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Cognitive trajectories diverge by genetic risk in a preclinical longitudinal cohort

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Abstract

INTRODUCTION: We sought to characterize the timing of changes in cognitive trajectories related to genetic risk using the apolipoprotein E (*APOE*) score, a continuous measure of Alzheimer's disease (AD) risk. We also aimed to determine if that timing was different when genetic risk was measured using an AD polygenic risk score (PRS) that contains *APOE*.

METHODS: We analyzed trajectories (N≈1135) for four neuropsychological composite scores using mixed effects regression for longitudinal change across *APOE* scores and PRS of participants in the Wisconsin Registry for Alzheimer's Prevention, a longitudinal study of adults aged 40–70 at baseline, with a median participant follow-up time of 7.8 years.

RESULTS: We found a significant non-linear age-by-*APOE* score interaction in predicting cognitive decline. Cognitive trajectories diverged by *APOE* score at approximately 65 years of age. A 0.5 SD difference in cognition between extreme percentiles of the PRS was predicted to occur 1–2 years before that of the *APOE* score.

DISCUSSION: Cognitive decline differs across time and *APOE* score. Estimates did not substantially shift with the AD PRS.

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Keywords

Genetics; *APOE*; cognition; longitudinal; cognitive decline; Alzheimer's disease; polygenic risk score; age

1. Introduction

Understanding the timing and order of cognitive changes preceding the clinical manifestation of Alzheimer's disease (AD) is critical for developing treatment and prevention strategies. Current theory suggests that pathological markers and cognition shift from normal to abnormal levels in a sigmoidal fashion over the 20 years preceding AD diagnosis.[1] It is still unclear what controls the timing of these changes.

Numerous genetic variants are associated with overall risk of AD and cognitive decline, but their interaction with age and how they affect timing of preclinical cognitive decline remains poorly understood. The apolipoprotein E (*APOE*) *ε4* allele is a major factor that increases risk of AD, with homozygotes relative to *APOE ε3*/*ε3* having an approximately 11-fold increased risk of clinically diagnosed AD and a 31-fold increased risk in neuropathologically confirmed AD.[2] It is associated with lower cognitive function, earlier onset of AD proteinopathy and clinical syndrome, and cognitive decline in people who were later determined to have clinical or autopsy-confirmed AD.[3–6] Although *APOE* is the strongest common genetic factor affecting risk of dementia due to AD, it is not the only one. AD is a genetically complex disease, and other variants are associated with AD clinical syndrome risk and dementia-related cognitive changes.[7,8] Mixed results have been reported for the effect of AD polygenic risk scores (PRS) on cognitive function and decline preceding AD onset, and some of the PRS findings have been mainly from the effects of *APOE*[7]. Although we know that genetics play an important role in overall cognitive function, AD risk, and cognitive decline post diagnosis, we know relatively little regarding how genetics influence the temporal evolution of cognitive decline preceding AD diagnosis.

Some evidence suggests that differences in decline by *APOE ε4* carrier status can be detected around age 60.[9,10] In contrast, other studies looking at *APOE ε4* carrier status and specific *APOE* allele combinations have suggested that the difference is detected after 65 or 70 depending on the cognitive domain.[11] While studies have evaluated the association between an AD PRS or variants besides those in *APOE* with the rate of cognitive decline,[12–15] to our knowledge, no studies have examined at what age cognitive function and decline differs by an AD PRS in a preclinical cohort. Understanding the interactions of genetic factors and time with respect to cognitive function and decline will contribute to mapping the preclinical mechanistic changes leading to the clinical manifestation of AD. This not only contributes to our temporal understanding of the biology of AD and related dementias, but it also informs us of the proper timing for clinical trial and lifestyle interventions that target cognitive decline.

Using data from the Wisconsin Registry for Alzheimer's Prevention (WRAP),[16] we estimate the age when individuals with different genetic risk of AD clinical syndrome diverge in their cognitive function and in their rate of cognitive decline. We use two genetic measures,

the *APOE* score and an AD PRS. We expand on previous research by (1) using cognitive composite scores from multiple domains as a measure of cognition instead of individual scores because composites have been shown to have lower intraindividual variability compared to single tests[17]; (2) representing *APOE* not as a count of *ε4* alleles but as a numeric score, which we call the *APOE* score, that accounts for all six *APOE* allele combinations and models non-linear risk of AD; (3) analyzing additional AD risk variants in the form of a PRS; and (4) analyzing these genetic factors in relation to non-linear age in a cohort with a relatively long follow-up time.

2. Methods

2.1. Study population

Participants for this study came from the WRAP, an ongoing longitudinal study of 1662 people.[16] WRAP is a convenience sample of people who were non-demented (preclinical) and 40 – 70 years old at baseline, who were fluent in English, and who had sufficient visual and auditory ability to participate in neuropsychological testing. It allows for the enrollment of siblings and is enriched for people with a parental history of AD, defined as a biological parent with autopsy-confirmed AD (~8%), probable AD dementia per medical record review (~83%), or dementia presumed due to AD based on the Dementia Questionnaire (~9%). Participants are followed up approximately every two years until a dementia diagnosis is made, or until drop out or death. Individuals provided signed informed consent, and this study was approved by the University of Wisconsin Institutional Review Board.

The WRAP sample as of the May 2020 data release contained 1662 participants. Of those, 1344 people were genotyped and 1282 people's samples passed quality control; 84 people of non-European genetic ancestry, as determined by principal component analysis of genome-wide data, were removed resulting in 1198 individuals.[18] We use a sample with European genetic ancestry because the weights for genetic variants were derived in that population. We excluded individuals who reported having a parent with an age of memory loss onset before 60 years (individuals more likely to have early-onset AD, 52 people) and individuals with missing outcome and covariate data (11–17 people, depending on outcome). No additional exclusions were made for events that could affect cognitive performance including incident stroke or traumatic brain injury. Because missing data varied by the outcome variable, the final sample sizes also varied slightly ranging from 1129 to 1135 (Supplemental Table 1).

2.2. Measures

2.2.1. Cognition—We used one global and three domain-specific cognitive composite scores as our measures of cognition. Cognitive composite scores were generated as previously described.[17] Each composite is the unweighted average of three psychometric test scores that were standardized (mean = 0, standard deviation [SD] = 1) prior to being averaged. The Trailmaking Test Part B (TMTb) score was multiplied by −1 before being included in a composite score so that higher values represent better performance, which is consistent with other tests. The immediate learning composite score is composed of the Rey Auditory Verbal Learning Test (RAVLT) total of five learning trials,[19] the Wechsler Memory Scale-Revised (WMS-R) Logical Memory-I immediate memory (total

of stories A and B),[20] and the Brief Visuospatial Memory Test-Revised (BVMT-R) total of three learning trials.[21] The delayed recall composite score is composed of the RAVLT delayed recall, the WMS-R Logical Memory-II delayed memory subtest (total of stories A and B), and the BVMT-R delayed memory subtest. The executive function composite score is composed of the TMTb,[22] the Stroop Color-Word Interference test,[23] and the Digit Symbol Wechsler Adult Intelligence Scale-Revised test.[24] The modified preclinical Alzheimer cognitive composite (PACC3), a measure of global cognition, was based on the test constructs described in Donohue et al.[25] and is composed of the RAVLT total of five learning trials, the WMS-R Logical Memory-II delayed memory subtest, and the Digit Symbol Wechsler Adult Intelligence Scale-Revised test.

2.2.2. Genetics—DNA was extracted from whole blood samples and genotyped using competitive allele-specific polymerase chain reaction (PCR) based KASP™ genotyping assays (LGC Genomics, Beverly, MA). DNA extraction and quality control were previously described.[26] DNA was also genotyped using the Illumina Multi-Ethnic Genotyping Array and taken through quality control as previously described.[18] For variants assessed with both technologies, we used values from the competitive allele-specific PCR-based technology instead of the array-based technology because of the higher quality of the allele-specific PCR genotyping (Supplemental Table 2).

The *APOE* score was derived from the rs429358 and rs7412 *APOE* variants. Because modeling *APOE* using *ε4* count does not account for non-linear AD risk between combinations of *ε2*, *ε3*, and *ε4* alleles,[27] we created and used the *APOE* score as our main measure of *APOE* risk. The *APOE* score is a continuous measure that is the natural logarithm of the odds ratio (OR) of the *APOE* genotype (*ε2*/*ε2*, *ε2*/*ε3*, *ε3*/*ε3*, *ε2*/*ε4*, *ε3*/*ε4*, *ε4*/*ε4*) with AD case control status, with higher values indicating higher genetic risk of AD.[26] *APOE* genotypes were derived from the two mentioned variants. Crude ORs for each genotype were calculated based on counts of AD cases and controls from the "Caucasian" population from the Alzgene database[28,29] using the *ε3*/*ε3* genotype as the reference category. The ORs for each *APOE* genotype were logarithm transformed to create the *APOE* score (Supplemental Table 3).

The PRS for AD was constructed based on a set of variants and summary statistics published by de Rojas et al.[30] in their "supplementary data 4" table. To calculate the PRS for a given individual, the number of risk alleles for a variant were weighted by the effect size of that variant's association with AD. Then all weighted variants were summed to form the PRS.[31] Higher PRS values indicate higher genetic risk of clinical AD. The polygenic risk score from de Rojas et al. has 39 variants, of which our data had 36 (Supplemental Table 2). Unlike de Rojas et al., we also included the *APOE* score and rs145999145 (*PLD3*) in the PRS, the latter of which was weighted using the log of the OR reported by Cruchaga et al.[32] This *PLD3* variant is rare, present in our study participants, and strongly associated with AD.[33]

2.2.3. Covariates—Covariates in the analyses included education (years, maximum 20 years), sex (binary, 1 = female), and cognitive assessment practice effects. Practice effects quantified how much cognitive testing practice a person had at each visit and was measured

as the number of previous tests a person took, which was equivalent to visit number – 1. To adjust for potential population stratification, genetic principal components were generated as previously described[18] and were added in a sensitivity analysis.

2.3. Statistical analyses

2.3.1. Regression model building—To evaluate whether age-related cognitive trajectories differ by genetic risk, we used mixed effects regression as follows. For each of four cognitive outcomes, we built models stepwise and tested if additions improved model fit using the Akaike Information Criterion (AIC) and an F-test with the "anova" function in R.[34] We started with a null model to determine if the individual (repeated measures correlation) and family-cluster (sibling correlation) random intercepts, and the random slope for age at the participant level significantly improved model fit. We then added fixed effects starting with the crude association of the *APOE* score. In the following step, we added linear age (centered at 65) along with covariates (sex, education, and practice effects). Next, based on recent WRAP publications showing that non-linear patterns of cognitive decline are beginning to emerge as the sample ages,[35,36] we evaluated if orthogonal polynomial terms for age ("poly" function in R), up to a cubic term, would improve the model fit. In the final modeling step, we added interactions between the *APOE* score and all age terms and compared that full model to the one without any interactions. If the full model was a better fit than the one without interactions, all interaction terms were retained even if one was not significant. For the PRS analysis, the fullest model for the *APOE* score was used replacing the *APOE* score with the AD PRS that contains the *APOE* score. For both the *APOE* score and AD PRS models, we conducted a sensitivity analysis adjusting the final model for the first five principal components of ancestry. All models used an unstructured variance-covariance structure; estimates were obtained using restricted maximum likelihood; the Kenward-Rodger approximation was used to determine degrees of freedom; and an alpha of 0.05 was the significance criterion. Regression diagnostics were performed for all models. This included evaluating mean structure and heteroscedasticity using residual versus fitted value plots and normality using quantile-quantile plots.

2.3.2. Estimate age of cognitive divergence by genetic risk—When there were significant age by *APOE* score interactions, we used the interaction model derived above to calculate adjusted means of cognitive scores and 95% confidence intervals (CI) at several genetic risk levels across the age range in our sample. The means and CIs were extracted using the "emmeans" package[37] in R and used to estimate the age when cognitive function began to differ between *APOE* scores. The age of divergence was the approximate 5-year age range when confidence intervals for the highest (2.54) and middle (0.00) *APOE* score mean cognitive levels no longer overlapped. To estimate the rate of cognitive change (i.e., simple *APOE* score slopes at various ages), we calculated the slope and 95% CI of the mean cognitive values extracted in the previous step. The Kenward-Rodger approximation was used to determine degrees of freedom. Similar steps were applied to estimate the mean cognition for the analyses with an age by PRS interaction.

2.3.3. Post Hoc: Compare APOE score and AD PRS with APOE age of cognitive divergence—To evaluate how additional genetic variants change the age when

differences in cognitive trajectories are observed, we compared the *APOE* score to an AD PRS—composed of the *APOE* score and additional variants. Using the estimates from the interaction models, we calculated the difference in mean cognition across age between high and low risk groups of each respective score. For each genetic measure, we extracted and compared the age when there was a 0.5 SD difference in the predicted cognition. A 0.5 SD difference is more clinically meaningful than the simple point when differences are statistically significant. The high and low values were 2.56 (*ε4/ε4*) and −0.7 (*ε2/ε2*) for the *APOE* score and 3.37 (100^{th} percentile) and −1.78 (0 percentile) for the PRS. We used extreme percentiles of the PRS because they are the closest conceptual equivalent to the two extreme *APOE* score risk levels. In addition, the extremes for the *APOE* score and the AD PRS with *APOE* were used to provide a best-case scenario comparison, the maximum extent of each score. However, we also plot mean cognitive differences relative to the 0.00 *APOE* score (*ε3/ε3*) and the 50^{th} percentile of the AD PRS for readers who wish to see estimates corresponding to commonly used reference points.

2.3.4. Software—Analysis was conducted in R v.4.0.3.[34] Various add-on packages were used for data management and visualization,[38] regression analysis,[39,40] and model estimates and predicted values extraction.[37,41]

3. Results

3.1. Sample characteristics

The WRAP analytic sample contains data from up to 6 study visits per person, with a median of 4 visits. This covers up to 13 years of follow-up, with a median participant follow-up time of 7.8 years and a mean time between visits of 2.5 years. At baseline (visit 2, as composite scores are not available for visit 1), the sample was mostly composed of females and people with the equivalent of a college degree, with a mean age of 59 years (Table 1). This sample includes individuals across all *APOE* genotypes (Supplemental Figure 1).

3.2. Association of the *APOE* score and age with cognitive composite scores

The final model for each cognitive outcome included random intercepts for individual and family, and a random slope for age at the participant level. Covariates included sex, education, practice effects (number of tests taken previously), and age (centered at 65 years). Age was modeled as a cubic polynomial for all outcomes except executive function where a quadratic polynomial provided the best fit. All final models included interactions between the *APOE* score and each age term.

The *APOE* score by age interaction was significant for all cognitive composite outcomes (Table 2). People with higher *APOE* scores have lower mean cognitive function at age 65 and higher rates of decline at older ages compared to people with lower *APOE* scores (Table 2, Figure 1). A sensitivity analysis adjusting for the first five principal components negligibly affected estimates (results not shown). Note that the *APOE* score was included as a continuous measure in the regression analyses. For ease of interpretation, estimates in

figures are provided for *APOE* scores that correspond to *APOE* genotypes as opposed to whole units or percentiles of the *APOE* score.

3.3. Age of cognitive divergence by *APOE* score

We identified the approximate 5-year age range when confidence intervals no longer overlapped for mean predicted cognitive levels between high (2.56) and middle (0.00) *APOE* score risk levels based on estimates from the interaction models (Table 2). For all cognitive composites, the age of detectable cognitive trajectory differences occurs very close to 65 years based on the models of our sample (Figure 1, Table 3). For executive function and PACC3 (global cognition), the divergence in trajectories occurs between 60 and 65 years. For immediate learning and delayed recall, the divergence occurs between 65 and 70 years.

3.4. Post-hoc: Difference in age of cognitive divergence between *APOE* score and AD PRS with *APOE*

We compared the age of cognitive divergence for the *APOE* score and an AD PRS (including the *APOE* score) to evaluate if additional genetic variants associated with AD shift the age when differences in cognitive levels between genetic risk categories are detected. For both the *APOE* score and AD PRS models (Supplemental Table 4), we calculated the age when the difference in cognition between the highest and lowest risk level of each genetic score reached 0.5 SD. For the *APOE* score, there was a 0.5 SD difference between an *APOE* score of −0.7 (*ε2*/*ε2*) and 2.56 (*ε4*/*ε4*) at age 69, 70, 70, and 69 for immediate learning, delayed recall, executive function, and PACC3, respectively (top row, Figure 2). For the AD PRS, there was a 0.5 SD difference between a PRS of −1.78 (0^{th} percentile) and 3.37 (100^{th} percentile) at age 68, 69, 68, and 67 for immediate learning, delayed recall, executive function, and PACC3, respectively (bottom row, Figure 2). In this descriptive assessment, the 0.5 SD difference in cognition between extreme values of each genetic measure is a year earlier for the PRS relative to the *APOE* score for immediate learning and delayed recall and two years earlier for executive function and PACC3.

4. Discussion

This project's goal was to evaluate the temporal relationship between genetic risk of dementia due to AD and cognitive decline in WRAP, a preclinical cohort with over 13 years of longitudinal cognitive assessment. We aimed to build on existing evidence that genetic factors are tied to cognitive decline rates by estimating the age when differences in cognition among genetic risk levels for AD emerge. We used a relatively novel measure, the *APOE* score, to model genetic risk of AD from *APOE* and found that *APOE* interacts with age non-linearly to affect four composite cognitive measures. For immediate learning, delayed recall, executive function, and global function (PACC3), higher *APOE* scores were associated with lower cognitive function at the centered age of 65 and increasing rates of cognitive decline over age. This is consistent with findings that *APOE* affects the age of clinical and pathological AD onset and is associated with cognitive decline not just overall cognitive function (i.e., associated with the rate of change in cognitive function not just cross-sectional cognitive differences).[42,43] Interestingly, similar analyses with slightly

different cognitive measures in the WRAP sample a few years ago did not yield any effect of *APOE* or the *APOE* by age interaction on cognition.[16] Additional follow-up time or the use of more sensitive composites may have led to these new findings. This kind of discrepancy in findings over age is highlighted in a meta-analysis of *APOE*'s effects on several cognitive domains in mid-life (35–60 years).[44] No combined *APOE* effects across studies were significant for any cognitive domain. However, the authors noted that several studies did demonstrate cognitive differences by *APOE* in participants older than 55 years.

We applied the regression models to estimate the age when differences between genetic risk levels would emerge in our sample. Across the four cognitive composite scores, predicted cognition began to diverge at approximately age 65 (Figure 1). Executive function and PACC3 changes occurred slightly earlier than those of immediate learning and delayed recall. Recent work examining the association of β-amyloid (Aβ) (which is influenced by *APOE*[45]) and cognitive function found that Aβ was associated with executive function but not measures of delayed recall.[46] Aβ is the first discernable pathological change to occur in AD,[47] so this association could explain why changes in executive function occurred earlier. PACC3 and the executive function composite score both include the Digit Symbol Wechsler Adult Intelligence Scale-Revised test, which could explain why PACC3 changes also occurred earlier. Our findings using the *APOE* score are a little later than what was reported by Caselli et al.[9,10,48] for memory domains and *APOE ε4* count, for which cognitive function differences were detectable around age 60. However, Caselli et al. did not find significant differences in cognitive performance across age by *APOE ε4* count for measures of executive function, whereas we did. The estimates in our sample are approximately the same as those reported by Gharbi-Meliani et al.[11] in the Whitehall II study. They reported that *APOE ε4* homozygotes performed worse compared to non-carriers on a composite measure of global cognition starting at age 65. Cognition for *APOE ε4* heterozygotes compared to non-carriers became worse between 70 and 75 years and was better before age 55. Any inconsistencies across studies could be due to the use of different cognitive measures, slight differences in modeling covariates, and population sample differences.

When we extended this analysis to evaluate how additional genetic variants added to the *APOE* score (in the form of an AD PRS with *APOE*) influence the age when cognitive differences emerge, we found that differences in cognition by PRS occurred one to two years earlier than by the *APOE* score alone. This difference is minimal in the context of making decisions about lifestyle interventions or clinical trial recruitment. This also implicates *APOE* as the main driver of these cognitive differences in the WRAP sample, which has also been reported in other samples.[13] In addition, a recent cross-sectional analysis of the UK Biobank,[49] which also evaluated the age of cognitive divergence by an AD PRS that included *APOE* and was composed of similar variants as ours, found in sensitivity analyses that the interaction between the PRS and age was not significant if *APOE* was taken out of the PRS and included as a separate term in the models. Our results as well as others that use a PRS could fluctuate with the addition of variants to the PRS. Many AD PRS exist, which were built on different principles. For measure reproducibility, we used a PRS[30] that included a specific set of variants instead of one based on a p-value threshold, whose variant composition can differ depending on a particular sample's linkage disequilibrium structure and other factors. Also, we chose PRS values at extreme high and low percentiles in this

estimate, which may not be stable across populations. However, using them illustrates the maximum extent the PRS could influence the age when cognitive differences emerge in this sample. Despite this, we only observed a difference of one year in immediate learning and delayed recall and two years in executive function and PACC3.

Relatively few studies have examined the specific timing of genetic effects on cognition in a preclinical cohort beyond the main effect of genetics on cognitive function and decline. Our study delves into this by using cognitive composite scores that are sensitive to aging related changes. We also add to existing research operationalizing *APOE* risk with the *APOE* score. Typically, *APOE* risk is modeled by *ε4* allele carrier status (carrier or non-carrier) or count (0, 1, 2), which have the disadvantage of masking risk variation by collapsing the six *APOE* allele combinations (*ε2*/*ε2*, *ε2*/*ε3*, *ε3*/*ε3*, *ε2*/*ε4*, *ε3*/*ε4*, *ε4*/*ε4*). When modeling all six allele combinations is desired, the *APOE* score also avoids power loss because it is a continuous instead of categorical variable. This approach to modeling *APOE* is relatively new but has been applied in a few other contexts.[2,26,50] Another strength of this study is that we model age non-linearly. Although including non-linear age in cognition models is not new, it is not standard practice. When possible, we recommend modeling age non-linearly to capture variation in the genetic effect on cognition. Several studies have shown the effects of PRS on AD, cognition, and cognitive decline, with mixed results.[7] To our knowledge, this study is the first to evaluate the specific timing of cognitive changes related to an AD PRS in a preclinical longitudinal cohort. The additional variants captured by a PRS could provide more insight on the biology of AD relating to the order of pathological changes in the preclinical stage. However, the PRS used in this study may not be directly comparable to that used in other studies because of variant composition.

Because WRAP is a convenience sample enriched for individuals with a family history of AD, these results should be interpreted as a preliminary step in understanding the temporal role of genetic factors in AD biology. Our age estimates may be biased towards an earlier age compared to estimates from a population-based sample because individuals in our sample may be more likely to experience earlier cognitive change resulting from their family history. However, convenience samples can have healthier volunteers than a population-based sample, which could result in better cognitive performance estimates for the former.[51] Because of model complexity and limited sample size, we were also not able to account for interactions or differences among sex, age, and *APOE*, which have been important in other analyses of cognition.[52,53] The inclusion of these terms may have provided more nuance to the sample estimates especially because our sample is predominantly female. The sample being predominantly white and female limits the generalizability of our findings. For example, the association between *APOE* ε4 carrier status and learning decline and verbal memory is stronger in females than in males,[54] which means that the age estimates from our study may be earlier than studies with more balanced proportions of males and females. Likewise, the *APOE* association with risk of AD and age of AD onset has been inconsistent and more often lacking in African-American populations.[55] Social and structural factors like more disadvantaged neighborhood environments can modify and even mask the effects of *APOE* on cognition.[56] Therefore, our estimates of age-related differences in *APOE*'s effects on cognition may not be generalizable to populations with higher proportions

of historically disadvantaged racial background groups, where the effects of *APOE* are potentially attenuated.

Future work in this area would benefit from evaluating cognitive trajectories among individuals who go on to develop dementia. Very few WRAP participants in our analytic sample had dementia, so we were not able to carry out analyses to understand how our findings relate to dementia-specific cognitive changes compared to non-dementia related ones. In addition, future research could investigate the temporal relationship between genetics and biomarkers of AD proteinopathy in relationship to cognitive decline. It is still not fully understood how these biomarker changes interact with each other. Investigating the timing of these effects can lead to better understanding of the order of the biomarker cascade[1] and insight about what risk factors initiate changes in other risk factors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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6. References

1. Jack CR, Knopman DS, Jagust WJ, et al. Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. Lancet Neurol. 2013;12(2):207–216. doi:10.1016/S1474-4422(12)70291-0 [PubMed: 23332364]
2. Reiman EM, Arboleda-Velasquez JF, Quiroz YT, et al. Exceptionally low likelihood of Alzheimer's dementia in *APOE2* homozygotes from a 5,000-person neuropathological study. Nat Commun. 2020;11(1):667–667. doi:10.1038/s41467-019-14279-8 [PubMed: 32015339]
3. Chang YL, Fennema-Notestine C, Holland D, et al. *APOE* interacts with age to modify rate of decline in cognitive and brain changes in Alzheimer's disease. Alzheimers Dement. 2014;10(3):336–348. doi:10.1016/j.jalz.2013.05.1763 [PubMed: 23896613]
4. Corder E, Saunders A, Strittmatter W, et al. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science. 1993;261(5123):921. doi:10.1126/science.8346443 [PubMed: 8346443]
5. Martins CAR, Oulhaj A, de Jager CA, Williams JH. *APOE* alleles predict the rate of cognitive decline in Alzheimer disease: A nonlinear model. Neurology. 2005;65(12):1888–1893. doi:10.1212/01.wnl.0000188871.74093.12 [PubMed: 16380608]
6. Qian J, Betensky RA, Hyman BT, Serrano-Pozo A. Association of *APOE* genotype with heterogeneity of cognitive decline rate in Alzheimer disease. Neurology. Published online March 26, 2021:10.1212/WNL.0000000000011883. doi:10.1212/WNL.0000000000011883
7. Andrews SJ, McFall GP, Booth A, Dixon RA, Anstey KJ. Association of Alzheimer's disease genetic risk loci with cognitive performance and decline: A systematic review. J Alzheimers Dis JAD. 2019;69(4):1109–1136. doi:10.3233/JAD-190342 [PubMed: 31156182]

8. Kunkle BW, Grenier-Boley B, Sims R, et al. Genetic meta-analysis of diagnosed Alzheimer's disease identifies new risk loci and implicates Aβ, tau, immunity and lipid processing. Nat Genet. 2019;51(3):414–430. doi:10.1038/s41588-019-0358-2 [PubMed: 30820047]
9. Caselli RJ, Locke DEC, Dueck AC, et al. The neuropsychology of normal aging and preclinical Alzheimer's disease. Alzheimers Dement. 2014;10(1):84–92. doi:10.1016/j.jalz.2013.01.004 [PubMed: 23541188]
10. Caselli RJ, Dueck AC, Osborne D, et al. Longitudinal modeling of age-related memory decline and the *APOE* ε4 effect. N Engl J Med. 2009;361(3):255–263. doi:10.1056/NEJMoa0809437 [PubMed: 19605830]
11. Gharbi-Meliani A, Dugravot A, Sabia S, et al. The association of APOE ε4 with cognitive function over the adult life course and incidence of dementia: 20 years follow-up of the Whitehall II study. Alzheimers Res Ther. 2021;13(1):5. doi:10.1186/s13195-020-00740-0 [PubMed: 33397450]
12. Ge T, Sabuncu MR, Smoller JW, Sperling RA, Mormino EC. Dissociable influences of *APOE ε4* and polygenic risk of AD dementia on amyloid and cognition. Neurology. 2018;90(18):e1605–e1612. doi:10.1212/WNL.0000000000005415 [PubMed: 29592889]
13. Gustavson DE, Reynolds CA, Hohman TJ, et al. Alzheimer's Disease Polygenic Scores Predict Changes in Episodic Memory and Executive Function Across 12 Years in Late Middle Age. J Int Neuropsychol Soc JINS. Published online February 21, 2022:1–12. doi:10.1017/S1355617722000108
14. Kumar A, Shoai M, Palmqvist S, et al. Genetic effects on longitudinal cognitive decline during the early stages of Alzheimer's disease. Sci Rep. 2021;11(1):19853. doi:10.1038/s41598-021-99310-z [PubMed: 34615922]
15. Pan G, King A, Wu F, et al. The potential roles of genetic factors in predicting ageing-related cognitive change and Alzheimer's disease. Ageing Res Rev. 2021;70:101402. doi:10.1016/j.arr.2021.101402 [PubMed: 34242808]
16. Johnson SC, Koscik RL, Jonaitis EM, et al. The Wisconsin Registry for Alzheimer's Prevention: A review of findings and current directions. Alzheimers Dement Diagn Assess Dis Monit. 2018;10(1):130–142. doi:10.1016/j.dadm.2017.11.007
17. Jonaitis EM, Koscik RL, Clark LR, et al. Measuring longitudinal cognition: Individual tests versus composites. Alzheimers Dement Diagn Assess Dis Monit. 2019;11(1):74–84. doi:10.1016/j.dadm.2018.11.006
18. Darst BF, Lu Q, Johnson SC, Engelman CD. Integrated analysis of genomics, longitudinal metabolomics, and Alzheimer's risk factors among 1,111 cohort participants. Genet Epidemiol. 2019;43(6):657–674. doi:10.1002/gepi.22211 [PubMed: 31104335]
19. Schmidt M Rey Auditory Verbal Learning Test: A Handbook. Western Psychological Services Los Angeles, CA; 1996.
20. Wechsler D Wechsler memory scale-revised. Psychol Corp. Published online 1987.
21. Benedict RH. Brief Visuospatial Memory Test--Revised. PAR; 1997.
22. Reitan RM. Validity of the Trail Making Test as an indicator of organic brain damage. Percept Mot Skills. 1958;8(3):271–276.
23. Trenerry MR, Crosson B, DeBoe J, Leber W. Stroop neuropsychological screening test. Odessa FL Psychol Assess Resour. Published online 1989.
24. Wechsler D WAIS-III : Administration and Scoring Manual : Wechsler Adult Intelligence Scale. Psychological Corporation; 1997.
25. Donohue MC, Sperling RA, Petersen R, Sun CK, Weiner MW, Aisen PS. Association between elevated brain amyloid and subsequent cognitive decline among cognitively normal persons. JAMA. 2017;317(22):2305–2316. doi:10.1001/jama.2017.6669 [PubMed: 28609533]
26. Darst BF, Koscik RL, Racine AM, et al. Pathway-specific polygenic risk scores as predictors of amyloid-β deposition and cognitive function in a sample at increased risk for Alzheimer's disease. J Alzheimers Dis. 2017;55(2):473–484. doi:10.3233/JAD-160195 [PubMed: 27662287]
27. Belloy ME, Napolioni V, Greicius MD. A quarter century of *APOE* and Alzheimer's disease: Progress to date and the path forward. Neuron. 2019;101(5):820–838. doi:10.1016/j.neuron.2019.01.056 [PubMed: 30844401]

28. ALZGENE database. AlzGene, meta-analysis of case-control AD associated studies. Published January 29, 2010. Accessed July 5, 2018. http://www.alzgene.org/meta.asp?geneID=83
29. Bertram L, McQueen MB, Mullin K, Blacker D, Tanzi RE. Systematic meta-analyses of Alzheimer disease genetic association studies: The AlzGene database. Nat Genet. 2007;39(1):17–23. doi:10.1038/ng1934 [PubMed: 17192785]
30. de Rojas I, Moreno-Grau S, Tesi N, et al. Common variants in Alzheimer's disease and risk stratification by polygenic risk scores. Nat Commun. 2021;12(1):3417. doi:10.1038/s41467-021-22491-8 [PubMed: 34099642]
31. Purcell SM, Wray NR, Stone JL, et al. Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. Nature. 2009;460(7256):748–752. doi:10.1038/nature08185 [PubMed: 19571811]
32. Cruchaga C, Karch CM, Jin SC, et al. Rare coding variants in the phospholipase D3 gene confer risk for Alzheimer's disease. Nature. 2014;505(7484):550–554. doi:10.1038/nature12825 [PubMed: 24336208]
33. Engelman CD, Darst BF, Bilgel M, et al. The effect of rare variants in *TREM2* and *PLD3* on longitudinal cognitive function in the Wisconsin Registry for Alzheimer's Prevention. Neurobiol Aging. 2018;66:177.e1–177.e5. doi:10.1016/j.neurobiolaging.2017.12.025
34. R Core Team. R: A language and environment for statistical computing. Published online 2020. https://www.R-project.org/
35. Allison SL, Jonaitis EM, Koscik RL, et al. Neurodegeneration, Alzheimer's disease biomarkers, and longitudinal verbal learning and memory performance in late middle age. Neurobiol Aging. 2021;102:151–160. doi:10.1016/j.neurobiolaging.2021.01.030 [PubMed: 33765428]
36. Koscik RL, Betthauser TJ, Jonaitis EM, et al. Amyloid duration is associated with preclinical cognitive decline and tau PET. Alzheimers Dement Diagn Assess Dis Monit. 2020;12(1):e12007. doi:10.1002/dad2.12007
37. Lenth RV. emmeans: Estimated marginal means, aka least-squares means. Published online 2020. https://CRAN.R-project.org/package=emmeans
38. Wickham H, Averick M, Bryan J, et al. Welcome to the tidyverse. J Open Source Softw. 2019;4(43):1686. doi:10.21105/joss.01686
39. Bates D, Mächler M, Bolker B, Walker S. Fitting linear mixed-effects models using lme4. J Stat Softw. 2015;67(1):1–48. doi:10.18637/jss.v067.i01
40. Kuznetsova A, Brockhoff PB, Christensen RHB. lmerTest package: Tests in linear mixed effects models. J Stat Softw. 2017;82(13):1–26. doi:10.18637/jss.v082.i13
41. Lüdecke D, Ben-Shachar MS, Patil I, Makowski D. Extracting, computing and exploring the parameters of statistical models using R. J Open Source Softw. 2020;5(53):2445. doi:10.21105/joss.02445
42. Bonham LW, Geier EG, Fan CC, et al. Age-dependent effects of *APOE ε4* in preclinical Alzheimer's disease. Ann Clin Transl Neurol. 2016;3(9):668–677. doi:10.1002/acn3.333 [PubMed: 27648456]
43. Del-Aguila JL, Fernández MV, Schindler S, et al. Assessment of the genetic architecture of Alzheimer's disease risk in rate of memory decline. J Alzheimers Dis JAD. 2018;62(2):745–756. doi:10.3233/JAD-170834 [PubMed: 29480181]
44. Lancaster C, Tabet N, Rusted J. The elusive nature of APOE ε4 in mid-adulthood: understanding the cognitive profile. J Int Neuropsychol Soc JINS. 2017;23(3):239–253. doi:10.1017/S1355617716000990 [PubMed: 28059047]
45. Serrano-Pozo A, Das S, Hyman BT. *APOE* and Alzheimer's disease: Advances in genetics, pathophysiology, and therapeutic approaches. Lancet Neurol. 2021;20(1):68–80. doi:10.1016/S1474-4422(20)30412-9 [PubMed: 33340485]
46. Tideman P, Stomrud E, Leuzy A, Mattsson-Carlgren N, Palmqvist S, Hansson O. Association of β-amyloid accumulation with executive function in adults with unimpaired cognition. Neurology. 2022;98(15):e1525. doi:10.1212/WNL.0000000000013299 [PubMed: 35022305]
47. Zetterberg H, Bendlin BB. Biomarkers for Alzheimer's disease—preparing for a new era of disease-modifying therapies. Mol Psychiatry. 2021;26(1):296–308. doi:10.1038/s41380-020-0721-9 [PubMed: 32251378]

48. Caselli RJ, Dueck AC, Locke DEC, et al. Longitudinal modeling of frontal cognition in *APOE* ε4 homozygotes, heterozygotes, and noncarriers. Neurology. 2011;76(16):1383–1388. doi:10.1212/WNL.0b013e3182167147 [PubMed: 21502596]

49. Zimmerman SC, Brenowitz WD, Calmasini C, et al. Association of Genetic Variants Linked to Late-Onset Alzheimer Disease With Cognitive Test Performance by Midlife. JAMA Netw Open. 2022;5(4):e225491–e225491. doi:10.1001/jamanetworkopen.2022.5491 [PubMed: 35377426]

50. Deming Y, Li Z, Kapoor M, et al. Genome-wide association study identifies four novel loci associated with Alzheimer's endophenotypes and disease modifiers. Acta Neuropathol (Berl). 2017;133(5):839–856. doi:10.1007/s00401-017-1685-y [PubMed: 28247064]

51. Brodaty H, Mothakunnel A, de Vel-Palumbo M, et al. Influence of population versus convenience sampling on sample characteristics in studies of cognitive aging. Ann Epidemiol. 2014;24(1):63–71. doi:10.1016/j.annepidem.2013.10.005 [PubMed: 24211070]

52. Koscik RL, Norton DL, Allison SL, et al. Characterizing the effects of sex, *APOE ε4*, and literacy on mid-life cognitive trajectories: application of information-theoretic model averaging and multi-model inference techniques to the Wisconsin Registry for Alzheimer's Prevention study. J Int Neuropsychol Soc JINS. 2019;25(2):119–133. doi:10.1017/S1355617718000954 [PubMed: 30522545]

53. Neu SC, Pa J, Kukull W, et al. Apolipoprotein E Genotype and Sex Risk Factors for Alzheimer Disease: A Meta-analysis. JAMA Neurol. 2017;74(10):1178–1189. doi:10.1001/jamaneurol.2017.2188 [PubMed: 28846757]

54. Beydoun MA, Boueiz A, Abougergi MS, et al. Sex differences in the association of the apolipoprotein E epsilon 4 allele with incidence of dementia, cognitive impairment, and decline. Neurobiol Aging. 2012;33(4):720–731.e4. doi:10.1016/j.neurobiolaging.2010.05.017 [PubMed: 20619505]

55. Reitz C, Mayeux R. Genetics of Alzheimer's disease in Caribbean Hispanic and African American populations. Dement Interface Psychiatry Neurol. 2014;75(7):534–541. doi:10.1016/j.biopsych.2013.06.003

56. Boardman JD, Barnes LL, Wilson RS, Evans DA, Mendes de Leon CF. Social disorder, *APOE-E4* genotype, and change in cognitive function among older adults living in Chicago. Soc Sci Med 1982. 2012;74(10):1584–1590. doi:10.1016/j.socscimed.2012.02.012

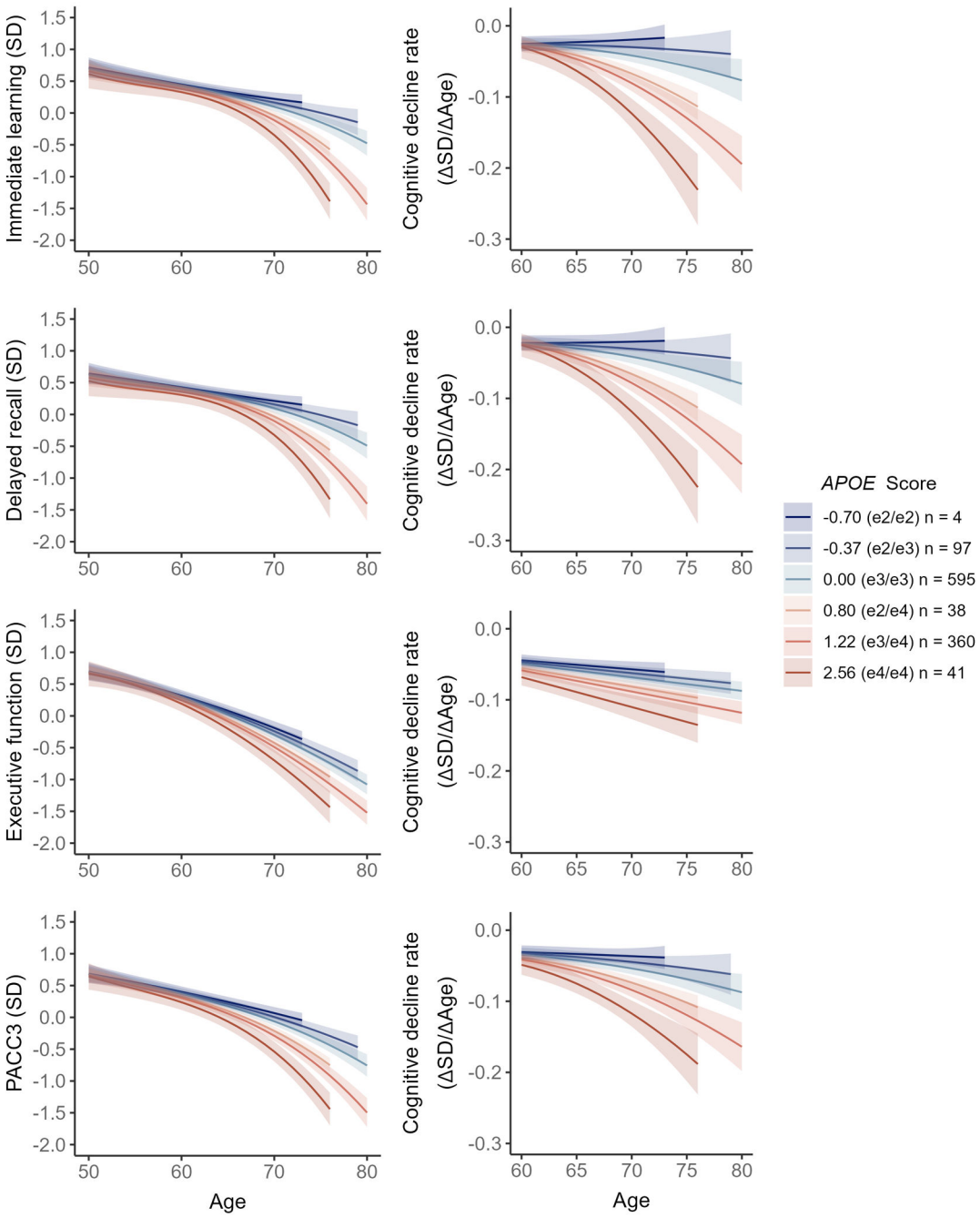

Figure 1: Predicted mean cognitive levels (left column) and slope of cognitive levels (right column) for *APOE* score groups across age from the *APOE* score by age interaction models.

The predicted mean cognitive level in SD (left) and the difference in SD across age (right) for each composite score is on the y-axis, and age in years is represented on the x-axis. Estimates come from regression models for immediate learning, delayed recall, executive function, and PACC3 that include the *APOE* score, age, age^2, age^3 (all except executive function), *APOE* score by age$^{[1-3]}$ (inclusive of all polynomial terms), sex, education, practice effects, random intercepts for individual and family, and random slope for age. Bands represent 95% CIs. For these estimates, sex was set to female, education to 16 years

(sample mean), and practice effects to 2 tests. Estimates are truncated to be within the age range of participants for a particular genetic group. Sample sizes for each genetic group are provided in the legend. Sample size varies slightly by cognitive outcome (see Supplemental Table 1). Values presented are for the outcome with largest sample size.

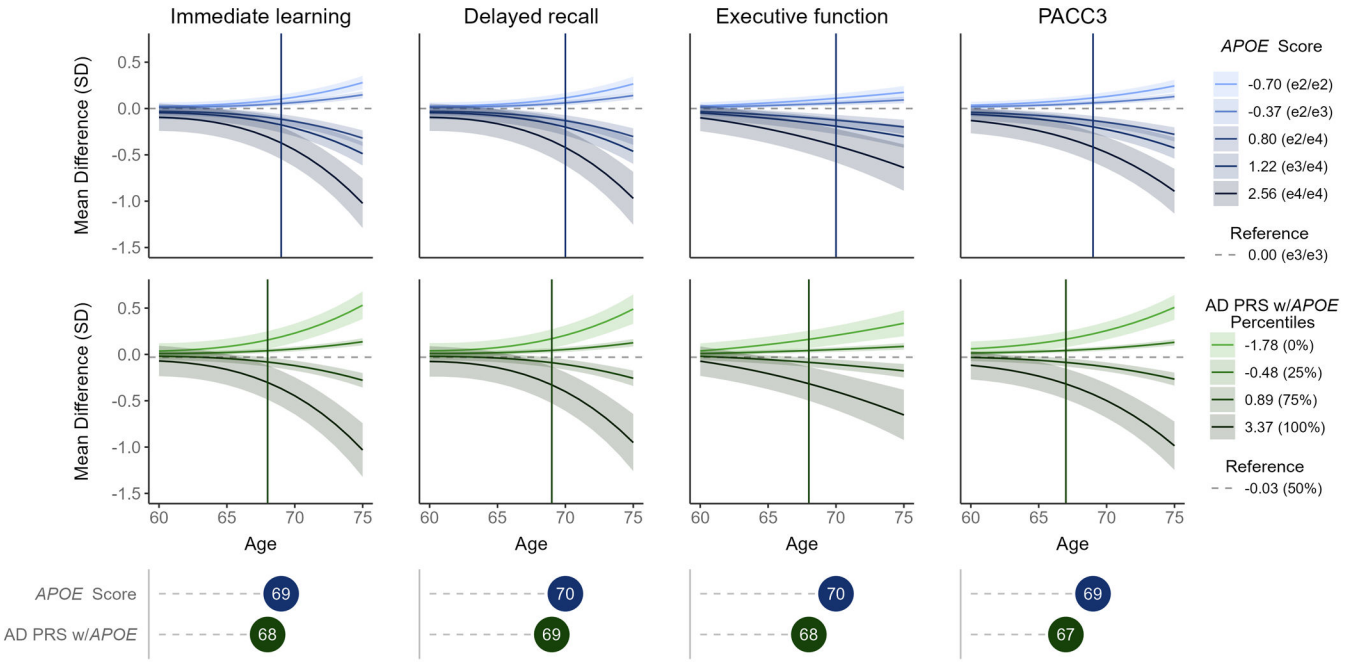

Figure 2: Difference in predicted mean cognition across age by genetic group and comparison of *APOE* score to AD PRS with *APOE*.

Immediate learning, delayed recall, executive function, and PACC3 differences (y-axis) across age (x-axis) are shown for *APOE* score groups (top row, blue) and the AD PRS with *APOE* (middle row, green) from a given genetic reference group (*APOE* score of 0 [e3/e3] and PRS of −0.03 [50th percentile]). A positive difference indicates better cognition than the reference, and a negative difference indicates worse cognition than the reference. Vertical lines mark the age when the difference in cognition is 0.5 SD between the extreme genetic risk categories (*APOE* score −0.7 and 2.56, and PRS of −1.78 and 3.37) is 0.5 SD. The bottom row shows the numerical value of those ages. Bands represent 95% CIs for the difference value. For these estimates, sex was set to female, education to 16 years (sample mean), and practice effects to 2 tests.

Table 1:

Participant characteristics at baseline by *APOE* genotype.

	Full analytic sample *, † (N = 1135)	***APOE ε2/ε2* (n = 4)**	***APOE ε2/ε3* (n = 97)**	***APOE ε3/ε3* (n = 595)**	***APOE ε2/ε4* (n = 38)**	***APOE ε3/ε4* (n = 360)**	***APOE ε4/ε4* (n = 41)**
Age, years (mean, SD)	59 (6)	54 (11)	60 (7)	59 (6)	57 (6)	58 (6)	58 (5)
Female (n, %)	794 (70%)	4 (100%)	73 (72%)	408 (69%)	23 (61%)	251 (70%)	39 (95%)
Education, years (mean, SD)	16 (2)	13 (1)	16 (2)	16 (2)	15 (2)	16 (2)	15 (2)
Immediate learning (mean, SD)	0.03 (0.78)	0.10 (0.33)	−0.02 (0.70)	0.06 (0.78)	−0.31 (0.80)	0.04 (0.78)	0.04 (0.79)
Delayed recall (mean, SD)	0.03 (0.78)	−0.08 (0.34)	0.01 (0.71)	0.05 (0.79)	−0.32 (0.78)	0.04 (0.77)	0.03 (0.74)
Executive function (mean, SD)	0.04 (0.77)	−0.24 (0.54)	−0.02 (0.69)	0.03 (0.78)	−0.06 (0.84)	0.08 (0.77)	0.06 (0.64)
Preclinical Alzheimer cognitive composite (mean, SD)	0.03 (0.75)	0.11 (0.41)	−0.00 (0.68)	0.05 (0.75)	−0.33 (0.84)	0.06 (0.75)	−0.01 (0.74)

Values are either mean (standard deviation [SD]) or count (percent)

* Sample size varies slightly by cognitive outcome (see Supplemental Table 1). Values presented are for the outcome with largest sample size.

† The sample consisted of 917 “family” groups, 85% of which were single unrelated individuals and 15% were families (siblings) ranging from 2–9 individuals.

Table 2:

Effect estimates from mixed effects regression of four cognitive composite outcomes with and without an *APOE* score by age interaction.

	Outcome							
Covariate	**Immediate learning Estimate (95% CI)**		**Delayed recall Estimate (95% CI)**		**Executive function Estimate (95% CI)**		**PACC3 Estimate (95% CI)**	
Intercept	−1.82*** (−2.12 to −1.53)	−1.83*** (−2.12 to −1.53)	−1.83*** (−2.13 to −1.53)	−1.82*** (−2.12 to −1.52)	−1.32*** (−1.62 to −1.01)	−1.31******* (−1.61 to −1.01)	−1.90*** (−2.18 to −1.62)	−1.91*** (−2.19 to −1.63)
***APOE* Score**	−0.07* (−0.13 to −0.02)	−0.10*** (−0.16 to −0.05)	−0.06* (−0.12 to −0.01)	−0.10*** (−0.15 to −0.04)	−0.05 (−0.11 to 0.01)	−0.09** (−0.14 to −0.03)	−0.08** (−0.13 to −0.03)	−0.11*** (−0.16 to −0.05)
Age (years, c = 65)	−17.60*** (−20.64 to −14.55)	−15.22*** (−18.41 to −12.03)	−16.01*** (−19.18 to −12.84)	−13.86*** (−17.19 to −10.53)	−27.24*** (−30.22 to −24.26)	−25.34*** (−28.45 to −22.24)	−21.53*** (−24.41 to −18.65)	−19.18*** (−22.19 to −16.18)
Age (2nd deg.)	−3.39*** (−4.67 to −2.11)	−1.98** (−3.46 to −0.50)	−4.03*** (−5.36 to −2.70)	−2.66*** (−4.21 to −1.12)	−4.49*** (−5.55 to −3.44)	−3.90*** (−5.13 to −2.67)	−3.97*** (−5.08 to −2.87)	−3.10*** (−4.39 to −1.82)
Age (3rd deg.)	−2.04*** (−3.15 to −0.93)	−1.32* (−2.58 to −0.05)	−2.01*** (−3.15 to −0.88)	−1.31* (−2.61 to −0.01)			−1.27** (−2.21 to −0.32)	−0.96 (−2.04 to 0.13)
***APOE* Score x Age**		−5.92*** (−8.32 to −3.53)		−5.48*** (−8.02 to −2.93)		−4.39*** (−6.43 to −2.34)		−5.74*** (−7.86 to −3.61)
***APOE* Score x Age (2nd deg.)**		−4.19*** (−5.99 to −2.39)		−4.03*** (−5.92 to −2.15)		−1.85* (−3.32 to −0.38)		−2.83*** (−4.39 to −1.26)
***APOE* Score x Age (3rd deg.)**		−2.30** (−3.82 to −0.77)		−2.23** (−3.79 to −0.67)				−1.26 (−2.57 to 0.04)
Marginal R2 / Conditional R2	0.21 / 0.78	0.21 / 0.79	0.19 / 0.79	0.19 / 0.80	0.26 / 0.89	0.26 / 0.89	0.28 / 0.85	0.29 / 0.85
AIC	6941	6889	6845	6802	4952	4929	5569	5526
N people	1134		1135		1129		1134	
N families	917		917		913		917	
N observations	4417		4414		4249		4404	

* p < 0.05

** p < 0.01

*** p < 0.001

CI: confidence interval; c: centered; AIC: Akaike information criterion; N: number

Models are adjusted for sex, years of education, and testing practice effects. All models included a random intercept for family and individual, and a random slope for age within individuals.

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Table 3:

Predicted mean cognitive levels (estimate [95% C])] and slope of cognitive levels (estimate [95% CI]) at particular *APOE* scores [*] across age from the *APOE* score by age interaction models.[†]

APOE score	Mean predicted cognitive values at specified age			Slope of predicted mean at specified age [‡]		
	60	65	70	60	65	70
Immediate learning						
−0.70 (*ε2*/*ε2*)	0.45 (0.36 to 0.54)	0.33 (0.24 to 0.41)	0.22 (0.12 to 0.32)	−0.03 (−0.04 to −0.01)	−0.02 (−0.03 to −0.01)	−0.02 (−0.03 to −0.01)
0.00 (*ε3*/*ε3*)	0.42 (0.36 to 0.49)	0.28 (0.22 to 0.34)	0.10 (0.03 to 0.17)	−0.03 (−0.03 to −0.02)	−0.03 (−0.04 to −0.02)	−0.04 (−0.05 to −0.03)
2.56 (*ε4*/*ε4*)	0.33 (0.20 to 0.46)	0.11 (−0.03 to 0.24)	−0.35 (−0.52 to −0.18)	−0.03 (−0.05 to −0.01)	−0.06 (−0.08 to −0.05)	−0.12 (−0.14 to −0.10)
Delayed recall						
−0.70 (*ε2*/*ε2*)	0.43 (0.34 to 0.52)	0.32 (0.23 to 0.40)	0.21 (0.11 to 0.32)	−0.02 (−0.03 to −0.01)	−0.02 (−0.03 to −0.01)	−0.02 (−0.03 to −0.01)
0.00 (*ε3*/*ε3*)	0.40 (0.34 to 0.46)	0.27 (0.21 to 0.33)	0.10 (0.02 to 0.17)	−0.02 (−0.03 to −0.02)	−0.03 (−0.04 to −0.02)	−0.04 (−0.05 to −0.03)
2.56 (*ε4*/*ε4*)	0.31 (0.18 to 0.44)	0.11 (−0.03 to 0.24)	−0.32 (−0.50 to −0.15)	−0.03 (−0.04 to −0.01)	−0.06 (−0.08 to −0.04)	−0.12 (−0.14 to −0.10)
Executive function						
−0.70 (*ε2*/*ε2*)	0.32 (0.23 to 0.41)	0.08 (−0.01 to 0.17)	−0.19 (−0.29 to −0.09)	−0.04 (−0.05 to −0.04)	−0.05 (−0.06 to −0.04)	−0.06 (−0.07 to −0.05)
0.00 (*ε3*/*ε3*)	0.29 (0.23 to 0.35)	0.02 (−0.04 to 0.08)	−0.30 (−0.37 to −0.23)	−0.05 (−0.06 to −0.04)	−0.06 (−0.07 to −0.05)	−0.07 (−0.08 to −0.06)
2.56 (*ε4*/*ε4*)	0.19 (0.06 to 0.32)	−0.20 (−0.34 to −0.07)	−0.70 (−0.87 to −0.53)	−0.07 (−0.08 to −0.06)	−0.09 (−0.10 to −0.08)	−0.11 (−0.13 to −0.09)
PACC3						
−0.70 (*ε2*/*ε2*)	0.40 (0.32 to 0.49)	0.24 (0.16 to 0.32)	0.07 (−0.03 to 0.16)	−0.03 (−0.04 to −0.02)	−0.03 (−0.04 to −0.02)	−0.04 (−0.05 to −0.03)
0.00 (*ε3*/*ε3*)	0.37 (0.31 to 0.43)	0.18 (0.12 to 0.23)	−0.06 (−0.13 to 0.00)	−0.03 (−0.04 to −0.03)	−0.04 (−0.05 to −0.04)	−0.05 (−0.06 to −0.05)
2.56 (*ε4*/*ε4*)	0.24 (0.12 to 0.36)	−0.06 (−0.19 to 0.06)	−0.54 (−0.69 to −0.38)	−0.05 (−0.06 to −0.03)	−0.08 (−0.09 to −0.06)	−0.12 (−0.14 to −0.10)

[*] Select *APOE* scores and ages are presented in this table, whereas the corresponding figure includes estimates for all *APOE* values.

[†] Estimates come from regression models for immediate learning, delayed recall, executive function, and PACC3 that include the *APOE* score, age, age^2, age^3 (all except executive function), *APOE* score by age$^{[1-3]}$ (inclusive of all polynomial terms), sex, education, practice effects, random intercepts for individual and family, and random slope for age. For these estimates, sex was set to female, education to 16 years (sample mean), and practice effects to 2 tests.

[‡] The slope is of the line tangent to the predicted mean curve at the specified age.