Apolipoprotein E allele combinations, plasma lipid profiles, and cognitive decline in a sample from the Seattle Longitudinal Study.

Joel Kennet, Ph.D.
K. Warner Schaie, Ph.D.

The Pennsylvania State University

Abstract

373 older participants (mean age in 1991 = 67) in the Seattle Longitudinal Study (SLS) were tested to determine apolipoprotein E (ApoE) genotype and plasma lipid levels. Psychometric test data from a majority of these participants were available from the 1984 and 1991 collection waves, and several were also tested in the 1998 wave. Three-timepoint data on the 5 Primary Mental Abilities (PMA's, Thurstone & Thurstone, 1949), and factor trend scores from a large battery of pencil-and-paper tests administered in 1984 and 1991 were analyzed for their relation to allele combination. In addition, raw PMA scores obtained in 1998 and ApoE allele combinations were examined for their concurrent relations to plasma lipid levels. ANCOVA with repeated measures, correcting for age and education, revealed a significant time x allele type interaction on PMA Reasoning and Intellectual ability. Seven-year changes in the factor scores for Spacial orientation and Numerical ability were also affected by allele type. PMA Reasoning scores in 1998 obtained a small but significant positive correlation with HDL cholesterol level. However, allele type was unrelated to HDL level, while it was related to overall cholesterol and LDL cholesterol levels.

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Introduction

The past few years have witnessed exciting findings by geneticists regarding the relation of the apolipoprotein E allele combination with the likelihood and time of onset of Alzheimer's Disease (AD). Specifically, the presence of the epsilon 4 allele has been linked to the disease in a dose-dependent fashion. Moreover, the presence of the epsilon 2 allele has been linked to lower LDL cholesterol levels and lower total/HDL cholesterol ratios, which may in turn be related to health outcomes that influence the severity of age-related cognitive decline and possibly the likelihood of diagnosis with dementia.

This study utilizes data from the Seattle Longitudinal Study (a long-term study of adult cognitive performance), combined with recently-obtained blood samples from a portion of the participants in that study. By analyzing the combination of alleles possessed by older individuals in the study, as well as plasma lipid profiles, we were able to examine patterns of cognitive decline as they related to allele combination, as well as concurrent relations between lipid levels and cognitive performance. In so doing, we identified specific cognitive abilities that were measurably affected by allele type in a normal, healthy population of older individuals. We were also able to examine the relationship between ApoE genotypes, cholesterol levels, and cognitive performance in later life.

Data continue to be collected in this study, so the results presented in this poster should be considered preliminary. When the study is completed, approximately twice as many participants will have had their blood drawn and tested. Moreover, information from autopsies performed on several of these individuals will become available in the coming years, thus allowing for confirmation of prior dementia diagnoses.

Method

Participants 373 individuals in older age groups (mean age in 1991 = 67.1; 53.9% female) in the Seattle Longitudinal Study (SLS) were given blood tests, allowing for determination of ApoE allele combination and plasma lipid levels. Participants in the SLS have been community-dwelling adults randomly selected from each 7-year age stratum of the membership of a metropolitan health maintenance organization.

The following frequencies (percentages) for ApoE allele combination were obtained: epsilon 2/2 = 1 (.27%), epsilon 3/2 = 49 (13.14%), epsilon 3/3 = 226 (60.59%), epsilon 4/2 = 9 (2.41%), epsilon 4/3 = 80 (21.45%), epsilon 4/4 = 8 (2.14%). These figures are roughly comparable to those obtained in other European and North American populations reported upon in other studies. Distributions of lipid counts also tended to be comparable to other, similar sample distributions. In general, participants in the SLS, especially returnees, tend to be higher-educated than the population at large. This particular sub-sample from the SLS completed a mean of 14.8 years of education.

Materials All participants received a battery of pencil-and-paper psychometric tests at each testing occasion (1984, 1991, 1998). The battery, when factored into its principal components, measures the primary cognitive abilities of inductive reasoning, spacial orientation, numerical ability, verbal ability, perceptual speed, and verbal memory. For a complete list of the specific measures employed, see Schaie (1996). For the purposes of this study, we will be examining raw subscores and composites obtained from the test of Primary Mental Abilities (PMA; Thurstone & Thurstone, 1949), which covers the domains of Reasoning, Space, Number, Verbal meaning, and Word fluency, along with standardized factor scores for the earlier-mentioned set of abilities. Data from the 1998 testing wave are incomplete; the present analyses are on 3-timepoint data from the PMA, and 7-year trend scores (1991 minus 1984) on the remainder of the psychometric measures.

Procedure The test battery mentioned above was administered to the participants on each of the three testing occasions (1984, 1991, and 1998). Testing occurred in small groups, each requiring two sessions. Total testing time was approximately 5 hours. Administration of the tests took place in a standard format, using a trained tester and a proctor. The group testing sessions took place in familiar locations close to the homes of the participants.

Design The present study utilizes analyses of covariance (ANCOVAs), controlling for participant age and educational level, to examine the effect of ApoE allele combination on a variety of measures of cognitive performance or change in cognitive performance. Other studies have treated ApoE allele combination as a frequency measure, with each possible allele (epsilon 2, 3, or 4) obtaining a value of 0, 1, or 2. In this study, ApoE allele combination is treated as a categorical variable with 5 groups (the epsilon 2/2 group was omitted due to its very low frequency), in order to facilitate interpretation of results. In addition to ANCOVAs, correlational analyses are used to examine concurrent relationships among plasma lipid levels, ApoE genotypes, and cognitive test scores.

Results

Table 1 consists of a summary of the results of the ANCOVA's on the 7-year trend scores, treating ApoE allele combination as a between -groups factor and covarying age and educational level. Among the 7-year change scores, significant differences were attributable to genotype on the Identical Pictures test (Ekstrom, French, Harman, & Derman, 1976), and the Spacial orientation and Numerical ability factor scores.

Post-hoc comparisons, using Tukey's honestly significant difference (HSD) test for unequal sample sizes, were conducted for each variable on which a significant effect obtained. No significant differences were obtained in the post-hoc test on the Identical Pictures test. For the factor scores, the epsilon 4/4 group was significantly different from the epsilon 4/2 group ($p < .05$) in Spacial orientation and in Numerical ability. Table 2 contains the means from the above analyses, and Figure 1 plots these means graphically.

The ANCOVAs with repeated measures on the 3-timepoint PMA data, again covarying age group and educational level, revealed a significant time x allele-type interaction on the Reasoning subtest and on the Intellectual Ability composite measure. Figure 2 plots mean scores obtained by each allele-type group at each timepoint on the PMA Reasoning subtest, and Figure 3 plots the composite measure.

A second set of analyses was concerned with the relation between ApoE allele combinations and plasma lipid levels. One-way ANOVAs were calculated, with allele combination as the between groups factor, on overall cholesterol, triglycerides, VLDL cholesterol, LDL cholesterol, and HDL cholesterol levels. Significant effects were observed on overall cholesterol (F 4, 356 = 6.58, $p < .001$), and on LDL cholesterol level (F 4, 356 = 6.86, $p < .001$). Table 3 provides summary statistics from this set of analyses.

Post-hoc tests (Tukey's HSD for unequal sample sizes) for group mean differences in overall cholesterol level showed significant differences between the ApoE allele groups epsilon 3/2 and 3/3, and between epsilon 3/2 and 4/3. The same pattern of differences was observed in the post-hoc tests for LDL cholesterol level. Table 4 contains the group means from this analysis.

Turning to the findings regarding plasma lipids and cognitive performance, correlations were calculated between cholesterol counts and the PMA scores obtained in the 1998 data collection wave. Table 5 contains these correlations. The majority of these are near zero, with the sole exception being the small, positive correlation obtained between HDL cholesterol and PMA Reasoning ($r = .13$, $p < .05$).

Discussion

Relationships among ApoE genotypes, plasma lipid levels, and cognitive test performance were investigated on a relatively small sample of older individuals participating in the SLS. As further data are collected, these relationships should become more clearly defined. At present, the discussion of these findings should be considered speculative.

Probably the most important result out of those described above is that ApoE genotyping can predict decline in cognitive test performance *prior* to diagnosis with dementia. Measurable differences in decline occurred in several cognitive ability domains. It has been noted that ApoE genotyping is far from perfect in its capacity to predict AD. However, particular patterns of decline in cognitive test performance might possibly be used as a cue to alert professionals of the potential need for further examination, including genotyping. Along these lines, it might be suggested that cognitive screening over the course of several years in later life might be utilized as a prerequisite to genotyping in order to reduce costs and potentially to produce more accurate predictions of likelihood and time until onset of AD than were possible with genotyping alone. The data to be collected in the future for this study should help to determine whether or not this might be the case.

Regarding the influence of allele type on plasma lipids, differences between groups were found only in the cases of overall cholesterol and LDL cholesterol levels. Among the findings relating plasma lipid levels to cognitive performance, we found no association except in the case of HDL cholesterol, which correlated positively with PMA Reasoning scores, and approached a significant correlation with Word fluency. Thus, the proposed role of plasma lipids as intermediating in the relationship between genotypes and change in cognitive performance in later life is questioned.

Table 1. ANCOVA results: Effect of allele type on 7-year change scores, controlling for age and education.

Dependent Variable	Mean Sqr Effect	Mean Sqr Error	F (4,239)	p
Identical Pictures	63.00	25.03	2.52	.04*
Number Comparison	7.60	18.62	.41	.80
Finding A's	16.32	31.33	.52	.72
Inductive Reasoning†	26.93	11.22	2.40	.05*
Spacial Orientation†	57.81	20.77	2.78	.03*
Perceptual Speed†	15.77	11.76	1.34	.26
Numerical Ability†	48.39	14.82	3.27	.01**
Verbal Ability†	2.02	11.36	.18	.95
Verbal Memory†	20.21	42.68	.47	.75

* $p \leq .05$
** $p \leq .01$

† Denotes factor score change, as opposed to change on individual tests.

Table 2. Allele-type group mean changes, over 7 years, on cognitive performance measures.

Allele type	3/2	3/3	4/2	4/3	4/4
Identical Pictures	-1.05	-1.52	5.00	-.29	-.80
Number Comparison	-.28	-.67	-.67	-1.25	-1.60
Finding A's	-.85	-.12	.00	.74	.00
Inductive Reasoning	.08	-.50	1.17	-.82	-4.00
Spacial Orientation	-1.36	-.96	1.83*	-.74	-6.60*
Perceptual Speed	-.41	-.87	2.50	-.65	-1.40
Numerical Ability	-1.36	-1.87	.17*	-2.16	-7.00*
Verbal Ability	.00	.14	.67	-.25	.20
Verbal Memory	-.90	-.41	3.33	-.61	-.80

* Denotes significant group mean difference, using Tukey's HSD test for unequal n.

Table 3. ANOVA results: Effect of allele type on plasma lipid levels.

Dependent Variable	Mean Sqr Effect	Mean Sqr Error	F (4,356)	p
Overall Cholesterol	7847.74	1192.30	6.58	.00**
Triglycerides	2840.48	6112.96	.46	.76
VLDL Cholesterol	115.49	244.52	.47	.76
LDL Cholesterol	6675.38	973.65	6.86	.00**
HDL Cholesterol	43.94	235.24	.19	.94

** $p < .01$

Table 4. Allele-type group mean plasma lipid levels.

Allele type	3/2	3/3	4/2	4/3	4/4
Overall Cholesterol	177.68*†	205.07*	198.00	204.62†	213.00
Triglycerides	133.00	142.80	116.11	145.68	148.90
VLDL Cholesterol	26.59	28.52	23.22	29.19	29.87
LDL Cholesterol	98.76*†	124.02*	118.44	122.74†	133.50
HDL Cholesterol	51.94	52.52	56.00	52.33	50.00

*, † Denote significant group mean differences, using Tukey's HSD test for unequal n.

Table 5. Correlations between plasma lipid levels and PMA performance measures.

	Overall Cholest-erol	Trigly-cerides	VLDL Chol.	LDL Chol.	HDL Chol.
Reasoning	.00	-.01	-.01	-.05	.13*
Space	-.06	-.03	-.04	-.04	-.03
Verbal	.01	.03	.03	-.04	.08
Number	-.06	-.02	-.02	-.06	-.02
Word Fluency	.03	.00	-.00	-.03	.11†
Intellectual Ability	-.04	-.01	-.02	-.07	.06
Educational Aptitude	.00	.02	.02	-.04	.10†

† $p < .10$
* $p < .05$

Figure 1. Comparison of allele-type groups on 7-year change in cognitive performance.

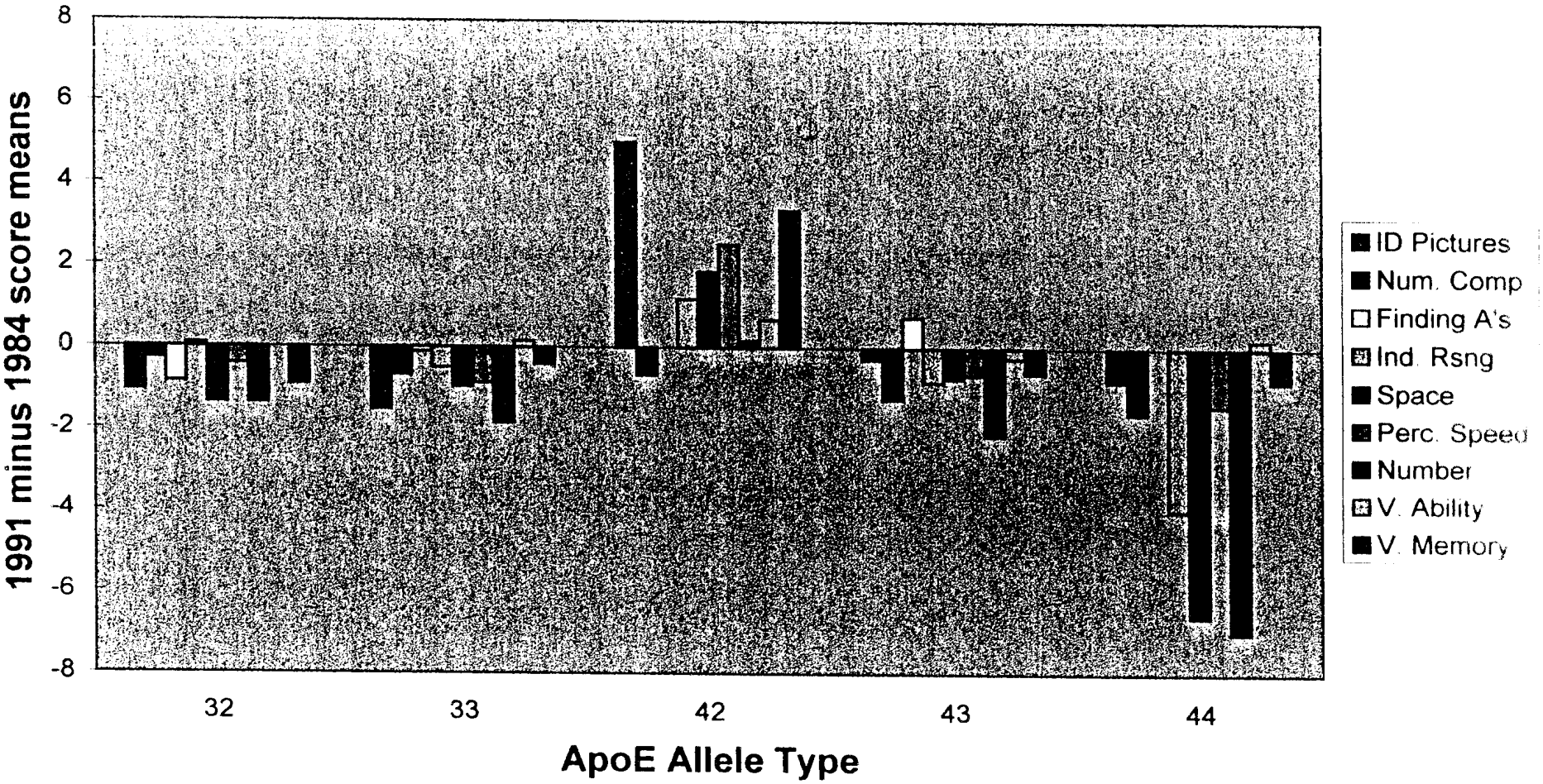

Figure 2. Change in Mean PMA Reasoning Scores by Allele Combination.

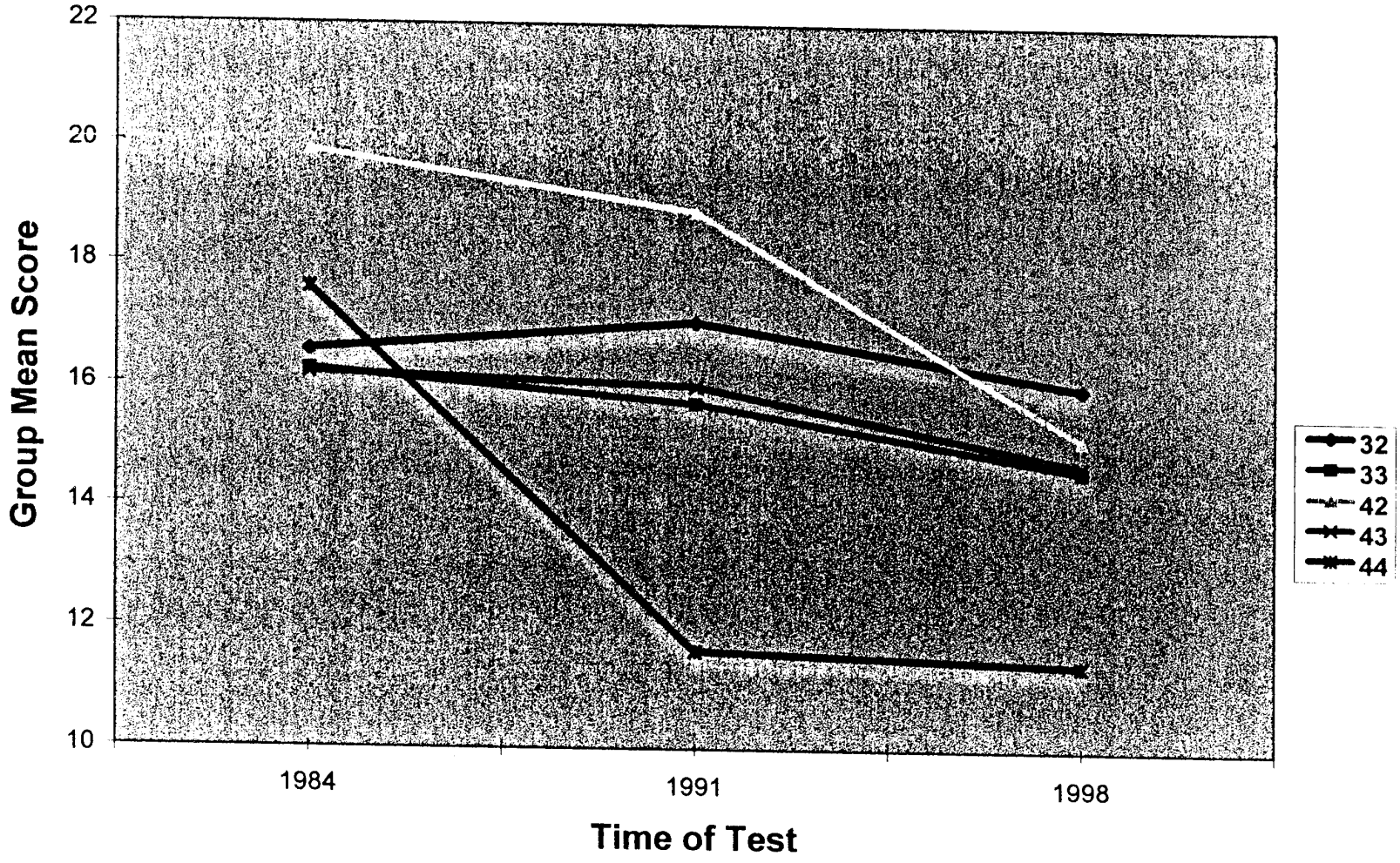

Figure 3. Change in PMA Intellectual Ability Composite Means by Allele Combination.