Association between MTHFR C677T/A1298C and susceptibility to autism spectrum disorders: a meta-analysis

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Abstract

Background: Autism spectrum disorder (ASD) is becoming increasingly prevalent of late. Methylenetetrahydrofolate reductase (MTHFR) has a significant role in folate metabolism. Owing to the inconsistencies and inconclusiveness on the association between MTHFR single nucleotide polymorphism (SNP) and ASD susceptibilities, a meta-analysis was conducted to settle the inconsistencies.

Methods: For this meta-analysis, a total of 15 manuscripts published up to January 26, 2020, were selected from PubMed, Google Scholar, Medline, WangFang, and CNKI databases using search terms “MTHFR” OR “methylenetetrahydrofolate reductase” AND “ASD” OR “Autism Spectrum Disorders” OR “Autism” AND “polymorphism” OR “susceptibility” OR “C677T” OR “A1298C”.

Results: The findings of the meta-analysis indicated that MTHFR C677T polymorphism is remarkably associated with ASD in the five genetic models, viz., allelic, dominant, recessive, heterozygote, and homozygote. However, the MTHFR A1298C polymorphism was not found to be significantly related to ASD in the five genetic models. Subgroup analyses revealed significant associations of ASD with the MTHFR (C677T and A1298C) polymorphism. Sensitivity analysis showed that this meta-analysis was stable and reliable. No publication bias was identified in the associations between MTHFR C677T polymorphisms and ASD in the five genetic models, except for the one with regard to the associations between MTHFR A1298C polymorphisms and ASD in the five genetic models.

Conclusion: This meta-analysis showed that MTHFR C677T polymorphism is a susceptibility factor for ASD, and MTHFR A1298C polymorphism is not associated with ASD susceptibility.

Keywords: Methylenetetrahydrofolate reductase, Autism spectrum disorder, Single nucleotide polymorphisms, Genetic models, Meta-analysis

Background

Autism spectrum disorder (ASD) is one of the complex neurodevelopmental disorders, which has been increasingly recognized as a public health issue [1]. It affects 9‰ of the entire population of children, and the estimated ratio between male and female (M:F) children is 4:1 [2]. The prevalence rates of ASD in terms of percentages are approximately 1.52‰ in the Middle East [2–5], 14.7‰ in the USA [6, 7], 1.66‰ in China [8], and 6‰ in Australia [1, 9].

The distinguishing features of ASD include a set of behavioral phenotypes such as social communication deficits, restrictive and repetitive behaviors [10, 11], and worsened quality of life and family functioning for children with ASD and their parents [12]. Brain and nervous system dysfunctions are indicated in ASD [13], which
occur as a result of pathophysiological and environmental factors. Folate/homocysteine (Hcy) levels act as a risk factor in ASD [14, 15], indicating the involvement of methylenetetrahydrofolate reductase (MTHFR) in ASD. Therefore, MTHFR has been the focal point of investigation on ASD, as inheritance validates the pathophysiological mechanism of ASD [16–18].

**MTHFR** locus has been mapped to chromosome1 (1p36.3) [19]. Conversion of 5, 10-methylenetetrahydrofolate to 5-methyltetrahydrofolate is performed by MTHFR, which regulates the intracellular levels of folate and Hcy [15, 20]. Single nucleotide polymorphisms (C677T and A1298C) are associated with the decline in MTHFR activity [21, 22], which is, in turn, correlated with Folate/Hcy levels [23, 24]. Homocysteinemia and low plasma folate are found in individuals with C677T and A1298C alleles [22, 25]. A reduction of approximately 50% ~ 60% in the MTHFR activity is correlated with compound heterozygosity for both C677T and A1298C [19, 22, 26–28]. A decline in the enzymatic activity to 35% ~ 70% in homozygotes T is linked to C677T polymorphism in MTHFR [29]. Generally, when compared to C677T mutation, A1298C mutation feebly affects MTHFR activity and Hcy and folate levels [25, 30].

Correlations between single nucleotide polymorphisms (C677T and A1298C) and susceptibility to ASD are still debatable. A correlation between MTHFR C677T polymorphism and a higher susceptibility to ASD has been reported by Boris et al. [22] among Caucasian children [27]. Guo et al. [31] evidenced that MTHFR C677T polymorphism is a risk factor for ASD among Chinese Han children [31]. El-baz et al. [32] recognized a significant correlation between MTHFR C677T polymorphisms and ASD among Egyptian children [32]. Nonetheless, Dos Santos et al. [28] found no correlation between MTHFR C677T polymorphism and ASD [28]. Studies by Khalil et al. [33] and El-baz et al. [32, 34] describe MTHFR A1298C polymorphism to represent a risk factor in correlation with ASD among Egyptian children. On the contrary, Mohammad et al. [35] evidenced that MTHFR A1298C polymorphism variant allele has no link with any independent risk of ASD [35]. In this meta-analysis, updated articles were gathered [26, 32, 36] to authenticate correlations between MTHFR polymorphism (C677T/A1298C) and susceptibility to ASD.

All full-text literature were scrutinized to determine whether the papers to be included.

### Selection criteria
The following criteria had to be satisfied by the studies to be incorporated in this meta-analysis: (1) Original studies on the correlation between MTHFR polymorphism (C677T/A1298C) and ASD; (2) Cohort or case-control designs; (3) All genotype frequency information is available; (4) Diagnostic criteria of ASD described in the Diagnostic and Statistical Manual of Mental Disorders (4th or 5th edition) [37, 38], and/or Childhood Autism Rating Scale [39].Certain earlier papers referred to the Manual of Mental Disorders (3rd edition) [40]. The exclusion criteria comprised the following: (1) Researches on the correlation between MTHFR polymorphism (C677T/A1298C) and ASD that are not original; (2) Studies that lack data and complete information; (3) Replicated studies; (4) Review studies.

### Data extraction
Two investigators, namely, Yan Li and Shuang Qiu, extracted all the relevant data with the help of a standardized protocol and data collection form. From every qualified study, data such as the name of the first author, year of publication, country, study population (ethnicity), study design, the definition of ASD, sample size of cases and controls, genotyping method, genotype information, and allele frequencies were gathered and documented. Disparities in the study selection were resolved through discussion or consensus with the third investigator (Yawen Liu). The corresponding authors of articles with missing data were emailed for the required data.

### Statistical analysis
Odds ratio (OR) and 95% confidence intervals (CI) were deduced to analyse how strongly MTHFR (C677T/ A1298C) polymorphism and the risk of ASD were correlated in the five genetic models, viz., allelic, dominant, recessive, heterozygote, and homozygote. Heterogeneity among studies was assessed through Q-test and $I^2$. Random effects model (DerSimonian-Laird methods) [41] was selected to pool data and in case of substantial heterogeneity ($Ph < 0.05$ and $I^2 > 50$); else, fixed effect model (Mantel-Haenszel methods) [42] was chosen. Furthermore, subgroup analyses were stratified according to the state with mandatory fortification of folate, population, sample source, and Hardy-Weinberg equilibrium (HWE). The included studies were tested for HWE in the control group utilizing Chi-square tests. Besides, the stability of the results was tested by performing a sensitivity analysis with the sequential omission of each study.

### Methods
#### Search strategy and identification of studies
Scientific literature published before January 26, 2020, in PubMed, Embase, Web of Science, Medline, WanFang database, and CNKI database were searched using specific search terms (Supplement file 1). The equivalent Chinese terms were used in the Chinese databases. Moreover, we retrieved related articles from the selected literature references to replenish data that had not been identified in the initial search.
conducted. Stata version 12.0 (StataCorp LP, College Station, TX, USA) was used to evaluate all analyses, and \( p < 0.05 \) was considered to be statistically significant.

**Results**

**Overall results**

Upon literature search and critical screening, about 15 studies from 125 articles were included in this meta-analysis, as already discussed in the Methods section (Fig. 1). A total of 2609 cases and 7496 controls were enrolled from the 15 articles published on the correlation between \( \text{MTHFR C677T} \) polymorphism and ASD susceptibility. Of those, only nine articles that included 1961 cases and 1652 controls qualified for the evaluation of the link between \( \text{MTHFR A1298C} \) and ASD as per the selection criteria. The characteristics of each primary study are summarized and presented in Tables 1 and 2.

**Association between MTHFR C677T polymorphism and ASD**

Random effect model (\( P_h < 0.05 \) or \( I^2 > 50\% \)) was used, and \( \text{MTHFR C677T} \) polymorphism was found to be remarkably linked to ASD susceptibility in allelic (T vs C: \( OR = 1.63, 95\% CI = 1.30–2.05, p < 0.05 \)), heterozygote (CT vs CC: \( OR = 1.66, 95\% CI = 1.31–2.11, p < 0.05 \)), homozygote (TT vs CC: \( OR = 2.03, 95\% CI = 1.33–3.09, p < 0.05 \)), dominant (TT + CT vs CC: \( OR = 1.82, 95\% CI = 1.39–2.37, p < 0.05 \)), and recessive models (TT vs CT + CC: \( OR = 1.59, 95\% CI = 1.14–2.22, p < 0.05 \); Table 3, Fig. 2a).

To further clarify the link between \( \text{MTHFR} \) polymorphisms and the risk of ASD, subgroup analysis was carried out. Firstly, no significant deviation of the correlation among the states with mandatory fortification of folate was recorded. \( \text{MTHFR C677T} \) polymorphism was not found to be linked to ASD susceptibility: allelic (T vs C: \( OR = 1.32, 95\% CI = 1.00–1.75, p > 0.05 \)), homozygote (TT vs CC: \( OR = 1.66, 95\% CI = 0.94–2.94, p > 0.05 \)), and recessive models (TT vs CT + CC: \( OR = 1.37, 95\% CI = 0.93–2.00, p > 0.05 \)). Nonetheless, it was observed to be associated with ASD susceptibility among the states without mandatory fortification of folate: allelic (T vs C: \( OR = 2.08, 95\% CI = 1.40–3.08, p > 0.05 \)), heterozygote (CT vs CC: \( OR = 1.95, 95\% CI = 1.34–2.82, p > 0.05 \)), homozygote (TT vs CC: \( OR = 2.78, 95\% CI = 1.35–5.73, p < 0.05 \)), dominant (TT + CT vs CC: \( OR = 2.22, 95\% CI = 1.46–3.36, p < 0.05 \)), and recessive models (TT vs CT + CC: \( OR = 2.23, 95\% CI = 1.13–4.38, p < 0.05 \)). Secondly, \( \text{MTHFR C677T} \) polymorphism was recorded to be correlated with ASD susceptibility in Caucasian population: allelic (T vs C: \( OR = 1.51, 95\% CI = 1.17–1.95, p < 0.05 \)), heterozygote (CT vs CC: \( OR = 1.62, 95\% CI = 1.20–2.18, p < 0.05 \)), homozygote (TT vs CC: \( OR = 1.92, 95\% CI = 1.16–3.16, p < 0.05 \)), and dominant models (TT + CT vs CC: \( OR = 1.73, 95\% CI = 1.25–2.41, p < 0.05 \)). Nonetheless, \( \text{MTHFR C677T} \) polymorphism was not found to be linked to ASD susceptibility among Asians: homozygote model (TT vs. CC: \( OR = 2.45, 95\% CI = 0.95–6.31, p > 0.05 \)). Thirdly, a hospital-based and population-based sample was adopted for this study. \( \text{MTHFR C677T} \) polymorphism was found to be linked
with ASD susceptibility under five genetic models in hospital- and population-based samples, respectively (all $p < 0.05$). Fourthly, our results showed that MTHFR C677T polymorphism was consistent/inconsistent with HWE; however, it was significantly associated with ASD susceptibility under five genetic models (all $p < 0.05$) (Table 3).

### Association between MTHFR A1298C polymorphism and ASD

Random effect model ($P_h < 0.05$ or $I^2 \geq 50\%$) was utilized, and no significant correlation between MTHFR A1298C polymorphism and ASD susceptibility in the five genetic models was identified (allelic, dominant, recessive, heterozygote, and homozygote; all $p > 0.05$; Table 4, Fig. 2b). As per the subgroup analyses, MTHFR A1298C polymorphism was found to be associated with ASD susceptibility among the states without mandatory fortification of folate: allelic model (C vs. A: OR = 1.84, 95% CI = 1.08–3.14, $p < 0.05$) and dominant model (CC + AC vs. AA: OR = 2.45, 95% CI = 1.16–5.15, $p < 0.05$). No significant correlation between MTHFR A1298C polymorphism and ASD susceptibility under the other genetic models in any subgroup was found (all $p > 0.05$) (Table 4).

### Sensitivity analysis and publication bias

The stability of the findings was evaluated through sensitivity analysis conducted by sequentially omitting each study, demonstrating that this meta-analysis is relatively

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**Table 1** Characteristics of included studies for MTHFR C677T polymorphism

| Author, year | Quality Score | Country | Ethnicity | Case N | CC | CT | TT | Control N | CC | CT | TT | Sample source | Folate | HWE |
|--------------|---------------|---------|-----------|--------|-----|-----|-----|-----------|-----|-----|-----|---------------|--------|------|
| Boris et al. 2004 [22] | 6 | USA | Caucasian | 168 | 35 | 94 | 39 | 5389 | 2570 | 2213 | 606 | Hospital-based | YES | 0 |
| James et al. 2006 [43] | 7 | USA | Caucasian | 356 | 134 | 176 | 46 | 205 | 93 | 90 | 22 | Hospital-based | YES | 0.974 |
| Mohammad et al. 2009 [35] | 7 | USA | Asian | 138 | 98 | 35 | 5 | 138 | 120 | 18 | 0 | Population-based | NO | 0.412 |
| Pasca et al. 2009 [27] | 8 | Romania | Caucasian | 39 | 21 | 14 | 4 | 80 | 46 | 28 | 6 | Population-based | NO | 0.551 |
| dos Santos et al. 2010 [28] | 7 | Brazil | Caucasian | 151 | 60 | 68 | 23 | 100 | 45 | 41 | 14 | Hospital-based | YES | 0.353 |
| Li et al. 2011 [44] | 7 | Canada | Caucasian | 205 | 68 | 98 | 39 | 384 | 177 | 166 | 41 | Population-based | YES | 0.823 |
| Liu et al. 2011 [44] | 7 | Canada | Caucasian | 400 | 167 | 179 | 54 | 384 | 177 | 166 | 41 | Population-based | YES | 0.823 |
| Schmidt et al. 2011 [45] | 8 | USA | Caucasian | 294 | 128 | 133 | 33 | 180 | 74 | 77 | 29 | Population-based | YES | 0.241 |
| Guo et al. 2012 [31] | 7 | China | Asian | 186 | 79 | 77 | 30 | 186 | 87 | 83 | 16 | Population-based | YES | 0.542 |
| Divyakolu et al. 2013 [46] | 6 | India | Asian | 50 | 27 | 22 | 1 | 50 | 42 | 8 | 0 | Hospital-based | NO | 0.539 |
| Park et al. 2014 [47] | 7 | Korea | Asian | 249 | 76 | 136 | 37 | 423 | 139 | 204 | 80 | Hospital-based | YES | 0.737 |
| Sener et al. 2014 [48] | 9 | Turkey | Caucasian | 98 | 44 | 51 | 3 | 70 | 37 | 33 | 0 | Population-based | NO | 0.009 |
| Shawkly et al. 2014 [46] | 6 | Egypt | Caucasian | 20 | 7 | 10 | 3 | 22 | 16 | 6 | 0 | Hospital-based | NO | 0.459 |
| Meguid et al. 2015 [49] | 8 | Egypt | Caucasian | 24 | 11 | 11 | 2 | 30 | 20 | 8 | 2 | Population-based | yes | 0.361 |
| El-baz et al. 2017 [32] | 6 | Egypt | Caucasian | 31 | 12 | 15 | 4 | 39 | 35 | 4 | 0 | Hospital-based | YES | 0.735 |
| Zhao et al. 2013 [36] | 9 | China | Asian | 200 | 91 | 59 | 50 | 200 | 144 | 39 | 17 | Hospital-based | NO | 0 |

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**Table 2** Characteristics of included studies for MTHFR A1298C polymorphism

| Author, year | Quality Score | Country | Ethnicity | Case N | AA | AC | CC | Control N | AA | AC | CC | Sample source | Folate | HWE |
|--------------|---------------|---------|-----------|--------|-----|-----|-----|-----------|-----|-----|-----|---------------|--------|------|
| Boris et al. 2004 [22] | 6 | USA | Caucasian | 168 | 93 | 65 | 10 | 159 | 70 | 75 | 14 | Hospital-based | YES | 0 |
| James et al. 2006 [43] | 7 | USA | Caucasian | 356 | 175 | 147 | 34 | 204 | 103 | 77 | 24 | Hospital-based | YES | 0.974 |
| Mohammad et al. 2009 [35] | 7 | USA | Asian | 138 | 35 | 59 | 44 | 138 | 48 | 32 | 58 | Population-based | NO | 0.412 |
| Liu et al. 2011 [44] | 8 | Canada | Caucasian | 205 | 109 | 81 | 15 | 382 | 170 | 175 | 37 | Population-based | YES | 0.823 |
| Liu et al. 2011 [44] | 7 | Canada | Caucasian | 307 | 134 | 133 | 40 | 382 | 170 | 175 | 37 | Population-based | YES | 0.823 |
| Schmidt et al. 2011 [45] | 8 | USA | Caucasian | 296 | 160 | 117 | 19 | 177 | 89 | 76 | 12 | Population-based | YES | 0.241 |
| Park et al. 2014 [47] | 6 | Korea | Asian | 236 | 147 | 75 | 14 | 323 | 198 | 114 | 11 | Hospital-based | NO | 0.737 |
| Meguid et al. 2015 [49] | 8 | Egypt | Caucasian | 24 | 0 | 23 | 1 | 30 | 12 | 16 | 2 | Population-based | NO | 0.361 |
| El-baz et al. 2017 [32] | 6 | Egypt | Caucasian | 31 | 7 | 13 | 11 | 39 | 31 | 7 | 1 | Hospital-based | YES | 0.451 |
| Zhao et al. 2013 [36] | 9 | China | Asian | 200 | 144 | 19 | 37 | 200 | 166 | 21 | 13 | Hospital-based | NO | 0 |
| Genetic Models | Fixed/ Random effect OR(95%CI) | Heterogeneity P | I²(%) | Publication Bias P of Egger's/Begg test |
|----------------|---------------------------------|-----------------|-------|--------------------------------------|
| Allele Contrast (T vs C) | 1.63 (1.30–2.05)\* | 0.000 | 84.3 | 0.029/0.017 |
| Mandatory fortification with folate | | | | |
| Yes | 1.32 (1.00–1.75)\* | 0.000 | 86.2 | 0.441/0.707 |
| No | 2.08 (1.40–3.08)\* | 0.000 | 84.4 | 0.044/0.032 |
| Population | | | | |
| Asian | 1.95 (1.14–3.33)\* | 0.000 | 90.3 | 0.178/0.221 |
| Caucasian | 1.51 (1.17–1.95)\* | 0.000 | 81.5 | 0.130/0.087 |
| Sample source | | | | |
| Hospital-based | 2.10 (1.34–3.14)\* | 0.000 | 89.6 | 0.062/0.174 |
| Population-based | 1.33 (1.11–1.65)\* | 0.006 | 64.3 | 0.267/0.386 |
| HWE | | | | |
| Yes | 1.46 (1.18–1.81)\* | 0.000 | 76.0 | 0.005/0.006 |
| No | 2.17 (1.52–3.10)\* | 0.030 | 71.4 | 0.779/1.000 |
| Heterozygote (CT vs CC) | 1.66 (1.31–2.11)\* | 0.000 | 69.2 | 0.017/0.008 |
| Mandatory fortification with folate | | | | |
| Yes | 1.45 (1.05–2.00)\* | 0.001 | 76.1 | 0.784/0.707 |
| No | 1.95 (1.34–2.82)\* | 0.002 | 66.4 | 0.031/0.020 |
| Population | | | | |
| Asian | 1.80 (1.15–2.80)\* | 0.005 | 72.7 | 0.044/0.221 |
| Caucasian | 1.62 (1.20–2.18)\* | 0.000 | 70.4 | 0.098/0.029 |
| Sample source | | | | |
| Hospital-based | 2.23 (1.48–3.35)\* | 0.000 | 76.3 | 0.048/0.108 |
| Population-based | 1.26 (1.07–1.48)\* | 0.249 | 22.6 | 0.191/0.266 |
| HWE | | | | |
| Yes | 1.49 (1.18–1.87)\* | 0.005 | 57.9 | 0.007/0.009 |
| No | 2.24 (1.40–3.58)\* | 0.064 | 63.6 | 0.001/0.296 |
| Homozygote (TT vs CC) | 2.03 (1.33–3.09)\* | 0.000 | 74.6 | 0.048/0.053 |
| Mandatory fortification with folate | | | | |
| Yes | 1.66 (0.94–2.94)\* | 0.000 | 84.7 | 0.355/0.700 |
| No | 2.78 (1.35–5.73)\* | 0.001 | 66.5 | 0.044/0.074 |
| Population | | | | |
| Asian | 2.45 (0.95–6.31)\* | 0.000 | 81.2 | 0.286/0.806 |
| Caucasian | 1.92 (1.16–3.16)\* | 0.000 | 73.7 | 0.147/0.119 |
| Sample source | | | | |
| Hospital-based | 2.54 (1.26–5.16)\* | 0.000 | 82.5 | 0.142/0.536 |
| Population-based | 1.61 (1.01–2.58)\* | 0.031 | 54.7 | 0.122/0.266 |
| HWE | | | | |
| Yes | 1.50 (1.05–2.13)\* | 0.012 | 53.4 | 0.006/0.012 |
| No | 4.72 (3.26–6.84)\* | 0.988 | 0.0 | 0.291/1.000 |
| Dominant (TT + CT vs CC) | 1.82 (1.39–2.37)\* | 0.000 | 78.6 | 0.021/0.010 |
| Mandatory fortification with folate | | | | |
| Yes | 1.49 (1.04–2.15)\* | 0.000 | 83.3 | 0.775/0.707 |
| No | 2.22 (1.46–3.36)\* | 0.000 | 76.3 | 0.051/0.049 |
### Table 3: Meta-analysis between MTHFR C677T polymorphism and ASD risk under genetic models (Continued)

| Genetic Models | Fixed/ Random effect OR (95% CI) | Heterogeneity | Publication Bias P of Egger’s/Begg test |
|----------------|----------------------------------|---------------|----------------------------------------|
| **Population** |                                  |               |                                        |
| Asian          | 2.03 (1.21–3.42)\(^b\)           | 0.000         | 82.7                                  |
| Caucasian      | 1.73 (1.25–2.41)\(^b\)           | 0.000         | 78.4                                  |
| **Sample source** |                                 |               |                                        |
| Hospital-based | 2.51 (1.57–4.02)\(^b\)           | 0.000         | 84.6                                  |
| Population-based | 1.32 (1.13–1.54)\(^b\)           | 0.066         | 47.2                                  |
| **HWE**        |                                  |               |                                        |
| Yes            | 1.59 (1.23–2.04)\(^b\)           | 0.000         | 68.3                                  |
| No             | 2.59 (1.60–4.18)\(^b\)           | 0.038         | 69.5                                  |
| **Recessive (TT vs CT + CC)** | 1.59 (1.14–2.22)\(^b\) | 0.000 | 65.6 | 0.033/0.053 |
| **Mandatory fortification with folate** | | | | |
| Yes            | 1.37 (0.93–2.00)\(^b\)           | 0.003         | 72.3                                  |
| No             | 2.23 (1.13–4.38)\(^b\)           | 0.002         | 65.1                                  |
| **Population** |                                  |               |                                        |
| Asian          | 2.07 (0.84–5.10)\(^b\)           | 0.000         | 81.5                                  |
| Caucasian      | 1.47 (1.04–2.07)\(^b\)           | 0.015         | 54.7                                  |
| **Sample source** |                                 |               |                                        |
| Hospital-based | 1.76 (1.02–3.04)\(^b\)           | 0.000         | 76.0                                  |
| Population-based | 1.41 (1.11–1.80)\(^b\)           | 0.057         | 48.9                                  |
| **HWE**        |                                  |               |                                        |
| Yes            | 1.23 (1.02–1.48)\(^b\)           | 0.025         | 48.7                                  |
| No             | 2.79 (2.05–3.80)\(^b\)           | 0.459         | 0.006                                  |

\(^a\)P < 0.05  
\(^b\)Fixed effect  
\(^b\)Random effect

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**Fig. 2** Association between MTHFR (C677T and A1298C) polymorphism and ASD susceptibility
Table 4 Meta-analysis of MTHFR A1298C polymorphism to ASD risk under the five genetic models

| Genetic Models | Fixed/ Random effect OR (95%CI) | Heterogeneity | Publication Bias of Egger’s/Begg test |
|----------------|---------------------------------|---------------|-------------------------------------|
| Allele Contrast (C vs A) | 1.17 (0.91–1.50)<sup>b</sup> | 0.000 | 81.7 | 0.210/0.010 |
| Mandatory fortification with folate | | | | |
| Yes | 0.91 (0.81–1.03)<sup>a</sup> | 0.153 | 40.3 | 0.086/0.098 |
| No | 1.84 (1.08–3.14)<sup>a</sup> | 0.002 | 86.0 | 0.086/0.095 |
| Population | | | | |
| Asian | 1.31 (0.81–2.14)<sup>a</sup> | 0.002 | 84.4 | 0.296/0.380 |
| Caucasian | 1.11 (0.82–1.49)<sup>a</sup> | 0.000 | 80.9 | 0.548/0.045 |
| Sample source | | | | |
| Hospital-based | 1.45 (0.88–2.39)<sup>a</sup> | 0.000 | 89.5 | 0.221/0.021 |
| Population-based | 0.96 (0.84–1.10)<sup>a</sup> | 0.074 | 53.0 | 0.204/0.462 |
| HWE | | | | |
| Yes | 1.13 (0.84–1.52)<sup>a</sup> | 0.000 | 80.9 | 0.368/0.043 |
| No | 1.25 (0.73–2.15)<sup>a</sup> | 0.000 | 87.2 | 0.282/0.296 |
| Heterozygote (AC vs AA) | 1.11 (0.82–1.50)<sup>a</sup> | 0.000 | 73.5 | 0.001/0.049 |
| Mandatory fortification with folate | | | | |
| Yes | 0.87 (0.74–1.02)<sup>a</sup> | 0.302 | 17.6 | 0.382/0.462 |
| No | 2.23 (0.98–5.09)<sup>a</sup> | 0.000 | 82.7 | 0.026/0.086 |
| Population | | | | |
| Asian | 1.29 (0.68–2.44)<sup>a</sup> | 0.015 | 76.3 | 0.532/1.000 |
| Caucasian | 1.04 (0.72–1.50)<sup>a</sup> | 0.001 | 74.7 | 0.002/0.230 |
| Sample source | | | | |
| Hospital-based | 1.11 (0.71–1.74)<sup>a</sup> | 0.004 | 74.0 | 0.090/0.462 |
| Population-based | 1.15 (0.72–1.86)<sup>a</sup> | 0.001 | 78.4 | 0.009/0.221 |
| HWE | | | | |
| Yes | 1.04 (0.73–1.50)<sup>a</sup> | 0.001 | 74.6 | 0.001/0.133 |
| No | 1.28 (0.66–2.47)<sup>a</sup> | 0.013 | 76.9 | 0.578/1.000 |
| Homozygote (CC vs AA) | 1.31 (0.82–2.09)<sup>a</sup> | 0.000 | 72.0 | 0.025/0.152 |
| Mandatory fortification with folate | | | | |
| Yes | 0.89 (0.67–1.18)<sup>a</sup> | 0.260 | 24.2 | 0.139/0.462 |
| No | 2.98 (1.17–7.58)<sup>a</sup> | 0.002 | 75.8 | 0.143/0.221 |
| Population | | | | |
| Asian | 1.78 (0.88–3.62)<sup>a</sup> | 0.041 | 68.8 | 0.811/1.000 |
| Caucasian | 1.11 (0.62–2.01)<sup>a</sup> | 0.002 | 70.5 | 0.073/0.368 |
| Sample source | | | | |
| Hospital-based | 1.87 (0.74–4.77)<sup>a</sup> | 0.000 | 83.6 | 0.044/0.462 |
| Population-based | 1.02 (0.76–1.34)<sup>a</sup> | 0.208 | 32.0 | 0.066/1.000 |
| HWE | | | | |
| Yes | 1.27 (0.68–2.35)<sup>a</sup> | 0.001 | 72.5 | 0.072/0.230 |
| No | 1.45 (0.65–3.24)<sup>a</sup> | 0.014 | 76.7 | 0.966/1.000 |
| Dominant (CC + AC vs AA) | 1.19 (0.87–1.64)<sup>a</sup> | 0.002 | 79.6 | 0.000/0.049 |
| Mandatory fortification with folate | | | | |
| Yes | 0.87 (0.74–1.02)<sup>a</sup> | 0.205 | 32.5 | 0.198/0.221 |
| No | 2.45 (1.16–5.15)<sup>a</sup> | 0.000 | 84.5 | 0.005/0.086 |
Table 4  Meta-analysis of MTHFR A1298C polymorphism to ASD risk under the five genetic models (Continued)

| Genetic Models | Fixed/ Random effect | Heterogeneity | Publication Bias of Egger’s/Begg test |
|----------------|----------------------|---------------|-------------------------------------|
|                | OR(95%CI)            | \(I^2(\%)\)  | P                                   |
| Population     |                      |               |                                     |
| Asian          | 1.38 (0.89–2.14)<sup>b</sup> | 0.054 | 65.8 | 0.291/1.000 |
| Caucasian      | 1.13 (0.75–1.72)<sup>b</sup> | 0.000 | 82.0 | 0.001/0.230 |
| Sample source  |                      |               |                                     |
| Hospital-based | 1.43 (0.81–2.50)<sup>b</sup> | 0.000 | 86.6 | 0.019/0.462 |
| Population-based | 1.03 (0.71–1.49)<sup>b</sup> | 0.011 | 69.2 | 0.014/0.221 |
| HWE            |                      |               |                                     |
| Yes            | 1.14 (0.76–1.73)<sup>b</sup> | 0.000 | 81.9 | 0.001/0.230 |
| No             | 1.34 (0.80–2.23)<sup>b</sup> | 0.023 | 73.4 | 0.306/1.000 |
| Recessive (CC vs AC + AA) | 1.17 (0.76–1.78)<sup>b</sup> | 0.001 | 69.4 | 0.081/0.152 |
| Mandatory fortification with folate |                      |               |                                     |
| Yes            | 0.94 (0.72–1.24)<sup>a</sup> | 0.363 | 7.7  | 0.192/0.462 |
| No             | 1.93 (0.70–1.25)<sup>b</sup> | 0.000 | 82.6 | 0.240/0.806 |
| Population     |                      |               |                                     |
| Asian          | 1.52 (0.54–4.33)<sup>b</sup> | 0.000 | 87.3 | 0.546/1.000 |
| Caucasian      | 0.99 (0.64–1.55)<sup>b</sup> | 0.486 | 52.8 | 0.174/0.368 |
| Sample source  |                      |               |                                     |
| Hospital-based | 1.74 (0.76–3.99)<sup>b</sup> | 0.000 | 80.3 | 0.063/0.462 |
| Population-based | 0.90 (0.69–1.19)<sup>a</sup> | 0.235 | 27.9 | 0.710/1.000 |
| HWE            |                      |               |                                     |
| Yes            | 1.12 (0.69–1.80)<sup>b</sup> | 0.025 | 58.5 | 0.163/0.368 |
| No             | 1.24 (0.46–3.36)<sup>b</sup> | 0.001 | 86.6 | 0.676/1.000 |

*<sup>a</sup>P < 0.05  
*<sup>b</sup>Fixed effect  
*<sup>c</sup>Random effect

Fig. 3  Sensitivity analysis between MTHFR (C677T and A1298C) polymorphism and ASD susceptibility
stable and credible (Fig. 3). To evaluate the publication bias, Begg’s funnel plot and Egger’s tests were carried out. No significant publication bias was detected in the correlation between MTHFR C677T polymorphisms and ASD risk in the five genetic models: allelic ($P_B = 0.029$, $P_E = 0.017$), heterozygote ($P_B = 0.048$, $P_E = 0.053$), dominant ($P_B = 0.021$, $P_E = 0.010$), and recessive models ($P_B = 0.033$, $P_E = 0.053$). However, publication bias was detected among the studies on the correlation between MTHFR A1298C polymorphisms and ASD risk in the following genetic models: allelic ($P_B = 0.210$, $P_E = 0.010$), heterozygote ($P_B = 0.001$, $P_E = 0.049$), homozygote ($P_B = 0.025$, $P_E = 0.152$), dominant ($P_B = 0.000$, $P_E = 0.049$), and recessive models ($P_B = 0.081$, $P_E = 0.152$) (Tables 3 and 4, Fig. 4).

Discussion
Relevant and up to date literature published prior to January 26, 2020 were selected for examining the correlation between MTHFR polymorphism (C677T and A1298C) and ASD risk in this meta-analysis. The findings of this study exhibit that MTHFR C677T polymorphism is a susceptibility factor of ASD, but MTHFR A1298C polymorphism is not linked with ASD susceptibility.

Several meta-analytic studies on the correlation between C677T polymorphism of MTHFR and ASD risk have been conducted. Frustaci et al. [24] studied six articles [22, 27, 28, 35, 43, 44], which consisted of 877 cases and 939 controls, mainly Caucasians, and found a remarkable correlation between C677T polymorphism of MTHFR and ASD risk [24]. Pu et al. [25] investigated eight articles [9, 18, 22, 27, 28, 31, 35, 43] involving 1672 cases and 6760 controls, also mainly Caucasians, evidenced a significant risk on the T allele mutation of MTHFR C677T in ASD [25]. Rai et al. [26] investigated 1978 cases and 7257 controls (Caucasians: 1355 cases and 6460 controls; Asians: 623 cases and 797 controls) in 13 studies [18, 22, 27, 28, 31, 33, 35, 43, 44, 46, 48, 50] and found that C677T polymorphism of MTHFR is a risk factor for ASD susceptibility as well [26]. Similarly, the current meta-analysis enrolled 2609 cases and 7496 controls (Caucasian: 1786 cases and 6499 controls, Asian: 823 cases and 997 controls) from 15 selected literature [9, 18, 22, 26–28, 31, 32, 33, 35, 43, 47, 48, 50], further confirmed the association between C677T polymorphism of MTHFR and ASD susceptibility.

A previous meta-analysis, conducted on the correlation between A1298C polymorphism of MTHFR and ASD risk [25] (included five literatures; 1470 cases and 1060 controls; Caucasians: 1332 cases and 922 controls, Asians: 138 cases and 138 controls, respectively) [18, 22, 35, 43, 44] reported that A1298C polymorphism of MTHFR is remarkably linked to reduced ASD risk but only in the recessive model [25].

In the present meta-analysis, eight of the selected articles [18, 22, 32, 35, 36, 43, 44, 47, 50] had enrolled 1961 cases and 1652 controls (Caucasians: 1387 cases and 991 controls, Asians: 574 cases and 661 controls), and it was recognized that A1298C polymorphism of MTHFR was not correlated with ASD susceptibility. However, Khalil et al. (42 cases and 48 controls) [49] and El-Baz et al. (31 cases and 39 controls) [32] revealed that MTHFR A1298C polymorphism represented a risk factor in association with ASD. This disagreement may be caused by small samples in the study.

There are several limitations for this study. First, the subgroup analyses of environmental risk factors, sex, and gene-environment interactions were not performed owing to insufficient information. Second, this meta-analysis was mainly focused on Caucasians and Asians, thus limiting the generalization of the findings to other ethnicities. Third, in agreement with the findings of
Frustaci et al. [24], Pu et al. [25] and Rai et al. [26], heterogeneity exists in this exploration. Fourth, publication bias was found in the association between MTHFR A1298C polymorphisms and ASD risk.

**Conclusion**

To conclude, this meta-analysis confirms that C677T polymorphism of MTHFR is remarkably linked with ASD risk. Nevertheless, the findings agree that the A1298C polymorphism of MTHFR is not significantly correlated with ASD. Exploring gene-gene and gene-environment interactions could throw more light on the genetic link between MTHFR variants and ASD risk.

**Supplementary information**

**Supplementary information** accompanies this paper at https://doi.org/10.1186/s12887-020-02390-3.

**Additional file 1 : Supplement file 1.** Search strategy: For this meta-analysis, a total of 15 manuscripts published up to January 26, 2020, were selected from PubMed, Google Scholar, Medline, WangFang, and CNKI databases using search terms “MTHFR” or “methylene tetrahydrofolate reductase” AND “ASD” or “Autism Spectrum Disorders” or “Autism” AND “polymorphism” or “susceptibility” OR “C677T” OR “A1298C”.

**Abbreviations**

ASD: Autism spectrum disorder; MTHFR: Methylentetrahydrofolate reductase; SNPs: Single nucleotide polymorphisms; HWE: Hardy-Weinberg equilibrium; OR: Odds ratio; CI: Confidence interval; AIC: Akaike’s information criterion; LD: Linkage disequilibrium

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**Authors’ contributions**

Conception and design: YL, YG, JS, and ZL; collection and assembly of data: YL, SQ; data analysis and interpretation: YL, SQ, ZL, YC, and YWL; manuscript writing: YL; revision of the manuscript: SQ, YG, JS, and ZL; collection and assembly of data: YL, SQ; data analysis and interpretation: YG, JS, and ZL; manuscript writing: YL, SQ; revision of the manuscript: YL, SQ, ZL, YC, and YWL; final approval of the manuscript: all authors.

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**Availability of data and materials**

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

**Ethics approval and consent to participate**

Not applicable.

**Consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

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