Association between variants of MTHFR genes and psychiatric disorders: A meta-analysis

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Background: Psychiatric disorders have seriously affected human life, one of the risk genes related to psychosis is the methylenetetrahydrofolate reductase (MTHFR) gene. This gene has a potential role in psychiatric disorders. Therefore, a meta-analysis is conducted to investigate the correlations between two prevalent MTHFR single nucleotide polymorphisms (SNPs), MTHFR C677T, A1298C, severe psychological disorders (schizophrenia, major depression, bipolar disorder).

Methods: A total of 81 published studies were screened and selected by a search of electronic databases up to April 2022. Odds ratios (ORs) with 95% confidence intervals (CIs) were used to assess the association between MTHFR polymorphism and psychiatric disorders susceptibility by using random effect models.

Results: We found that MTHFR C677T polymorphism is significantly related to schizophrenia and major depression in the overall population. MTHFR C677T has been linked to an increased risk of bipolar disorder in the recessive model (TT vs. CT + CC). Ethnic subgroup analysis shows that schizophrenia and major depression significantly correlate with MTHFR C677T and A1298C in Asian populations but not Caucasians. Besides, schizophrenia is correlated substantially with MTHFR C677T in the African population. However, the MTHFR A1298C polymorphism is only marginally linked to major depression.

Conclusion: Findings of the current study revealed that MTHFR may contribute to the common pathogenesis of psychiatric diseases and that its variants may be essential in controlling the expression of psychosis-related genes. This study could help the researchers and health specialists in the early diagnosis and treatment of psychiatric disorders.

KEYWORDS
MTHFR C677T, MTHFR A1298C, disorders, meta-analysis, gene variants
Introduction

Mental disorders have seriously affected human life, causing considerable familial and social burden (1). They are among the leading causes of disability globally and have been related to an increase in premature mortality (2). Major psychiatric disorders include schizophrenia (SZ), major depression (MD), bipolar disorder (BPD), and others (3). These mental disorders are more likely to occur in families, suggesting that they are related to genetic factors (4, 5). Many susceptible genes have been found through unbiased genome-wide association studies (GWAS), a kind of analysis comparing allele frequencies of all available polymorphic markers with specific symptoms or disease states (6, 7). GWAS and many other follow-up replication studies have suggested that methylenetetrahydrofolatereductase (MTHFR) polymorphisms are associated with psychiatric disorders.

The MTHFR is a crucial enzyme in the one-carbon metabolism (OCM) process, which involves folate and homocysteine (Hcy) metabolisms. It transforms 5,10-methylenetetrahydrofolate (5,10-methylene THF) to 5-methyltetrahydrofolate (5-methyl THF), and it is involved in folate and homocysteine conversion, which is linked to DNA methylation (8–10). A number of mutations in the MTHFR gene have been found, and the most common mutations are C677T (rs1801133) and A1298C (rs1801131), which are correlated with enzyme deficiency (11–14). In addition, MTHFR polymorphism may significantly decrease MTHFR activity, affect the concentration of Hcy in plasma, and lead to a wide range of mental, neurological, and vascular dysfunction (15).

The human Methylenetetrahydrofolatereductase (MTHFR) gene is located in chromosomal region 1p36.3 (16). The MTHFR gene has 14 common or rare single nucleotide polymorphisms linked with enzyme defects, the most prevalent of which are C677T and A1298C. The C677T gene location is one of the most researched and clinically significant variants in exon 4. The variation in C677T is due to the replacement of thymine by thymine, which leads to the conversion of valine to alanine at codon 222 (11). The polymorphism of A1298C is due to the adenine substitution by cytosine, leading to the conversion of glutamic acid to alanine at residue 429 (10). The replacement of 677 and 1,298 nucleotides C-T and A-C in the MTHFR gene reduces enzyme activity, and this decrease in MTHFR activity may affect the OCM cycle (17). Abnormal OCM might impair cortical and hippocampal neurogenesis during development and affect brain maturation and function (18–20).

The association between MTHFR polymorphism and mental illnesses has already been explored, but the influence of MTHFR on psychiatric disorders is still disputed, and limited studies have been found (21–23). These inconsistencies might be attributed to limited sample sizes, ethnic heterogeneity, and differences in population substructure. So, in current study these limitations have been overcome and summarized the conflicting data. A meta-analysis is performed to explore the connection of MTHFR C677T and A1298C polymorphisms with major mental disorders (including SZ, MD, and BPD). We also assessed whether ethnicity would affect the results. Therefore, it will provide more powerful evidence of whether MTHFR variants influence psychiatric diseases.

Materials and methods

Search strategy

We initially searched PubMed, Embase, Proquest, Web of Science, CNKI (Chinese National Knowledge Infrastructure), VIP (Chinese) database, and Wanfang (Chinese) database for the following terms: MTHFR (methylenetetrahydrofolatereductase), gene (gene or genetic or polymorphism or variants or variation), and psychiatric disorders (psychiatry disorders or mental illness or mental disorders or psychosis). We discovered that most research concentrated on MTHFR C677T and MTHFR A1298C. The researchers investigated the relationships between MTHFR gene variants and susceptibility to mental diseases such as schizophrenia, bipolar disorder, and depression. To guarantee that we missed no studies, we searched these databases again using these gene terms (MTHFR C677T and A1298C) and major mental disorders such as “schizophrenia,” “bipolar disorder,” “depression,” and so on. All of the research was completed and published by April 2022. After that, we selected relevant papers and examined their bibliographies to find additional references.

Study selection

Selection of articles for analysis purposes was made based on the following criteria: (1) case-control studies; (2) giving comprehensive data of formally diagnosed patients with unrelated healthy control subjects for generating an odds ratio (OR) with a 95% confidence interval (CI); (3) Case status was classified as having a DSM-IV-diagnosed mental condition, with control patients having no history of psychiatric disorders or other neurological abnormalities; (4) the studies used samples that did not overlap with other studies; (5) the use of internationally recognized loci gene polymorphism detection techniques (such as polymerase chain reactionrestriction fragment length polymorphism, real-time quantitative polymerase chain reaction, or amplification block mutation system-polymerase
chain reaction); and (6) the demographic characteristics of the control group, such as gender and age, were comparable to those of the case group. In addition, articles were excluded if they (1) not reported the target genotype frequencies, (2) were reviews, letters, or commentaries, or (3) were duplicate reports.

Data extraction and management

Two reviewers independently extracted the following information from all eligible studies: author, year of publication, country, ethnicity (categorized as Asian, Caucasian, and African populations), and the number of distinct genotypes in cases and controls for C677T or A1298C genotype. In the case of a disagreement, a discussion was held, and if no agreement could be achieved, a third person was consulted for consensus.

Statistical analysis

We investigated the potential of conducting a meta-analysis of all eligible studies. The odds ratio (OR) and associated 95% confidence intervals (CIs) were used to examine the strength of the connection between MTHFR polymorphism and mental disorders: the allele model (T vs. C, C vs. A), the dominant model (TT + CT vs. CC, CC + AC vs. AA), the homozygote model (TT vs. CC, CC vs. AA) and the recessive model (TT vs. CT + CC, CC vs. AC + AA). The Chi-square test was used to analyze the genotype distribution in the control groups for Hardy Weinberg equilibrium (HWE). The Cochran’s (Q) $X^2$ test and $I^2$ statistic were used to assess the heterogeneity between individual studies (24). Considering the heterogeneity of studies, this meta-analysis adopted a random effect model (25). Subgroup analyses were performed using ethnicity stratification, and sensitivity analyses were undertaken.
TABLE 1  Overview of MTHFR C677T genotype distribution of psychosis patients and controls, with information about country, ethnicity, and disease.

| References          | Year  | Country | Ethnicity | Case | Control | Case | Control | P_HWE |
|---------------------|-------|---------|-----------|------|---------|------|---------|-------|
| Schizophrenia       |       |         |           |      |         |      |         |       |
| Arinami et al. (27) | 1997  | Japanese| Asian     | 297  | 419     | 96   | 138     | 63    |
| Kunugi et al. (28)  | 1998  | Japanese| Asian     | 343  | 258     | 121  | 168     | 54    |
| Virgos et al. (29)  | 1999  | Spain   | Caucasian | 210  | 218     | 81   | 98      | 31    |
| Joober et al. (30)  | 2000  | Canada  | Caucasian | 105  | 90      | 30   | 52      | 23    |
| Saci et al. (31)    | 2003  | Turkey  | Caucasian | 130  | 226     | 59   | 49      | 22    |
| Tan et al. (32)     | 2004  | Singapore| Asian     | 236  | 120     | 136  | 84      | 16    |
| Yu et al. (33)      | 2004  | China   | Asian     | 230  | 251     | 91   | 96      | 43    |
| Yu et al. (33)      | 2005  | Scotland| Caucasian | 426  | 628     | 199  | 186     | 41    |
| Saci et al. (34)    | 2005  | Turkey  | Asian     | 297  | 341     | 144  | 115     | 38    |
| Vilella et al. (35) | 2005  | Spain   | Caucasian | 158  | 234     | 58   | 75      | 25    |
| Kempisty et al. (36)| 2006  | Poland  | Caucasian | 200  | 300     | 113  | 68      | 19    |
| Philibert et al. (37)| 2006  | United States| Caucasian | 206  | 359     | 107  | 83      | 16    |
| Lee et al. (38)     | 2006  | South Korea| Caucasian | 215  | 235     | 74   | 128     | 33    |
| Yang et al. (39)    | 2007  | China   | Asian     | 100  | 100     | 33   | 51      | 16    |
| Jonsson et al. (40) | 2007  | Denmark | Asian     | 419  | 1006    | 200  | 177     | 42    |
| Jonsson et al. (40) | 2008  | Norway  | Caucasian | 163  | 177     | 75   | 70      | 18    |
| Jonsson et al. (40) | 2008  | Sweden  | Caucasian | 258  | 293     | 137  | 104     | 17    |
| Muntjewerff (41)    | 2008  | Netherlands| Caucasian | 252  | 405     | 110  | 111     | 31    |
| Ruffman et al. (42) | 2008  | United States| Caucasian | 130  | 208     | 81   | 98      | 31    |
| Feng et al. (43)    | 2009  | China   | Asian     | 123  | 123     | 17   | 67      | 39    |
| Betcheva et al. (44)| 2009  | Bulgaria| Caucasian | 185  | 182     | 76   | 85      | 24    |
| Garcia-Miss et al. (45)| 2010  | Mexico  | Caucasian | 105  | 108     | 29   | 45      | 31    |
| Kang et al. (46)    | 2010  | Korean  | Asian     | 360  | 348     | 125  | 176     | 59    |
| Ye et al. (47)      | 2010  | China   | Asian     | 104  | 56      | 12   | 58      | 34    |
| Bouaziz et al. (48) | 2010  | Tunisia | African   | 25   | 25      | 18   | 4       | 3     |
| Arrzaghi et al. (49) | 2011  | Iran    | Asian     | 66   | 94      | 35   | 27      | 4     |
| Kim et al. (50)     | 2011  | Korea   | Asian     | 201  | 350     | 62   | 101     | 38    |
| Muntjewerff et al. (51)| 2011  | Netherlands| Caucasian | 739  | 886     | 334  | 319     | 86    |
| Tsutsumi et al. (52)| 2011  | Japan   | Asian     | 413  | 385     | 160  | 184     | 69    |
| Zhang et al. (53)   | 2012  | China   | Asian     | 235  | 102     | 96   | 113     | 26    |
| Lochman et al. (54) | 2013  | Czechia | Caucasian | 186  | 209     | 72   | 90      | 24    |
| Zhang et al. (55)   | 2013  | China   | Asian     | 1002 | 1036    | 166  | 450     | 384   |
| Kontis et al. (56)  | 2013  | Greece  | Caucasian | 90   | 55      | 40   | 37      | 13    |
| El-Hadidy et al. (57)| 2014  | Egypt   | African   | 103  | 149     | 52   | 36      | 15    |
| Her et al. (58)     | 2014  | China   | Asian     | 130  | 80      | 17   | 65      | 48    |
| Nishi et al. (59)   | 2014  | Japan   | Asian     | 621  | 486     | 220  | 309     | 92    |
| Nishi et al. (59)   | 2014  | Japan   | Asian     | 1,149| 2,742   | 417  | 530     | 202   |
| Foroughmand et al. (60)| 2015  | Iran    | Asian     | 200  | 200     | 104  | 76      | 20    |
| Misiaik et al. (61) | 2016  | Poland  | Caucasian | 135  | 146     | 64   | 52      | 16    |
| Takano et al. (62)  | 2016  | Japan   | Asian     | 45   | 30      | 17   | 18      | 10    |
| Wang et al. (63)    | 2017  | China   | Asian     | 254  | 339     | 79   | 129     | 46    |
| Oniki et al. (64)   | 2017  | Japan   | Asian     | 256  | 194     | 89   | 135     | 32    |
| Debost et al. (65)  | 2017  | Denmark | Caucasian | 1699 | 1681    | 839  | 704     | 156   |
| Zhilyaeva et al. (66)| 2018  | Russia  | Caucasian | 500  | 499     | 245  | 212     | 43    |
| Ota et al. (67)     | 2019  | Japan   | Asian     | 538  | 1263    | 181  | 255     | 102   |
| Wan et al. (68)     | 2019  | China   | Asian     | 97   | 92      | 24   | 47      | 26    |
| Wan, L (69)         | 2019  | China   | Asian     | 242  | 234     | 45   | 122     | 75    |
| References                  | Year | Country        | Ethnicity | Case Control | Case Control | $P_{HWE}$ |
|-----------------------------|------|----------------|-----------|--------------|--------------|-----------|
|                            |      |                |           | CC CT TT     | CC CT TT     |           |
| **Major depression**        |      |                |           |              |              |           |
| Arinami et al. (27)         | 1997 | Japanese       | Asian     | 32 419 9 14 9 154 | 214 51       | 0.074     |
| Kunugi et al. (28)          | 1998 | Japanese       | Asian     | 71 258 10 31 30 95 | 129 34       | 0.342     |
| Tan et al. (32)             | 2004 | Singapore      | Asian     | 88 120 49 34 5 80 | 33 7         | 0.165     |
| Kelly et al. (70)           | 2004 | United Kingdom | Caucasian | 100 89 30 56 14 40 | 37 12        | 0.467     |
| Reif et al. (71)            | 2005 | Germany        | Caucasian | 46 176 23 17 6 75 | 80 21        | 0.962     |
| Yuan et al. (72)            | 2005 | China          | Asian     | 60 80 22 27 11 27 | 38 15        | 0.801     |
| Chen-Sheng et al. (73)      | 2005 | China          | Asian     | 39 20 22 15 2 11 9 | 0 0.194     |
| Yuan (74)                   | 2007 | China          | Asian     | 60 80 22 27 11 27 | 38 15        | 0.801     |
| Silprien et al. (75)        | 2008 | Poland         | Caucasian | 83 89 26 38 19 46 | 36 7         | 0.991     |
| Zhao (76)                   | 2008 | China          | Asian     | 77 85 12 37 28 21 | 48 16        | 0.219     |
| Yuan et al. (77)            | 2008 | China          | Asian     | 116 80 46 48 22 27 | 38 15        | 0.801     |
| Hong et al. (78)            | 2009 | China          | Asian     | 178 85 75 84 19 32 | 44 9         | 0.28      |
| Kim et al. (79)             | 2009 | China          | Asian     | 63 458 16 28 19 84 | 248 126      | 0.63      |
| Pan et al. (80)             | 2009 | United States  | Caucasian | 170 83 72 79 19 30 | 44 9         | 0.598     |
| Cao et al. (81)             | 2010 | China          | Asian     | 50 59 9 23 18 24 | 27 8         | 0.926     |
| Zeman et al. (82)           | 2010 | Czechia        | Caucasian | 42 41 15 18 9 16 | 17 8         | 0.377     |
| Feng et al. (83)            | 2010 | China          | Asian     | 152 152 32 66 54 51 | 81 20        | 0.167     |
| Li et al. (84)              | 2010 | China          | Asian     | 402 600 132 192 78 156 | 343 101 <0.001* |
| Song (85)                   | 2010 | China          | Asian     | 156 123 33 68 55 35 | 74 14        | 0.008*    |
| Lizer et al. (96)           | 2011 | United States  | Caucasian | 82 74 31 34 17 33 | 28 13        | 0.114     |
| Zhao et al. (87)            | 2011 | China          | Asian     | 94 98 24 43 27 36 | 45 17        | 0.651     |
| Chojnicka et al. (88)       | 2012 | Poland         | Caucasian | 710 2547 342 300 68 1213 | 1081 253 0.593 |
| Evinova et al. (89)         | 2012 | Slovak         | Caucasian | 134 143 70 54 10 58 | 73 12        | 0.1       |
| Qiao et al. (90)            | 2012 | China          | Asian     | 94 98 24 43 27 36 | 45 17        | 0.651     |
| Shen et al. (91)            | 2014 | China          | Asian     | 368 219 88 259 21 113 | 91 15        | 0.563     |
| Sayadi et al. (92)          | 2016 | Tunisia        | African   | 208 187 105 80 23 80 | 93 14        | 0.066     |
| Mei et al. (93)             | 2016 | China          | Asian     | 37 65 9 26 2 32 | 7 6          | 0.59      |
| Huang et al. (94)           | 2017 | China          | Asian     | 80 80 20 36 24 30 | 38 12        | 0.995     |
| Li et al. (95)              | 2017 | China          | Asian     | 218 582 97 93 28 461 | 89 32 <0.001* |
| Mei et al. (96)             | 2018 | China          | Asian     | 106 175 25 75 6 90 | 73 12        | 0.59      |
| Saraswathy et al. (97)      | 2019 | India          | African   | 91 206 78 12 1 183 | 22 1         | 0.68      |
| **Bipolar disorder**        |      |                |           |              |              |           |
| Arinami et al. (27)         | 1997 | Japanese       | Asian     | 40 419 15 20 5 154 | 214 51       | 0.074     |
| Kunugi et al. (28)          | 1998 | Japanese       | Asian     | 143 258 41 74 28 95 | 129 34       | 0.342     |
| Tan et al. (32)             | 2004 | Singapore      | Asian     | 167 120 99 60 8 80 | 33 7         | 0.165     |
| Reif et al. (71)            | 2005 | Germany        | Caucasian | 92 176 48 34 10 75 | 80 21        | 0.962     |
| Kempisty et al. (36)        | 2006 | Poland         | Caucasian | 200 300 108 73 19 210 | 79 11        | 0.303     |
| Zhao et al. (98)            | 2008 | China          | Asian     | 61 73 12 28 21 18 | 40 15        | 0.404     |
| Ozbek et al. (99)           | 2008 | Turkey         | Caucasian | 197 238 104 76 17 116 | 97 25        | 0.603     |
| Jonsson et al. (40)         | 2008 | Norway         | Caucasian | 117 177 58 49 10 80 | 75 22        | 0.501     |
| Chen et al. (100)           | 2009 | China          | Asian     | 501 461 178 231 | 92 153 235 | 73 0.272 |
| Ezzafer et al. (101)        | 2011 | Tunisia        | African   | 92 170 41 40 11 94 | 62 14        | 0.411     |
| Arzaghi et al. (49)         | 2011 | Iran           | Asian     | 90 94 52 34 4 54 | 38 2         | 0.11      |
| El-Hadidy et al. (57)       | 2013 | Egypt          | African   | 134 149 46 70 18 114 | 30 5         | 0.239     |
| Permoda-Osip et al. (102)   | 2014 | Poland         | Caucasian | 112 164 51 50 11 66 | 82 16        | 0.657     |
| Wang et al. (103)           | 2015 | China          | Asian     | 531 447 287 206 38 215 | 199 33       | 0.16      |
| Rahimi et al. (104)         | 2016 | Iran           | Caucasian | 150 148 69 67 14 81 | 62 5         | 0.093     |

*P < 0.05.
### TABLE 2  Overview of MTHFR A1298C genotype distribution of psychosis patients and controls, with information about country, ethnicity, and disease.

| First author      | Year | Country | Ethnicity | Case AA | Case AC | Case CC | Control AA | Control AC | Control CC | PHWE   |
|-------------------|------|---------|-----------|---------|---------|---------|------------|------------|------------|--------|
| **Schizophrenia** |      |         |           |         |         |         |            |            |            |        |
| Sazci et al. (31) | 2003 | Turkey  | Caucasian | 130     | 226     | 57      | 59         | 14         | 114        | 93      | 19    | 0.996  |
| Yu et al. (33)   | 2004 | China   | Asian     | 230     | 251     | 130     | 78         | 22         | 154        | 81      | 16    | 0.235  |
|                  |      | Scotland | Caucasian | 426     | 628     | 177     | 209        | 40         | 292        | 272     | 64    | 0.955  |
| Sazci et al. (34) | 2005 | Turkey  | Caucasian | 297     | 341     | 130     | 129        | 38         | 159        | 155     | 27    | 0.201  |
| Vilella et al. (35) | 2005 | Spain   | Caucasian | 158     | 234     | 76      | 68         | 14         | 124        | 97      | 13    | 0.286  |
| Lee et al. (38)  | 2006 | South Korea | Asian | 235     | 236     | 157     | 7          | 71         | 145        | 14      | 77    | <0.001* |
| Kempisty et al. (105) | 2007 | Poland  | Caucasian | 200     | 300     | 109     | 74         | 17         | 185        | 105     | 10    | 0.29   |
| Jonsson et al. (40) | 2008 | Denmark | Caucasian | 418     | 1004    | 184     | 186        | 48         | 462        | 419     | 123   | 0.052  |
|                  |      | Norway  | Caucasian | 163     | 177     | 89      | 60         | 14         | 82         | 79      | 16    | 0.625  |
|                  |      | Sweden  | Caucasian | 258     | 293     | 110     | 113        | 35         | 122        | 129     | 42    | 0.406  |
| Betcheva et al. (44) | 2009 | Bulgaria | Caucasian | 181     | 183     | 91      | 72         | 18         | 80         | 79      | 24    | 0.406  |
| Kang et al. (46)  | 2010 | Korea   | Asian     | 360     | 348     | 248     | 105        | 7          | 239        | 100     | 9    | 0.703  |
| Zhang et al. (106) | 2010 | China   | Asian     | 379     | 380     | 230     | 127        | 22         | 260        | 108     | 12    | 0.848  |
| Kim et al. (50)   | 2011 | Korea   | Asian     | 201     | 350     | 129     | 67         | 5          | 240        | 105     | 5    | 0.083  |
| Zhang et al. (53) | 2012 | China   | Asian     | 235     | 102     | 126     | 91         | 18         | 62         | 33      | 7     | 0.376  |
| Foroughmand et al. (60) | 2015 | Iran    | Asian     | 200     | 200     | 65      | 108        | 27         | 60         | 89      | 51    | 0.126  |
| Misiak et al. (61) | 2016 | Poland  | Caucasian | 135     | 146     | 55      | 64         | 13         | 55         | 72      | 19    | 0.64   |
| Takano et al. (62) | 2016 | Japan   | Asian     | 45      | 30      | 34      | 8          | 3          | 21         | 9       | 0    | 0.2    |
| Oniki et al. (64) | 2017 | Japan   | Asian     | 256     | 194     | 173     | 75         | 8          | 124        | 65      | 5    | 0.597  |
| Ota et al. (67)   | 2019 | Japan   | Asian     | 537     | 1262    | 358     | 163        | 16         | 820        | 395     | 47    | 0.947  |
| Wan et al. (68)   | 2019 | China   | Asian     | 97      | 92      | 66      | 29         | 2          | 69         | 22      | 1     | 0.603  |
| Wan et al. (69)   | 2019 | China   | Asian     | 242     | 234     | 174     | 63         | 5          | 171        | 58      | 5    | 0.975  |
| **Major depression** |      |         |           |         |         |         |            |            |            |        |
| Reif et al. (71)  | 2005 | Germany | Caucasian | 46      | 184     | 16      | 21         | 9          | 75         | 96      | 13    | 0.016* |
| Zeman et al. (82) | 2010 | Czechia | Caucasian | 42      | 41      | 22      | 17         | 3          | 20         | 18      | 3    | 0.495  |
| Feng et al. (83)  | 2010 | China   | Asian     | 152     | 152     | 122     | 28         | 2          | 115        | 35      | 2    | 0.716  |
| Evinova et al. (89) | 2012 | Slovak  | Caucasian | 134     | 143     | 49      | 65         | 20         | 70         | 61      | 12    | 0.801  |
| Li et al. (93)    | 2017 | China   | Asian     | 218     | 582     | 86      | 75         | 57         | 396        | 144     | 42    | <0.001* |
| **Bipolar disorder** |      |         |           |         |         |         |            |            |            |        |
| Reif et al. (71)  | 2005 | Germany | Caucasian | 92      | 184     | 30      | 47         | 15         | 75         | 96      | 13    | 0.016* |
| Kempisty et al. (105) | 2007 | Poland  | Caucasian | 200     | 300     | 99      | 78         | 23         | 185        | 105     | 10    | 0.29   |
| Jonsson et al. (40) | 2008 | Norway  | Caucasian | 115     | 177     | 47      | 56         | 12         | 82         | 79      | 16    | 0.624  |
| Ozbek et al. (99) | 2008 | Turkey  | Caucasian | 197     | 238     | 91      | 84         | 22         | 113        | 101     | 24    | 0.848  |
| Permoda-Osip et al. (102) | 2014 | Poland  | Caucasian | 111     | 156     | 51      | 50         | 10         | 60         | 74      | 22    | 0.915  |

*P < 0.05.

by excluding papers from the meta-analysis that were not in HWE. The funnel plots were displayed and evaluated using Egger's linear regression test to control publication bias (26). Stata 14.0 was used to conduct all statistical analyses (StataCorp, College Station, TX, United States). A P-value of less than 0.05 was regarded as statistically significant. The article mainly showed the forest plots of T vs. C of MTHFR C677T and C vs. A of MTHFR A1298C; the other results were shown in the tables.

**Results**

**Characteristics of eligible studies**

Out of screened articles, 843 unduplicated association studies were found. Figure 1 depicts a flow chart of the research process, the eliminated studies, and the reasons for their exclusion. Following an initial literature search and further screening, 81 (27–106) publications were retrieved.
Our meta-analysis comprised 49,775 subjects (20,981 patients and 28,794 controls) with MTHFR C677T genotyping and 16,058 subjects (6,690 patients and 9,368 controls) with MTHFR A1298C genotyping. Detailed information (first author, year of publication, country, ethnicity, case/control, genotype, and \(P_{HWE}\)) of included articles are summarized in Tables 1, 2.

### Methylenetetrahydrofolate reductase C677T/A1298C and psychiatric disorders

#### Association between the methylenetetrahydrofolate reductase C677T/A1298C polymorphisms and schizophrenia

Findings of the association and the heterogeneity test is shown in Table 3. MTHFR C677T polymorphism was shown to be highly associated with an increased risk of developing SZ in all statistical models (for T vs. C, OR = 1.16, 95% CI = 1.10–1.23, \(P < 0.001\); for TT + CT vs. CC: OR = 1.18, 95% CI = 1.10–1.27, \(P < 0.001\); for TT vs. CT + CC: OR = 1.25, 95% CI = 1.13–1.37, \(P < 0.001\); for TT vs. CC: OR = 1.35, 95% CI = 1.19–1.52, \(P < 0.001\)) (Figure 2 and Table 3).

An ethnic subgroup analysis revealed a substantial association between MTHFR C677T polymorphism and SZ among Asian populations (for T vs. C: OR = 1.19, 95% CI = 1.11–1.29, \(P < 0.001\); for TT + CT vs. CC: OR = 1.22, 95% CI = 1.10–1.35, \(P < 0.001\); for TT vs. CT + CC: OR = 1.31, 95% CI = 1.16–1.48, \(P < 0.001\); for TT vs. CC: OR = 1.46, 95% CI = 1.24–1.72, \(P < 0.001\)); in Caucasian populations, a significant association was found with the allele model (for T vs. C: OR = 1.09, 95% CI = 1.01–1.17, \(P = 0.036\)) and the dominant model (for TT + CT vs. CC: OR = 1.12, 95% CI = 1.06–1.18, \(P = 0.002\)); in African populations, there was a significant association with the allele model (for T vs. C: OR = 2.58, 95% CI = 1.45–4.57, \(P < 0.001\)).

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**TABLE 3** Odds ratios and heterogeneity results for the 4 genetic models of the MTHFR C677T and A1298C for SZ.

| MTHFR     | Comparison model | OR (95% CI) | \(P_{OR}\) | Heterogeneity |
|-----------|------------------|-------------|-------------|---------------|
|           | \(Q\) within     | \(P\)-value | \(I^2\) (%) |
| MTHFRC677T| All studies      |             |             |               |
| T vs. C   | 1.16(1.10–1.23)  | <0.001      | 116.30      | <0.001        | 60.4         |
| TT + CT vs. CC | 1.18(1.10–1.27) | <0.001      | 93.38       | <0.001        | 50.7         |
| TT vs. CT + CC | 1.25(1.13–1.37) | <0.001      | 80.44       | 0.001         | 42.8         |
| TT vs. CC  | 1.35(1.19–1.52)  | <0.001      | 103.78      | <0.001        | 55.7         |
| Asian     | T vs. C          | 1.19(1.11–1.29) | <0.001      | 56.46        | 0.001        | 57.5         |
| TT + CT vs. CC | 1.22(1.10–1.35) | <0.001      | 48.36       | 0.002         | 50.4         |
| TT vs. CT + CC | 1.31(1.16–1.48) | <0.001      | 41.63       | 0.014         | 42.3         |
| TT vs. CC  | 1.46(1.24–1.72)  | <0.001      | 57.48       | <0.001        | 58.2         |
| Caucasian | T vs. C          | 1.09(1.01–1.17) | 0.036      | 35.29        | 0.013        | 46.2         |
| TT + CT vs. CC | 1.11(1.01–1.21) | 0.034      | 28.48       | 0.075         | 33.3         |
| TT vs. CT + CC | 1.12(0.97–1.29) | 0.132      | 27.66       | 0.088         | 31.6         |
| TT vs. CC  | 1.16(0.98–1.37)  | 0.082      | 32.08       | 0.031         | 40.8         |
| African   | T vs. C          | 2.58(1.45–4.57) | 0.001      | 1.36         | 0.243        | 26.6         |
| TT + CT vs. CC | 2.37(1.00–5.64) | 0.050      | 1.84        | 0.175         | 45.6         |
| TT vs. CT + CC | 4.59(1.77–11.92) | 0.002     | 0.10        | 0.756         | 0            |
| TT vs. CC  | 5.81(1.20–15.32) | <0.001      | 0.31        | <0.001        | 0            |
| MTHFRA1298C| All studies      |             |             |               |
| C vs. A   | 1.04(0.96–1.13)  | 0.305      | 33.40       | 0.042         | 37.1         |
| CC + AC vs. AA | 1.06(0.98–1.15) | 0.165      | 23.60       | 0.313         | 11.0         |
| CC vs. AC + AA | 1.05(0.88–1.25) | 0.622      | 31.24       | 0.07          | 32.8         |
| CC vs. AA  | 1.08(0.89–1.29)  | 0.438      | 31.32       | 0.069         | 32.9         |
| Caucasian | C vs. A          | 1.05(0.95–1.17) | 0.327      | 14.04        | 0.121        | 35.9         |
| CC + AC vs. AA | 1.07(0.95–1.20) | 0.289      | 11.04       | 0.273         | 18.5         |
| CC vs. AC + AA | 1.09(0.87–1.37) | 0.434      | 13.54       | 0.14          | 33.5         |
| CC vs. AA  | 1.12(0.88–1.44)  | 0.357      | 14.85       | 0.095         | 39.4         |
| Asian     | C vs. A          | 1.03(0.92–1.16) | 0.602      | 18.98        | 0.061        | 42.0         |
| CC + AC vs. AA | 1.05(0.94–1.18) | 0.418      | 12.42       | 0.333         | 11.5         |
| CC vs. AC + AA | 1.00(0.74–1.34) | 0.981      | 16.80       | 0.114         | 34.5         |
| CC vs. AA  | 1.02(0.77–1.37)  | 0.870      | 15.70       | 0.153         | 29.9         |
95% CI = 1.45–4.57, \( P = 0.001 \)), the recessive model (TT vs. CT + CC: OR = 4.59, 95% CI = 1.77–11.92, \( P = 0.002 \)) and the homozygote model (for TT vs. CC: OR = 5.81, 95% CI = 1.20–15.32, \( P < 0.001 \)). All these findings are summarized in Table 3. Subgroup analysis reveals that the association between MTHFR C677T polymorphism and SZ exists in Asian (all genetic models) and African populations (allele models, recessive models, and homozygous models) but not in Caucasian (only allele models and dominant models).

The MTHFR A1298C polymorphism was not statistically correlated with SZ in all models (Figure 3 and Table 3).

Moreover, subgroup analysis revealed no correlation between the MTHFR A1298C polymorphism and SZ in Asian or Caucasian populations (Figure 3 and Table 3). African populations were not included in the study because of the small number of studies.

There were two articles not in Hardy–Weinberg equilibrium (37, 38) (Tables 1, 2). Sensitivity analysis revealed that the overall association between MTHFR C677T polymorphism and SZ remained unchanged after omitting these two samples from the meta-analysis (for T vs. C: OR = 1.17, 95% CI = 1.10–1.24, \( P < 0.001 \), Supplementary Figure 6; for TT + CT vs. CT + CC: OR = 1.21, 95% CI = 1.14–1.28, \( P < 0.001 \).)
FIGURE 3
Forest plots for the associations between MTHFR A1298C polymorphisms and SZ for the allele model with random effect model.

Subgroup analysis by ethnicity revealed a substantial correlation between the MTHFR C677T polymorphism and MD in Asian populations (for T vs. C: OR = 1.46, 95% CI = 1.21–1.77, \( P < 0.001 \); for TT + CT vs. CC: OR = 1.52, 95% CI = 1.11–2.08, \( P = 0.009 \); for TT vs. CT + CC: OR = 1.75, 95% CI = 1.34–2.28, \( P < 0.001 \); for TT vs. CC: OR = 1.89, 95% CI = 1.40–2.57, \( P < 0.001 \)), but not in Caucasian and African populations (Figure 4 and Table 4).

The MTHFR A1298C polymorphism was found to be highly associated with MD in the recessive model (for CC vs. AC + AA: OR = 2.63, 95% CI: 1.49–4.65, \( P = 0.001 \)) and the homozygote model (for CC vs. AA: OR = 2.14, 95% CI = 1.23–3.71, \( P = 0.007 \); for CC vs. AA: OR = 2.36, 95% CI = 1.31–4.26, \( P = 0.004 \)) (Figure 5 and Table 4). Nonetheless, there was no statistical correlation

CC: OR = 1.18, 95% CI = 1.10–1.28, \( P < 0.001 \); for TT vs. CT + CC: OR = 1.25, 95% CI = 1.14–1.38, \( P < 0.001 \); for TT vs. CC: OR = 1.35, 95% CI = 1.20–1.53, \( P < 0.001 \). Sensitivity analysis for the MTHFR A1298C polymorphism revealed that excluding Lee et al. (38) had no impact on the conclusion of the meta-analysis (Supplementary Figure 7).

Association between the methylenetetrahydrofolate reductase C677T/A1298C polymorphisms and major depression

Table 4 shows the main results as well as the heterogeneity test. MTHFR C677T polymorphism was shown to be highly associated with an increased risk of developing MD in all statistical models (for T vs. C: OR = 1.33, 95% CI = 1.15–1.55, \( P < 0.001 \); for TT + CT vs. CC: OR = 1.35, 95% CI = 1.08–1.70, \( P = 0.009 \); for TT vs. CT + CC: OR = 1.58, 95% CI = 1.28–1.95, \( P < 0.001 \); for TT vs. CC: OR = 1.66, 95% CI = 1.31–2.11, \( P < 0.001 \)) (Figure 4 and Table 4).
between A1298C polymorphism and MD in Asian populations (Figure 5 and Table 4). Subgroup analysis shows that the correlation between MTHFR C677T polymorphism and MD exists in the Asian population (all genetic models) but not in Caucasian and African populations.

Four articles were not found in Hardy–Weinberg equilibrium (71, 84, 85, 95) (Tables 1, 2). Sensitivity analysis revealed that the overall correlation between MTHFR C677T polymorphism and MD remained unchanged after eliminating these data from the meta-analysis (Supplementary Figure 8). Sensitivity analyses for MTHFR A1298C polymorphism revealed that excluding Reif A. et al. (71) and Li et al. (95) resulted in a decreasing statistical correlation with MD; nonetheless, all statistical models revealed that MTHFR A1298C polymorphism was not significantly correlated with MD (Supplementary Figure 9).

### Association between the methylenetetrahydrofolatereductase C677T/A1298C polymorphisms and bipolar disorder

Table 5 displays the main results and the heterogeneity test. There was a marginal correlation between the MTHFR C677T polymorphism and BPD in the recessive model (for TT vs. CT + CC: OR = 1.31, 95% CI: 1.03–1.67, \(P = 0.028\)) and the homozygote model (for TT vs. CC: OR = 1.40, 95% CI = 1.00–1.94, \(P = 0.049\)) (Table 5). Moreover, subgroup analysis indicated no statistical correlation between the MTHFR C677T polymorphism and BPD in Asian, African, or Caucasian populations (Figure 6 and Table 5). Additionally, all models revealed that the MTHFR A1298C polymorphism was not statistically correlated with BPD (Figure 7 and Table 5).

Only one study was not in Hardy–Weinberg equilibrium (71) (Table 2), and there was no statistical association between

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**Table 4** Odds ratios and heterogeneity results for the 4 genetic models of the MTHFR C677T and A1298C for MD.

| MTHFR       | Comparison model      | OR (95% CI)    | \(P_{OR}\)  | Heterogeneity | Q within | \(P\)-value | \(I^2\) (%) |
|-------------|----------------------|----------------|------------|--------------|-----------|-------------|------------|
| MTHFR C677T | All studies         | T vs. C       | 1.33(1.15–1.55) | <0.001       | 159.05    | <0.001      | 81.1       |
|             |                      | TT + CT vs. CC | 1.35(1.08–1.70) | 0.009        | 183.95    | <0.001      | 83.7       |
|             |                      | TT vs. CT + CC | 1.58(1.24–1.95) | <0.001       | 75.2      | <0.001      | 60.1       |
|             |                      | TT vs. CC     | 1.66(1.31–2.11) | <0.001       | 80.47     | <0.001      | 62.7       |
|             | Asian                | T vs. C       | 1.46(1.21–1.77) | <0.001       | 107.45    | <0.001      | 81.4       |
|             |                      | TT + CT vs. CC | 1.52(1.11–2.08) | 0.009        | 135.03    | <0.001      | 85.2       |
|             |                      | TT vs. CT + CC | 1.75(1.34–2.28) | <0.001       | 54.54     | <0.001      | 63.3       |
|             |                      | TT vs. CC     | 1.89(1.40–2.57) | <0.001       | 56.63     | <0.001      | 64.7       |
|             | Caucasian            | T vs. C       | 1.09(0.88–1.34) | 0.445        | 17.97     | 0.012       | 61.0       |
|             |                      | TT + CT vs. CC | 1.08(0.81–1.44) | 0.616        | 18.02     | 0.012       | 61.2       |
|             |                      | TT vs. CT + CC | 1.07(0.86–1.34) | 0.527        | 7.11      | 0.417       | 1.6        |
|             |                      | TT vs. CC     | 1.20(0.83–1.73) | 0.337        | 11.59     | 0.115       | 39.6       |
|             | African              | T vs. C       | 0.98(0.72–1.32) | 0.879        | 1.07      | 0.301       | 6.5        |
|             |                      | TT + CT vs. CC | 0.91(0.52–1.59) | 0.735        | 1.95      | 0.162       | 48.8       |
|             |                      | TT vs. CT + CC | 1.57(0.80–3.09) | 0.189        | 0.07      | 0.788       | 0          |
|             |                      | TT vs. CC     | 1.30(0.65–2.63) | 0.460        | 0.18      | 0.669       | 0          |
| MTHFR A1298C| All studies         | C vs. A       | 1.44(0.84–2.48) | 0.191        | 35.80     | <0.001      | 88.8       |
|             |                      | CC + AC vs. AA | 1.42(0.77–2.61) | 0.263        | 26.32     | <0.001      | 84.8       |
|             |                      | CC vs. AC + AA | 2.63(1.49–4.65) | 0.001        | 7.55      | 0.109       | 47         |
|             |                      | CC vs. AA     | 2.83(1.39–5.77) | 0.004        | 10.27     | 0.036       | 61         |
|             | Caucasian            | C vs. A       | 1.40(1.01–1.82) | 0.011        | 1.83      | 0.4        | 0          |
|             |                      | CC + AC vs. AA | 1.39(0.97–1.98) | 0.073        | 1.74      | 0.418       | 0          |
|             |                      | CC vs. AC + AA | 2.14(1.23–3.71) | 0.007        | 1.68      | 0.433       | 0          |
|             |                      | CC vs. AA     | 2.36(1.31–4.36) | 0.004        | 1.58      | 0.454       | 0          |
|             | Asian                | C vs. A       | 1.61(0.42–6.17) | 0.484        | 23.67     | <0.001      | 95.8       |
|             |                      | CC + AC vs. AA | 1.61(0.39–6.68) | 0.513        | 20.23     | <0.001      | 95.1       |
|             |                      | CC vs. AC + AA | 2.93(0.76–11.29) | 0.118       | 2.16      | 0.142       | 53.7       |
|             |                      | CC vs. AA     | 3.13(0.53–18.66) | 0.210        | 3.34      | 0.068       | 70         |
A1298C polymorphism and BPD after removing this study (Supplementary Figure 10).

Association between the methylenetetrahydrofolatereductase C677T/A1298C polymorphisms and psychiatric disorders

Significant publication biases were found when all diseases were considered (Supplementary Figure 5 and Supplementary Table 2). Therefore, analyses between MTHFR C677T and mental disorders were unsuitable here. However, the main results and the heterogeneity tests between MTHFR C677T and mental disorders were shown in Supplementary Table 1. Furthermore, the forest plots indicated that MTHFR C677T was strongly associated with psychiatric disorders, and sensitivity analysis did not affect the results (Supplementary Figures 1, 2).

Most studies were not in Hardy–Weinberg equilibrium when all diseases were considered. Moreover, analysis between MTHFR A1298C and psychiatric disorders was also unsuitable. Significant correlations were detected between the MTHFR A1298C polymorphism and psychiatric disorders (Supplementary Figure 3). However, sensitivity analysis revealed that excluding did change the conclusion (Supplementary Figure 4).

Publication bias

In order to evaluate publication bias, we used formal statistical methods (Egger’s regression test). Table 6 and Figure 8 presented the funnel plots for the meta-analysis. We observed that for SZ, no publication bias could be observed except in the dominant model (TT + CT vs. CC, $P_{\text{Egger}} = 0.01$). The Egger’s test results for MD were substantial in two genetic models of overall populations (allele model: C vs. A, $P_{\text{Egger}} = 0.03$; homozygote model: CC vs. AA, $P_{\text{Egger}} = 0.02$). And there was
FIGURE 5
Forest plots for the associations between MTHFR A1298C polymorphisms and MD for the allele model with random effect model.

TABLE 5
Odds ratios and heterogeneity results for the 4 genetic models of the MTHFR C677T and A1298C for BPD.

| MTHFR   | Comparison model | OR (95% CI) | P < OR | Heterogeneity |
|---------|------------------|-------------|--------|---------------|
|         |                  |             | Q within | P-value | I^2 (%) |
| MTHFR C677T | All studies     | T vs. C     | 1.20 (0.98–1.46) | 0.073 | 76.32 | -0.001 | 81.7 |
|          |                  | TT vs. CT + CC | 1.51 (0.93–1.57) | 0.028 | 22.71 | 0.065 | 38.4 |
|          |                  | TT vs. CT + CC | 1.40 (1.01–1.94) | 0.049 | 36.79 | 0.001 | 61.9 |
| Asian   | T vs. C          | 1.17 (0.91–1.49) | 0.216 | 6.03  | 0.42  | 0.4   |
|          | TT vs. CT + CC   | 1.23 (0.99–1.54) | 0.063 | 4.61  | 0.60  | 0     |
|          | TT vs. CT + CC   | 1.40 (1.01–1.94) | 0.049 | 36.79 | 0.001 | 61.9 |
|          | TT vs. CT + CC   | 1.50 (0.87–1.98) | 0.048 | 11.67 | 0.04  | 57.2 |
| African | T vs. C          | 1.19 (0.65–2.18) | 0.566 | 15.96 | 0.007 | 68.7 |
|          | TT vs. CT + CC   | 3.09 (0.79–12.18) | 0.106 | 14.15 | <0.001 | 92.9 |
|          | TT vs. CT + CC   | 2.50 (0.87–7.19) | 0.09  | 2.59  | 0.107 | 61.4 |
|          | TT vs. CT + CC   | 3.90 (0.81–18.69) | 0.089 | 5.29  | 0.021 | 81.1 |
| MTHFRA1298C | All studies(Caucasian) | C vs. A | 1.19 (0.91–1.56) | 0.208 | 13.67 | 0.008 | 70.7 |
|          | CC + AC vs. AA   | 1.19 (0.91–1.56) | 0.200 | 7.54  | 0.110 | 0.110 |
|          | CC vs. AC + AA   | 1.50 (0.81–2.77) | 0.200 | 13.66 | 0.008 | 70.7 |
|          | CC vs. AA        | 1.58 (0.79–3.16) | 0.200 | 15.85 | 0.003 | 74.8 |
**FIGURE 6**
Forest plots for the associations between MTHFR C677T polymorphisms and BPD for the allele model with random effect model.

**FIGURE 7**
Forest plots for the associations between MTHFR A1298C polymorphisms and BPD for the allele model with random effect model.

NOTE: Weights are from random effects analysis.
TABLE 6 Publication bias risk in this meta-analysis.

| Disease         | MTHFR                        | $P_{Egger}$ | 95% CL |
|-----------------|------------------------------|-------------|--------|
| Schizophrenia C677T | T vs. C                      | 0.05        | 0.02-2.10 |
|                 | TT + CT vs. CC               | 0.01        | 0.27-2.08 |
|                 | TT vs. CT + CC               | 0.24        | −0.34-1.32 |
|                 | TT vs. CC                    | 0.06        | −0.05-1.86 |
| A1298C          | C vs. A                      | 0.73        | −1.60-2.25 |
|                 | CC + AC vs. AA               | 0.66        | −2.03-1.31 |
|                 | CC vs. AC + AA               | 0.09        | −0.17-2.39 |
|                 | CC vs. AA                    | 0.14        | −0.35-2.32 |
| Major depression C677T | T vs. C                      | 0.18        | −0.64-3.33 |
|                 | TT + CT vs. CC               | 0.35        | −1.09-3.00 |
|                 | TT vs. CT + CC               | 0.40        | −0.80-1.97 |
|                 | TT vs. CC                    | 0.09        | −0.21-2.52 |
| A1298C          | C vs. A                      | 0.03        | −12.82-1.28 |
|                 | CC + AC vs. AA               | 0.08        | −13.00-1.10 |
|                 | CC vs. AC + AA               | 0.05        | −4.48-0.02 |
|                 | CC vs. AA                    | 0.02        | −4.78-0.81 |
| Bipolar disorder C677T | T vs. C                      | 0.19        | −1.45-6.66 |
|                 | TT + CT vs. CC               | 0.21        | −1.62-6.66 |
|                 | TT vs. CT + CC               | 0.31        | −0.95-2.81 |
|                 | TT vs. CC                    | 0.18        | −0.82-4.02 |
| A1298C          | C vs. A                      | 0.54        | −30.72-19.79 |
|                 | CC + AC vs. AA               | 0.54        | −17.02-10.90 |
|                 | CC vs. AC + AA               | 0.75        | −24.98-31.11 |
|                 | CC vs. AA                    | 0.82        | −26.75-31.41 |

no publication bias for BPD. Publication bias may correlate to the editor’s decision for publication. However, it is common that only the positive results are published, and negative findings are unavailable. So, we could not exclude this kind of possibility.

Discussion

A mental disorder is a neurological disease with complicated etiology, which may be closely related to genetic factors. A great number of research on the susceptibility to mental illnesses (including SZ, MD, and BPD) have been undertaken using MTHFR gene polymorphism. Some studies supported the susceptibility variation of MTHFR in mental diseases (27, 31, 70, 96, 105, 69), whereas other studies showed a negative correlation (28, 29, 33, 46, 102, 46). These variations might be due to the type of disease, ethnicity, or sample size. Our meta-analysis incorporates all previous research and provides more reliable evidence for the association between mental illness and MTHFR SNPs.

For Sz, our meta-analysis found a substantial association between MTHFR C677T polymorphism and higher incidence of SZ, which is consistent with research by Hu et al. (22) and Peerbooms et al. (23). In addition, we found that MTHFR A1298C polymorphism was not correlated with increased SZ risk, which is consistent with Peerbooms et al. (23). However, Hu et al. (22) discovered a marginal correlation between the MTHFR A1298C polymorphism and SZ. The inconsistency may be mainly owing to the limited sample size in the previous meta-analyses. For MTHFR C677T and A1298C, the sensitivity analysis has no substantial change to the results. As a result, the study’s findings are relatively consistent.

For MD, our meta-analysis’s results showed a significant correlation between MTHFR C677T polymorphism and increased risk of MD. The meta-analysis of Wu et al. (107) supports our view, whereas Gaysina et al. (108) and Peerbooms et al. (23) discovered no association between the C677T and MD. These discrepancies might be due to ethnicity, sample size, and other factors. Sensitivity analysis showed no change in the overall correlation between C677T polymorphism and MD. Also, we found a correlation between the A1298C polymorphism and MD (in recessive models and homozygous models). However, after excluding two studies not in Hardy–Weinberg equilibrium (38, 95), we discovered that A1298C polymorphism was not correlated with depression. We suspect that the reason for this is the insufficient number of studies included.

For BPD, meta-analysis reveals that MTHFR C677T polymorphism is weakly related to the occurrence of diseases (in recessive models and homozygous models). The meta-analysis of Hu et al. (22) found a marginal connection of C677T with an elevated risk of BPD (the recessive model), but some studies (21, 109, 110) found no associations. Different numbers of studies included may cause the inconsistency. Our meta-analysis included all current research, providing more reliable evidence for the association between MTHFR C677T polymorphism and BPD. As for A1298C, we only found studies in Caucasian people, and we did not find any association in these studies. The sensitivity analysis has no change to the results. Therefore, the results of this study are generally robust.

Many researchers have discovered that MTHFR is closely related to cognitive function, such as verbal fluency, visual–motor coordination, attention selectivity, and distribution (111–113). MTHFR polymorphism may also cause central nerve injury and microvascular injury, affect the synthesis of central neurotransmitters and the methylation of central neural system amines and phospholipids, and eventually lead to various mental diseases (114). All these impairments are not specific to one disease; therefore, we guess MTHFR may work on the common pathogenesis of these psychiatric disorders.

Some limitations of this meta-analysis should be considered when interpreting the findings. Firstly, we can only search for English and Chinese articles with some language limitations. Second, publication bias cannot be ignored in the current study.
since Egger test findings are substantial in several SZ and MD genetic models. It may correlate to the editor’s decision for publication and so on. However, it is common that only the positive results are published, and negative findings are unavailable. And we could not exclude this kind of possibility. Furthermore, the number of articles on A1298C polymorphism with MD are insufficient to provide conclusive evidence. More original research is required to validate our results. Despite some limitations, our current research also has some value. First of all, our meta-analysis includes a large sample size, which can reduce errors. Secondly, we fully considered and analyzed the impact of race on the disease.
Conclusion

Our meta-analysis findings demonstrate that MTHFR C677T polymorphism increases the risk of schizophrenia and severe depression in the general population, and a marginal correlation of MTHFR C677T with a higher risk of bipolar disorder has also been reported for the recessive model. More original research and a bigger sample size are required to validate our results. Nevertheless, the findings of our meta-analysis imply that MTHFR may play a significant role in the common pathogenesis of mental illness and that its variation may be involved in controlling the expression of genes associated with it. It would help in the early diagnosis and treatment of related mental disorders. Moreover, studies on risk factor analysis could be performed on psychiatric disorders to better prevent these mental health problems.

Data availability statement

The original contributions presented in this study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

Y-XZ: conceptualization, software, data curation, and writing – original draft preparation. DH: conceptualization, methodology, and funding acquisition. L-PY: data curation and validation. CG: visualization and investigation. C-CC: software and validation. Z-YG: writing – reviewing and editing. H-MS: project administration and supervision. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.976428/full#supplementary-material

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