PAPER

The apolipoprotein E ϵ2 allele and decline in episodic memory

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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 (ϵ2/2, ϵ2/3; n=86), and ϵ4 (ϵ3/4, ϵ4/4; 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 (ϵ2/2, ϵ2/3,ϵ2/4,ϵ3/3,ϵ3/4, ϵ4/4). Possession of one or more copies of the ϵ4 allele is associated with an increased risk of AD.[1 2] The ϵ4 allele is also associated with more rapid cognitive decline in older persons,[3–5] especially in episodic memory.[6 7] 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,[8 9] 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,[3 10–13] few of these have assessed multiple domains of cognition,[10] 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,[7] 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.[10]

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

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

Variable	ApoE subgroup†		
	ε2	ε3	ε4
Number of persons	86	425	158
Mean (SD) age (y)	75.7 (7.3)	75.7(6.7)	74.8 (6.3)
Mean (SD) education (y)	17.7 (2.8)	18.1 (3.4)	18.6 (3.3)
Women (%)	67.4	65.7	62.7
White, non-Hispanic (%)	93.0	93.2	92.4
Mean (SD) MMSE	28.3 (1.8)	28.4 (1.7)	28.5 (1.6)

†The ε2 subgroup included ε2/2 and ε2/3 genotypes, ε3 included ε3/3, and ε4 included ε3/4 and ε4/4.

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

Model term†	Estimate	SE
Time	–0.022*	0.009
ε2	0.089	0.061
ε2 × time	0.038*	0.019
ε4	–0.061	0.049
ε4 × time	–0.051***	0.015

†Those with the ε3/3 genotype were the reference group for contrasts with the ε2 (ε2/2, ε3/3) and ε4 (ε3/4, ε4/4) subgroups. *p<0.05; ***p<0.001.

examination, cognitive function assessment, and review of brain scan if available, as previously described.[14–17] 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 [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[19] and immediate and delayed recall of Story A from Logical Memory[20] and of the East Boston Story.[21] Semantic memory was assessed with Verbal Fluency,[19] a 20 item subset of the Boston Naming test,[22] a 20 item version of the National Adult Reading Test,[23] and a 15 item version of Extended Range Vocabulary.[24] Four working memory tests were administered: Digits Forward and Digits Backward,[20] Digit Ordering,[25] and Alpha Span.[26] Perceptual speed was assessed with the Symbol Digit Modalities Test[27] and Number Comparison,[24]and visuospatial ability was assessed with subsets of items from Judgment of Line Orientation[28] and Standard Progressive Matrices.[29]

We used composite measures in analyses rather than individual tests to reduce measurement error, especially floor and ceiling artefacts. As previously described,[17] 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.[7 14 15 17]

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.[30]

Data analysis

Participants were divided into three apoE subgroups for all analyses: ε2, consisting of the ε2/2 and ε2/3 genotypes; ε3, consisting of ε3/3; and ε4, consisting of ε3/4 and ε4/4. Because we wanted to assess the independent contributions of ε2 and ε4 to cognition, those with the ε2/4 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 ε2 and ε4 subgroups compared with the ε3 reference group, controlling for the potentially confounding effects of age, sex, and education.[31]

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.[32] 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 ε3/3 genotype served as the reference group in all analyses. Each model included terms for time since baseline (in years), apoE subgroups ε2 and ε4 (each contrasted with the ε3 reference group), and the interaction of each subgroup with time. The term for time indicates the average annual rate of change in the ε3/3 reference group. The

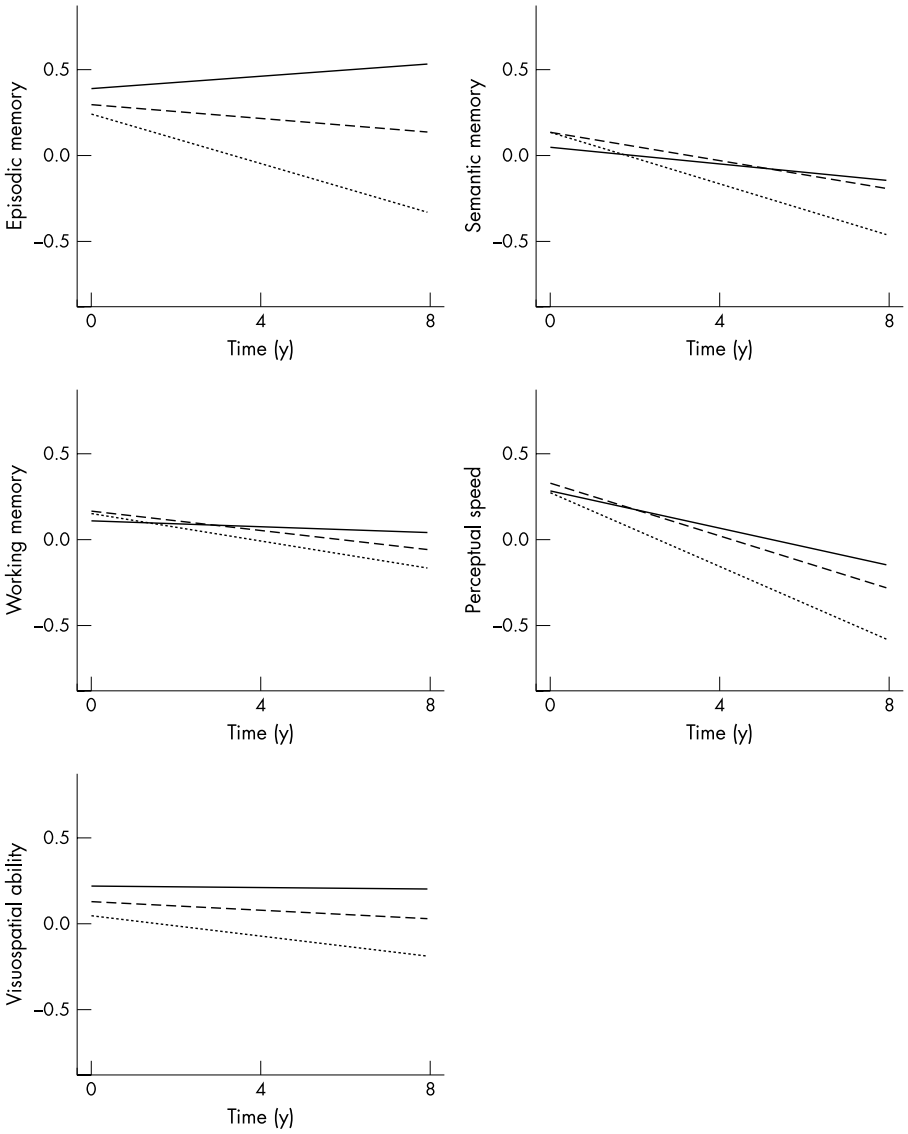

Figure 1 Average paths of eight year change in different cognitive domains in typical persons from the ϵ2 (solid line), ϵ3 (dashed line), and ϵ4 (dotted line) apoE subgroups.

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.[33]

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.[9 34 35] 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.[6 7] 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

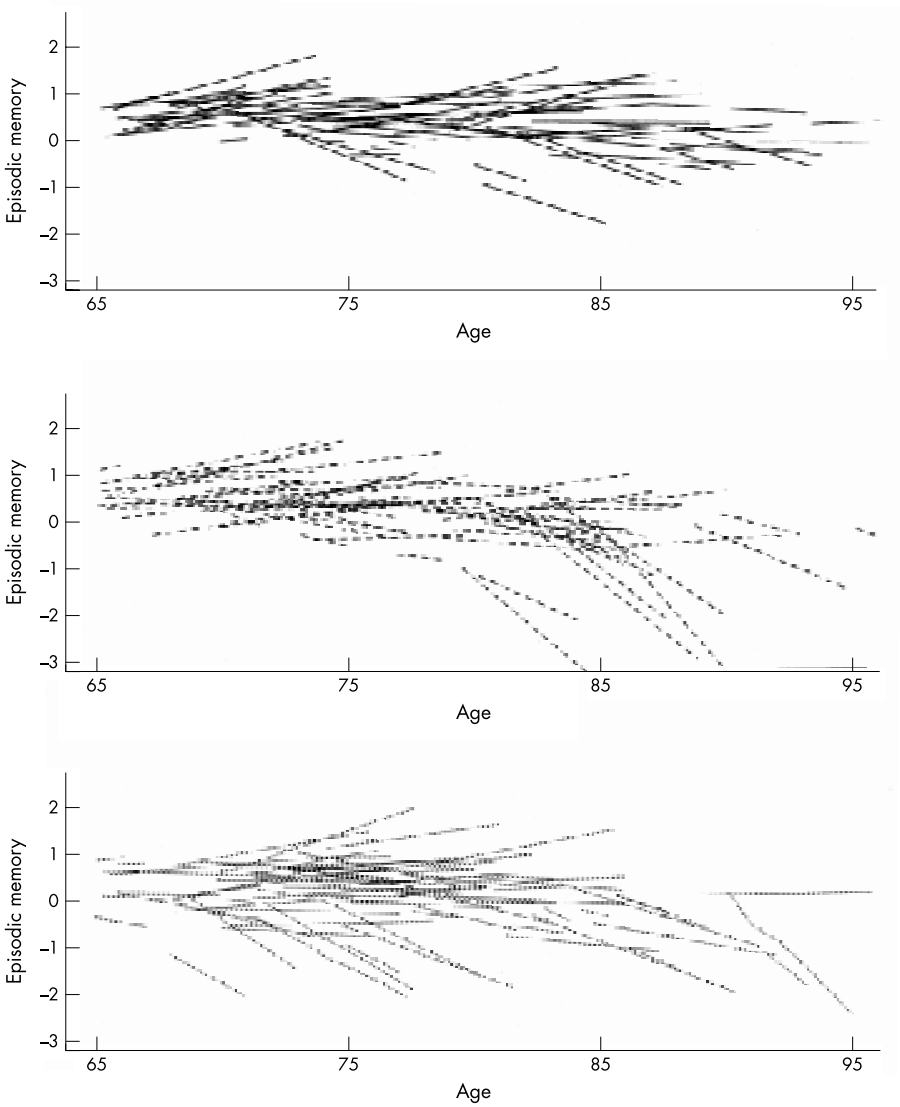

Figure 2 Individual paths of change in episodic memory in all persons from the ϵ2 subgroup (solid line) and equal numbers of persons randomly selected from the ϵ3 (dashed line) and ϵ4 (dotted line) apoE subgroups.

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 ϵ3/3 reference group, the beneficial effect of ϵ2 and the deleterious effect of ϵ4 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 over the study period for everyone in the ϵ2 group and for equal numbers of persons randomly selected from the ϵ3 and ϵ4 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 ϵ2 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 ϵ3/3 genotype declined in each cognitive domain. The ϵ2 subgroup did not significantly differ from the ϵ3/3 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 ϵ4 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 ϵ2 subgroup, 72 (17%) in the ϵ3 subgroup, and 39 (25%) in the ϵ4 subgroup. The relative risk of incident AD was 0.76 (95%CI 0.40 to 1.44) in the ϵ2 subgroup and 1.86 (95% CI 1.22 to 2.82) in the ϵ4 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 ϵ2 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 ϵ2 allele. By contrast, episodic memory declined slightly in those with the ϵ3/3 genotype and more sharply in those with at least one ϵ4 allele. The results suggest that the apoE ϵ2 allele protects against episodic memory decline in older persons.

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

Cognitive measure	Model term†	Estimate	SE
Semantic memory	Time	–0.042***	0.008
	ε2	–0.089	0.065
	ε2 × time	0.017	0.017
	ε4	0.005	0.051
	ε4 × time	–0.034*	0.014
Working memory	Time	–0.030***	0.006
	ε2	–0.060	0.069
	ε2 × time	0.020	0.012
	ε4	–0.019	0.054
	ε4 × time	–0.011	0.009
Perceptual speed	Time	–0.077***	0.009
	ε2	–0.046	0.086
	ε2 × time	0.022	0.018
	ε4	–0.057	0.068
	ε4 × time	–0.030*	0.014
Visuospatial ability	Time	–0.014*	0.007
	ε2	0.091	0.075
	ε2 × time	0.011	0.014
	ε4	–0.080	0.059
	ε4 × time	–0.017	0.011

†Those with the ε3/3 genotype were the reference group for contrasts with the ε2 (ε2/2, ε2/3) and ε4 (ε3/4, ε4/4) subgroups. *p<0.05; ***p<0.001.

As noted above, previous research on the relation of the ε2 allele to change in cognitive function has yielded mixed results. In the only previous study to assess multiple cognitive domains, those with the ε2/3 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 ε3/3, but analyses were not adjusted for the potentially confounding effects of demographic variables, and no ε4 effects were observed.[10] In other studies, ε2 was associated with reduced episodic memory decline (but other cognitive functions were not assessed)[11] and with reduced decline on one of two perceptual speed measures.[13] By contrast, ε2 was unrelated to change in cognitive function, including measures of episodic memory, in two other studies.[3 12]

These inconsistent results probably reflect several factors. Firstly, the ε2 allele is comparatively rare, with a frequency of about 0.08 in American and European white populations,[36] limiting statistical power. Secondly, 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,[3 10 12] 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 ε2 effects. Some studies, like the present one, have excluded ε2/4 from the ε2 subgroup,[10] but other studies have included it for some[11–13] or all[3] analyses. Because meta-analyses suggest that the ε2/4 genotype is associated with increased risk of AD,[37] its inclusion in an ε2 subgroup may tend to obscure a beneficial effect of ε2 on cognition. In addition, the ε2 comparison group in this and some previous studies has been restricted to those with the ε3/3 genotype,[10 12] but other studies have included all persons without an ε2 allele, thereby confounding ε2 and ε4 effects.[3 11 13]

Progressive loss of episodic memory is a defining feature of AD. That ε2, like ε4,[6 7] 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 ε2 and ε4 alleles to change in cognitive function. We found that ε2 effects on cognitive decline were about equal to those of ε4, 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.[38]

The risk of developing AD was increased in those with ε4. AD incidence was reduced among those with ε2 but not significantly so, perhaps because of limited statistical power and the lack of an ε2 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 ε2 effects on cognitive function in more representative groups. Also, we had only one participant with the ε2/2 genotype, precluding a comparison of ε2 homozygotes and heterozygotes.

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