Influence of genetic polymorphisms in homocysteine and lipid metabolism systems on antidepressant drug response

**CURRENT STATUS:** UNDER REVIEW

**Baoyu Yuan**  
Southeast University Zhongda Hospital Department of Neurology

**Xiaoyan Sun**  
Southeast University Zhongda Hospital

**Zhi Xu**  
Southeast University Zhongda Hospital

**Mengjia Pu**  
Southeast University Zhongda Hospital

**Yonggui Yuan**  
Southeast University Zhongda Hospital Department of Psychiatry

**Zhijun Zhang**  
Southeast University

✉ janemengzhang@vip.163.com**Corresponding Author**  
**ORCID:** 0000-0001-5480-0888

**DOI:**  
10.21203/rs.2.20389/v2

**SUBJECT AREAS**  
Psychiatry

**KEYWORDS**  
Depression, Antidepressant, MTHFR, ApoE, ApoA4, Genetic polymorphism
Abstract

Background: Variation in genes implicated in homocysteine and lipid metabolism systems may influence antidepressant response. This study was aimed to investigate how the MTHFR, ApoE and ApoA4 polymorphisms determine this response to treatment.

Methods: A total of 281 Han Chinese patients received a single antidepressant drug (SSRI or SNRI) for at least 6 weeks. The Hamilton Depression Rating Scale (HDRS-17) was used to evaluate the severity of depressive symptoms and the therapeutic effects of the drug administered. Eight single nucleotide polymorphisms (SNPs) of MTHFR, ApoE and ApoA4 genes were detected using gene chips. Differences in clinical variables between the responders and non-responders, as well as between remission and non-remission groups, were examined using the independent samples t test and Pearson’s χ² test. In addition, the associations of single loci and haplotypes with treatment response were analyzed.

Results: Haplotype (C-A) in MTHFR (rs1801133 and rs1801131) was significantly associated with better antidepressant response in the 8-week antidepressant group overall (P = 0.0007), and in the male subgroup (P = 0.003), and SNRI subgroup (P = 0.001). The ApoE rs405509 C allele was significantly associated with worse antidepressant response in the 6-week male subgroup (P = 0.004), while the 405509 AA genotype was associated with better antidepressant efficacy in the 6-week group overall (P = 0.006) and male subgroup (P = 0.002). Haplotype (G-A) in APOE (rs7412 and rs405509) was significantly associated with better antidepressant response in 6-week male subgroup (P = 0.003), G-C haplotype was associated with better response in 6-week SNRI subgroup, APOA4 rs5092 G allele was associated with worse antidepressant response in 6-weeks male subgroup (P = 0.037), SNRIs subgroup (P = 0.097) and 8-weeks female subgroup (P = 0.045), APOA4 rs5092 GG genotype was associated with worse antidepressant efficacy in 6-week SNRI subgroup (P = 0.008).
Conclusions: The haplotype in MTHFR (rs1801131-rs1801133) C-A type was associated with better antidepressant efficacy, especially in males and in patients using SNRIs. The efficacy of antidepressants may be better in ApoE rs405509 A allele and AA genotype carriers, but worse in ApoA4 rs5092 G allele and GG genotype carriers.

Background

Major depressive disorder (MDD) is a common mental disorder with high rates of morbidity, recurrence, and suicide [1, 2]. Although newer antidepressant drugs are generally well tolerated and relatively effective, only 30–40% of patients achieve full remission [3]. Partial remission results in greater suffering among patients, as well as higher costs [4]. The variability in antidepressant drug response can be attributed to several factors, including genetic and environmental influences [5]. Therefore, several authors have attempted to identify variables that could predict antidepressant response, and have suggested several predictors, including clinical, psychosocial, psychophysiological, neuropsychological, neuroimaging, and genetic markers. It has also been suggested that combinations of these variables may improve predictions of treatment response [6-8]. Meta-analyses and consensus suggested that genetic factors are thought to play a pivotal role in individual responses to antidepressant treatment [9, 10]. Genetic research generally focuses on polymorphisms of target proteins, which are related to the mechanisms of action of antidepressant drugs.

Several studies have shown high folate deficiency prevalence rates in depression [11, 12], presumably because of its impact on neurotransmitter synthesis, which relies on the folate-dependent one-carbon pathway. Low folate level may dampen antidepressant response, increase the risk of depressive relapse, and delay improvement in individuals treated with antidepressants [13]. Folate supplementation appears to improve the response to selective serotonin reuptake inhibitors (SSRIs) [14, 15]. One particular focus
with respect to the connection between folate and depression has been the enzyme
methylenetetrahydrofolate reductase (MTHFR) [16], which synthesizes 5-
methyltetrahydrofolate, a carbon donor involved in the methylation of homocysteine (Hcy)
to methionine. This enzyme is encoded by the MTHFR gene on chromosome 1 locus q36.3
in humans. A1298C missense mutation (cytosine-to-thymine) in the MTHFR gene results in
an alanine-to valine substitution that renders MTHFR thermolabile, and may lead to
elevated plasma Hcy, a vascular risk factor [17]. Many recent studies on vascular
depression have suggested that chronic lesions in small blood vessels and capillaries
could play a role in the pathogenesis of depression [18]. Furthermore, various lines of
research have suggested MTHFR polymorphisms might enhance the environmental risks
(such as low folate intake) for MDD via the interaction between genetic and environmental
factors [19]. Several studies performed the association between MTHFR polymorphisms
and antidepressant treatment response in different populations, which the results were
contradictory [20-24]. Therefore, the first purpose of this study was to investigate how
MTHFR polymorphisms affect antidepressant efficacy in Chinese Han MDD population.

Apolipoproteins (Apo) are lipid-binding proteins involved in the transport of lipids in
plasma. Several studies suggested that changes in serum lipid composition may be related
to MDD [25]. Apolipoprotein E (ApoE) is essential for the normal catabolism of triglyceride-
rich lipoprotein constituents. Accumulating evidence indicates that apoE polymorphism
affects multiple physiopathological pathways in coronary heart disease and Alzheimer’s
disease (AD) [26, 27]. ApoE including epsilon 2 (ε2), ε3, and ε4 alleles, is encoded by a
polymorphic gene located on chromosome 19 [28]. Although protective effects of ApoE ε2
have been reported in MDD, and ApoE ε4 may be associated with late-onset depression
[29], the conclusions of previous studies were not in complete agreement. The present
study focused on the ApoE gene promoter region and coding region to investigate the
relationships between polymorphic loci and antidepressant efficacy. Apolipoprotein A4 (ApoA4) is another protein involved in lipid metabolic regulation, and has been shown to activate lecithin-cholesterol acyltransferase and cholesterylster transfer protein [30]. Data-driven analysis showed that ApoA4 has very high accuracy for discriminating individuals with remitted late-life depression (LLD) compared to never-depressed control participants [31].

A single genetic variant cannot explain the consistent variability observed in patient response to psychiatric treatment [32]. Multiple genetic variations in the Hcy and lipid metabolism pathways could explain more of the variance than a single genetic polymorphism. Therefore, in the present study, we enrolled highly homogeneous MDD patients, evaluated the efficacy of antidepressant therapy every two weeks after received a single antidepressant drug[]and defined response and remission at 6 weeks and 8 weeks respectively. Furthermore, we intended to confirm the association of MTHFR, ApoE and ApoA4 with MDD and antidepressant response to gain a better understanding of the roles of both genetic and clinical factors in the response to antidepressant treatment.

Methods

Subjects

The subjects were Han Chinese inpatients referred to five psychiatric hospitals (Beijing, Changsha, Huaian, Nanjing, and Yangzhou). All patients were 18–60 years old and fulfilled the criteria for a diagnosis of MDD according to the Diagnostic and Statistical Manual of the American Psychiatric Association (DSM-IV) [33]. All subjects had a new diagnosis, or had recently relapsed, and all were drug-free for over 2 weeks and had a baseline score ≥ 18 on the 17-item HAMA(HDRS-17) [34], having presented with depressive symptoms for at least 2 weeks before entry into the study. The diagnoses were made by two independent senior psychiatrists and were confirmed by a third psychiatrist blinded to the
previous evaluations. Exclusion criteria included documented history of a diagnosis on Axis 1 (including substance misuse, schizophrenia, schizoaffective disorder, bipolar disorder, generalized anxiety disorder, panic disorder or obsessive-compulsive disorder) of DSM-IV, personality disorder, mental retardation, pregnancy, lactation, primary organic disease or other illness impairing psychiatric evaluation, or a history of electroconvulsive therapy within the previous 6 months. Newly diagnosed patients were also excluded if they had a manic episode in the 12 months following entry. All subjects provided written informed consent for participation in the study, which was approved by the ethics committee of each participating hospital, in accordance with the Declaration of Helsinki. A flow chart of subject recruitment is shown in Chart 1.

**Antidepressant treatment and clinical evaluation**

A total of 281 Han Chinese patients received a single antidepressant drug (SSRI or SNRI) prescribed according to local clinical practice guidelines for at least 6 weeks, and 275 cases were followed up for 8 weeks. We interviewed each patient biweekly and recorded treatment duration, dosage, outcome, and compliance, using the HDRS-17 to assess the severity of symptoms and therapeutic efficacy while blinded to patient genotypes. A meeting was held for investigators from the different sites before commencement of the study for assessment, training, and standardization of techniques. The assessing psychiatrists at different clinical centers showed high interrater agreement regarding outcomes and side effects. Dose increases of the antidepressant drugs prescribed at baseline were allowed if the patient had not achieved Clinical Global Impression (CGI) change scores indicating “much improved” or “very much improved.” Concomitant psychotropic medications were not permitted, except for low-dose benzodiazepine anxiolytic (alprazolam, 0.4–0.8 mg/day; estazolam, 1–2 mg/day) for alleviation of insomnia. Drug side effects were assessed with the Treatment Emergent Symptom Scale
(TESS) (Guy, 1976) every 2 weeks, and drug compliance was also monitored routinely via interviews with nursing staff. “Response” was defined as a reduction of at least 50% in the HDRS-17 total score after 6 weeks of treatment, while “remission” was defined as a total HDRS-17 score ≤ 7 points after 8 weeks of treatment, according to the Guidelines for Biological Treatment of Unipolar Depressive Disorders of the World Federation of Societies of Biological Psychiatry [35]. Patients requiring a change in antidepressant drug or demonstrating non-adherence were excluded from the study.

**Gene selection and genotyping methods**

Three candidate genes were selected based on evidence for the involvement of vascular risk factors and lipid metabolism in the mechanism of depression, including *MTHFR*, *ApoE*, and *ApoA4* genes. Eight single nucleotide polymorphisms (SNPs) were detected with minor allele frequency (MAF) values of > 5% in the Asian population, according to the dbSNP and HapMap databases and using gene chips (Table S1).

Blood was collected in 5-ml EDTA vacutainers and stored at −80°C until genotyping. Genomic DNA was extracted using an NPK-100 Magextractor-genome kit (Toyobo, Osaka, Japan). After quality assessment, DNA samples (250 ng each) were genotyped by Berkeley Biotech Inc. (Menlo Park, CA) using GoldenGate assays (Illumina Inc., San Diego, CA). All of the SNPs selected for the custom oligo pooled assays had Illumina design scores > 0.6. All of our samples had Illumina 10% GenCall scores > 0.4 and call rates > 90%. Genotype data on SNPs were generated using Beadstudio 3.0 (Illumina) and were exported in Excel format for further analysis.

**Statistical analysis**

Differences in clinical variables between responder and non-responder groups, as well as remission and non-remission groups, were evaluated by Student’s *t* test or Pearson’s *χ*² test using SPSS software (version 13.0; SPSS Inc., Chicago, IL). Haploview 4.0 was used to
analyze Hardy–Weinberg equilibrium (HWE), MAF, percentage of successful genotyping for each marker (%gene), and linkage disequilibrium (LD; both D' and r2).

Population power analysis indicates that our sample of 281 subjects has 88.6% power to detect significant (p < 0.05) differences between response rates of 71 and 77%, i.e. group differences in the proportion of responders are less than 12.3%. In addition, genetic polymorphisms were associated with therapeutic effects by comparing allele, genotype and haplotype distributions of MTHFR, APOE, and APOA4 between responders and non-responders, remitters and non-remitters using UNPHASED 3.0.13 (Dudbridge, 2003), and correct the results using age, baseline HDRS-17 score, gender and drug type as covariates. To investigate these relationships in the context of sex and drug type subgroups, we used logistic regression analysis (SPSS version 13.0) to explore the interactions between genotypes and gender or drug type on treatment outcome, using age and HDRS-17 baseline score as covariates. 1000 random permutations were performed using UNPHASED 3.0.13 software to correct p-values for multiple testing in the allelic, genotypic and haplotype association analyses, P <0.05 was considered statistical significance.

Results

(1) Characteristics of study participants

A total of 281 patients completed a 6-week antidepressant treatment course. Among these patients, 205 achieved a response and the response rates about 72.9%. The demographic and clinical characteristics of patients in the responder and non-responder groups are shown in Table 1. There were no significant differences between the 6-week responder and non-responder groups in sex, age, drugs used, years of education, or family history of mood disorders. However, the baseline HDRS-17 score was significantly different between these two groups (t = 2.891, P=0.004).
A total of 275 patients completed 8-week antidepressant treatment. Among these patients, 144 achieved remission and the remission rates about 52.4%. There were no significant differences in age, number of years of education, family history, baseline HDRS-17 score, or antidepressant agents used between remission and non-remission groups (all $P > 0.05$), while the proportion of male patients and number of episodes were significantly higher in the non-remission group than the remission group ($t = 2.381, P=0.018$ and $t = -1.983, P=0.049$, respectively), as shown in Table 1 and 2.

(2) Allele frequency and linkage disequilibrium

Among the eight SNPs of the three genes investigated, two (ApoA4 rs5101 and rs675) were eliminated as they had MAF < 5%, while the remaining six SNPs were subjected to further statistical analyses (table S1). LD analysis showed that two SNPs (rs1801133, rs1801131) of the MTHFR gene were in near 100% LD ($D' = 1.0, r^2 = 0.177$), while two other SNPs (rs405509, rs439401) of the ApoE gene were in strong LD ($D' = 0.961, r^2 = 0.505$). The other SNPs showed no LD.

(3) Single polymorphism associations for the MTHFR, ApoE and ApoA4

Analysis of single-locus effects revealed that genotypes of the SNPs: rs1801131 and rs1801133 (MTHFR) had no significant association with antidepressant response in 6 weeks (The detail negative results see the supplement material Table S2, S3). However, MTHFR rs1801133 TT genotype was related to the efficacy of antidepressants, and its distribution frequency is significantly higher in the non-remission group than in the remission group (group overall: $\chi^2 = 6.328, P = 0.012$; female subgroup: $\chi^2 = 4.145, P = 0.042$; SSRI subgroup: $\chi^2 = 5.808, P = 0.016$), but the results did not withstand permutation correction (The detail negative results see the supplement material Tables S4 and S5).
The ApoE rs405509 C allele was significantly associated with the efficacy of antidepressants at 6 weeks (Overall group: $\chi^2 = 6.27, P = 0.012$, Male subgroup: $\chi^2 = 8.445, P = 0.004$); SNRI subgroup: $\chi^2 = 6.707, P = 0.0096$), compared with the A allele, the antidepressant efficacy of the C allele carrier is worse (Overall group: OR = 0.6, 95% CI = 0.4-0.9; Male subgroup: OR = 0.41 95% CI = 0.22-0.75; SNRI subgroup: OR = 0.42, 95% CI = 0.22-0.82), in which the results only in the male subgroup withstood 1000 permutations testing ($P^* < 0.05$); The C allele was also compared with the 8-week SNRI subgroup The worse antidepressant efficacy was related ($P = 0.031$, OR = 0.70), but the results did not withstand permutation testing. The rs405509 AA genotype was significantly associated with the efficacy of antidepressants at 6 weeks (Overall group: $\chi^2 = 7.41, P = 0.006$; Male subgroup: $\chi^2 = 9.77, P = 0.002$; SNRI subgroup: $\chi^2 = 6.41, P = 0.011$), compared with AC genotype, AA genotype carriers have better antidepressant effect (Overall group: 95% CI =0.48(0.28-0.84); Male subgroup: OR = 0.28 95% CI = 0.12-0.66; SNRI subgroup: OR = 0.34, 95% CI = 0.13-0.87). The results in the Overall group ($P^* = 0.04$) and SNRI subgroup ($P^* = 0.009$) withstood permutation testing. (Table 3)

The APOE rs7412 G allele was associated with better antidepressant efficacy in the male subgroup (6-week male subgroup: $P = 0.009$, OR = 3.15; 8-week male subgroup: $P = 0.0109$, OR = 3.92), but none of the results did not withstand permutation testing. There was no significant correlation between the ApoE rs7412 genotype and the efficacy of antidepressants (all $P> 0.05$). There was no significant correlation between APOE rs439401 allele and antidepressant efficacy (all $P > 0.05$). The rs439401 GG genotype was associated with better antidepressant efficacy in the 8-week SSRI subgroup ($\chi^2=4.313, P=0.038$, OR=2.07, 95% CI = 0.81-5.2), but the results did not withstand permutation testing (The detail negative results see the supplement material Table S6, S7, S8 and S9).

The ApoA4 rs5092 G allele was associated with antidepressant response, of which the
antidepressant effect of G allele carriers was poor in 6-week male subgroup ($\chi^2 = 4.334, P = 0.037, OR = 0.55, 95\% CI = 0.31-0.97$), 6-week SNRI subgroup ($\chi^2 = 7.241, P = 0.007, OR = 0.42, 95\% CI = 0.22-0.80$) and 8-week female subgroup ($\chi^2 = 4.014, P = 0.045, OR=0.64 95\% CI = 0.41-0.99$), the result withstood permutation testing (6-week male subgroup: $P^* = 0.03$, 6-week SNRI subgroup: $P^* = 0.005$, 8-week female subgroup: $P^* = 0.03$) (Table 3). Furthermore, the ApoA4 rs5092 GG genotype was significantly associated with antidepressant efficacy in the 6-week male subgroup ($\chi^2 = 4.059, P = 0.034$) and SNRI subgroup ($\chi^2 = 6.964, P = 0.008$). Compared to the AA and AG haplotypes, the GG haplotype was associated with reduced likelihood of a good response (male subgroup, $OR = 0.26, 95\% CI = 0.08-0.87$; SNRI subgroup, $OR = 0.13, 95\% CI = 0.02-0.65$), but only the SNRI subgroup withstood permutation correction ($P^* = 0.019$) (Table 3). The other negative results see the supplement material Table S10, S11, S12 and S13.

(4) Haplotype associations for the MTHFR and ApoE

We examined the associations of haplotypes derived from the SNPs in MTHFR and ApoE with antidepressant response, limiting our analysis to haplotypes with a frequency of 5%. Table 4 shows that the haplotype (C-A) in MTHFR (rs1801133 and rs1801131) was significantly associated with antidepressant response in the 8-week antidepressant group overall ($\chi^2 = 11.39, P = 0.0007$), male subgroup ($\chi^2 = 8.767, P = 0.003$), and SNRI subgroup ($\chi^2 = 10.51, P = 0.001$). In comparison to the T-A haplotype and C-C haplotype, the C-A haplotype was associated with increased likelihood of good remission in the group overall (OR = 1.718, 95\% CI = 1.178-2.505), and in the male subgroup (OR = 1.971, 95\% CI = 1.088-3.572) and SNRI subgroup (OR = 2.251, 95\% CI = 1.24-4.085), all of the results outlined above withstood permutation testing (overall: $P^* = 0.02$, male subgroup: $P^* = 0.012$, SNRI subgroup: $P^* = 0.002$) (Table 4). The haplotype in MTHFR (rs1801133 and
rs1801131) was no significant association with antidepressant response in the 6-week (all P >0.05), and the detail results were provided in the supplement material S14, S15).

Another analysis of haplotype effects demonstrated that haplotype (G-A) of ApoE (rs7412 and rs405509) was significantly associated with antidepressant response in the 6-week male subgroup ($\chi^2 = 8.687, P = 0.003$) In comparison to the A-A haplotype, the G-A haplotype was associated with increased likelihood of a better response (OR = 1.24, 95% CI = 0.12–12.9). Haplotype (G-C) in ApoE (rs7412 and rs405509) was significantly associated with antidepressant response in the 6-week SNRI subgroup ($\chi^2 = 8.24, P=0.0041$). In comparison with the A-A haplotype, the G-C haplotype was associated with increased likelihood of a better response (OR = 1.04, 95% CI = 0.19–5.64). All of the results outlined above withstood permutations testing (male subgroup: $P^* < 0.05$, SNRI subgroup: $P^* = 0.049$) (Table 5).

We also found that in the overall group, haplotypes G-A and G-C (rs7412 and rs405509), haplotypes CG (rs405509 and rs439401), and haplotypes GCG (rs7412, rs405509, and rs439401) was significantly associated with antidepressant response in the 6-week (rs7412-rs405509: G-A, $\chi^2 = 5.046, P= 0.025$; G-C, $\chi^2 = 4.313, P = 0.038$; rs405509-rs439401: $\chi^2 = 5.13, P = 0.024$; rs7412-rs405509-rs439401: $\chi^2 = 3.907, P = 0.048$); In the male subgroup, haplotypes A-G, C-G (rs405509 and rs439401), and haplotypes GAG (rs7412, rs405509, and rs439401) were associated with antidepressant response (rs405509-rs405509: A-G, $\chi^2 = 5.876 , P = 0.015$; C-G, $\chi^2 = 6.136, P = 0.013$; rs7412-rs405509-rs439401: GAG, $\chi^2 = 5.842, P = 0.016$); In the SNRI subgroup, haplotype GA(rs405509 and rs439401) ,A-A, C-G, and GAG, GCG, (rs7412, rs405509, and -rs439401) was significantly associated with antidepressant response in the 6-week , (rs7412-rs405509: $\chi^2 = 7.658, P = 0.006$; rs405509-rs439401: AA $\chi^2 = 4.02, P = 0.045$, C-G, $\chi^2 =
5.392, $P = 0.02$; rs7412-rs405509-rs439401: G-A-A, $\chi^2 = 4.367, P = 0.037$, G-C-G, $\chi^2 = 6.517, P = 0.011$). However, all of the results outlined above did not withstand permutation testing (see Table S16).

In the SNRI subgroup, the haplotype G-A (rs7412 and rs405509), and C-G (rs405509 and rs439401) of ApoE was significantly associated with worse antidepressant response in the 8-week (rs7412-rs405509: $P = 0.044$, OR = 0.91, rs405509-rs439401: $P = 0.047$, OR = 0.55), but the results outlined above did not withstand permutations (see Table S17).

**Discussion**

We investigated the association of genetic variation in folate and lipid metabolism-related genes with antidepressant response in patients with major depression, and found significant effects of single polymorphisms in *MTHFR, ApoE*, and *ApoA4*.

In the *MTHFR* gene, C677T (rs1801133) and A1298C (rs1801131) are the most investigated SNPs associated with MDD. The C677T variant results from a single nucleotide substitution at this position, in which cytosine (C) is replaced by thymine (T) resulting a conversion of alanine to valine residue which diminishes the enzyme activity diminishes the enzyme activity. Another common polymorphism is A1298C, in which adenine (A) is replaced by cytosine (C) resulting a conversion of glutamate to alanine, which also diminishes the enzyme activity. In the present study, the haplotypes C-A of rs1801133 and rs1801131 were associated with better antidepressant effects in the group overall, male and SNRI subgroups. This may have been because there are mutations in both T-A and C-C haplotypes that result in decreased MTHFR enzyme activity, increased blood Hcy levels, and decreased folate levels [36]. Bottilieri et al. reported that folic acid supplementation can protect brain function by reducing Hcy [37, 38], and also that increased levels of Hcy and/or decreased levels of folate resulted in decreased levels of S-adenosyl methionine (SAM) in cerebrospinal fluid; meanwhile, SAM as a methyl donor for serotonin (5-HT) and
catecholamine pathways exerted significant antidepressant effects and was shown to have better efficacy than imipramine [39]. However, it has been suggested [40] that folic acid and vitamin B12 do not clearly enhance the efficacy of antidepressants, and that the use of folic acid and vitamin B12 can only prevent further increases in Hcy but cannot reduce its level; this may be related to differences among studies in the folic acid and vitamin B12 doses used.

This study further showed that only C-A haplotype carriers in the male subgroup experienced higher antidepressant efficacy; this was not seen in the female subgroup. This may have been due to the higher folate concentrations and lower Hcy levels in women [41], which compensates for reduced MTHFR enzyme activity, thus making it difficult to detect the relationship between this gene polymorphism and antidepressant efficacy. In addition, women have higher estrogen levels, and estrogen can also weaken the correlation between MTHFR polymorphism and antidepressant efficacy to some extent by lowering Hcy levels [42].

In addition, the efficacy of antidepressants was greater in C-A haplotype carriers in the SNRI subgroup. As we all known, SSRIs mainly selectively inhibit the reuptake of 5-HT by the presynaptic membrane. In contrast to SSRIs, SNRIs have a 5-HT reuptake inhibitory effect, as well as noradrenaline (NE) and mild dopamine (DA) reuptake inhibition. It has been reported that depressed patients with high plasma hcy concentrations have significantly lower concentrations of the CSF monoamine metabolites 5-hydroxyindoleacetic acid (5-HIAA), homovanillic acid (HVA), and 4-hydroxy-3-methoxyphenylethylene (MHPG) suggesting an impairment in the metabolism of 5-HT, DA and NE [43]. Therefore, SNRIs maybe have greater effects against the neurotoxicity associated with a high Hcy level. SSRIs have a single drug target, so there was little difference in efficacy between haplotypes in the SSRI subgroup.
In our present study, we also notice that single locus association analysis has found no association between SNPs rs1801131 and rs1801133 with antidepressant response, in agreement with the findings from several studies. Mei F et al [23] found that the mutation of MTHFR gene C677T polymorphism was significantly associated with the increased risk of PSD, but not with antidepressant treatment response. Mischoulon, D et al [24]. reported that MTHFR C677T and MS A2756G polymorphism did not affect the antidepressant response of fluoxetine treatment. We speculate that a single SNP has less effect on gene function than a haplotype, which is not enough to affect the efficacy of antidepressants. The ApoE gene plays an important role in regulating lipid metabolism and maintaining cholesterol balance. The SNP, rs7412 (C526T), is a functional site in the ApoE gene; it is mutated, resulting in replacement of arginine with cysteine. which indicated that this polymorphism is closely related to lipid metabolism. Although rs405509 (219A/C), which is located in the promoter region upstream of the gene, has not been confirmed to be a functional site, which showed that its polymorphism is associated with antidepressant efficacy. Therefore, further studies regarding this site are required.

Studies showed that serum cholesterol levels in patients with depression were significantly lower than those in healthy people[44]. Furthermore, Sonawalla et al. reported that serum cholesterol levels have also been shown to be associated with the efficacy of antidepressants[45]. Their study found that patients with depression treated with a standard dose of fluoxetine (20 mg/d) had high serum cholesterol levels (≥ 200 mg/dl); with lower cholesterol levels, the curative effect is diminished, the tendency toward chronic disease is greater, and the possibility of recurrence is higher; related research on refractory depression reached a similar conclusion. The above studies suggested that the effects of the ApoE gene polymorphism on the efficacy of antidepressants may be related to the concentration of cholesterol in the body. Excessive
cholesterol concentration may affect 5-HT transporters and/or various 5-HT receptors[46]. The function of the 5HT neurons cytomembrane structure has an adverse effect. As another possible explanation, patients with hypercholesterolemia are more likely to have vascular and anxiety disorders, which would affect the efficacy of antidepressants[47]. However, studies have yielded inconsistent results, suggesting that the incidence of depression is lower in the higher blood lipid state, and that high blood lipids may have certain antidepressant effects. For example, Mase et al. [48] reported that low serum high-density lipoprotein (HDL-C) is a marker of suicidal behavior in depression, and may induce immune or inflammatory reactions in depression. Mischoulon et al. [49] also reported that foods rich in docosahexaenoic acid (DHA) are associated with a lower incidence of depression, while DHA deficiency (e.g., alcoholism and postpartum) is associated with a higher incidence of depression. The discrepancies between the above studies may be related to differences in the subjects and indicators of blood lipid levels. In addition, studies on the association between the ApoE gene and depression and antidepressant efficacy have focused on the common alleles of this gene, ε2, ε3, and ε4, and some studies confirmed that the ApoE gene ε4 allele was associated with greater efficacy of antidepressants [50-52]. Bizzarro et al. [53] reported a significant association between AD and rs405509 CC genotypes when exploring the association between AD and an ApoE gene promoter, suggesting that rs405509 may play a role in the pathogenesis of AD. Lescai et al. [54] also reported that haplotype A-ε4, consisting of rs4905509 and ε4, can increase the risk of late-onset AD by reducing ApoE expression levels. Therefore, we hypothesized that the rs405509 polymorphism may have strong LD with other functional SNPs, such as the ε4 allele, and thus alter the biological function of the ApoE gene to influence the efficacy of antidepressants.

The function of rs5092 (29A/G) located in the promoter region of the ApoA4 gene, is still
unclear and there have been few studies related to this site. However, in an exploration of
gene function, the polymorphism of the ApoA1/C3/A4 gene cluster on chromosome 11q23-
24 was shown to be related to blood lipids. These three genes show a high degree of
identity and evolved from the same ancestral gene. The ApoA1 and ApoA4 genes have the
same transcriptional direction, while ApoC3 is transcribed in the opposite direction [54];
moreover, its polymorphic variation can lead to hypertriglyceridemia [55]. This site may
affect the synthesis of ApoA4, and the blood lipid level, by altering transcription of the
ApoA4 gene.
Analyses of the ApoE and ApoA4 genes indicated correlations between each polymorphic
site and the efficacy of antidepressants in the male subgroup, but not in the female
subgroup; the latter also required a longer treatment cycle (8 weeks). This may have been
related to differences in lipid levels between male and female patients, and to differences
in the pharmacokinetics of antidepressants. Rare studies have involved gender differences
in lipid metabolism gene polymorphisms, the specific mechanism still needs further
research.
Our study has limitations as follows. Firstly, there was no placebo control group in our
present study, it is difficult to exclude such effects and other non-pharmaceutical factors.
In further research, we can consider establishing a placebo control group to better
observe the efficacy of antidepressants. Second, only three genes polymorphism in Hcy
and lipid metabolic pathways were included in the present study, their treatment response
may be not enough. Regarding the sites shown to be associated with the efficacy of
antidepressants studies with larger sample sizes are needed to verify their accuracy and
lay a foundation for personalized medicine.
Conclusions
This study demonstrates that genetic polymorphisms of MTHFR, ApoE, and ApoA4 may be
associated with the efficacy of antidepressants, in which the haplotype (rs1801131-rs1801133) A–C type was associated with better antidepressant efficacy, especially in males and in patients using SNRIs. The efficacy of antidepressants may be better in ApoE rs405509 A allele and AA genotype carriers, but worse in ApoA4 rs5092 G allele and GG genotype carriers. Confirmation of these preliminary results across independent populations and further pharmacogenomics exploration might lead to novel strategies for individualized, rational and successful antidepressant drug treatment.

List Of Abbreviations

5-HIAA: 5-hydroxyindoleacetic acid
5-HT: 5-hydroxytryptamine, serotonin
AD: Alzheimer’s disease
ApoA4: Apolipoprotein A4
ApoE: Apolipoprotein E
CGI: Clinical Global Impression
DA: Dopamine
DHA: Docosahexaenoic acid
DSM-IV: Diagnostic and Statistical Manual of the American Psychiatric Association
Hcy: Homocysteine
HDL-C: High-density lipoprotein
HDRS: Hamilton Depression Rating Scale
HVA: Homovanillic acid
HWE: Hardy-Weinberg equilibrium
LLD: Late-life depression
MAF: Minor allele frequency
MDD: Major depressive disorder
MHPG: 4-hydroxy-3-methoxyphenylglycol

MTHFR: Methylenetetrahydrofolate reductase

NE: Norepinephrine

SAM: S-adenosyl methionine

SNPs: Single nucleotide polymorphisms

SNRI: Serotonin norepinephrine reuptake inhibitor

SSRIs: Serotonin reuptake inhibitors

TESS: Treatment Emergent Symptom Scale

Declarations

**Ethics approval and consent to participate**

The authors state that the study was established according to the ethical guidelines of the Helsinki Declaration and was approved by the ethics committee of all participating hospitals, including Beijing Anding Hospital, the Second Xiangya Hospital of Central South University, Huaian No. 3 People’s Hospital, Wutaishan Hospital of Yangzhou, Affiliated ZhongDa Hospital of Southeast University. Written informed consent was obtained from all subjects or guardian participants.

**Consent for publication**

Not applicable.

**Availability of data and materials**

The raw/processed data required to reproduce these findings cannot be shared at this time as the data also forms part of an ongoing study. The de-identified dataset used and/or analysed during the current study are available from the corresponding author on reasonable request.

**Competing interests**

The authors declare that Yonggui Yuan as a member of Editorial Board.
**Funding**

The study has been partly supported by the National Basic Research Program of China (973 Program, No. 2007CB512308 Zhijun Zhang and No. 2009CB918303 Lingjiang Li), National Hi-Tech Research and Development Program of China (863 Program, No. 2008AA02Z413 Zhijun Zhang) and Scientific Research Program of Jiangsu Provincial Commission of Health and Family Planning (No. H2017007, Baoyu Yuan).

**Authors’ contributions**

Zhijun Zhang and Yuan Yonggui designed the research protocol, Sun Xiaoyan, Xu Zhi and Pu Mengjia analyzed data; Yuan Baoyu and Zhang Zhijun wrote the paper. All authors read and approved the final manuscript.

**Acknowledgements**

We thank colleagues involved in collecting clinical data: Professor Chuanyue Wang of Beijing Anding Hospital; Professor Zhening Liu of the Second Xiangya Hospital of Central South University; Congjie Wang of Huaian No. 3 People’s Hospital; Xiaobin Zhang, Yumei Zhang and Honghui Zhou of Yangzhou Wutaishang Hospital. We thank Ning Sun and Kerang Zhang from the First Hospital of Shanxi Medical for providing control group information. We thank Qiang Wang of West China Hospital, Haijian Guo of JiangSu Province Center for Disease Control and Prevention and Juncheng Dai of Nanjing Medical University for statistical advice and analyses.

**References**

1. Vandeleur CL, Fassassi S, Castelao E, Glaus J, Strippoli MF, Lasserre AM, Rudaz D, Gebreab S, Pistis G, Aubry JM et al: *Prevalence and correlates of DSM-5 major depressive and related disorders in the community*. Psychiatry research 2017, **250**:50-58.

2. Huang Y, Wang Y, Wang H, Liu Z, Yu X, Yan J, Yu Y, Kou C, Xu X, Lu J et al:
Prevalence of mental disorders in China: a cross-sectional epidemiological study. The Lancet Psychiatry 2019, 6(3):211-224.

3. Kelley ME, Dunlop BW, Nemeroff CB, Lori A, Carrillo-Roa T, Binder EB, Kutner MH, Rivera VA, Craighead WE, Mayberg HS: Response rate profiles for major depressive disorder: Characterizing early response and longitudinal nonresponse. Depression and anxiety 2018, 35(10):992-1000.

4. Tranter R, O'Donovan C, Chandarana P, Kennedy S: Prevalence and outcome of partial remission in depression. Journal of Psychiatry & Neuroscience Jpn 2002, 27(4):241-247.

5. Lohoff FW, Ferraro TN: Pharmacogenetic considerations in the treatment of psychiatric disorders. Expert opinion on pharmacotherapy 2010, 11(3):423-439.

6. Mocking RJ, Figueroa CA, Rive MM, Geugies H, Servaas MN, Assies J, Koeter MW, Vaz FM, Wichers M, van Straalen JP et al: Vulnerability for new episodes in recurrent major depressive disorder: protocol for the longitudinal DELTA-neuroimaging cohort study. BMJ open 2016, 6(3):e009510.

7. Bigdeli TB, Ripke S, Peterson RE, Trzaskowski M, Bacanu SA, Abdellaoui A, Andlauer TF, Beekman AT, Berger K, Blackwood DH et al: Genetic effects influencing risk for major depressive disorder in China and Europe. Translational psychiatry 2017, 7(3):e1074.

8. Vall E, Wade TD: Predictors of treatment outcome in individuals with eating disorders: A systematic review and meta-analysis. The International journal of eating disorders 2015, 48(7):946-971.

9. Fabbri C, Hosak L, Mössner R, Giegling I, Serretti AJWJoBP: Consensus paper of the WFSBP Task Force on Genetics: Genetics, epigenetics and gene expression markers of major depressive disorder and antidepressant response. 2016,
10. Kato M, Serretti A: Review and meta-analysis of antidepressant pharmacogenetic findings in major depressive disorder. *Molecular psychiatry* 2010, 15(5):473-500.

11. Alpert JE, Mischoulon D, Nierenberg AA, Fava M: Nutrition and depression: focus on folate. *Nutrition* 2000, 16(7-8):544.

12. Tiemeier H, van Tuijl HR, Hofman A, Meijer J, Kiliaan AJ, Breteler MM: Vitamin B12, folate, and homocysteine in depression: the Rotterdam Study. *American Journal of Psychiatry* 2002, 159(12):2099.

13. Jain R, Jackson WC: Beyond the resistance: how novel neurobiological understandings of depression may lead to advanced treatment strategies. *The Journal of clinical psychiatry* 2012, 73(11):e30.

14. Alpert JE, Mischoulon D, Rubenstein GEF, Bottonari K, Nierenberg AA, Fava M: Folinic Acid (Leucovorin) as an Adjunctive Treatment for SSRI-Refractory Depression. *Annals of Clinical Psychiatry* 2002, 14(1):33-38.

15. Hintikka J, Tolmunen T, Tanskanen A, Viinamaki H: High vitamin B12 level and good treatment outcome may be associated in major depressive disorder. *BMC psychiatry* 2003, 3:17.

16. McGuffin P, Knight J, Breen G, Brewster S, Boyd PR, Craddock N, Gill M, Korszun A, Maier W, Middleton L et al: Whole genome linkage scan of recurrent depressive disorder from the depression network study. *Human molecular genetics* 2005, 14(22):3337-3345.

17. Cortese C, Motti C: MTHFR gene polymorphism, homocysteine and cardiovascular disease. *Public health nutrition* 2001, 4(2B):493-497.

18. Santos M, Kovari E, Hof PR, Gold G, Bouras C, Giannakopoulos P: The impact of
vascular burden on late-life depression. *Brain research reviews* 2009, *62*(1):19-32.

19. Wan L, Li Y, Zhang Z, Sun Z, He Y, Li R: *Methylenetetrahydrofolate reductase and psychiatric diseases*. *Translational psychiatry* 2018, *8*(1):242.

20. Shen X, Wu Y, Guan T, Wang X, Qian M, Lin M, Shen Z, Sun J, Zhong H, Yang J et al: Association analysis of COMT/MTHFR polymorphisms and major depressive disorder in Chinese Han population. *Journal of affective disorders* 2014, *161*:73-78.

21. Jamerson BD, Payne ME, Garrett ME, Ashley-Koch AE, Speer MC, Steffens DC: *Folate metabolism genes, dietary folate and response to antidepressant medications in late-life depression*. *International journal of geriatric psychiatry* 2013, *28*(9):925-932.

22. Lanctôt KL, Rapoport MJ, Chan F, Rajaram RD, Strauss J, Sicard T, McCullagh S, Feinstein A, Kiss A, Kennedy JL et al: Genetic predictors of response to treatment with citalopram in depression secondary to traumatic brain injury. *Brain Inj* 2010, *24*(7-8):959-969.

23. Mei F, Wu Y, Ding G, Pan F, Chen L, Wu J: Association of methylenetetrahydrofolate reductase gene 677C>T polymorphism with post-stroke depression risk and antidepressant treatment response in Han Chinese. *JPMA The Journal of the Pakistan Medical Association* 2018, *68*(7):888-892.

24. Mischoulon D, Lamon-Fava S, Selhub J, Katz J, Papakostas GI, Iosifescu DV, Yeung AS, Dording CM, Farabaugh AH, Clain AJ et al: Prevalence of MTHFR C677T and MS A2756G polymorphisms in major depressive disorder, and their impact on response to fluoxetine treatment. *CNS spectrums* 2012, *17*(2):76-86.

25. Maes M, Smith R, Christophe A, Vandoolaeghe E, Gastel AV, Neels H, Demedts P,
Wauters A, Meltzer HY: **Lower serum high-density lipoprotein cholesterol (HDL-C) in major depression and in depressed men with serious suicidal attempts: relationship with immune-inflammatory markers.** *Acta psychi**atr**ica Sc**andinav**ica* 1997, **95**(3):212.

26. Nikolac Perkovic M, Pivac N: **Genetic Markers of Alzheimer's Disease.** *Adv Exp Med Biol* 2019, **1192**:27-52.

27. Chen W, Jin F, Cao G, Mei R, Wang Y, Long P, Wang X, Ge W: **ApoE4 May be a Promising Target for Treatment of Coronary Heart Disease and Alzheimer's Disease.** *Current drug targets* 2018, **19**(9):1038-1044.

28. Mahley RW, Weisgraber KH, Huang Y: **Apolipoprotein E4: a causative factor and therapeutic target in neuropathology, including Alzheimer's disease.** *Proceedings of the National Academy of Sciences of the United States of America* 2006, **103**(15):5644-5651.

29. F. Sharpley C: **The Role of Genes (and Environmental Stress) in Depression: An Update.** *Current Psychiatry Reviews* 2011, **7**(2):84-95.

30. Kim YS, Gu BH, Choi BC, Kim MS, Song S, Yun JH, Chung MK, Choi CH, Baek KH: **Apolipoprotein A-IV as a novel gene associated with polycystic ovary syndrome.** *International journal of molecular medicine* 2013, **31**(3):707-716.

31. Diniz BS, Lin CW, Sibille E, Tseng G, Lotrich F, Aizenstein Hj, Reynolds CF, Butters MA: **Circulating biosignatures of late-life depression (LLD): Towards a comprehensive, data-driven approach to understanding LLD pathophysiology.** *Journal of psychiatric research* 2016, **82**:1-7.

32. Pickar D, Rubinow K: **Pharmacogenomics of psychiatric disorders.** *Trends in Pharmacological Sciences* 2001, **22**(2):75-83.

33. Association AP: **Diagnostic and statistic manual of mental disorders 5 (DSM-5).**
Diabetes 1994, 11(Suppl)(1):97-98.

34. Takahashi: **Rating scale for depression.** *Journal of Neurology Neurosurgery & Psychiatry* 1998, 23(1): 56-62.

35. Bauer M, Whybrow PC, Angst J, Versiani M, Moller HJ: **World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Unipolar Depressive Disorders, Part 1: Acute and continuation treatment of major depressive disorder.** *The world journal of biological psychiatry: the official journal of the World Federation of Societies of Biological Psychiatry* 2002, 3(1): 5-43.

36. Kamphuis MH, Geerlings Ml, Grobbee DE, Kromhout D: **Dietary intake of B(6-9-12) vitamins, serum homocysteine levels and their association with depressive symptoms: the Zutphen Elderly Study.** *European journal of clinical nutrition* 2008, 62(8): 939-945.

37. Bottiglieri T: **Homocysteine and folate metabolism in depression.** *Progress in neuro-psychopharmacology & biological psychiatry* 2005, 29(7): 1103-1112.

38. Herrmann W, Obeid R: **Biomarkers of folate and vitamin B(12) status in cerebrospinal fluid.** *Clinical chemistry and laboratory medicine* 2007, 45(12): 1614-1620.

39. Bell KM, Plon L, Bunney WE, Jr., Potkin SG: **S-adenosylmethionine treatment of depression: a controlled clinical trial.** *The American journal of psychiatry* 1988, 145(9): 1110-1114.

40. Christensen H, Aiken A, Batterham PJ, Walker J, Mackinnon AJ, Fenech M, Hickie IB: **No clear potentiation of antidepressant medication effects by folic acid+vitamin B12 in a large community sample.** *Journal of affective disorders* 2011, 130(1-2): 37-45.
41. Nanri A, Mizoue T, Matsushita Y, Sasaki S, Ohta M, Sato M, Mishima N: Serum folate and homocysteine and depressive symptoms among Japanese men and women. *European journal of clinical nutrition* 2010, 64(3):289-296.

42. Kalra DK: Homocysteine and cardiovascular disease. *Current atherosclerosis reports* 2004, 6(2):101-106.

43. Bottiglieri T, Laundy M, Crellin R, Toone BK, Carney MW, Reynolds EH: Homocysteine, folate, methylation, and monoamine metabolism in depression. *Journal of neurology, neurosurgery, and psychiatry* 2000, 69(2):228-232.

44. Kim EJ, Hong J, Hwang J-W: The Association between Depressive Mood and Cholesterol Levels in Korean Adolescents. *Psychiatry investigation* 2019, 16(10):737-744.

45. Sonawalla SB, Papakostas GI, Petersen TJ, Yeung AS, Smith MM, Sickinger AH, Gordon J, Israel JA, Tedlow JR, Lamon-Fava S et al: Elevated cholesterol levels associated with nonresponse to fluoxetine treatment in major depressive disorder. *Psychosomatics* 2002, 43(4):310-316.

46. Pucadyil TJ, Chattopadhyay A: Cholesterol modulates the antagonist-binding function of hippocampal serotonin1A receptors. *Biochimica et Biophysica Acta (BBA) - Biomembranes* 2005, 1714(1):35-42.

47. Suárez Bagnasco M: Psychological issues and cognitive impairment in adults with familial hypercholesterolemia. *Family practice* 2017, 34(5):520-524.

48. Maes M, Smith R, Christophe A, Vandoolaeghe E, Van Gastel A, Neels H, Demedts P, Wauters A, Meltzer HY: Lower serum high-density lipoprotein cholesterol (HDL-C) in major depression and in depressed men with serious suicidal attempts: relationship with immune-inflammatory markers. *Acta psychiatrica Scandinavica*
1997, **95**(3):212-221.

49. Mischoulon D, Fava M: **Docosahexanoic acid and omega-3 fatty acids in depression.** *The Psychiatric clinics of North America* 2000, **23**(4):785-794.

50. Murphy GM, Kremer C, Rodrigues H, Schatzberg AF: **The apolipoprotein E epsilon4 allele and antidepressant efficacy in cognitively intact elderly depressed patients.** *Biological psychiatry* 2003, **54**(7):665-673.

51. Schmand B, Hooijer C, Jonker C, Lindeboom J, Havekes LM: **Apolipoprotein E phenotype is not related to late-life depression in a population-based sample.** *Social psychiatry and psychiatric epidemiology* 1998, **33**(1):21-26.

52. Mauricio M, O'Hara R, Yesavage JA, Friedman L, Kraemer HC, Van De Water M, Murphy GM, Jr.: **A longitudinal study of apolipoprotein-E genotype and depressive symptoms in community-dwelling older adults.** *The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry* 2000, **8**(3):196-200.

53. Bizzarro A, Seripa D, Acciarri A, Matera MG, Pilotto A, Tiziano FD, Brahe C, Masullo C: **The complex interaction between APOE promoter and AD: an Italian case-control study.** *European journal of human genetics : EJHG* 2009, **17**(7):938-945.

54. Lescai F, Chiamenti AM, Codemo A, Pirazzini C, D'Agostino G, Ruarò C, Ghidoni R, Benussi L, Galimberti D, Esposito F et al: **An APOE haplotype associated with decreased epsilon4 expression increases the risk of late onset Alzheimer's disease.** *Journal of Alzheimer's disease : JAD* 2011, **24**(2):235-245.

55. Groenendijk M, Cantor RM, de Bruin TW, Dallinga-Thie GM: **The apoAI-CIII-AIV gene cluster.** *Atherosclerosis* 2001, **157**(1):1-11.

**Tables**

Table 1. Demographic characteristics of MDD patients and baseline HDRS-17 scores:
comparison between responder and non-responder groups

| Demographic characteristics | Responder (n=205) | Non-responder (n=76) | t / χ² | P  |
|-----------------------------|------------------|----------------------|-------|----|
| Gender (male/female)        | 81/124           | 35/41                | 0.987 | 0.324 |
| Age (years)                 | 38.99±12.93      | 36.18±13.36          | 1.599 | 0.111 |
| Education (years)           | 11.27±3.84       | 12.20±3.82           | −1.800 | 0.073 |
| Family history of mood disorder (yes/no) | 29 (14.15%) | 15 (19.74%) | −1.031 | 0.305 |
| Baseline HDRS-17 score      | 28.18±5.68       | 26.01±5.32           | 2.891 | 0.004 |
| Number of episodes          | 2.01±1.57        | 2.33±2.03            | −1.394 | 0.164 |
| Antidepressant (SSRI/SNRI)  | 114/91           | 50/26                | 1.569 | 0.119 |

Abbreviations: HDRS-17, 17-item Hamilton Depression Rating Scale; SNRI, serotonin norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

Table 2. Demographic characteristics of MDD patients and HDRS-17 scores: comparison between remission and non-remission groups

| Demographic characteristics | remission (n=144) | non-remission (n=131) | t / χ² | P  |
|-----------------------------|-------------------|-----------------------|-------|----|
| Gender (male/female)        | 49/95             | 63/68                 | 2.381 | 0.018 |
| Age (years)                 | 38.38±11.99       | 38.14±14.11           | 0.150 | 0.881 |
| Education (years)           | 11.28±3.65        | 11.73±4.07            | −0.957 | 0.340 |
| Family history of mood disorders (yes/no) | 20 (13.89%) | 22 (16.79%) | −0.645 | 0.519 |
| Baseline HDRS-17 score      | 27.03±5.71        | 28.00±5.36            | −1.452 | 0.148 |
| Number of episodes          | 1.88±1.30         | 2.30±2.06             | −1.983 | 0.049 |
| Antidepressant (SSRI/SNRI)  | 76/68             | 83/48                 | 1.781 | 0.076 |

Abbreviations: HDRS-17, 17-item Hamilton Depression Rating Scale; SNRI, serotonin norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.
norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

Table 3. Genetic association analysis (genotypic/allelic) of SNPs versus response status in each subgroups

| Groups                  | SNPs (Gene/rs#) | Allele/Genotype | Response (%) | Non-response (%) |
|-------------------------|-----------------|-----------------|--------------|------------------|
| Overall (6-week)        | ApoE/rs405509   | AA              | 113 (55)     | 28 (37)          |
|                         |                 | AC              | 82 (40)      | 42 (55)          |
|                         |                 | A               | 129 (80)     | 43 (61)          |
|                         |                 | C               | 33 (20)      | 27 (39)          |
|                         |                 | AA              | 51 (63)      | 11 (31)          |
|                         |                 | AC              | 27 (33)      | 21 (60)          |
| Male subgroup (6-week)  | ApoE/rs405509   | A               | 129 (80)     | 43 (61)          |
|                         |                 | C               | 33 (20)      | 27 (39)          |
|                         |                 | AA              | 51 (63)      | 11 (31)          |
|                         |                 | AC              | 27 (33)      | 21 (60)          |
| Male subgroup (6-week)  | ApoA4/rs5092    | A               | 98 (60)      | 32 (46)          |
| SNRI subgroup (6-week)  | ApoA4/rs5092    | A               | 98 (54)      | 17 (33)          |
|                         |                 | G               | 64 (40)      | 38 (54)          |
|                         |                 | AA              | 23 (25)      | 2 (8)            |
|                         |                 | AG              | 62 (54)      | 32 (64)          |
|                         |                 | GG              | 16 (18)      | 11 (42)          |
| Female subgroup (8-week)| ApoA4/rs5092    | A               | 101 (53)     | 57 (42)          |
|                         |                 | G               | 89 (47)      | 49 (58)          |

Abbreviations: SNPs, single nucleotide polymorphisms; SNRI, serotonin norepinephrine reuptake inhibitor; OR, odds ratio; CI, confidence interval

*Adjusted P-value from 1,000 permutation tests

Table 4. Estimated haplotype frequency of the two MTHFR SNPs (rs1801133 and rs1801131) and results of haplotype analysis in remission and non-remission groups

| Group                | haplotype | remission (%) | non-remission (%) | OR (95%CI)       |
|----------------------|-----------|---------------|-------------------|------------------|
| Overall              | T-A       | 117 (41)      | 125 (48)          | 1                |
|                      | C-A       | 127 (44)      | 79 (30)           | 1.72 (1.18-2.51) |
|                      | C-C       | 44 (15)       | 58 (22)           | 0.81 (0.51-1.29) |
|                      | T-A       | 40 (15)       | 60 (48)           | 1                |
| Male subgroup        | C-A       | 46 (47)       | 35 (28)           | 1.97 (1.09-3.51) |
| SNRI subgroup        | C-C       | 12 (12)       | 31 (25)           | 0.58 (0.27-1.27) |
|                      | T-A       | 58 (43)       | 51 (53)           | 1                |
|                      | C-A       | 64 (47)       | 25 (26)           | 2.25 (1.24-4.11) |
|                      | C-C       | 14 (10)       | 20 (21)           | 0.62 (0.28-1.42) |

Abbreviations: SNRI, serotonin noradrenaline reuptake inhibitor; OR, odds ratio; CI, confidence interval

*Adjusted P-value from 1,000 permutation tests

Table 5. Estimated haplotype frequencies of the two ApoE SNPs (rs7412 and rs405509)
and the results of haplotype analysis in responders and non-responders

| Group          | haplotype       | response (%) | non-response (%) |
|----------------|-----------------|--------------|------------------|
| Male subgroup  | rs7412-rs405509 | G-A          | 125 (77)         |
|                |                 | G-C          | 27 (17)          |
| SNRI subgroup  | rs7412-rs405509 | A-C          | 12 (7)           |
|                |                 | G-A          | 139 (77)         |
|                |                 | G-C          | 26 (14)          |

Abbreviations: RM, remission; NR, non-remission; SNRI, serotonin noradrenaline reuptake inhibitor; OR, odds ratio; CI, confidence interval

*Adjusted P-value from 1,000 permutation tests

Figures
Flow chart of recruited subjects. Abbreviations: SNRI, serotonin norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

Supplementary Files

This is a list of supplementary files associated with the primary manuscript. Click to download.

Supplementary tables.docx