Association between cognitive impairment and apolipoprotein A1 or apolipoprotein B levels is regulated by apolipoprotein E variant rs429358 in patients with chronic schizophrenia

Wenwang Rao1,2, Yunshu Zhang1,3, Keqing Li1,3, Xiang Yang Zhang4

1Institute of Mental Health, Hebei Mental Health Centre, Hebei Province, China
2Unit of Psychiatry, Department of Public Health and Medicinal Administration & Institute of Translational Medicine, Faculty of Health Sciences, University of Macau, Macao SAR, China
3Department of Sleep Medicine, Hebei Psychiatric Hospital, Hebei Province, China
4CAS Key Laboratory of Mental Health, Institute of Psychology, Chinese Academy of Sciences, Beijing, China

Correspondence to: Xiang Yang Zhang; email: zhangxy@psych.ac.cn
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ABSTRACT

ApoE gene polymorphism may be involved in the change in blood lipid profile and cognitive impairment of the general population. However, few studies explored the effects of ApoE gene polymorphism on blood lipid levels and cognition in schizophrenia. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) was employed to evaluate the cognition and the SNPStats was used to investigate the association of ApoE rs429358 with schizophrenia. The models of analysis of covariance and multivariate analysis were conducted to investigate the effect of ApoE rs429358 on cognition in schizophrenia. Altogether, 637 patients with schizophrenia and 467 healthy controls were recruited in this study. The findings in the case group found that both the ApoA1 and ApoB levels were predictors for RBANS total score ($p < 0.001$ vs. $p = 0.011$), immediate memory ($p < 0.001$ vs. $p = 0.019$), language ($p < 0.001$ vs. $p = 0.013$), attention ($p < 0.001$ vs. $p < 0.001$), except ApoA1 level only was a predictor for visuospatial/constructional ($p = 0.014$) and delayed memory ($p < 0.001$). When the association was examined in different ApoE rs429358 genotype subgroups, the association between ApoA1 level and RBANS scores (except for the language score) or between ApoB level and RBANS scores (except for the attention score) was regulated by ApoE rs429358. Our results suggest that patients with schizophrenia have broad cognitive impairment compared with healthy controls. For patients with schizophrenia, both ApoA1 and ApoB levels were positively associated with cognition. There was a significant association between ApoA1 or ApoB levels and cognition in schizophrenia, which was regulated by the ApoE rs429358.

INTRODUCTION

Schizophrenia is a severe long-term mental illness with an estimated lifetime prevalence rate of 0.4–0.88% [1–4], which is associated with serious adverse consequences during the deterioration of the disease, such as high disability [5], premature mortality [6], potential years of life loss [7] and functional and cognitive decline [8]. In addition, previous studies have shown that schizophrenia may lead to a high financial burden [9, 10]. A large number of literatures have revealed that patients with schizophrenia are characterized by changes in blood lipid profiles [11, 12] and various cognitive disorders, including learning, memory, attention, executive function, and information processing [13, 14]. However, the pathophysiological
mechanisms of underlying cognitive impairment and blood lipid profile changes in patients with schizophrenia are still unclear.

The human apolipoprotein E (ApoE) variant originates from two functional polymorphisms (rs429358 and rs7412) in exon 4 of the ApoE gene, which can be combined to form three major subtypes (2,3 and 4) [15]. Previous studies have shown that ApoE gene polymorphism may affect the level of lipoprotein [16–18] and also affect the development of schizophrenia [19, 20]. For example, one study found a significant association between ApoE 3 gene variation and schizophrenia in Asian populations [19]; Another study found a significant association between ApoE rs429358 or ApoE rs7412 polymorphisms and low-density lipoprotein levels (LDL) in whites and African Americans [21]. In addition, the ApoE gene polymorphisms were also associated with cognitive impairment [22]. Some studies have shown that ApoE 4 gene mutations were associated with postoperative cognitive impairment [23], as well as certain areas of cognitive function, including episodic memory, global cognitive ability, executive function and perceptual speed [24]. Young people with ApoE 4 gene mutations performed better in episodic and working memory, executive function and language fluency [25, 26]. Interestingly, one study found that ApoE4 carriers had better language fluency in the 51-65 age group than ApoE3 carriers [27].

Apolipoproteins A1 (ApoA1) and apolipoproteins B (ApoB) are common apolipoproteins (Apos) related to β-including plasma chylomicrons, very-low-density lipoprotein (VLDL) and LDL [32], which can be used as a biomarker of schizophrenia [33]. On the one hand, numerous studies have observed the mixed changes in ApoA1 and ApoB levels in patients with schizophrenia, such as an increase in ApoA1 [31, 34, 35] or ApoB [33, 36, 37] and reduction of ApoA1 [37, 38], or ApoB [35]. On the other hand, ApoA1 and ApoB levels may be associated with cognitive decline [39, 40], which has been indirectly verified by a number of mouse experiments [41, 42]. Specifically, Lewis et al. found that using a triple transgenic mouse model, the over-expression of ApoA1 prevented the development of age-related learning and memory deficits, despite the continued Aβ deposition. Bereczki et al. found that over-expression of human ApoB caused the formation of amyloid plaques and extensive neuronal death in the serum of transgenic mice. In addition, ApoE gene polymorphism may affect expression levels of ApoA1 and ApoB [40, 43, 44]. Nevertheless, few studies have been performed on this topic. Some speculations have been proposed. For example, one study has proposed that genetic variation in the coding region of the ApoE gene (Apoε2/ε3/ε4) plays a critical role in modulating atherogenic ApoA1/B-containing lipoproteins [45, 46]. Another study has hypothesized that assembly or structure of lipoprotein particles is affected, which in turn may alter the half-lives of their various apolipoprotein components [47].

Numerous empirical results suggested there was an association between ApoE gene and Alzheimer's disease [48, 49], between ApoE gene and lipid levels [50], as well as between ApoE gene and cognition [51]. However, few studies have explored the effects of ApoE gene polymorphism on blood lipid levels and cognition in schizophrenia. Therefore, we conducted this study to explore the relationship between cognitive impairment and ApoA1 and ApoB levels in patients with schizophrenia, because it may be altered by the ApoE polymorphism rs429358. We hypothesized that the ApoE polymorphism rs429358 would lead to the changes in ApoA1 and ApoB levels, thereby playing a role in cognitive impairment in schizophrenia. This study had 3 main purposes: (1) to examine the effect of ApoE polymorphism rs429358 on cognitive function of patients with schizophrenia and healthy controls; (2) to investigate the relationship between ApoA1 or ApoB levels and cognitive function in patients with schizophrenia; and (3) to investigate whether the relationship between ApoA1 or ApoB levels and cognitive function is regulated by the ApoE polymorphism rs429358.

**METHODS**

**Study participants**

A total of 637 patients with schizophrenia were recruited from Beijing Hui-Long-Guan hospital, and Hebei Rongjun Hospital in Baoding city near Beijing. All patients met the following inclusion criteria:(a) according to the Structure Clinical Interview for DSM-IV (SCID), schizophrenia was diagnosed by two psychiatrists with a Kappa value greater than 0.80; (b) at least 12 months of the course of disease; (c) had a stable dose of oral antipsychotic medicines for at least 12 weeks before entering this study. The average antipsychotic dose (equivalent to chlorpromazine) was 391.72 ± 181.22 mg/day [52–54]. The exclusion criteria were as follows: (a) diagnosis of drug or alcohol abuse/dependence; (b) suffering from major physical diseases, including head injury, epilepsy, cardiovascular disease, cerebrovascular disease, infection, cancer, and diabetes; (c) being pregnant.
A total of 467 healthy controls were recruited from a local community in Haidian District, Beijing. They had no self-reported personal or family history of any mental illness. They were in good physical health, and any subjects with medical illnesses or drug and alcohol abuse/dependence except for tobacco smoking were excluded.

All participants voluntarily participated in this study and gave written informed consent before entering the study. The protocol was approved by the Ethics Committee of Beijing Hui-Long-Guan hospital, and it was implemented in accordance with the Declaration of Helsinki [55].

Data collection and measures

Well-trained researchers collected general information, socio-demographic characteristics, and medical conditions from pre-designed questionnaires and medical records. The well-validated Chinese version of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS, Form A) [56–59] was used to assess neurocognitive function by three clinical psychologists. After training, an intraclass correlation coefficient (ICC) was greater than 0.8 among these three psychologists. The RBANS includes 12 subscales, which are used to calculate a total score and 5 age-adjusted index scores (attention, language, delayed memory, immediate memory and visuospatial/construction). The RBANS was evaluated on the same day or the next day of the blood draw. A higher score denotes better ability.

DNA extraction and SNP genotyping

Genomic DNA was extracted from 5 ml of peripheral venous blood in each sample using standard salting-out procedures [60], and then stored at −80 degree. The ApoE polymorphism rs429358 was genotyped by using Matrix-Assisted Laser Desorption/Ionization Time of Flight Mass Spectrometry (MALDI-TOF-MS) (Sequenom Inc., San Diego, CA, USA) according to the protocol [61]. After consulting the NCBI GenBank database for reference sequences, the primers and extension probes were generated. Re-genotyping was performed by trained researchers without knowing the clinical information in 5% randomly selected samples for quality control, with an error rate of less than 0.1%.

Serum ApoA1 and ApoB levels measurement

Blood sampling and measurement of serum apolipoprotein (ApoA1 and ApoB) levels were described in detail in our previous study [62], which was performed by immunoturbidimetric method (Beijing Leadman Biotechnology, China) on the Olympus AU2700 analyzer [12, 63].

Statistical analysis

Since all demographic and clinical variables, as well as ApoA1 and ApoB levels were normally distributed in patients and normal controls (Kolmogorov–Smirnov one sample test; all p > 0.05), the principal outcome analysis consisted of an independent two-sample t-test for continuous variables between cases and controls. Chi-squared (χ2) was used for categorical variables between cases and controls. The SNPStats program (a network tool for SNP analysis; https://www.snpstats.net/start.htm) was used to examine the deviation from Hardy-Weinberg disequilibrium (HWD) and genetic model (i.e., dominant, dominant, recessive, and over dominant) analysis for ApoE rs429358 [64]. Furthermore, in order to identify the effect of ApoE variant rs429358 on susceptibility to schizophrenia, logistic regression analysis was used to control for confounding factors. Since almost no homozygous variant CC genotypes were detected in our study (appropriate 0.8% of patients and 0.5% of healthy controls), we considered the CC and TC genotypes as a group in the following association analysis.

An independent two-sample t-test was used to assess between-group differences in continuous variables grouped by genotypes, and Chi-squared (χ2) was used for dichotomous variables. Pearson correlation analysis was used to analyze the correlation between variables, and the partial correlation analysis was carried out with age, gender, education level, BMI and age of onset as covariates. Stepwise regression analysis was used to explore whether there were differences in the relationship between ApoA1 or ApoB levels and RBANS scores among the ApoE rs429358 subgroups. In each ApoE rs429358 subgroup, the RBANS total or subscale scores were taken as the dependent variables, and ApoA1 and ApoB levels were used as independent variables, adjusting for age, gender, education, BMI and age of onset. Based on the ApoE rs429358 genotype subgroups, a two-way analysis of variance (two-way ANCOVA) was used to explore the differences in cognitive scores between patients with schizophrenia and healthy controls. First, the 2 × 2 MANCOVA (genotype × diagnosis) model was used to report the overall p value, and then in this model, the main effects of diagnosis, genotype, and genotype × diagnosis were tested. In this model, diagnosis and ApoE rs429358 genotype were used as independent variables, and the score of each cognitive domain and the total score of RBANS were used as dependent variables, with age,
gender, education level and BMI as covariates. Bonferroni correction was applied to each test to adjust for multiple tests ($P_{\text{corr}} = P \times 6$), since six comparisons were made between the ApoA1 or ApoB levels and RBANS scores.

Power analysis was conducted using the Quanto software (Version 1.2.3) under log additive, recessive and dominant models, assuming that the prevalence rate of schizophrenia in the population was 1%. All data analyses were performed using SPSS, version 26.0 (IBM SPSS, IBM Corp., Armonk, NY, USA), with a significance level of 0.05 (two-sided).

**RESULTS**

**Association analysis of ApoE rs429358 with schizophrenia**

The demographic and clinical information between schizophrenia and healthy controls are summarized in Table 1. There were significant differences in gender, BMI and age between patients and healthy controls (all $p < 0.05$), which were adjusted as covariates in the following analyses.

The HWD test revealed that the genotype distributions of ApoE rs429358 in both schizophrenia and controls were consistent with HWD (case: $p = 0.52$; control: $p = 1.0$; all: $p = 0.82$). We did not observe a significant difference in ApoE rs429358 genotype distributions under the inheritance model (all $p > 0.05$). After adjusting for age, gender and BMI, there were still no significant differences in the distribution of alleles and genotypes (all $p > 0.05$).

**Cognition between patients and controls**

A total of 815 subjects (415 patients and 400 healthy controls) completed the cognitive assessment. Except for the years of education, there were significant differences in gender, age and BMI between patients and controls (all $p < 0.05$). Therefore, these significant variables were used as covariates in the following analyses. The ANOVA analysis indicated that RBANS total score and its subscale scores (except for visuospatial/constructional score) of healthy controls were significantly greater than those of patients with schizophrenia (all $p < 0.05$). Moreover, after adjusting for covariates including sex, age and BMI, the ANCOVA analysis showed that there were significant differences in immediate memory score ($F = 136.97, p < 0.001$), language score ($F = 121.80, p < 0.001$), attention score ($F = 117.13, p < 0.001$), delayed memory score ($F = 197.49, p < 0.001$) and RBANS total score ($F = 159.94, p < 0.001$) between the two groups.

**Effects of ApoE rs429358 on cognition in patients and controls**

Two-way ANOVA analysis showed that diagnosis had a significant effect on all RBANS scores except for visuospatial/constructional score. However, genotype and genotype X diagnosis had no significant effect on any RBANS scores (all $p > 0.05$; Table 2). When controlling for sex, age BMI and education, the above results did not change significantly. In addition, in the patient group, there was no significant difference in RBANS scores between the ApoE rs429358 genotype groups (all $p > 0.05$).

**Genotype effects on serum ApoA1 and ApoB levels between patients**

ApoA1 levels were available for 507 patients, while ApoB levels were available for 505 patients. There were no ApoA1 and ApoB levels available for healthy controls. There was a significant difference in serum ApoA1 levels between the ApoE rs429358 genotype groups, showing that patients with TT genotype had higher ApoA1 levels than patients with CT+CC genotype ($p = 0.010$, Table 3). After adjusting the BMI, the difference remained significant ($p = 0.005$). In addition, there was no significant difference in ApoB levels between ApoE rs429358 genotype groups ($p = 0.545$).

**Relationship between serum ApoA1 levels and cognition in patients**

Pearson correlation analysis showed a significant association between ApoA1 level and RBANS total score ($r = 0.343, n = 318, p < 0.001, P_{\text{corr}} < 0.006$), immediate memory ($r = 0.251, n = 318, p < 0.001, P_{\text{corr}} < 0.006$), language ($r = 0.243, n = 318, p < 0.001, P_{\text{corr}} < 0.006$), attention ($r = 0.401, n = 318, p < 0.001, P_{\text{corr}} < 0.006$), visuospatial/ constructional ($r = 0.230, n = 318, p < 0.001, P_{\text{corr}} < 0.006$) or delayed memory ($r = 0.261, n = 318, p < 0.001, P_{\text{corr}} < 0.006$). Furthermore, after controlling for age, gender, BMI, years of education, and age of onset, ApoA1 level was still correlated with the RBANS total score ($r = 0.287, n = 211, p < 0.001, P_{\text{corr}} < 0.006$), immediate memory ($r = 0.252, n = 211, p < 0.001, P_{\text{corr}} < 0.006$), language ($r = 0.321 n = 211, p < 0.001, P_{\text{corr}} < 0.006$), attention ($r = 0.321, n = 211, p < 0.001, P_{\text{corr}} < 0.006$), visuospatial/ constructional ($r = 0.168, n = 211, p = 0.014, P_{\text{corr}} = 0.084$) and delayed memory domains ($r = 0.198, n = 211, p = 0.004, P_{\text{corr}} = 0.024$). In addition, linear regression analyses identified that ApoA1 level was a predictor for RBANS total score ($t = 4.359, p < 0.001, P_{\text{corr}} < 0.006$), immediate memory ($t = 3.790, p < 0.001, P_{\text{corr}} < 0.006$), language ($t = 4.924, p < 0.001, P_{\text{corr}} < 0.006$), attention ($t = 4.925,
Table 1. Demographic profiles in patients with schizophrenia and controls (Mean ± SD).

| Variables               | Association between rs429358 and schizophrenia | Association between rs429358 and cognition score |
|-------------------------|-----------------------------------------------|-----------------------------------------------|
|                        | Cases (n = 637) | Controls (n = 467) | t/X²  | P value | Cases (n = 415) | Controls (n = 400) | t/X²  | P value |
| Age (year)              | 47.52 ± 10.61  | 44.94 ± 13.63      | −3.392 | 0.001   | 48.19 ± 9.25    | 45.84 ± 13.37      | −2.867 | 0.004   |
| Sex                     |                 |                   |       |         |                 |                   |       |         |
| Female (%)              | 156 (24.5)      | 274 (58.7)         | 132.406 | <0.001  | 73 (17.6)       | 230 (57.5)          | 138.902 | <0.001  |
| Male (%)                | 481 (75.5)      | 193 (41.3)         | 0.955  | 0.340   | 342 (82.4)      | 170 (42.5)          | 0.473  | 0.636   |
| Year of education       | 9.30 ± 6.81     | 9.66 ± 5.33        | 0.11   | 0.904   | 9.19 ± 6.77     | 9.40 ± 5.59         | 0.473  | 0.636   |
| Body mass index         | 24.45 ± 4.00    | 25.14 ± 4.18       | 2.538  | 0.011   | 24.68 ± 3.89    | 25.41 ± 4.14        | 2.378  | 0.018   |
| Age of onset            | 23.20 ± 5.16    |                   |       |         | 23.12 ± 4.67    |                   |       |         |
| Illness of course (year)| 24.43 ± 10.52   |                   |       |         | 25.23 ± 9.49    |                   |       |         |
| Mean daily dose (mg/day)|(chlorpromazine equivalents) | 39.72 ± 181.22 |       |         | 388.78 ± 171.19 |                   |       |         |
| ApoA1 level (g/L)       | 1.53 ± 0.38     |                   |       |         | 1.50 ± 0.38     |                   |       |         |
| ApoB level (g/L)        | 0.89 ± 0.24     |                   |       |         | 0.88 ± 0.25     |                   |       |         |
| RBANS Total score       |                   |                   |       |         | 64.60 ± 15.66  | 80.04 ± 15.12      | 14.308 | <0.001  |
| Immediate memory score  |                   |                   |       |         | 65.68 ± 16.82  | 75.69 ± 17.31      | 14.219 | <0.001  |
| Attention score         |                   |                   |       |         | 70.21 ± 18.13  | 76.14 ± 20.26      | 12.687 | <0.001  |
| Language score          |                   |                   |       |         | 81.06 ± 15.45  | 93.89 ± 13.09      | 12.810 | <0.001  |
| visuospatial/           |                   |                   |       |         | 81.06 ± 15.45  | 92.89 ± 13.09      | 12.810 | <0.001  |
| Constructional score    |                   |                   |       |         | 76.09 ± 19.45  | 79.62 ± 15.59      | 1.313  | 0.190   |
| Delayed memory score    |                   |                   |       |         | 66.24 ± 19.27  | 86.25 ± 15.26      | 16.465 | <0.001  |

Table 2. Comparisons among the RBANS total and five subscale scores by diagnostic and genotypic groupings (Mean ± SD).

| RBANS scores          | Cases               | Controls             | Diagnosis        | Genotype        | Diagnosis × genotype |
|-----------------------|---------------------|----------------------|------------------|-----------------|----------------------|
|                       | TT (n = 315)        | CC + CT (n = 53)     | TT (n = 336)     | CC + CT (n = 64) | F (p value)          |
| Immediate memory      | 56.67 ± 15.50       | 61.17 ± 20.10        | 75.91 ± 17.33    | 74.52 ± 17.28   | 86.860 (<0.001)      |
| Attention             | 70.13 ± 17.94       | 72.09 ± 15.85        | 87.76 ± 20.38    | 85.75 ± 20.31   | 65.908 (<0.001)      |
| Language              | 80.68 ± 15.23       | 81.42 ± 16.20        | 93.78 ± 12.60    | 94.47 ± 15.49   | 83.125 (<0.001)      |
| visuospatial/         | 76.68 ± 18.60       | 76.68 ± 20.12        | 79.61 ± 15.51    | 79.67 ± 16.15   | 0.709 (0.400)        |
| Constructional score  | 64.88 ± 18.70       | 68.28 ± 20.59        | 86.39 ± 15.08    | 85.52 ± 16.29   | 125.553 (<0.001)     |
| Delayed memory        | 63.48 ± 14.24       | 65.00 ± 18.97        | 80.16 ± 14.97    | 79.44 ± 16.04   | 104.854 (<0.001)     |
| Total                 |                     |                      |                  |                 | 0.069 (0.792)        |

p < 0.001, p_{cor} < 0.006), visuospatial/constructional (r = 2.474, p = 0.014, p_{cor} = 0.084) and delayed memory domains (r = 2.934, p < 0.001, p_{cor} < 0.006).

Relationship between serum ApoB levels and cognition in patients

The ApoB level was associated with RBANS total score (r = 0.245, n = 316, p < 0.001, p_{cor} < 0.006), immediate memory (r = 0.211, n = 316, p < 0.001, p_{cor} < 0.006), language (r = 0.185, n = 316, p = 0.001, p_{cor} < 0.006), attention (r = 0.315, n = 316, p < 0.001, p_{cor} < 0.006), visuospatial/constructional (r = 0.166, n = 316, p = 0.003, p_{cor} = 0.018) and delayed memory (r = 0.181, n = 316, p = 0.001, p_{cor} = 0.006). After controlling for age, gender, BMI, years of education and age of onset, the ApoB level was still correlated with RBANS total score (r = 0.175, n = 209, p = 0.011, p_{cor} = 0.066), immediate memory (r = 0.161, n = 209, p = 0.019, p_{cor} = 0.114), language (r = 0.171, n = 209, p = 0.013, p_{cor} = 0.078), and attention (r = 0.334, n = 209, p < 0.001, p_{cor} < 0.006). In addition, linear regression analyses identified that the ApoB level was a predictor for RBANS total score (r = 0.257, p = 0.011, p_{cor} = 0.066), immediate memory (r = 0.237, p = 0.019, p_{cor} = 0.114), language (r = 0.251, p = 0.013, p_{cor} = 0.078), and attention (r = 0.512, p < 0.001, p_{cor} < 0.006).
Table 3. Demographic and clinical information according to ApoE rs429358 genotype of cases and controls in a Chinese sample.

| Variables                      | Cases (n = 506) | Health Controls (n = 421) |
|--------------------------------|----------------|--------------------------|
| Age (year)                     | CT+CC (n = 73) | TT (n = 433) | t/X² | P value | CT+CC (n = 67) | TT (n = 354) | t/X² | P value |
| Sex                            | 47.45 ± 10.04 | 47.36 ± 9.66 | −0.077 | 0.939 | 46.15 ± 13.14 | 46.16 ± 13.27 | 0.006 | 0.995 |
| Female (%)                     | 19 (26.0)     | 91 (21.0)     | 0.922 | 0.337 | 38 (56.7)     | 210 (59.3)    | 0.158 | 0.691 |
| Male (%)                       | 54 (74.0)     | 342 (79.0)    |       |       | 29 (43.3)     | 144 (40.7)    |       |       |
| Year of education              | 10.21 ± 10.91 | 8.72 ± 2.60   | −1.159 | 0.250 | 10.80 ± 11.52 | 9.14 ± 3.32   | −1.164 | 0.248 |
| Body mass index                | 23.53 ± 4.12  | 24.73 ± 3.85  | 2.131 | 0.034 | 25.00 ± 3.58  | 25.41 ± 4.20  | 0.734 | 0.464 |
| Age of onset                   | 23.34 ± 5.58  | 22.98 ± 4.77  | −0.587 | 0.558 |       |             |       |       |
| Illness of course (year)       | 24.11 ± 9.56  | 24.53 ± 10.07 | 0.335 | 0.738 |       |             |       |       |
| Mean daily dose (mg/day)       | 413.29 ± 178.79 | 380.97 ± 159.69 | −1.166 | 0.245 |       |             |       |       |
| (chlorpromazine equivalents)   |               |             |       |       |       |             |       |       |
| ApoA1 level (g/L)              | 1.38 ± 0.40   | 1.52 ± 0.37   | 2.586 | 0.010 |       |             |       |       |
| ApoB level (g/L)               | 0.86 ± 0.26   | 0.88 ± 0.26   | 0.606 | 0.545 |       |             |       |       |

Genotype effects on serum ApoA1 level and cognition in patients

In the T homozygote group, Pearson correlation analysis showed a significant positive association between ApoA1 level and RBANS total score, ($r = 0.384, n = 234, p < 0.001, p_{corr} < 0.006$), immediate memory index ($r = 0.233, n = 234, p < 0.001, p_{corr} < 0.006$), visuospatial/constructional index ($r = 0.260, n = 234, p < 0.001, p_{corr} < 0.006$), language index ($r = 0.268, n = 234, p < 0.001, p_{corr} < 0.006$), attention index ($r = 0.408, n = 234, p < 0.001, p_{corr} < 0.006$) and delayed memory index ($r = 0.253, n = 234, p < 0.001, p_{corr} < 0.006$). Moreover, after controlling for age, gender, BMI, years of education and age of onset, the ApoA1 level still positively associated with the RBANS total score ($r = 0.398, n = 163, p < 0.001, p_{corr} < 0.006$), immediate memory index ($r = 0.308, n = 163, p < 0.001, p_{corr} < 0.006$), visuospatial/constructional index ($r = 0.198, n = 163, p = 0.011, p_{corr} = 0.066$), language index ($r = 0.357, n = 163, p < 0.001, p_{corr} < 0.006$), attention index ($r = 0.338, n = 163, p < 0.001, p_{corr} < 0.006$) and delayed memory index ($r = 0.245, n = 163, p = 0.001, p_{corr} = 0.006$). Further regression analysis confirmed that ApoA1 level was significantly associated with RBANS total score ($t = 6.272, p < 0.001, p_{corr} < 0.006$), immediate memory index ($t = 4.789, p < 0.001, p_{corr} < 0.006$), visuospatial/constructional index ($t = 2.704, p = 0.008, p_{corr} = 0.048$), language index ($t = 5.215, p < 0.001, p_{corr} < 0.006$), attention index ($t = 5.444, p < 0.001, p_{corr} < 0.006$) and delayed memory index ($t = 3.672, p < 0.001, p_{corr} < 0.006$).

In the C allele carriers, ApoA1 level was significantly associated with RBANS total score ($r = 0.448, n = 42, p = 0.003, p_{corr} = 0.012$), immediate memory index ($r = 0.522, n = 42, p < 0.001, p_{corr} < 0.006$), visuospatial/constructional index ($r = 0.357, n = 42, p = 0.020, p_{corr} = 0.120$), language index ($r = 0.542, n = 42, p < 0.001, p_{corr} < 0.006$), attention index ($r = 0.608, n = 42, p < 0.001, p_{corr} < 0.006$) and delayed memory index ($r = 0.440, n = 42, p = 0.004, p_{corr} = 0.024$). After controlling for age, gender, BMI, duration of education and age of onset, ApoA1 level was only associated with language index ($r = 0.431, n = 25, p = 0.025, p_{corr} = 0.150$).

Genotype effects on serum ApoB level and cognition in patients

In the T homozygote group, there was a significant association between ApoB levels and the RBANS total score ($r = 0.260, n = 233, p < 0.001, p_{corr} < 0.006$), immediate memory index ($r = 0.222, n = 233, p = 0.001, p_{corr} = 0.006$), visuospatial/constructional index ($r = 0.152, n = 233, p = 0.020, p_{corr} = 0.120$), language index ($r = 0.161, n = 233, p = 0.014, p_{corr} = 0.084$), attention index ($r = 0.293, n = 233, p < 0.001, p_{corr} < 0.006$) and delayed memory index ($r = 0.173, n = 233, p = 0.008, p_{corr} = 0.048$). When controlling for age, gender, BMI, duration of education and age of onset, RBANS total score ($r = 0.231, n = 162, p = 0.003, p_{corr} = 0.018$), immediate memory index ($r = 0.172, n = 162, p = 0.028, p_{corr} = 0.168$), language index ($r = 0.170, n = 162, p = 0.029, p_{corr} = 0.174$), and attention index ($r = 0.332, n = 162, p < 0.001, p_{corr} < 0.006$) remained significant. Furthermore, regression analysis showed that ApoB level was significantly associated with the RBANS total score ($t = 2.971, p = 0.003, p_{corr} = 0.018$), immediate memory index ($t = 2.333, p = 0.021, p_{corr} = 0.126$), language index ($t = 2.540, p = 0.012, p_{corr} = 0.072$) and attention index ($t = 5.012, p < 0.001, p_{corr} < 0.006$).

In the C allele carriers, Pearson correlation analysis showed a significant association between ApoB level
DISCUSSION

To our best knowledge, this is the first report to explore the relationship between ApoE rs429358 and cognitive impairment in patients with schizophrenia. This study had several main findings. (1) ApoE rs429358 may not be associated with susceptibility to schizophrenia. (2) In patients, serum ApoA1 level was significantly higher in the ApoE rs429358 TT genotype group than that in the CT + CC genotype group. (3) Except for the visuospatial/constructional domain, RBANS total score and all other domains of patients with schizophrenia were significantly lower than those of healthy controls. (4) ApoE rs429358 genotype was not associated with any cognitive performance shown on the RBANS. (5) Except for the visuospatial/constructional domain delayed memory domain, the RBANS total score and the other 3 domains were correlated with serum ApoA1 and ApoB levels. (6) The association between serum ApoA1 level and RBANS scores (except language score) or between serum ApoB level and RBANS scores (except attention score) was regulated by ApoE rs429358.

This study did not find any association between ApoE rs429358 and schizophrenia, which is consistent with previous studies [65–67]. Nevertheless, an early meta-analysis showed an association of ApoE ε3 with schizophrenia in Asian populations [19], but not in other populations. Meanwhile, a highly significant association was found between ApoE genotype and schizophrenia in the Chinese population [68]. Moreover, an association study and meta-analysis revealed an association between schizophrenia and ApoE ε2ε3 genotype in French male samples but not in the entire French sample [69]. In addition, there was an association between undifferentiated type of schizophrenia and ApoE ε3ε3 genotype in the Serbian population [70]. Interestingly, both ApoE ε3 and ApoE-219G haplotypes increased the risk of schizophrenia in siblings [71]. By comparing the above studies, we speculate that these different results between our current study and other studies may be partly due to differences in population, sample composition, types of schizophrenia and synergy/interaction with other variants.

The Apolipoprotein E (ApoE) gene (4 exons and 3 introns) plays a key role in receptor-mediated endocytosis of lipoproteins in the brain [72] and affects downstream proteins, such as brain-derived neurotrophic factor (BDNF) [73, 74], which may be involved in neuropsychiatric genetics [74, 75], especially in cognition-related diseases [76]. In addition, ApoB level are associated with the low-density lipoprotein receptor (LDLR) [77, 78], which is expressed in brain capillary endothelial cells and astrocytes, and plays an important role in cholesterol and Aβ clearance [79]. ApoA1 level plays a major role in cholesterol transport in the central nervous system (CNS) [80, 81]. Brain cholesterol is considered to be involved in the development of blood-brain barrier [82–84]. Blood-brain barrier damage is associated with the occurrence and development of cognitive impairment [85].

It is well-known that ApoE gene polymorphism was associated with cognitive decline, which has been confirmed by some studies [86, 87], mouse experiments [88, 89], clinical studies [90, 91] and meta-analysis [24]. Moreover, previous studies have revealed an association between the ApoE variant rs429358 (rather than rs7412) and cognitive decline in the aging population [51, 92, 93]. However, our research did not support this association. One possible explanation is that abnormalities caused by schizophrenia may affect the impact of rs429358 on cognitive function. In addition, a study found that schizophrenia patients with ApoEε4 carriers had significantly lower verbal memory score assessed by the Brief Assessment of Cognition in Schizophrenia (BACS) [22]. Another study showed an interaction between the ApoE ε4 allele, first-episode psychosis (FEP), and the improvement in verbal memory over time measured by California Verbal Learning Test (CVLT) [94]. These inconsistent findings of cognitive deficits in patients with schizophrenia may be partly due to the combined effects of different cognitive measurement tools and ApoE genotypes.

Interestingly, to our best knowledge, this is a first report showing that ApoA1 level was positively associated with all domains of RBANS scores in patients with schizophrenia, while ApoB level was correlated with the RBANS total score and other 3 domains, except for visuospatial/constructional domain and delayed memory domain. Similarly, a study reported that ApoA1 level was independently associated with cognitive impairment as shown by the Mini Mental Status Examination (MMSE) in elderly men [95]. Another study of the Swedish Adoption Twin Study of Aging of 50 years and older demonstrated that ApoA1 level was significantly associated with perceptual speed in women, while ApoB level was associated with perceptual speed in men and verbal ability in women [39]. These consistent results may suggest that the impacts of ApoA1 and ApoB levels on cognitive function may not be affected by schizophrenia.
Moreover, the association between serum ApoA1 level and RBANS scores (except for the language score) or between serum ApoB level and RBANS scores (except for the attention score) was regulated by the ApoE rs429358 genotype. We speculate that this regulatory effect of ApoE rs429358 may be achieved by controlling the expression levels of ApoA1 and ApoB. Although there was no significant difference in ApoB levels between different ApoE rs429358 genotype groups in our study, many studies have found that ApoE gene polymorphisms affect the expression levels of ApoA1 and ApoB [40, 43, 44].

This study has several limitations. First, the controls were different from the cases in several key demographics (like age, sex and BMI), which may make the case vs control analysis less relevant. Although we adjusted these different key demographics in the statistical analysis models, it may still lead to bias in the statistical analysis due to these different variables between cases and controls, which should be remedied in future studies that will select the controls to match the cases. Second, owing to the cross-sectional study design, the causality between ApoE rs429358, ApoA1 and ApoB levels, and cognition impairment in patients with schizophrenia was not directly revealed. Third, compared with typical psychiatric outpatients or first-episode patients with schizophrenia and aboriginal patients, the inpatients in this study had more severe psychopathology, cognitive decline and longer duration of disease and antipsychotic treatment, which may limit the generalization of our findings of this study. Fourth, ApoE rs429358 has a rare CC genotype. Therefore, this study combined CC and TC genotypes as a group for association analysis, which may cause uncertainty in the results. Fifth, in this study, we only examined the effects of a single genetic polymorphism, and it is necessary to detect other functional variants of the ApoE gene (e.g., rs7412), because other polymorphisms, haplotypes, gene interaction or gene-environment interaction may be associated with schizophrenia or with cognitive dysfunction in patients with schizophrenia. Sixth, the RBANS is unable to assess all cognitive domains that may be altered in patients, such as motor ability or executive function. Although the RBANS scale has been well verified for the Chinese general population and patients with schizophrenia, its lacks of norm value restricts its use in the Chinese population.

In summary, the ApoE rs429358 gene polymorphism did not directly affect the susceptibility to schizophrenia and cognitive function of schizophrenia. However, the serum ApoA1 and ApoB levels were positively correlated with the degree of cognitive function in patients with schizophrenia, indicating that serum ApoA1 and ApoB levels may be biomarkers of general cognitive function in schizophrenia patients. The association between serum ApoA1 or ApoB levels and cognitive impairment in patients with schizophrenia were regulated by the existence of ApoE rs429358 polymorphism. However, due to the limited sample size and relatively low statistical power, our findings are still preliminary. Therefore, future studies are needed to confirm our current findings in larger samples from different ethnicities, and the biological mechanisms of cognitive impairments in schizophrenia involved in ApoE rs429358 should also be further studied.

**AUTHOR CONTRIBUTIONS**

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by WWR, YSZ, KQL and XYZ. The first draft of the manuscript was written by WWR and XYZ revised the manuscript. All authors read and approved the final manuscript.

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**CONFLICTS OF INTEREST**

The authors declare no conflicts of interest related to this study.

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**REFERENCES**

1. Saha S, Chant D, Welham J, McGrath J. A systematic review of the prevalence of schizophrenia. PLoS Med. 2005; 2:e141. [https://doi.org/10.1371/journal.pmed.0020141](https://doi.org/10.1371/journal.pmed.0020141) PMID: 15916472

2. Moreno-Küstner B, Martin C, Pastor L. Prevalence of psychotic disorders and its association with methodological issues. A systematic review and meta-analyses. PLoS One. 2018; 13:e0195687. [https://doi.org/10.1371/journal.pone.0195687](https://doi.org/10.1371/journal.pone.0195687) PMID: 29649252
3. Phanthunane P, Vos T, Whiteford H, Bertram M, Udomratn P. Schizophrenia in Thailand: prevalence and burden of disease. Popul Health Metr. 2010; 8:24. https://doi.org/10.1186/1478-7954-8-24 PMID: 20712909

4. Huang Y, Wang Y, Wang H, Liu Z, Yu X, Yan J, Yu Y, Kou C, Xu X, Lu J, Wang Z, He S, Xu Y, et al. Prevalence of mental disorders in China: a cross-sectional epidemiological study. Lancet Psychiatry. 2019; 6:211–24. https://doi.org/10.1016/S2215-0366(18)30511-X PMID: 30792114

5. Vos T, Barber RM, Bell B, Bertozi-Villa A, Biryukov S, Bolliger I, Charlson F, Davis A, Degenhardt L, Dicker D, Duan L, Erskine H, Feigin VL, et al, and Global Burden of Disease Study 2013 Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. The Lancet. 2015; 386:743–800. https://doi.org/10.1016/s0140-6736(15)60692-4 PMID: 26063472

6. Olsson M, Gerhard T, Huang C, Crystal S, Stroup TS. Premature Mortality Among Adults With Schizophrenia in the United States. JAMA Psychiatry. 2015; 72:1172–81. https://doi.org/10.1001/jamapsychiatry.2015.1737 PMID: 26509694

7. Hjorthøj C, Stürup AE, McGrath JJ, Nordentoft M. Years of potential life lost and life expectancy in schizophrenia: a systematic review and meta-analysis. Lancet Psychiatry. 2017; 4:295–301. https://doi.org/10.1016/S2215-0366(17)30078-0 PMID: 28237639

8. Chen YL, Pan CH, Chang CK, Chen PH, Chang HM, Tai MH, Su SS, Tsai SY, Chen CC, Kuo CJ. Physical Illnesses Before Diagnosed as Schizophrenia: A Nationwide Case-Control Study. Schizophr Bull. 2020; 46:785–94. https://doi.org/10.1093/schbul/sbbaa009 PMID: 32052838

9. Chong HY, Teoh SL, Wu DB, Kotirum S, Chiou CF, Chaiyakunapruk N. Global economic burden of schizophrenia: a systematic review. Neuropsychiatr Dis Treat. 2016; 12:357–73. https://doi.org/10.2147/NDT.S96649 PMID: 26937191

10. Charlson FJ, Ferrari AJ, Santomauro DF, Diminic S, Stockings E, Scott JG, McGrath JJ, Whiteford HA. Global Epidemiology and Burden of Schizophrenia: Findings From the Global Burden of Disease Study 2016. Schizophr Bull. 2018; 44:1195–203. https://doi.org/10.1093/schbul/sby058 PMID: 29762765

11. Yogaratnam J, Biswas N, Vadivel R, Jacob R. Metabolic complications of schizophrenia and antipsychotic medications—an updated review. East Asian Arch Psychiatry. 2013; 23:21–28. PMID: 23535629

12. An HM, Tan YL, Tan SP, Shi J, WangZR, Yang FD, Huang XF, Soars JC, Kosten TR, Zhang XY. Smoking and Serum Lipid Profiles in Schizophrenia. Neurosci Bull. 2016; 32:383–88. https://doi.org/10.1007/s12264-016-0022-0 PMID: 27017941

13. Hui L, Rao WW, Yu Q, Kou C, Wu IQ, He JC, Ye MJ, Liu JH, Xu XJ, Zheng K, Ruan LN, Liu HY, Hu WM, et al. TCF4 gene polymorphism is associated with cognition in patients with schizophrenia and healthy controls. J Psychiatr Res. 2015; 69:95–101. https://doi.org/10.1016/j.jpsychires.2015.07.022 PMID: 26343600

14. Xi MH, Tian L, Chen S, Tan YL, Chen DC, Chen J, Chen N, De Yang F, Licinio J, Kosten TR, Soares JC, Zhang XY. Contribution of IL-10 and its -592 A/C polymorphism to cognitive functions in first-episode drug-naïve schizophrenia. Brain Behav Immun. 2016; 57:116–24. https://doi.org/10.1016/j.bbi.2016.03.005 PMID: 26971470

15. Eisenberg DT, Kuzawa CW, Hayes MG. Worldwide allele frequencies of the human apolipoprotein E gene: climate, local adaptations, and evolutionary history. Am J Phys Anthropol. 2010; 143:100–11. https://doi.org/10.1002/ajpa.21298 PMID: 20734437

16. Li W. Association of APOE E2 and low-density lipoprotein with depressive symptoms in Chinese senile schizophrenia inpatients: A cross-sectional study. Schizophr Res Cogn. 2020; 23:100193. https://doi.org/10.1016/j.sgcog.2020.100193 PMID: 33294393

17. Ban C, Zhang Q, Feng J, Li H, Qiu Q, Tian Y, Li X. Low prevalence of lipid metabolism abnormalities in APOE e2-genotype and male patients 60 years or older with schizophrenia. BMC Psychiatry. 2017; 17:395. https://doi.org/10.1186/s12888-017-1530-9 PMID: 29233125

18. Li W, Ban C, Yue L, Sun L, Li X, Xiao S. Homozygosity in the APOE 3 Polymorphism Is Associated With Less Depression and Higher Serum Low-Density Lipoprotein in Chinese Elderly Schizophrenics. Front Endocrinol (Lausanne). 2020; 11:642. https://doi.org/10.3389/fendo.2020.00642 PMID: 33178131

19. González-Castro TB, Tomela-Zárate CA, Hernández-Díaz Y, Fresán A, Juárez-Rojop IE, Ble-Castillo JL,
20. Al-Asmary SM, Kadasah S, Arfin M, Tariq M, Al-Asmari A. Apolipoprotein E polymorphism is associated with susceptibility to schizophrenia among Saudis. Arch Med Sci. 2015; 11:869–76. https://doi.org/10.5114/ams.2015.53308 PMID:26322100

21. Radwan ZH, Wang X, Waqar F, Pirim D, Niemiri V, Hokanson JE, Hamman RF, Bunker CH, Barmada MM, Demirci FY, Kamboh MI. Comprehensive evaluation of the association of APOE genetic variation with plasma lipoprotein traits in U.S. whites and African blacks. PLoS One. 2014; 9:e114618. https://doi.org/10.1371/journal.pone.0114618 PMID:25502880

22. Ward KM, Kraal AZ, Flowers SA, Ellingrod VL. Cardiovascular Pharmacogenomics and Cognitive Function in Patients with Schizophrenia. Pharmacotherapy. 2017; 37:1122–30. https://doi.org/10.1002/phar.1968 PMID:28605058

23. Cao L, Wang K, Gu T, Du B, Song J. Association between APOE epsilon 4 allele and postoperative cognitive dysfunction: a meta-analysis. Int J Neurosci. 2014; 124:478–85. https://doi.org/10.3109/00207454.2013.860601 PMID:24168388

24. Wisdom NM, Callahan JL, Hawkins KA. The effects of apolipoprotein E on non-impaired cognitive functioning: a meta-analysis. Neurobiol Aging. 2011; 32:63–74. https://doi.org/10.1016/j.neurobiolaging.2009.02.003 PMID:19285755

25. Bunce D, Anstey KJ, Burns R, Christensen H, Easteal S. Does possession of apolipoprotein E ε4 benefit cognitive function in healthy young adults? Neuropsychologia. 2011; 49:1693–97. https://doi.org/10.1016/j.neuropsychologia.2011.02.042 PMID:21396385

26. Rusted JM, Evans SL, King SL, Dowell N, Tabet N, Tofts PS. APOE ε4 polymorphism in young adults is associated with improved attention and indexed by distinct neural signatures. Neuroimage. 2013; 65:364–73. https://doi.org/10.1016/j.neuroimage.2012.10.010 PMID:23063453

27. Alexander DM, Williams LM, Gatt JM, Dobson-Stone C, Kuan SA, Todd EG, Schofield PR, Cooper NJ, Gordon E. The contribution of apolipoprotein E alleles on cognitive performance and dynamic neural activity over six decades. Biol Psychol. 2007; 75:229–38. https://doi.org/10.1016/j.biopsych.2007.03.001 PMID:17433528

28. Woods AG, Sokolowska I, Taurines R, Gerlach M, Dudley E, Thome J, Darie CC. Potential biomarkers in psychiatry: focus on the cholesterol system. J Cell Mol Med. 2012; 16:1184–95. https://doi.org/10.1111/j.1582-4934.2012.01543.x PMID:22304330

29. Takechi R, Galloway S, Pallebage-Gamarallage MM, Wellington CL, Johnsen RD, Dhaliwal SS, Mamo JC. Differential effects of dietary fatty acids on the cerebral distribution of plasma-derived apo B lipoproteins with amyloid-beta. Br J Nutr. 2010; 103:652–62. https://doi.org/10.1017/S0007114509992194 PMID:19860996

30. Thambisetty M, Simmons A, Velayudhan L, Hye A, Campbell J, Zhang Y, Wahlund LO, Westman E, Kinsey A, Güntert A, Proitsi P, Powell J, Causevic M, et al. Association of plasma clusterin concentration with severity, pathology, and progression in Alzheimer disease. Arch Gen Psychiatry. 2010; 67:739–48. https://doi.org/10.1001/archgenpsychiatry.2010.78 PMID:20603455

31. Boiko AS, Mednova IA, Kornetova EG, Semke AV, Bokhan NA, Loonen AJM, Ivanova SA. Apolipoprotein serum levels related to metabolic syndrome in patients with schizophrenia. Heliyon. 2019; 5:e02033. https://doi.org/10.1016/j.heliyon.2019.e02033 PMID:31317083

32. Demmer LA, Levin MS, Elovson J, Reuben MA, Lusis AJ, Gordon JI. Tissue-specific expression and developmental regulation of the rat apolipoprotein B gene. Proc Natl Acad Sci U S A. 1986; 83:8102–06. https://doi.org/10.1073/pnas.83.21.8102 PMID:3464945

33. Walss-Bass C, Lokesh GLR, Dyukova E, Gorenstein DG, Roberts DL, Velligan D, Volk DE. X-Aptamer Technology Identifies C4A and ApoB in Blood as Potential Markers for Schizophrenia. Mol Neuropsychiatry. 2019; 5:52–59. https://doi.org/10.1159/000492331 PMID:31019918

34. Martins-De-Souza D, Wobrock T, Zerr I, Schmitt A, Gawinecka J, Schneider-Axmann T, Falkai P, Turck CW. Different apolipoprotein E, apolipoprotein A1 and prostaglandin-H2 D-isomerase levels in cerebrospinal fluid of schizophrenia patients and healthy controls. World J Biol Psychiatry. 2010; 11:719–28. https://doi.org/10.3109/15622971003758748 PMID:20446881
35. Wen F, Tan J. Effects of phenothiazine drugs on serum levels of apolipoproteins and lipoproteins in schizophrenic subjects. Acta Pharmacol Sin. 2003; 24:1001–05. PMID:14531942

36. Ozornin A, Govorin N. Blood lipid spectrum changes in first-episode schizophrenia patients treated with risperidone and haloperidol. Eur Psychiatry. 2013; 28:1. https://doi.org/10.1016/S0924-9338(13)76615-X

37. Mabrouk H, Mechria H, Mechri A, Azizi I, Neffati F, Douki W, Gaha L, Najjar MF. Paraoxonase 1 activity and lipid profile in schizophrenic patients. Asian J Psychiatr. 2014; 9:36–40. https://doi.org/10.1016/j.ajp.2013.12.019 PMID:24813034

38. Huang JT, Wang L, Prabakaran S, Wengenroth M, Lockstone HE, Koethe D, Gerth CW, Gross S, Schreiber D, Lilley K, Wayland M, Oxley D, Leweke FM, et al. Independent protein-profiling studies show a decrease in apolipoprotein A1 levels in schizophrenia CSF, brain and peripheral tissues. Mol Psychiatry. 2008; 13:1118–28. https://doi.org/10.1038/sj.mp.4002108 PMID:17938634

39. Reynolds CA, Gatz M, Prince JA, Berg S, Pedersen NL. Serum lipid levels and cognitive change in late life. J Am Geriatr Soc. 2010; 58:501–09. https://doi.org/10.1111/j.1532-5415.2010.02739.x PMID:20398119

40. Song F, Poljak A, Crawford J, Kochan NA, Wen W, Cameron B, Lux O, Brodaty H, Mather K, Smythe GA, Sachdev PS. Plasma apolipoprotein levels are associated with cognitive status and decline in a community cohort of older individuals. PLoS One. 2012; 7:e34078. https://doi.org/10.1371/journal.pone.0034078 PMID:22701550

41. Lewis TL, Cao D, Lu H, Mans RA, Su YR, Jungbauer L, Linton MF, Fazio S, LaDu MJ, Li L. Overexpression of human apolipoprotein A-I preserves cognitive function and attenuates neuroinflammation and cerebral amyloid angiopathy in a mouse model of Alzheimer disease. J Biol Chem. 2010; 285:36958–68. https://doi.org/10.1074/jbc.M110.127829 PMID:20847045

42. Bereczki E, Bernát G, Csont T, Ferdinandy P, Scheich H, Sántha M. Overexpression of human apolipoprotein B-100 induces severe neurodegeneration in transgenic mice. J Proteome Res. 2008; 7:2246–52. https://doi.org/10.1021/pr7006329 PMID:18473452

43. Han S, Xu Y, Gao M, Wang Y, Wang J, Liu Y, Wang M, Zhang X. Serum apolipoprotein E concentration and polymorphism influence serum lipid levels in Chinese Shandong Han population. Medicine (Baltimore). 2016; 95:e5639. https://doi.org/10.1097/MD.0000000000005639 PMID:27977609

44. Eichner JE, Dunn ST, Perveen G, Thompson DM, Stewart KE, Stroehla BC. Apolipoprotein E polymorphism and cardiovascular disease: a HuGE review. Am J Epidemiol. 2002; 155:487–95. https://doi.org/10.1093/aje/155.6.487 PMID:11882522

45. Davignon J, Gregg RE, Sing CF. Apolipoprotein E polymorphism and atherosclerosis. Arteriosclerosis. 1988; 8:1–21. https://doi.org/10.1161/01.atv.8.1.1 PMID:3277611

46. Ozturk Z, Enkhmaa B, Shachter NS, Berglund A, Anuurad E. Integrated role of two apolipoprotein E polymorphisms on apolipoprotein B levels and coronary artery disease in a biethnic population. Metab Syndr Relat Disord. 2010; 8:531–38. https://doi.org/10.1089/met.2010.0034 PMID:20715976

47. Muenchhoff J, Song F, Poljak A, Crawford JD, Mather KA, Kochan NA, Yang Z, Trollor JN, Reppermund S, Maston K, Theobald A, Kirchner-Adelhardt S, Kwok JB, et al. Plasma apolipoproteins and physical and cognitive health in very old individuals. Neurobiol Aging. 2017; 55:49–60. https://doi.org/10.1016/j.neurobiolaging.2017.02.017 PMID:28419892

48. Nordestgaard LT, Tybjærg-Hansen A, Rasmussen KL, Nordestgaard BG, Frikke-Schmidt R. Genetic variation in clusterin and risk of dementia and ischemic vascular disease in the general population: cohort studies and meta-analyses of 362,338 individuals. BMC Med. 2018; 16:39. https://doi.org/10.1186/s12916-018-1029-3 PMID:29534716

49. Palmer ND, Kahali B, Kuppa A, Chen Y, Du X, Feitosa MF, Bielak LF, O’Connell JR, Musani SK, Guo X, Smith AV, Ryan KA, Eirksdottir G, et al. Allele Specific Variation at APOE Increases Non-alcoholic Fatty Liver Disease and Obesity but Decreases Risk of Alzheimer’s Disease and Myocardial Infarction. Hum Mol Genet. 2021; 30:27977609

50. Husain MA, Laurent B, Plourde M. APOE and Alzheimer’s Disease: From Lipid Transport to Physiopathology and Therapeutics. Front Neurosci. 2021; 15:630502.
51. Zhen J, Huang X, Van Halm-Lutterodt N, Dong S, Ma W, Xiao R, Yuan L. ApoE rs429358 and rs7412 Polymorphism and Gender Differences of Serum Lipid Profile and Cognition in Aging Chinese Population. Front Aging Neurosci. 2017; 9:248. https://doi.org/10.3389/fnagi.2017.00248 PMID:28824412

52. Kane JM, Aguglia E, Altamura AC, Ayuso Gutierrez JL, Brunello N, Fleischhacker WW, Gaebel W, Gerlach J, Guelfi JD, Kissling W, Lapierre YD, Lindström E, Mendlewicz J, et al. Guidelines for depot antipsychotic treatment in schizophrenia. European Neuropsychopharmacology Consensus Conference in Siena, Italy. Eur Neuropsychopharmacol. 1998; 8:55–66. https://doi.org/10.1016/s0924-977x(97)00045-x PMID:9452941

53. Lehman AF, Lieberman JA, Dixon LB, McGlashan TH, Miller AL, Perkins DO, Kreyenbuhl J, and American Psychiatric Association, and Steering Committee on Practice Guidelines. Practice guideline for the treatment of patients with schizophrenia, second edition. Am J Psychiatry. 2004 (Suppl 2); 161:1–56. PMID:15000267

54. Woods SW. Chlorpromazine equivalent doses for the newer atypical antipsychotics. J Clin Psychiatry. 2003; 64:663–67. https://doi.org/10.4088/jcp.v64n0607 PMID:12823080

55. Williams JR. The Declaration of Helsinki and public health. Bull World Health Organ. 2008; 86:650–52. https://doi.org/10.2471/blt.08.050955 PMID:18796267

56. Randolph C, Tierney MC, Mohr E, Chase TN. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): preliminary clinical validity. J Clin Exp Neuropsychol. 1998; 20:310–19. https://doi.org/10.1076/jcen.20.3.310.823 PMID:9845158

57. Cheng Y, Wu W, Wang J, Feng W, Wu X, Li C. Reliability and validity of the Repeatable Battery for the Assessment of Neuropsychological Status in community-dwelling elderly. Arch Med Sci. 2011; 7:850–57. https://doi.org/10.5114/aoms.2011.25561 PMID:22291831

58. Zhang BH, Tang YL, Zhang WF, Wang ZR, Yang GG, Shi C, Zhang XY, Zhou DF. [Repeatable Battery for the Assessment of Neuropsychological Status as a Screening Test in Chinese: reliability and Validity]. Chin Ment Health J. 2008; 22:865–69. https://doi.org/10.3321/j.issn:1000-6729.2008.12.001

59. Wang JH, Li CB, Cheng Y, Yi ZH, Long B, Wang JJ. [Reliability and validity of repeatable battery for the assessment of neuropsychological status (RBANS) in schizophrenic patients: a preliminary study]. Shanghai Arch Psychiatry. 2009; 21:265–68. https://doi.org/10.3969/j.issn.1002-0829.2009.05.003

60. Tian W, Zeng XM, Li LX, Jin HK, Luo QZ, Wang F, Guo SS, Cao Y. Gender-specific associations between MICA-STR and nasopharyngeal carcinoma in a southern Chinese Han population. Immunogenetics. 2006; 58:113–21. https://doi.org/10.1007/s00251-006-0993-6 PMID:16547745

61. Jurinke C, Oeth P, van den Boom D. MALDI-TOF mass spectrometry: a versatile tool for high-performance DNA analysis. Mol Biotechnol. 2004; 26:147–64. https://doi.org/10.1385/MB:26:2:147 PMID:14764940

62. Zhang XY, Tan YL, Cao LY, Wu GY, Xu Q, Shen Y, Zhou DF. Antioxidant enzymes and lipid peroxidation in different forms of schizophrenia treated with typical and atypical antipsychotics. Schizophr Res. 2006; 81:291–300. https://doi.org/10.1016/j.schres.2005.10.011 PMID:16309894

63. An H, Du X, Huang X, Qi L, Jia Q, Yin G, Xiao C, Huang XF, Ning Y, Cassidy RM, Wang L, Soares JC, Zhang XY. Obesity, altered oxidative stress, and clinical correlates in chronic schizophrenia patients. Transl Psychiatry. 2018; 8:258. https://doi.org/10.1038/s41398-018-0303-7 PMID:30498208

64. Solé X, Guiné E, Valls J, Iniesta R, Moreno V. SNPStats: a web tool for the analysis of association studies. Bioinformatics. 2006; 22:1928–29. https://doi.org/10.1093/bioinformatics/btl268 PMID:16720584

65. Martorell L, Virgos C, Valero J, Coll G, Figuera L, Joven J, Pocoví M, Martorell L, Virgos C, Valero J, Coll G, Figuera L, Joven J, Pocoví M, Labad A, Villegas E. Schizophrenic women with the APOE epsilon 4 allele have a worse prognosis than those without it. Mol Psychiatry. 2001; 6:307–10. https://doi.org/10.1038/sj.mp.4000855 PMID:11326299

66. Xia X, Meng Z, Wu X, Chen S, Wu X, Han Z. Association between APOE polymorphism with the onset of schizophrenia and cognitive function. J Nat Med. 2020; 51:672. https://doi.org/10.3969/j.issn.0253-9802.2020.09.006
67. Pickar D, Malhotra AK, Rooney W, Breier A, Goldman D. Apolipoprotein E epsilon 4 and clinical phenotype in schizophrenia. Lancet. 1997; 350:930–31. https://doi.org/10.1016/S0140-6736(05)63266-7 PMID:9314875

68. Liu W, Breen G, Zhang J, Li S, Gu N, Feng G, Bai S, Shen T, Yu A, Xue H, St Clair D, He L. Association of APOE gene with schizophrenia in Chinese: a possible risk factor in times of malnutrition. Schizophr Res. 2003; 62:225–30. https://doi.org/10.1016/s0920-9964(02)00384-5 PMID:12837518

69. Schürhoff F, Krebs MO, Szöke A, Loze JY, Goldberger C, Quignon V, Tignol J, Rouillon F, Laplanche JL, Leboyer M. Apolipoprotein E in schizophrenia: a French association study and meta-analysis. Am J Med Genet B Neuropsychiatr Genet. 2003; 119B:18–23. https://doi.org/10.1002/ajmg.b.20007 PMID:12707932

70. Kecmanović M, Dobricić V, Dimitrijević R, Keckarević D, Savić-Pavičević D, Keckarević-Marković M, Ivkovic M, Romac S. Schizophrenia and apolipoprotein E gene polymorphism in Serbian population. Int J Neurosci. 2010; 120:502–06. https://doi.org/10.3109/00207451003765956 PMID:20583903

71. Tovilla-Zarate C, Medellin BC, Fresan A, Apiquian R, Dassori A, Rolando M, Escamilla M, Nicolini H. APOE-epsilon3 and APOE-219G haplotypes increase the risk for schizophrenia in sibling pairs. J Neuropsychiatry Clin Neurosci. 2009; 21:440–44. https://doi.org/10.1176/appi.neuropsych.21.4.440 PMID:19996253

72. Puglielli L, Tanzi RE, Kovacs DM. Alzheimer’s disease: the cholesterol connection. Nat Neurosci. 2003; 6:345–51. https://doi.org/10.1038/nn0403-345 PMID:12658281

73. Holtzman DM, Herz J, Bu G. Apolipoprotein E and apolipoprotein E receptors: normal biology and roles in Alzheimer disease. Cold Spring Harb Perspect Med. 2012; 2:a006312. https://doi.org/10.1101/cshperspect.a006312 PMID:22393530

74. Forero DA, López-León S, González-Giraldo Y, Dries DR, Pereira-Morales AJ, Jiménez KM, Franco-Restrepo JE. APOE gene and neuropsychiatric disorders and endophenotypes: A comprehensive review. Am J Med Genet B Neuropsychiatr Genet. 2018; 177:126–42. https://doi.org/10.1002/ajmg.b.32516 PMID:27943569

75. Villeneuve S, Brisson D, Marchant NL, Gaudet D. The potential applications of Apolipoprotein E in personalized medicine. Front Aging Neurosci. 2014; 6:154. https://doi.org/10.3389/fnagi.2014.00154 PMID:25071563

76. Liu CC, Liu CC, Kanekiyto T, Xu H, Bu G. Apolipoprotein E and Alzheimer disease: risk, mechanisms and therapy. Nat Rev Neurol. 2013; 9:106–18. https://doi.org/10.1038/nrneurol.2012.263 PMID:23296339

77. Vitali C, Wellington CL, Calabresi L. HDL and cholesterol handling in the brain. Cardiovasc Res. 2014; 103:405–13. https://doi.org/10.1093/cvr/cvu148 PMID:24907980

78. Twisk J, Gillian-Daniel DL, Tebon A, Wang L, Barrett PH, Attie AD. The role of the LDL receptor in apolipoprotein B secretion. J Clin Invest. 2000; 105:521–32. https://doi.org/10.1172/JCI8623 PMID:10683382

79. Castellano JM, Deane R, Gottesdiener AJ, Verghese PB, Stewart FR, West T, Paoletti AC, Kasper TR, DeMattos RB, Zlokovic BV, Holtzman DM. Low-density lipoprotein receptor overexpression enhances the rate of brain-to-blood Aβ clearance in a mouse model of β-amyloidosis. Proc Natl Acad Sci U S A. 2012; 109:15502–07. https://doi.org/10.1073/pnas.1206446109 PMID:22927427

80. Mahley RW, Innerarity TL, Rall SC Jr, Weissgraber KH. Plasma lipoproteins: apolipoprotein structure and function. J Lipid Res. 1984; 25:1277–94. https://doi.org/10.1194/jdr/25/9/1277 PMID:6099394

81. Elliott DA, Weickert CS, Garner B. Apolipoproteins in the brain: implications for neurological and psychiatric disorders. Clin Lipidol. 2010; 51:555–73. https://doi.org/10.2217/CLP.10.37 PMID:21423873

82. Iuliano L, Crick PJ, Zerbinati C, Tritapepe L, Abdel-Maguid W, DeMattos RB, Zlokovic BV, Holtzman DM. Low-density lipoprotein receptor overexpression enhances the rate of brain-to-blood Aβ clearance in a mouse model of β-amyloidosis. Proc Natl Acad Sci U S A. 2012; 109:15502–07. https://doi.org/10.1073/pnas.1206446109 PMID:22927427

83. Abbott NJ, Friedman A. Overview and introduction: the blood-brain barrier in health and disease. Epilepsia. 2012 (Suppl 6); 53:1–6. https://doi.org/10.1111/j.1528-1167.2012.03696.x PMID:23134489

84. Dias HK, Brown CL, Polidori MC, Lip GY, Griffiths HR. LDL-lipids from patients with hypercholesterolaemia
and Alzheimer’s disease are inflammatory to microvascular endothelial cells: mitigation by statin intervention. Clin Sci (Lond). 2015; 129:1195–206. [https://doi.org/10.1042/CS20150351] PMID:26399707

85. Li R, Wang TJ, Lyu PY, Liu Y, Chen WH, Fan MY, Xu J. Effects of Plasma Lipids and Statins on Cognitive Function. Chin Med J (Engl). 2018; 131:171–76. [https://doi.org/10.4103/0366-6999.225062] PMID:29451153

86. Chu CS, Lu T, Tsai SJ, Hong CJ, Yeh HL, Yang AC, Liu ME. APOE ε4 polymorphism and cognitive deficit among the very old Chinese veteran men without dementia. Neurosci Lett. 2014; 576:17–21. [https://doi.org/10.1016/j.neulet.2014.05.046] PMID:24887584

87. Sinclair LI, Button KS, Munafò MR, Day IN, Lewis G. Possible Association of APOE Genotype with Working Memory in Young Adults. PLoS One. 2015; 10:e0135894. [https://doi.org/10.1371/journal.pone.0135894] PMID:26287823

88. Siegel JA, Benice TS, Van Meer P, Park BS, Raber J. Acetylcholine receptor and behavioral deficits in mice lacking apolipoprotein E. Neurobiol Aging. 2011; 32:75–84. [https://doi.org/10.1016/j.neurobiolaging.2008.12.006] PMID:19178986

89. Lane-Donovan C, Wong WM, Durakoglugil MS, Wasser CR, Jiang S, Xian X, Herz J. Genetic Restoration of Plasma ApoE Improves Cognition and Partially RestoresSynaptic Defects in ApoE-Deficient Mice. J Neurosci. 2016; 36:10141–50. [https://doi.org/10.1523/JNEUROSCI.1054-16.2016] PMID:27683909

90. Shinohara M, Kanekiyo T, Yang L, Linthicum D, Shinohara M, Fu Y, Price L, Frisch-Dailey JL, Han X, Fryer JD, Bu G. APOE2 eases cognitive decline during Aging: Clinical and preclinical evaluations. Ann Neurol. 2016; 79:758–74. [https://doi.org/10.1002/ana.24628] PMID:26933942

91. Su YY, Zhang XD, Schoepf UJ, Varga-Szemes A, Stubenrauch A, Liang X, Zheng LJ, Zheng G, Kong X, Xu Q, Wang SJ, QI RF, Lu GM, et al. Lower functional connectivity of default mode network in cognitively normal young adults with mutation of APP, presenilins and APOE ε4. Brain Imaging Behav. 2017; 11:818–28. [https://doi.org/10.1007/s11682-016-9556-z] PMID:27189159

92. Prada D, Colicino E, Power MC, Cox DG, Weisskopf MG, Hou L, Spiri lii A, Vokonas P, Zhong J, Sanchez-Guerra M, Herrera LA, Schwartz J, Baccarelli AA. Influence of multiple APOE genetic variants on cognitive function in a cohort of older men - results from the Normative Aging Study. BMC Psychiatry. 2014; 14:223. [https://doi.org/10.1186/s12888-014-0223-x] PMID:25085564

93. Davies G, Harris SE, Reynolds CA, Payton A, Knight HM, Liewald DC, Lopez LM, Luciano M, Gow AJ, Corley J, Henderson R, Murray C, Pattie A, et al. A genome-wide association study implicates the APOE locus in nonpathological cognitive ageing. Mol Psychiatry. 2014; 19:76–87. [https://doi.org/10.1038/mp.2012.159] PMID:23207651

94. Vila-Rodriguez F, Lang DJ, Baizt H, Gicas K, Thorton AE, Ehmnn TS, Smith GN, Barr AM, Torres JI, Kopala LC, MacEwan GW, Müller DJ, Kennedy JL, et al. Verbal memory improvement in first-episode psychosis APOE-ε4 carriers: a pleiotropic effect? Neuropsychiatr Dis Treat. 2017; 13:2945–53. [https://doi.org/10.2147/NDT.S150488] PMID:29263671

95. Ma C, Li J, Bao Z, Ruan Q, Yu Z. Serum Levels of ApoA1 and ApoA2 Are Associated with Cognitive Status in Older Men. Biomed Res Int. 2015; 2015:481621. [https://doi.org/10.1155/2015/481621] PMID:26682220