APOE polymorphism, socioeconomic status and cognitive function in mid-life–the Whitehall II longitudinal study.

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Abstract

Objective The aim of this study was to investigate the association of the common apolipoprotein E gene (*APOE*) variants with cognitive function and cognitive decline in adult mid-life, and explore the possibility that *APOE* genotype mediates the link between socioeconomic status (SES) and cognitive function. *Methods* Data on cognitive function, as measured by five cognitive tests, together with *APOE* genotype were obtained in an occupational cohort (the Whitehall II study) of 6,004 participants aged 44-69 years (1997-1999). Cognitive change was examined in 2,717 participants who had cognitive function measured at baseline (1991-1993). *Results* SES based on civil service employment grade was strongly related to cognitive function. There was no association between *APOE* genotype and employment grade. In women, participants with *APOE*-ε4 had a lower memory score ($p<0.05$) but the result was sensitive to data from a small number of individuals. A marginal cross-sectional difference in the semantic fluency score was found ($p=0.07$) and there was a relative decline at follow-up ($p<0.001$, net change =-1.19, 95%CI = –1.90 ~ -0.49) in those with *APOE*-ε4 genotypes. *Conclusions* *APOE*-ε4 has little influence on cognitive decline in mid-life while SES is a strong determinant, although *APOE* genotype may emerge as an important factor in cognitive function in later life.

KEYWORDS: Cognitive function, *APOE* polymorphism, Socioeconomic status, longitudinal study

Introduction

Although individual differences in adult cognitive function are reportedly subject to substantial genetic influence [1; 2], identification of the specific genes involved and the corresponding gene-environment interactions remains a challenging task. The apolipoprotein E gene (*APOE*) has attracted considerable attention in this regard. The *APOE* gene has three common alleles (ε2, ε3 and ε4) which form six genotypes (ε2/ε2, ε2/ε3, ε3/ε3, ε2/ε4, ε3/ε4 and ε4/ε4). *APOE*-ε4 carriers have an increased risk of Alzheimer's disease [3; 4] and it may be that the *APOE*-ε4 allele is also associated with faster cognitive ageing. Besides many cross-sectional studies, some prospective studies of elderly, apparently non-demented, individuals support an *APOE* effect on memory, speed of information processing and other aspects of cognitive function [5-14] while others find effects in women only [15; 16] or no association in either sex [17-19].

The Whitehall II study [20] is investigating the influence of socioeconomic position on adult cognitive function [21]. Previous population-based studies show a strong association: the higher an individual's socioeconomic status (SES), the higher the cognitive performance and the slower the cognitive decline [22; 23]. While the role of environment on cognitive function is well established, the influence of common genetic variation in the social patterning of cognitive function is unclear. *APOE* could be associated with achieved level of cognitive function and contribute to socioeconomic differences in cognitive function in mid-life as a consequence of a difference in the age of onset of cognitive decline, dependent on ε4 carrier status [11], or *APOE*-ε4 may modify the association between socioeconomic status and cognitive decline [24].

In this paper we set out to characterise the influences of the common *APOE* variants and SES on cognitive function of individuals in the Whitehall II study, and examine the inter-relationship between *APOE* genotype, SES, and cognitive function through two related questions: (a) Is the *APOE*-ε4 allele related to cognitive function and cognitive decline in this cohort? (b) Does *APOE* genotype modify the link between SES and cognitive function? We have used data on five domains of cognitive function at two phases of the Whitehall II study for the investigation.

Methods

The Whitehall II study

The Whitehall II Study was set up in 1985 to investigate the socioeconomic gradient in health and disease in 10,308 British civil servants (6,895 men, 3,413 women) aged 35-55. Baseline and follow-up examinations involved a clinical screening and a self-administered questionnaire containing sections on sociodemographic characteristics, health and lifestyle factors. The data used in current analysis were from phases 3 (1991-1993) and 5 (1997-1999), consisting of 8,815 and 7,830 respondents, respectively. The study was approved by UCL Research Ethics Committee, and participants gave informed consent to each aspect of the study.

Measures of cognitive function

The battery of cognitive tests involved 5 standard tasks: The **verbal memory test** is a twenty-word free recall test of short-term memory. Participants were given an audiotaped

list of twenty single or double syllable words at two-second intervals and asked to recall them in writing within two minutes. The **AH 4-I** [25] is a test of inductive reasoning, consisting of 65 verbal and numeric items to be completed within 10 minutes. The **Mill Hill** [26] assesses the participant's vocabulary and ability to recognise and comprehend words. The participants were given thirty-three groups of words, each containing a word in capital letters and six other words. The participants had ten minutes to choose from the six words in each group which means the same as the word in capital letters in that group. Finally, **phonemic and semantic fluency tests** [27] require the participant to recall in writing as many words beginning with the letter "S" in one minute and as many "animal" words in one minute. The AH4 tests for fluid ability which is associated with reasoning and induction and Mill Hill tests for crystallised ability which is associated with accumulation of knowledge and vocabulary. These tests are scored according to the number of correct answers given, with maximum possible values 20, 33 and 65 for memory, AH4 and Mill Hill tests and no apparent upper bounds for phonemic and semantic fluency tests.

Measures of SES and covariates

We used civil service employment grade as measure of adult SES: 1 = unified grade 1-6, 2 = unified grade 7, 3 = senior executive officer, 4 = higher executive officer, 5 = executive officer, 6 = clerical officer/office support; from which three categories were created: 1 = high (unified grades), 2 = medium (executive officers), 3 = low (clerical officer/office support). People in different grades differ with respect to salary, social status and level of responsibility. A five-category definition was used for education: 1 =

no formal qualification, 2 = lower secondary school education, 3 = higher secondary school education, 4 = university degree, 5 = higher university degree; corresponding to a three-category definition: 1 = no qualification, 2 = up to secondary school qualification, 3 = university qualification. Women generally had lower education and lower employment status than men. The 30-item general health questionnaire (GHQ) [28] was used to evaluate differences in psychological state with total GHQ score dichotomised into low (<5) and high (>=5) to apply the cut-off between those who did and did not report distress.

APOE genotyping

APOE genotype was determined using a standard PCR assay [29] of DNA extracted from whole blood using the salting out method [30]. Genotype was read blind by two independent observers and any discrepancies were resolved by repeating PCR analysis.

Study sample

The main sample consisted of attenders at phase 5 who completed the cognitive tests and provided DNA for *APOE* genotyping. Between April 1997 and January 1999, 6,543 participants (4,638 men, 1,905 women) attended the screening clinic, among whom 6,073 (4,295 men, 1,778 women) finished their cognitive testing and there were no sex differences in participation rates. The participation rate was unrelated to age and education and greater than 95% in each employment grade.

Cognitive tests were administered to 4,128 participants (2,869 men, 1,259 women) attending the phase 3 screening clinic (September 1991 -- December 1992). These tests were only administered after March 1992, and 3,518 participants (2,518 men, 1,000 women) finished their cognitive testing and accounted for about 40% of the total sample at phase 3. The participation rate in cognitive tests was higher ($p<0.0001$) in men (87.7%) than in women (79.4%) with 75% or higher in each age group in women. The participation rate was unrelated to education and GHQ caseness. In men, there was a relatively small number of participants (n=156) in the clerical/support group with lower participation rate (73.2%) In women the participation rate was 75% or higher in each employment grade. A similar pattern of participation rates by employment grade was observed among those who attended phase 5 cognitive testing.

There were 6,996 participants (4,884 men, 2,112 women) where *APOE* genotyping was successful. One individual with the *APOE* genotype ε3/ε4 had a change in Mill Hill score of 16 and was considered to be an outlier and excluded from the analysis. Non-European participants were excluded from the analysis because they accounted for a small proportion of the total sample and were predominantly in the lowest employment grade with *APOE*-ε4 allele frequencies (South Asians 9.2%, Afro-Caribbeans 24.3%) ($p<0.0001$) being significantly different from that in Europeans (15.0%). There were 6,004 European participants (4,331 men, 1,673 women) with cognitive scores or *APOE* genotypes at phase 5, among whom 5,244 had cognitive scores and 5,090 had *APOE* genotypes. There were 2,717 European participants (1,992 men, 725 women) with cognitive scores at phase 3. Among 2,423 (1,799 men, 624 women) and 4,330 Europeans

(3,168 men, 1,162 women) with *APOE* genotype and cognitive scores at phases 3 and 5, 2,106 (1,591 men, 515 women) had cognitive scores at both phases and *APOE* genotypes.

Statistical analyses

The analysis was carried out in SAS 8.2, AMOS 4.01 and Mplus 3.01. Due to possible sex differences in *APOE*-ε4 effects, sex-specific analyses were conducted. Trend tests of cognitive scores with respect to age, education and employment grade were conducted using linear regression. The relative importance of age, education, employment grade and *APOE* on cognitive function was assessed using regression R^2. A five-group age (1 = 45-49, 2 = 50-54, 3 = 55-59, 4 = 60-64 and 5 = 65-69) together with the six-grade employment and the five-level education were used to adjust for nonlinear effects and to facilitate the interpretation of interactions terms when included in the models. Conditional regression was conducted in which a given cognitive score at phase 5 was regressed on its score and age at phase 3 plus their interaction. The difference between cognitive scores of phase 5 and phase 3 was used as change score and analysed with respect to age groups (1 = 39-44, 2 = 45-49, 3 = 50-54 and 4 = 55-62) and employment grade at phase 3. Correlation structure of domains of cognitive function was explored through a confirmatory factor analysis involving all five cognitive tests, with goodness of fit of the model being assessed by χ^2, the root mean square error of approximation (RMSEA) and comparative fit index (CFI).

The change score for each cognitive test was examined according to the associated phase 3 score being low, medium or high, in order to identify ceiling and floor effects, or

regression towards the mean. As suggested [31], a test of cohort effect was conducted by comparing the first test scores of attenders at phases 3 and 5, matched by the age range of 45~62, given that differential selection of participants via the administration of cognitive tests at phase 3 was rather unlikely. The test of practice effect [32] was carried out using phase 5 scores between those who attended and did not attend cognitive tests at phase 3. The strength of association was also examined via bootstrap analyses involving association between employment grade and *APOE-ε4* and *APOE*-ε4 effect in the joint model including age, *APOE*-ε4, employment grade, indicator variable for practice effect and cognitive scores at phases 3 and 5, each with 10,000 replicates.

Results

Age, SES and cognitive function

Cognitive scores at phase 5 according to sociodemographic characteristics of participants are shown in Table 1. Men had a lower age-adjusted mean memory score than women, but significantly higher age-adjusted scores on AH4, Mill Hill and semantic fluency tests than women. In general, cognitive scores were lower in older age groups, those with less education and lower employment grade. When cognitive scores were adjusted for employment grade, the sex difference in memory scores increased ($p<0.0001$) and women had significantly higher phonemic and semantic scores than men (both $p<0.0001$). The trend to lower Mill Hill score with age in women was greatly attenuated by adjustment for employment grade. There was generally no age by employment grade interaction except Mill Hill score (men $p=0.025$, women $p=0.0002$) and AH4 score in

women (p=0.007), where there was a suggestion that vocabulary tended to improving with age in higher grade staff only.

[Insert Table 1 here]

Education and employment grade accounted for a substantial part of the total variation (R^2) of cognitive scores as measured by regression. In men, age accounted for R^2=0.02 of the AH4 score but this increased to 0.27 after adjusting for education and employment grade. In women, age alone gave an R^2 of 0.08 from the Mill Hill score but this became 0.52 after similar adjustment. In general, models including employment grade had a relatively higher R^2 than those including education only. However, for memory score in women and Mill Hill scores in both sexes, adjustment for education produced a larger R^2 than employment grade. Memory had the smallest education and employment grade adjusted R^2. The small increase over age of Mill Hill score in men was non-significant (p=0.11) when adding employment grade.

Phase 3 score accounted for much of the variance of scores at phase 5, with R^2 ranging from under 20% for memory to about 70% for the Mill Hill score, while age and its interaction with test scores at phase 3 explained at most 1~4% and 1% of the variance at phase 5. Small increases in cognitive scores were observed at phase 5 compared with phase 3 in men and women (p<0.005). In both sexes, smaller improvements were seen in older age groups. Linear modelling showed change scores of memory, AH4, phonemic fluency and semantic fluency in men and semantic fluency in women were negatively associated with age at phase 3. The change score was not related to employment grade (all with p>0.15).

Confirmatory factor analysis revealed a two-factor model in which memory and semantic fluency were loaded on one factor and Mill Hill (χ^2=3.75, df=2, p=0.15, RMSEA=0.012, CFI=1.0) from the other, whereas AH4 and phonemic fluency were on both factors.

APOE genotype, SES and cognitive function

The distribution of *APOE* alleles by sex and employment grade is shown in Table 2. There was no *APOE* genotypic (p=0.19 for men, p=0.42 for women) or *APOE*-ε4 allelic (p=0.20 for men, p=0.47 for women) association with employment grade. The trend tests of *APOE* alleles by employment grade were non-significant (all with p>=0.20). Similarly, there were no *APOE* genotypic (p=0.99 for men, p=0.13 for women) or *APOE*-ε4 allelic (p=0.85 for men and p=0.40 for women) association with education. Bootstrap-adjusted p values between employment grade and *APOE*-ε4 were 0.35 for men and 0.41 for women.

[Insert Table 2 here]

At phase 5, the strongest adverse *APOE*-ε4 effect was observed on the memory test score in women, after adjusting for age (p=0.047; difference = -0.33, 95%CI = -0.66~-0.004). The effect on semantic fluency -0.51 (95%CI –-1.06~0.04) was marginally significant (p=0.07). In contrast to the substantial increase of R^2 when including education and employment grade, entering *APOE*-ε4 into the regression caused much smaller changes. A significant *APOE*-ε4 by employment grade interaction was seen for memory score in men (p=0.025) but the main *APOE* effect was not significant (p=0.22). No significant interactions were seen for other cognitive tests in men and all cognitive tests in women. When employment grade and *APOE*-ε4 were in the same regression equation, *APOE*-ε4

effect in women on memory and semantic fluency approached significance (both p=0.06). The *APOE*-ε4 effect on memory score was mainly detected in the age group 50-54. When three individuals with memory scores of 0, 2, 2, and *APOE* genotype ε3/ε4, ε3/ε4, ε4/ε4 largely were excluded, the age-adjusted *APOE*-ε4 memory effect became non-significant (p=0.10). The size of the effect that would be attributed to the mediating effect of *APOE*-ε4 carrier status in the cross-sectional association between SES and memory in women was estimated by linear regression, containing age as a covariate; adding *APOE*-ε4 led to a 1.5% decrease of the regression coefficient for employment grade.

APOE genotype, SES and cognitive decline

Changes in cognitive scores (mean and SE) by sex, age group and *APOE*-ε4 carrier status are shown in Table 3. In women, *APOE*-ε4 carriers generally showed smaller improvement compared to non-ε4 carriers, especially for semantic fluency score. Although most cognitive change scores stratified by age group were statistically non-significant between *APOE*-ε4 and non-ε4 groups, decreases of semantic fluency scores at age groups 45-49 (p=0.030) and 60-69 (p=0.040) were found. The adverse *APOE*-ε4 effect on semantic fluency in women remained significant (p<0.001, net change = -1.19, 95%CI = -1.90~-0.49) after adjusting for age. When adjusting for both age and employment grade the results were largely unchanged (p<0.001; net change=-1.23, 95%CI=-1.94~-0.52). No *APOE*-ε4 by age interaction was observed on change scores (all with p>0.10).

[Insert Table 3 here]

Ceiling, floor, cohort and practice effects

The distributions of cognitive scores at both phases did not show strong ceiling or floor effects. Participants scoring low at phase 3 showed an overall improvement, while those scoring high at phase 3 showed decline, indicating regression towards the mean. In both men and women matched for age, the phase 5 scores of phase 3 non-attenders were higher than those of phase 3 attenders, except for the Mill Hill score in men, suggesting a cohort effect. Furthermore, phase 5 scores of phase 3 attenders were higher than those of phase 3 non-attenders, except for the Mill Hill scores in women, indicating practice effects. The joint model of age, employment grade, *APOE*-ε4 and practice effect had RMSEA=0.018, CFI=0.999. An *APOE*-ε4 effect was found in semantic fluency in women (estimate = -0.66, z= -2.78, 99%CI = -0.31 ~ -0.41) but not men. The practice effect on phase 5 score was significant in women (estimate=0.45, z=2.27, 99%CI = -0.31 ~ 0.30) but not men.

Discussion

Our study provides a novel insight into influences on cognitive function in healthy men and women in mid-life. There was some evidence of relative cognitive decline over the six years of follow up, and evidence of only a modest *APOE* effect at this stage of the life course. While the influence of *APOE* may emerge with further ageing, we found that cognition around 50 years of age was largely influenced by education and occupational status, both of which were strongly related to the five cognitive domains tested in men and in women. We are unable to examine genetic influences on cognitive development earlier in life, however *APOE* genotype did not appear to influence civil service

employment grade destination. Given the endowment acquired during childhood and adolescence, our results suggest a substantial influence of environment on cognitive function in mid-life though genetic influences are also likely to operate. These findings are based on a sensitive measure of SES. All participants were initially employed in the civil service where employment grade is a marker of substantial differences in material circumstances, psychosocial environment and behaviour at home and at work over the life course.

Age, SES and cognitive function

The larger age effect on cognitive function from cross-sectional data than a longitudinal time effect is as expected [31; 33], and reflects either a cohort effect (birth years ranging between 1930-53), a practice effect due to retest, or a combination of the two. Women performed better in the short-term memory test than men, as reported elsewhere [34]. Here, the sex difference in memory score is evident at each level of the civil service (Table 1). Similarly, the unadjusted sex difference in semantic fluency score favouring men reflects the non-uniform distribution of men and women across employment grades. In general, the influence of employment grade on cognitive function appeared to be larger than education, but it has been reported that there is a strong association between education and crystallised intelligence such as Mill Hill test, particularly in women [22]. The lack of age by employment grade interaction in most tests indicates that for each employment grade cognitive scores did not differ significantly across age groups except the AH4 score in women and Mill Hill vocabulary score in both sexes. The larger than age effect of social class were also in line with other report [35]. As cognitive impairment

is related to functional decline, dependent living and mortality, it remains to assess if poor functioning starts from mid-life and clusters in certain individuals in the cohort, which will have both clinical importance and public health implications.

APOE genotype, SES and cognitive function

APOE allele frequencies in the cohort were consistent with other studies [7; 36]. We found no association between employment grade and *APOE* polymorphism, and overall no evidence of an interaction between employment grade and *APOE*-ε4 on cognitive function. In agreement with report showing no association between *APOE*-ε4 and education [13], this study provides no support for the proposal that *APOE*-ε4 influences social position [37], either through level of educational attainment or occupational status, as measured by civil service employment grade, or that it mediates the association between SES and cognitive function. The *APOE*-ε4 by employment interaction observed for memory in men was not accompanied by a main *APOE*-ε4 effect and is probably a chance finding.

APOE genotype, SES and cognitive decline

A memory-associated cognitive decline attributable to *APOE*-ε4 in women is in accordance with other reports on nondemented [11; 15; 16] and demented [8] subjects. This finding supports an *APOE*-ε4 effect on cognitive function, which we expect will increase with age (Table 3). The test scores in our study were generally lower and their improvements smaller in the older age groups, consistent with onset of cognitive decline after age 50. Additionally, the tendency to smaller improvement of test scores in older

women with *APOE*-ε4, significantly in the case of semantic fluency, suggests *APOE* may play a role in the decline. Our observation that SES was more associated with cognitive function than with cognitive decline was also reported with education status [31]. However, due to the presence of the practice effects, it is inappropriate to conclude that there was no association between SES and cognitive change based on change score.

Ceiling, floor, cohort and practice effects

Since a large proportion of the variance in cognitive function at phase 5 can be accounted by phase 3 scores, cognitive function appears to be relatively stable in the age range examined. However, interpretation of these findings is hampered by possible cohort effects, linking with different sociohistorical experiences [38], and practice effects. This could be greatly facilitated with data from further phase of Whitehall II study. Cognitive improvement has been observed even in a cohort after age 65 years [31]. Being actively employed in civil service would help participants to maintain or enhance an active lifestyle and therefore cognitive function [39]. Cognitive function in later life has been shown to be associated with cognition in childhood and across the life course [23], and this path could have a substantial initial input from parental SES [14; 40]. The Whitehall II data add to the body of literature of cognitive function in the fifth and sixth decades showing that it is relatively stable compared to findings from population-based cohorts usually aged 65 and over [5; 7; 8; 10; 14].

Conclusions

We observed small negative *APOE*-ε4 effects involving memory and semantic fluency in women but not in men, while SES is a strong determinant of cognitive function. There is little support for an *APOE*-ε4 modification effect of the association between SES and cognitive function. Study of the *APOE*-ε4 effect on cognitive decline should take into account dimensions of SES and other specific environmental factors. We plan to examine the link between *APOE*-ε4 and cognitive function in conjunction with other genetic and environmental factors, and to obtain estimates of cognitive changes in relation to SES and *APOE* polymorphism [13] as the cohort ages and moves into retirement..

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Table 1 Cognitive scores at phase 5 by sex, according to age, education and SES

	Sample size	Memory	AH4	Mill Hill	Phonemic fluency	Semantic fluency
Age-adjusted mean (SD)¶ by sex (N=5244)						
Men	3811	6.75(2.27)	49.0(9.03)	26.0(3.36)	16.9(4.26)	16.6(3.89)
Women	1433	6.96(2.63)	42.8(11.3)	24.0(4.69)	16.8(4.78)	16.2(4.49)
Difference p		0.005	<0.0001	<0.0001	0.45	0.0004
Mean by age group						
Men						
45-49	868	7.58	50.8	25.7	17.9	17.8
50-59	1920	7.10	50.2	26.1	17.5	17.1
60-69	1023	6.16	47.9	26.3	16.0	15.9
Trend p		<0.0001	<0.0001	0.0004	<0.0001	<0.0001
Women						
45-49	302	8.06	49.2	25.9	18.8	18.6
50-59	681	7.18	44.5	24.3	17.2	16.8
60-69	450	6.33	37.5	22.4	15.4	14.4
Trend p		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Age-adjusted mean by education						
Men						
No qualification	216	6.01	39.4	22.3	14.1	13.8
Secondary	2000	6.63	48.6	25.7	16.6	16.5
University	1416	7.23	53.2	27.8	18.0	17.7
Trend p		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Women						
No qualification	287	5.94	34.1	19.9	14.5	13.6
Secondary	645	7.03	43.6	24.4	17.0	16.2
University	354	7.72	50.7	27.9	18.9	18.9
Trend p		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Age-adjusted mean by employment grade						
Men						
High	2067	7.10	52.2	27.1	17.8	17.5
Medium	1566	6.46	46.9	25.3	16.0	16.0
Low	156	5.69	34.7	21.4	13.4	12.8
Trend p		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Women						
High	332	7.54	50.9	27.4	19.3	18.7
Medium	698	7.07	43.3	24.5	16.9	16.3
Low	389	6.17	34.2	20.0	14.6	13.8
Trend p		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

¶ the standard deviation (SD) was not age-adjusted. The sample sizes in all categories were the largest (usually the Mill Hill test) among five cognitive scores.

Table 2 The distribution of *APOE* alleles (% and 95% CI) by sex and employment grade (phase 5) and trend tests of individual alleles versus others

Sex	Employment grade	Total alleles	APOE alleles		
			ε2	ε3	ε4
Men	Admin	3966	7.84 (7.0-8.7)	76.9 (75.5-78.2)	15.3 (14.2-16.5)
	Prof/Exec	3060	8.07 (7.1-9.1)	77.2 (75.6-78.6)	14.8 (13.5-16.1)
	Cl/Supp	312	4.81 (2.7-7.8)	76.0 (70.8-80.6)	19.2 (15.0-24.1)
	Trend *p*		0.42	0.59	0.98
Women	Admin	646	7.12 (5.3-9.4)	78.0 (74.6-81.2)	14.9 (12.2-17.8)
	Prof/Exec	1338	7.17 (5.9-8.7)	78.5 (76.2-80.7)	14.3 (12.5-16.3)
	Cl/Supp	796	5.65 (4.2-7.5)	80.2 (77.2-82.9)	14.2 (11.8-16.8)
	Trend *p*		0.20	0.53	0.85

Table 3 Changes (mean and SE) in cognitive scores from phase 3 to phase 5 by sex, age group and *APOE*-ε4 carrier status

Sex	Cognitive test	*APOE*	Mean change (SE) by age at phase 5		
			45-49	50-59	60-69
Men	Memory	Non-ε4	1.37 (0.15)	1.41 (0.10)	0.96 (0.16)
		ε4	1.67 (0.20)	1.44 (0.17)	0.76 (0.25)
	AH4	Non-ε4	1.54 (0.35)	1.48 (0.24)	0.53 (0.34)
		ε4	1.03 (0.42)	2.00 (0.39)	0.95 (0.59)
	Mill Hill	non-ε4	0.48 (0.11)	0.25 (0.08)	0.03 (0.13)
		ε4	0.26 (0.18)	0.43 (0.11)	0.33 (0.18)
	Phonemic fluency	non-ε4	0.83 (0.21)	0.55 (0.15)	-0.32 (0.21)
		ε4	0.88 (0.29)	0.62 (0.23)	0.12 (0.39)
	Semantic fluency	non-ε4	1.40 (0.17)	0.95 (0.14)	0.45 (0.19)
		ε4	1.29 (0.32)	1.06 (0.22)	0.60 (0.29)
Women	Memory	non-ε4	1.80 (0.33)	1.07 (0.19)	1.34 (0.26)
		ε4	1.84 (0.46)	1.07 (0.31)	0.57 (0.46)
	AH4	non-ε4	1.42 (0.58)	1.82 (0.44)	1.36 (0.52)
		ε4	1.32 (0.87)	1.85 (0.91)	0.39 (1.33)
	Mill Hill	non-ε4	0.53 (0.23)	0.31 (0.16)	0.55 (0.19)
		ε4	0.84 (0.31)	0.78 (0.32)	0.13 (0.34)
	Phonemic Fluency	non-ε4	0.44 (0.40)	0.76 (0.30)	-0.01 (0.43)
		ε4	0.45 (0.58)	-0.08 (0.50)	-0.03 (0.49)
	Semantic Fluency	**non-ε4**	**2.31 (0.42)**	1.66 (0.28)	**0.86 (0.27)**
		ε4**	**0.58 (0.74)***	0.75 (0.30)	**-0.31 (0.51)***

* p=0.030 and 0.040 for semantic fluency score (age groups 45-49 and 60-69)
** p=0.001 with age adjustment.