The apolipoprotein E ε2 allele and decline in episodic memory

R S Wilson, J L Bienias, E Berry-Kravis, D A Evans, D A Bennett

Objectives: The apolipoprotein E (apoE) ε4 allele is related to decline in multiple cognitive domains, especially episodic memory, but the effect of the ε2 allele on change in different forms of cognitive function has been difficult to establish.

Methods: Participants are from the Religious Orders Study. At baseline, they were at least 65 years old and free of clinical evidence of dementia. For up to eight years, they underwent annual clinical evaluations that included detailed cognitive function assessment from which previously established summary measures of episodic memory, semantic memory, working memory, perceptual speed, and visuospatial ability were derived. Growth curve models were used to assess change in each measure and its relation to apoE genotype, controlling for age, sex, education, and baseline level of cognition. Follow up data were available in 669 persons (98% of those eligible). We treated those with the ε3/3 genotype as the reference group (n=425), which was contrasted with ε2/ε2 (n=22), ε2/ε3 (n=16), and ε4 (n=4/ε4; n=158) subgroups.

Results: Rate of episodic memory change in the three subgroups significantly differed, with an average annual increase of 0.016 units in the ε2 subgroup and annual decreases of 0.022 units in those with ε3/3 and of 0.073 units in the ε4 subgroup. The ε2 subgroup did not differ from those with ε3/3 in rate of decline in other cognitive systems. The ε4 subgroup declined more rapidly than those with ε3/3 in semantic memory and perceptual speed but not in working memory or visuospatial ability.

Conclusion: Possession of one or more apoE ε2 alleles is associated with reduced decline in episodic memory in older persons.

Alzheimer’s disease (AD) is the most common cause of dementia in older persons. Although a small proportion of disease can be explained by rare mutations on one of three chromosomes, most AD is thought to result from a complex interaction between environmental and genetic risk factors. One well established risk factor for AD is apolipoprotein E (apoE) status. The apoE gene has three important alleles (ε2, ε3, ε4), which yield six genotypes (ε2/ε2, ε2/ε3, ε2/ε4, ε3/ε3, ε3/ε4, ε4/ε4). Possession of one or more copies of the ε4 allele is associated with increased risk of AD. The ε4 allele is also associated with more rapid cognitive decline in older persons, especially in episodic memory. Because impaired episodic memory is an early and defining feature of AD, these findings suggest that ε4 affects risk of AD mainly by augmenting the usual biological process that leads to disease.

Knowledge about the comparatively rarer ε2 allele has been slower to accumulate. Possession of the ε2 allele has been associated with a reduced risk of AD in some studies, but it has been hard to establish whether ε2 protects against cognitive decline and if so, whether this effect, like that of ε4, is especially pronounced in episodic memory. Few longitudinal cognitive function studies have focused on the ε2 allele, and few of these have assessed multiple domains of cognition, and results have been varied.

We used data from the Religious Orders Study, a longitudinal clinical-pathological study of aging and AD, to examine the association of the apoE ε2 allele with change in different cognitive systems. For up to eight years, older Catholic clergy members underwent annual clinical evaluations, including detailed cognitive function testing from which previously established composite measures of episodic memory and other cognitive functions were derived. To assess ε2 effects, we contrasted an ε2 subgroup (consisting of ε2/2 and ε2/3) with an ε3/3 reference group. We assessed ε4 effects in a similar manner, by contrasting an ε4 subgroup (ε3/4, ε4/4) with ε3/3 to provide another point of comparison for ε2, and because most previous research on ε4, including an earlier study of this cohort, has grouped ε2/2, ε2/3, ε3/3 into a single “no ε4” comparison group, with the result that few published estimates of ε4 effects on cognitive decline are independent of ε2 effects.

METHODS

Subjects

Participants are from the Religious Orders Study, a clinical-pathological investigation of aging and AD in older Catholic clergy members. They were recruited from about 40 groups across the USA (see acknowledgements) and agreed to annual clinical evaluations and brain donation at death. The study was approved by the Institutional Review Board of Rush-Presbyterian-St Luke’s Medical Center.

Clinical evaluations began in January of 1994 and new participants continue to be enrolled. Of 908 persons who had completed the baseline evaluation at the time of these analyses, apoE genotype was unavailable in 111, and 72 met dementia criteria (see below). Because we wanted to assess the independent effects associated with the ε2 and ε4 alleles, we also excluded those with the ε2/4 genotype (n=16). This left 709 persons eligible at baseline, 25 of whom died before their first follow up evaluation, leaving 684 persons who were eligible for follow up. Of these, 669 persons (98%) completed at least one follow up evaluation (mean of 6.0 evaluations per person, range: 2 to 9). Analyses are based on this group.

Clinical evaluation

At baseline, each participant underwent a uniform clinical evaluation that included a medical history, neurological

Abbreviations: AD, Alzheimer’s disease; apoE, apolipoprotein E
examination, cognitive function assessment, and review of brain scan if available, as previously described.\textsuperscript{16,17} The evaluation was repeated annually thereafter with examiners blinded to previously collected data. Based on this evaluation, a board certified or board eligible neurologist or geriatrician classified participants with respect to AD and other common conditions of old age. The diagnosis of AD followed the criteria of the joint working group of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association (NINCDS/ADRDA criteria\textsuperscript{18}). These criteria require a history of cognitive decline and impairment in at least two cognitive domains, one of which must be memory to meet AD criteria.

### Cognitive function assessment

As part of each evaluation, 19 cognitive tests were administered. Seven tests assessed episodic memory: Word List Memory, Recall, and Recognition\textsuperscript{19} and immediate and delayed recall of Story A from Logical Memory\textsuperscript{20} and of the East Boston Story.\textsuperscript{21} Semantic memory was assessed with Verbal Fluency,\textsuperscript{19} a 20 item subset of the Boston Naming test,\textsuperscript{22} a 20 item version of the National Adult Reading Test,\textsuperscript{23} and a 15 item version of Extended Range Vocabulary.\textsuperscript{24} Four working memory tests were administered: Digits Forward and Digits Backward,\textsuperscript{24} Digit Ordering,\textsuperscript{22} and Alpha Span.\textsuperscript{25} Perceptual speed was assessed with the Symbol Digit Modalities Test\textsuperscript{27} and Number Comparison,\textsuperscript{28} and visuospatial ability was assessed with subsets of items from Judgment of Line Orientation\textsuperscript{29} and Standard Progressive Matrices.\textsuperscript{30}

We used composite measures in analyses rather than individual tests to reduce measurement error, especially floor and ceiling artefacts. As previously described,\textsuperscript{31} we hypothesised that the tests could be grouped into domains of episodic memory, semantic memory, working memory, perceptual speed, and visuospatial ability, as outlined above. We tested this hypothesis in two steps. Firstly, we performed a principal components factor analysis of the 19 tests at baseline and grouped tests with loadings of 0.50 or higher on the same factor. Secondly, we used Rand’s statistic to assess the agreement between the conceptually based and empirically based groupings. The overall agreement was 0.79 (p<0.01), supporting the hypothesised grouping. We formed composite measures of episodic memory, semantic memory, working memory, perceptual speed, and visuospatial ability by converting raw scores on each component test to a z score, using the baseline mean and standard deviation, and computing the average. At least half of the component tests had to have valid scores to compute the composite. Over 95% of the component tests had valid scores for each composite measure computed in this study. Further psychometric information about the individual cognitive function tests and the composite measures is published elsewhere.\textsuperscript{31–33}

### Apolipoprotein E genotyping

Blood was collected at each site with acid citrate dextrose anticoagulant and stored at room temperature until undergoing lymphocyte separation within 24 hours of collection. DNA was extracted from about two to three million cells. Genotyping was performed by an investigator blinded to all clinical and postmortem data following the method of Hixon and Vernier.\textsuperscript{34}

### Data analysis

Participants were divided into three apoE subgroups for all analyses: e2, consisting of the e2/2 and e2/3 genotypes; e3, consisting of e3/3; and e4, consisting of e3/4 and e4/4. Because we wanted to assess the independent contributions of e2 and e4 to cognition, those with the e2/4 genotype were excluded from all analyses except the computation of allele frequencies at baseline.

We used a proportional hazards model to assess the relative risk of developing AD in the e2 and e4 subgroups compared with the e3 reference group, controlling for the potentially confounding effects of age, sex, and education.\textsuperscript{35}

We used random effects regression models to characterise individual paths of change in each cognitive measure and to test the association of apoE genotype with initial level of function and rate of change.\textsuperscript{18} In this approach, variation is partitioned into that coming from persons following different paths and that coming from the observed measurements deviating from these paths. Each person’s path was assumed to follow the path of the group except for random effects that caused a given person’s baseline level of function (random intercept) to be at a higher or lower level and the rate of change (random slope) to be faster or slower. These two components of between person variability were used to estimate individual growth curves which were plotted.

Those with the e3/3 genotype served as the reference group in all analyses. Each model included terms for time since baseline (in years), apoE subgroups e2 and e4 (each contrasted with the e3 reference group), and the interaction of each subgroup with time. The term for time indicates the average annual rate of change in the e3/3 reference group. The

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**Table 1** Descriptive information about participants in the apoE subgroups at baseline.

<table>
<thead>
<tr>
<th>Variable</th>
<th>ApoE subgroup†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>e2</td>
</tr>
<tr>
<td>Number of persons</td>
<td>86</td>
</tr>
<tr>
<td>Mean (SD) age (y)</td>
<td>75.7(7.3)</td>
</tr>
<tr>
<td>Mean (SD) education (y)</td>
<td>17.7(2.8)</td>
</tr>
<tr>
<td>Women (%)</td>
<td>67.4</td>
</tr>
<tr>
<td>White, non-Hispanic (%)</td>
<td>93.0</td>
</tr>
<tr>
<td>Mean (SD) MMSE</td>
<td>28.3(1.8)</td>
</tr>
</tbody>
</table>

†The e2 subgroup included e2/2 and e2/3 genotypes, e3 included e3/3, and e4 included e3/4 and e4/4.

**Table 2** Summary of random effects model examining the association of time, apoE subgroup, and their interaction with episodic memory function. Terms for age, sex, education, and their interactions with time were also included.

<table>
<thead>
<tr>
<th>Model term†</th>
<th>Estimate</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time</td>
<td>−0.022*</td>
<td>0.009</td>
</tr>
<tr>
<td>e2</td>
<td>0.089</td>
<td>0.061</td>
</tr>
<tr>
<td>e2 × time</td>
<td>0.038*</td>
<td>0.019</td>
</tr>
<tr>
<td>e4</td>
<td>−0.061</td>
<td>0.049</td>
</tr>
<tr>
<td>e4 × time</td>
<td>−0.051***</td>
<td>0.015</td>
</tr>
</tbody>
</table>

†Those with the e3/3 genotype were the reference group for contrasts with the e2 (e2/2, e2/3) and e4 (e3/4, e4/4) subgroups. *p<0.05; **p<0.001.
terms for apoE subgroup (ε2 or ε4) indicates the average difference at baseline between each apoE subgroup and the reference group. The interaction terms denote the average difference in annual rate of change between each apoE subgroup and the reference group. Because of the association of cognitive function with demographic variables, all models also included terms for age, sex, education, and their interactions with time.

Model assumptions of linearity, normality, and independence and homoscedasticity of errors were evaluated graphically and analytically and were found to be adequately met. All analyses were carried out in SAS.

RESULTS
ApoE subgroups
The allele frequencies in the cohort at baseline, 0.077 for ε2, 0.788 for ε3, and 0.136 for ε4, are comparable to those observed in population-based studies. Because we wanted to assess the independent contributions of the ε2 and ε4 alleles to cognitive function, we excluded persons with the ε2/4 genotype (n=16) and formed three subgroups: ε2 (ε2/2=1; ε2/3=85), ε3 (ε3/3=425), and ε4 (ε3/4=149, ε4/4=9). The distributions of demographic variables and of baseline MMSE scores were similar in the three subgroups (table 1). In each subgroup, more than 95% of those eligible participated in follow up, with an average of 5.9 to 6.0 completed evaluations per person, which represents more than 95% of possible evaluations in survivors.

Change in episodic memory in apoE subgroups
We began analyses with episodic memory because of its strong association with apoE ε4. At baseline, the summary measure of episodic memory ranged from −2.851 to 1.555 (mean=0.117; SD=0.616), with higher scores indicating better memory function. We constructed a random effects model to test whether the apoE subgroups differed in rate of change in episodic memory, controlling for baseline level of memory and for the potentially confounding effects of age, sex, and education (table 2).

Persons with the ε3/3 genotype declined an average of 0.022 units per year (95% CI −0.004 to −0.040), as shown by the term for time. At baseline, episodic memory in the ε2 subgroup was similar to the ε3/3 reference group, as shown by the term for ε2. By contrast, annual episodic memory change in the ε2 subgroup was 0.038 units less than the reference group (p<0.05). Thus, on average, episodic memory performance in the ε2 subgroup increased by 0.016 units per year. Episodic memory in the ε4 subgroup did not differ from the reference
group at baseline, but it declined by an additional 0.051 units per year (p<0.001).

To visually examine these effects, we plotted the paths of change in episodic memory during the eight years of observation in each apoE subgroup as estimated from the model (fig 1, upper left). In comparison with the e3/3 reference group, the beneficial effect of e2 and the deleterious effect of e4 on change in episodic memory are of comparable size.

To examine individual differences within the apoE subgroups, we estimated from the model the person specific paths of change in episodic memory during the eight years of observation for every individual in the e2 group and for equal numbers of persons randomly selected from the e3 and e4 groups (fig 2). The horizontal axis shows the person's age at each evaluation, and the length of each line relative to the horizontal axis shows the years of observation on that person. Heterogeneity is evident in each subgroup, but the relative absence of decline in the e2 subgroup is striking.

**Change in other cognitive domains in apoE subgroups**

We repeated the initial analysis on the summary measures of semantic memory, working memory, perceptual speed, and visuospatial ability (table 3, fig 1). On average, those with the e3/3 genotype declined in each cognitive domain. The e2 subgroup did not significantly differ from the e3/3 reference group in baseline level of function or rate of change in any of the cognitive domains, though there was a trend for reduced decline in working memory (p=0.096). The e4 subgroup did not differ from the reference group at baseline and declined more rapidly in semantic memory and perceptual speed but not in working memory or visuospatial ability.

**Incident AD in apoE subgroups**

During follow up, 124 persons developed AD, 13 (15%) in the e2 subgroup, 72 (17%) in the e3 subgroup, and 39 (25%) in the e4 subgroup. The relative risk of incident AD was 0.76 (95%CI 0.40 to 1.44) in the e2 subgroup and 1.86 (95% CI 1.22 to 2.82) in the e4 subgroup, as estimated in a proportional hazards model adjusted for age, sex, and education.

**DISCUSSION**

In a large cohort of older persons examined annually for an average of five years, possession of one or more copies of the apoE e2 allele was associated with rate of change in episodic memory but not with change in other cognitive systems. Episodic memory performance improved slightly in those with at least one e2 allele. By contrast, episodic memory declined slightly in those with the e3/3 genotype and more sharply in those with at least one e4 allele. The results suggest that the apoE e2 allele protects against episodic memory decline in older persons.
As noted above, previous research on the relation of the e2 allele to change in cognitive function has yielded mixed results. In the only previous study to assess multiple cognitive domains, those with the e2/3 genotype had reduced decline on two of five episodic memory measures and on one of five measures of other cognitive functions compared with those with e3/3, but analyses were not adjusted for the potentially confounding effects of demographic variables, and no e4 effects were observed.10 In other studies, e2 was associated with reduced episodic memory decline (but other cognitive functions were not assessed)10 and with reduced decline on one of two perceptual speed measures.11 By contrast, e2 was unrelated to change in cognitive function, including measures of episodic memory, in two other studies.12

These inconsistent results probably reflect several factors. Firstly, the e2 allele is comparatively rare, with a frequency of about 0.08 in American and European white populations,13 limiting statistical power. Second, because cognition changes gradually in older persons and is measured with error, the ability to reliably assess change in individuals depends on the length of the study period, the number of observations per person within that period, and the use of psychometrically sound outcomes. Yet some previous studies were based on three years or less of observation,10 12 13 and all were based on two observations per person and used individual tests as outcomes, increasing the possibility of floor and ceiling artefacts. Another issue is the variable composition of subgroups formed to assess e2 effects. Some studies, like the present one, have excluded e2/4 from the e2 subgroup,11 12 but other studies have included it for some13 14 or all15 analyses. Because meta-analyses suggest that the e2/4 genotype is associated with increased risk of AD,13 its inclusion in an e2 subgroup may tend to obscure a beneficial effect of e2 on cognition. In addition, the e2 comparison group in this and some previous studies has been restricted to those with the e3/3 genotype,10 13 but other studies have included all persons without an e2 allele, thereby confounding e2 and e4 effects.10 13 14

Progressive loss of episodic memory is a defining feature of AD. That e2, like e4, seems to have a comparatively selective effect on episodic memory is consistent with the idea that apoE genotype affects risk of AD mainly by augmenting or retarding the usual biological process leading to disease rather than through some other mechanism. Clinical-pathological studies will be needed to investigate these issues.

Few previous longitudinal studies have assessed the independent contributions of the e2 and e4 alleles to change in cognitive function. We found that e2 effects on cognitive decline were about equal to those of e4, or slightly smaller, but in the opposite direction. This finding underscores the limitation of binary apoE measures that contrast people with and without a given allele and suggests that ordinal approaches to scaling the overall impact of apoE may be feasible.14 The risk of developing AD was increased in those with e4. AD incidence was reduced among those with e2 but not significantly so, perhaps because of limited statistical power and the lack of an e2 effect on forms of cognition other than episodic memory.

This study has several strengths. In each apoE subgroup there was an average of about six annual evaluations per person with more than 95% follow up participation in survivors, and previously established, composite measures of specific cognitive systems were used as outcomes, increasing our ability to reliably characterise individual patterns of change in cognitive function and their relation to apoE genotype. The principal limitation is that the cohort is selected and differs in important ways from the US population. It will be important, therefore, to assess e2 effects on cognitive function in more representative groups. Also, we had only one participant with the e2/2 genotype, precluding a comparison of e2 homozygotes and heterozygotes.

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**Table 3** Summary of random effects models examining the association of time, apoE subgroup, and their interaction with function in different cognitive domains. Terms for age, sex, education, and their interactions with time were included in each model.

<table>
<thead>
<tr>
<th>Cognitive measure</th>
<th>Model term†</th>
<th>Estimate</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Semantic memory</td>
<td>Time</td>
<td>-0.042***</td>
<td>0.008</td>
</tr>
<tr>
<td></td>
<td>e2</td>
<td>-0.089</td>
<td>0.065</td>
</tr>
<tr>
<td></td>
<td>e2 × time</td>
<td>0.017</td>
<td>0.017</td>
</tr>
<tr>
<td></td>
<td>e4</td>
<td>0.005</td>
<td>0.051</td>
</tr>
<tr>
<td></td>
<td>e4 × time</td>
<td>-0.034*</td>
<td>0.014</td>
</tr>
<tr>
<td>Working memory</td>
<td>Time</td>
<td>-0.030***</td>
<td>0.006</td>
</tr>
<tr>
<td></td>
<td>e2</td>
<td>-0.060</td>
<td>0.069</td>
</tr>
<tr>
<td></td>
<td>e2 × time</td>
<td>0.020</td>
<td>0.012</td>
</tr>
<tr>
<td></td>
<td>e4</td>
<td>-0.019</td>
<td>0.054</td>
</tr>
<tr>
<td></td>
<td>e4 × time</td>
<td>-0.011</td>
<td>0.009</td>
</tr>
<tr>
<td>Perceptual speed</td>
<td>Time</td>
<td>-0.077***</td>
<td>0.009</td>
</tr>
<tr>
<td></td>
<td>e2</td>
<td>-0.046</td>
<td>0.086</td>
</tr>
<tr>
<td></td>
<td>e2 × time</td>
<td>0.022</td>
<td>0.018</td>
</tr>
<tr>
<td></td>
<td>e4</td>
<td>-0.057</td>
<td>0.068</td>
</tr>
<tr>
<td></td>
<td>e4 × time</td>
<td>-0.030*</td>
<td>0.014</td>
</tr>
<tr>
<td>Visuospatial ability</td>
<td>Time</td>
<td>-0.014*</td>
<td>0.007</td>
</tr>
<tr>
<td></td>
<td>e2</td>
<td>0.091</td>
<td>0.075</td>
</tr>
<tr>
<td></td>
<td>e2 × time</td>
<td>0.011</td>
<td>0.014</td>
</tr>
<tr>
<td></td>
<td>e4</td>
<td>-0.080</td>
<td>0.059</td>
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<tr>
<td></td>
<td>e4 × time</td>
<td>-0.017</td>
<td>0.011</td>
</tr>
</tbody>
</table>

† Those with the e3/3 genotype were the reference group for contrasts with the e2 [e2/2, e2/3] and e4 [e3/4, e4/4] subgroups. *p<0.05; ***p<0.001.
Sisters; Techny, IL; Maryknolls; Los Altos, CA and Maryknolls, NY; Nurturity, Inc; DePaul, W; Oblate Sisters of Providence; Baltimore, MD; Passionists; Chicago, IL; Presentation Sisters, BVM; Dubuque, IA; Servites; Chicago, IL; Sinsinawa Dominican Sisters; Chicago, IL and Sisinawwa, WI; Sisters of Charity, BVM; Chicago, IL and Dubuque, IA; Sisters of the Holy Family; New Orleans, LA; Sisters of the Holy Family of Nazareth; Des Plaines, IL; Sisters of Mercy of the Americas; Chicago, IL; Aurora, IL and Eric, PA; Sisters of St Benedict; St. Cloud and St. Joseph, MN; Sisters of St Casimir; Chicago, IL; Sisters of St Francis of Mary Immaculate, Joliet, IL; Sisters of St Joseph of LaGrange; LaGrange Park, IL; Society of Divine Word; Techny, IL; Trappists; Getsemani, KY and Prosta, IA; Wheaton Franciscan Sisters; Wheaton, IL.

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