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Apolipoprotein E ε4 and later life decline in cognitive function and grip strength

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Abstract

Objectives: Presence of the apolipoprotein E (*APOE*) ε4 allele is a risk factor for dementia, while the ε2 allele offers protection against dementia. There is also evidence for a relationship between *APOE* genotype and changes in cognitive function. It is not clear however, whether this relationship stems from undetected disease in persons genetically more vulnerable to dementia. This study examined whether *APOE* genotype was associated with either initial performance or change in performance on a range of cognitive and non-cognitive tasks, after accounting for possible preclinical dementia.

Design: A population-based cohort was assessed up to four times over 12 years.

Participants: The sample was an Australian cohort of 590 participants aged 70 and over who were genotyped for *APOE*.

Measurements: The outcomes were processing speed, verbal fluency, episodic memory, word recognition, face recognition, grip strength and reaction time.

Results: Adjusted latent growth models indicated that ε4 carriers had significantly poorer initial memory performance and greater declines in processing speed and word recognition, compared to ε2 and ε3 carriers. In addition, ε2 carriers exhibited significantly less decline in right grip strength than ε3 carriers. However, after excluding 125 participants with low global cognition scores, all genotype effects became non-significant.

Conclusions: Over a 12 year period, findings indicate that *APOE* ε4-related cognitive decline in older community-dwelling populations is due to a higher likelihood of preclinical dementia among ε4 carriers. When possible dementia cases are removed from the analyses, ε4 associations with cognitive decline become statistically unreliable.

Introduction

The apolipoprotein E (*APOE*) ε4 allele is an established risk factor for dementia (e.g., 1) while, conversely, the ε2 allele offers protection against the disease (e.g., 2). Meta-analyses also suggest both ε4-related cognitive deficits, and ε2-related cognitive benefits, in later life (3, 4). However, there is accumulating evidence that the subclinical phase of dementia precedes eventual diagnosis by several years, even decades. For instance, histopathological work (5, 6) suggests the neuropathological markers of the disease are present in middle-age and early adulthood, while cognitive deficits have been detected up to ten years before clinical diagnosis (7). A key question, therefore, is whether *APOE* genotype exerts a direct influence on cognition independently of dementia-related neuropathology as numerous studies suggest, or whether ε4-related cognitive deficits represent a behavioral marker of the, as yet, undetected disease in persons genetically more vulnerable to earlier onset of dementia. It is this important question that motivates the present study.

There is already evidence that the latter may be the case. For example, longitudinal studies suggest that when future dementia is taken in to account, *APOE* genotype-related variation in cognitive change is minimal (8, 9), and two recent large-scale studies suggest that the more marked cognitive decline observed in ε4 carriers was probably associated with the presence of subclinical dementia-related neuropathology (10, 11).

The present study builds upon this research and also extends the earlier work of Hofer et al. (12), who examined the effects of *APOE* on cognition in the present community-based population. Using the first three measurement points from the Canberra Longitudinal Study cohort (13), Hofer and colleagues examined the effects of *APOE* genotype on memory, processing speed and verbal ability, which were measured as latent constructs derived from multiple cognitive tasks. They found that the ε4 allele was associated with poorer initial processing speed and greater declines in both speed and memory. In a cognitively intact

subsample, the effects on memory remained while the processing speed effects became non-significant. However, the investigators were not able to control for possible neuropathology beyond the seven year assessment period of that study. The present analysis, therefore, used all four waves of the Canberra Longitudinal Study spanning 12 years, examined a broader range of cognitive measures that were not investigated in that earlier study individually, and adjusted for potential neuropathology over the entire 12-year period. We also investigated grip strength because decreased grip strength has been identified as a strong predictor of cognitive aging (14, 15) and is associated with Alzheimer pathology and disease progression (16).

Importantly, to test whether any effects of *APOE* on cognition were due to possible subclinical dementia pathology, we used broader exclusion criteria for possible dementia. Instead of using the Canberra Interview for the Elderly, a diagnostic instrument for dementia (17) used in the earlier study, a cut-off of 24 on the Mini-Mental State Examination (18) was used to exclude participants possibly in the preclinical dementia phase during the study period. Given evidence that the $\varepsilon 2$ allele may delay dementia onset and help preserve late-life cognitive performance (19), we additionally extended the earlier study (12) by examining the specific effects of the $\varepsilon 2$ allele on cognitive change.

Following from the earlier work, we hypothesized that the *APOE* $\varepsilon 4$ allele would be associated with more precipitous decline in memory performance and processing speed. A non-specific protective effect of $\varepsilon 2$ on cognitive performance was also expected. However, *APOE*-related associations were expected to attenuate when possible dementia was taken into account. We also predicted that the $\varepsilon 4$ allele would be associated with weaker grip strength. More specifically, given evidence that dementia pathology has an earlier and more pronounced effect on the left cerebral hemisphere (20), and recent evidence that children with an $\varepsilon 2$ allele are more likely to be left handed (21), it was predicted that right-hand grip

strength, controlled by the left hemisphere, would exhibit greater decline in ε4 carriers than non-carriers.

Methods

Participants

The Canberra Longitudinal Study is an epidemiological survey of mental health and cognitive functioning in people aged 70 and over (13). Eight hundred and ninety-six participants (456 men and 440 women) were recruited for the baseline assessment in 1990. All participants were initially living in the community in the cities of Canberra or Queanbeyan, Australia. Participants were sampled from the compulsory electoral roll, with 69% responding to a letter and/or phone call (see 22 for further description of the recruitment), and the sample was stratified by age and gender. Approval for the research was obtained from the Ethics in Human Experimentation Committee of The Australian National University and all participants provided written informed consent.

The present sample (n = 590) comprised individuals successfully genotyped for *APOE* at Wave 2 of the study, excluding ten participants with genotype ε2/4 and five participants whose genotype could not be established. We excluded persons with the ε2/4 genotype because the respective alleles exert opposing influences on cognition and dementia and, therefore, may cancel one another out. Of the 590 participants included in the analysis who completed Waves 1 and 2, 360 (61.0%) completed the Wave 3 assessment (152 deceased, 78 dropouts) and 203 (34.4%) completed the Wave 4 assessment (295 deceased, 92 dropouts). Participants who completed the second interview have previously been reported to be younger, more educated, less disabled, have fewer diseases, have stronger grip strength, and have fewer depression symptoms than those who were not included in the analysis (23).

Survey Procedure

Participants were interviewed up to four times over 12 years by trained professional interviewers. Baseline interviews lasted approximately two hours, and included a survey that covered background characteristics, physical health and disease status, mental health status, cognitive performance and social support. Interviews also included physical assessment of blood pressure, lung function, grip strength, vision and reaction time.

APOE Genotype

APOE genotyping was performed using DNA extracted from buccal swabs using a modification of the method of Richards et al. (24). Polymerase chain reaction amplification of a 234 base-pair fragment of exon 4 of the apoE gene followed by digestion with *CfoI* was used to determine *APOE* genotype. These were separated by polyacrylamide gel electrophoresis and displayed by silver staining. Of the 605 participants tested, *APOE* genotype was successfully determined for 600. After excluding the 10 participants who had an ε2/4 genotype, the sample (n = 590) consisted of 11.0% having an ε2 gene (n = 2 with ε2/2; n = 63 with ε2/3), 23.2% having an ε4 gene (n = 127 with ε3/4; n = 10 with ε4/4) and the remaining 65.8% being homozygous for ε3 (n = 388).

Measures

A range of cognitive tests was administered at each interview. *Speed of processing* was measured by the Symbol-Letter Modalities Test (SLMT), a task similar to Smith's (25) Symbol-Digit Modalities Test and Wechsler's (26) Digit-Symbol Substitution. The number of correct symbol-letter pairs made in 90 seconds was summed. *Verbal fluency* was assessed as the number of animals named in 30 seconds [adapted from (27) to reduce participant burden]. An *episodic memory* task consisted of four brief episodic memory tasks testing

word, face, name and address recall and figure reproduction (28). *Face and word recognition* tasks were based on the Rivermead Behavioural Memory Test (29). To facilitate comparisons between tests, all of the cognitive and grip strength measures were standardized to a common metric, with a mean of 100 and standard deviation of 10 for the complete baseline sample.

To measure *choice reaction time*, participants were asked to press a button with their left or right hand depending on which of two stimulus lights were illuminated (interstimulus intervals ranged from 0.5 to 2.0 seconds) (30), and choice reaction time was measured as the mean response time over 20 trials. *Grip strength* was taken using a Smedley hand dynamometer which measures the force exerted in kilograms (30). Measurements were taken for both right and left hands.

The Mini-Mental State Examination (MMSE: 18), scored out of 30, was used to screen for possible preclinical dementia. Following consideration of the broader literature (31, 32), participants with MMSE scores ≤ 24 at any assessment were excluded to assess whether any effects of *APOE* on cognitive performance were attributable to possible dementia. Norms for the MMSE indicate sensitivity of 95% and specificity of 82% for detecting Alzheimer's Disease at this cut point in community-based individuals who are 80 years or older with nine or more years of education (most participants in the present study were in this category by the second wave) (33).

Additional control variables included in each model were age, gender and years of education. Years of education were assessed using a single self-report item.

Analysis

Latent growth models estimating the level (intercept) and slope of performance on each of the eight outcome measures were run. Latent growth models are a class of structural equation models that represent individual level data in terms of an initial level of performance

latent variable or factor (level), a rate of change factor (slope), and error (residual) parameters (12, 34). These structures are analogous to random intercept and slope terms in mixed models. However, latent growth modeling uses a multivariate approach, such that an outcome variable measured at four occasions gives rise to a four-variate outcome vector (35). Like mixed models, latent growth models accommodate missing data, appropriately accommodate unequal numbers of individual observations, account for dependencies among observations within individuals, and account for individual differences in the rates of cognitive decline (36).

Separate models were used to assess the role of *APOE* genotype on each of the outcome variables. In order to delineate and maximize allelic influence while retaining statistical power, the genotype combinations used in the models were as follows: $\varepsilon 2 = \varepsilon 2/2 + \varepsilon 2/3$; $\varepsilon 3 = \varepsilon 3/3$; $\varepsilon 4 = \varepsilon 3/4 + \varepsilon 4/4$. To assess all possible genotype comparisons, the models were run using $\varepsilon 3$ as the reference category, then repeated with $\varepsilon 2$ as the reference category. These models were each estimated twice: once with all participants and once excluding participants with possible preclinical dementia (MMSE $\leq$ 24 at any assessment). Mplus version 6 was used to estimate the latent growth models which incorporated all available data under the missing at random assumption. To illustrate the effects found in the models, mixed model repeated measures analyses of variance were used to estimate cognitive performance over time, adjusting for age, gender, education and genotype. Finally, a logistic regression analysis was used to examine baseline predictors of having MMSE $\leq$ 24 at any time point. PASW version 18 was used to estimate both the mixed effects models and logistic regression model.

Results

Individuals in the analysis sample were an average age of 76.2 years at the first assessment (*SD* = 4.7, range = 70-93 years), and had mean 11.5 years of education (*SD* = 2.6). Due to the gender stratification, the sample was 49.0% men and 51.0% women. The analysis sample was significantly younger (76.2 vs. 77.2 years; $F_{1,894} = 9.29$, $p = 0.002$) and better educated (11.5 vs. 11.0 years; $F_{1,892} = 7.45$, $p = 0.006$) than the full sample, but did not differ in gender distribution ($\chi^2_1 = 2.52$, $p = 0.112$). Descriptive statistics for the analysis sample are shown in Table 1, both overall and by *APOE* genotype group. As indicated in the table, there were no differences across genotype groups as assessed at the initial assessment, with the exception of word recognition where ε4 carriers performed significantly worse than ε2 and ε3 carriers. There was also some indication of poorer performance on episodic memory and MMSE in ε4 carriers compared to ε2 and ε3 carriers, although the differences were not significant ($p = 0.07$). Mixed effects models indicated that performance on all of the outcomes declined significantly over time. Adjusted for age, gender, education and *APOE*, the effect of time was significant at $p < 0.001$ for all outcomes ($F_{3, 202\text{-}370}$ range: 11.1 – 226.2). In Table 2, the latent growth model shows that the rate of decline in processing speed (SLMT) was significantly greater for $\varepsilon 4$ relative to both $\varepsilon 3$ ($p = 0.002$) and $\varepsilon 2$ ($p = 0.048$) carriers. The initial level of episodic memory performance was significantly lower for $\varepsilon 4$ allele than for $\varepsilon 2$ ($p = 0.015$). The level of word recognition performance was significantly lower for $\varepsilon 4$ than for both $\varepsilon 3$ ($p = 0.031$) and $\varepsilon 2$ ($p = 0.007$), while there was significantly greater decline in word recognition performance among $\varepsilon 4$ carriers compared to $\varepsilon 3$ ($p = 0.006$). Initial face recognition performance was significantly poorer for $\varepsilon 4$ than $\varepsilon 2$ ($p = 0.028$). Right hand grip strength declined significantly less in $\varepsilon 2$ participants relative to $\varepsilon 3$ ($p = 0.031$).

The effect of genotype on cognition is illustrated in Figure 1, which shows word recognition performance for participants 70-79 and ≥ 80 across the four time points. Values in the figure are based on estimated marginal means from a mixed model repeated measures ANOVA adjusted for age group, gender, education and genotype. The effect of $\varepsilon 4$ is evident in terms of both the poorer performance at baseline (particularly among the 70-79 group) and the greater decline in performance of both $\varepsilon 4$ groups over the four waves.

Importantly however, after excluding participants (n = 125) with possible preclinical dementia (i.e., persons with MMSE score ≤ 24 at any time point), the estimated genotype effects were greatly attenuated such that none of the original effects remained significant (Table 3). Participants who met this criterion performed significantly more poorly on all of the cognitive tests administered at the second assessment, scoring one SD lower on SLMT, word recognition, face recognition and episodic memory ($t_{559\text{-}570}$ = 8.04-11.33, p < 0.001 for all), suggesting some indication of cognitive deficit. The genotype distribution in this analysis was significantly different to the analysis without the exclusion. Notably, a greater proportion of $\varepsilon 4$ carriers had low MMSE scores ($\varepsilon 2$: n = 56 included/14% excluded, $\varepsilon 3$: n = 313 included/19% excluded, $\varepsilon 4$: n = 96 included/30% excluded; χ^2 = 9.2, p = 0.01). Nevertheless, the analysis had sufficient power to detect small differences between the $\varepsilon 3$ and $\varepsilon 4$ groups (conservatively assuming n = 96 per group, the power to detect an effect size of 0.2 between group effects was 0.93). The attenuation is illustrated in Figure 2 which shows the word recognition effect for those participants who did not have MMSE ≤24 at any time point. The values in this figure were estimated in the same way as those in Figure 1. The attenuation of the *APOE* effect can be seen in the overlap between the six groups. Also of note is that the slopes of all groups in Figure 2 appear to be relatively flat, suggesting much of the performance decline in the initial analyses was due to possible preclinical dementia as

opposed to age-based effects. Note that no participants with the $\varepsilon 4$ genotype in the 80s group remained by the fourth wave after excluding for MMSE ≤ 24, a result specific to the present cohort.

To investigate possible mediators of the relationship between $\varepsilon 4$ and low MMSE scores, baseline predictors of having MMSE ≤ 24 at any time point were examined in a logistic regression model. The model simultaneously included the effects of age, gender, years of education, marital status (married, single, widowed, divorced/separated), depression and anxiety symptoms (37), disease count (from a list of 14 conditions), physical functioning (38) and smoking status (never, past, current), all reported at the baseline assessment. Only increased age [OR = 1.07, χ^2 (1) = 12.0, p = 0.001], fewer years of education [OR = 0.86, χ^2 (1) = 15.5, p = 0.001] and being widowed or divorced/separated were significantly associated with low MMSE scores [marital status omnibus χ^2 (3) = 9.1, p = 0.028; widowed vs. married: OR = 1.69, χ^2 (1) = 5.9, p = 0.016; divorced/separated vs. married: OR = 2.39, χ^2 (1) = 5.0, p = 0.026], reflecting previously reported associations (39).

Discussion

This study possesses several important features. First, we assessed cognitive change in old age across a range of cognitive and non-cognitive variables as a function of *APOE* genotype over a 12 year period. To our knowledge, there are no other longitudinal studies of *APOE* and cognitive change over this length of time in older community-based populations that have controlled for possible dementia. Second, we carefully delineated between *APOE* genotype in order to assess the primary effects of the $\varepsilon 2$ allele (protective effect) relative to the $\varepsilon 3$ allele (neutral) and, in turn, the $\varepsilon 4$ allele (high vulnerability), in relation to cognitive decline. Additionally, in a repeat analysis, we removed persons considered high-risk for subclinical dementia. There were several important findings arising from the study. First,

persons possessing the ε4 allele exhibited lower initial scores in episodic memory, word recognition and face recognition than non-ε4 carriers. ε4 carriers also showed more marked decline over time in processing speed and word recognition. Second, although the protective effect of the ε2 allele was not demonstrated in relation to the cognitive variables, ε2 carriers declined less in right-hand grip strength than ε3 carriers. Importantly however, when persons with possible dementia neuropathology were removed from the sample, all of these *APOE*-related effects became non-significant.

The findings build upon earlier work on this dataset (12) by extending the analysis period to 12 years, examining a broader range of cognitive and non-cognitive variables, and using broader exclusion criteria for possible dementia. The findings have some important implications. First, they suggest that ε4-related cognitive decline in old age is associated with the preclinical phase of, as yet, undetected dementia rather than an independent effect of *APOE* genotype on cognition. Although we did not formally assess clinical dementia, when persons with low MMSE scores were removed from the sample, *APOE*-related effects disappeared. As low MMSE scores are associated with a higher likelihood of dementia (31, 32), this finding is consistent with several other studies (e.g., 8, 9, 10) that demonstrate null ε4-related effects when future dementia is controlled for. Given accumulating evidence that the subclinical phase of the disease extends years, and perhaps decades, ahead of the eventual clinical manifestations, the findings support the view that both *APOE* genotype and neuropsychological assessment could be taken into account in procedures for the early detection of dementia.

It also appears that the protective effect of the ε2 allele may reflect the hemispheric specificity of incipient neuropathology. As we expected, an *APOE* effect was detected for grip strength in the right hand. This prediction was made because it is now well documented

that brain aging and dementia-related pathology affect the left hemisphere earlier and more strongly than the right (20). Since the left hemisphere controls the right hand, deficits in grip strength would be expected first in the right hand. While we detected a protective effect for the $\varepsilon 2$ relative to the $\varepsilon 3$ allele for right hand grip strength, what is surprising is that we did not find an association between weaker grip strength and the $\varepsilon 4$ allele. This suggests a protective effect of the $\varepsilon 2$ allele against neuropathology, particularly since this disappeared in analyses that excluded persons with low MMSE scores.

A major concern in any study where significant effects disappear when participants are removed from the analyses is that reducing sample size affected statistical power. In the present context, this raises the question of whether our null results in the repeated analyses simply reflect a Type II error. We are confident that this was not the case, as a conservative post hoc power analysis found 93% power to detect an effect size of 0.2 between the $\varepsilon 3$ and $\varepsilon 4$ carriers. However, it is important to note that in our repeat analyses significantly more $\varepsilon 4$ carriers were removed from the sample due to low MMSE scores. As $\varepsilon 4$ carriers are genetically more vulnerable to earlier onset of dementia, this finding is consistent with the possibility that those excluded persons were more likely to be in the subclinical phase of the disease.

The study does possess several limitations that we should acknowledge. First, although we removed persons with low MMSE scores due to the higher likelihood that they may be experiencing dementia-related neuropathology, we were unable to confirm diagnosis. However, the MMSE criterion used in the present study drew upon work elsewhere (31, 32), and was broader in excluding possible dementia cases than the Canberra Interview for the Elderly criteria which in the earlier study detected only 30 dementia cases at any time point (compared to n = 125 with MMSE ≤24 here). Although the MMSE is not a conclusive

screening tool for dementia, we believe our approach represents a reasonable method of excluding possible dementia cases, given the constraints of available data. The present findings would be strengthened if replicated in other samples using mediation analyses with clinical measures assessing preclinical dementia. Second, as is unfortunately inevitable in studies of this age group, there was a high level of mortality by Wave 4. Although we still retained a reasonable sample size compared to other late-life cohort studies, our findings accordingly should be treated with appropriate caution. Third, although our neuropsychological battery assessed a comprehensive range of cognitive domains including executive function and episodic memory, both shown to be sensitive to ε4-related effects (3, 4), it remains possible that our battery was insufficiently broad to capture the effects of interest. Future work from our laboratories will address this issue using other datasets. Fourth, the available data were not sufficient for investigating quadratic or exponential changes in cognition (across four waves) and did not provide sufficient numbers of e2/2 and e4/4 homozygotes to separate homozygotes from heterozygotes. Finally, *APOE* genotyping took place at Wave 2 of the study, and therefore excluded those who died or withdrew after baseline assessment. This may have led to a genetically more homogeneous sample resulting in more conservative estimates.

To conclude, this study adds to evidence that *APOE* ε4-related cognitive decline in older community-dwelling populations is due to a higher likelihood of, as yet, undetected dementia among ε4 carriers. Moreover, the findings also suggest a protective effect for persons in possession of the ε2 allele. It is important that further longitudinal work is undertaken in community-based populations to confirm these findings. If the more precipitous cognitive decline commonly reported among older ε4 carriers is due to a greater proportion of those persons eventually becoming demented, it suggests that both

neuropsychological testing and *APOE* genotyping could inform early detection programs for dementia in early old age.

References

1. Farrer LA, Cupples LA, Haines JL, et al: Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium. Jama 1997; 278:1349-1356

2. Corder EH, Saunders AM, Risch NJ, et al: Protective effect of apolipoprotein E type 2 allele for late onset Alzheimer disease. Nat Genet 1994; 7:180-184

3. Small BJ, Rosnick CB, Fratiglioni L, et al: Apolipoprotein E and cognitive performance: a meta-analysis. Psychol Aging 2004; 19:592-600

4. Wisdom NM, Callahan JL,Hawkins KA: The effects of apolipoprotein E on non-impaired cognitive functioning: A meta-analysis. Neurobiology of Aging 2011; 32:63-74

5. Ohm TG, Muller H, Braak H, et al: Close-meshed prevalence rates of different stages as a tool to uncover the rate of Alzheimer's disease-related neurofibrillary changes. Neuroscience 1995; 64:209-217

6. Ghebremedhin E, Schultz C, Braak E, et al: High frequency of apolipoprotein E epsilon4 allele in young individuals with very mild Alzheimer's disease-related neurofibrillary changes. Exp Neurol 1998; 153:152-155

7. Amieva H, Le Goff M, Millet X, et al: Prodromal Alzheimer's disease: successive emergence of the clinical symptoms. Ann Neurol 2008; 64:492-498

8. Bondi MW, Salmon DP, Galasko D, et al: Neuropsychological function and apolipoprotein E genotype in the preclinical detection of Alzheimer's disease. Psychol Aging 1999; 14:295-303

9. Bunce D, Fratiglioni L, Small BJ, et al: APOE and cognitive decline in preclinical Alzheimer disease and non-demented aging. Neurology 2004; 63:816-821

10. Caselli RJ, Dueck AC, Osborne D, et al: Longitudinal modeling of age-related memory decline and the APOE epsilon4 effect. N Engl J Med 2009; 361:255-263

11. Caselli RJ, Dueck AC, Locke DE, et al: Longitudinal modeling of frontal cognition in APOE epsilon4 homozygotes, heterozygotes, and noncarriers. Neurology 2011; 76:1383-1388

12. Hofer SM, Christensen H, Mackinnon AJ, et al: Change in cognitive functioning associated with apoE genotype in a community sample of older adults. Psychol Aging 2002; 17:194-208

13. Christensen H, Mackinnon A, Jorm AF, et al: The Canberra longitudinal study: Design, aims, methodology, outcomes and recent empirical investigations. Aging, Neuropsychology, and Cognition 2004; 11:169-195

14. Anstey KJ,Smith GA: Interrelationships among biological markers of aging, health, activity, acculturation, and cognitive performance in late adulthood. Psychol Aging 1999; 14:605-618

15. Taekema DG, Gussekloo J, Maier AB, et al: Handgrip strength as a predictor of functional, psychological and social health. A prospective population-based study among the oldest old. Age Ageing 2010; 39:331-337

16. Buchman AS, Schneider JA, Leurgans S, et al: Physical frailty in older persons is associated with Alzheimer disease pathology. Neurology 2008; 71:499-504

17. Mackinnon A, Christensen H, Cullen JS, et al: The Canberra Interview for the Elderly: assessment of its validity in the diagnosis of dementia and depression. Acta Psychiatr Scand 1993; 87:146-151

18. Folstein MF, Folstein SE,McHugh PR: "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975; 12:189-198

19. Berlau DJ, Corrada MM, Head E, et al: APOE epsilon2 is associated with intact cognition but increased Alzheimer pathology in the oldest old. Neurology 2009; 72:829-834

20. Thompson PM, Hayashi KM, de Zubicaray G, et al: Dynamics of gray matter loss in Alzheimer's disease. J Neurosci 2003; 23:994-1005

21. Bloss CS, Delis DC, Salmon DP, et al: APOE genotype is associated with left-handedness and visuospatial skills in children. Neurobiol Aging 2010; 31:787-795

22. Henderson AS, Jorm AF, MacKinnon A, et al: The prevalence of depressive disorders and the distribution of depressive symptoms in later life: a survey using Draft ICD-10 and DSM-III-R. Psychol Med 1993; 23:719-729

23. Batterham PJ, Mackinnon AJ,Christensen H: The association between change in cognitive ability and cause-specific mortality in a community sample of older adults. Psychol Aging in press;

24. Richards B, Skoletsky J, Shuber AP, et al: Multiplex PCR amplification from the CFTR gene using DNA prepared from buccal brushes/swabs. Hum Mol Genet 1993; 2:159-163

25. Smith A: The Symbol Digit Modalities Test, Los Angeles, Western Psychological Services, 1973

26. Wechsler D: Manual for the Wechsler Adult Intelligence Scale - revised, New York, The Psychological Corporation, 1981

27. Lezak MD: Neuropsychological assessment (3rd ed.), New York, NY, Oxford University Press; US, 1995

28. Jorm AF: Use of informants' reports to study memory changes in dementia, in Memory Functioning in Dementia. Edited by Backman L. Amsterdam, North-Holland, 1992, pp 267-282

29. Wilson B, Cockburn J, Baddeley A, et al: The development and validation of a test battery for detecting and monitoring everyday memory problems. Journal of Clinical and Experimental Neuropsychology 1989; 11:855-870

30. Christensen H, Korten AE, Mackinnon AJ, et al: Are changes in sensory disability, reaction time, and grip strength associated with changes in memory and crystallized Intelligence? A longitudinal analysis in an elderly community sample. Gerontology 2000; 46:276-292

31. Holsinger T, Deveau J, Boustani M, et al: Does this patient have dementia? Jama 2007; 297:2391-2404

32. McDowell I, Kristjansson B, Hill GB, et al: Community screening for dementia: the Mini Mental State Exam (MMSE) and Modified Mini-Mental State Exam (3MS) compared. J Clin Epidemiol 1997; 50:377-383

33. Tombaugh TN, McDowell I, Kristjansson B, et al: Mini-Mental State Examination (MMSE) and the Modified MMSE (3MS): A Psychometric Comparison and Normative Data. Psychological Assessment 1996; 8:48-59

34. McArdle JJ,Epstein D: Latent growth curves within developmental structural equation models. Child Dev 1987; 58:110-133

35. Muthén LK,Muthén BO: Mplus User's Guide. (Sixth Edition), Los Angeles, CA, Muthén & Muthén, 2010

36. Bäckman L,MacDonald SWS: Death and cognition: Synthesis and outlook. European Psychologist 2006; 11:224-235

37. Goldberg D, Bridges K, Duncan-Jones P, et al: Detecting anxiety and depression in general medical settings. BMJ 1988; 297:897-899

38. Christensen H, Jorm AF, Henderson AS, et al: The relationship between health and cognitive functioning in a sample of elderly people in the community. Age Ageing 1994; 23:204-212

39. Helmer C, Damon D, Letenneur L, et al: Marital status and risk of Alzheimer's disease: a French population-based cohort study. Neurology 1999; 53:1953-1958

Table 1: Descriptive statistics at the initial interview for participants included in the analysis, both overall and by genotype

	Total (n = 590)		APOE e2 group (n = 65)		APOE e3 group (n = 388)		APOE e4 group (n = 137)		*Comparison of APOE groups*	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	F	p
Age	76.19	4.70	76.17	4.22	76.38	4.75	75.68	4.75	1.126	0.325
Years of education	11.52	2.64	11.23	2.52	11.57	2.66	11.52	2.64	0.436	0.647
Disease count	2.72	1.65	2.58	1.59	2.81	1.67	2.53	1.60	1.777	0.170
Goldberg depression	1.85	1.83	2.03	2.02	1.89	1.85	1.66	1.67	1.145	0.319
Goldberg anxiety	2.41	2.22	2.44	2.50	2.32	2.17	2.63	2.22	0.996	0.370
Activities of daily living score	1.56	2.03	2.05	2.40	1.49	1.98	1.54	1.96	2.139	0.119
Symbol-Letter Modalities	99.31	15.01	100.42	15.50	99.71	15.13	97.69	14.42	1.102	0.333
Verbal fluency	11.26	3.39	11.46	3.05	11.22	3.45	11.28	3.39	0.142	0.868
Episodic memory	13.65	1.94	14.06	1.56	13.66	2.05	13.39	1.73	2.689	0.069
Word recognition	0.96	0.07	0.97	0.06	0.96	0.07	0.94	0.09	4.477	0.012
Face recognition	0.79	0.09	0.80	0.08	0.79	0.10	0.78	0.10	1.259	0.285
Choice reaction time	471.52	140.38	467.69	121.34	475.11	140.93	463.19	147.73	0.360	0.698
Right grip strength	26.39	10.30	24.88	9.29	26.31	10.18	27.34	11.04	1.277	0.280
Left grip strength	24.15	9.80	23.65	9.45	24.03	9.75	24.76	10.13	0.378	0.685
Mini-Mental State Exam	27.85	1.98	27.96	1.65	27.96	1.96	27.52	2.15	2.612	0.074

	Total (n = 590)		APOE e2 group (n = 65)		APOE e3 group (n = 388)		APOE e4 group (n = 137)		*Comparison of APOE groups*	
	Count	*%*	*Count*	*%*	*Count*	*%*	*Count*	*%*	χ^2	*p*
Female gender	301	51.0%	36	55.4%	197	50.8%	68	49.6%	0.610	0.737
Current smoker	254	43.1%	24	36.9%	172	44.3%	58	42.3%	4.675	0.322
Marital status										
Married	337	57.1%	39	60.0%	217	55.9%	81	59.1%	2.585	0.859
Widowed	208	35.3%	22	33.8%	143	36.9%	43	31.4%		
Divorced/separated	21	3.6%	2	3.1%	12	3.1%	7	5.1%		
Single	24	4.1%	2	3.1%	16	4.1%	6	4.4%		

Table 2: Latent growth curve models of cognitive performance, reaction time and grip strength, adjusted for gender, initial age and education (n ≤ 590)

		APOE 2 vs. 3		*APOE* 4 vs. 3		*APOE* 4 vs. 2	
		Estimate	p	Estimate	p	Estimate	p
SLMT	intercept	0.567	0.590	-1.146	0.137	-1.713	0.146
	slope	-0.047	0.920	-1.110	**0.002**	-1.063	**0.048**
Verbal fluency	intercept	-0.436	0.726	0.214	0.814	0.650	0.641
	slope	0.889	0.161	-0.449	0.357	-1.338	0.066
Episodic memory	**intercept**	1.457	0.142	-1.265	0.085	-2.721	**0.015**
	slope	0.250	0.701	-0.239	0.635	-0.489	0.512
Word recognition	**intercept**	1.492	0.144	-1.626	**0.031**	-3.118	**0.007**
	slope	-0.205	0.805	-1.768	**0.006**	-1.564	0.098
Face recognition	**intercept**	1.220	0.248	-1.377	0.074	-2.597	**0.028**
	slope	-1.040	0.104	-0.924	0.060	0.117	0.873
Choice RT	intercept	-1.231	0.146	0.017	0.978	1.249	0.189
	slope	0.133	0.844	-0.314	0.543	-0.447	0.562
Right grip	intercept	-0.573	0.508	0.415	0.518	0.989	0.310
	slope	0.765	**0.031**	0.138	0.622	-0.627	0.125
Left grip	intercept	0.247	0.753	0.029	0.961	-0.218	0.805
	slope	0.184	0.576	0.055	0.831	-0.129	0.734

Notes: ***Bold*** *values indicate p < 0.05; APOE 2: apolipoprotein E genotypes 22/23; APOE 3: apolipoprotein E genotype 33; APOE 4: apolipoprotein E genotypes 34/44; SLMT: Symbol-Letter Modalities Test; Choice RT: choice reaction time*

Table 3: Latent growth curve models excluding participants with MMSE ≤ 24 at any time point, adjusted for gender, initial age and education (n ≤ 465)

		APOE 2 vs. 3		*APOE* 4 vs. 3		*APOE* 4 vs. 2	
		Estimate	p	Estimate	p	Estimate	p
SLMT	intercept	0.911	0.403	0.179	0.836	-0.732	0.561
	slope	-0.576	0.190	-0.595	0.095	-0.018	0.972
Verbal fluency	intercept	0.049	0.971	-0.054	0.959	-0.103	0.947
	slope	0.442	0.503	-0.242	0.653	-0.684	0.381
Episodic memory	intercept	1.426	0.095	-0.367	0.589	-1.793	0.070
	slope	-0.110	0.845	-0.017	0.971	0.093	0.888
Word recognition	intercept	0.956	0.194	-0.700	0.232	-1.656	0.052
	slope	0.186	0.765	0.276	0.595	0.090	0.902
Face recognition	intercept	0.432	0.681	-0.397	0.630	-0.829	0.494
	slope	-0.555	0.355	-0.455	0.349	0.100	0.887
Choice RT	intercept	-1.334	0.099	0.034	0.958	1.368	0.144
	slope	0.102	0.866	-0.237	0.629	-0.339	0.632
Right grip	intercept	-0.032	0.972	0.541	0.457	0.573	0.586
	slope	0.603	0.100	0.247	0.427	-0.356	0.415
Left grip	intercept	0.497	0.551	-0.077	0.909	-0.574	0.554
	slope	0.122	0.725	0.247	0.397	0.125	0.760

Notes: ***Bold*** *values indicate p < 0.05; APOE 2: apolipoprotein E genotypes 22/23; APOE 3: apolipoprotein E genotype 33; APOE 4: apolipoprotein E genotypes 34/44; SLMT: Symbol-Letter Modalities Test; Choice RT: choice reaction time*

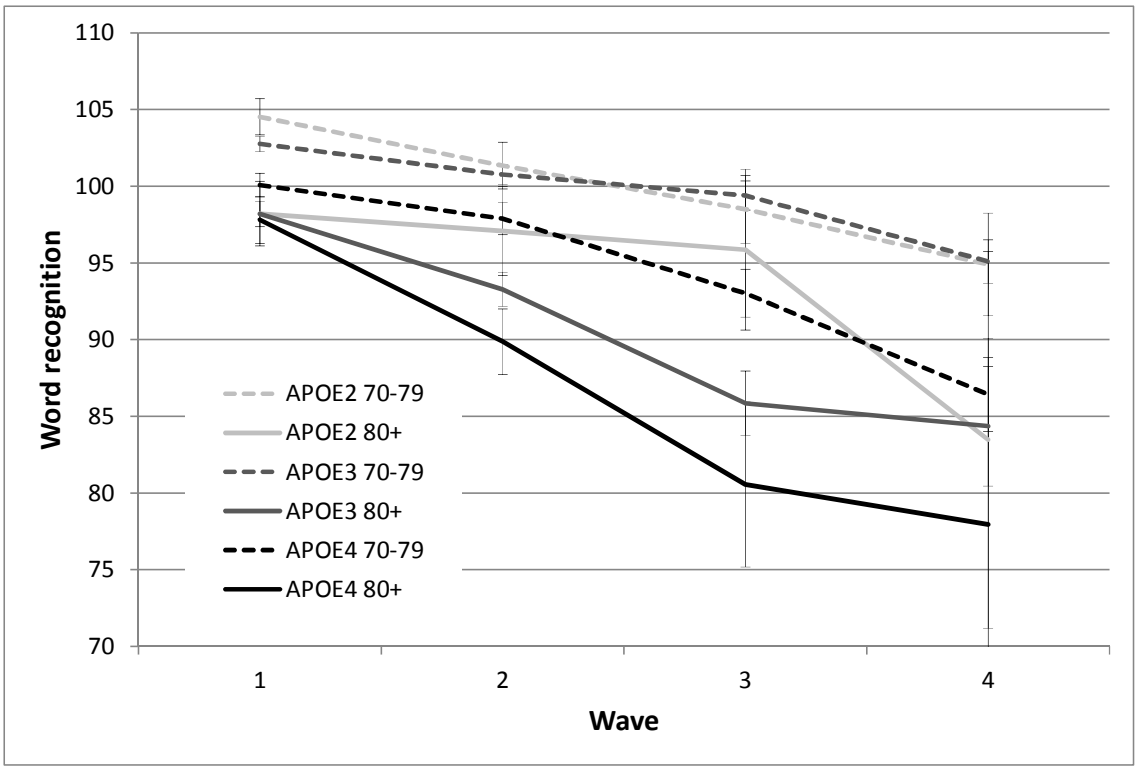

Figure 1: Effect of *APOE* genotype and age group on word recognition performance across the four time points

Notes: Values are estimates from mixed model repeated measures ANOVA; error bars represent standard errors; APOE: apolipoprotein E; Scores were standardized at baseline to M =*100 and* SD = *10*

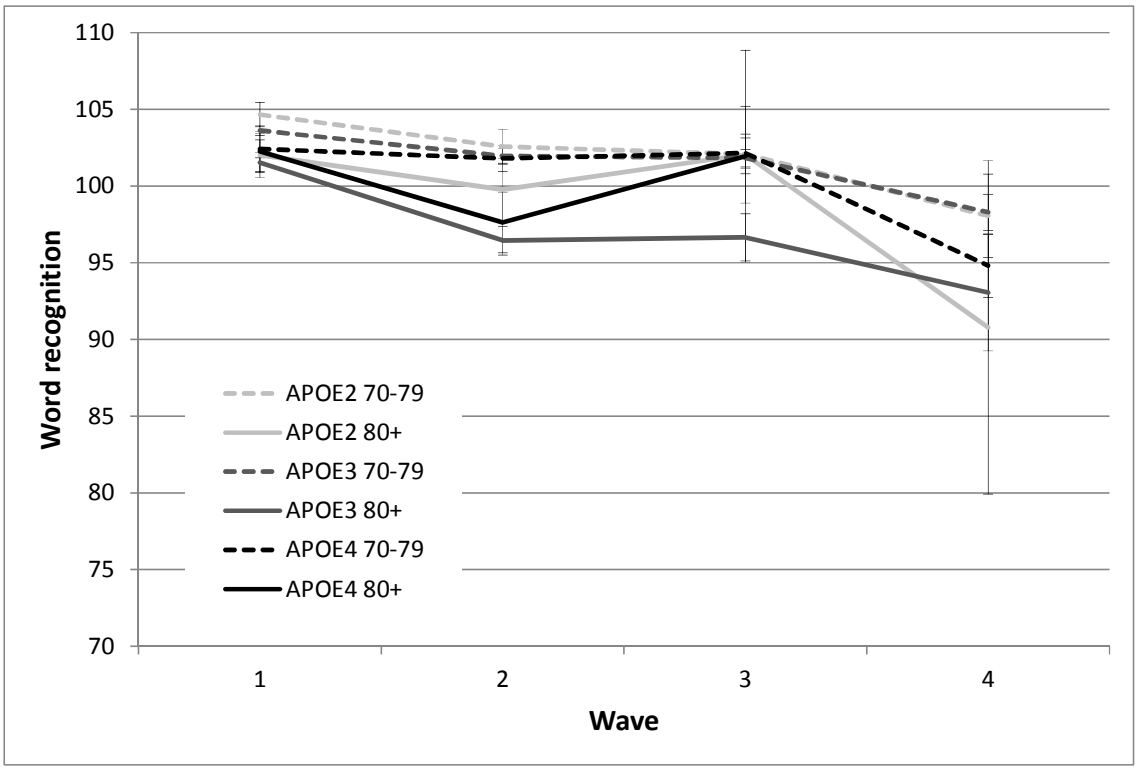

Figure 2: Effect of *APOE* genotype and age group on word recognition performance across the four time points, excluding participants with MMSE ≤ 24 at any time point

Notes: Values are estimates from mixed model repeated measures ANOVA; error bars represent standard errors; APOE = apolipoprotein E; Scores were standardized at baseline to M =*100 and* SD = *10*