

## Apolipoprotein E Gene Variability and Cognitive Functions at Age 79: A Follow-Up of the Scottish Mental Survey of 1932

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Apolipoprotein E (*APOE*) genotype is a possible influence on nonpathological cognitive aging. The authors studied 462 community-dwelling, 79-year-old people born in 1921, whose childhood IQ had been assessed in the Scottish Mental Survey of 1932 (Scottish Council for Research in Education, 1933). Adjusting for sex, childhood IQ, and self-reported illnesses, the authors found that those with an *APOE*  $\epsilon 4$  allele had significantly lower Wechsler Logical Memory (D. Wechsler, 1987) scores than those without an  $\epsilon 4$  allele. Those people with *APOE*  $\epsilon 2/\epsilon 3$  genotypes had significantly higher Wechsler Logical Memory scores than  $\epsilon 3/\epsilon 3$ , who were significantly higher than  $\epsilon 3/\epsilon 4$ . Neither nonverbal reasoning nor verbal fluency were affected. In this sample, *APOE* genotype contributed to verbal memory in old age.

As humans grow older, mean scores on some cognitive function tests decline, even in the absence of dementia (Schaie, 1996; Wilson, Beckett, et al., 2002). This includes abilities such as memory, reasoning, processing speed, and spatial ability (Salt-house & Ferrer-Caja, 2003). There is an association between cognitive decline and loss of independence, and lower quality of life (National Research Council [NRC], 2000). Therefore, finding influences on nonpathological cognitive aging has practical and scientific value.

Correlates of normal cognitive aging include genetic, medical, psychological, and social factors (Anstey & Christensen, 2000; Fillit et al., 2002; McDonald, 2002; NRC, 2000; Richards, Hardy, & Wadsworth, 2003). The most studied genetic influence on cognitive aging is the gene coding for apolipoprotein E (apoE) (Anstey & Christensen, 2000; Smith, 2002). ApoE is involved in lipid transport and immune regulation (Mahley & Rall, 2000). It has three main isoforms, apoE2, apoE3, and apoE4, coded for by the  $\epsilon 2$ ,  $\epsilon 3$ , and  $\epsilon 4$  alleles of the *APOE* gene on chromosome 19 in humans. Possession of the  $\epsilon 4$  allele of the *APOE* gene is associated with earlier death and increased risk of cardiovascular disease, stroke, and Alzheimer's dementia (Farrer et al., 1997; Smith, 2002). The *APOE* gene is associated with mild cognitive impairment (DeCarli et al., 2001) and perhaps with cognitive decline after head injury (Samatovicz, 2000), cardiac bypass surgery (Robson et al., 2002), and diabetes (Ferguson et al., 2003).

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There is uncertainty whether variability in the *APOE* gene relates to normal cognitive aging in humans. In some cross-sectional studies, *APOE*  $\epsilon 4$  allele status was significantly related to cognitive function in middle-aged and older adults (Smith, 2002) but probably not in children (Turic, Fisher, Plomin, & Owen, 2001). Some longitudinal studies revealed that, among nondemented people, cognitive decline proceeds faster in those with an  $\epsilon 4$  allele (Anstey & Christensen, 2000; Deary et al., 2002; Hofer et al., 2002; Smith, 2002); others disagree (Pendleton et al., 2002). We examined the influence of the  $\epsilon 4$  allele on normal cognitive aging in the Lothian Birth Cohort of 1921 study in Edinburgh, Scotland (Deary, Whiteman, Starr, Whalley, & Fox, 2004). Participants took the same verbal reasoning test (Moray House Test [MHT]) at age 11 in 1932 and at age 79 or so in 1999–2001. There was a significant detrimental effect of *APOE*  $\epsilon 4$  on changes in MHT scores from age 11 to 79 (Deary et al., 2002). However, in a separate sample, the Aberdeen Birth Cohort of 1921, there was no significant effect of *APOE*  $\epsilon 4$  on the Raven's Standard Pro-

gressive Matrices test of nonverbal reasoning at age 77 (Deary et al., 2003).

Memory is among the cognitive functions most likely to show relative deterioration in those with an *APOE*  $\epsilon 4$  allele (Flory, Manuk, Ferrell, Ryan, & Muldoon, 2000; Hofer et al., 2002; Mayeux, Small, Tang, Tycko, & Stern, 2001). On the other hand, the *APOE*  $\epsilon 2$  allele might protect memory. In a longitudinal study, possession of an *APOE*  $\epsilon 2$  allele was associated with a lesser amount of decline in episodic memory in old age (Wilson, Bienias, Berry-Kravis, Evans, & Bennett, 2002).

Some (Mortensen & Hogh, 2001) but not all (Deary et al., 2002) studies that use general population samples revealed that the influence of the  $\epsilon 4$  allele on cognitive decline occurs in women but not in men. A Sex  $\times$   $\epsilon 4$  interaction on cognitive function was found among people with diabetes (Ferguson et al., 2003).

Smith (2002) urged more research on *APOE*'s effects on normal cognitive aging and on whether they are specific to women. The present study examines the effect of the *APOE*  $\epsilon 4$  and  $\epsilon 2$  alleles on verbal memory, nonverbal reasoning, and verbal fluency at age 79 years in the Lothian Birth Cohort of 1921 sample. Because *APOE* genotype influences dementia and cardiovascular disease (Kolovou, Daskalova, & Mikhailidis, 2003), and both are causes of cognitive impairment (O'Brien et al., 2003), these factors were taken into account.

## Method

### Participants

We studied 462 people (188 men, 274 women) who completed the MHT in the Scottish Mental Survey of 1932. All participants were born in 1921. Mean age at retest was 79.1 years ( $SD = 0.6$  years; range = 77.8 to 80.6 years). Recruitment for retesting was through the Community Health Index of general medical practitioners' patient lists and advertisements and announcements in the media (Deary et al., 2004). Participants included in the analyses met the following criteria at retest: (a) scored  $\geq 24$  on the Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975), had no history of dementia, and completed cognitive testing. All participants lived independently in the community and were able to travel to the laboratory. Medical history and physical investigations were undertaken (Deary et al., 2004). Positive cardiovascular disease history included myocardial infarction, angina, coronary bypass surgery, and atrial fibrillation. A code of *unclassified* was given if there was no indication of ischaemic disease but there was a history of, for example, rheumatic heart disease. By recording medical history, we found that (a) 79 people had cardiovascular disease, 62 had angina only or were unsure, 316 had no cardiovascular disease, and 5 were unclassified; (b) 195 participants had hypertension, 264 did not have hypertension, 2 were unsure, and 1 was unclassified; (c) 36 participants had cerebrovascular disease, 423 did not have cerebrovascular disease, and 3 were unsure; and (d) 20 participants had diabetes, and 442 participants did not have diabetes.

### Measures

#### *APOE* Genotyping

Venous blood was drawn for DNA extraction. *APOE* genotypes were analyzed by polymerase chain reaction (PCR) amplification of a 227 base pair (bp) fragment of the *APOE* gene, containing two polymorphic sites that account for the three alleles,  $\epsilon 2$ ,  $\epsilon 3$ , and  $\epsilon 4$  (Wenham, Price, & Blundell, 1991). The alleles were distinguished by restriction digest of the PCR products with the restriction enzyme *CfoI*, followed by electrophore-

sis in 4% Nusieve gels (Cambrex Bioscience, Wokingham, Berkshire, United Kingdom).

### Cognitive Tests

*Moray House Test.* Participants took the Moray House Test on June 1, 1932, when they were between 10.5 and 11.5 years old (Deary, Whalley, Lemmon, Crawford, & Starr, 2000; Scottish Council for Research in Education, 1933). Verbal reasoning material predominates in the test. Raw scores were corrected for age (in days) and converted to IQ ( $M = 100$ ,  $SD = 15$ ).

*MMSE.* The MMSE is a standard screening test for clinical cognitive impairment (Folstein et al., 1975). The maximum score is 30.

*Logical Memory subtest.* The Logical Memory subtest is from the Wechsler Memory Scale—Revised (Wechsler, 1987). Participants hear a short story (story "A") containing 25 memory items. Immediately after this the participants recall as much of the story as possible. The process is repeated with a second story (story "B"). After a minimum delay of 30 min, participants recall as much as they can about each story. Because the immediate and delayed recall scores were highly correlated ( $r_s = .79$  and  $.81$  for stories A and B, respectively), the component scores were summed to form a single score that could range from 0 to 100.

*Raven's Standard Progressive Matrices.* Raven's Standard Progressive Matrices is a test of nonverbal reasoning (Raven, Court, & Raven, 1977), involving rule induction and application, and pattern completion. The test has 60 items, and participants were given a time limit of 20 min.

*Verbal fluency.* Verbal fluency is described as a test of executive function (Lezak, 1995). The participants are given 1 min to name as many words as possible beginning with the letter C. The process is repeated for the letters F and L.

## Results

### Descriptive Statistics

One hundred and twenty (26.0%) of the 462 participants possessed at least one copy of the *APOE*  $\epsilon 4$  allele. Genotypes occurred as follows:  $\epsilon 2\epsilon 2 = 2$  (0.4%),  $\epsilon 2\epsilon 3 = 66$  (14.3%),  $\epsilon 2\epsilon 4 = 16$  (3.5%),  $\epsilon 3\epsilon 3 = 274$  (59.3%),  $\epsilon 3\epsilon 4 = 101$  (21.9%), and  $\epsilon 4\epsilon 4 = 3$  (0.6%). Allele frequencies in the sample were  $\epsilon 2 = 9.3\%$ ,  $\epsilon 3 = 77.4\%$ , and  $\epsilon 4 = 13.3\%$ . The sample did not differ significantly from Hardy–Weinberg equilibrium,  $\chi^2(3) = 6.48$ ,  $p > .05$ , exact test. Means and standard deviations of, and correlations among, mental tests are shown in Table 1.

### Models Comparing *APOE* $\epsilon 4+$ With *APOE* $\epsilon 4-$

No significant difference existed between those with and without a copy of the *APOE*  $\epsilon 4$  allele in age 11 years IQ,  $t(460) = 0.73$ ,  $p = .46$ ; or MMSE scores at age 79 years,  $t(460) = 1.67$ ,  $p = .10$  (see Table 1).

General linear modeling (SPSS, Version 11.0) was run with Raven's Standard Progressive Matrices, Logical Memory subtest, and Verbal Fluency test scores together as dependent variables. Full factorial models were run first, and they were then run again, excluding nonsignificant interaction effects. There were no significant interactions between fixed factors (*APOE*  $\epsilon 4$  allele status and sex) and the covariate age 11 years IQ. There were significant multivariate effects (Wilks's lambda) of *APOE*  $\epsilon 4$  allele status,  $F(3, 455) = 2.71$ ,  $p = .045$ ,  $\eta^2 = .018$ ; age 11 years IQ,  $F(3, 455) = 49.80$ ,  $p < .001$ ,  $\eta^2 = .247$ ; and sex,  $F(3, 455) = 4.45$ ,  $p = .004$ ,  $\eta^2 = .028$ . *APOE*  $\epsilon 4$  allele status contributed significantly to

Table 1  
Correlations Among, and Descriptive Statistics for, Cognitive Tests Used in the Present Study

Test	1	3	4	5	Whole sample ( <i>n</i> = 462)		APOE ε4– ( <i>n</i> = 342)		APOE ε4+ ( <i>n</i> = 120)	
					<i>M</i>	( <i>SD</i> )	<i>M</i>	( <i>SD</i> )	<i>M</i>	( <i>SD</i> )
1. MHT at age 11	—	.25	.44	.31	100.5	(14.6)	100.8	(14.5)	99.7	(15.1)
2. MMSE	.27	.22	.36	.21	28.3	(1.4)	28.4	(1.4)	28.1	(1.5)
3. Logical Memory total score	.25	—			31.8	(12.6)				
4. Raven	.44	.34	—		31.3	(8.6)				
5. Verbal Fluency	.31	.11*	.24	—	40.0	(12.2)				

Note. APOE = Apolipoprotein E; MHT = Moray House Test; MMSE = Mini-Mental State Examination; Raven = Raven's Standard Progressive Matrices. ε4+ indicates someone who has at least one copy of the epsilon 4 allele of the gene for apolipoprotein E. ε4– indicates someone who does not have a copy of the epsilon 4 allele of the gene for apolipoprotein E. All correlations are significant at  $p < .01$ , except \*  $p = .02$ .

Logical Memory,  $F(1, 457) = 7.84, p = .005, \eta^2 = .017$ ; ε4+ participants scored lower (Table 2). APOE ε4 status had no significant effect on Raven's Standard Progressive Matrices,  $F(1, 457) = 1.46, p = .23, \eta^2 = .003$ , or Verbal Fluency,  $F(1, 457) = 0.01, p = .92, \eta^2 \leq .001$ . Estimated marginal means in Table 2 show the adjusted effect of APOE ε4 status on all three cognitive tests. Sex contributed significantly to Raven's Standard Progressive Matrices,  $F(1, 457) = 11.58, p = .001, \eta^2 = .025$  (men scored higher, as reported in Deary et al., 2004), but not to Logical Memory,  $F(1, 457) = 3.25, p = .07, \eta^2 = .007$ , or to Verbal Fluency,  $F(1, 457) = 0.24, p = .62, \eta^2 = .001$ . There was no significant Sex  $\times$  APOE ε4 status interaction,  $F(3, 455) = 0.98, p = .40, \eta^2 = .006$ . Age 11 years IQ contributed significantly to all three outcomes at age 79: Raven's Standard Progressive Matrices,  $F(1, 457) = 113.02, p < .001, \eta^2 = .198$ ; Logical Memory subtest total score,  $F(1, 457) = 28.73, p < .001, \eta^2 = .059$ ; and Verbal Fluency,  $F(1, 457) = 46.79, p < .001, \eta^2 = .093$ .

The same model was repeated four times for the Logical Memory dependent variable adding the MMSE score as an additional covariate and history of one of four diseases (cardiovascular, cerebrovascular, diabetes, or hypertension) as a between-subjects factor after APOE status. Although MMSE was related to Logical Memory,  $F(1, 450) = 11.01, p = .001, \eta^2 = .024$ , APOE ε4 allele status remained significant,  $F(1, 450) = 9.06, p = .003, \eta^2 = .020$ . The only illness that contributed significantly to poorer logical memory was hypertension,  $F(2, 454) = 3.31, p = .037, \eta^2 = .014$ .

#### Models Comparing APOE ε2ε3, ε3ε3, and ε3ε4

Models described in the previous section were run again after replacing APOE ε4 status with a fixed effect of three APOE

genotypes, ε2/ε3, ε3/ε3, ε3/ε4. The contributions of IQ at age 11 and sex were very similar to those found in the previous analyses; therefore, these effects are not presented here (details are available from the authors). There were no significant interactions. With sex and IQ at age 11 in the multivariate model, APOE genotype contributed significantly to Logical Memory scores,  $F(2, 434) = 8.52, p < .001, \eta^2 = .038$ , but not to Raven's Standard Progressive Matrices or Verbal Fluency scores. Estimated marginal means for the effect of APOE genotype in the model are shown in Table 2. Those with ε2/ε3 genotypes scored significantly higher on Logical Memory than did ε3/ε3 ( $p = .003$ ), who scored higher than ε3/ε4 ( $p < .001$ ).

Models were run with Logical Memory as the sole dependent variable. MMSE was a covariate. Cardiovascular disease, cerebrovascular disease, diabetes, and hypertension were included individually in separate models. Only hypertension contributed significantly to poorer Logical Memory,  $F(2, 432) = 3.18, p = .042, \eta^2 = .015$ . The effect of APOE genotype was significant in all models at  $p < .001$ , and partial  $\eta^2$  was consistent, from .038 to .041. The three pairwise comparisons among genotypes were significant in all models, with the same rank order of Logical Memory test total scores (ε2/ε3 > ε3/ε3 > ε3/ε4) and similar  $p$  values to those in the multivariate model.

#### Discussion

Our results agree with the suggested association between APOE ε4 and memory scores (Bondi et al., 1995; Bondi, Salmon, Galasko, Thomas, & Thal, 1999; Chey, Kim, & Cho, 2000) and rate of decline in memory scores (Hofer et al., 2002; Mayeux et al.,

Table 2  
Estimated Marginal Means (95% Confidence Interval) for the Effect of APOE Genotypes on Cognitive Test Scores

Test	ε4– ( <i>n</i> = 342)	ε4+ ( <i>n</i> = 120)	ε2/ε3 ( <i>n</i> = 66)	ε3/ε3 ( <i>n</i> = 274)	ε3/ε4 ( <i>n</i> = 101)
Logical Memory	32.9 <sup>a</sup> (31.6–34.2)	29.2 (26.9–31.4)	36.9 (33.9–39.9)	31.9 <sup>b</sup> (30.4–33.3)	28.8 (26.4–31.2)
Raven	31.8 (31.0–32.6)	30.8 (29.4–32.2)	32.5 (30.6–34.4)	31.5 (30.6–32.5)	31.0 (29.5–32.6)
Verbal Fluency	39.9 (38.7–41.2)	40.1 (37.9–42.2)	39.1 (36.2–42.0)	40.0 (38.6–41.4)	40.0 (37.4–42.1)

Note. Marginal means are adjusted for sex and IQ at age 11. ε4+ indicates someone who has at least one copy of the epsilon 4 allele of the gene for apolipoprotein E. ε4– indicates someone who does not have a copy of the epsilon 4 allele of the gene for apolipoprotein E. ε3/ε3 indicates someone who has 2 epsilon 3 alleles of the gene for apolipoprotein E, and so forth. Raven = Raven's Standard Progressive Matrices. Pairwise comparisons are based on estimated marginal means: <sup>a</sup> APOE ε4– vs. APOE ε4+,  $p < .01$ ; <sup>b</sup> ε3/ε3 vs. ε2/ε3,  $p = .003$ ; ε3/ε3 vs. ε3/ε4,  $p < .01$ .

2001; Wilson, Schneider, et al., 2002) in older people without dementia. They also agree with the suggested protective effect of the  $\epsilon 2$  allele on memory (Farrer et al., 1997; Wilson, Bienias, et al., 2002).

Not all studies find that *APOE*  $\epsilon 4$  status is related to memory or other cognitive functions in nondemented older people. There are various possible reasons for this. The effect size of *APOE* genotype is relatively small, and therefore large numbers of participants are required. The method of defining cognition as the outcome variable might be important. There is less power if cognition is defined as a dichotomy between impaired and not impaired (Dik et al., 2000) versus a continuum as was used here. The mental test battery is potentially important in a situation where some tests are more sensitive to the effects of *APOE* genotype than others. For example, Pendleton et al. (2002) found no effect of *APOE* genotype on fluid intelligence as measured by the Alice Heim (Heim, 1970) test. Similarly, we found no effect of *APOE* genotype on Raven's Standard Progressive Matrices in our study and elsewhere (Deary et al., 2003).

Why should Logical Memory but not fluid intelligence be affected by *APOE* genotype? One possible reason is because there are substantial aging effects on the cognitive domain of memory that are not shared with the effect of age on general cognition (Salthouse & Ferrer-Caja, 2003). However, in addition to memory, *APOE* status might influence verbal reasoning (Deary et al., 2002), verbal fluency (Robson et al., 2002), and visual attention (Greenwood, Sunderland, Friz, & Parasuraman, 2000).

The effect size of the  $\epsilon 4$  allele on memory scores was modest, at about 2% of the variance. In models including  $\epsilon 2/\epsilon 3$ ,  $\epsilon 3/\epsilon 3$ , and  $\epsilon 3/\epsilon 4$ , *APOE* accounted for about 4% of the variance. These are contributions to total variance in memory scores, but not all of that variance is genetic in origin. For example, imagine that the genetic contribution to memory scores was 50%. The above estimates for *APOE* would represent 4% (2% of 100 = 4% of 50) and 8%, respectively, of the genetic variance. Future research might establish additional genetic contributions, for example, the val66met polymorphism on the gene for brain-derived neurotrophic factor (Egan et al., 2003).

It is unlikely that the present effects of *APOE* were substantially due to incipient dementia. Participants lived independently, were relatively healthy, had no history of dementia, and scored 24 or more on the MMSE. Effects remained after adjusting for MMSE score. Given valid assumptions about the effect of the *APOE*  $\epsilon 4$  allele on dementia (Breitner et al., 1999) those with "incipient Alzheimer's dementia" would require an untenably high mean difference (from the nonincipient-dementia participants) of over 90 points each fully to cause the Logical Memory differences found in this study. Details of this computation are available from the authors. There were no outliers on the Logical Memory test in either of the *APOE*  $\epsilon 4$  groups, and the two groups had almost identical standard deviations. However, we cannot rule out the possibility that incipient Alzheimer's disease could account for some of the effect. The Logical Memory test score appears to be a sensitive, early indicator of Alzheimer's disease (Howieson et al., 2003), as does delayed recall from the California Verbal Learning Test (Bondi et al., 1999, 1995). Also, people with early dementia will not always present as outliers in a cognitive score distribution, as there is a continuum of cognitive decline from normal aging to moderate Alzheimer's dementia (Paykel, Huppert,

& Brayne, 1998). Moreover, in a nondemented sample of older people, those with the *APOE*  $\epsilon 4$  allele subsequently were more likely to develop probable or questionable Alzheimer's disease (Bondi et al., 1999).

There are neuronal pathologies other than Alzheimer's disease that could account for the effect of *APOE* genotype. Among the normal population *APOE*  $\epsilon 4$  appears to be a "frailty gene, predisposing one to be more susceptible to injury and less likely to recover from trauma once it occurs" (Smith, 2002, p. 356). Those who produce the E4 protein isoform have relatively poor neuronal repair and protection, leading to neurodegeneration (Mahley & Rall, 2000).

These considerations emphasize that finding associations of cognitive aging—either genetic or other factors—is not an end in itself. The associations achieve importance insofar as they suggest further investigations into the mechanisms that underlie individual differences in cognitive change with age. Understanding mechanisms might lead to effective interventions to prevent, delay, or ameliorate the more damaging age-related changes to cognition.

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