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*Original Article*

# Meta-analysis of association between MTHFR C677T polymorphism and risk of myocardial infarction: evidence from forty-four case-control studies

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**Abstract:** The results from previous researches on the association between methylenetetrahydrofolate reductase (MTHFR) C677T polymorphism and risk of myocardial infarction (MI) remain conflicting. A meta-analysis was conducted to clarify the effect of MTHFR polymorphism on the risk of MI. An electronic search of PubMed, EMBASE, Cochrane library and China Knowledge Resource Integrated Database for papers on C677T polymorphism and risk of MI was performed. The software STATA (Version 13.0) was used for statistical analysis. Statistical heterogeneity, test of publication bias and sensitivity analysis was performed. Forty-four studies including 9,693 cases and 12,554 controls were included in this study. The MTHFR C677T polymorphism showed pooled odds ratios for the homozygote comparison (OR = 0.927, 95% CI [0.771, 1.114]), heterozygote comparison (OR = 0.977, 95% CI [0.917, 1.041]), dominant model (OR = 0.973, 95% CI [0.877, 1.080]), recessive model (OR = 0.944, 95% CI [0.805, 1.107]), and an additive model (OR = 0.972, 95% CI [0.888, 1.063]). In summary, the current meta-analysis, based on the most updated information, showed no significant association between MTHFR C677T polymorphism and MI risk. Future researches should investigate not only individual genes, but also gene–gene interactions, genetic-nutritional interactions, and other SNPs.

**Keywords:** MTHFR, C677T, polymorphism, myocardial infarction, meta-analysis

## Introduction

Despite improvements in lifestyle and the advancement of percutaneous coronary intervention, myocardial infarction (MI) remains the principal cause of death in many countries [1]. According to report from NHANES (National Health and Nutrition Examination Survey) 2003 to 2006 the overall prevalence of MI is 3.6% in US adults over the age of 20, with rates of 4.7% for male and 2.6% for female [2]. MI is a multifactorial disease with a complex pathogenesis where lifestyle, individual genetic background and environmental risk factors are involved. Previous studies have investigated the association of genetic variants in DNA repair pathways, lipid-related pathways, fibrinolytic system, renin angiotensin aldosterone system, nitric oxide synthase and methylenetetrahydrofolate reductase with MI risk [3-8].

Numerous studies have reported that hyperhomocysteinemia is an independent risk factor for cardiovascular diseases (CVD) and MI and that elevated total plasma homocysteine level has a negative effect on prognosis [9-11]. Previous experimental evidence shows that homocysteine (Hcy)-induced CVD was associated with endothelial dysfunction and injury followed by platelet activation and thrombus formation [12, 13]. The enzyme MTHFR plays a critical role in the folate metabolism pathway, regulates the intracellular folate pool for synthesis and methylation of DNA and reduces $5^1$,$10^1$-methylenetetrahydrofolate to $5^1$-methylenetetrahydrofolate, the latter being the methyl donor for the re-methylation of Hcy to methionine [14, 15]. The MTHFR gene is located on chromosome 1 at the end of the short arm (1p36.6) and is 2.2 kb in length with a total of 11 exons [16]. Previous researches have demonstrated that

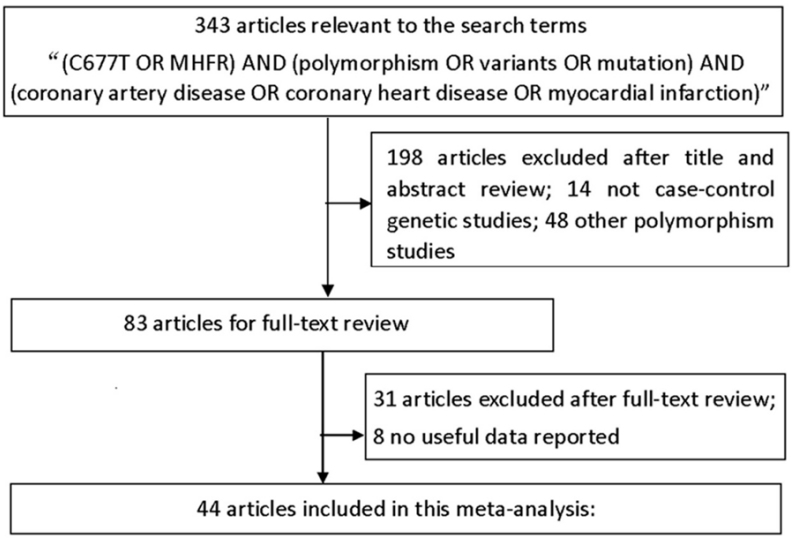


**Figure 1.** Flow diagram of search strategy and study selection.

low-level expression of MTHFR gene was often associated with an increase in plasma tHcy concentrations [17]. The C-to-T transition at nucleotide 677 in exon 4 is a point mutation that converts a cytosine (C) to a thymine (T), resulting in an amino acid substitution of alanine to valine, which can decrease the thermal stability and lead a 50% reduction of MTHFR enzyme activity, an increase of plasma homocysteine concentration and a decrease of plasma folic acid concentration [18].

Numberous studies have reported the association between the MTHFR gene C677T polymorphism and risk of MI, but the results remain controversial. Considering the relatively small sample size in each of the published studies, a meta-analysis of forty-four studies including 9,693 cases and 12,554 controls was conducted to clarify the effect of MTHFR polymorphism on the risk of MI.

## Materials and methods

### *Search strategy*

We performed this meta-analysis following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) criteria [19]. We sought relevant studies that had been published before January 1, 2015 and reported on associations of MTHFR gene C677T polymorphism and risk of MI. Computer searches of PubMed, EMBASE and China National Knowledge Infrastructure (CNKI) were searched using search terms as "(C677T OR MHFR) AND (polymorphism OR variants OR mutation) AND (coronary artery disease OR coronary heart disease OR myocardial infarction)". Only studies published in English or in Chinese language were included. Related reference articles were also searched to identify other relevant publications. Unpublished data and further information were also obtained from the corresponding authors.

### *Inclusion and exclusion criteria*

Any observational studies, regardless of sample size, were included, if they fulfilled the following criteria: 1) MTHFR C677T polymorphism and risk of MI; 2) myocardial infarction was defined by World Health Organization criteria, or typical ECG changes/increased serum enzymes; 3) human case-control design; 4) studies that reported the frequency of the MTHFR C677T polymorphism as number of cancer cases and controls according to the three variant genotypes of either polymorphisms; and 5) published in English or Chinese.

The criteria for the exclusion of studies are as follows: 1) not related to the MTHFR C677T polymorphism and risk of MI; 2) not a primary case-control study; 3) no usable or sufficient genotype data reported; 4) case reports, letter to Editor, book chapters or reviews.

### *Data extraction*

Two investigators independently extracted the data from all qualified studies according to a standardized protocol listed above and the result was reviewed by a third investigator. Discrepancies were solved through discussion until agreement was reached. We extracted the following information: the first author's name, year of publication, the country in which the study was conducted, ethnicity, the source of control group evidence of Hardy-Weinberg equilibrium (HWE) in controls, the sample size, num-

**Table 1.** Characteristics of studies included in this meta-analysis

| Author | Year | Region | Ethnicity | Case | | | | Control | | | | Hardy Weinberg (P) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| MTHFR C677T | | | | Total | CC | CT | TT | Total | CC | CT | TT | |
| Shen et al., 2001 | 2001 | USA | Caucasian | 550 | 241 | 252 | 57 | 554 | 245 | 252 | 57 | 0.508 |
| Jeng et al., 2003 | 2003 | China | Asian | 59 | 36 | 22 | 1 | 232 | 123 | 95 | 14 | 0.438 |
| Siemianowicz et al., 2003 | 2003 | Poland | Caucasian | 146 | 38 | 60 | 48 | 44 | 18 | 20 | 6 | 0.906 |
| Heijmans et al., 2003 | 2003 | Netherlands | Caucasian | 44 | 23 | 17 | 4 | 793 | 399 | 329 | 65 | 0.806 |
| Shi et al., 2005 | 2005 | USA | Caucasian | 1051 | 483 | 468 | 100 | 1141 | 498 | 519 | 124 | 0.516 |
| Zhang et al., 2005 | 2005 | China | Asian | 505 | 120 | 230 | 155 | 500 | 160 | 231 | 109 | 0.138 |
| Shen et al., 2005 | 2005 | China | Asian | 116 | 33 | 65 | 18 | 111 | 53 | 42 | 16 | 0.117 |
| Zou et al., 2006 | 2006 | China | Asian | 100 | 24 | 52 | 24 | 100 | 39 | 48 | 13 | 0.767 |
| Jin et al., 2007 | 2007 | China | Asian | 100 | 24 | 52 | 24 | 100 | 39 | 48 | 13 | 0.767 |
| Suzuki et al., 2007 | 2007 | Japan | Asian | 515 | 182 | 256 | 77 | 1030 | 379 | 474 | 177 | 0.170 |
| Gemignani et al., 2007 | 2007 | European | Caucasian | 247 | 104 | 107 | 36 | 259 | 131 | 103 | 25 | 0.473 |
| Hung et al., 2007 | 2007 | France | Caucasian | 2169 | 1009 | 929 | 231 | 2803 | 1397 | 1147 | 259 | 0.288 |
| Liu et al., 2008 | 2008 | China | Asian | 500 | 157 | 245 | 98 | 424 | 149 | 265 | 10 | P < 0.05 |
| Liu et al., 2009 | 2009 | Taiwan | Asian | 358 | 205 | 124 | 29 | 716 | 362 | 291 | 63 | 0.679 |
| Yang et al., 2010 | 2010 | China | Asian | 120 | 49 | 52 | 19 | 165 | 62 | 75 | 28 | 0.516 |
| Yao et al., 2010 | 2010 | China | Asian | 93 | 27 | 46 | 20 | 106 | 36 | 51 | 19 | 0.899 |
| Kiyohara et al., 2011 | 2011 | Japan | Asian | 462 | 153 | 201 | 108 | 379 | 158 | 170 | 51 | 0.624 |
| Arslan et al., 2011 | 2011 | Turkey | Caucasian | 64 | 30 | 27 | 7 | 61 | 29 | 29 | 3 | 0.206 |
| Cui et al., 2011 | 2011 | China | Asian | 438 | 58 | 240 | 140 | 641 | 121 | 325 | 195 | 0.483 |
| Cheng et al., 2011 | 2011 | China | Asian | 178 | 49 | 58 | 71 | 180 | 47 | 88 | 45 | 0.767 |
| Cui et al., 2011 | 2011 | Korean | Asian | 3938 | 1361 | 1909 | 668 | 1700 | 540 | 862 | 298 | 0.148 |
| Cheng et al., 2012b | 2012 | China | Asian | 94 | 26 | 33 | 35 | 78 | 21 | 39 | 18 | 0.990 |
| Ma et al., 2012 | 2012 | China | Asian | 120 | 20 | 54 | 46 | 60 | 22 | 28 | 10 | 0.830 |
| Cavic et al., 2014 | 2014 | Serbia | Caucasian | 55 | 34 | 18 | 3 | 53 | 13 | 33 | 7 | 0.057 |
| Yilmaz et al., 2014 | 2014 | Turkey | Caucasian | 100 | 55 | 38 | 7 | 100 | 51 | 43 | 6 | 0.433 |
| Cai et al., 2014 | 2014 | China | Asian | 202 | 54 | 102 | 46 | 202 | 69 | 112 | 21 | P < 0.05 |
| MTHFR A1298C | | | | Total | AA | AC | CC | Total | AA | AC | CC | |
| Shen et al., 2001 | 2001 | USA | Caucasian | 550 | 261 | 246 | 43 | 554 | 265 | 249 | 40 | 0.072 |
| Siemianowicz et al., 2003 | 2003 | Poland | Caucasian | 146 | 32 | 76 | 38 | 44 | 12 | 24 | 8 | 0.507 |
| Shi et al., 2005 | 2005 | USA | Caucasian | 1051 | 480 | 462 | 109 | 1141 | 554 | 496 | 91 | 0.168 |
| Zhang et al., 2005 | 2005 | China | Asian | 505 | 355 | 141 | 9 | 500 | 345 | 150 | 5 | P < 0.05 |
| Shen et al., 2005 | 2005 | China | Asian | 114 | 71 | 41 | 2 | 109 | 69 | 34 | 6 | 0.509 |
| Jin et al., 2007 | 2007 | China | Asian | 100 | 70 | 28 | 2 | 100 | 68 | 30 | 2 | 0.528 |
| Suzuki et al., 2007 | 2007 | Japan | Asian | 512 | 341 | 149 | 22 | 1019 | 652 | 322 | 45 | 0.515 |
| Hung et al., 2007 | 2007 | France | Caucasian | 2209 | 1031 | 960 | 218 | 2865 | 1285 | 1268 | 312 | 0.976 |
| Liu et al., 2008 | 2008 | China | Asian | 500 | 341 | 141 | 18 | 517 | 364 | 142 | 11 | 0.509 |
| Liu et al., 2009 | 2009 | Taiwan | Asian | 358 | 228 | 115 | 15 | 716 | 467 | 226 | 23 | 0.491 |
| Kiyohara et al., 2011 | 2011 | Japan | Asian | 462 | 278 | 154 | 30 | 379 | 239 | 122 | 18 | 0.633 |
| Arslan et al., 2011 | 2011 | Turkey | Caucasian | 64 | 29 | 29 | 6 | 61 | 28 | 29 | 4 | 0.543 |
| Cai et al., 2014 | 2014 | China | Asian | 202 | 55 | 106 | 41 | 202 | 65 | 102 | 35 | 0.642 |

ber of cases and controls with the CC/CT/TT genotypes.

*Statistical analysis*

STATA software (Version 13.0) was used for all statistical analyses. Two-sided *P* values less than 0.05 were considered statistically significant. For the control groups for each study, the observed genotype frequencies of the MTHFR C677T polymorphism were evaluated for Hardy-Weinberg equilibrium (HWE; P < 0.05 was considered significant), and if the genotype distributions in the controls significantly deviated from HWE then the study was excluded from our sensitive analysis [20]. The strength of the

**Table 2.** Results of the overall meta-analysis

| MTHFR C677T | | | |
|---|---|---|---|
| Contrast | OR, 95% CI | Heterogeneity | Z and P |
| TT versus CC | 1.518, [1.220, 1.890] | chi-squared = 120.84 (d.f. = 25) P = 0.000, I-squared = 79.3% | Z = 3.74 P = 0.000 |
| CT versus CC | 1.053, [0.940, 1.179] | chi-squared = 65.32 (d.f. = 25) P = 0.000, I-squared = 61.7% | Z = 0.89 P = 0.372 |
| CT + TT versus CC | 1.143, [1.013, 1.291] | chi-squared = 86.41 (d.f. = 25) P = 0.000, I-squared = 71.1% | Z = 2.16 P = 0.031 |
| TT versus CT + CC | 1.435, [1.190, 1.730] | chi-squared = 108.37 (d.f. = 25) P = 0.000, I-squared = 76.9% | Z = 3.78 P = 0.000 |
| T versus C | 1.176, [1.066, 1.298] | chi-squared = 120.43 (d.f. = 25) P = 0.000, I-squared =79.2% | Z = 3.23 P = 0.001 |
| MTHFR A1298C | | | |
| Contrast | OR, 95% CI | Heterogeneity | Z and P |
| CC versus AA | 1.073, [0.943, 1.221] | chi-squared = 15.07 (d.f. = 12) P = 0.238, I-squared = 20.4% | Z = 1.07 P = 0.283 |
| AC versus AA | 0.992, [0.925, 1.064] | chi-squared = 4.96 (d.f. = 12) P = 0.959, I-squared = 0.0% | Z = 0.22 P = 0.829 |
| AC + CC versus AA | 1.004, [0.940, 1.074] | chi-squared = 8.12 (d.f. = 12) P = 0.775, I-squared = 0.0% | Z = 0.13 P = 0.898 |
| CC versus AC + AA | 1.073, [0.948, 1.214] | chi-squared = 13.01 (d.f. = 12) P = 0.368, I-squared = 7.7% | Z = 1.12 P = 0.263 |
| C versus A | 1.015, [0.964, 1.070] | chi-squared = 12.17 (d.f. = 12) P = 0.432, I-squared = 1.4% | Z = 0.57 P = 0.565 |

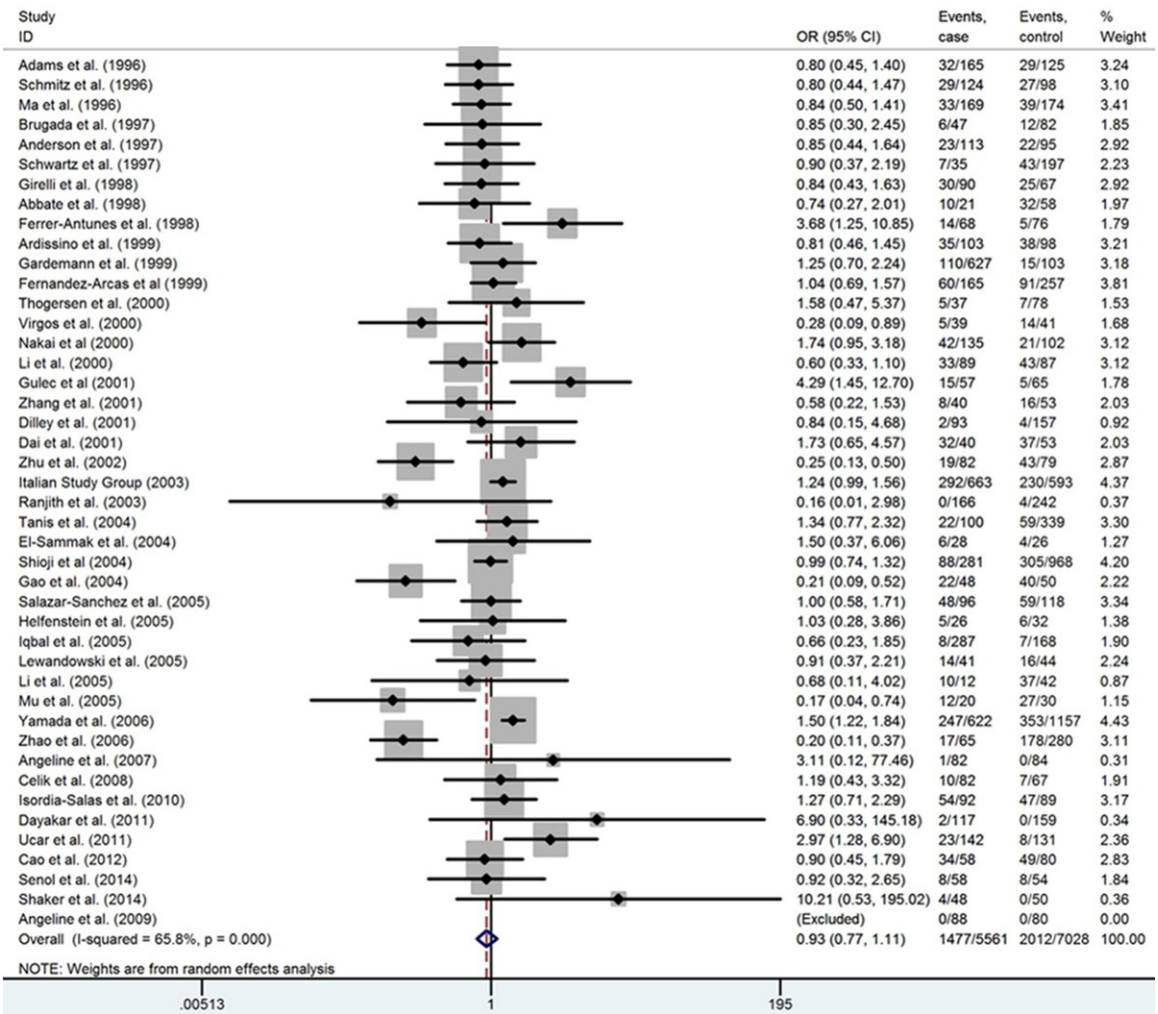


**Figure 2.** Random effect forest plot of homozygote model (TT vs. CC) of MTHFR C677T Polymorphism.

association between the MTHFR C677T polymorphism and MI risk was assessed using the odds ratios (ORs) with 95% 95% confidence interval (CI). The pooled ORs were calculated for the homozygote model, heterozygote model, dominant model, recessive model, and an addi-

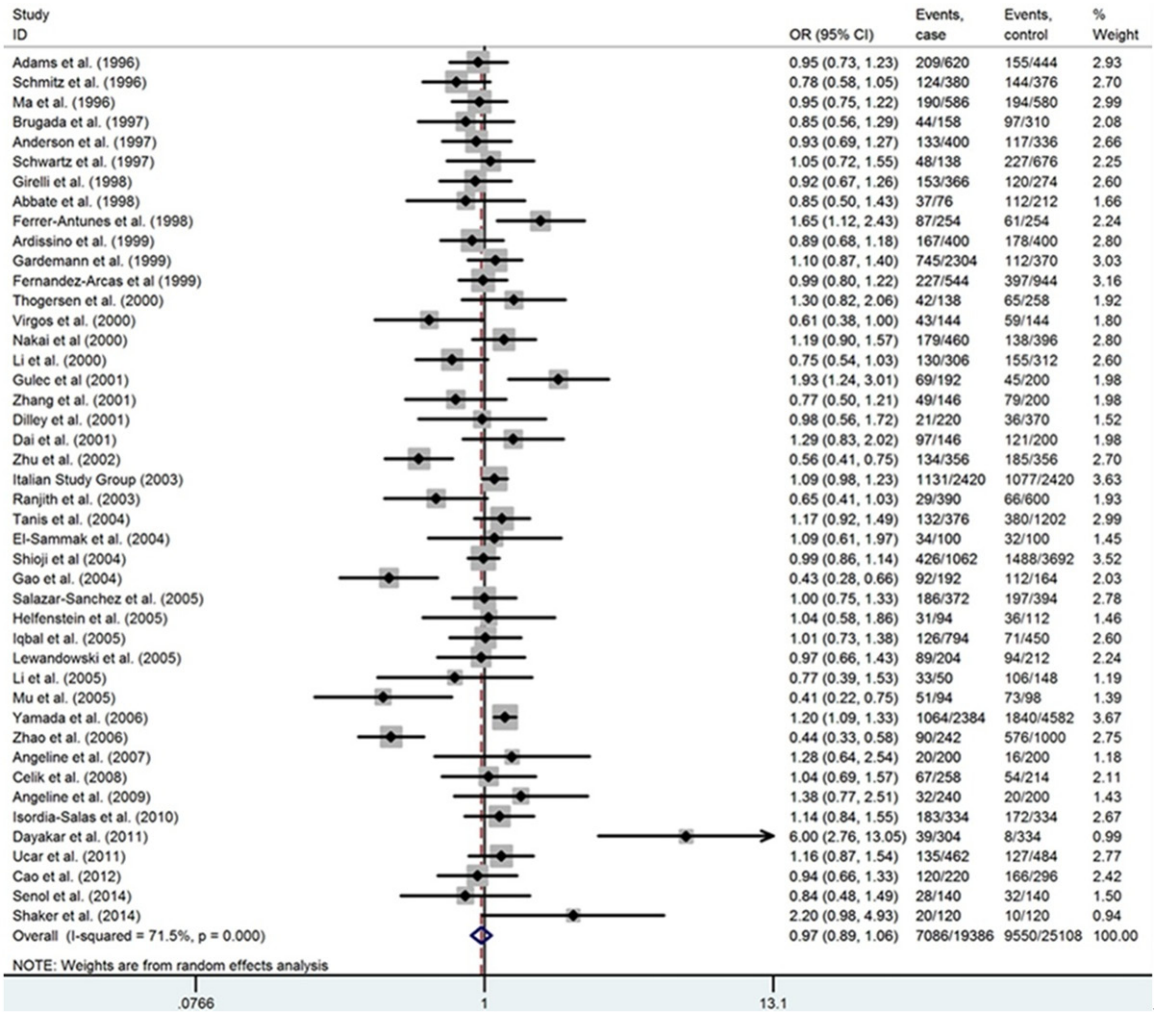


**Figure 3.** Random effect forest plot of additive model (T vs. C) of MTHFR C677T Polymorphism.

tive model [21]. Cochran's Q-statistic and the $I^2$ metric were conducted to assess heterogeneity between studies, with values < 25% indicating low, 25-50% indicating moderate, and > 50% indicating high heterogeneity [22, 23]. If the heterogeneity test result returned P > 0.1, the pooled ORs were analyzed using the random-effects model [24], or else, the fixed effects model was used [25]. Sensitivity analyses were also performed after sequential removal of each study [26, 27]. Lastly, Begg's funnel plot and Egger's test were used to examine statistically any publication bias [28].

## Results

*Characteristics of the included studies*

In accordance with the inclusion criteria, forty-four case-control studies [29-72] with 9,693 cases and 12,554 controls were included based on the search criteria for risk of MI related to the MTHFR C677T polymorphism. The study inclusion and exclusion procedures are summarized in **Figure 1**. All of the forty-four studies were published between 1996 and 2014. Studies were conducted in three major ethnic populations, with one on African-Americans, sixteen on Asians and twenty-seven on Caucasians. No overlap occurred between the studies based on case or control participation. The genotype distributions in the controls for all studies were consistent with the Hardy-Weinberg equilibrium [73], except for four studies [62, 64, 69, 71]. The characteristics of all included studies are summarized in **Table 1**.

*Results of the overall meta-analysis*

The main results of meta-analysis on the association between the MTHFR C677T polymorphism and MI are listed in **Table 2**. The MTHFR

**Table 3.** Sub-group analysis stratified by ethnicity

| MTHFR C677T | | | | | | |
|---|---|---|---|---|---|---|
| Ethnicity | Comparisons | TT versus CC (OR, 95% CI, Z, P) | CT versus CC (OR, 95% CI, Z, P) | CT + TT versus CC (OR, 95% CI, Z, P) | TT versus CT + CC (OR, 95% CI, Z, P) | T versus C (OR, 95% CI, Z, P) |
| Caucasian | 9 | 1.170, [0.859, 1.593]<br>Z = 1.00, P = 0.319 | 0.978, [0.815, 1.174]<br>Z = 0.24, P = 0.813 | 1.005, [0.822, 1.229]<br>Z = 0.05, P = 0.960 | 1.146, [0.910, 1.444]<br>Z = 1.16, P = 0.247 | 1.043, [0.888, 1.224]<br>Z = 0.51, P = 0.610 |
| Asian | 17 | 1.722, [1.271, 2.334]<br>Z = 3.51, P = 0.000 | 1.107, [0.948, 1.292]<br>Z = 1.28, P = 0.201 | 1.235, [1.046, 1.458]<br>Z = 2.49, P = 0.013 | 1.572, [1.215, 2.033]<br>Z = 3.45, P = 0.001 | 1.251, [1.096, 1.429]<br>Z = 3.31, P = 0.001 |
| Overall | 26 | 1.518, [1.220, 1.890]<br>Z = 3.74, P = 0.000 | 1.053, [0.940, 1.179]<br>Z = 0.89, P = 0.372 | 1.143, [1.013, 1.291]<br>Z = 2.16, P = 0.031 | 1.435, [1.190, 1.730]<br>Z = 3.78, P = 0.000 | 1.176, [1.066, 1.298]<br>Z = 3.23, P = 0.001 |
| MTHFR A1298C | | | | | | |
| Ethnicity | Comparisons | CC versus AA (OR, 95% CI, Z, P) | AC versus AA (OR, 95% CI, Z, P) | AC + CC versus AA (OR, 95% CI, Z, P) | CC versus AC + AA (OR, 95% CI, Z, P) | C versus A (OR, 95% CI, Z, P) |
| Caucasian | 5 | 1.021, [0.879, 1.185]<br>Z = 0.27, P = 0.789 | 0.987, [0.903, 1.079]<br>Z = 0.29, P = 0.774 | 0.993, [0.912, 1.081]<br>Z = 0.17, P = 0.865 | 1.030, [0.893, 1.187]<br>Z = 0.40, P = 0.686 | 1.002, [0.939, 1.068]<br>Z = 0.05, P = 0.957 |
| Asian | 8 | 1.247, [0.964, 1.612]<br>Z = 1.68, P = 0.092 | 1.001, [0.895, 1.119]<br>Z = 0.01, P = 0.990 | 1.023, [0.919, 1.139]<br>Z = 0.42, P = 0.674 | 1.215, [0.949, 1.556]<br>Z = 1.54, P = 0.123 | 1.043, [0.953, 1.141]<br>Z = 0.91, P = 0.361 |
| Overall | 13 | 1.073, [0.943, 1.221]<br>Z = 1.07, P = 0.283 | 0.992, [0.925, 1.064]<br>Z = 0.22, P = 0.829 | 1.004, [0.940, 1.074]<br>Z = 0.13, P = 0.898 | 1.073, [0.948, 1.214]<br>Z = 1.12, P = 0.263 | 1.015, [0.964, 1.070]<br>Z = 0.57, P = 0.565 |

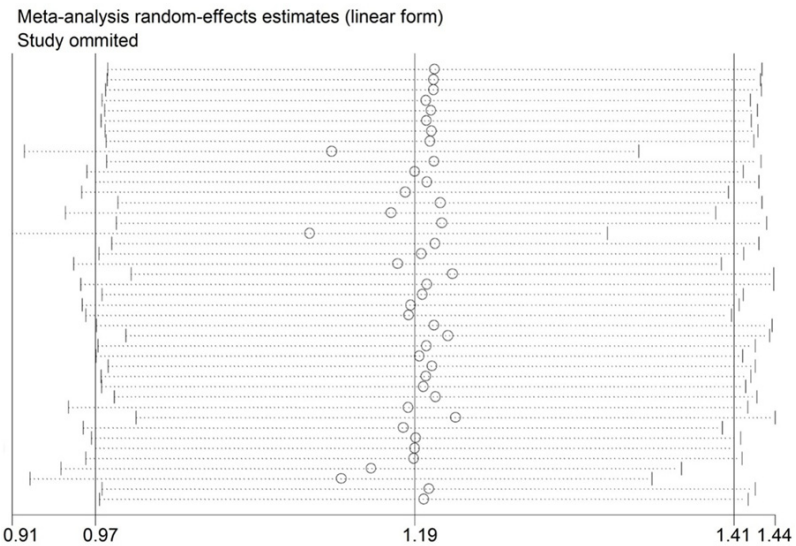


**Figure 4.** Sensitivity analysis.

C677T polymorphism showed pooled odds ratios for the homozygote comparison (TT versus CC: OR = 0.927, 95% CI [0.771, 1.114]; P = 0.419), heterozygote comparison (CT versus CC: OR = 0.977, 95% CI [0.917, 1.041]; P = 0.470), dominant model (CT + TT versus CC: OR = 0.973, 95% CI [0.877, 1.080]; P = 0.609), recessive model (TT versus CT + CC: OR = 0.944, 95% CI [0.805, 1.107]; P = 0.478), and an additive model (T versus C: OR = 0.972, 95% CI [0.888, 1.063]; P = 0.533) (**Figures 2** and **3**).

*Sub-group analysis*

We performed a sub-group analysis stratified by ethnicity. We found no significant association between the MTHFR C677T polymorphism and MI risk in Asian, Caucasian and African-American groups in any genetic models. In homozygote comparison (TT versus CC), the pooled OR was 0.656 (95% CI [0.428, 1.005]) for Asian population, 1.084 (95% CI [0.925, 1.271]) for Caucasianpopulation, 0.841 (95% CI [0.151, 4.681]) for African-American population. In recessive comparison (TT versus CT + CC), the pooled OR was 0.721 (95% CI [0.513, 1.014]) for Asian population, 1.091 (95% CI [0.940, 1.267]) for Caucasian population, 0.838 (95% CI [0.151, 4.652]) for African-American population. We also performed a sub-group analysis stratified by gender. No significant association between the MTHFR C677T polymorphism and MI risk was found in Mixed, Male or Female group. The main results of sub-group analysis are summarized in **Table 3**.

*Test for heterogeneity*

There was a significant heterogeneity: for homozygote comparison (TT versus CC), chi-squared = 122.84 (d.f. = 42), P = 0.000, I-squared = 65.8%; for recessive model (TT versus CT + CC), chi-squared = 117.26 (d.f. = 42), P = 0.000, I-squared = 64.2%. We assessed the source of heterogeneity by region, publication year, and sample size. However, we did not observe any sources that contributed to the substantial heterogeneity.

*Sensitivity analysis*

We performed a sensitivity analysis to ascertain the primary origin of the heterogeneity. Through sensitivity analysis, the present study showed that no individual study had remarkable effect on the pooled ORs (**Figure 4**).

*Publication bias*

Funnel plot was used to assess publication bias (**Figure 5**). Begg's test and Egger's test were performed to evaluate funnel plot symmetry statistically. The results showed no publication bias: Begg's test: Pr > |z| = 0.061; Egger's test: P > |t| = 0.588.

## Discussion

Myocardial infarction (MI) was regarded as a polygenic disease with high mortality rate that results from the mutual action of environmental and genetic factors [74]. Previous genome association and candidate gene studies have been performed to identify MI susceptible genes and help susceptible individuals prevent the development of MI [75, 76]. Several studies have reported that homocysteine level was significantly higher in acute MI in patients without any risk factors and were considered low risk according to the Framingham risk score [77, 78]. Their results support the hypothesis that homocysteine level may be an independent risk factor for coronary artery disease. Hagar performed a study which aimed to assess the effect of folic acid and Vitamin B (12) supplementation on isoprenaline-induced myocardial

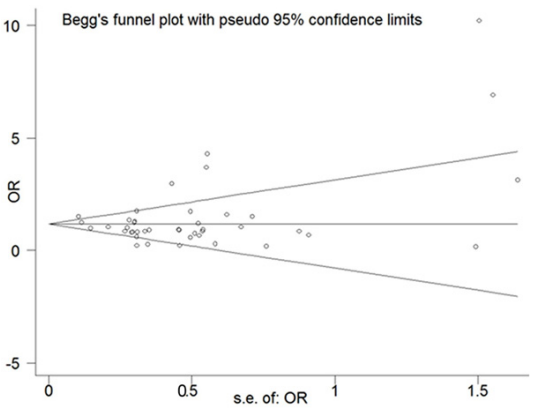


**Figure 5.** Test for publication bias.

infarction in hyperhomocysteinemic rats and the results suggested that Hhcy aggravates MI via oxidative stress mechanisms and that lowering homocysteinemia level with folic acid and Vitamin B (12) can ameliorate the detrimental effects of hyperhomocysteinemia and may reduce the risk of MI [79].

The enzyme MTHFR plays a critical role in the folate metabolism pathway. Adams et al. first examined the association between the MTHFR gene polymorphisms and the risk of MI [29]. After that, a number of case-control studies were conducted but the results remain controversial. Small sample size, various ethnic group, diet, environment and methodologies might be responsible for the discrepancy. Chao et al. performed a meta-analysis based on 30 case-control studies in 2011 (most of their included studies were before 2008) and concluded that the MTHFR C677T polymorphism was associated with risk of MI in young or middle-aged Caucasians [80]. Considering a series of novel studies have been published after that, an updated meta-analysis based on 44 case-control studies was conducted by us. The current meta-analysis, based on the most updated information,showed no significant association between MTHFR C677T polymorphism and MI risk.

We performed a sub-group analysis stratified by ethnicity and a sub-group analysis stratified by gender. However, we didn't find any significant association between MTHFR C677T polymorphism and MI risk in sub-groups in any genetic models. We observed that there was a significant heterogeneity, but sensitivity analysis did not show any single study strongly affecting the combined results. Begg's test and Egger's test showed no publication bias. By means of meta-analysis, a statistical method for combining the results from independent studies, we drew a more reliable conclusion on the influence of MTHFR C677T polymorphism on MI risk. However, MI is a "multi-factorial" result, with many factors, genetic and/or environmental. Future researches should investigate not only individual genes, but also gene-gene interactions, genetic-nutritional interactions, and other SNPs [81-83].

Two potential limitations of this meta-analysis should be discussed: 1) although the funnel plot and Begg's test showed no publication bias, selection bias may have occurred since only studies in English or Chinese were selected; 2) there was a significant heterogeneity; Despite the limitations listed above, our meta-analysis has some clear advantages: 1) this is the meta-analysis with a maximum sample size up to date; 2) we performed a sub-group analysis stratified by ethnicity and a sub-group analysis stratified by gender; 3) sensitivity analysis showed no individual study had remarkable effect on the pooled results; 4) the well-designed search and selection method significantly increased the statistical power of this meta-analysis; 5) no publication bias was detected, indicating that our pooled results are likely to be reliable.

In summary, the current meta-analysis, based on the most updated information, showed no significant association between MTHFR C677T polymorphism and MI risk. Future researches should investigate not only individual genes, but also gene-gene interactions, genetic-nutritional interactions, and other SNPs.

## Disclosure of conflict of interest

None.

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