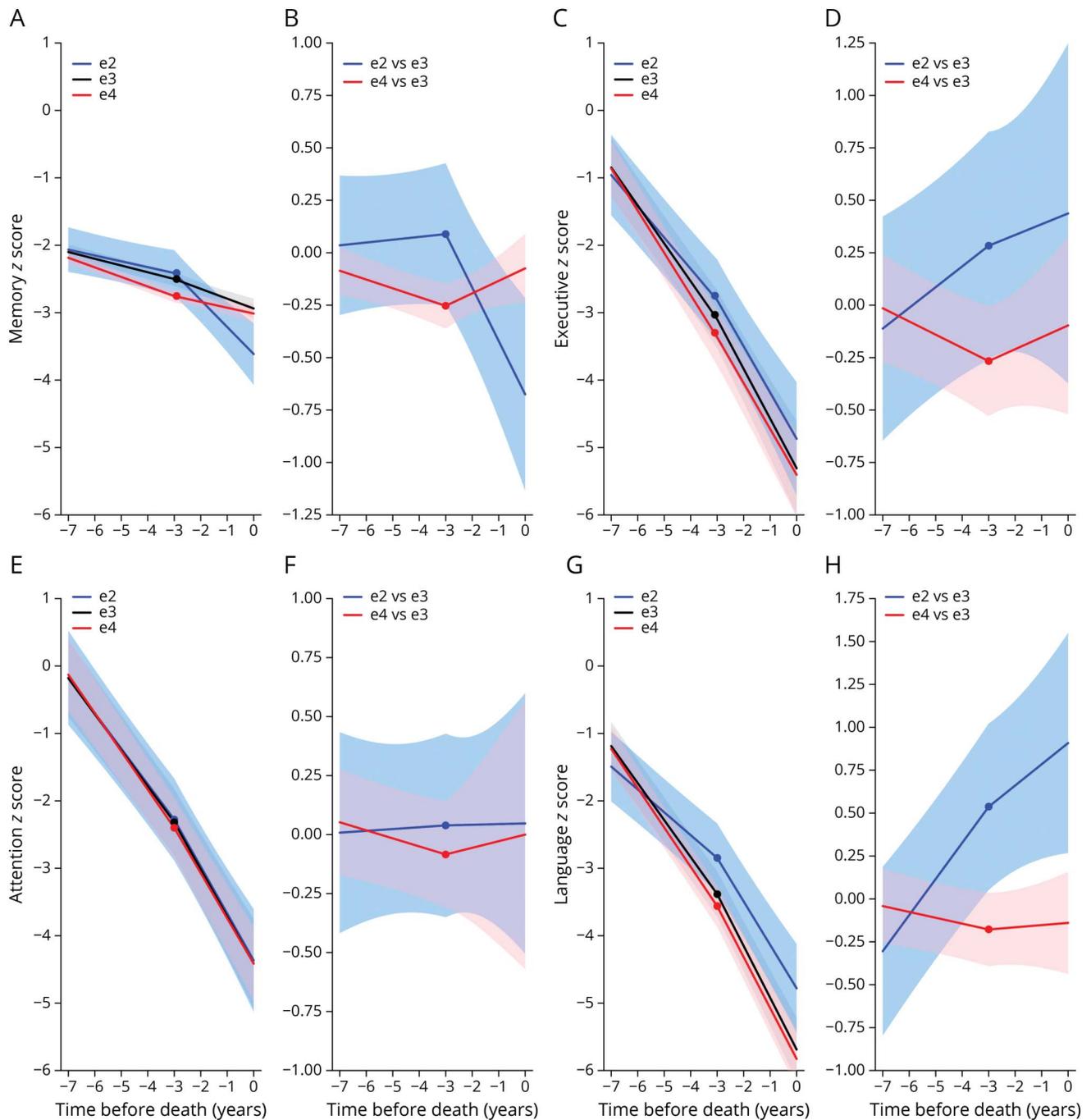
In this large, national, clinicopathologic sample, selected to be representative of participants in clinical trials with biomarker-

based eligibility criteria, we found a statistically significant difference in cognitive trajectory across *APOE* genotypes. In general, *APOE* $\epsilon 2$ carriers exhibited a slower decline and *APOE* $\epsilon 4$ carriers a faster decline than *APOE* $\epsilon 3/\epsilon 3$ carriers.

Our reverse longitudinal modeling approach enabled us to use information from patients with definite AD, to control for neuropathologic comorbidities that may affect rate of progression, and to focus on the effect of *APOE* genotype. Previous disparate results on the cognitive impact of the *APOE* genotype may have reflected the lack of autopsy confirmation and noise introduced by variation in the extent and severity of ADNC and concurrent pathologies.⁶⁻¹⁵ Moreover, the 3-year change point is consistent with a prior report on the Religious Orders Study and Rush Memory and Aging Project (ROS-MAP) cohort³⁶ and allowed us to identify and remove the expected ceiling/floor effects of cognitive outcome measures in advanced AD stages, providing data most relevant to mild and moderate dementia stages. Thus, our findings are consistent with a scenario in which the *APOE* $\epsilon 4$ allele not only anticipates the onset of cognitive decline but also accelerates its progression later in the disease course, with the *APOE* $\epsilon 2$ allele having opposite effects.

The magnitude of these differences approached clinical relevance even after controlling for the presence and severity of ADNC and concurrent pathologies (i.e., ≈ 0.7 points of CDR-SOB score per year and ≈ 0.5 points of MMSE score per year in *APOE* $\epsilon 4$ carriers vs *APOE* $\epsilon 3/\epsilon 3$ carriers). Thus, our current results may help inform clinical trial design. While randomization would ensure matching of treatment and placebo groups by *APOE* genotype and *APOE*-based post hoc analyses are usual practice,³⁷ stratification at enrollment by *APOE* genotype might be considered regardless of expected *APOE*-driven differences in drug response or frequency of drug adverse effects. Some clinical trials have specified

Figure 3 Effect of *APOE* Alleles on Cognitive Domain-Specific Composite Measures



(A, C, E, and G) Model-based cognitive trajectories of (A) memory, (C) executive, (E) attention, and (G) language composite-measures z scores by *APOE* allele with the intercept at the time of death calculated for an 82-year-old woman with 15 years of education and autopsy findings of frequent Consortium to Establish a Registry of Alzheimer's Disease (CERAD) neuritic plaque score and Braak neurofibrillary tangle stage V/VI and no comorbid pathologies and with adjustments for the effect of Alzheimer disease neuropathologic variables (CERAD and Braak) on the rate of cognitive decline and for comorbid pathologies (model 2). (B, D, F, and H) Difference of model-based cognitive trajectories of (B) memory, (D) executive, (F) attention, and (H) language composite-measures z scores between *APOE* allele groups (*APOE* ϵ 2 and *APOE* ϵ 4 vs *APOE* ϵ 3/ ϵ 3 carriers) under model 2. Shaded areas represent the corresponding 95% confidence intervals.

alternative protocols for *APOE* ϵ 4 carriers^{38,39} because *APOE* ϵ 4 increases the risk of blood-brain barrier disruption caused by monoclonal anti-A β antibodies leading to amyloid-related imaging abnormalities,⁴⁰ which could in addition affect the relative rates of progression among treatment groups.

Moreover, although some of the concurrent pathologies controlled for here cannot be accurately ascertained ante-mortem, the data illustrate the importance of using available biomarkers to account for as many variables as possible in a clinical trial setting.

Of note, our results are at odds with the hypothesis that the *APOE* genotype drives different AD clinical phenotypes, that is, an amnesic/temporo-limbic presentation in *APOE* $\epsilon 4$ carriers vs a dysexecutive/frontoparietal in *APOE* $\epsilon 4$ noncarriers.⁴¹⁻⁴³ *APOE* $\epsilon 4$ carriers had a significantly faster decline in all cognitive domains examined (memory, attention, executive, and language) compared to *APOE* $\epsilon 3/\epsilon 3$ carriers in models not adjusted by ADNC effects on rate of cognitive decline and concurrent pathologies, and in both memory and executive function in adjusted models. Larger clinical and multimodal imaging studies including higher numbers of *APOE* $\epsilon 2$ carriers across AD preclinical and clinical stages are needed to confirm this hypothesis.

Our findings also provide important pathophysiologic insights. We were able to compare estimates between models with and without adjustment for the impact of ADNC on rate of cognitive decline and for comorbid pathologies. Overall, the results from both models were largely comparable: adjusting for interactions between ADNC and the slope of cognitive decline and for concurrent pathologies (model 2) rendered statistically significant point slope estimates that were only 3% to 24% smaller than those obtained without including these neuropathologic covariates (model 1), and some of the estimates for *APOE* $\epsilon 2$ allele in model 2 were even larger than their counterparts in model 1 (table 3). Therefore, these results suggest that, relative to the *APOE* $\epsilon 3$ allele, the *APOE* $\epsilon 2$ allele confers protection against cognitive decline beyond its known protective effects against ADNC, whereas the *APOE* $\epsilon 4$ allele accelerates cognitive decline beyond its known promoting effects of ADNC and concurrent pathologies, that is, cerebrovascular disease,²² LB disease,²³ and transactive response DNA-binding protein 43kDa (TDP-43) proteinopathy²⁴ (controlled here by the presence/absence of HScl). The cognitive protective effects of the *APOE* $\epsilon 2$ allele observed in this moderate/high ADNC sample are reminiscent of the cognitive resilience to ADNC recently reported for both the Christchurch homozygous mutation in the *APOE* gene⁴⁴ and *APOE* $\epsilon 2$ homozygosity.⁴⁵ Multiple $A\beta$ -dependent and -independent mechanisms could explain these *APOE*-mediated differences in cognitive decline rate: impaired glucose utilization⁴⁶; stabilization of synaptotoxic $A\beta$ oligomers⁴⁷; increased colocalization of $A\beta$ oligomers with synapses⁴⁸; altered synaptic pruning⁴⁹; exacerbated microglial inflammation, tau spreading, and neurodegeneration^{9,50}; and impaired neuroprotective mechanisms.⁵¹

Some limitations of our study pertinent to available or collected data should be acknowledged. This moderate/high ADNC sample is not suited to capture possible differences in rate of cognitive decline or phenotypic presentation differences across *APOE* genotypes at the earliest clinical stages. Thus, our study participants do not resemble those enrolled in current therapeutic clinical trials targeting subjective or very mild cognitive impairment or in secondary prevention trials (i.e., cognitively intact individuals with positive AD biomarkers). The underrepresentation of *APOE* $\epsilon 2$ carriers with

substantial ADNC ($n = 44$) is expected given the protective effect of this allele against AD; *APOE* $\epsilon 4$ carriers would also be underrepresented in a sample of cognitively intact individuals with low ADNC.^{5,45} In addition, the effects of *APOE* genotype on the visuospatial/perceptive domain could not be studied due to insufficient specific neuropsychological tests for these skills in the first 2 NACC UDS iterations,²⁶ and we had to use the presence of HScl as an imperfect surrogate of TDP-43 pathology because this has been recorded only since January 2014.⁵² Other limitations concern the statistical modeling. To be able to use the autopsy variables as baseline covariates and to apply reverse longitudinal modeling, we assumed that amyloid plaque burden plateaus early in the clinical course of AD and that the sequence of Braak NFT stages from limbic (III/IV) to neocortical (V/VI) is valid over the extent of the follow-up; these assumptions are well supported by prior $A\beta$ and tau PET imaging studies.^{34,35} The complexity of our modeling strategy prevented us from including some terms in the models due to risk of overfitting such as a participant-specific change point as a random variable and interaction terms between *APOE* genotype and comorbid pathologies or between comorbid pathologies and slope of cognitive decline.

The *APOE* $\epsilon 2$ and *APOE* $\epsilon 4$ alleles have opposing effects on the rate of cognitive decline compared to the most common *APOE* $\epsilon 3/\epsilon 3$ genotype. These effects are clinically relevant, detectable in samples comparable in size and demographics to those enrolled in prototypical clinical trials, and largely independent of their known effects on measured ADNC and comorbid pathologies. Thus, besides neuropathology, other *APOE*-related phenotypes—perhaps microglial and astrocytic reactions^{9,49,50}—might drive AD clinical progression. Further research to understand this *APOE* $\epsilon 2$ -mediated resilience and *APOE* $\epsilon 4$ -linked adversity is warranted.

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Disclosure

B.T. Hyman has a family member who works at Novartis and owns stock in Novartis; he serves on the scientific advisory board of Dewpoint and owns stock; he serves on a scientific advisory board or is a consultant for Abbvie, Arvinas, Biogen, Novartis, Cell Signaling, the US Department of Justice, Takeda, Vigil, W20 group, and Seer; and his laboratory is supported by sponsored research agreements with Abbvie, Amgen, Arvinas, Biogen, Denali, Dewpoint, Fidelity Biosciences, F Prime, General Electric, Eli Lilly, Merck, Sangamo, and Spark, as well as research grants from the NIH (PI), Cure Alzheimer's Fund (PI), Tau Consortium (PI), the JPB Foundation (PI), Alzheimer's Association (mentor), and Brightfocus (mentor). R.A. Betensky serves on the National Cancer Institute Board of Scientific Counselors for Clinical Sciences and Epidemiology, Biogen, Alexion, Reata, and PTC Therapeutics; she is consultant for Cowen Inc and has served as expert witness for Amarin, Actavis, Amazon, and Apotex and as consultant for Pfizer and Amgen. Drs. Qian and Serrano-Pozo have no disclosures. Go to Neurology.org/N for full disclosures.

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Appendix Authors

Name	Location	Contribution
Jing Qian, PhD	University of Massachusetts, Amherst	Analyzed and interpreted the data, performed statistical analysis, revised the manuscript for intellectual content

Appendix (continued)

Name	Location	Contribution
Rebecca A. Betensky, PhD	New York University, New York City	Designed the study, interpreted the data, performed statistical analysis, revised the manuscript for intellectual content
Bradley T. Hyman, MD, PhD	Massachusetts General Hospital, Boston	Designed the study, interpreted the data, revised the manuscript for intellectual content
Alberto Serrano-Pozo, MD, PhD	Massachusetts General Hospital, Boston	Conceptualized and designed the study, interpreted the data, drafted the manuscript for intellectual content

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