MTHFR A1298C gene polymorphism on stroke risk: an updated meta-analysis

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Abstract

Background: Previous studies have shown the effect of MTHFR A1298C gene polymorphism on stroke risk. But the results of published studies remained inconclusive and controversial. So we conducted a meta-analysis to accurately estimate the potential association between MTHFR A1298C gene polymorphism and stroke susceptibility.

Methods: A systematic literature search on Embase, Pubmed, Web of Science, Cochrane Library, China National Knowledge Infrastructure (CNKI) and WanFang electronic database identified 40 articles including 5725 cases and 8655 controls. Strength of association was evaluated by pooled odds ratio (OR), 95% confidence interval (CI) and p value. Funnel plots and Begger’s regression test were applied for testing the publication bias. Statistical analysis of all data was performed by Stata 12.0.

Results: The meta-analysis results indicated a significant relationship between MTHFR gene A1298C polymorphisms and stroke risk under the C allelic genetic model (OR = 1.19, 95%CI = 1.07–1.32, p = 0.001), dominant genetic model (OR = 1.19, 95%CI = 1.06–1.33, p = 0.004) and recessive genetic model (OR = 1.43, 95%CI = 1.15–1.77, p = 0.001). In subgroup analysis, we discovered obvious correlation in three genetic model of Asian, stroke type, adult by ethnicity, population, stroke type, source of control and case size. Additionally, in studies of control from hospital and case size equal 100, obvious correlation was also found in the three genetic model.

Conclusions: Our meta-analysis results indicated that there was evidence to support the correlation between MTHFR A1298C polymorphism and stroke susceptibility, especially in adults and ischemic stroke.

Keywords: MTHFR A1298C, Polymorphism, Stroke, Meta-analysis

Introduction

Stroke was a type of clinical syndrome caused by sudden neurological deficits after cerebral blood vessel rupture or occlusion. It had a very high rate of disability and was classified into ischemic stroke (IS) and hemorrhagic stroke (HS) [1, 2]. Genetic genes, high blood sugar, unhealthy lifestyles, high blood pressure, and hyperlipidemia were all high-risk factors for stroke, which similarly to high-risk factors for cardiovascular disease [3, 4].

Methylenetetrahydrofolate reductase (MTHFR) was a key enzyme that folic acid metabolizes in vivo. The activity of this enzyme can directly affect the plasma homocysteine content in the human body [5, 6]. C677T and A1298C were two common mutants in MTHFR. Their missense mutations resulted in the replacement of 677 base C with T and the substitution of A with C in 1298, which changed the amino acid structure of MTHFR and caused the decrease of MTHFR enzyme activity [7–10]. The homocysteine cannot be converted into the word methionine normally, which causes a significant increase in the homocysteine content in the blood, which increases the stroke susceptibility [11].

A meta-analysis study performed in 2013 firstly reported the association among MTHFR A1298C and...
stroke risk [12]. A meta-analysis study performed in 2014 reported the correlation between MTHFR A1298C polymorphism and adult stroke [13]. Although Kumar et al. [14] conducted a meta-analysis and indicated that genotyping of MTHFR gene A1298C polymorphism may be used as a predictor for the occurrence of ischemic stroke. However, just 20 articles were included in this study, and some articles published in Chinese journal were not included in the analysis. Incomplete article search may lead to unstable results. Later a meta-analysis study performed in 2018 reported the association among MTHFR A1298C polymorphism and IS risk [15]. In recent years, many studies [16–20] have reported the association among MTHFR A1298C polymorphism and stroke risk. But the results were still inconsistent. Therefore, the purpose of this meta-analysis was to investigate the relationship among MTHFR A1298C polymorphism and stroke risk by updating previous meta-analyses.

Materials and methods

Publication search

Search in electronic databases such as PubMed, Cochrane Library, Web of Science, Embase, CNKI and WanFang using following terms: ("methylene tetrahydrofolate reductase" OR "A1298C" OR "MTHFR") AND ("apoplexy" OR "stroke" OR "brain infarction" OR "cerebrovascular disorder") AND ("polymorphism" OR "variant" OR "mutation") until August 2019. To ensure the relevant studies are included, two investigators independently searched the relevant literature and manually checked some major articles and reviews.

Selection criteria

ALL selected studies complied with the inclusion criteria: (1) Full text can be searched in electronic databases; (2) Case-control studies on MTHFR A1298C and stroke susceptibility; (3) MTHFR A1298C genotype frequency can be provided. The main exclusion criteria include the following: (1) Repeat articles in other electronic databases (2) The design was not a case-control study; (3) Unpublished studies, meta-analysis and systematic reviews; (4) The genotype frequency of MTHFR A1298C was not provided. Referring to the systematic review and meta-analysis [PRISMA], we screened all retrieved documents and constructed an information flow chart using the final qualified data.

Data extraction

Two researchers screened the retrieved studies by inclusion and exclusion standard. We selected following information from the included researches: first author, publication years, study country / region, type of stroke, study population, control group source, sample size (case and control) and genotype type. we evaluated each included study by Newcastle-Ottawa Scale (NOS) [21]. And we used Hardy-Weinberg-equilibrium (HWE) to assess the gene distribution in control group [22]. In order to ensure the accuracy of the information extracted from the research, the third researcher will review the accuracy of the information extracted by the first two researchers, and the three researchers will resolve the disputed results through negotiation.

Statistical analysis

Odds ratio (OR) and 95% confidence interval (CI) were calculated to estimate the relationship among MTHFR A1298C polymorphism and stroke susceptibility by different genetic comparison models: the C allele model (C and A), recessive model (CC and AA + CA) and dominant model (CC + CA and AA). Heterogeneities of different genetic comparison models was evaluated by the χ² based Q-statistic and I² [23, 24]. Significant Q statistic (p < 0.10) or I² > 50% indicates that there was heterogeneity between studies. The pooled OR was estimated by fixed effect model (Mantel–Haenszel) when no heterogeneity existed. Otherwise, the pooled OR was estimated by random effect model. To determine the possible causes of heterogeneity, ethnicity (African, Caucasian and Asian), study population (children and adults), type of stroke (ischemic and hemorrhagic), control source (based on population and Hospitals) and case group sample sizes (less than 100 and greater than or equal to 100) were analyzed in subgroups. In addition, sensitivity analysis was performed on different genetic comparison models to evaluate the effect of a single research on pooled OR. We used Egger test and funnel plots to evaluate the potential publication bias [25]. Stata 12.0 was used to perform statistical analysis of all genetic comparison models.

Results

Literature Search and Study Characteristics

Flowcharts of the detailed selection process were shown in Fig. 1. A total of 5475 publications were searched in several electronic databases. After carefully reading the research title, content and abstract, the two researchers excluded 1496 duplicate documents, 3851 irrelevant papers, and read the remaining 128 articles in full text. Finally, our meta-analysis included 40 case-control publications that met the inclusion criteria (involving 5725 cases and 8655 controls). Four of the control groups did not meet HWE balance (p < 0.05). In the 40 case-control studies, 22 were conducted among Asian populations, 16 were Caucasian, and 2 were African population. Thirty-one studies were based on adults. Other 9 studies were based on children. Ten studies were based on IS. Four studies based on HS and other...
studies based on both (MIXED). Four studies based on population (PB), 21 studies based on hospital (HB), other studies based on no report (NR) in this article. The sample group of 21 studies was less than 100, and the sample group of the other 19 studies was greater than or equal to 100. The main features of the study and the genotype distribution results of the HWE test were shown in Table 1.

**Meta-analysis results**

The meta-analysis included 14,380 participants (5725 cases and 8655 controls) in 40 case-control studies (Table 2). The meta-analysis results indicated the polymorphisms in *MTHFR* A1298C gene had significant association with stroke risk under the C allelic genetic model (OR = 1.19, 95%CI = 1.07–1.32, *p* = 0.001), dominant genetic model (OR = 1.19, 95%CI = 1.06–1.33, *p* = 0.004) and recessive genetic model (OR = 1.43, 95%CI = 1.15–1.77, *p* = 0.001).

In ethnic subgroup analysis, *MTHFR* A1298C polymorphism was obviously correlated with increased risk of stroke under three genetic models of Asian population (C vs A: OR = 1.18, 95%CI = 1.07–1.32, *p* = 0.002; CC + CA vs AA: OR = 1.19, 95%CI = 1.06–1.34, *p* = 0.008; CC vs CA + AA: OR = 1.48, 95%CI = 1.16–1.89, *p* = 0.002). There was no obvious association among *MTHFR* A1298C polymorphism and children stroke risk. Stratified analysis by stroke type found that *MTHFR* A1298C polymorphism was obviously correlated with increased stroke risk in the three genetic models of ischemic stroke (C vs A: OR = 1.22, 95%CI = 1.09–1.37, *p* = 0.002; CC + CA vs AA: OR = 1.24, 95%CI = 1.09–1.42, *p* = 0.002; CC vs CA + AA: OR = 1.38, 95%CI = 1.12–1.69, *p* = 0.002). In the control source stratification, three control genetic models from hospitals found an obvious correlation among the *MTHFR* A1298C polymorphism and increased stroke risk (C vs A: OR = 1.24, 95%CI = 1.08–1.42, *p* = 0.002; CC + CA vs AA: OR = 1.23, 95%CI = 1.06–1.44, *p* = 0.008; CC vs CA + AA: OR = 1.54, 95%CI = 1.28–1.86, *p* = 0.007). Finally, we stratified the case group according to whether the sample size was greater than or equal to 100. The study discovered that *MTHFR* A1298C polymorphism was obviously correlated with increased stroke risk under the three genetic models with a sample size of 100 or more (C vs A: OR =
| Author | Year | Country | Type   | Population | Source of control | Sample size | NOS score | HWE |
|--------|------|---------|--------|------------|-------------------|-------------|-----------|-----|
| Akar et al | 2001 | Turkey | IS     | Children   | NR                | 46 68       | 13 27     | 6 53 39 | 31 32 5 94 42 7 0.399 |
| Lin et al | 2004 | China  | IS     | Adults     | HB                | 68 50       | 50 16 2 116 20 | 35 15 0 | 85 15 8 0.212 |
| Linnebank et al | 2005 | Germany | IS     | Adults     | PB                | 159 159     | 80 65 14 225 93 | 73 64 | 22 210 108 8 0.196 |
| Sun et al | 2005 | China  | IS     | Adults     | NR                | 97 94       | 55 40 2 150 44 | 60 31 3 | 151 37 8 0.676 |
| Komitopoulou et al | 2006 | Greece | IS     | Children   | HB                | 89 103      | 35 45 9 115 63 | 50 40 | 13 140 66 7 0.272 |
| Sazci et al | 2006 | Turkey | IS     | Adults     | NR                | 92 259      | 36 37 19 109 75 | 130 108 | 21 368 150 8 0.828 |
| Sazci et al | 2006 | Turkey | HS     | Adults     | NR                | 28 259      | 16 9 3 41 15 | 130 108 | 21 368 150 8 0.828 |
| Dikmen et al | 2006 | Turkey | IS     | Adults     | NR                | 154 55      | 59 79 16 197 111 | 19 33 | 3 71 39 7 0.021 |
| Dikmen et al | 2006 | Turkey | HS     | Adults     | NR                | 49 55       | 19 23 7 61 37 | 19 33 | 3 71 39 7 0.021 |
| Zhang et al | 2007 | China  | IS     | Adults     | NR                | 100 100     | 56 40 4 152 48 | 64 33 | 3 161 39 8 0.609 |
| Sirachainan et al | 2008 | Thailand | IS     | Children   | HB                | 44 164      | 22 19 3 63 25 | 82 69 | 13 233 95 6 0.774 |
| Biswas et al | 2009 | India  | IS     | Children   | NR                | 58 58       | 38 14 6 90 26 | 50 7 1 | 107 9 8 0.232 |
| Morita et al | 2009 | America | IS     | Children   | PB                | 23 90       | 17 6 0 40 6 | 41 36 | 13 118 62 6 0.278 |
| Sawula et al | 2009 | Poland | IS     | Adults     | HB                | 128 59      | 53 57 18 163 93 | 26 22 | 11 74 44 7 0.119 |
| Almawi et al | 2009 | Bahrain | MIXED  | Adults     | HB                | 118 120     | 50 38 30 138 98 | 54 60 | 6 168 72 6 0.037 |
| Biswas et al | 2009 | India  | IS     | Adults     | HB                | 120 120     | 80 31 9 191 49 | 90 24 | 6 204 36 7 0.018 |
| Chen et al | 2010 | China  | IS     | Adults     | HB                | 470 495     | 354 109 7 817 123 | 387 105 | 3 879 111 7 0.146 |
| Han et al | 2010 | Korea  | IS     | Adults     | HB                | 264 234     | 179 80 5 438 90 | 182 51 | 1 415 53 8 0.193 |
| Giusti et al | 2010 | Italy  | IS     | Adults     | HB                | 501 1211    | 248 197 56 693 309 | 572 529 | 110 1673 749 7 0.434 |
| Hultdin et al | 2011 | Sweden | IS     | Adults     | NR                | 314 767     | 135 142 37 412 216 | 328 346 | 93 1002 532 7 0.905 |
| Hultdin et al | 2011 | Sweden | HS     | Adults     | NR                | 59 767      | 29 29 1 87 31 | 328 346 | 93 1002 532 7 0.905 |
| Arsene et al | 2011 | Bahrain | IS     | Adults     | HB                | 67 60       | 30 28 9 88 46 | 25 27 | 8 77 43 7 0.868 |
| Zhang et al | 2012 | China  | IS     | Adults     | HB                | 67 71       | 38 29 0 105 29 | 57 14 | 0 128 14 7 0.357 |
| Xu et al | 2012 | China  | MIXED  | Adults     | HB                | 70 50       | 7 41 22 55 85 | 12 30 | 8 54 46 8 0.142 |
| Zhang et al | 2012 | China  | IS     | Adults     | HB                | 40 40       | 27 12 1 66 14 | 33 7 0 | 73 7 8 0.544 |
| Fekih-Mrissa et al | 2013 | Tunisia | IS     | Adults     | HB                | 84 100      | 58 15 11 131 37 | 93 7 | 0 193 7 7 0.717 |
| Gelfand et al | 2013 | America | IS     | Children   | PB                | 13 84       | 4 7 2 15 11 | 39 41 | 4 119 49 8 0.097 |
| Zhou et al | 2014 | China  | IS     | Adults     | HB                | 542 654     | 333 174 35 840 244 | 448 182 | 24 1078 230 8 0.308 |
| Balcerzyk et al | 2015 | Poland | IS     | Children   | NR                | 88 111      | 51 30 7 132 44 | 53 47 | 11 153 69 7 0.902 |
| Lv et al | 2015 | China  | IS     | Adults     | NR                | 199 241     | 31 97 71 159 239 | 71 110 | 60 252 230 8 0.186 |
| Wei et al | 2015 | Malaysia | IS     | Adults     | NR                | 297 297     | 184 95 18 463 131 | 186 104 | 7 476 118 6 0.085 |
| Author          | Year | Country | Type | Population | Source of control | Sample size case | Sample size control | NOS | HWE |
|-----------------|------|---------|------|------------|-------------------|------------------|---------------------|-----|-----|
| Kamberi et al   | 2016 | Albania | IS   | Adults     | PB                | 39  102           | 18  20  1  56  22  54  44  4  152 | 52  8  0.171 |
| Herak et al     | 2017 | Croatia | IS   | Children   | HB                | 73  100           | 34  33  6  101  45  52  39  9  143 | 57  8  0.667 |
| Wang et al      | 2017 | China   | MIXED| Adults     | NR                | 225  169          | 130  85  10  345  105  99  65  5  263 | 75  6  0.139 |
| Zhao et al      | 2017 | China   | IS   | Adults     | HB                | 130  100          | 98  32  0  228  32  68  32  0  168 | 32  8  0.057 |
| Hu et al        | 2017 | China   | IS   | Adults     | HB                | 181  169          | 106  67  8  279  83  99  65  5  263 | 75  8  0.139 |
| Abidi et al     | 2018 | Morocco | HS   | Adults     | HB                | 113  323          | 64  46  3  174  52  186  120 17  492 | 154 8  0.678 |
| Hashemi et al   | 2019 | Iran    | IS   | Adults     | NR                | 106  157          | 72  31  3  175  37  120  32 5  272 | 42  8  0.131 |
| Xiong et al     | 2019 | China   | MIXED| Adults     | HB                | 92  140           | 64  24  4  152  32  90  44  6  224 | 56  8  0.833 |
| Mazdeh et al    | 2020 | Iran    | IS   | Children   | HB                | 318  400          | 170 121 27  461 175  235 147 18  617 | 183 8  0.406 |
1.16, 95%CI = 1.05–1.28, \( p = 0.003; \) CC + CA vs AA: OR = 1.14, 95%CI = 1.02–1.28, \( p = 0.020; \) CC vs CA + AA: OR = 1.46, 95%CI = 1.12–1.88, \( p = 0.004 \) (Fig. 2).

In order to evaluate the stability of this meta-analysis, the sensitivity analysis of this study excluded each included study one by one to compare the difference between the pooled OR before and after exclusion. The results of this analysis were very stable (Fig. 3). We used Begg’s funnel plot to estimate publication bias and found no publication in the three genetic models (C vs A: \( p = 0.742; \) CC + CA vs AA: \( p = 0.825; \) CC vs CA + AA: \( p = 0.138 \) ) (Fig. 4).

### Discussion

In recent years, there have been many studies on MTHFR A1298C polymorphism and stroke susceptibility [17, 19, 26–50]. In 2001, Akar et al. firstly found no association among MTHFR A1298C polymorphism and the ischemic stroke risk in Turkish children [51]. In 2004, the study by Lin et al. focused on adult ischemic stroke in China and found that the CC genotype and C allele frequency had no obvious difference between the cases and controls [52]. Biswas et al. [53] found that MTHFR 1298 A > C showed significant alleles and genotypes associated with disease phenotypes in the Indian child population. With increasing research among MTHFR A1298C polymorphism and stroke susceptibility, Lv et al. [12] performed a meta-analysis of MTHFR gene A1298C and stroke. In this meta-analysis, 13 studies with 1974 cases and 2660 controls were extracted to assess the potential correlation. Overall analysis indicated that MTHFR A1298C was significantly associated with the stroke risk only in the heterozygote comparison and in the dominant model. Zhang constructed a meta-analysis of MTHFR A1298C polymorphism and stroke risk in adults [13]. 15 researches with 2361 cases and 2653 controls were included in final meta-analysis. Comprehensive analysis results showed that the polymorphism of MTHFR gene A1298C was significantly correlated with adult stroke in allelic model, dominant, additive and recessive models. Because the two meta-analyses came from different populations and sample sizes are different, these studies have shown inconsistent results. Since 2014, there have been another 25 studies on MTHFR gene A1298C polymorphism and stroke. Therefore, we upgraded a meta-analysis of MTHFR gene A1298C polymorphism and stroke susceptibility.

This meta-analysis resolved the correlation among MTHFR A1298C polymorphism and stroke susceptibility. The comprehensive data of the study showed that MTHFR A1298C polymorphism was a probable risk factor for stroke in dominant model (CC + CA vs AA), recessive model (CC vs CA + AA) and allele model (C vs A). In stratified analysis based on race, study population, population, and source of control, the results showed consistent results. Comprehensive analysis results showed that the polymorphism of MTHFR gene A1298C was significantly correlated with stroke susceptibility in Chinese population, and the correlation was stronger in adults than in children. Therefore, the results of this meta-analysis provide new insights into the association between MTHFR A1298C polymorphism and stroke susceptibility.

### Table 2: Pooled ORs and 95%CIs of the association between MTHFR A1298C polymorphism and stroke

| Total and subgroups | Studies | CC + CA vs AA | CC vs CA + AA | C VS A |
|--------------------|---------|---------------|---------------|--------|
|                    | OR  | 95%CI         | \( I^2 \) | \( P \) | OR  | 95%CI         | \( I^2 \) | \( P \) | OR  | 95%CI         | \( I^2 \) | \( P \) |
| **Total**          | 40  | 1.19 1.06–1.33 | 51.8% | <0.001 | 1.43 1.15–1.77 | 40.6% | <0.006 | 1.19 1.07–1.32 | 61.1% | <0.001 |
| **Ethnicity**      |      |               |         |        |               |       |        |               |       |        |
| Asian              | 22  | 1.28 1.17–1.47 | 40.9% | 0.025  | 1.84 1.49–2.27 | 0.0%  | 0.057  | 1.29 1.16–1.44 | 36.8% | 0.044  |
| Caucasian          | 16  | 0.99 0.85–1.17 | 29.2% | 0.131  | 1.10 0.81–1.50 | 44.0% | 0.031  | 1.01 0.88–1.16 | 48.0% | 0.017  |
| African            | 2   | 2.38 0.43–13.19 | 91.6% | 0.001  | 3.31 0.04–276.07 | 87.8% | 0.004  | 2.63 0.33–20.97 | 95.2% | <0.001 |
| **Population**     |      |               |         |        |               |       |        |               |       |        |
| Child              | 9   | 1.20 0.85–1.69 | 58.9% | 0.013  | 1.25 0.79–2.00 | 29.0% | 0.187  | 1.15 0.86–1.54 | 66.1% | 0.003  |
| Adult              | 31  | 1.19 1.06–1.34 | 51.1% | 0.001  | 1.48 1.16–1.89 | 45.0% | 0.005  | 1.18 1.07–1.32 | 60.9% | <0.001 |
| **Stroke type**    |      |               |         |        |               |       |        |               |       |        |
| IS                 | 32  | 1.24 1.09–1.42 | 56.6% | <0.001 | 1.38 1.12–1.69 | 28.4% | 0.076  | 1.22 1.09–1.37 | 63.0% | <0.001 |
| HS                 | 4   | 0.89 0.67–1.18 | 0.0%  | 0.811  | 0.79 0.23–2.65 | 64.5% | 0.037  | 0.88 0.70–1.10 | 0.0%  | 0.494  |
| MIXED              | 4   | 1.09 0.77–1.56 | 36.8% | <0.001 | 2.39 1.09–5.22 | 55.9% | 0.078  | 1.27 0.91–1.78 | 60.2% | 0.057  |
| **Source of control** |      |               |         |        |               |       |        |               |       |        |
| HB                 | 21  | 1.23 1.06–1.44 | 51.4% | 0.011  | 1.54 1.28–1.86 | 40.9% | 0.033  | 1.24 1.08–1.42 | 60.7% | <0.001 |
| PB                 | 4   | 0.88 0.47–1.62 | 52.7% | 0.003  | 0.61 0.33–1.11 | 39.5% | 0.175  | 0.86 0.49–1.50 | 68.8% | 0.022  |
| NR                 | 15  | 1.19 0.98–1.44 | 57.9% | 0.068  | 1.38 1.12–1.70 | 37.4% | 0.071  | 1.18 1.01–1.39 | 59.2% | 0.002  |
| **Case size**      |      |               |         |        |               |       |        |               |       |        |
| <100               | 21  | 1.28 1.00–1.65 | 61.3% | <0.001 | 1.36 0.92–2.01 | 36.9% | 0.050  | 1.25 1.00–1.57 | 69.8% | <0.001 |
| \( \geq 100 \)     | 19  | 1.14 1.02–1.28 | 36.8% | 0.055  | 1.46 1.12–1.88 | 47.5% | 0.013  | 1.16 1.05–1.28 | 46.8% | 0.013  |
stroke type, source of controls population and sample size of cases, a significant association was discovered among MTHFR A1298C polymorphism and stroke in three genetic models of Asians. In Caucasian and African, MTHFR A1298C polymorphism was not significantly correlated with stroke. In stratified analysis according to study population, it was discovered that MTHFR A1298C polymorphism was obviously correlated with stroke in adults. But the correlation between MTHFR A1298C polymorphism and stroke in children lacked corresponding evidence. In stratified analysis of stroke
Fig. 4 Beggs's funnel plot for publication bias analysis. a is the model of CC + CA VS TT; b is the model of CC VS CA + AA; c is the model of C VS A.
types, the association among MTHFR A1298C polymorphism and stroke was found only in ischemic stroke. The stratified analysis of source of the control group showed that there was obvious correlation among MTHFR A1298C polymorphism and stroke in hospital study. The stratified analysis of the sample size showed that the correlation among MTHFR A1298C polymorphism and stroke was found only when the number of samples in the case group was greater than or equal to 100. The above analysis showed that the source of control group and the sample size of case group may be the influencing factors of the correlation study among MTHFR A1298C polymorphism and stroke. This was undiscovered in early meta-analysis. Although Kumar et al. [14] conducted a meta-analysis on association between A1298C polymorphism and risk of ischemic stroke. However, just 20 articles were included in this study, and some articles published in Chinese journal were not included in the analysis. The biological mechanism of the association between A1298C and stroke has not been confirmed. Study [54] indicated that MTHFR gene can encode MTHFR enzyme, which plays a key role in regulating cellular homocysteine (Hcy) and folate metabolism by catalyzing the conversion of 5,10-methylpentylenetetrahydrofolate to 5-methyltetrahydrofolate, and elevated homocysteine level in blood circulation is considered as an independent risk factor for cerebral, coronary and peripheral atherosclerosis [55].

This meta-analysis has several limitations. Our results show the genetic differences in ethnic differences and stroke risk, but the study only includes Asian, Caucasian and African populations, and there are few studies in African populations, and there are no corresponding studies for other ethnic populations. The occurrence of stroke is often caused by the interaction of genetic factors and environmental factors. This study is only conducted from the perspective of genetics without the influence of environmental exposure. In previous studies, especially in meta-analysis, the data was still insufficient. We have checked as many articles as possible, but many studies have omitted data, such as control sources and genetic testing methods.

In conclusion, we found obvious correlation among MTHFR A1298C and stroke risk in Asians, adults and ischemic strokes. However, for the Caucasian, African, children and hemorrhagic stroke, the risk of MTHFR A1298C could not be confirmed because of the relatively limited sample size. In addition, sample size of case group and source of control group would also have an impact on the results in the stratified analysis of this study. Therefore, in future research, we can explore more about the correlation among MTHFR A1298C and stroke in other races (except for Asian population), children, and hemorrhagic stroke.

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Ethical Statement
Not applicable.

Authors’ contributions
Manuscript writing, editing and review were conducted by XD and GW. JW participated in the articles search; LW and YD performed data analysis and evaluation the quality of the selected studies. The author(s) read and approved the final manuscript.

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Competing interests
The authors declare that they have no competing interests.

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