

# Apolipoprotein E $\epsilon$ 4 is superior to apolipoprotein E $\epsilon$ 2 in predicting cognitive scores over 30 months

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**Background:** The purpose of this study was to compare apolipoprotein E  $\epsilon$ 4 (Apo E  $\epsilon$ 4) and apolipoprotein E  $\epsilon$ 2 (Apo E  $\epsilon$ 2) as predictors of cognitive and functional trajectories over 30 months.

**Methods:** This prospective cohort study included 287 community-dwelling memory clinic patients with dementia, mild cognitive impairment, or no cognitive impairment. The Addenbrooke Cognitive Examination, Mini-Mental State Examination, Montreal Cognitive Assessment, Delirium Index, and Nottingham Instrumental Activities of Daily Living tests were administered to each subject.

**Results:** One hundred and nine subjects (40%) carried Apo E  $\epsilon$ 4 and 48 (16.7%) carried Apo E  $\epsilon$ 2. One hundred and nine  $\epsilon$ 4-positive subjects differed significantly from 178  $\epsilon$ 4-negative subjects in 19/52 comparisons (36.5%), whereas 46 Apo E  $\epsilon$ 2-positive subjects had 0/52 significant differences from 239  $\epsilon$ 2-negative subjects ( $P < 0.0001$ ). The variables most affected by  $\epsilon$ 4 were the Delirium Index and Mini-Mental State Examination. Instrumental Activities of Daily Living score and residence were unrelated to Apo E  $\epsilon$ 4 or  $\epsilon$ 2.

**Conclusion:** Apo E  $\epsilon$ 4 positivity predicted four cognitive scores measured every 6 months over 30 months. Apo E  $\epsilon$ 2 scores predicted none of 52 comparisons.

**Keywords:** apolipoprotein E genotype, dementia, mild cognitive impairment

## Introduction

The apolipoprotein E (Apo E) genotype has been studied primarily with respect to the initial diagnosis of Alzheimer's disease. We reviewed 15 Apo E papers<sup>1-15</sup> representing 21,651 subjects. Apo E  $\epsilon$ 4 was present in 4,689 of 20,356 subjects (23.0%) in 12/15 studies in which Apo E  $\epsilon$ 4 was reported. Apo E  $\epsilon$ 2 was present in 1,680 subjects of 21,651 (7.7%) in 11/15 studies in which Apo E  $\epsilon$ 2 was reported.

Albert et al<sup>1</sup> studied 216 community-dwelling elderly subjects free of dementia using the Schwab and England Activities of Daily Living (SEADL) scale (0, bedridden; 100 completely independent), Blessed Dementia Rating Scale, and Barthel Activities of Daily Living Index.<sup>16,17,18</sup> The SEADL score was 80.9 in the  $\epsilon$ 4 group versus 87.3 in non- $\epsilon$ 4 group ( $P < 0.05$ ). Apo E  $\epsilon$ 2/ $\epsilon$ 2 or  $\epsilon$ 2/ $\epsilon$ 3 had an odds ratio of 2.6 for independence on the Barthel Activities of Daily Living Index and SEADL.

Blacker et al<sup>14</sup> followed 342 subjects aged  $\geq 57$  years for 5 years; of these, 107 had no cognitive impairment and 235 had mild cognitive impairment. They measured 22 neuropsychologic scores from six tests. Allele numbers for no cognitive impairment/mild cognitive impairment/all 342 subjects were  $\epsilon$ 2 9/19/28,  $\epsilon$ 3 84/178/262, and  $\epsilon$ 4 14/38/52, respectively. Allele frequencies were 79% for  $\epsilon$ 3, 13% for  $\epsilon$ 4, and 8% for

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ε2. Comparing 107 no cognitive impairment versus 235 mild cognitive impairment at baseline. 87/235 mild cognitive impairment reverted to no cognitive impairment. Apo E ε2 had a hazard ratio (HR) of 0.13 for conversion from no cognitive impairment to mild cognitive impairment. Multivariate model of time to progression from no cognitive impairment to mild cognitive impairment included California Verbal Learning Test total score (HR 0.58,  $P = 0.003$ ) and ε2 (HR 0.14,  $P = 0.006$ ). ε4 predicted time to dementia but not time to mild cognitive impairment.

Bonner-Jackson et al<sup>5</sup> followed 795 subjects, comparing 225 healthy controls, 381 patients with amnesic mild cognitive impairment, and 189 with Alzheimer's disease (mean age 75.9 years versus 74.8 years versus 75.3 years, respectively,  $P = 0.13$ ; Apo E ε2 [non ε4] 14.7% versus 3.9% versus 2.6%,  $P < 0.001$ ). Comparing Apo E ε2 versus non-ε2, the baseline Functional Activities Questionnaire score (0 best, 30 worst) was 2.83 versus 5.13; the 12-month Functional Activities Questionnaire score was 3.53 versus 6.90 ( $P < 0.001$ ); the 24-month Functional Activities Questionnaire score was 3.29 versus 8.66 ( $P < 0.001$ ); the digit span score was  $8.2 \pm 2.3$  versus  $8.2 \pm 2.0$  ( $P = 0.96$ ); the Trail Making Test Version A score seconds (sec) was 44.1 versus 48.2 ( $P = 0.29$ ); the Mini-Mental State Examination (MMSE) score was 27.7 versus 26.7 ( $P = 0.006$ ); the composite delayed memory from logical memory and Rey Auditory Verbal Learning Test score was 1.56 versus  $-0.11$  ( $P < 0.001$ ); the composite executive function score was 1.21 versus 0.003 ( $P = 0.02$ ); the Trail Making Test part B sec score was 120.1 versus 135.8 ( $P = 0.02$ ); the category fluency for animals score was 17.3 versus 16.1 (no  $P$ -value listed); the category fluency for vegetables score was 12.8 versus 11.0 (no  $P$ -value listed); and the clock drawing score was 4.4 versus 4.1 (no  $P$ -value listed).

## Materials and methods

Wyong Hospital is 100 km north of Sydney, Australia, and has 370 beds. The Wyong memory clinic is staffed by a geriatrician (PR) and a clinical nurse consultant (EH), both of whom assess each patient and arrive at a consensus diagnosis of dementia, mild cognitive impairment, or no cognitive impairment. The diagnosis of dementia and mild cognitive impairment uses the Nottingham Instrumental Activities of Daily Living (IADL, with 0 indicating worst and 22 indicating best) to measure functional decline. The IADL instrument includes driving, cooking, house cleaning, laundry, reading, and 17 other items, but does not include self-medication or finances.<sup>19</sup> Other clinical

measurements include the MMSE (0 indicating worst and 30 indicating best),<sup>20</sup> Montreal Cognitive Assessment (MoCA, with 0 indicating worst and 30 indicating best),<sup>21</sup> Addenbrooke Cognitive Examination (ACE-R, 0 indicating worst and 100 indicating best),<sup>22</sup> and Delirium Index (DI, 0 indicating best and 21 indicating worst).<sup>23</sup> The principal reason for measuring DI is to have a baseline in the event of subsequent delirium. The diagnosis of dementia was made by the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV) in a consensus meeting between the geriatrician (PR) and clinical nurse consultant (EH). Patients who did not meet the criteria for dementia but had cognitive impairment and only a minor change in IADL were classified as having mild cognitive impairment. Patients were assessed every 6 months. When patients arrived in clinic unwell or with limited tolerance for cognitive testing, the MMSE and DI were measured first. If that was tolerated, the MoCA was administered next, followed by the ACE-R. Caregivers or informants completed the IADL questionnaire.

Weight was measured using an Omron digital floor scale (OMRON Healthcare Europe B.V., Hoofddorp, the Netherlands) accurate to 400 g. Height was measured using a stadiometer and body mass index was calculated from measurements taken at the first clinic visit. Approximately 70% of the patients had computed tomographic brain scans, 5% had magnetic resonance imaging, and 0% had fluorodeoxyglucose or Pittsburgh Compound B positron emission tomography. Comorbidity was measured using the Cumulative Illness Rating Scale (0, no comorbidity; 52, maximal comorbidity).<sup>24</sup>

Inclusion criteria for this study were: age  $\geq 65$  years; community-dwelling; memory clinic follow-up for at least 6 months; and vision adequate to perform the cognitive scales using enlarged drawings of, eg, the dual pentagons for the MMSE, clock, cube in the MoCA, and naming objects in the ACE-R. Apo E genotyping was performed during evaluation in the memory clinic. Baseline values were denoted by the suffix "1". Values at 6, 12, 18, 24, and 30 months carry the suffixes of 6, 12, 18, 24, and 30, respectively.

## Statistical analysis

We used the abbreviation DFM to denote the difference in means between two groups. This is a more concise figure than 95% confidence intervals. It was defined as the absolute difference in means divided by the mean of group one. Comparison of subgroups was done using a Microsoft Access 2003 database (Microsoft Corporation, Redmond, WA, USA). This was exported to Microsoft Excel 2003

(Microsoft Corporation) to calculate body mass index and duration of follow-up. The spreadsheet was then exported to Stats Direct version 2.7.8b ([statsdirect.com/update.aspx](http://statsdirect.com/update.aspx)) to calculate the mean ± standard deviation, chi-square and Fisher's exact tests for proportions, and the Mann–Whitney *U*-test for nonparametric comparison of groups of different sizes (eg, 109 ε4-positive with 178 ε4-negative). Bonferroni correction was made for the five scores at each point in time. This was an audit of practice, with no new or different methods of measurements used. The North Sydney Central Coast Research Ethics Committee did not require informed consent to be sought from subjects.

## Results

The 287 patients were recruited from the Wyong Memory Clinic between January 2009 and February 2012. Their mean age was 79.8 ± 6.5 years, with 51.5% being female. Fifty-four percent (156/287) had dementia and 37% (106/287) had mild cognitive impairment (by consensus conference). Mean years of education was 9.9. Mean follow-up was 21 months. Cumulative deaths were zero at 3 months, three at 12 months, five at 18 months, seven at 24 months, and seven at 30 months.

### Apo E ε4-negative subjects versus ε4-positive subjects at baseline

One hundred and nine of 287 subjects (40%) were Apo E ε4-positive; 14 were ε4/ε4 and 95 carried one ε4 allele. Comparing the 178 ε4-negative subjects with the 109 ε4-positive subjects in Table 1, the Apo E ε4-positive group was significantly older and had a lower prevalence of diabetes and lower comorbidity score (Table 1). The DI was significantly worse in the Apo E ε4-positive group at all time intervals. Prior to Bonferroni correction, the MMSE was lower in the Apo E ε4-positive group at months 6, 12, 24, and 30 (Table 1), MoCA was significantly lower in the ε4-positive group at months 6, 12, and 18 (Table 1), and ACE-R was lower at months 12 and 24. After Bonferroni correction, the differences were significant only for age, diabetes, and MMSE at 6 and 12 months, and for DI at 12 and 18 months.

### Residence of Apo E ε4-negative survivors versus ε4-positive survivors

The percentages of Apo E ε4-negative survivors and ε4-positive survivors living in the community at 6 months were 96.6% versus 99.1%, respectively ( $P = 0.217$ ); 94.3%

**Table 1** Comparison of 178 Apo E ε4 negative subjects with 109 Apo E ε4 positive subjects

Parameter	Apo E Neg	Apo E Pos	P/BonP/DFM
<b>Mean age</b>	80.6 ± 6.7	78.5 ± 5.9	0.0116/NA/2.6%
Female (%)	48.3	56.9	0.16
Living alone (%)	30.3	30.2	0.99
Married (%)	53.9	56.9	0.83
Education, years	9.8 ± 2.0	10.0 ± 1.8	0.33/NA/2.0%
Dementia at baseline (%)	51.7	58.7	0.249
Diabetes at baseline (%)	25.8	10.1	0.001/0.01 n = 10
Atrial fibrillation at baseline (%)	11.8	9.2	0.31
Weight, kg	70.1 ± 16.3	67.8 ± 14.4	0.175/3.3%
BMI	26.8 ± 5.3	25.8 ± 4.5	0.195/3.7%
<b>CIRS</b>	7.77 ± 2.13	6.57 ± 2.41	0.007/0.07/15.4%
<b>IADL-1 (0–22)</b>	14.2 ± 5.0	14.4 ± 5.7	0.543/NA/1.4%
<b>MMSE-1 (0–30)</b>	23.3 ± 4.6	22.3 ± 6.0	0.061/0.61/4.3%
<b>MoCA-1 (0–30)</b>	18.0 ± 5.8	16.5 ± 6.1	0.071/0.671/8.3%
<b>ACE-R (0–100)</b>	66.8 ± 16.5	63.9 ± 18.1	0.320/NA/4.3%
<b>DI-1 (0, best; 21, worst)</b>	3.15 ± 2.00	3.90 ± 1.81	0.041/0.41/23.8%
<b>Six months IADL-6</b>	13.8 ± 5.5	13.7 ± 5.9	0.920/NA/0.7%
<b>MMSE-6</b>	23.4 ± 4.9	21.7 ± 5.3	0.01/0.05/7.3%
<b>MoCA-6</b>	17.8 ± 6.0	16.1 ± 6.2	0.048/0.24/9.6%
<b>ACE-6</b>	69.1 ± 13.7	65.4 ± 14.5	0.0636/0.32/5.3%
<b>DI-6</b>	3.34 ± 2.07	4.27 ± 1.88	0.013/0.065/27.8%
<b>12 months IADL-12</b>	13.3 ± 5.9	13.0 ± 5.7	0.527/NA/2.2%
<b>MMSE-12</b>	22.9 ± 5.2	21.9 ± 5.6	0.0081/0.040/4.4%
<b>MoCA-12</b>	17.9 ± 6.7	16.0 ± 6.2	0.032/0.16/10.6%
<b>ACE-12</b>	69.6 ± 15.4	64.6 ± 15.7	0.032/0.16/7.2%
<b>DI-12</b>	3.32 ± 2.25	4.36 ± 1.94	0.0053/0.026/31.3%
<b>18 months IADL-18</b>	12.0 ± 6.5	11.4 ± 5.5	0.523/NA/5.0%
<b>MMSE-18</b>	22.1 ± 5.4	20.2 ± 6.4	0.064/0.32/8.6%
<b>MoCA-18</b>	17.5 ± 6.4	14.8 ± 6.5	0.017/0.085/15.4%
<b>ACE-18</b>	66.5 ± 15.4	61.6 ± 18.0	0.10/0.50/7.4%
<b>DI-18</b>	3.83 ± 2.30	4.82 ± 2.12	0.007/0.035/25.8%
<b>24 months IADL-24</b>	11.6 ± 6.5	10.2 ± 6.1	0.245/NA/12.1%
<b>MMSE-24</b>	22.6 ± 6.7	20.6 ± 6.2	0.040/0.20/8.8%
<b>MoCA-24</b>	17.7 ± 7.1	15.6 ± 7.5	0.117/0.58/11.9%
<b>ACE-24</b>	68.9 ± 17.8	60.7 ± 18.5	0.023/0.11/11.9%
<b>DI-24</b>	3.36 ± 2.35	4.46 ± 2.40	0.018/0.09/32.7%
<b>30 months IADL-30</b>	11.3 ± 6.5	10.2 ± 5.8	0.443/NA/9.3%
<b>MMSE-30</b>	22.8 ± 5.8	19.2 ± 6.5	0.032/0.16/15.8%
<b>MoCA-30</b>	17.4 ± 6.5	15.2 ± 7.6	0.244/NA/12.6%
<b>ACE-30</b>	69.6 ± 11.9	60.2 ± 21.2	0.15/NA/13.5%
<b>DI-30</b>	3.63 ± 2.20	4.79 ± 2.24	0.034/0.17/34.5%

**Notes:** The suffix "1" denotes baseline, "6" denotes 6 months, "12" denotes 12 months, "18" denotes 18 months. Significant differences are depicted in bold. DFM calculated as mean for Apo E-negative minus mean Apo E-positive/mean Apo E-negative. Bonferroni correction was made for the five scores at each point in time and is designated as Bon No Bon P. P-values for weight, kg and BMI.

**Abbreviations:** Apo E Neg, apolipoprotein E-negative; Apo E Pos, apolipoprotein E-positive; NA, not applicable; DFM, difference between means; ACE, Addenbrooke Cognitive Examination; BMI, body mass index; CIRS, Cumulative Illness Rating Scale; DFM, percentage difference between the means of the two groups; DI, delirium index; IADL, Nottingham instrumental activities of daily living; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; P, P-value; Bon, bonferroni.

versus 96.8% ( $P = 0.39$ ) at 12 months; 91.4% versus 94.0% ( $P = 0.54$ ) at 18 months; 89.4% versus 84.0% ( $P = 0.37$ ) at 24 months; and 90.7% versus 85.7% ( $P = 0.51$ ) at 30 months.

## Important differences between Apo E $\epsilon$ 4-negative and $\epsilon$ 4-positive subjects

DI was significantly worse in  $\epsilon$ 4-positive subjects at all six time points, with a mean DFM of 29.6%; MoCA was significantly worse in  $\epsilon$ 4-positive subjects at three of six time points, with a mean DFM of 11.4%; MMSE was significantly worse in  $\epsilon$ 4-positive subjects at four of six time points, but the mean DFM of 8.2% was less than that for MoCA measurements at the six time points; ACE-R was significantly worse in  $\epsilon$ 4-positive subjects at two of six time points and the DFM of 8.3% was similar to that for MMSE; age was 2.6% older in  $\epsilon$ 4-negative subjects; diabetes was 15.7% more common in  $\epsilon$ 4-negative subjects; and the Cumulative Illness Rating Scale score was 15.4% higher in  $\epsilon$ 4-negative subjects.

## Comparison of Apo E $\epsilon$ 2-negative and $\epsilon$ 2-positive subjects

The 239 Apo E  $\epsilon$ 2-negative subjects did not differ at a  $P < 0.05$  level in any of the 52 comparisons with the 48  $\epsilon$ 2-positive subjects. In contrast, the Apo E  $\epsilon$ 4-negative versus Apo E  $\epsilon$ 4-positive comparison was significant in 19/52 subjects (36.5%).

## Discussion

We did not anticipate three major findings in this study of 287 community-dwelling elderly subjects. First, we were surprised that Apo E  $\epsilon$ 2 was of no value in predicting MMSE, MoCA, ACE-R, DI, or IADL scores at 6-monthly intervals through to 30 months ( $P < 0.05$  in 0/52 comparisons) in view of the published research.<sup>5</sup> In contrast, Apo E  $\epsilon$ 4 was a significant predictor in 19/52 comparisons. The probability that this is due to chance is  $<0.0001$  by both chi-square and Fisher's exact tests.

The second unexpected finding was of the DI being more sensitive to differences between Apo E  $\epsilon$ 4-positive and Apo E  $\epsilon$ 4-negative subjects ( $P < 0.05$  at all six time points) than MMSE (4/6), MoCA (3/6), or ACE-R (2/6). DI has seven items and can be administered in less than 4 minutes in subjects without cognitive impairment (2 minutes in severe dementia). DI shares several items with the other cognitive tests used in this study. DI item 1 (attention/spell "world" backwards) is part of the MMSE and ACE-R, and the MoCA uses digit span for testing attention. Item 4 (orientation to date, month, year, date of birth, name of hospital) is included in the MMSE, MoCA, and ACE-R. DI item 4 (three-word recall over several minutes) is part of

the MMSE and ACE-R, and MoCA uses five-word recall over a longer interval.

The final unexpected finding was that Apo E  $\epsilon$ 4-positive subjects had a significantly lower comorbidity score than Apo E  $\epsilon$ 4-negative subjects. The Cumulative Illness Rating Scale<sup>24</sup> assesses comorbidity in 13 domains, and is therefore superior to the Charlson comorbidity index, which excludes psychiatric illness. The 15 Apo E papers reviewed did not analyze comorbidity scores in relation to Apo E  $\epsilon$ 4 or  $\epsilon$ 2, so our finding needs verification. Comorbidity can be calculated post hoc from a review of medical diagnoses in clinical letters and discharge summaries.

Bonner-Jackson et al<sup>5</sup> followed 795 subjects using the Functional Activities Questionnaire as an IADL scale, comprising 225 subjects without cognitive impairment, 381 with amnesic mild cognitive impairment, and 189 with Alzheimer's dementia. Comparing 53/795 subjects with Apo E  $\epsilon$ 2 (6.7%) with 742 who were non- $\epsilon$ 2, the Functional Activities Questionnaire score at baseline was  $2.83 \pm 6.4$  versus  $5.13 \pm 6.6$ , respectively,  $3.53 \pm 6.7$  versus  $6.9 \pm 8.2$  ( $P < 0.001$ ) at 12 months, and  $3.29 \pm 6.8$  versus  $8.66 \pm 9.5$  ( $P < 0.001$ ) at 24 months. They did not report on Apo E  $\epsilon$ 4, so we cannot determine if  $\epsilon$ 4 was a more powerful predictor than  $\epsilon$ 2.

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## Author contributions

PR was involved in every aspect of this research. BN was involved in data analysis and manuscript revisions. EH measured MMSE, ACE, and aided on consensus definition of dementia. All authors were involved in the critical revision of the manuscript and gave final approval of the proof to be published.

## Disclosure

The authors report no potential conflicts of interest in this work.

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