Running head: SERUM CHOLESTEROL LEVEL

Serum Cholesterol Level and Age Group as Moderators of the Relationship of APOE Genotype on Cognitive Performance

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Abstract

Genetic and health risk factors for Alzheimer's disease, such as apolipoprotein E-e4 (APOE-e4) and high cholesterol, have been investigated separately in relation to cognitive decline, yet few studies have examined domain-specific cognitive deficits associated with APOE (Small, Basun, & Bäckman, 1998) or how this may be moderated by serum cholesterol level. We examined whether APOE-e4 (n=121) and non-e4 carriers (n=347) showed significant mean level differences in four domains of neuropsychological measures. The sample included 468 normal, community-dwelling older adults (M=73.52, SD=8.26, range=59-95) from the Seattle Longitudinal Study who had complete data on all measures, including lipids, and APOE genotype. A two (APOE group: e4 carriers, non-e4 carriers) X two (age group: 58-74, 75-95) X two (total cholesterol level: low risk, borderline/high risk) MANOVA was calculated for each of the four domains, covarying for age, education, and gender. Significant genotype X age group interactions were observed for the global cognitive functioning domain ($p<.01$) and the memory recall/recognition domain ($p<.05$). For these domains, e4 carriers who were in the old-old age group performed more poorly on neuropsychological measures than those in any other group. Significant differences by cholesterol level ($p<.01$) were found only for the memory recall and recognition domain. Individuals with high cholesterol risk had higher scores on average for one of the memory recall and recognition measures, though this difference was not significant. Evaluating these differences in comparison to other lipid types may provide additional evidence.

Serum Cholesterol Level and Age Group as Moderators of the Relationship of APOE Genotype on Cognitive Performance

Some researchers have speculated that the relationships between apolipoprotein E epsilon-4 (APOE-e4) and cognitive impairment or Alzheimer's disease may be explained by elevated lipid levels (Chandra & Pandav, 1998; Stewart et al., 2001). Yet, few studies have examined lipid levels in relation to cognitive ability and APOE genotype in a normal aging population.

APOE appears to be involved in lipid metabolism given its function in the transport of very-low-density lipoprotein (VLDL; Heininger, 2000). Not yet know is whether one APOE genotype is more associated with particular lipid levels than other APOE genotypes. Some research has found that APOE-e2 is associated with lower lipoprotein levels and APOE-e4 is associated with higher or elevated lipoprotein levels, particularly for total cholesterol and low-density lipoprotein cholesterol (LDL-c; Davignon, Gregg, & Sing, 1988; Mahley, 1988; Notkola et al., 1998; Smith, 2000). Other research was not able to find an association between total cholesterol and triglyceride levels and e4 carrier status (Stewart et al., 2001). Similarly, a large population-based sample (N=2212; ages 65 and over) found increased total cholesterol associated with increased risk of AD, but not with e4 carrier status (Evans et al., 2000).

Several studies have found evidence of higher lipoproteins in those with probable or definite AD (Lehtonen & Luntonen, 1986; Giubilei et al., 1990; Bonarek et al., 2000; Lesser et al., 2001). However, the findings of Bonarek and colleagues (2000) found no statistically significant differences in lipoprotein levels (total cholesterol, LDL-c, protein plasma) between nondemented and demented groups; higher high-density lipoprotein cholesterol (HDL-c) was associated with a decreased risk of dementia. Bonarek et al. (2000) speculated that the negative

effects of LDL-c in AD (i.e., whereby LDL stimulates production of free radicals and thus oxidative stress) may be reduced by HDL-c (i.e., which protects against oxidative stress). In this situation, HDL-c acts as a protective factor which, when present, prevents the atherosclerotic and degenerative mechanisms in the pathogenesis of AD (Bonarek et al., 2000).

In addition to variations in the association between lipoprotein types and APOE allele combinations, there is also little research which has examined domain-specific cognitive deficits associated with APOE (Small, Basun, & Bäckman, 1998) or the strength of the effect of APOE in different age groups (Small et al., 2000). Some evidence for potential effects between areas of cognitive functioning, APOE, and age was found by researchers from The Mayo Clinic. Findings indicated an interaction for age by group for the APOE-e4 homozygotes and also for the non-e4 group on WAIS-R Digit Span, Auditory Verbal Learning Test (AVLT) Total score, and Trial 5 of the AVLT (Caselli et al., 1999). Research from the Cache County Study has found that there is a low association between e4 and AD for those in the old-old stage of adulthood (Breitner et al., 1999; Breitner & Miech, 2000). Findings from the Nun Study, which implicitly also involve age effects (age range 75-98), found that there was less decline on CERAD cognitive measures for those without an e4 allele than those with an e4 allele; those with one e4 allele were twice as likely to decline from intact status to impaired status (Riley et al., 2000).

For this study, we investigated serum total cholesterol and age group as moderators of the relationship of APOE, specifically e4 carriers and non-e4 carriers, over four domains of cognitive functioning. For comparison purposes, an additional lipid type, HDL-c was also examined using the same methods.

Method

Participants

The sample for this investigation was comprised of community-dwelling older adults (N=468) ages 59-95 (M=73.52, SD=8.26) from the larger Seattle Longitudinal Study (SLS; Schaie, 1996) who volunteered to complete a series of neuropsychological assessments in addition to their participation in at least one wave of SLS. The neuropsychological assessments were administered in order to study cognitive change in later adulthood with specific interest in detecting the early precursors to cognitive impairment. In this investigation, the sample includes individuals with one time point of data between 1997 and 2000, who had complete data on all measures for the four domains, complete lipid profiles, and had been genotyped for APOE.

Measures

These measures come primarily from the CERAD battery (Morris et al., 1989, 1993), but also include measures used in clinical practice for dementia diagnosis such as selected subtests from the WAIS-R and the WMS-R, the Mattis Dementia Rating Scale, and a memory measure often included in clinical trials called the Fuld Object Memory Test (Fuld, 1977).

Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975; Tombaugh & McIntyre, 1992) is a brief cognitive screening measure composed of 30-items which assess orientation to person, place, and time, as well as immediate and delayed recall, ability to follow simple instructions, concentration, constructional praxis, and language. It is included primarily because it is used in most all clinical research by varying levels of health professionals, though it is also a measure of the CERAD battery.

Verbal Fluency (Animals category; Borkowski, Benton, & Spreen, 1967; Welsh et al., 1994) measures verbal production, semantic memory, and language. Participants are given 60 seconds in which to name as many animals as they are able. Verbal fluency has been found to be sensitive in the detection of cognitive decline (Flicker, Ferris, & Reisberg, 1991; Berg, Danziger, & Storandt, 1984) and is also a measure from the CERAD battery.

Word List Memory Recall (immediate and delayed; Atkinson & Shiffrin, 1971; Cahn et al., 1995) is a measure of immediate and delayed memory recall. Participants are given a list of 10 words and asked to recall as many as they are able at three trials, followed by a delay.

Word List Recognition (Cahn et al., 1995; Mohs, Kim, Dunn, Davis, & Johns, 1986) is a measure of semantic memory recognition, where participants are to select the 10 words among a list which includes 10 distractor words.

Constructional Praxis (Rosen, Mohs, & Davis, 1984; Welsh et al., 1994) is a visuospatial measure requiring psychomotor skills and is untimed. It consists of four line drawings of two and three-dimensional figures which become increasingly complex (circle, diamond, rectangle, cube). Both immediate and delayed recall of the figures is included in these analyses.

Modified Boston Naming (Kaplan, Goodglass, & Weintraub, 1994) measures impairment in language functions and is helpful for identifying those with semantic, as well as phonetic difficulties. The test consists of 15, two-dimensional pictures which the participant is asked to name in 20 seconds. If not produced in that time period, the individual is given a semantic cue and given 20 seconds to respond. If the individual does not respond correctly, a second phonetic cue is given. If only the second phonetic cue is responded to correctly, then the response is recorded but no credit is given.

Subtests from the Wechsler Adult Intelligence Scale – Revised (WAIS-R; Wechsler, 1981) measure several abilities from both the verbal and performance sections of the test, which are used most often in clinical settings for the detection of cognitive functioning. Vocabulary and Comprehension subtests will not be included, as verbal ability is less associated with early cognitive decline or dementia.

Digit symbol substitution. This subtest measures visual-motor speed, coordination, accuracy, sustained effort, visual-lexical learning potential, and short-term working memory.

Block Design. This subtest measures general nonverbal intelligence, visual abstraction, planning and anticipation, manipulative dexterity, problem-solving potential, abstract form, and perceptual organization.

Digit Span. This subtest measures working-term auditory memory, concentration, freedom from distractibility, mental control, immediate trace memory sequencing, and ability to hold traces while verbalizing digits.

Wechsler Memory Scale – Revised (WMS-R; Wechsler, 1987; Cahn et al., 1995) is included in the SLS neuropsychology battery, but only includes the subtests of Logical Memory Tests I and II, as the other portions of the WMS-R content are covered in other parts of the Neuropsychological Battery. Logical Memory subtests measure immediate and delayed verbal recall to story passages that are read aloud.

Fuld Object Memory Test (Fuld, 1977) is a free recall measure of objects. Included in this investigation are the scores for retrieval and rapid verbal retrieval.

Mattis Dementia Rating Scale (DRS; Mattis, 1988) is routinely used in clinical settings to distinguish cognitively impaired persons from non-impaired persons. It has a total score and five subscale scores (Attention, initiation and perseveration, construction, conceptualization, and

memory). It has been found to be sensitive at distinguishing varying levels of AD (Vitaliano et al., 1984; Smith et al., 1994). Only the total score will be included in these analyses.

The neuropsychological assessments were grouped into four domains. These domains were global cognitive status, verbal ability, memory recall and recognition, and perceptual organization. The measures that were included under the Global Cognitive Status domain included the Mini-Mental Status Examination total score and the Mattis Dementia Rating Test. The Verbal Ability domain included the neuropsychological measures of Verbal Fluency, WAIS-R Comprehension and Vocabulary total scores, and the modified Boston Naming Test. The Memory Recall and Recognition domain included Word List Recognition and Recall, Constructional Praxis Recognition and Recall, WMS-R immediate and delayed recall, and FULD retrieval and rapid verbal retrieval measures. The Perceptual Organization domain included WAIS-R digit symbol, digit span, and block design.

APOE genotyping and lipids. Individuals who participated in the SLS Neuropsychology Study or who volunteered before participating in the 7th wave (also known as the 1998 replicate) of the larger SLS were invited to also participate in APOE genotyping and lipid levels assessment. APOE genotyping (e2/2, e2/3, e2/4, e3/3, e3/4, e4/4) and lipid profiles (total serum plasma cholesterol, low-density lipoprotein, high-density lipoprotein, very-low-density lipoprotein, and triglycerides) of whole blood and individual cell lines were processed through DNA cryopreservation after 20cc of blood was obtained by a trained phlebotomist. The blood was collected through a collaborative agreement with the Puget Sound Blood Program and analyzed at Northwest Lipid Research Laboratory of the University of Washington.

For this investigation, APOE genotypes are grouped into two types: non-e4 carriers (e2/2, e2/3, e3/3), and e4 carriers (e2/4, e3/4, e4/4). This grouping system is common and has been used in several previous studies by other investigators. Complete descriptive data by carrier group is provided in Table 1.

Statistical Analyses

A two (APOE group: e4 carriers, non-e4 carriers) X two (age group: young-old: 59-74, old-old: 75-95) X two (total cholesterol level: low risk, borderline/high risk) MANOVA was calculated for each of the four cognitive domains, covarying for age, education, and gender. All pairwise comparisons of the means were assessed with Tukey adjusted multiple comparisons (Milliken & Johnson, 2002; Tukey, 1991). The age group variable was calculated as integer age at each individual's actual time of testing without rounding. This was done to assure that age and the classification for age group were as accurate as possible for each individual.

To further confirm whether the initial findings for serum total cholesterol were found in other lipid types, an additional MANOVA model was specified, yet for high-density lipoprotein (HDL-c). While the larger study included several lipid types, the literature on HDL-c is much broader than that on triglycerides or very-low density lipoproteins. Previous investigations with individuals with one time point of neuropsychological data from this study have indicated that there is greater variability in the HDL-c for this sample than for LDL-c. For these reasons, HDL-c was selected as the comparison model to serum total cholesterol. A two (APOE group: e4 carriers, non-e4 carriers) X two (age group: young-old: 59-74, old-old: 75-95) X two (high-density lipoprotein: low risk, high risk) MANOVA was calculated for each of the four cognitive domains, covarying for age, education, and gender. Unlike serum total cholesterol, HDL-c is a

good cholesterol type for which higher numbers indicate lower risk. Risk was reverse coded to correct for this (low risk=61 mg/dL and over; high risk=0=60 mg/dL). Similar to the previous model for serum total cholesterol, age was calculated in the same way and Tukey adjusted multiple comparisons were also used for all pairwise mean-level, post-hoc comparisons.

Results

Person-specific characteristics

Several demographic groups were necessary in order to calculate the manovas for this study. Age group was comprised of young-old (59-74 years; n=251) and old-old (75-95 years, n=217). Education group included low education (7-12 years, n=110) and high education (13-20 years, n=358). The gender variable was divided into males (n=213) and females (n=255). This investigation included a dichotomous grouping of e4 carriers (n=121) and non-e4 carriers (n=347). Serum total cholesterol, also known as plasma cholesterol, was composed of two groups based on the National Cholesterol Education Program (2001) guidelines from the National Heart, Lung, and Blood Institute. These two groups were categorized as low risk (0-199 mg/dL; n=226) and high risk (200 mg/dL or above; n=242) for total cholesterol. As a comparison lipid type, high-density lipoprotein cholesterol (HDL-c) was also included in the analyses. The two groups for HDL-c were low risk (61 mg/dL and above; n=122) and high risk (0-60 mg/dL; n=346).

Mean-level differences

Statistically significant APOE by age group interactions were observed for the global cognitive functioning domain ($p<.01$) and the memory recall/recognition domain ($p<.05$). For both of these domains, e4 carriers who were in the old-old age group performed more poorly on

the neuropsychological measures than those in any other group ($p<.001$). Multivariate analysis of variance effects are presented for serum total cholesterol in Table 2. Mean-level differences for interactions and main effects for serum total cholesterol are presented in Tables 3.1-3.3.

Main effects were found for the relationship between APOE and each of the domains of global cognitive functioning ($p<.05$), memory recall/recognition ($p<.001$), and perceptual organization ($p<.05$). Main effects for the demographics of age group and also of education were found for all four domains ($p<.001$), whereas main effects for sex were found for all but the verbal ability domain. For serum total cholesterol, the young-old group performed better on all cognitive measures of the four domains ($p<.05$).

Significant differences for serum total cholesterol were found for only the memory recall/recognition domain ($p<.05$). Contrary to the expected direction, individuals with high cholesterol risk (total cholesterol of 200 mg/dl or higher) had higher scores on average for the Word List Recall measure ($p<.05$), as indicated by significant differences in Tukey adjusted means. However, this pattern was reversed for the significant interaction of genotype X age X serum total cholesterol on the FULD retrieval subtest ($p<.05$), where the e4 carriers who were in the old-old group and high risk for total cholesterol, performed most poorly of any group.

Results for HDL-c were comparable to those for serum total cholesterol for demographic and APOE main effects. However, the strength of the relationships was lessened for APOE: There were no main effects for HDL-c and only one significant interaction (for APOE by age for global cognitive status, indicating that e4 carriers in the old-old age group performed more poorly). Main effects were found for the relationship between APOE and the domains of global cognitive functioning ($p<.05$) and memory recall/recognition ($p<.05$). Main effects for the demographics of age group and also of education were found for all four domains ($p<.001$), whereas main

effects for sex were found for all but the perceptual organization domain. For HDL-c, the young-old group performed better on all cognitive measures of the four domains ($p<.05$). Multivariate analysis of variance effects are presented for HDL-c in Table 4. Mean-level differences for the main effects for HDL-c are presented in Tables 5.1-5.2.

Discussion

Several relationships were tested in this study. The literature on APOE polymorphism, lipid type, and age-related cognitive changes has been sparse, particularly in normal aging populations. Several studies have investigated one or two of the variables of interest, though few have examined more dynamic models or models which control for inherent demographics or person-specific characteristics.

By examining serum total cholesterol and high-density lipoprotein, we found that significant differences by the former was associated with the memory recognition and recall domain. More specifically, multivariate analysis indicated that individuals who were at risk for high total cholesterol had higher scores on the memory recognition and recall domain. This finding is contrary to what would be expected, that if high cholesterol is associated with Alzheimer's (e.g., Bonarek et al., 2000, Lesser et al., 2001), then cognitive performance for these high cholesterol risk individuals would seem to be lower. Yet, at the test-specific level, these mean-level differences between cholesterol risk and cognitive performance were rarely statistically significant using Tukey adjusted means (exception was with Word List Recall). Also at the univariate, test-specific level, there was a three-way interaction for APOE X Age X serum cholesterol for the FULD retrieval subtest. Individuals who were high risk, e4 carriers, and in the old-old group performed significantly more poorly on this measure of memory recall than high

risk non-e4 carriers in the young-old group. Given the interaction for both age group and allele type, it is not clear what drove the effect most. Further, since this effect was not found in any other domain, one could argue that the omnibus F effect observed for the memory domain and by affiliation the univariate test-specific results are not robust enough to offer a clear interpretation as to the effect of cholesterol on APOE and cognitive functioning.

Similar to the work of prior investigators, it might also be said that the data lends itself to risk assessment using an alternative analysis method, such as multinomial logistic regression. By having complete data on all measures, this data might also reveal more intuitively appealing findings with structural equation modeling, which implicitly has fewer assumptions to maintain. Still, the findings here are supportive of previous work on the relationships between APOE and cognitive functioning, particularly that individuals with at least one e4 allele show more decline on cognitive measures than do individuals without an e4 allele (Hofer et al., 2002; Hyman et al., 1996; O'Hara et al., 1998; Riley et al., 2000), while others have found significant age group effects on WAIS-R digit span and memory recall measures (Casselli et al., 1999).

The finding that individuals in the old-old age group performed more poorly on neuropsychological measures than those in the young-old age group is congruent with past research (e.g., Libon et al., 1994; Mazaux et al., 1995) and even for studies like this one where the measures were largely untimed. Reasons for age differences have included the dual processing for encoding and storage, required during memory tasks (Bäckman, Small, & Wahlin, 2001), as well as individual variability in the context of genetic influences (Harris, Pedersen, McClearn, Plomin, & Nesselroade, 1992), and increased perservations with age (Lezak, 1995).

Despite supportive evidence for the relationships between APOE and cognition and age group, there are still unanswered questions in regard to cholesterol risk and cognitive

impairment. With no interactions between total cholesterol or HDL-c and APOE for the cognitive domains in this investigation, it is unknown how these are associated, possibly through or in concert with another moderating or mediating variable. Only additional analyses will provide clarity as to these associations and the additional risk that lipids may manifest in cognitive impairment, characteristic of Alzheimer's disease.

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Table 1.

Person-specific characteristics by APOE allele type.

Variable	APOE-non-e4 carriers		APOE-e4 carriers	
	Young-old (n=182)	Old-old (n=165)	Young-old (n=69)	Old-old (n=52)
Years of age	67.08 (4.51)	81.10 (4.80)	67.38 (4.62)	80.19 (4.42)
% Female	56.6	52.1	55.1	53.8
Years of Education	15.47 (2.68)	14.57 (2.89)	15.99 (2.69)	14.73 (2.74)
MMSE Total Score	28.76 (1.37)	28.11 (1.86)	28.97 (1.55)	27.02 (2.64)

Note. Years of age, years of education, and MMSE Total Scores are provided as Mean (SD). The allelic frequencies for the original six polymorphisms across the whole sample (N=468) are as follows: e2/e2=2 (0.4%), e3/e2=61(13.0%), e3/e3=284 (60.7%), e4/e2=14 (3.0%), e4/e3=97 (20.7%), e4/e4=10 (2.1%). For this study, APOE allele types were grouped into two types (74.1% and 25.9% of the total sample, respectively): non-e4 carriers (e2/e2, e3/e2, e3/e3), and e4 carriers (e4/e2, e4/e3, e4/e4).

Table 2.

Serum Total Cholesterol: Multivariate analyses of variance F ratios for mean-level differences for the 4 cognitive domains (N=468)

	MANOVA			
	Verbal Ability	Global Cognitive	Memory Recall/Recognition	Perceptual Organization
Variable	F(5, 454)	F(2, 459)	F(8, 451)	F(3, 456)
APOE (E)	--	3.71*	5.01***	3.11*
Age Group (A)	13.10***	29.22***	12.67***	38.82***
Total Cholesterol (P)	--	--	2.18*	--
ExA	--	6.63**	2.43*	--
ExP	--	--	--	--
ExAxP	--	--	--	--
AxP	--	--	--	--
Sex	--	7.40***	8.85***	3.05*
Education	25.13***	11.04***	5.29***	12.27***

Note. F ratios are Wilks' approximation of Fs. MANOVA=multivariate analysis of variance. Risk groups for serum total cholesterol were low risk (0-199 mg/dL; n=226) and high risk (200 mg/dL and above; n=242).

*p < .05. **p < .01. ***p < .001.

Table 3.1

Univariate Tests on APOE allele type (non-e4, e4), age group (young-old, old-old), and serum total cholesterol (low/high risk), covarying for education and gender, for significant between factors for Global Cognitive (N=468)

Domain	Variable and source	DF effect	SS Type III	F	Tukey Adjusted Means
Global Cognitive					
	MMSE				
	Between Factors (Overall)	9	213.13	7.90***	--
	Allele Type (AT)	1	19.12	6.38*	no4=28.44, e4=27.98*
	Age Group (A)	1	117.03	39.06***	young=28.80, old=27.62***
	AT*A	1	35.72	11.92***	1) non-e4, young=28.71 2) non-e4, old=28.17 3) e4, young=28.86 4) e4, old=27.07 1, 2*; 2, 4***; 3, 4***
	Education	1	40.41	13.49***	
	Sex	1	20.12	6.72**	
	Residual Error	458	1372.18	--	--
	Mattis				
	Between Factors (Overall)	1	1863.32	9.48***	
	Allele Type (AT)	1	142.83	6.54*	no4=138.95, e4=137.67*
	Age Group (A)	1	607.73	27.84***	young=139.65, old=136.97***
	Education	1	387.20	17.73***	
	Sex	1	294.61	13.49***	
	Residual Error	458	9999.58	--	--

Note. Only statistically significant between factors are listed above to minimize space.

*p < .05. **p < .01. ***p < .001.

Table 3.2

Univariate Tests on APOE allele type (non-e4, e4), age group (young-old, old-old), and serum total cholesterol (low/high risk), covarying for education and gender, for significant between factors for Memory Recall and Recognition (N=468)

Domain	Variable and source	DF effect	SS Type III	F	Tukey Adjusted Means
Memory Recall & Recognitn					
	Word List Recall				
	Between Factors (Overall)	9	493.26	13.39***	--
	Allele Type (AT)	1	100.52	24.56***	non-e4=7.63, e4=6.56***
	Age Group (A)	1	194.81	47.60**	young=7.85, old=6.33***
	AT*A	1	23.30	5.69*	1) non-e4, young=8.13 2) non-e4, old=7.13 3) e4, young=7.57 4) e4, old=5.54 1, 2***; 2, 4***; 3, 4***
	Plasma	1	18.92	4.62*	Low risk=6.86, high risk=7.32*
	Education	1	20.37	4.98*	
	Sex	1	98.98	24.19***	
	Residual Error	458	1874.49	--	--
	Word List Recogn				
	Between Factors (Overall)	9	26.55	7.11***	
	Allele Type (AT)	1	9.65	23.23***	non-e4=9.84, e4=9.50***
	Age Group (A)	1	13.49	32.48***	young=9.87, old=9.47***
	AT*A	1	6.81	16.41***	1) non-e4, young=9.90 2) non-e4, old=9.78 3) e4, young=9.84 4) e4, old=9.16 1, 4***; 2, 4***; 3, 4***
	Residual Error	458	190.12	--	--
	Constructional Praxis Delayed				
	Between Factors (Overall)	9	440.70	7.70***	
	Allele Type (AT)	1	43.86	6.90**	non-e4=8.01, e4=7.30**
	Age Group (A)	1	248.05	39.01	young=8.51, old=6.80***
	Education	1	58.23	9.16**	
	Residual Error	458	2911.96	--	--

Note. Only statistically significant between factors are listed above to minimize space. Memory Recall and Recognition is the full name of this domain.

*p < .05. **p < .01. ***p < .001.

Table 3.2 (continued)

Univariate Tests on APOE allele type (non-e4, e4), age group (young-old, old-old), and serum total cholesterol (low/high risk), covarying for education and gender, for significant between factors for Memory Recall and Recognition (N=468)

Domain	Variable and source	DF effect	SS Type III	F	Tukey Adjusted Means
Memory Recall & Recognitn					
	Constructional Praxis Immediate				
	Between Factors (Overall)	9	17.91	2.30*	--
	Education	1	4.72	5.45*	--
	Residual Error	458	396.32	--	--
	WMSR Immediate				
	Between Factors (Overall)	9	3961.76	8.24***	
	Allele Type (AT)	1	389.46	7.29**	non-e4=27.22, e4=25.11**
	Age Group (A)	1	1401.75	26.24***	young=28.20, old=24.13***
	Education	1	956.64	17.91***	
	Residual Error	458	24466.54	--	--
	WMSR Delayed				
	Between Factors (Overall)	9	6157.44	9.55***	
	Allele Type (AT)	1	492.54	6.87**	non-e4=21.71, e4=19.33**
	Age Group (A)	1	2848.83	39.75***	young=23.42, old=17.61***
	Education	1	1094.45	15.27***	
	Residual Error	458	32823.76	--	--
	FULD Rapid Verbal Retrieval				
	Between Factors (Overall)	9	26819.56	18.84***	
	Age Group (A)	1	8876.77	56.12***	young=69.24, old=58.99***
	Education	1	4632.66	29.29***	
	Sex	1	6279.32	39.70***	
	Residual Error	458	72444.41	--	--
	FULD Retrieval				
	Between Factors (Overall)	9	2733.72	10.60***	
	Allele Type (AT)	1	198.84	6.94**	no4=43.41, e4=41.89**
	Age Group (A)	1	1685.25	58.83***	young=44.88, old=40.42***
	AT*A*P	1	114.73	4.01*	Non-e4 young high risk=45.13, E4, old, high risk=37.34***
	Education	1	120.60	4.21*	
	Sex	1	128.01	4.47*	
	Residual Error	458	13119.20	--	--

Note. Only statistically significant between factors are listed above to minimize space. P=serum total cholesterol. Memory recall and recognition is the full name of this domain. *$p < .05$. **$p < .01$. ***$p < .001$.

Table 3.3

Univariate Tests on APOE allele type (non-e4, e4), age group (young-old, old-old), and serum total cholesterol (low/high risk), covarying for education and gender, for significant between factors for Perceptual Organization (N=468)

Domain	Variable and source	DF effect	SS Type III	F	Tukey Adjusted Means
Perceptual Organizatn					
	WAISR Block Design				
	Between Factors (Overall)	9	10505.07	16.88***	--
	Age Group (A)	1	5223.66	75.56***	Young=31.19, old=23.33***
	Allele Type*P	1	309.19	4.47*	ns
	Education	1	1646.02	23.81***	
	Sex	1	318.03	4.60*	
	Residual Error	458	31661.61	--	--
	WAISR Digit Span				
	Between Factors (Overall)	9	640.08	4.63***	
	Allele Type (AT)	1	101.86	6.63*	no4=15.65, e4=14.58*
	Age Group (A)	1	214.91	13.95***	young=15.91, old=14.32***
	Education	1	229.84	14.95***	
	Residual Error	458	7040.86	--	--
	WAISR Digit Symbol				
	Between Factors (Overall)	9	18626.81	20.22***	
	Age Group (A)	1	9302.04	90.86***	young=48.05, old=37.56***
	Education	1	2120.75	20.71***	
	Residual Error	458	46890.17	--	--

Note. Only statistically significant between factors are listed above to minimize space. P=serum total cholesterol. Perceptual organization is the full name of this domain.

*p < .05. **p < .01. ***p < .001.

Table 4.

High-density lipoprotein cholesterol: Multivariate analyses of variance F ratios for mean-level differences for the 4 cognitive domains (N=468)

	MANOVA			
	Verbal Ability	Global Cognitive	Memory Recall/Recognition	Perceptual Organization
Variable	F(5, 454)	F(2, 457)	F(8, 451)	F(3, 456)
APOE (E)	--	3.97*	3.55***	2.39^
Age Group (A)	11.95***	19.22***	9.76***	25.04***
HDL-c (H)	--	--	2.18*	2.58^
ExA	--	3.17*	1.81^	--
ExH	--	--	--	--
ExAxH	--	--	--	--
AxH	--	--	--	--
Sex	2.70*	5.45**	8.68***	--
Education	24.36***	10.66***	5.12***	12.23***

Note. F ratios are Wilks' approximation of Fs. MANOVA=multivariate analysis of variance. HDL-c=High-density lipoprotein cholesterol. Risk groups for HDL-c are low risk (61 mg/dL and above; n=122) and high risk (0-60 mg/dL; n=346).

^ $p < .10$

*$p < .05$. **$p < .01$. ***$p < .001$.

Table 5.1

Univariate Tests on APOE allele type (non-e4, e4), age group (young-old, old-old), and HDL-c (low/high risk), covarying for education and gender, for significant between factors for Global Cognitive (N=468)

Domain	Variable and source	DF effect	SS Type III	F	Tukey Adjusted Means
Global Cognitive					
	MMSE				
	Between Factors (Overall)	9	222.52	8.31***	
	Age Group (A)	1	104.50	35.12***	young=28.85, old=27.60***
	AT*A	1	18.00	6.05*	1) non-e4, young=28.79 2) non-e4, old=28.05 3) e4, young=28.92 4) e4, old=27.15 1, 2**; 2, 4***; 3, 4***
	Education	1	40.52	13.62***	
	Sex	1	15.76	5.30*	
	Residual Error	458	1362.79	--	--
	Mattis				
	Between Factors (Overall)	1	1854.89	9.43***	
	Allele Type (AT)	1	161.69	7.40**	no4=139.21, e4=137.68**
	Age Group (A)	1	385.00	17.62***	young=139.64, old=137.24***
	Education	1	365.77	16.74***	
	Sex	1	213.92	9.79**	
	Residual Error	458	10008.00	--	--

Note. Only statistically significant between factors are listed above to minimize space. HDL-c=High-density lipoprotein cholesterol.

*p < .05. **p < .01. ***p < .001.

Table 5.2

Univariate Tests on APOE allele type (non-e4, e4), age group (young-old, old-old), and HDL-c (low/high risk), covarying for education and gender, for significant between factors for Memory Recall and Recognition (N=468)

Domain	Variable and source	DF effect	SS Type III	F	Tukey Adjusted Means
Memory Recall & Recognitn					
	Word List Recall				
	Between Factors (Overall)	9	468.88	12.57***	--
	Allele Type (AT)	1	62.07	14.97***	non-e4=7.58, e4=6.62***
	Age Group (A)	1	146.26	35.28***	young=7.83, old=6.36***
	AT*A	1	19.80	4.78*	1) non-e4, young=8.05 2) non-e4, old=7.11 3) e4, young=7.63 4) e4, old=5.62 1, 2***; 2, 4***; 3, 4***
	Education	1	20.02	4.83*	
	Sex	1	115.54	27.87***	
	Residual Error	458	1898.87	--	--
	Word List Recogn				
	Between Factors (Overall)	9	24.52	6.50***	
	Allele Type (AT)	1	6.48	15.45***	non-e4=9.82, e4=9.51***
	Age Group (A)	1	9.15	21.81***	young=9.85, old=9.48***
	AT*A	1	3.89	9.27**	1) non-e4, young=9.88 2) non-e4, old=9.78 3) e4, young=9.82 4) e4, old=9.21 1, 4***; 2, 4***; 3, 4***
	Residual Error	458	192.15	--	--
	Constructional Praxis Delayed				
	Between Factors (Overall)	9	454.13	7.97***	
	Allele Type (AT)	1	49.03	7.75**	non-e4=8.00, e4=7.16**
	Age Group (A)	1	173.38	27.40***	young=8.38, old=6.78***
	Education	1	60.41	9.55**	
	Residual Error	458	2898.53	--	--

Note. Only statistically significant between factors are listed above to minimize space. Memory recall and recognition is the full name of this domain.

*p < .05. **p < .01. ***p < .001.

Table 5.2 (continued)

Univariate Tests on APOE allele type (non-e4, e4), age group (young-old, old-old), and HDL-c (low/high risk), covarying for education and gender, for significant between factors for Memory Recall and Recognition (N=468)

Domain	Variable and source	DF effect	SS Type III	F	Tukey Adjusted Means
Memory Recall & Recognitn					
	Constructional Praxis Immediate				
	Between Factors (Overall)	9	16.62	2.13*	--
	AT*A*H	1	3.87	4.46*	ns
	Education	1	4.75	5.48*	--
	Residual Error	458	397.61	--	--
	WMSR Immediate				
	Between Factors (Overall)	9	3751.34	7.74***	
	Allele Type (AT)	1	387.83	7.20**	non-e4=27.48, e4=25.10**
	Age Group (A)	1	966.56	17.94***	young=28.20, old=24.40***
	Education	1	927.25	17.21***	
	Residual Error	458	24676.96	--	--
	WMSR Delayed				
	Between Factors (Overall)	9	5825.31	8.94***	
	Allele Type (AT)	1	400.28	5.53*	non-e4=21.90, e4=19.49**
	Age Group (A)	1	2139.39	29.55***	young=23.52, old=17.87***
	Education	1	1063.71	14.69***	
	Residual Error	458	33155.88	--	--
	FULD Rapid Verbal Retrieval				
	Between Factors (Overall)	9	26124.28	18.18***	
	Age Group (A)	1	7135.51	44.68***	young=69.54, old=59.23***
	Education	1	4566.74	28.60***	
	Sex	1	5539.88	34.69***	
	Residual Error	458	73139.69	--	--
	FULD Retrieval				
	Between Factors (Overall)	9	2563.06	9.81***	
	Allele Type (AT)	1	192.06	6.62*	non-e4=43.47, e4=41.80**
	Age Group (A)	1	1410.82	48.62***	young=44.93, old=40.35***
	AT*A	1	123.62	4.26*	1) non-e4, young=45.10 2) non-e4, old=41.85 3) e4, young=44.76 4) e4, old=38.83 1, 2***; 2, 4**; 3, 4***
	Education	1	129.72	4.47*	
	Residual Error	458	13289.87	--	--

Note. Only statistically significant between factors are listed above to minimize space. HDL-c=high density lipoprotein cholesterol. Memory recall and recognition is the full name of this domain. *$p < .05$. **$p < .01$. ***$p < .001$.