Association between MTHFR (677C>T and 1298A>C) polymorphisms and psychiatric disorder: A meta-analysis

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Abstract

Recent studies showed that genetic polymorphism of 5,10-methylenetetrahydrofolate reductase (MTHFR) is related to attention-deficit hyperactivity disorder (ADHD), bipolar disorder (BD) and schizophrenia (SCZ). However, no consistent conclusion has been determined. This meta-analysis aims to interrogate the relationship between MTHFR gene polymorphisms (677C>T and 1298A>C) and the occurrence of ADHD, BD and SCZ. We retrieved case-control studies that met the inclusion criteria from the PubMed database. Associations between MTHFR polymorphisms (677C>T and 1298A>C) and ADHD, BD and SCZ were measured by means of odds ratios (ORs) using a random effects model and 95% confidence intervals (CIs). Additionally, sensitivity analysis and publication bias were performed. After inclusion criteria were met, a total of five studies with ADHD including 434 cases and 670 controls, 18 studies with BD including 4167 cases and 5901 controls and 44 studies with SCZ including 16,098 cases and 19913 controls were finally included in our meta-analysis. Overall, our meta-analytical results provided evidence that the MTHFR 677C>T was associated with occurrence of BD and SCZ, while the 1298A>C polymorphism was related to ADHD and BD, and additionally the sensitivity analysis indicated these results were stable and reliable. This may provide useful information for relevant studies on the etiology of psychiatric disorders.

Introduction

Folic acid, a member of the vitamin B complex, is considered to be strongly associated with the function and development of the central nervous system, which plays an important role in cellular processes including nucleotide synthesis and methylation [1]. The enzyme 5,10-methylenetetrahydrofolate reductase (MTHFR) functions in the pathway that converts folate into metabolites that may be used for cellular processes including methylation of gene promoter enhancers and protein, RNA, DNA, amino acid and phospholipid synthesis. Specifically, this enzyme converts 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, which
is required for the multistep process that converts the amino acid homocysteine to methionine. Methionine is used to synthesize proteins and other important compounds [2]. The MTHFR gene is located at 1p36.22 [3]. Genetic variation in this gene influences susceptibility to occlusive vascular disease, neural tube defects, colon cancer and acute leukemia, and mutations in this gene are associated with MTHFR deficiency. Among the variations of the MTHFR gene, the polymorphisms of C677T and A1298C affect both nucleotide synthesis and DNA methylation. Compared with wild genotype (CC), the heterozygote (CT) and mutation homozygote (TT) lead to declines in enzyme activity of about 34% and 75%, respectively [4]. Homozygous carriers of the 1298C allele have a more moderate 30–40% reduction of the enzyme activity, but its function remains controversial.

Epidemiological research has reported that attention-deficit hyperactivity disorder (ADHD), bipolar disorder (BD) and schizophrenia (SCZ) are multimorbid conditions that are typically accompanied by cognitive advantages or deficits, suggesting that common biological mechanisms may underlie these phenotypes [5]. The complex neurodevelopmental disorder ADHD affects around 5% of school-aged children [6], and 65% of them can be still affected when they are grown up, which has significant social, academic and occupational effects [7]. Its prevalence in adults is approximately 2.5% [8]. The etiology of ADHD is not fully understood and remains inconclusive. Family, twin and adoption studies have identified the impact of genetic variation on ADHD risk. Not only environment, such as maternal smoking, but genetic factors also play an important role. Molecular genetics research has gradually ascertained the inherited susceptible genes for ADHD. Recent investigations reported that the average heritability was estimated at 76% [9, 10] in childhood and 30–50% [11–13] or even higher in adulthood [14, 15].

Characterized by alternating episodes of depression and mania [16], BD is a serious common chronic mental illness with population prevalence of about 1–2% [17]. Although it is more common than previously thought, it has received less attention in terms of research than other major psychiatric disorders. Family, twin and adoption studies have identified the impact of genetic variation on the risk of BD [18]. Age at onset and polarity at onset are related to the indicators of BD severity. The patients at an earlier onset show an increased polygenic liability of psychiatric disorders [19]. Both ADHD and BD are neurodevelopmental disorders with onset in childhood and early adolescence, and common persistence in adulthood [20].

Affected by the mutual influence of multiple genetic and environmental factors, SCZ is a common mental disorder with heritability up to 80% [21]. Patients with SCZ experience higher mortality rates than the general population, especially due to suicide [22]. Large-scale epidemiological studies have consistently shown that infections, autoimmune diseases and atopic disorders are associated with increased risk of SCZ and that SCZ is associated with increased levels of immune markers at diagnosis [23].

Recent studies showed that MTHFR genetic polymorphism is related to neuropsychiatric diseases such as ADHD, BD and SCZ [24–27]. Polymorphisms of MTHFR C677T are likely to be associated with the risk of developing BD and SCZ and influence the age at onset of BD but not for SCZ [28]. A regression model found the TT genotype of the C677T locus was associated with the lowest global methylation. Moreover, the C677T allele might represent different liability according to gender [29]. However, some studies failed to find any association between MTHFR C667T polymorphism and risk of SCZ and BD [30, 31]. Due to the small number of studies and the limited sample size, conclusions are not clear.

Meta-analysis is a widely used statistical method in medical studies, particularly for topics that are being extensively studied with controversial results [32]. No meta-analysis has yet reported on association between MTHFR polymorphism and ADHD occurrence. One meta-analysis reported that the MTHFR C677T locus was significantly associated with BD in 2011.
There have been four meta-analyses concerning the association of SCZ [33–36]. The latest study found that MTHFR A1298C polymorphism was a risk factor for SCZ, which included 19 studies with 4049 cases and 5488 controls [36]. To better understand the role of MTHFR in the occurrence of psychiatric disorders, we conducted a meta-analysis of all published case-control studies exploring the associations between two common polymorphisms (677C>T and 1298A>C) of MTHFR and three psychiatric disorders: ADHD, BD and SCZ. This will provide a more comprehensive assessment of the association between this polymorphism and ADHD, BD and SCZ.

**Materials and methods**

**Identification and eligibility of relevant studies**

To identify eligible studies for inclusion in this meta-analysis, we searched the PubMed electronic database up to December 2021, without restriction on article type in English. The following keywords were used in the literature search: 5,10-methylenetetrahydrofolate reductase, MTHFR, and one of the following three words: ADHD, BD or SCZ. The selected studies met the following inclusion criteria: (1) case-control design, (2) including patients with one of the three diseases and (3) stating available allele or genotype frequencies. Of the studies with the same or overlapping data published by the same authors, the latest articles were selected. Major reasons for exclusion follow: (1) no control population, (2) duplicate of an earlier publication and (3) lack of usable genotype frequency data. If we needed to retrieve additional data that were not contained in the original report, we contacted the corresponding authors for additional details (e.g., allele or genotype frequencies or sample characteristics).

**Data extraction**

Based on the inclusion criteria, two reviewers (Mao-ling Sun and Jun Yao) independently extracted information from all the included studies. Disagreements were resolved by discussion until the two reviewers reached a consensus. The following data were extracted from each study: first author’s family name, publication year, country and number of genotypes between cases and controls. To delineate potential moderating influences on the effects obtained from the case-control studies considered, we also included the following variables: (1) diagnostic criteria, (2) controls source, (3) mean age of cases and (4) proportion of males in the disease sample.

**Quality assessment**

Two authors (Mao-ling Sun and Jun Yao) independently assessed the quality of the included studies according to the Newcastle Ottawa Scale (NOS) (www.ohri.ca/programs/clinical_epidemiology/oxford.asp). This scale consists of three components related to sample selection, comparability and ascertainment of exposure. A score of five or more was considered “high quality”; studies with scores from zero to four were assessed as “low quality”.

**Statistical analysis**

Hardy–Weinberg equilibrium (HWE) in the genotype distribution of controls was tested using the chi-square goodness of fit. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to measure the strength of the association between the target locus and the disease. Pooled effect sizes across studies were determined using five genetic models (allele contrast, homozygous codominant, heterozygous codominant, dominant and recessive) by a random effects model, which could reduce the bias due to the heterogeneity from multiple
studies. The degree of heterogeneity between studies was determined by Q-statistic, with \( p > 0.05 \) indicating a lack of heterogeneity and \( p < 0.05 \) indicating heterogeneity. Moreover, \( I^2 \) was calculated to quantify the apparent inconsistency; its conventional interpretation for existing heterogeneity is low (<25%), moderate (approximately 50%) and high (>75%). Additionally, Begg's funnel plot and Egger's test were used to evaluate publication bias.

Sensitivity analysis was performed to assess the potential influences of a single study on the pooled effect size. It was performed by omitting single studies one at a time for each meta-analysis to screen for significant alterations to pooled effect size.

All statistical tests were two-sided, with \( p < 0.05 \) considered significant. The meta-analysis was conducted using Stata version 16.0 software (Stata Corp., College Station, TX, USA).

**Results**

After the removal of overlapping articles and those that did not meet the inclusion criteria (Fig 1), a total of five studies with ADHD including 434 cases and 670 controls [2, 37–40], 18 studies with BD including 4167 cases and 5901 controls [28–31, 41–53] and 44 studies with SCZ including 16,098 cases and 19,913 controls were finally included in our meta-analysis [28–31, 42, 46, 47, 52, 54–76]. The key characteristics of the studies and NOS scale information are presented in Table 1. The NOS scale results showed that 66 studies were of high quality and one
Table 1. Baseline characteristics of qualified studies in this meta-analysis.

| Author   | Year | Country  | Disease | Diagnostic criteria | Controls source | Mean age of cases (years) | Male (%) | NOS scores |
|----------|------|----------|---------|---------------------|-----------------|---------------------------|----------|------------|
| Baykal   | 2019 | Turkey   | ADHD    | DSM-V               | hospital-based  | 8.70±2.77                 | 78.1     | 5          |
| Ergul    | 2012 | Turkey   | ADHD    | DSM-IV             | hospital-based  | 8.87±2.55                 | 80.0     | 5          |
| Gokcen   | 2011 | Turkey   | ADHD    | DSM-IV             | population-based| 9.77±2.3                  | 77.5     | 7          |
| Krull    | 2008 | U.S.     | ADHD    | -                  | -               | 8.70±2.77                 | 78.1     | 4          |
| Sadeghiyeh | 2020 | Aryan    | ADHD    | DSM-IV             | population-based| 8.13±1.34                | 82.2     | 7          |
| Agnieszka| 2014 | Poland   | BD      | DSM-IV-TR          | hospital-based  | 51±14                     | 20.7     | 7          |
| Arinami  | 1997 | Japan    | BD      | DSM-IV             | population-based| -                        | -        | 5          |
| Arzaghi  | 2011 | Iran     | BD      | DSM-IV             | hospital-based  | 35±8                     | 56.7     | 7          |
| Chen     | 2009 | China    | BD      | DSM-IV             | population-based| 36.6±7.2                 | -        | 7          |
| El-Hadidy| 2014 | Egypt    | BD      | DSM-IV-TR          | hospital-based  | 32.2±10.9                | 53.7     | 7          |
| El-Hadidy| 2013 | Egypt    | BD      | DSM-IV             | hospital-based  | -                        | -        | 5          |
| Ezzaher  | 2011 | Tunisia  | BD      | DSM-IV             | hospital-based  | 36±11.1                  | 67.3     | 7          |
| Jasson   | 2008 | Norway   | BD      | DSM-IV             | population-based| 41±12.2                 | 39.3     | 8          |
| Kempsy   | 2006 | Poland   | BD      | DSM-IV             | population-based| 44.5±13.5                | 52.5     | 8          |
| Kempsy   | 2007 | Poland   | BD      | DSM-IV             | population-based| 43.5±13.5                | 52.5     | 8          |
| Kunugi   | 1998 | Japan    | BD      | DSM-IV             | population-based| 47.9±13.6                | 37.1     | 8          |
| Ozbek    | 2008 | Turkey   | BD      | DSM-IV             | population-based| 40.5±12.33              | 37.6     | 8          |
| Rahimi   | 2016 | Iran     | BD      | DSM-IV-TR          | hospital-based  | 35.4±12.3                | 50.0     | 7          |
| Reif     | 2005 | Germany  | BD      | DSM-IV             | population-based| 50.0                     | -        | 7          |
| Sarah Woods | 2010 | UK, Canada| BD      | DSM-IV             | population-based| 47.15±11.94             | 37.7     | 8          |
| Tan      | 2004 | Singapore| BD      | DSM-IV             | hospital-based  | 43.3±14                  | 34.1     | 7          |
| Wang     | 2015 | China    | BD      | DSM-IV-TR          | population-based| 31.9±11.5               | 48.8     | 8          |
| Zhao     | 2008 | China    | BD      | DSM-IV             | population-based| -                       | -        | 7          |
| Gao      | 2020 | China    | SCZ     | DSM-IV             | population-based| 47.8±10.2               | 81.8     | 8          |
| Arinami  | 1997 | Japan    | SCZ     | DSM-IV             | -               | -                        | -        | 5          |
| Arzaghi  | 2011 | Iran     | SCZ     | DSM-IV             | hospital-based  | 29.4                    | 68.18    | 7          |
| Betcheva | 2009 | Bulgaria | SCZ     | DSM-IV             | -               | -                        | -        | 5          |
| Bouaziz  | 2010 | Tunisia  | SCZ     | DSM-IV-TR          | population-based| 36.0±9.0                | 100.0    | 8          |
| El-Hadidy| 2014 | Egypt    | SCZ     | DSM-IV-TR          | hospital-based  | 33.9±9.4                | 36.46    | 7          |
| Feng     | 2009 | China    | SCZ     | DSM-IV             | hospital-based  | 31.7                    | 40.65    | 7          |
| Foroughmand AM | 2015 | Iran    | SCZ     | DSM-IV-TR          | population-based| 43.3±11.3              | 58.5     | 7          |
| Garcia-Miss Mdel | 2010 | Mexico | SCZ     | DSM-IV-TR          | population-based| 38.9                  | 70.48    | 8          |
| Hei      | 2014 | China    | SCZ     | DSM-IV             | hospital-based  | 27±12                   | 54.6     | 7          |
| Jonsson  | 2008 | Norway   | SCZ     | DSM-IV             | population-based| 36.6±9.8                | 53.99    | 8          |
| Jonsson  | 2008 | Denmark  | SCZ     | ICD-10             | population-based| 44.4±11.2              | 57.52    | 8          |
| Jonsson  | 2008 | Sweden   | SCZ     | DSM-III-R          | population-based| 55.7±15.6              | 62.02    | 8          |
| Joober   | 2000 | Canada   | SCZ     | DSM-IV             | population-based| -                      | -        | 7          |
| Kang,HJ  | 2010 | Korean   | SCZ     | DSM-IV             | population-based| 38.3±3.93              | 54.0     | 8          |
| Kempisty | 2007 | Poland   | SCZ     | DSM-IV             | population-based| 43.5±13.5              | 52.5     | 8          |
| Kempisty | 2006 | Poland   | SCZ     | DSM-IV             | population-based| 10.39                  | 50.5     | 8          |
| Kim      | 2011 | Korean   | SCZ     | DSM-IV             | hospital-based  | 32.89±7.76             | 66.17    | 7          |
| Kontis,D | 2013 | Greece   | SCZ     | DSM-IV             | population-based| 42.91±10               | 64.44    | 8          |
| Kunugi   | 1998 | Japan    | SCZ     | DSM-IV             | population-based| 42.2±12.8              | 48.69    | 8          |
| Lajin,B  | 2012 | Syrian   | SCZ     | DSM-IV             | hospital-based  | 37±10                  | 70.59    | 7          |
| Lee      | 2006 | Korea    | SCZ     | DSM-IV             | population-based| -                      | 42.55    | 7          |

(Continued)
The study was of low quality. Genotype and allele frequencies, HWE and sample size are given in Tables 2–4, respectively. Of the total of 67 studies, four showed significant deviations from HWE ($p < 0.05$).

### Association between MTHFR 677C>T and ADHD

Table 5 and Fig 2 show results generated for five genetic models evaluating the association between 677C>T variation and ADHD risk under a random effects model. Results indicated no association between 677C>T locus and ADHD occurrence.
Table 3. Distribution of genotype and allele frequencies of the MTHFR 677C>T and 1298A>C polymorphisms in bipolar disorder patients.

| Author       | Cases, n | Controls, n | Cases, n | Controls, n | Sample size |
|--------------|----------|-------------|----------|-------------|-------------|
|              | CC CT TT | CC CT TT    | AA AC CC | AA AC CC    | P_HWE       |
| Agnieszka    | 51 50 11 | 66 85 16    | 0.1266   |             | 112 167     |
| Arinami      | 15 20 5  | 154 214 51  | 0.0743   |             | 40 419      |
| Arzaghi      | 52 34 4  | 54 38 2     | 0.1096   |             | 90 94       |
| Chen         | 178 231 92 | 153 235 73 | 0.2718   |             | 501 461     |
| El-Hadidy    | 46 70 18 | 114 30 5    | 0.1026   |             | 134 149     |
| El-Hadidy    | 42 40 8  | 72 30 6     | 0.2390   |             | 90 108      |
| Ezzaher      | 41 40 11 | 94 62 14    | 0.4106   |             | 92 170      |
| Jasson       | 58 49 10 | 80 75 22    | 0.5008   | 47 56 12    | 82 79 16    | 0.6243   | 232 354     |
| Kempisy      | 108 73 19 | 210 79 11  | 0.3027   |             |             | 200 300     |
| Arinami      | 96 138 63 | 154 214 51 | 0.0743   |             |             | 297 419     |
| Arzaghi      | 35 27 4  | 54 38 2     | 0.1096   |             |             | 66 94       |
| Betcheva     | 76 85 24 | 84 76 22    | 0.4565   | 91 72 18    | 80 79 24    | 0.5213   | 366 365     |
| Bouaziz      | 18 4 3  | 19 5 1      | 0.3969   |             |             | 25 25       |
| El-Hadidy    | 48 28 20 | 72 30 6     | 0.2390   |             |             | 96 108      |
| Fong         | 17 67 39 | 40 65 18    | 0.3084   |             |             | 123 123     |
| Foroughmand.AM | 104 76 20 | 123 64 13  | 0.2437   | 60 89 51    | 65 108 27   | 0.0885   | 400 400     |
| Joober       | 30 52 23 | 41 36 13    | 0.2783   |             |             | 105 90      |
| Kang,HJ      | 125 176 59 | 130 158 60 | 0.3168   | 248 105 7   | 239 100 9   | 0.7026   | 720 696     |
| Kontis.D     | 40 37 13 | 21 22 12    | 0.1868   |             |             | 90 55       |

Note: $P_{HWE}$ represents the $P$ value of Hardy-Weinberg equilibrium test in the genotype distribution of controls.

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Table 4. Distribution of genotype and allele frequencies of the MTHFR 677C>T and 1298A>C polymorphisms in schizophrenia patients.

| Author         | Cases, n | Controls, n | Cases, n | Controls, n | Sample size |
|----------------|----------|-------------|----------|-------------|-------------|
|                | CC CT TT | CC CT TT    | AA AC CC | AA AC CC    | P_HWE       |
| Arinami        | 96 138 63 | 154 214 51 | 0.0743   |             | 297 419     |
| Arzaghi        | 35 27 4  | 54 38 2     | 0.1096   |             | 66 94       |
| Betcheva       | 76 85 24 | 84 76 22    | 0.4565   | 91 72 18    | 80 79 24    | 0.5213   | 366 365     |
| Bouaziz        | 18 4 3  | 19 5 1      | 0.3969   |             |             | 25 25       |
| El-Hadidy      | 48 28 20 | 72 30 6     | 0.2390   |             |             | 96 108      |
| Fong           | 17 67 39 | 40 65 18    | 0.3084   |             |             | 123 123     |
| Foroughmand.AM | 104 76 20 | 123 64 13  | 0.2437   | 60 89 51    | 65 108 27   | 0.0885   | 400 400     |
| Joober         | 30 52 23 | 41 36 13    | 0.2783   |             |             | 105 90      |
| Kang,HJ        | 125 176 59 | 130 158 60 | 0.3168   | 248 105 7   | 239 100 9   | 0.7026   | 720 696     |
| Kontis.D       | 40 37 13 | 21 22 12    | 0.1868   |             |             | 90 55       |

Note: $P_{HWE}$ represents the $P$ value of Hardy-Weinberg equilibrium test in the genotype distribution of controls.

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(Continued)
Table 4. (Continued)

| Author       | CC, n | CT, n | TT, n | CC, n | CT, n | TT, n | \(P_{\text{HWE}}\) |
|--------------|-------|-------|-------|-------|-------|-------|---------------------|
| Kunugi       | 121   | 168   | 54    | 95    | 129   | 34    | 0.3416             |
| Lajin.B      | 47    | 26    | 12    | 58    | 58    | 10    | 0.3879             |
| Lee          | 74    | 128   | 33    | 99    | 115   | 21    | 0.1257             |
| Misiak.B     | 64    | 52    | 16    | 71    | 53    | 22    | 0.0280             |
| Muntjewerff  | 110   | 111   | 31    | 205   | 165   | 35    | 0.8261             |
| Muntjewerff.JW | 334  | 319   | 86    | 405   | 389   | 92    | 0.9213             |
| Nishi        | 220   | 309   | 92    | 174   | 239   | 73    | 0.5380             |
| Nishi        | 417   | 530   | 202   | 1,072 | 2,160 | 410   | 0.2074             |
| Philibert    | 107   | 83    | 16    | 176   | 137   | 46    | 0.0212             |
| Roffman      | 41    | 27    | 11    | 35    | 32    | 8     | 0.0280             |
| Sazci        | 144   | 115   | 38    | 161   | 156   | 24    | 0.0926             |
| Sazci        | 59    | 49    | 22    | 106   | 103   | 17    | 0.2361             |
| Tan          | 136   | 84    | 16    | 80    | 33    | 7     | 0.1645             |
| Tsutsumi     | 160   | 184   | 69    | 138   | 183   | 64    | 0.8004             |
| Vilella      | 58    | 75    | 25    | 85    | 110   | 39    | 0.7360             |
| Virgos       | 81    | 98    | 31    | 79    | 106   | 33    | 0.7928             |
| Wan          | 45    | 122   | 75    | 71    | 113   | 50    | 0.6869             |
| Wan          | 24    | 47    | 26    | 24    | 43    | 25    | 0.5323             |
| Ye           | 12    | 58    | 34    | 14    | 32    | 10    | 0.2658             |
| Yu           | 91    | 96    | 43    | 85    | 126   | 40    | 0.5543             |
| Yu           | 199   | 186   | 41    | 306   | 260   | 62    | 0.5351             |
| Zhang        | 166   | 450   | 384   | 213   | 505   | 318   | 0.6297             |
| Zhang        | 96    | 113   | 26    | 52    | 45    | 5     | 0.2248             |
| Zhilyaeva.TV | 245   | 212   | 43    | 280   | 188   | 31    | 0.9406             |

Note: \(P_{\text{HWE}}\) represents the \(P\) value of Hardy-Weinberg equilibrium test in the genotype distribution of controls.

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Table 5. Summarized ORs with 95% CIs for the association between MTHFR polymorphisms and ADHD.

| Polymorphism | Genetic model | n | Statistical model | OR     | 95% CI | \(p_z\) | \(I^2(\%)\) | \(p_h\) | \(p_e\) |
|--------------|---------------|---|------------------|--------|--------|--------|-----------|--------|--------|
| 677C>T       | Allele contrast | 5 | Random           | 1.161  | 0.962–1.400 | 0.119  | 0.0        | 0.712  | 0.367  |
|              | Homozygous codominant | 3 | Random           | 1.317  | 0.870–1.993 | 0.193  | 0.0        | 0.436  | 0.427  |
|              | Heterozygous codominant | 5 | Random           | 1.168  | 0.883–1.543 | 0.277  | 0.0        | 0.852  | 0.779  |
|              | Dominant      | 5 | Random           | 1.205  | 0.924–1.571 | 0.169  | 0.0        | 0.794  | 0.544  |
|              | Recessive     | 3 | Random           | 1.229  | 0.852–1.774 | 0.270  | 0.0        | 0.452  | 0.401  |
| 1298A>C      | Allele contrast | 5 | Random           | 1.206  | 1.003–1.450 | 0.047  | 0.0        | 0.453  | 0.681  |
|              | Homozygous codominant | 3 | Random           | 1.255  | 0.650–2.420 | 0.497  | 44.1       | 0.167  | 0.873  |
|              | Heterozygous codominant | 5 | Random           | 1.321  | 0.987–1.767 | 0.061  | 0.0        | 0.428  | 0.352  |
|              | Dominant      | 5 | Random           | 1.337  | 1.012–1.766 | 0.041  | 0.0        | 0.442  | 0.337  |
|              | Recessive     | 3 | Random           | 1.132  | 0.558–2.927 | 0.731  | 59.0       | 0.087  | 0.850  |

Note: \(n\), the number of studies; \(p_z\), \(P\) value for association test; \(p_h\), \(P\) value for heterogeneity test; \(p_e\), \(P\) value for publication bias test.

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Table 5 and Fig 3 show results for five genetic models evaluating associations between 1298A>C variation and ADHD risk under a random effects model. Results showed an association between 1298A>C and ADHD occurrence as a risk factor in the allele contrast ($p = 0.047$, OR = 1.206, 95% CI = 1.003–1.450) and the dominant models ($p = 0.041$, OR = 1.337, 95% CI = 1.012–1.766).

Table 6 and Fig 4 show the results for five genetic models evaluating the association between 677C>T variation and BD risk under a random effects model. The results indicated an association between 677C>T variation and BD occurrence as a protective factor in the allele contrast ($p = 0.024$, OR = 0.822, 95% CI = 0.693–0.974) and as a risk factor in the dominant model ($p = 0.044$, OR = 1.254, 95% CI = 1.006–1.562).

Fig 2. Forest plot of the association between 667C>T variation and risk of ADHD in the five genetic models: A, allele contrast; B, homozygous codominant; C, heterozygous codominant; D, dominant; and E, recessive.

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Association between MTHFR 1298A>C and ADHD

Table 5 and Fig 3 show results for five genetic models evaluating associations between 1298A>C variation and ADHD risk under a random effects model. Results showed an association between 1298A>C and ADHD occurrence as a risk factor in the allele contrast ($p = 0.047$, OR = 1.206, 95% CI = 1.003–1.450) and the dominant models ($p = 0.041$, OR = 1.337, 95% CI = 1.012–1.766).

Association between MTHFR 667C>T and BD

Table 6 and Fig 4 show the results for five genetic models evaluating the association between 677C>T variation and BD risk under a random effects model. The results indicated an association between 677C>T locus and BD occurrence as a protective factor in the allele contrast model ($p = 0.024$, OR = 0.822, 95% CI = 0.693–0.974) and as a risk factor in the dominant model ($p = 0.044$, OR = 1.254, 95% CI = 1.006–1.562).
Fig 3. Forest plot of the associations between 1298A>C variation and risk of ADHD in the five genetic models: A, allele contrast; B, homozygous codominant; C, heterozygous codominant; D, dominant; and E, recessive.

Table 6. Summarized ORs with 95% CIs for the association between MTHFR polymorphisms and bipolar disorder.

| Polymorphism | Genetic model | n  | Statistical model | OR    | 95% CI     | p_z  | I² (%) | p_h  | p_e  |
|--------------|---------------|----|-------------------|-------|------------|------|--------|------|------|
| 677C>T       | Allele contrast | 17 | Random            | 0.822 | 0.693–0.974 | 0.024 | 81.1   | 0.000 | 0.058 |
|              | Homozygous codominant | 17 | Random            | 0.744 | 0.553–1.001 | 0.050 | 64.9   | 0.000 | 0.025 |
|              | Heterozygous codominant | 17 | Random            | 1.079 | 0.905–1.287 | 0.396 | 12.7   | 0.305 | 0.128 |
|              | Dominant       | 17 | Random            | 1.254 | 1.006–1.562 | 0.044 | 79.8   | 0.000 | 0.138 |
|              | Recessive      | 17 | Random            | 0.810 | 0.640–1.026 | 0.080 | 50.4   | 0.009 | 0.036 |
| 1298A>C      | Allele contrast | 4  | Random            | 0.756 | 0.602–0.950 | 0.017 | 50.8   | 0.107 | 0.991 |
|              | Homozygous codominant | 4  | Random            | 0.493 | 0.259–0.937 | 0.031 | 64.0   | 0.040 | 0.436 |
|              | Heterozygous codominant | 4  | Random            | 2.030 | 1.068–3.862 | 0.031 | 64.0   | 0.040 | 0.436 |
|              | Dominant       | 4  | Random            | 1.326 | 1.075–1.636 | 0.008 | 0.0    | 0.409 | 0.941 |
|              | Recessive      | 4  | Random            | 0.541 | 0.300–0.977 | 0.042 | 61.4   | 0.051 | 0.413 |

Note: n, the number of studies; p_z, P value for association test; p_h, p value for heterogeneity test; p_e, p value for publication bias test.

https://doi.org/10.1371/journal.pone.0271170.t006
Table 6 and Fig 5 show the results for five genetic models evaluating associations between 1298A>C variation and BD risk under a random effects model. Our results showed an association between 1298A>C and BD occurrence as a protective factor in the allele contrast ($p = 0.017$, OR = 0.756, 95% CI = 0.602–0.950), homozygous codominant ($p = 0.031$, OR = 0.493, 95% CI = 0.259–0.937) and recessive models ($p = 0.042$, OR = 0.541, 95% CI = 0.300–0.977). However, the MTHFR 1298A>C increased the BD occurrence in the heterozygous codominant ($p = 0.031$, OR = 2.030, 95% CI = 1.068–3.862) and dominant models ($p = 0.008$, OR = 1.326, 95% CI = 1.075–1.636).

**Fig 4.** Forest plot of the association between 667C>T variation and risk of bipolar disorder in the five genetic models: A, allele contrast; B, homozygous codominant; C, heterozygous codominant; D, dominant; and E, recessive.

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**Association between MTHFR 1298A>C and BD**

Table 6 and Fig 5 show the results for five genetic models evaluating associations between 1298A>C variation and BD risk under a random effects model. Our results showed an association between 1298A>C and BD occurrence as a protective factor in the allele contrast ($p = 0.017$, OR = 0.756, 95% CI = 0.602–0.950), homozygous codominant ($p = 0.031$, OR = 0.493, 95% CI = 0.259–0.937) and recessive models ($p = 0.042$, OR = 0.541, 95% CI = 0.300–0.977). However, the MTHFR 1298A>C increased the BD occurrence in the heterozygous codominant ($p = 0.031$, OR = 2.030, 95% CI = 1.068–3.862) and dominant models ($p = 0.008$, OR = 1.326, 95% CI = 1.075–1.636).
Fig 5. Forest plot of the associations between 1298A>C variation and risk of bipolar disorder in the five genetic models: A, allele contrast; B, homozygous codominant; C, heterozygous codominant; D, dominant; and E, recessive.

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Table 7. Summarized ORs with 95% CIs for the association between MTHFR polymorphisms and schizophrenia.

| Polymorphism | Genetic model | n   | Statistical model | OR  | 95% CI     | p   | I²(%) | p_h  | p_e  |
|--------------|---------------|-----|------------------|-----|------------|-----|-------|------|------|
| 677C>T       | Allele contrast | 43  | Random           | 0.867 | 0.815-0.923 | 0.000 | 58.6  | 0.000 | 0.125 |
|              | Homozygous codominant | 43  | Random           | 0.735 | 0.643-0.841 | 0.000 | 57.7  | 0.000 | 0.055 |
|              | Heterozygous codominant | 43  | Random           | 1.211 | 1.100-1.333 | 0.000 | 26.5  | 0.060 | 0.196 |
|              | Dominant      | 43  | Random           | 1.153 | 1.066-1.246 | 0.000 | 47.9  | 0.000 | 0.104 |
|              | Recessive     | 43  | Random           | 0.787 | 0.707-0.876 | 0.000 | 45.2  | 0.001 | 0.136 |
| 1298A>C      | Allele contrast | 17  | Random           | 0.925 | 0.845-1.013 | 0.094 | 41.4  | 0.038 | 0.851 |
|              | Homozygous codominant | 17  | Random           | 0.852 | 0.691-1.052 | 0.136 | 35.4  | 0.074 | 0.833 |
|              | Heterozygous codominant | 17  | Random           | 1.113 | 0.926-1.338 | 0.254 | 18.4  | 0.239 | 0.756 |
|              | Dominant      | 17  | Random           | 1.085 | 0.984-1.196 | 0.103 | 18.2  | 0.240 | 0.788 |
|              | Recessive     | 17  | Random           | 0.867 | 0.711-1.057 | 0.138 | 34.0  | 0.084 | 0.800 |

Note: n, the number of studies; p, P value for association test; p_h, p value for heterogeneity test; p_e, p value for publication bias test.

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Table 7 and Fig 6 show the results for five genetic models evaluating the association between 667C>T variation and SCZ risk under a random effects model. The results indicated an association between 677C>T locus and SCZ occurrence as a protective factor in the allele contrast ($p < 0.001$, OR = 0.867, 95% CI = 0.815–0.923), homozygous codominant ($p < 0.001$, OR = 0.735, 95% CI = 0.643–0.841) and recessive models ($p < 0.001$, OR = 0.787, 95% CI = 0.707–0.876) and as a risk factor in the heterozygous codominant ($p < 0.001$, OR = 1.211, 95% CI = 1.100–1.333) and dominant models ($p < 0.001$, OR = 1.153, 95% CI = 1.066–1.246).

**Fig 6.** Forest plot of the association between 667C>T variation and risk of schizophrenia in the five genetic models: A, allele contrast; B, homozygous codominant; C, heterozygous codominant; D, dominant; and E, recessive.

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**Association between MTHFR 667C>T and SCZ**

Table 7 and Fig 6 show the results for five genetic models evaluating the association between 667C>T variation and SCZ risk under a random effects model. The results indicated an association between 677C>T locus and SCZ occurrence as a protective factor in the allele contrast ($p < 0.001$, OR = 0.867, 95% CI = 0.815–0.923), homozygous codominant ($p < 0.001$, OR = 0.735, 95% CI = 0.643–0.841) and recessive models ($p < 0.001$, OR = 0.787, 95% CI = 0.707–0.876) and as a risk factor in the heterozygous codominant ($p < 0.001$, OR = 1.211, 95% CI = 1.100–1.333) and dominant models ($p < 0.001$, OR = 1.153, 95% CI = 1.066–1.246).
Table 7 and Fig 7 show the results for five genetic models evaluating associations between 1298A>C variation and SCZ risk under a random effects model. The results showed no association between 1298A>C and SCZ occurrence in the five genetic models.

Sensitivity analysis

We examined the influence of individual studies in the pooled ORs for 667C>T and 1298A>C loci via sensitivity analysis involving omitting each study in each genetic model; the results did not change. This indicates that our results were statistically robust for all five genetic models.
models examining associations between MTHFR polymorphisms and susceptibility to ADHD, BD and SCZ.

**Publication bias**

We assessed possible publication bias using a Begg’s funnel plot and Egger’s test. No obvious asymmetry was observed in the funnel plot and Begg’s test results, indicating a lack of publication bias ($p > 0.05$) except for the homozygous codominant model of $677C>T$ locus in BD ($p = 0.025$) (Figs 8–13).

**Discussion**

The present meta-analysis included 66 studies that investigated the association between MTHFR ($677C>T$ and $1298A>C$) polymorphisms and occurrence of ADHD, BD and SCZ. Overall, our meta-analytical results provided evidence that MTHFR $677C>T$ was associated
with occurrence of BD and SCZ, while the 1298A>C polymorphism was related to ADHD and BD. The sensitivity analysis indicated that these results were stable and reliable.

Five previous retrospective studies investigated the association between MTHFR polymorphisms and ADHD [2, 37–39, 77]. Our results were very similar to those of Tahereh Sadeghiyeh [77], but not exactly the same as those of Saliha Baykal and Emel Ergul [37, 38]. A total of five retrospective studies were included, which represented MTHFR polymorphisms more accurately than previous published studies. This is the first meta-analysis to include recent published studies concerning the association between MTHFR polymorphism and ADHD occurrence. Therefore, to some extent, our study provides a more reliable assessment of the association between MTHFR polymorphisms and ADHD. Additionally, some previous studies showed that ADHD occurrence was affected by various environmental factors [78]. It is possible that epigenetic risk mechanisms in ADHD responding to environmental risk factors or trans-regulatory and gene × environment effects in the development of child psychopathology might play a consequential role in ADHD etiology [79]. In addition, ADHD subtypes represent distinct clinical entities and may have different genetic backgrounds [80].
To date, case-control studies and meta-analyses have explored the role of MTHFR polymorphisms in BD occurrence [24, 31, 33, 43, 51, 81–83] but with no consistent conclusion. Additionally, The MTHFR gene polymorphism is unlikely to play a major role in the pathogenesis of obsessive-compulsive disorder [84]. Our study showed that the 677C>T and 1298A>C polymorphisms were involved in the occurrence of BD. Moreover, a genome-wide association study suggested that the MTHFR gene polymorphism was related to mood disorder [85]. The Genotypes of 677C>T were related to total homocysteine (tHcy), folate and B12. Individuals with TT genotype have elevated tHcy and reduced folate and B12 levels, which may be a susceptible factor for the BD [48]. The interaction of BDNF Val66Met and MTHFR C677T may reduce the hippocampal size in both healthy controls and patients with first-episode psychosis [86].

The C677T polymorphisms of MTHFR had an influence on SCZ symptoms. However, the effect of the T allele on the negative symptoms of SCZ could be further enhanced by folate deficiency [87]. Additionally, there was a significant association between the 677TT genotype and SCZ under the recessive model in the male patient subgroup, and CT genotype under the

Fig 10. Funnel plot analysis depicting publication bias in the association between MTHFR 677C>T polymorphism and bipolar disorder in the five genetic models (A, allele contrast; B, homozygous codominant; C, heterozygous codominant; D, dominant; and E, recessive).

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overdominant model in the total patient group [65]. The OR for patient with BD and SCZ in 1298CC homozygous state was 3.768 (P = 0.0003) and 2.694 (P = 0.0123), respectively. After the stratification of patients based on gender, only a significant association of 1298CC genotype with BD in female patients was observed (P = 0.0005) [46]. Moreover, a previous meta-analysis indicated that the T allele and TT genotype of C677T carriers showed significantly increased risk of major psychiatric disorders including SCZ and BD [33]. Moreover, the activity of MTHFR will be affected by multiple single-nucleotide polymorphisms. However, variations other than the 677C>T and 1298A>C polymorphisms have received little attention. In addition, aggravating symptoms, increased MTHFR polymorphisms, and reduced genomic methylation levels can be observed in patients with early-onset SCZ [88]. MTHFR 677T allele carriers have lower levels of total cholesterol and low-density lipoprotein cholesterol than those with the 677CC genotype [89]. There was a positive association between the COMT—MTHFR interaction and attention in inpatients suffering from recent onset SCZ [90]. MTHFR A1298C, but not C677T, was associated with the metabolic syndrome, its CC genotype having a 2.4 times higher risk compared to AA genotype [91]. In addition, the C allele of MTHFR was associated with BMI reduction in the schizophrenia patients following switching of antipsychotics to aripiprazole and ziprasidone [92].

There were several potential limitations to the present study. First, the most important was sample size. Small samples with limited participants are usually accompanied by selection
biases. These studies lack sufficient power to support or refute meaningful conclusions [93].
Second, subgroup analysis cannot be carried out with limited samples, so the influence of some factors (e.g. ethnicity, source of controls and diagnostic criteria) were ignored. The discrepancies of the studies may result from population stratifications, explicitly, socio-economic status [94]. Finally, clinical subtypes of the mental disorder, gene–gene interaction and epigenetics were not examined in this study due to insufficient information.

Conclusions
Our findings suggest that the MTHFR 677C>T was associated with occurrence of BD and SCZ, while the 1298A>C polymorphism was related to ADHD and BD. Studies involving larger sample sizes will be necessary to confirm the meta-analysis results, particularly in different ethnicities and to address the epigenetic mechanisms and environmental influences on the occurrence of common mental disorders.
Supporting information

S1 Checklist. Meta-analysis on genetic association studies checklist.
(DOCX)
Author Contributions

Conceptualization: Ji-long Zheng, Jun Yao.

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