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Apolipoprotein A1 And Depression: A Two-Sample Mendelian Randomization Analysis

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Abstract

Object: Although some observational studies have reported the correlation between lipid metabolites and depression, the causal relationship remains uncertain. In this study, we aimed to assess the causal relationship between apolipoprotein A1(ApoA1) and depression, especially with broad depression.

Materials and Methods: We used 10 independent single nucleotide polymorphisms associated with ApoA1 as instrumental variables (IVs) in the large genome-wide association study (GWAS) of circulating metabolites from a UK biobank. Corresponding data on depression and its subtypes were obtained from 113,769 depression patients and 208,811 controls in 3 GWAS studies. The inverse variance weighting (IVW) method was used to calculate the random estimate, and several alternative methods and multiple sensitivities were used for analysis.

Results: We found that genetic predisposition to lower expression of ApoA1 was associated with higher risk of broad depression, with an odds ratio (OR) of 0.990 (95% confidence interval (CI),0.981–0.999; p = 0.005) per log-odds increment in expression of ApoA1, but not with probable major depressive disorder (OR, 0.997; 95, CI 0.992-1.000; p = 0.065). The association of ApoA1 with broad depression was overall robust to sensitivity analyses. While the IVW result showed that ApoA1 is related to International Classification of Diseases (ICD, version 9 or 10)-coded MDD (OR, 0.991; 95% CI, 0.983 to 0.999; P = 0.038)), but the sensitivity analysis of ApoA1 and depression showed no statistical significance in nucleotide polymorphisms (SNPs).

Conclusion: We provided evidence for a possible causal effect of ApoA1 on decreased risk of broad depression. However, future research is required to investigate whether rational intervention on ApoA1 may help to reduce societal burden of broad depression.

Keywords: Mendelian randomization analysis; Depression; Apolipoprotein A1

Introduction

Depression is an affective mental disease characterized by a significant and persistent low mood. Most of the patients are depressed and pessimistic. In recent years, the incidence of depression has been increasing year by year [1]. Depression patients often have cognitive abnormalities such as attention function, memory function, processing speed, executive function and selective cognitive control. However, the mechanism and related influencing factors of cognitive impairment in depression patients are not clear. At present, research on cognitive dysfunction mainly focuses on patients with depression, schizophrenia and elderly people with chronic diseases.

The lipids in serum are divided into fat (mainly triglycerides) and lipoids (including cholesterol, sugar, fat and phospholipids). Lipids are the main source of energy in the human body, which can maintain body temperature and protect organs. At present, clinical detection of basic blood lipid includes TC, TG, LDL-C and HDL-C [2]. The clinical application value of ApoA1, apolipoprotein B, and lipoprotein LP (a) has attracted increasing attention. Research evidence indicate that blood lipid metabolism levels are associated with depression. Abnormal lipid metabolism can lead to a variety of chronic diseases, among which lipid metabolism is closely related to depression and anxiety disorders [3].

Mendelian randomization analysis is an important method for causal inference in observational studies. It uses exposure- related genotypes as IVs. However, traditional Mendelian randomization analysis requires genotype and exposure and outcome data from the same individual, and the cost of data detection is relatively high. In recent years, two-sample Mendelian randomization analysis (2MR) has been gradually developed. Compared with traditional Mendelian randomization analysis, it allows the data of gene associated with exposure and outcome from two

independent sample populations, which has greatly improved the efficiency and feasibility of etiology research and has been widely used in the study of causal association between risk factors and disease. In this study, the 2MR was used to select single SNP sites as IVs. The causal association between ApoA1 and depression was explored based on a publicly available GWAS database, and the effect size was estimated, and the stability of the results was evaluated through sensitivity analysis.

In summary, although traditional observational epidemiological studies have confirmed the relationship between ApoA1 and depression, the causal relationship between the two is still controversial. This study intends to use the 2MR method to investigate the causal association between ApoA1 and depression combined with the principle and adaptive conditions of the 2MR method.

Materials and Methods

Date source and single-nucleotide polymorphism selection

ApoA1 related SNPs data was from a large GWAS study on circulating metabolites published in Nat Commun, 2016 [4]. In order to minimize the potential bias caused by population stratification and make the two samples have similar genetic characteristics, the European population database was selected for research. The sample size of the database is 20,687, including 11,760,646 SNPs. In order to avoid the possible bias caused by the strong linkage disequilibrium (LD) between SNPs, independent SNPs with genome-wide significance associated with ApoA1 were screened from the database in this study. The screening criteria were: ①P < 5*10-8 of the correlation effect between ApoA1 and IVs; ②the physical distance between every two genes was >10000kb, and the R2 of LD between genes was < 0.001. Finally, 10 SNPs meeting the above conditions were included in the study. Effect allele (EA), **β** value, SE and P value were extracted from the database.

The data on the effect between SNPs and depression were extracted from a meta-analysis of a GWAS study of depression in European population published in Nat Commun, 2018 [5]. The data included 113,769 depression patients and 208,811 control in 3 GWAS study. The 10 SNPs selected in this study can find corresponding information in the database. Then, we extract the Log (OR) value, the corresponding standard error and P value information of the effector gene from the database.

Statistical analyses and assessment of pleiotropy

In order to satisfy the premise that the effect of instrumental variables on depression can only be achieved by ApoA1, we used the method of Egger regression to test the hypothesis of the direct pleiotropy of IVs [6]. IVW method was used to estimate the causal effect between ApoA1 and depression, and the final result was shown by forest graph [7]. In order to ensure the accuracy of the results and eliminate the influence of research methods on the accuracy of the results, various 2MR analysis methods (MR Egger, Maximum likelihood, Weighted median) were used in this study to test the accuracy of the results [6,8,9]. The heterogeneity of the SNPs was tested by Cochran's Q test [10]. Leave one out (LOO) method was used for sensitivity analysis of the results, that is one of the SNPs was eliminated in turn, and the remaining SNPs were used as instrumental variables for analysis of the two samples [11]. IVW method was used to estimate the total effect and observe the stability of effect estimation, so as to determine the degree of influence of individual SNPs on the estimated value of causal correlation. To avoid possible association with confounding factors that might influence the results of the study, the site was retrieved in Pheno Scanner [12]. Steiger analysis was performed to rule out the reverse causal association and verify the causal relationship [13]. Two Sample MR packets in R version 3.5.3 were used for all statistical analyses.

Results

10 instrumental variables were preliminarily selected from the GWAS database of ApoA1 and all of them met the requirements of P>5*10-8 in the depression database. Table 1 lists the relevant information of the 10 gene data analyzed in this study.

Table 1: The strength of the effect SNP alleles associated with ApoA1 and broad depression.

SNP	EA	非EA	ApoA1			Broad depression		
			P 值	Beta	Se	P 值	Beta	Se
rs11632618	A	G	7.76E-13	0.174133	0.024085	0.014388	-0.00563	0.002301
rs144064722	G	A	8.30E-09	0.203723	0.035039	0.878284	0.000597	0.003898
rs1461729	G	A	1.77E-08	0.086363	0.015193	0.473489	0.001391	0.001941
rs174594	A	C	1.32E-11	0.071714	0.010504	0.137316	-0.00181	0.001218
rs1883025	T	C	2.86E-09	-0.079839	0.013321	0.549516	0.0008099	0.001353
rs247617	A	C	7.90E-63	0.197243	0.011688	0.98546	-2.29E-05	0.001258
rs261291	C	T	2.58E-39	0.144314	0.010905	0.51434	0.0008018	0.00123
rs6507939	C	A	5.03E-14	0.108424	0.014268	0.081433	-0.002881	0.001653
rs73424577	G	A	9.78E-10	0.186041	0.030161	0.021291	-0.008149	0.003539
rs75835816	C	G	1.67E-08	-0.22095	0.038801	0.11513	0.0071292	0.004525

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Associations of genetically determined risk of ApoA1 with broad depression using multiple MR methods are reflected in Figure 1.We found evidence of a detrimental causal effect of ApoA1 on broad depression in the primary analysis (IVW OR, 0.990 for broad depression per log-odds increment in ApoA1 risk, 95% CI 0.981–0.999; p = 0.005; Figure 2), and the heterogeneity between each gene was low (Q = 13.330, P = 0.101); The effect estimates of the MR-Egger method, the weighted median method, and the maximum likelihood estimation method are OR = 0.996 (95% CI: 0.969-1.023; P = 0.762), OR = 0.990 (95% CI: 0.983-0.998; P = 0.015) and OR = 0.990 (95% CI: 0.982-0.997; P = 0.009).Although the estimated value of MR Egger's method was not statistically significant due to its relatively low self-test efficiency, the effect estimates of the weighted median method and the maximum likelihood estimation method were close to that of the IVW method.

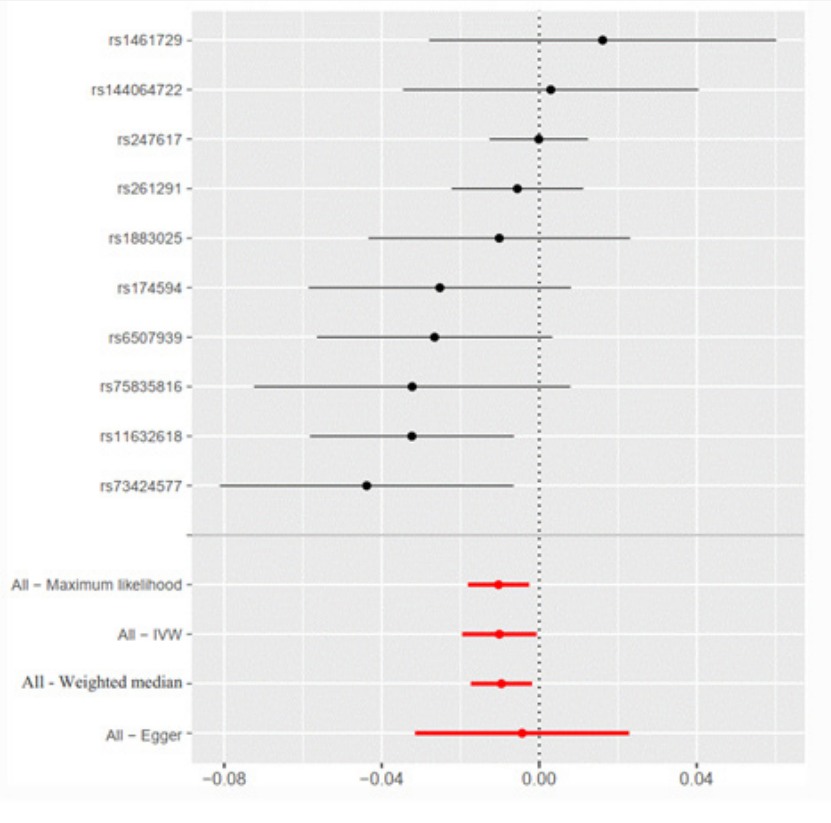

Figure 1: Two-sample Mendelian randomization estimates of ApoA1 with broad depression from MR Egger, Maximum likelihood, Weighted median.

The results of sensitivity analysis in this study were shown in the Table 2 and Figure 2. It showed that the comprehensive effect of all IVs was OR=0.990, (95%CI: 0.980-0.999, P=0.035<0.05), indicating that ApoA1 was a protective factor for generalized depression. The results of directional test were shown in the Table 3. The statistical analysis results suggested that ApoA1 was the cause and depression was the effect.

Table 2: The results of leave one out method.

leave One out SNP	OR	95% CI	P
rs11632618	0.968183	0.943-0.994	0.014386
rs144064722	1.002935	0.966-1.041	0.878284
rs1461729	1.016237	0.972-1.062	0.473482
rs174594	0.975079	0.943-1.008	0.137311
rs1883025	0.989907	0.958-1.023	0.549511

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rs247617	0.999884	0.987-1.012	0.98546
rs261291	0.994459	0.978-1.011	0.514327
rs6507939	0.973782	0.945-1.000	0.081432
rs73424577	0.957143	0.922-0.993	0.021287
rs75835816	0.968249	0.930-1.007	0.11513
rs11632618	0.968183	0.981-0.999	0.014386
rs144064722	1.002935	0.969-1.023	0.878284
rs1461729	1.016237	0.943-0.994	0.473482

Table 3: The results of directional test.

Exposure	Outcome	SNP_R2. Exposure	SNP_R2. Outcome	Correct_Causal_Direction	Steiger_pval
Apolipoprotein A1	Depression (broad)	0.041862	6.31E-05	TRUE	1.98E-153

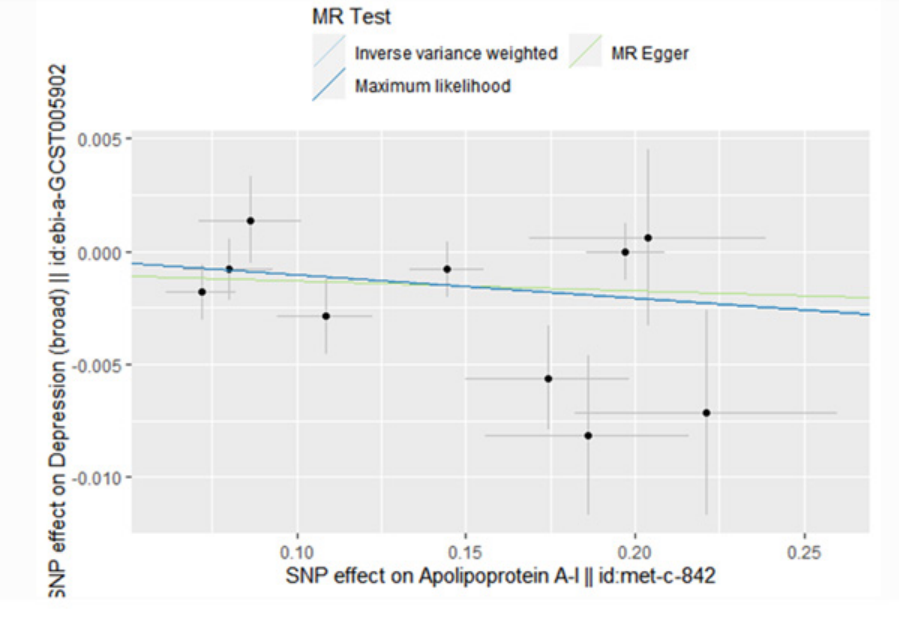

Figure 2: Scatterplot of SNP potential effects on ApoA1 vs broad depression, with the slope of each line corresponding to estimated MR effect per method.

Conversely, ApoA1 was not causally related to probable major depressive disorder (OR 0.997; 95CI 0.992-1.000; p = 0.065). While the IVW result showed that ApoA1 was related to MDD (OR, 0.991; 95% CI, 0.983 to 0.999; P = 0.038)), but the association of ApoA1 with MDD was no statistical significance to sensitivity analyses.

Discussion

According to the current research, the symptoms of depression accompanied by cognitive impairment will continue to occur from the onset stage to the remission stage, and the depression will seriously affect the cognitive such as memory, attention, language, visual span, executive function and so on [14]. In recent years, epidemiological investigations have found abnormal blood lipid metabolism in patients with depressive disorders. The cause may be related to poor appetite and weight loss caused by depression, which reduces lipid metabolism levels, or decreased lipid synthesis caused by depression [15]. Current studies have confirmed that the metabolic levels of TG, TC and LDL-C are closely related to the changes of cognitive function in patients with depression [16]. However, there is still no rigorous and systematic theory to elucidate the causes and specific pathogenesis of cognitive impairment in patients with depression. However, other socio-demographic data, lipidomic, proteomics, genetics, or other biological indicators and the causes and mechanisms of cognitive function are still relatively unclear. More importantly,

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the relationship between abnormal lipid metabolism and the occurrence of cognitive dysfunction in depressed patients still needs to be further studied and confirmed, which is the research focus and direction that we should pay attention to in the future.

Therefore, this study used two large-scale GWAS databases to conduct a two-sample Mendelian randomized analysis to explore the causal relationship between ApoA1 and depression. We found that genetic predisposition to lower expression of ApoA1 was associated with higher risk of broad depression (0R,0.990; 95% CI,0.981–0.999; p= 0.005), which suggests ApoA1 is a protective factor for depression. The causal association between apolipoprotein A1 and depression was investigated in terms of etiology, and a large sample size ensured a high degree of final causal effect value. This study provides clearer clues for the prevention of depression and has greater significance for the prevention of depression in the general population. However, this study also has some limitations. First, the 2MR analysis requires that the two data come from the same population but do not overlap two samples. This study ensures that both databases are from European populations as much as possible, and try to avoid racial bias, but due to the lack of individuals the data does not strictly guarantee the independence of the two samples. In addition, we used only one of the many genetic variants studied by the GWAS, which may lead to a decrease in the accuracy of IVs in predicting the risk of depression.

In summary, our study demonstrated the existence of a causal link between apolipoprotein A1 and depression in plasma by using Mendelian randomization analysis, thereby proving a causal association between apolipoprotein A1 concentration and depression at the genetic level.

Ethics Approval and Consent to Participate

This study was approved by the human ethics committee of the Seven Affiliated Hospital at Sun Yat-Sen University, and written informed consent was obtained from each participant.

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