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—two 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 ε4 carriers exhibited ≈1.5 times faster CDR-SOB increase than APOE ε3/ε3 carriers (2.12 points per year vs 1.44 points per year) and ≈1.3 times faster increase than APOE ε2 carriers (1.65 points per year), whereas APOE ε2 vs APOE ε3/ε3 difference was not statistically significant. APOE ε4 carriers had ≈1.1 times faster MMSE decline than APOE ε3/ε3 carriers (−3.45 vs −3.03 points per year) and ≈1.4 times faster decline than APOE ε2 carriers (−2.43 points per year), whereas APOE ε2 carriers had ≈1.2 times slower decline than APOE ε3/ε3 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 ε3/ε3 reference genotype, the APOE ε2 and ε4 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.
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. 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 ε4 and ε2 alleles on AD risk, age at symptom onset, and AD neuropathologic changes (ADNC). However, prior longitudinal clinical studies after symptom onset have reported conflicting results—accelerating neutral and slowing effects for APOE ε4 vs slowing effects for APOE ε2. —likely due, at least in part, to the suboptimal accuracy of a clinically based AD diagnosis. Another proposed driver is the co-occurrence of ≥2 brain pathologies, each of which could independently contribute to cognitive impairment and could be influenced by the APOE genotype.

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.

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 [HScI] 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. 

Glossary
Aβ = 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; HScI = hippocampal sclerosis; LB = Lewy bodies; MMSE = Mini-Mental State Examination; NACC = National Alzheimer’s Coordinating Center; NFT = neurofibrillary tangle; NP = neurtic plaque; ROSMAP = Religious Orders Study and Rush Memory and Aging Project; TDP-43 = transactive response DNA-binding protein 43kDa; UDS = Uniform Data Set.
Table 1  Characteristics of This NACC Autopsy Cohort

| Characteristic                              | Total (n = 1,109) | APOE ε2 | APOE ε3/ε3 | APOE ε4 |
|--------------------------------------------|-------------------|---------|------------|---------|
| APOE genotype, n (%)                       | 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                    | 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) |
| Arteriosclerosis, 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
Statistics
Statistical analyses were run in R software version 3.6 using R package lmm (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 structure 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. 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.

The covariates used in the mixed-effects submodel for the longitudinal cognitive trajectory analyses and in Cox
proportional hazards submodel for the time-to-event analyses included sex, education, age at death, APOE genotype (presence vs absence of ε2 allele, and presence vs absence of ε4 allele, with ε3/ε3 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 HScI 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

Figure 1 Flowchart of Study Participants

ADNC = Alzheimer disease neuropathological changes; CERAD = Consortium to Establish a Registry of Alzheimer’s Disease; NACC = National Alzheimer’s Coordinating Center; NP = neuritic plaque; UDS = Uniform Data Set.
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 arteriolosclerosis 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 HScI. 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, HScI, and arteriolosclerosis) 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 HScI was associated with worse memory (−0.294 ± 0.63, 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 arteriolosclerosis 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 2 Associations of APOE Alleles With Neuropathologic Findings at Autopsy

| Neuropathologic outcome measure | APOE ε4 allele | APOE ε4 dose | APOE ε2 allele | APOE ε2 dose |
|--------------------------------|---------------|-------------|---------------|-------------|
| Presence of APOE 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) |
| Presence of APOE ε2 allele | 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) |
| Presence of 2 APOE alleles | 0.75 (0.56 to 0.95) | 0.75 (0.56 to 0.95) | 0.75 (0.56 to 0.95) | 0.75 (0.56 to 0.95) |
| Presence of 1 APOE 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) |
| Presence of CAA | −0.18 (−0.55 to 0.21) | −0.18 (−0.55 to 0.21) | −0.18 (−0.55 to 0.21) | −0.18 (−0.55 to 0.21) |
| Presence of LB | 0.04 (−0.02 to 0.10) | 0.04 (−0.02 to 0.10) | 0.04 (−0.02 to 0.10) | 0.04 (−0.02 to 0.10) |
| Presence of HScI | 0.02 (−0.06 to 0.14) | 0.02 (−0.06 to 0.14) | 0.02 (−0.06 to 0.14) | 0.02 (−0.06 to 0.14) |
| Presence of mild CAA | 0.16 (0.01 to 0.30) | 0.16 (0.01 to 0.30) | 0.16 (0.01 to 0.30) | 0.16 (0.01 to 0.30) |
| Presence of moderate CAA | 0.01 (−0.06 to 0.10) | 0.01 (−0.06 to 0.10) | 0.01 (−0.06 to 0.10) | 0.01 (−0.06 to 0.10) |
| Presence of severe CAA | 0.22 (0.002 to 0.44) | 0.22 (0.002 to 0.44) | 0.22 (0.002 to 0.44) | 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; HScI = hippocampal sclerosis; LB = Lewy bodies; NFT = neurofibrillary tangle; NP = neuritic plaque; OR = odds ratio.
| Outcome contrast | No.  | Model 1 Estimate | SE | 95% CI       | Model 2 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 |
| APOE 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 |
| APOE 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 |
| APOE 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 |
| APOE 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 |
| APOE 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 |
Table 3 Effects of APOE Alleles on Cognitive Trajectories in Forward Time Scale >3 Years From Death (continued)

| Outcome contrast | Model 1 | | | | Model 2 |
|------------------|---------|-----------------|-----------------|---------------|-----------|-----------|
| Braak NFT V/VI vs III/IV | No. | Estimate | SE | 95% CI | Estimate | SE | 95% CI |
| APOE genotype | | | | | | | |
| ε2 vs ε3/ε3 | | 0.119 | 0.039 | 0.043 to 0.194 | 0.210 | 0.037 | 0.137 to 0.283 |
| ε4 vs ε3/ε3 | | −0.053 | 0.021 | −0.094 to −0.011 | −0.034 | 0.018 | −0.069 to 0.001 |
| ε2 vs ε4 | | 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 ε4 carriers exhibited ≈1.5 times faster progression by CDR-SOB score than APOE ε3/ε3 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 ε2 carriers (2.12 vs 1.65 points per year, 95% CI 0.22–0.72), but APOE ε2 carriers did not significantly differ from APOE ε3/ε3 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 ε4 carriers had ≈1.1 times faster decline than APOE ε3/ε3 carriers (−3.45 vs −3.03 points per year, 95% CI −0.62 to −0.24) and ≈1.4 times faster decline than APOE ε2 carriers (−3.45 vs −2.43 points per year, 95% CI −1.41 to −0.64), whereas APOE ε2 carriers had ≈1.2 times slower decline than APOE ε3/ε3 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 ε4 carriers exhibited ≈1.6 times faster clinical progression by CDR-SOB score than APOE ε3/ε3 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 ε2 carriers (1.80 vs 1.34 points per year, 95% CI 0.19–0.72). In contrast, APOE ε2 carriers did not significantly differ from APOE ε3/ε3 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 ε4 carriers had ≈1.2 times faster decline than APOE ε3/ε3 carriers (−2.90 vs −2.43 points per year, 95% CI −0.68 to −0.27) and ≈1.4 times faster decline than APOE ε2 carriers (−2.90 vs −2.04 points per year, 95% CI −1.26 to −0.45), whereas APOE ε2 carriers had ≈1.2 times slower decline than APOE ε3/ε3 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 ε2 carriers exhibited a significantly slower increase in CDR-SOB score compared to the APOE ε3/ε3 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 ε4 group is apparent, with a slower decline relative to the APOE ε3/ε3 group (2.02 vs 2.28 points per year, 95% CI −0.06 to −0.45). Indeed, 29% APOE ε4 carriers had already reached the maximum CDR-SOB score of 18 at the 3-year change time point compared to 19% of APOE ε3/ε3 carriers. Similarly, the APOE ε4 carriers showed a significantly faster decline in MMSE score than the APOE ε3/ε3 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 ε3/ε3 group, causing APOE ε2 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 ε3/ε3 carriers had reached an MMSE score ≤3 at the 3-year change time point vs none of the APOE ε2 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 ε4 carriers had a significantly faster decline in all 4 domains analyzed.
APOE e2 carriers had a significantly slower decline in language compared to APOE e3/e3 carriers and in both memory and language compared to APOE e4 carriers (table 3, figure 3, and figure e-1 available from Dryad: doi.org/10.5061/dryad.w0vt4b8qk). The models controlling

(memory, executive, attention, language) compared to APOE e3/e3 carriers, whereas APOE e2 carriers had a significantly slower decline in language compared to APOE e3/e3 carriers

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 e3/e3, APOE e2, and APOE e4 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 e2 and APOE e4 vs APOE e3/e3 carriers) under models 1 (B and F) and 2 (D and H). Shaded areas represent the corresponding 95% confidence intervals.
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  | 0.311   |         |
| Braak NFT V/VI vs III/IV          | NA   | NA      | NA      | 0.246   | 0.138   | −0.024  | 0.517   |         |
| APOE genotype                     |      |         |         |         |         |         |         |         |
| e2 vs e3/e3                       | −0.599| 0.246   | −1.082  | −0.016  | −0.575  | 0.252   | −1.070  | −0.080  |
| e4 vs e3/e3                       | −0.212| 0.098   | −0.403  | −0.020  | −0.256  | 0.099   | −0.451  | −0.062  |
| e2 vs e4                          | −0.388| 0.244   | −0.866  | 0.091   | −0.319  | 0.251   | −0.811  | 0.173   |
| MMSE score                        | 988  |         |         |         |         |         |         |         |
| CERAD NP FREQ vs MOD              | NA   | NA      | NA      | −0.450  | 0.219   | −0.878  | −0.021  |         |
| Braak NFT V/VI vs III/IV          | NA   | NA      | NA      | −0.417  | 0.242   | −0.892  | 0.058   |         |
| APOE genotype                     |      |         |         |         |         |         |         |         |
| e2 vs e3/e3                       | −0.233| 0.411   | −1.039  | 0.574   | −0.565  | 0.463   | −1.472  | 0.341   |
| e4 vs e3/e3                       | −0.449| 0.184   | −0.810  | −0.088  | −0.396  | 0.201   | −0.789  | −0.002  |
| e2 vs e4                          | 0.216 | 0.408   | −0.583  | 1.016   | −0.170  | 0.466   | −1.083  | 0.743   |
| Memory                            | 814  |         |         |         |         |         |         |         |
| CERAD NP FREQ vs MOD              | NA   | NA      | NA      | 0.019   | 0.034   | −0.047  | 0.086   |         |
| Braak NFT V/VI vs III/IV          | NA   | NA      | NA      | 0.013   | 0.036   | −0.058  | 0.084   |         |
| APOE genotype                     |      |         |         |         |         |         |         |         |
| e2 vs e3/e3                       | −0.279| 0.073   | −0.421  | −0.137  | −0.255  | 0.073   | −0.398  | −0.111  |
| e4 vs e3/e3                       | 0.064 | 0.031   | 0.004   | 0.124   | 0.060   | 0.031   | −0.001  | 0.120   |
| e2 vs e4                          | −0.343| 0.072   | −0.485  | −0.202  | −0.314  | 0.073   | −0.458  | −0.171  |
| Attention                         | 826  |         |         |         |         |         |         |         |
| CERAD NP FREQ vs MOD              | NA   | NA      | NA      | −0.104  | 0.045   | −0.191  | −0.016  |         |
| Braak NFT V/VI vs III/IV          | NA   | NA      | NA      | −0.029  | 0.048   | −0.123  | 0.064   |         |
| APOE genotype                     |      |         |         |         |         |         |         |         |
| e2 vs e3/e3                       | 0.049 | 0.076   | −0.100  | 0.198   | 0.003   | 0.090   | −0.173  | 0.179   |
| e4 vs e3/e3                       | 0.012 | 0.036   | −0.059  | 0.083   | 0.028   | 0.074   | −0.118  | 0.174   |
| e2 vs e4                          | 0.037 | 0.076   | −0.112  | 0.187   | −0.025  | 0.099   | −0.219  | 0.169   |
| Executive                         | 611  |         |         |         |         |         |         |         |
| CERAD NP FREQ vs MOD              | NA   | NA      | NA      | 0.060   | 0.061   | −0.060  | 0.179   |         |
| Braak NFT V/VI vs III/IV          | NA   | NA      | NA      | −0.142  | 0.062   | −0.263  | −0.020  |         |
| APOE genotype                     |      |         |         |         |         |         |         |         |
| e2 vs e3/e3                       | 0.018 | 0.111   | −0.201  | 0.236   | 0.051   | 0.117   | −0.179  | 0.281   |
| e4 vs e3/e3                       | 0.029 | 0.061   | −0.090  | 0.149   | 0.057   | 0.064   | −0.069  | 0.182   |
| e2 vs e4                          | −0.012| 0.112   | −0.232  | 0.208   | −0.005  | 0.116   | −0.232  | 0.221   |
| Language                          | 826  |         |         |         |         |         |         |         |

Continued
for ADNC 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 ε4 allele was associated with a significantly faster decline compared to the APOE ε3/ε3 reference group in only the memory and executive domains, whereas APOE ε2 carriers had a slower decline in language and executive functions than both APOE ε3/ε3 carriers and APOE ε4 carriers (table 3, figure 3, and figure e-1 available from Dryad). On the other hand, within 3 years before death, the APOE ε2 carriers declined significantly faster than the APOE ε4 and APOE ε3/ε3 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, 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 ε2 carriers exhibited a slower decline and APOE ε4 carriers a faster decline than APOE ε3/ε3 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. 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) cohort 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 ε4 allele not only anticipates the onset of cognitive decline but also accelerates its progression later in the disease course, with the APOE ε2 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 ε4 carriers vs APOE ε3/ε3 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, 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

| Outcome contrast | 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 |

**APOE genotype**

| APOE genotype | Estimate | SE | 95% CI | Estimate | SE | 95% CI |
|---------------|----------|----|--------|----------|----|--------|
| ε2 vs ε3/ε3  | 0.089    | 0.081 | −0.069 to 0.248 | 0.124 | 0.080 | −0.032 to 0.280 |
| ε4 vs ε3/ε3  | −0.068   | 0.039 | −0.145 to 0.009 | 0.013 | 0.040 | −0.066 to 0.091 |
| ε2 vs ε4     | 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 (CDR-SOB 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.
alternative protocols for APOE ε4 carriers because APOE ε4 increases the risk of blood-brain barrier disruption caused by monoclonal anti-Aβ antibodies leading to amyloid-related imaging abnormalities, 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 amnestic/temporo-limbic presentation in APOE ε4 carriers vs a dysexecutive/frontoparietal in APOE ε4 noncarriers.41-43 APOE ε4 carriers had a significantly faster decline in all cognitive domains examined (memory, attention, executive, and language) compared to APOE ε3/ε3 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 ε2 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 ε2 allele in model 2 were even larger than their counterparts in model 1 (table 3). Therefore, these results suggest that, relative to the APOE ε3 allele, the APOE ε2 allele confers protection against cognitive decline beyond its known protective effects against ADNC, whereas the APOE ε4 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 ε2 allele observed in this moderate/high ADNC sample are reminiscent of the cognitive resilience to ADNC recently reported for both the Christchurch homoygous mutation in the APOE gene44 and APOE ε2 homozygosity.45 Multiple Aβ-dependent and -independent mechanisms could explain these APOE-mediated differences in cognitive decline rate: impaired glucose utilization46; stabilization of synaptotoxic Aβ oligomers47; increased colocalization of Aβ oligomers with synapses48; altered synaptic pruning49; exacerbated microglial inflammation, tau spreading, and neurodegeneration50; 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 ε2 carriers with substantial ADNC (n = 44) is expected given the protective effect of this allele against AD; APOE ε4 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 Aβ and tau PET imaging studies.36,38 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 ε2 and APOE ε4 alleles have opposing effects on the rate of cognitive decline compared to the most common APOE ε3/ε3 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 reactions9,49,50—might drive AD clinical progression. Further research to understand this APOE ε2–mediated resilience and APOE ε4–linked adversity is warranted.

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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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