The apolipoprotein E ε4 allele-dependent relationship between serum lipid levels and cognitive function: A population-based cross-sectional study

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Abstract
Background: Till now, the effect of serum lipid levels on cognitive function is still controversial. The apolipoprotein E ε4 (APOE) allele is the most critical genetic risk factor for Alzheimer’s disease and cognitive impairment. Additionally, APOE ε4 allele has a major impact on lipid metabolism. The aim of this study was to investigate the APOE genotype-dependent relationship between peripheral serum lipid levels and cognitive impairment.

Method: 1273 subjects aged 40-86 years participated in this cross-sectional study. Serum lipid levels and the APOE genotype were detected. Mini-mental state examination was used to diagnose the cognitive impairment or not. Univariate and multivariate analyses were used to analyze the relationships between APOE genotype, serum lipid levels and cognition function.

Result: After controlling for all possible covariates, a significant interaction between low serum high density lipoprotein and the APOE ε4 allele on cognitive impairment (Wald’s chi-square=4.269, df=1, OR=20.094, p=0.039) (Table 1) was found in the total participants. In APOE ε4 carriers, low serum high density lipoprotein was positively associated with cognitive impairment (Wald’s chi-square=8.200, df=1, OR=60.335, p=0.004) (Table 2), and serum high density lipoprotein levels were positively correlated with Mini-mental state examination score (r=0.217, df=176, p=0.004). There was no significant correlation between serum total cholesterol, low-density lipoprotein, triglycerides levels and cognitive impairment in either the total participants or APOE ε4 carriers/non-carriers. (Figure 1).

Conclusion: APOE ε4 carriers, but not non-carriers, with lower serum high-density lipoprotein had a higher prevalence of cognitive impairment and a lower Mini-mental state examination score. These results suggest that the APOE ε4 allele may affect the relationship between serum lipid levels and cognitive impairment. However, the specific mechanism needs to be further elucidated.
**FIGURE 1**

**TABLE 1**

| Table 1. The relationships between serum lipid parameters and cognitive impairment with binary logistic regression in the total samples |
|---------------------------------|
|                                | B  | SE  | Wald's chi-square | OR   | 95%CI | P-value |
| Model 1                         |    |     |                  |      |       |         |
| High TC                        | -0.195 | 0.222 | 0.771          | 0.823 | 0.533-1.271 | 0.380 |
| High TG                        | -0.167 | 0.239 | 0.487          | 0.846 | 0.529-1.353 | 0.485 |
| High LDL-c                     | -0.062 | 0.312 | 0.039          | 0.940 | 0.511-1.732 | 0.843 |
| Low HDL-c                      | 0.595 | 0.655 | 0.824          | 1.813 | 0.502-6.544 | 0.364 |
| Model 2                         |    |     |                  |      |       |         |
| High TC                        | -0.161 | 0.226 | 0.506          | 0.641 | 0.496-1.236 | 0.477 |
| High TG                        | -0.144 | 0.250 | 0.333          | 0.766 | 0.536-1.315 | 0.516 |
| High LDL-c                     | -0.061 | 0.319 | 0.036          | 0.941 | 0.504-1.757 | 0.849 |
| Low HDL-c                      | 0.718 | 0.655 | 1.293          | 1.982 | 0.658-7.404 | 0.273 |
| Model 3                         |    |     |                  |      |       |         |
| High TC                        | -0.077 | 0.248 | 0.396          | 0.926 | 0.569-1.907 | 0.757 |
| High TC by APOE ε4 status      | -0.462 | 0.568 | 0.476          | 0.628 | 0.415-1.503 | 0.416 |
| High TG                        | -0.174 | 0.279 | 0.676          | 0.840 | 0.446-1.532 | 0.532 |
| High TG by APOE ε4 status      | 0.146 | 0.592 | 0.390          | 0.630 | 0.349-1.135 | 0.507 |
| High LDL-c by APOE ε4 status   | 0.180 | 0.382 | 0.222          | 0.385 | 0.193-0.776 | 0.677 |
| High LDL-c by APOE ε4 status   | -0.435 | 0.381 | 0.390          | 0.630 | 0.349-1.135 | 0.507 |
| Low HDL-c                      | -0.354 | 1.061 | 0.011          | 0.702 | 0.088-5.614 | 0.739 |
| Low HDL-c by APOE ε4 status    | 3.000 | 1.452 | 2.594          | 2.094 | 1.167-3.465 | 0.029 |

Binary logistic regression model was used for data analysis, df=1.
APOE ε4 carrier status: dummy coded with ε4 carriers=1, non-carriers=0.
Model 1 was adjusted for age, gender and education years.
Model 2 was adjusted for age, gender, education years, smoking, drinking, intensity of physical activity, body mass index, log-transformed fasting blood glucose, mean arterial pressure, pulse rate, heart disease and APOE ε4 carrier status.
Model 3 was adjusted for the covariates included in model 2 as well as the interaction terms of APOE ε4 carrier status by serum lipids.
**Table 2. The relationships between serum lipid parameters and cognitive impairment with binary logistic regression in the subgroups according APOE e4 status.**

| Participants | B     | SE    | Wald's chi-square | OR    | 95%CI  | P-value |
|--------------|-------|-------|-------------------|-------|--------|---------|
| **APOE e4 carriers** |       |       |                   |       |        |         |
| Model 4      |       |       |                   |       |        |         |
| High TC      | -0.716| 0.545 | 1.724             | 0.489 | 0.168-1.423 | 0.189   |
| High TG      | 0.098 | 0.556 | 0.031             | 1.103 | 0.371-3.284 | 0.860   |
| High LDL-c   | 0.166 | 0.618 | 0.072             | 1.181 | 0.352-3.965 | 0.788   |
| Low HDL-c    | 3.172 | 1.203 | 6.957             | 23.847| 2.259-251.772| 0.008   |
| Model 5      |       |       |                   |       |        |         |
| High TC      | -0.946| 0.594 | 2.540             | 0.388 | 0.121-1.243 | 0.111   |
| High TG      | -0.238| 0.615 | 0.150             | 0.788 | 0.236-2.628 | 0.698   |
| High LDL-c   | 0.060 | 0.665 | 0.008             | 1.062 | 0.288-3.914 | 0.928   |
| Low HDL-c    | 4.100 | 1.432 | 8.200             | 60.335| 3.646-998.364| 0.004   |
| **APOE e4 non-carriers** |       |       |                   |       |        |         |
| Model 4      |       |       |                   |       |        |         |
| High TC      | -0.103| 0.245 | 0.176             | 0.902 | 0.558-1.458 | 0.675   |
| High TG      | -0.247| 0.270 | 0.840             | 0.781 | 0.460-1.325 | 0.359   |
| High LDL-c   | -0.219| 0.376 | 0.339             | 0.803 | 0.384-1.680 | 0.561   |
| Low HDL-c    | -0.453| 1.057 | 0.184             | 0.636 | 0.080-5.043 | 0.668   |
| Model 5      |       |       |                   |       |        |         |
| High TC      | -0.052| 0.250 | 0.043             | 0.950 | 0.582-1.549 | 0.836   |
| High TG      | -0.176| 0.283 | 0.385             | 0.839 | 0.482-1.461 | 0.535   |
| High LDL-c   | -0.166| 0.383 | 0.187             | 0.847 | 0.400-1.795 | 0.665   |
| Low HDL-c    | -0.254| 1.062 | 0.057             | 0.776 | 0.097-6.221 | 0.811   |

Binary logistic regression model was used for data analysis, df=1. Model 4 and 5 were analyzed in APOE e4 carriers. Model 6 and 7 were analyzed in APOE e4 non-carriers.

APOE e4 carrier status: dummy coded with e4 carriers=1, non-carriers=0.

Model 4 and 6 were adjusted for age, gender, education years.

Model 5 and 7 were adjusted for age, gender, education years, smoking, drinking, intensity of physical activity, body mass index, log-transformed fasting blood glucose, mean arterial pressure, pulse rate and heart disease.