Methylenetetrahydrofolate Reductase C677T Polymorphism and Type 2 Diabetes Mellitus in Chinese Population: A Meta-Analysis of 29 Case-Control Studies

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Abstract

Background: Methylenetetrahydrofolate reductase (MTHFR), a key enzyme in folate metabolism, had significant effects on the homocysteine levels. The common functional MTHFR C677T polymorphism had been extensively researched. Several studies had evaluated the relationship between MTHFR C677T polymorphism and type 2 diabetes mellitus (T2DM), but the results were still controversial in the Chinese Han population. This meta-analysis was conducted to evaluate the relationship between MTHFR C677T polymorphism and T2DM in the Chinese Han population.

Methods: We searched the relevant studies in multiple electronic databases, which published up to December 2013. We reviewed and extracted data from all the included studies on the relationship between MTHFR C677T polymorphism and T2DM in the Chinese Han population. The odds ratios (ORs) and their 95% confidence intervals (95%CIs) were used to evaluate the relationship. Fixed-effects and random-effects meta-analysis were used to pool ORs by the heterogeneity. Publication bias and sensitivity analysis were also examined.

Results: 29 studies were finally included in our meta-analysis, which contained 4656 individuals with T2DM and 2127 healthy controls. There was a significant relationship between MTHFR C677T polymorphism and T2DM under dominant (OR: 1.70, 95% CI: 1.42–2.02), recessive (OR: 1.48, 95% CI: 1.21–1.80), homozygous (OR: 1.89, 95% CI: 1.47–2.42), heterozygous (OR: 1.58, 95% CI: 1.33–1.87), and additive (OR: 1.46, 95% CI: 1.28–1.68) genetic model in a random-effects model. Subgroup analysis also reached similar results. Sensitivity analysis indicated that the overall result were dependable.

Conclusions: There was a significant relationship between MTHFR C677T polymorphism and T2DM in the Chinese Han population. The results of our meta-analysis suggested that MTHFR 677T allele might be a risk genetic factor of T2DM in the Chinese Han population.

Introduction

Type 2 diabetes mellitus (T2DM) is one of public health problems, seriously affects individual life quality, and increases individual economic burden. WHO estimates the number of people with diabetes will increase by 114% between 2000 and 2030, and China will become the major site of diabetes epidemic. In a systematic review of 22 studies on diabetes prevalence in China from 2000 to 2010, it increased from 2.6% to 9.7% during this decade [1]. It is estimated that China will have 380 million people with diabetes by 2025 [2]. However, the pathogenesis of T2DM remains unclear [3]. Currently, the research on genetic polymorphisms is one of the most attention areas in the pathogenesis of T2DM, and some studies indicate that genetic polymorphisms have critical roles in the etiology of T2DM [4,5]. Methylenetetrahydrofolate reductase (MTHFR) is a critical enzyme involved in folate metabolism, which converts 5, 10-methylene tetrahydrofolate to 5-methyl tetrahydrofolate. Mice deficient in MTHFR have reduced S-adenosylmethionine and increased S-adenosylhomocysteine, show hyperhomocysteinemia and global DNA hypomethylation [6]. The MTHFR C677T polymorphism is the most important genetic variation, which causes hyperhomocysteinemia [7]. The C677T polymorphism is a C to T transition at base pair 677, which will lead to the amino acid transition from Ala to Val and is associated with reduction of MTHFR activity. The variation of MTHFR C677T polymorphism may decrease enzyme activity by 65% and increase plasma total homocysteine levels particularly in the conditions of low dietary folate [8]. Some studies suggested that elevated plasma total homocysteine was associated with insulin resistance, which...
was the major cause of T2DM [3,9,10]. Homocysteine exposure can decline the viability of insulin-secreting cells, reduce glucokinase phosphorolyzing ability, and diminish insulin secretory responsiveness, lead to cell death [11]. Therefore, the MTHFR C677T polymorphism has been widely considered a genetic candidate for T2DM [12].

In recent years, numerous studies had demonstrated an association between MTHFR C677T polymorphism and T2DM. However, the results were not consistent [13–19]. A systematic review on Arab ethnicity found that MTHFR C677T polymorphism was significantly associated with T2DM [14], but another systematic review found that there was no association between MTHFR C677T polymorphism and T2DM around the world, similar results were repeated for ethnic group (Asian, Caucasian, African) [13]. Furthermore, previous studies also showed that the prevalence of MTHFR C677T polymorphism varies in different geographical regions and ethnic groups [20], and people from different ethnic groups had different genetic susceptibility with T2DM[21]. These findings suggested the study on the association between MTHFR C677T polymorphism and T2DM should be based on one single ethnical population to provide a precise estimation. Therefore, we conducted a meta-analysis to evaluate the association between MTHFR C677T polymorphism and T2DM specifically in Chinese Han population.

Materials and Methods

Search Strategy and Identification of Relevant Studies

A search strategy was carried out in multiple electronic databases (Cochrane, EMBASE, PubMed, CQVIP, CNKI (China National Knowledge Infrastructure), CBM (China Biological Medicine Database), and Wanfang databases) before December 2013. The following subject terms were used for searching by ‘methyltetrahydrofolate reductase or MTHFR’, ‘gene or polymorphism or genetic polymorphism’, ‘Chinese or China’, and ‘diabetes or mellitus or diabetes mellitus or T2DM’. The papers were limited on humans and published in English or Chinese. In order to further identify any additional relevant data, we carefully searched the references in the selected studies.

Data Extraction

The data from all included studies were independently extracted by two authors (BZ and XW) according to a standard protocol. If the third author (LL) resolved the disagreement between two authors. We excluded the studies that did not follow the inclusion criteria, that lacked of sufficient data, or that considered duplicated articles. If we found the same data in different studies, we used the data only one time. The following items were extracted from all included studies: the first author’s name, year of publication, region (province), total number of study, gender, genotypic distribution, allele frequencies.

Inclusion Criteria

We set the inclusion criteria according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement[22]. a) Give information on the criteria and methods for selection. b) Describe laboratory methods, including source and storage of DNA, genotyping methods and platforms. c) Clearly define genetic variants using a widely used nomenclature system. d) State whether Hardy-Weinberg equilibrium was considered and, if so, how. e) Report numbers in each genotype category.

Statistical Analysis

STATA 11.0 software (StatCorp, College Station, TX, USA) was used to perform the meta-analysis. We used five genetic models, which included dominant (TT+CT vs. CC), recessive (TT vs. CC+CT), homozygous (TT vs. CC), heterozygous (CT vs. CC), and additive (T vs. C) models. The odds ratios (ORs) and their 95% confidence intervals (95%CIs) were used to evaluate the association between MTHFR C677T polymorphism and T2DM. We used Chi-square-based Q-tests to assess the heterogeneity between the individual studies [23]. If there was a significant heterogeneity among the individual studies, the random-effect model (DerSimonian and Laird method) was carried out to assess the pooled OR. Otherwise, the fixed-effect model (the Mantel–Haenszel method) was carried out.

We also conducted meta-regression and subgroup analysis to explore the sources of heterogeneity. To assess the reliability of the outcomes in the meta-analysis, a sensitivity analysis was performed by excluding one study at a time. Publication bias was assessed using the Egger’s test [24]. We also conducted the Duval and Tweedie nonparametric “trim and fill” procedure to further assess the effect of publication bias in each genetic model [25]. Hardy-Weinbery equilibrium (HWE) in controls was assessed by the goodness-of-fit x² test in each included study. The significance set at the P<0.05 in all analyses.

Results

Characteristics of Including Studies

Figure 1 showed the procedure by which article was selected. A comprehensive search yielded 103 articles. After the removal of duplicated literatures and articles containing unspecific data that did not meet our criteria, a total of 29 studies was finally identified in our meta-analysis. Table 1 illustrated the characteristics of all the included studies in this meta-analysis. The data contained 4656 T2DM cases and 2127 healthy controls [15–17,26–51]. The provinces of 29 studies included Heilongjiang, Beijing, Gansu, Shanxi, Zhejiang, Shanghai, Neimenggu, Guizhou, Tianjin, Guangdong, Hubei, Shandong, Jiangsu, Hebei, and Jilin. Except for 7 studies, the distribution of genotypes in the controls was consistent with HWE.

Results of the Overall Meta-Analysis

Table 2 showed the ORs with their 95% CIs for the association between MTHFR C677T polymorphism and T2DM in the recessive, dominant, homozygous, heterozygous, and additive genetic model. There was a significant association between MTHFR C677T polymorphism and T2DM under dominant model (OR: 1.93, 95% CI: 1.74–2.14), recessive (OR: 1.48, 95% CI: 1.21–1.80), homozygous (OR: 1.89, 95% CI: 1.47–2.42), heterozygous (OR: 1.58, 95% CI: 1.33–1.87), and additive (OR: 1.46, 95% CI: 1.28–1.68) genetic model in a random-effects model.

Meta-Regression and Stratified Analysis

There was a significant heterogeneity in each genetic model (Table 2), we used meta-regression to explore the sources of heterogeneity in each genetic model separately. Similarly, heterogeneity can be explained by the number of the control group in each genetic model (Table 3). In the subgroup analysis based on region, we divided the included studies into two major group, the northern and the southern [20]. The northern group included Beijing, Gansu, Heilongjiang, Hebei, Tianjin, Jilin, Neimenggu, Shandong, Shanxi, and the southern group included Hubei, Jiangsu, Shanghai, Guizhou, Zhejiang, and Guangdong. There was a
significant association between MTHFR C677T polymorphism and T2DM under each genetic model in both groups. Likewise, we performed subgroup analysis on studies in which the MTHFR alleles in the control group were in HWE and on studies in which they were not in HWE, there was a significant association between MTHFR C677T polymorphism and T2DM under each genetic model in both groups (Table 2).

Sensitivity Analysis
Table 4 showed the pooled ORs and their 95% CIs of sensitivity analysis by excluding one study at a time in each genetic model, the results in the five genetic models indicated that the overall result was dependable.

Assessment of Publication Bias
As shown in table 2, Egger’s test suggested no publication bias in dominant and heterozygous, but not in recessive, homozygous and
| Number | Author | Year | Region | Total number of study | Male (%) | Genotypic distribution | Allele frequencies | HWE |
|--------|--------|------|--------|------------------------|----------|------------------------|-------------------|-----|
|        |        |      |        |                        |          | CC case | CT case | TT case | C case | C control | T case | T control |        |
| 1      | Sun, Liang | 2013 | Beijing | 549                  | 51.37    | 180 30  | 243 42  | 48 6    | 603 102  | 339 54   | Yes      |
| 2      | Mei, Qingbu | 2012 | Heilongjiang | 215          | No       | 17 17    | 51 70   | 23 37   | 85 104   | 97 144   | Yes      |
| 3      | Dai, Hongshuang | 2012 | Heilongjiang | 180           | 55.00    | 51 31    | 54 27   | 15 2    | 156 89   | 84 31    | Yes      |
| 4      | Chen, Arong | 2010 | Gansu | 219                  | 59.62    | 57 34    | 74 17   | 33 4    | 188 85   | 128 25   | Yes      |
| 5      | Zhang, Qiaohui | 2009 | Shanxi | 278                  | 60.79    | 66 26    | 94 17   | 66 9    | 226 69   | 226 35   | Yes      |
| 6      | Qiu, Yi | 2009 | Zhejiang | 299               | 54.85    | 83 53    | 68 29   | 48 18   | 234 135  | 164 65   | No       |
| 7      | Hu, Ling | 2009 | Shanxi | 211                | 62.56    | 47 26    | 63 17   | 49 9    | 157 69   | 163 35   | Yes      |
| 8      | Wen, Jie | 2008 | Shanghai | 211              | 52.13    | 43 27    | 82 25   | 29 5    | 168 79   | 140 35   | Yes      |
| 9      | Luo, Dan | 2008 | Beijing | 226             | 47.79    | 59 43    | 63 31   | 19 11   | 181 117  | 101 53   | Yes      |
| 10     | Chen, Ping | 2008 | Heilongjiang | 240           | No       | 19 14    | 70 73   | 27 37   | 108 101  | 124 147  | No       |
| 11     | Zhang, Chunyu | 2007 | Neimenggu | 141            | 51.77    | 28 34    | 29 19   | 19 12   | 85 87    | 67 43    | No       |
| 12     | Luo, Dan | 2007 | Beijing | 274             | 52.64    | 55 42    | 102 35  | 26 14   | 222 119  | 154 63   | Yes      |
| 13     | Yue, Hong | 2006 | Shanxi | 282                | 53.09    | 66 17    | 131 11  | 55 2    | 263 45   | 241 15   | Yes      |
| 14     | Xiao, Yan | 2006 | Guizhou | 146            | No       | 16 47    | 53 25   | 4 1     | 85 119   | 61 27    | Yes      |
| 15     | Sun, Ying | 2005 | Tianjin | 355             | 50.00    | 113 47   | 85 25   | 68 17   | 311 119  | 221 49   | No       |
| 16     | Shi, Chengjun | 2006 | Guangdong | 295           | No       | 108 68   | 60 34   | 18 7    | 276 170  | 96 48    | Yes      |
| 17     | Liang, Wenchang | 2005 | Zhejiang | 122             | No       | 33 17    | 34 18   | 15 5    | 100 52   | 64 28    | Yes      |
| 18     | Guo, Lixin | 2005 | Beijing | 288             | 57.29    | 60 58    | 51 34   | 50 35   | 171 150  | 151 104  | No       |
| 19     | Sun, Jiazhong, X | 2005 | Hubei | 342         | 67.25    | 101 63   | 78 31   | 49 20   | 280 57   | 176 71   | No       |
| 20     | Zhou, Jun | 2004 | Heilongjiang | 208           | No       | 16 8     | 78 31   | 45 30   | 110 47   | 168 91   | Yes      |
| 21     | Sun, Le | 2004 | Shandong | 155            | 47.44    | 27 29    | 52 18   | 27 2    | 106 75   | 106 24   | Yes      |
| 22     | Mao, L | 2004 | Jiangsu | 122           | 46.92    | 35 18    | 37 18   | 11 3    | 107 70   | 59 24    | Yes      |
| 23     | Chen, Arong | 2004 | Gansu | 126                 | 64.29    | 24 21    | 45 9    | 22 5    | 93 51    | 89 19    | No       |
| 24     | Xu, Jinheng | 2003 | Hebei | 175              | 45.14    | 30 7     | 54 25   | 39 20   | 114 39   | 132 65   | Yes      |
| 25     | Zhang, Guodong | 2002 | Shanghai | 298            | No       | 56 40    | 108 49  | 34 11   | 220 129  | 176 71   | Yes      |
| 26     | Shi, Jieping | 2002 | Jilin | 106            | No       | 12 22    | 31 29   | 7 5     | 55 55    | 45 45    | Yes      |
| 27     | Yang, Guoqing | 2001 | Beijing | 288           | 53.61    | 57 26    | 113 28  | 56 8    | 227 80   | 225 44   | Yes      |
| 28     | Wang, Longqing | 2001 | Guangdong | 264           | 52.27    | 65 37    | 75 38   | 39 10   | 205 112  | 153 58   | Yes      |
| 29     | Hu, Sheng | 2001 | Hubei | 168            | 55.36    | 49 30    | 48 24   | 16 1    | 146 84   | 80 26    | Yes      |

HWE: Hardy-Weinbery equilibrium; a: The distribution of gender between case and control group is in balance; b: The distribution of age between case and control group is in balance; c: The distribution of BMI between case and control group is in balance.

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additive genetic model. Because of this, we used the trim and fill method, the pooled analysis incorporating the hypothetical studies continued to show a statistically significant association between MTHFR C677T polymorphism and T2DM under recessive (OR: 1.26, 95% CI: 1.02–1.54), homozygous (OR: 1.60, 95% CI: 1.23–2.08) and additive (OR: 1.29, 95% CI: 1.12–1.49) genetic model.

**Discussion**

This current study, to our knowledge, was the first to use a meta-analysis to evaluate the association between MTHFR C677T polymorphism and T2DM specifically in China. There was a significant relationship between MTHFR C677T polymorphism and T2DM in each genetic model. The prevalence of MTHFR C677T polymorphism varies in the different regions in China [20], so we separated northern group from southern group, and still got similar results, which compared to the overall results. According to whether HWE in control, we also found that there was a significant association between MTHFR C677T polymorphism and T2DM in each genetic model. Sensitivity analysis indicated there was no significant change on the overall results by removing one study in each turn. Egger's test suggested publication bias in recessive, homozygous and additive genetic model. The trim and fill analysis did not change the general results in the three genetic models (although the strength of the association was slightly attenuated), suggesting that the results of our analysis were credible. Based on the results of our meta-

| Genetic Model | Subgroup | Model for meta-analysis | OR(95% CI) | P for heterogeneity | I² (%) | P for Egger’s test |
|---------------|----------|-------------------------|------------|---------------------|--------|--------------------|
| Dominant      | overall  | R                       | 1.70(1.42–2.02) | 0.00 | 56.9 | 0.45 |
|               | Region   |                         |            |                     |        |                    |
|               | Southern China | R | 1.71(1.32,2.21) | 0.04 | 49.6 |            |
|               | Northern China | R | 1.68(1.32,2.14) | 0.00 | 61.9 |            |
|               | HWE      |                         |            |                     |        |                    |
|               | Yes      | R                       | 1.73(1.39,2.15) | 0.00 | 60.5 |            |
|               | No       | F                       | 1.57(1.28,1.93) | 0.07 | 47.8 |            |
| Recessive     | overall  | R                       | 1.48(1.21–1.80) | 0.02 | 37.7 | 0.00 |
|               | Region   |                         |            |                     |        |                    |
|               | Southern China | F | 1.70(1.29–2.23) | 0.81 | 0.00 |            |
|               | Northern China | R | 1.39(1.07–1.81) | 0.01 | 50.4 |            |
|               | HWE      |                         |            |                     |        |                    |
|               | Yes      | R                       | 1.61(1.23–2.09) | 0.01 | 44.3 |            |
|               | No       | F                       | 1.28(1.00–1.63) | 0.34 | 11.6 |            |
| Homozygous    | overall  | R                       | 1.89(1.47–2.42) | 0.00 | 50.0 | 0.01 |
|               | Region   |                         |            |                     |        |                    |
|               | Southern China | F | 2.07(1.56,2.76) | 0.60 | 0.00 |            |
|               | Northern China | R | 1.81(1.28,2.56) | 0.00 | 62.1 |            |
|               | HWE      |                         |            |                     |        |                    |
|               | Yes      | R                       | 2.13(1.53,2.95) | 0.00 | 53.2 |            |
|               | No       | F                       | 1.51(1.16,1.96) | 0.18 | 32.6 |            |
| Heterozygous  | overall  | R                       | 1.58(1.33–1.87) | 0.00 | 46.4 | 0.33 |
|               | Region   |                         |            |                     |        |                    |
|               | Southern China | R | 1.57(1.18,2.08) | 0.03 | 52.3 |            |
|               | Northern China | R | 1.58(1.28,1.97) | 0.02 | 46.0 |            |
|               | HWE      |                         |            |                     |        |                    |
|               | Yes      | R                       | 1.59(1.30,1.95) | 0.00 | 51.1 |            |
|               | No       | F                       | 1.52(1.20,1.92) | 0.16 | 35.1 |            |
| Additive      | overall  | R                       | 1.46(1.28–1.68) | 0.00 | 64.5 | 0.01 |
|               | Region   |                         |            |                     |        |                    |
|               | Southern China | R | 1.53(1.34,1.75) | 0.29 | 16.6 |            |
|               | Northern China | R | 1.42(1.17,1.72) | 0.00 | 72.7 |            |
|               | HWE      |                         |            |                     |        |                    |
|               | Yes      | R                       | 1.48(1.26,1.75) | 0.00 | 66.9 |            |
|               | No       | R                       | 1.41(1.11,1.78) | 0.02 | 64.5 |            |

OR: odds ratio; R: random-effects model; F: fix-effects model. HWE: Hardy-Weinbery equilibrium. doi:10.1371/journal.pone.0102443.t002
As an essential intermediate, homocysteine plays an important role between folate and activated methyl cycle, which is involved in the transfer of activated methyl groups from tetrahydrofolate to S-adenosylmethionine [52]. The methyl cycle has effects on global and gene promoter-specific DNA methylation in regulating gene expression [53,54]. Some studies suggested that homocysteine exposure had adverse effects on beta cell glucose metabolism and cell viability, and impaired insulin secretory function [55]. There was a significant association between homocysteine level and insulin resistance [9,56]. Due to its biological relevance and its association with metabolic disorders, homocysteine metabolism is an important candidate pathway for T2DM. The C677T variant of MTHFR plays an important role on homocysteine metabolism [57]. The homozygous 677TT and heterozygous 677CT genotypes have decreased 70% and 35% in the enzyme activity of MTHFR respectively, compared to the 677CC genotype [58]. Individuals with the homozygous 677TT genotype have higher plasma homocysteine and lower plasma folate levels than those with 677CC genotype [59]. MTHFR C677T polymorphism has also been reported to be associated with type 2 diabetes, and its complications [17,30,31,37,60].

In 2013, Khalid et al. found that there was a significant association between MTHFR C677T polymorphism and T2DM in Arab population [14], and Zhong et al. also conducted a meta-analysis of the relationship between MTHFR C677T polymorphism and T2DM, and concluded that there was no association between MTHFR C677T polymorphism and T2DM, regardless of the ethnicity of the patient or the presence of serious DM-related complications [13]. Our meta-analysis showed a significant relationship between MTHFR C677T polymorphism and T2DM under five genetic models in Chinese Han population. The results in our meta-analysis were similar to Khalid’s study, and different from Zhong’s study. There are several reasons for this difference. First, Zhong et al. conducted the meta-analysis all over the world, only loosely classified the study population as African, Asian, or Caucasian. Because MTHFR C677T polymorphism distribution varies among different ethnic groups, the relationship between

### Table 3. The results of meta-regression in the five genetic models.

| Genetic Model | Variables | P for meta-regression |
|---------------|-----------|-----------------------|
| Dominant      | year      | 0.521                 |
|               | total number of study | 0.175             |
|               | number of control     | 0.008                 |
|               | number of case        | 0.504                 |
|               | male (%)              | 0.152                 |
| Recessive     | year      | 0.534                 |
|               | total number of study | 0.738                 |
|               | number of control     | 0.013                 |
|               | number of case        | 0.530                 |
|               | male (%)              | 0.396                 |
| Homozygous    | year      | 0.479                 |
|               | total number of study | 0.373                 |
|               | number of control     | 0.003                 |
|               | number of case        | 0.995                 |
|               | male (%)              | 0.347                 |
| Heterozygous  | year      | 0.580                 |
|               | total number of study | 0.150                 |
|               | number of control     | 0.028                 |
|               | number of case        | 0.367                 |
|               | male (%)              | 0.152                 |
| Additive      | year      | 0.683                 |
|               | total number of study | 0.419                 |
|               | number of control     | 0.008                 |
|               | number of case        | 0.952                 |
|               | male (%)              | 0.116                 |

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analysis, we can speculate that MTHFR 677T allele might increase the risk of T2DM in the Chinese Han population.

As an essential intermediate, homocysteine plays an important role between folate and activated methyl cycle, which is involved in the transfer of activated methyl groups from tetrahydrofolate to S-adenosylmethionine [52]. The methyl cycle has effects on global and gene promoter-specific DNA methylation in regulating gene expression [53,54]. Some studies suggested that homocysteine exposure had adverse effects on beta cell glucose metabolism and cell viability, and impaired insulin secretory function [55]. There was a significant association between homocysteine level and insulin resistance [9,56]. Due to its biological relevance and its association with metabolic disorders, homocysteine metabolism is an important candidate pathway for T2DM. The C677T variant of MTHFR plays an important role on homocysteine metabolism [57]. The homozygous 677TT and heterozygous 677CT genotypes have decreased 70% and 35% in the enzyme activity of MTHFR respectively, compared to the 677CC genotype [58]. Individuals with the homozygous 677TT genotype have higher plasma homocysteine and lower plasma folate levels than those with 677CC genotype [59]. MTHFR C677T polymorphism has also been reported to be associated with type 2 diabetes, and its complications [17,30,31,37,60].
MTHFR C677T polymorphism and T2DM should be studied on a single ethnic group. Therefore, our study focused on the Chinese Han population to derive an accurate evaluation. Second, more than a third of included studies focused on the Chinese Han population in Zhong’s study, but he just conducted subgroup analysis in Asian population, did not further analyze the association in Chinese Han population. Third, Zhong’s study only included 16 studies on the Chinese Han population, while our study included 29 studies. We think the number of included studies for Zhong’s meta-analysis was inadequate, for example Sun et al., Qiu et al., they had suggested that ACE insertion/deletion (I/D) polymorphism may act synergistically with MTHFR C677T polymorphism to increase the risk of T2DM. Because of the limitations in our study, more large-scale studies were needed to assess the association between MTHFR C677T polymorphism and T2DM. And due to lack of necessary personal information in the included studies, we were unable to further perform subgroup analysis for the relevant influential factors (gender, age, BMI and so on). Second, all included studies were cross-sectional design and all the subjects came from hospitals, their results were not adjusted by the relevant influential factors. They could not infer cause-effect relationship.

In conclusion, our meta-analysis suggested there was a significant association between MTHFR C677T polymorphism and T2DM in the Chinese Han population, and indicated that MTHFR 677T allele might be a risk genetic factor in developing T2DM [62].

Supporting Information

Checklist S1  PRISMA Checklist of this systematic review. (DOC)
Checklist S2 Meta-analysis on Genetic Association Studies Checklist.
(DOCX)

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