Available online at www.sciencedirect.com

Metabolism

www.metabolismjournal.com

Meta-analysis

Association between methylenetetrahydrofolate reductase (MTHFR) C677T/A1298C polymorphisms and essential hypertension: A systematic review and meta-analysis

Yi-Le Wu[a,1], Cai-Yun Hu[a,1], Shan-Shan Lu[a], Feng-Feng Gong[a], Fang Feng[a], Zhen-Zhong Qian[a], Xiu-Xiu Ding[b], Hui-Yun Yang[a], Ye-Huan Sun[a,c,*]

[a] Department of Epidemiology and Health Statistics, School of Public Health, Anhui Medical University, No. 81 Meishan Road, Hefei 230032, Anhui, China

[b] Department of Maternal, Child and Adolescent Health, School of Public Health, Anhui Medical University, No. 81 MeiShan Road, Hefei 230032, Anhui, China

[c] Centre for Evidence-Based Practice, Anhui Medical University, No. 81 Meishan Road, Hefei 230032, Anhui, China

ARTICLE INFO

Article history:
Received 10 April 2014
Accepted 1 October 2014

Keywords:
Hypertension
Methylenetetrahydrofolate reductase
MTHFR
Polymorphism
Meta-analysis

ABSTRACT

Objective. Many studies have investigated the role of 5,10-methylenetetrahydrofolate reductase gene (MTHFR) C677T/A1298C polymorphisms in essential hypertension (EH), but results are inconclusive. The purpose of this meta-analysis was to clarify the effects of MTHFR C677T/A1298C polymorphisms on the risk of EH.

Methods. Electronic databases were searched to identify relevant studies published until January 2014. Data were extracted by two independent authors. Odds ratios (ORs) with 95% confidence intervals (CIs) were used to assess the association between MTHFR C677T/A1298C polymorphisms and the risk of EH using random effect models or fixed effect models. Finally, 30 studies with 5207 cases and 5383 controls were included for C677T polymorphism and 6 studies with 1009 cases and 994 controls were included for A1298C polymorphism.

Results. Meta-analysis results indicated that MTHFR C677T polymorphism contributed to an increased risk of EH (for T vs. C: OR = 1.30, 95%CI = 1.18–1.43; for TT + CT vs. CC: OR = 1.34, 95%CI = 1.24–1.46; for TT vs. CC: OR = 1.62, 95%CI = 1.32–1.99; for TT vs. CT + CC: OR = 1.41, 95%CI = 1.26–1.59). However, no significant association was detected between MTHFR A1298C polymorphism and the risk of EH.

Conclusion. This meta-analysis supports that MTHFR C677T polymorphism plays a role in developing EH. MTHFR A1298C polymorphism may not be associated with an increased risk of EH. Further large and well-designed studies are warranted to confirm these findings.

Abbreviations: *MTHFR*, Methylenetetrahydrofolate reductase; *EH*, Essential hypertension; *Hcy*, Homocysteine; *ORs*, Odds ratios; *CIs*, Confidence intervals; *HWE*, Hardy–Weinberg equilibrium.

* *Corresponding author at:* Department of Epidemiology and Health Statistics, School of Public Health, Anhui Medical University, No. 81 Meishan Road, Hefei 230032, Anhui, China. Tel./fax: +86 551 65143334.
E-mail address: yhsun_ahmu_edu@yeah.net (Y.-H. Sun).

[1] Contributed equally to this work.

http://dx.doi.org/10.1016/j.metabol.2014.10.001
0026-0495/

1. Introduction

Hypertension is one of the leading death causes worldwide and the third cause of disability-adjusted life-years [1,2]. One pooled analysis reported that the overall prevalence of hypertension was estimated to be 26.4% (26.6% of men and 26.1% of women) among adults in the world in 2000 and the number would increase by about 60% to a total of 1.56 billion in 2025 [1]. Essential hypertension (EH) is a complex disease that is likely to result from the interaction of multiple genetic and environmental factors [3]. It was estimated that the genetic factors contributed to blood pressure variation ranging from 30% to 50% [4]. During recent decades, the candidate gene association study has been a commonly used method to identify the related risk genes of hypertension [5].

Methylenetetrahydrofolate reductase (MTHFR) is a crucial enzyme that catalyzes the conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, an important enzymatic process in folate metabolism and in remethylation of homocysteine (Hcy) into methionine. Two common single nucleotide polymorphisms, C677T and A1298C, are known to affect the enzyme function and have shown potential clinical significance. For the MTHFR C677T polymorphism, a C to T transition at nucleotide position 677 in exon 4 generates an alanine to valine change at amino acid 222. As a result, the homozygous MTHFR 677TT genotype possesses a thermolabile enzyme with reduced activity [6], which results in decreased folate concentration and enhanced plasma Hcy concentration [7,8]. Previous meta-analyses have indicated that MTHFR C677T polymorphism was associated with an increased risk of coronary artery disease [9] and diabetic nephropathy [10]. Similarly, another polymorphism in MTHFR, an A to C transversion at nucleotide 1298, results in an amino acid substitution of glutamic acid for alanine at codon 429, which may also reduce the enzyme activity to a lesser extent [11]. Hcy contributes to oxidative stress and endothelial damage [12], regarded as a risk factor for coronary artery disease [13,14]. Elevated plasma Hcy has been found in hypertensive patients and shown a positive association with blood pressure [15,16]. A 2-year, randomized, placebo-controlled trial [17] showed that individuals who were randomized to homocysteine-lowering treatment, would have a decrease in blood pressure. This may provide an evidence to support the association between Hcy and blood pressure.

Over the last two decades, a number of studies examined the association between MTHFR C677T/A1298C polymorphisms and EH risk among different populations. However, these results were controversial. With respect to MTHFR C677T polymorphism, a meta-analysis by Qian et al. [18] indicated that MTHFR C677T polymorphism was a risk factor of hypertension; however, the meta-analysis included all types of hypertension, rather than specially investigated EH. Furthermore, some new studies were included in the present meta-analysis, which made the conclusion more powerful than the aforementioned meta-analysis [18]. Regarding to MTHFR A1298C polymorphism, no meta-analysis on this issue has ever been conducted to date. Consequently, this meta-analysis was performed to more precisely estimate the potential effects of MTHFR C677T/A1298C polymorphisms on EH using all newly eligible studies. In these analyses, the effect modification by publication year and ethnicity was examined.

2. Materials and methods

2.1. Identification and selection of studies

Before the study, we consulted the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement (PRIMSA) [19].

A comprehensive literature search was independently performed by two investigators (Ding, Yang) for all potential studies related to MTHFR C677T/A1289C polymorphisms and EH published until January 2014 from PubMed, EMBASE, CBM (Chinese Biomedical Database), CNKI (Chinese National Knowledge Infrastructure), VIP (Chinese) Database and Wanfang (Chinese) Database. The following key words: ("Methylenetetrahydrofolate reductase" or "MTHFR" or "C677T" or "A1298C") and ("polymorphism" or 'variation' or 'mutations') and ("hypertension" or "essential hypertension" or "blood pressure" or "high blood pressure") or relevant Chinese technical terms were used to search for relevant studies. Furthermore, the reference lists of retrieved articles were also reviewed to identify additional eligible studies. When there were multiple publications from the same study sample, the one with the largest sample size was included to avoid double counting.

2.2. Inclusion and exclusion criteria

Eligible studies must meet the following inclusion criteria: (1) exploration of associations between MTHFR polymorphisms (including C677T or A1298C or both) and EH; (2) case–control studies; (3) providing complete information on genotype frequencies of MTHFR C677T and/or A1298C polymorphism(s) or sufficient data for calculating an odd ratio (OR) with 95% confidence interval (CI); (4) hypertension was defined as systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg or treatment with anti-hypertensive medication; (5) using healthy individuals as controls. The exclusion criteria were as follows: (1) a review, case report, editorial, or comment; (2) a duplicated study; (3) a study on secondary hypertension or with other serious diseases.

2.3. Data extraction

Two reviewers (Lu, Gong) independently extracted the following information from each study included: name of the first author, year of publication, origin of country, ethnicity, diagnostic criteria for EH, numbers of cases and controls, and distribution of genotypes in the case and control groups. Disagreements were resolved by consensus.

2.4. Statistical analysis

The strength of associations between MTHFR C677T/A1298C polymorphisms and EH was assessed by calculating the pooled ORs with 95% CIs. The pooled ORs were performed

for the allele model (T vs. C), the dominant model (TT + CT vs. CC), the homozygote model (TT vs. CC) and the recessive model (TT vs. CT + CC). Taking possible between-study heterogeneity into consideration, I^2 statistics were used to estimate the degree of heterogeneity among the studies. $I^2 > 50\%$ indicated an obvious between-study heterogeneity [20], and OR (95% CI) was calculated by the random effects model [21]; otherwise, the fixed effects model was used [22]. Hardy–Weinberg equilibrium (HWE) of the observed genotypes frequencies in control group of each reviewed study was examined by the Chi-square test. In addition, cumulative meta-analysis [23] was performed to evaluate whether the association changed over time. Meta-regression analysis was used to investigate effect modification by year of publication and ethnicity. Sensitivity analyses were performed for control samples not in HWE ($p < 0.05$) to assess the impact of these studies. Publication bias was detected by several methods. Asymmetry of the funnel plot indicated the possible publication bias. In addition, the Begg's test and Egger's test were also used [24]. All statistical analyses were conducted using Stata 9.0 (Stata Corporation, College Station, TX). A *P* value less than 0.05 was considered statistically significant.

3. Results

3.1. Characteristics of eligible studies

Based on our search strategy, 402 records were identified through our initial search. After removing the overlapping records and screening titles and abstracts, 93 records were considered potentially eligible and needed to further evaluate. Full texts of these 93 studies were achieved and reviewed thoroughly, and 61 of these were excluded. Finally, a total of 32 studies [25–56] were included in this meta-analysis. The process of study selection was summarized in the flow diagram (Fig. 1). Of the 32 studies, 26 studies only examined the C677T polymorphism, 2 studies only examined the A1298C polymorphism, and 4 studies examined both the C677T and A1298C polymorphisms. In terms of ethnicity, 20 studies were performed in Asian population, while 12 studies were conducted in White population. Detailed characteristics of included studies are summarized in Table 1.

3.2. Quantitative synthesis

3.2.1. *MTHFR C677T polymorphism and EH*

A total of 30 studies (5207 cases and 5383 controls) assessed the association between MTHFR C677T polymorphism and EH. As shown in Table 2, the pooled results indicated that MTHFR C677T polymorphism was significantly associated with an increased risk of EH in all genetic models (for T vs. C: OR = 1.30, 95%CI = 1.18–1.43; for TT + CT vs. CC: OR = 1.34, 95%CI = 1.24–1.46; for TT vs. CC: OR = 1.62, 95%CI = 1.32–1.99; for TT vs. CT + CC: OR = 1.41, 95%CI = 1.26–1.59, forest plot was shown in Fig. 2). Meta-regression analyses indicated no significant modification of the meta-analytic effect size by year of publication and ethnicity (Table 3).

Five of 30 control samples were not in Hardy–Weinberg equilibrium [28,30,41,48,52]. The overall association between

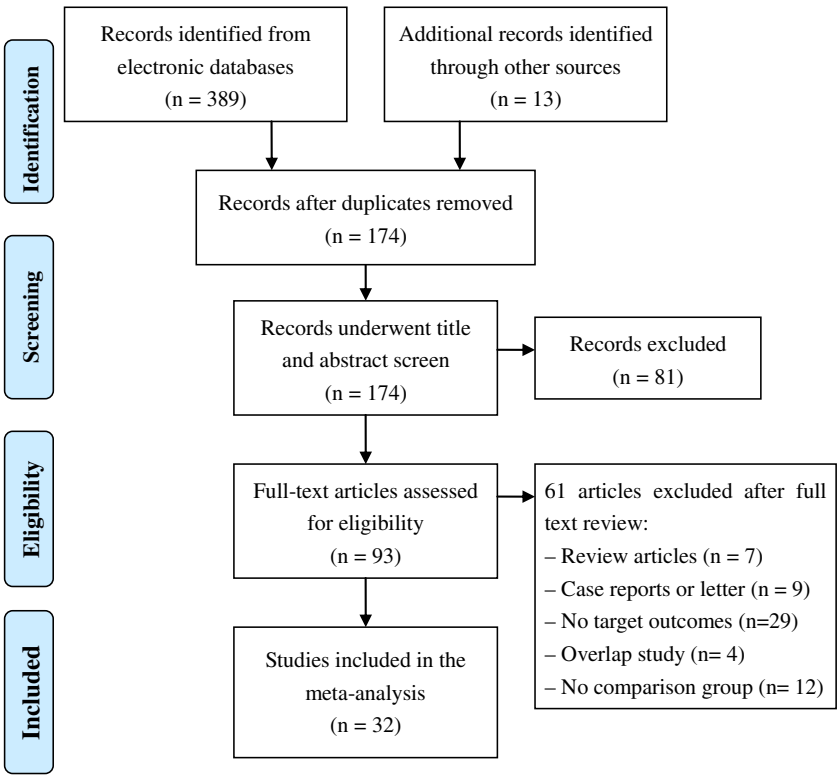

Fig. 1 – PRISMA flow diagram for inclusion of the studies examining the association between MTHFR polymorphisms and essential hypertension.

Table 1 – Main characteristics of studies included in this meta-analysis.

First author	Year	Country	Ethnicity	Diagnostic standard		Distribution of MTHFR C677T genotype							Distribution of MTHFR A1298C genotype						
						Cases			Controls			P_{HWE}	Cases			Controls			P_{HWE}
				SBP	DBP	CC	CT	TT	CC	CT	TT		AA	AC	CC	AA	AC	CC	
Nishio [25]	1996	Japan	Asian	>140	>90	16	26	5	29	44	9	0.202							
Nakata [26]	1998	Japan	Asian	>160	>95	63	91	19	65	83	36	0.309							
Gao [27]	1999	China	Asian	>140	>90	44	68	15	62	84	24	0.393							
Benes [28]	2001	Czech Republic	White	>140	>90	73	93	27	86	106	17	0.045*							
Wang [29]	2002	China	Asian	>140	>90	17	51	37	14	23	9	0.935							
Kahleová [30]	2002	Czech Republic	White	>140	>90	82	55	27	86	69	18	0.045*	79	62	23	77	75	21	0.679
Sun [31]	2003	China	Asian	>140	—	6	22	27	14	23	9	0.935							
Rodríguez-Esparragón [32]	2003	Spain	White	>140	>90	83	115	34	95	100	20	0.386							
Heux [33]	2004	New Zealand	White	>140	>95	87	125	35	105	119	25	0.299							
Tylicki [34]	2005	Austria/Poland	White	>140	>90	40	39	11	42	38	10	0.752							
Liu [35]	2005	China	Asian	>140	>90	29	45	26	31	50	19	0.884							
Lwin [36]	2006	Japan	Asian	>140	>90	39	58	19	64	117	38	0.215							
Li [37]	2006	China	Asian	>140	>90	18	6	2	21	7	2	0.227							
Hu [38]	2006	China	Asian	>140	>90	55	39	16	61	42	12	0.249							
Hui [39]	2007	Japan	Asian	>160	>100	83	129	49	104	123	44	0.454							
Markan [40]	2007	India	Asian	>140	>90	105	40	8	105	28	0	0.175	99	43	11	112	17	4	0.004*
Xing [41]	2007	China	Asian	>140	>90	202	309	184	182	222	105	0.016*							
Tang [42]	2007	China	Asian	>140	>90	139	93	20	138	51	6	0.630							
Lin [43]	2008	China	Asian	>140	>90	19	27	4	73	44	6	0.848							
Ilhan [44]	2008	Turkey	White	>140	>90	36	32	10	72	26	2	0.845							
Deshmukh [45]	2009	United States	White	>140	>90	22	16	4	52	48	18	0.221							
Ng [46]	2009	Australia	White	>140	>90	14	14	10	40	32	8	0.670	37	35	7	22	14	3	0.714
Wang [47]	2010	China	Asian	>140	>90								132	56	7	134	68	11	0.539
Liu [48]	2011	China	Asian	>140	>90	58	70	27	74	47	19	0.015*							
Demirel [49]	2011	Turkey	White	>140	>90								25	19	6	14	33	3	0.006*
Zhang [50]	2012	China	Asian	>140	>90	128	53	8	117	41	7	0.176							
Cao [51]	2012	China	Asian	>140	>90	33	53	26	49	68	30	0.474							
Yin [52]	2012	China	Asian	>140	>90	244	358	68	322	309	51	0.047*							
Fowdar [53]	2012	Australia	White	>140	>90	170	174	33	175	183	35	0.186	165	151	52	162	173	51	0.072
Bayramoglu [54]	2013	Turkey	White	>140	>90	65	38	22	56	38	5	0.654							
Yao [55]	2013	China	Asian	>140	>90	32	69	49	61	67	22	0.608							
Fridman [56]	2013	Argentina	White	>140	>90	29	40	6	71	64	15	0.917							

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; P_{HWE}, *P*-value for Hardy-Weinberg Equilibrium in control group.

Table 2 – Summary of pooled odds ratios (ORs) with confidence intervals (CIs) in the meta-analysis.

MTHFR genotype	Comparison model	Studies (cases/controls)	Test of association			M*	I^2(%)	P (publication bias test)		Sensitivity analysis	
			OR	95%CI	P_{OR}			Begg's test	Egger's test	OR	95%CI
MTHFR C677T	T vs. C	30 (5207/5383)	1.30	1.18-1.43	<0.001	R	58.7	0.28	0.35	1.31	1.15-1.49
	TT + CT vs. CC	30 (5207/5383)	1.34	1.24-1.46	<0.001	F	40.8	0.39	0.15	1.31	1.19-1.45
	TT vs. CC	30 (5207/5383)	1.62	1.32-1.99	<0.001	R	50.9	0.28	0.41	1.63	1.24-2.15
	TT vs. CT + CC	30 (5207/5383)	1.41	1.26-1.59	<0.001	F	44.3	0.23	0.58	1.44	1.14-1.82
MTHFR A1298C	C vs. A	6 (1009/994)	1.09	0.81-1.46	0.577	R	71.2	0.71	0.52	0.95	0.81-1.10
	CC + AC vs. AA	6 (1009/994)	1.06	0.70-1.61	0.778	R	76.3	1.00	0.76	0.93	0.77-1.45
	CC vs. AA	6 (1009/994)	1.09	0.80-1.48	0.493	F	0.0	0.45	0.64	0.98	0.70-1.37
	CC vs. AC + AA	6 (1009/994)	1.16	0.86-1.56	0.326	F	0.0	0.45	0.76	1.05	0.77-1.45

M*, model of meta-analysis; R, random effect model; F, fixed effect model.

the MTHFR C677T polymorphism and EH was unchanged after an exclusion of these five samples from the meta-analysis, indicating that the results from this meta-analysis were statistically robust (Table 2). Cumulative meta-analysis by year of publication indicated that the association between MTHFR C677T polymorphism and EH was increased in strength and magnitude over the years (Fig. 3).

3.2.2. *MTHFR A1298C polymorphism and EH*

Based on 6 studies (1009 cases and 994 controls), no association was detected between the MTHFR A1298C polymorphism and EH in all the genetic models (for C vs. A: OR = 1.09, 95%CI = 0.81–1.46; for CC + AC vs. AA: OR = 1.06, 95%CI = 0.70–1.61; for CC vs. AA: OR = 1.09, 95%CI = 0.80–1.48; for CC vs. AC + AA: OR = 1.16, 95%CI = 0.86–1.56, Table 2, forest plot was shown in Fig. S1). Similarly to MTHFR C677T polymorphism, meta-regression analyses indicated no significant effect modification by year of publication and ethnicity (Table 3). Hardy–Weinberg disequilibrium was observed in two studies [40,49]. The exclusion of these two studies did not change the results (Table 2).

3.2.3. *Publication bias*

No obvious publication bias was detected according to the shapes of the funnel plot for MTHFR C677T and A1298C

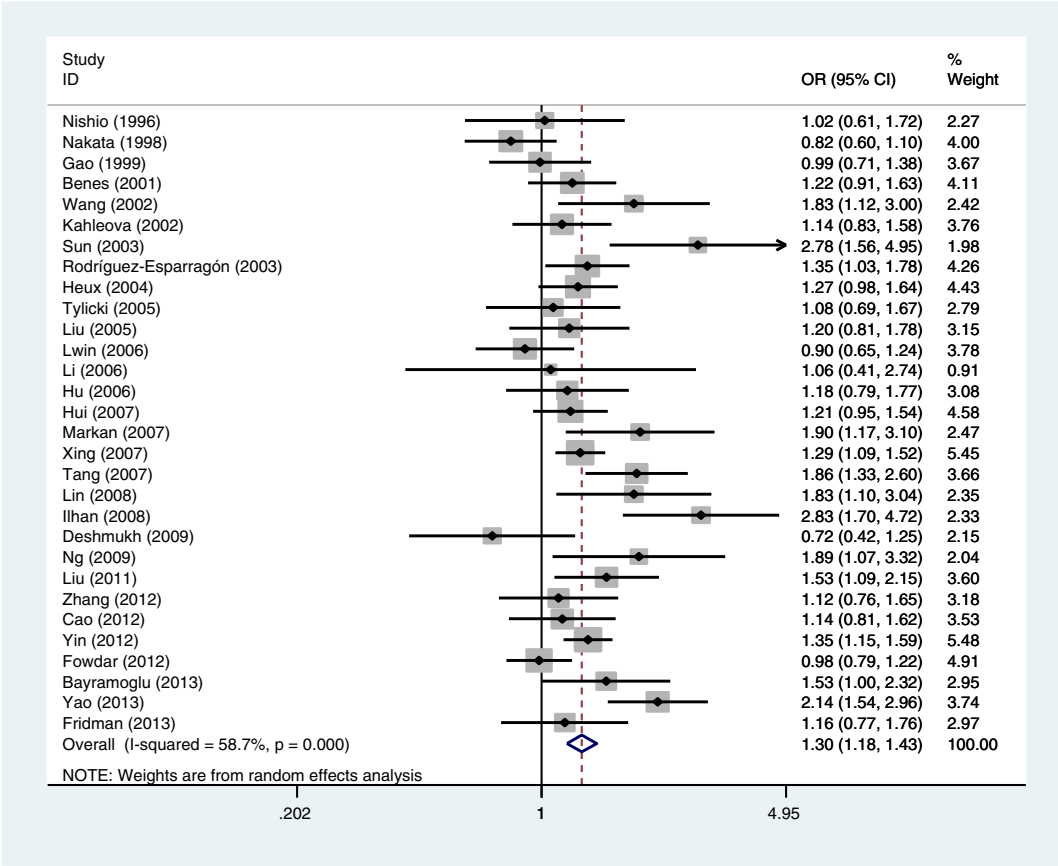

Fig. 2 – Results of the random effect meta-analysis of MTHFR C677T polymorphism and essential hypertension as tested in the allele model (T vs. C).

Table 3 – Results of the meta-regression analyses of the MTHFR C677T and A1298C meta-analyses for the 4 genetic models tested, including year of publication and ethnic group as possible modifiers in separate (one modifier) and combined analyses (multiple modifiers).

	Year of publication (coef; P-value)		Ethnic group (coef; P-value)	
	One modifier	Multiple modifier	One modifier	Multiple modifier
MTHFR C677T				
T vs. C	0.02; 0.20	0.02; 0.20	−0.05; 0.68	−0.05; 0.65
TT + CT vs. CC	0.02; 0.18	0.02; 0.19	−0.14; 0.26	−0.14; 0.27
TT vs. CC	0.03; 0.25	0.03; 0.26	0.03; 0.89	0.04; 0.88
TT vs. CT + CC	0.02; 0.32	0.02; 0.32	0.12; 0.57	0.12; 0.55
MTHFR A1298C				
C vs. A	−0.03; 0.65	−0.03; 0.65	−0.36; 0.41	−0.37; 0.46
CC + AC vs. AA	−0.07; 0.43	−0.70; 0.44	−0.52; 0.40	−0.53; 0.42
CC vs. AA	−0.02; 0.67	−0.02; 0.73	−0.16; 0.73	−0.19; 0.76
CC vs. AC + AA	−0.01; 0.72	−0.01; 0.78	−0.01; 0.99	−0.01; 0.99

polymorphisms (Fig. S2). Moreover, neither the Begg's test nor Egger's test detected any obvious evidence of the publication bias in all genetic models (Table 2).

4. Discussion

To date, many studies have investigated the association between MTHFR C677T/A1298C polymorphisms and the risk of EH among different ethnic populations. However, findings from these studies were controversial due to their small sample size or ethnic difference. Meta-analysis is a powerful tool for pooling data from different studies to strengthen the statistical power. It is also used to elucidate the effect of a genetic factor on the risk of disease. The strength of this study is based on the aggregation of available published studies giving greater power to detect gene frequency differences [57].

The present meta-analysis examining MTHFR C677T polymorphism with 5207 patients and 5383 control subjects indicated that carriers of the T allele and TT genotype significantly increased the risk of EH in all genetic models. This finding is consistent with a recent genome-wide association study [58], which reported a significant association between MTHFR C677T polymorphism and hypertension. However, no significant association was detected between MTHFR A1298C polymorphism and EH in this meta-analysis. Cumulative meta-analyses showed that the association between MTHFR C677T polymorphism and EH gradually increased in strength and magnitude over the years, and the corresponding CIs narrowed down with the increase in the number of available studies in the order of publication year. Additionally, sensitivity analysis indicated that an omission of studies which departure from HWE did not alter the magnitude of observed effect, suggesting that the results were generally robust. Finally, the meta-regression study was carried out to evaluate the potential moderators. Nevertheless, no moderating effect was observed for year of publication or ethnic groups.

It has been well documented that the T allele of MTHFR C677T polymorphism produced a thermolabile variant of MTHFR enzyme resulting in reduced MTHFR activity and subsequent higher plasma concentrations of Hcy [6]. The Hcy pathway has emerged as a strong candidate for EH and many studies have been conducted to investigate genetic variation underlying hyperhomocysteinemia [53]. Findings from the Third National Health and Nutrition Examination Survey (NHANES III) indicated that people with the highest level of Hcy had a 2–3 fold increase in the risk of hypertension than those with the lowest Hcy level [14]. The hypothesis that Hcy may be involved in the pathogenesis of EH is based on the fact that plasma Hcy could induce arteriolar constriction, renal dysfunction, and increased sodium reabsorption, and also increase arterial stiffness [56,59]. The MTHFR A1298C polymorphism contributes to less effect on MTHFR enzyme activity and Hcy concentrations [11]. Consequently, A1298C polymorphism does not seem to be powerful enough to affect plasma Hcy level compared with C677T polymorphism. It may be expected that the MTHFR A1298C polymorphism is also a risk factor for EH, but with a smaller relative risk than the MTHFR C677T polymorphism, thus the risk effect could not be detected. This may partly explain why MTHFR C677T polymorphism but not A1298C polymorphism was significantly associated with EH. Similarly to MTHFR A1298C polymorphism, a recent meta-analysis [60] also revealed that another polymorphism (A1572G) in MTHFR was not associated with EH. However, the underlying mechanism by which MTHFR C677T polymorphism is associated with EH remains unclear, and further studies are needed to elucidate the roles of different MTHFR polymorphisms in developing EH.

4.1. *Limitations and strengths*

Several limitations of this meta-analysis should be mentioned. First, findings from this study were based on individual unadjusted estimates, while a more precise estimate should be adjusted for potentially confounding factors, including gender, age, body mass index (BMI), smoking status, and other environmental factors. Second, the meta-analysis on MTHFR A1298C polymorphism was performed based on a small sample size, which suggested that type II error cannot be dismissed. Third, although genetic and environmental risk factors are experientially recognized as sharing a role in increasing the risk of EH, the gene–gene and gene–environment interactions could not be taken into account for limited data from included studies. Finally, matching of control subjects was not always performed in all included studies in this meta-analysis. In spite

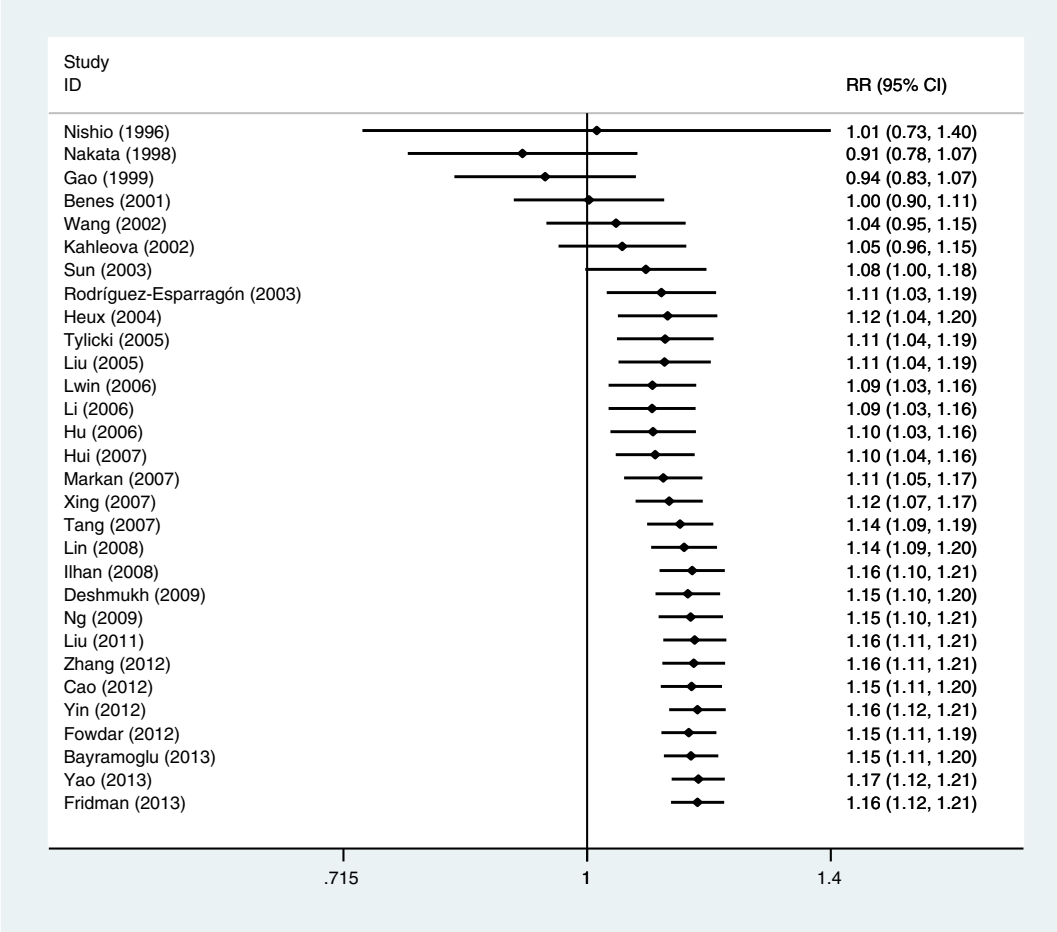

Fig. 3 – Cumulative results of the meta-analysis of the association between MTHFR C677T polymorphism and essential hypertension according to year of publication.

of these limitations, some advantages in this meta-analysis should be acknowledged. First, a systematic review of the association between MTHFR C677T/A1298C polymorphisms and the risk of EH is more powerful than individual study. Second, the quality of included studies in this meta-analysis was satisfactory based on our preset selection criteria. Third, no publication bias was detected in all genetic models, suggesting that the results were relatively reliable.

5. Conclusion

In conclusion, this meta-analysis confirms that MTHFR C677T polymorphism is associated with an increased risk of EH, and indicates a lack of significant association between MTHFR A1298C polymorphism and the risk of EH. These findings provide an important evidence-based reference that MTHFR C677T polymorphism may be a new marker for clinical evaluation and gene-targeted therapy of EH. Future prospective studies with larger sample size are expected to further examine the association between these two polymorphisms in MTHFR and the risk of EH.

Author contributions

Wu Y-L and Hu C-Y designed the study and wrote the manuscript; Lu S-S, Qian Z-Z, Gong F-F and Feng F collected and analyzed the data; Ding X-X and Yang H-Y collected the data and contributed to the discussion; Sun Y-H supervised the work and revised the manuscript. All authors approved the final manuscript.

Funding

This study was supported by grants from National Natural Science Foundation of China (no. 81172763).

Acknowledgments

None.

Conflicts of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.metabol.2014.10.001.

REFERENCES

[1] Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. Lancet 2005;365:217–23.

[2] Ezzati M, Lopez AD, Rodgers A, Vander Hoorn S, Murray CJ, Comparative Risk Assessment Collaborating Group. Selected major risk factors and global and regional burden of disease. Lancet 2002;360:1347–60.

[3] Kunes J, Zicha J. Developmental windows and environment as important factors in the expression of genetic information: a cardiovascular physiologist's view. Clin Sci (Lond) 2006;111: 295–305.

[4] Tanira MO, Al Balushi KA. Genetic variations related to hypertension: a review. J Hum Hypertens 2005;19:7–19.

[5] Harrison M, Maresso K, Broeckel U. Genetic determinants of hypertension: an update. Curr Hypertens Rep 2008;10:488–95.

[6] Frosst P, Blom HJ, Milos R, Goyette P, Sheppard CA, Matthews RG, et al. A candidate genetic risk factor for vascular disease: a common mutation in methylenetetrahydrofolate reductase. Nat Genet 1995;10:111–3.

[7] Pereira AC, Schettert IT, Morandini Filho AA, Guerra-Shinohara EM, Krieger JE. Methylenetetrahydrofolate reductase (MTHFR) c677t gene variant modulates the homocysteine folate correlation in a mild folate-deficient population. Clin Chim Acta 2004;340:99–105.

[8] Dankner R, Chetrit A, Murad H, Sela BA, Frystyk J, Raz I, et al. Serum adiponectin is associated with homocysteine in elderly men and women, and with 5,10-methylenetetrahydrofolate reductase (MTHFR) in a sex-dependent manner. Metabolism 2010;59:1767–74.

[9] Li YY. Methylenetetrahydrofolate reductase C677T gene polymorphism and coronary artery disease in a Chinese Han population: a meta-analysis. Metabolism 2012;61:846–52.

[10] Yang S, Zhang J, Feng C, Huang G. MTHFR 677 T variant contributes to diabetic nephropathy risk in Caucasian individuals with type 2 diabetes: a meta-analysis. Metabolism 2013;62:586–94.

[11] van der Put NM, Gabreëls F, Stevens EM, Smeitink JA, Trijbels FJ, Eskes TK, et al. A second common mutation in the methylenetetrahydrofolate reductase gene: an additional risk factor for neural-tube defects? Am J Hum Genet 1998;62: 1044–51.

[12] Schroecksnadel K, Frick B, Winkler C, Wirleitner B, Weiss G, Fuchs D. Atorvastatin suppresses homocysteine formation in stimulated human peripheral blood mononuclear cells. Clin Chem Lab Med 2005;43:1373–6.

[13] Halilovic E, Kabil E, Halilovic E. Homocysteine in angiographically proven coronary disease. Med Arh 2009;63:252–6.

[14] Ghassibe-Sabbagh M, Platt DE, Youhanna S, Abchee AB, Stewart K, Badro DA, et al. Genetic and environmental influences on total plasma homocysteine and its role in coronary artery disease risk. Atherosclerosis 2012;222:180–6.

[15] Lim U, Cassano PA. Homocysteine and blood pressure in the Third National Health and Nutrition Examination Survey, 1988–1994. Am J Epidemiol 2002;156:1105–13.

[16] Sundström J, Sullivan L, D'Agostino RB, Jacques PF, Selhub J, Rosenberg IH, et al. Plasma homocysteine, hypertension incidence, and blood pressure tracking: the Framingham Heart Study. Hypertension 2003;42:1100–5.

[17] van Dijk RA, Rauwerda JA, Steyn M, Twisk JW, Stehouwer CD. Long-term homocysteine-lowering treatment with folic acid plus pyridoxine is associated with decreased blood pressure but not with improved brachial artery endothelium-dependent vasodilation or carotid artery stiffness: a 2-year, randomized, placebo-controlled trial. Arterioscler Thromb Vasc Biol 2001;21:2072–9.

[18] Qian X, Lu Z, Tan M, Liu H, Lu D. A meta-analysis of association between C677T polymorphism in the methylenetetrahydrofolate reductase gene and hypertension. Eur J Hum Genet 2007;15: 1239–45.

[19] Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 2009; 151:264–9.

[20] Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.

[21] DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–88.

[22] Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 1959;22:719–48.

[23] Lau J, Antman EM, Jimenez-Silva J, Kupelnick B, Mosteller F, Chalmers TC. Cumulative meta-analysis of therapeutic trials for myocardial infarction. N Engl J Med 1992;327:248–54.

[24] Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315:629–34.

[25] Nishio H, Lee MJ, Fujii M, Kario K, Kayaba K, Shimada K, et al. A common mutation in methylenetetrahydrofolate reductase gene among the Japanese population. Jpn J Hum Genet 1996;41:247–51.

[26] Nakata Y, Katsuya T, Takami S, Sato N, Fu Y, Ishikawa K, et al. Methylenetetrahydrofolate reductase gene polymorphism: relation to blood pressure and cerebrovascular disease. Am J Hypertens 1998;11:1019–23.

[27] Gao YY, Zhan SY, Yin XJ, Hu YH, Li LM. The relationship between methylenetetrahydrofolate reductase polymorphism and risk of essential hypertension. J Beijing Med Univ 1999;31: 370–2 [in Chinese].

[28] Benes P, Kanková K, Muzík J, Groch L, Benedík J, Elbl L, et al. Methylenetetrahydrofolate reductase polymorphism, type II diabetes mellitus, coronary artery disease, and essential hypertension in the Czech population. Mol Genet Metab 2001; 73:188–95.

[29] Wang L, Guo H, Li YM. MTHFR gene C 677 T polymorphisms and variation of plasma homocysteine levels in primary hypertension. Tianjin Med J 2002;30:579–82 [in Chinese].

[30] Kahleová R, Palyzová D, Zvára K, Zvárová J, Hrach K, Nováková I, et al. Essential hypertension in adolescents: association with insulin resistance and with metabolism of homocysteine and vitamins. Am J Hypertens 2002;15:857–64.

[31] Sun XN, Li YM, Guo H. The gene polymorphisms of homocysteine metabolism-related enzymes and the associated factors in isolated systolic hypertension. Chin J Cardiol 2003;31:269–73.

[32] Rodríguez-Esparragón F, Hernández-Perera O, Rodríguez-Pérez JC, Anábitarte A, Díaz-Cremades JM, Losada A, et al. The effect of methylenetetrahydrofolate reductase C677T common variant on hypertensive risk is not solely explained by increased plasma homocysteine values. Clin Exp Hypertens 2003;25:209–20.

[33] Heux S, Morin F, Lea RA, Ovcaric M, Tajouri L, Griffiths LR. The methylentetrahydrofolate reductase gene variant (C677T) as a risk factor for essential hypertension in Caucasians. Hypertens Res 2004;27:663–7.
[34] Tylicki L, Födinger M, Puttinger H, Rutkowski P, Strozecki P, Tyszko S, et al. Methylenetetrahydrofolate reductase gene polymorphisms in essential hypertension relation: with the development of hypertensive end-stage renal disease. Am J Hypertens 2005;18: 1442–8.
[35] Liu JW, Ye L, Liu J, Li XY. Study on homocysteine metabolism-related enzymes gene polymorphisms in elderly essential hypertension patients with peripheral arterial occlusive disease. Chin J Geriatr 2005;24:332–5 [in Chinese].
[36] Lwin H, Yokoyama T, Yoshiike N, Saito K, Yamamoto A, Tanaka H, et al. Polymorphism of methylenetetrahydrofolate reductase gene (C677T MTHFR) is not a confounding factor of the relationship between serum uric acid level and the prevalence of hypertension in Japanese men. Circ J 2006;70:83–7.
[37] Li XJ, Huang W. The analysis of MTHFR gene polymorphism in patients with renal damage caused by hypertension and patients with renal parenchymal hypertension. J Cap Univ Med Sci 2006;27:497–500 [in Chinese].
[38] Hu RL, Niu GM, Zhao SG, Zhang CM, Hu RL, Wang ZG, et al. The association between gene polymorphisms of N5,10-methylenetetrahydrofolate reductase and Mongolian patients with primary hypertension. ChinJ Hypertens 2006;14: 274–6 [in Chinese].
[39] Hui P, Nakayama T, Morita A, Sato N, Hishiki M, Saito K, et al. Common single nucleotide polymorphisms in Japanese patients with essential hypertension: aldehyde dehydrogenase 2 gene as a risk factor independent of alcohol consumption. Hypertens Res 2007;30:585–92.
[40] Markan S, Sachdeva M, Sehrawat BS, Kumari S, Jain S, Khullar M. MTHFR 677 CT/MTHFR 1298 CC genotypes are associated with increased risk of hypertension in Indians. Mol Cell Biochem 2007;302:125–31.
[41] Xing XR, Hua Q. Relationships between the polymorphism of methylenetetrahydrofolate reductase gene C677T and hypertension, cardiac structure and function. Med J Chin People's Liberation Army 2007;32:741–4 [in Chinese].
[42] Tang Y, Chen H, Wu XY. The C677T point mutation of N5,10-methylene-tetrahydrofolate reductase (MTHFR) and essential hypertension. Mol Cardiol China 2007;7:205–7 [in Chinese].
[43] Lin PT, Cheng CH, Wei JC, Huang YC. Low plasma pyridoxal 5'-phosphate concentration and MTHFR 677C– > T genotypes are associated with increased risk of hypertension. Int J Vitam Nutr Res 2008;78:33–40.
[44] Ilhan N, Kucuksu M, Kaman D, Ilhan N, Ozbay Y, et al. The 677 C/T MTHFR polymorphism is associated with essential hypertension, coronary artery disease, and higher homocysteine levels. Arch Med Res 2008;39:125–30.
[45] Deshmukh A, Rodrigue KM, Kennedy KM, Land S, Jacobs BS, Raz N. Synergistic effects of the MTHFR C677T polymorphism and hypertension on spatial navigation. Biol Psychol 2009;80:240–5.
[46] Ng X, Boyd L, Dufficy L, Naumovski N, Blades B, Travers C, et al. Folate nutritional genetics and risk for hypertension in an elderly population sample. J Nutrigenet Nutrigenomics 2009;2:1–8.
[47] Wang H, Wu GZ, Zhang Y, Zhang XY, Chen YL, Ai SK. Association of homocysteine and its metabolic enzyme genes polymorphisms with essential hypertension in Xinjiang Kazakhs. J Clin Rehab Tissue Eng Res 2010;14: 6247–52 [in Chinese].
[48] Liu HY, Ma P, Xu QB. The correlation between polymorphisms of N5,10-methylene-tetrahydrofolate reductase and essential hypertension in Han population in Ningxia. Guangdong Med J 2011;32:1977–80 [in Chinese].
[49] Demirel Y, Dogan S, Uludag A, Silan C, Atik S, Silan F, et al. Combined effect of Factor V Leiden, MTHFR, and angiotensin-converting enzyme (insertion/deletion) gene mutations in hypertensive adult individuals: a population-based study from Sivas and Canakkale, Turkey. Genet Test Mol Biomarkers 2011;15:785–91.
[50] Zhang Y, Wang H, Zhang XY, Wang L, Wu GZ. Relationship between homocysteine, methylenetetrahydrofolate reductase C677T polymorphisms and essential hypertension in Kazak nationality in Xinjiang. J Clin Cardiol 2012;28:570–3 [in Chinese].
[51] Cao ZY. The association between methylenetetrahydrofolate reductase C677T polymorphism and elderly hypertension with acute myocardial infarction. Chin J Gerontol 2012;32: 5118–20 [in Chinese].
[52] Yin RX, Wu JZ, Liu WY, Wu DF, Cao XL, Miao L, et al. Association of several lipid-related gene polymorphisms and blood pressure variation in the Bai Ku Yao population. Am J Hypertens 2012;25:927–36.
[53] Fowdar JY, Lason MV, Szvetko AL, Lea RA, Griffiths LR. Investigation of homocysteine-pathway-related variants in essential hypertension. Int J Hypertens 2012;2012:190923.
[54] Bayramoglu A, Urhan Kucuk M, Guler HI, Abaci O, Kucukkaya Y, Colak E. Is there any genetic predisposition of MMP-9 gene C1562T and MTHFR gene C677T polymorphisms with essential hypertension? 2013 [Epub ahead of print].
[55] Yao R, Zhang HM, Zhang JL, Li DB, Fan YY. Association of MTHFR C677T polymorphism with essential hypertension in Henan Hans of China. Chin J Gerontol 2013;33:1001–3 [in Chinese].
[56] Fridman O, Porcile R, Morales AV, Gariglio LO, Potenzoni MA, Turk Noceto PC. Association of methylenetetrahydrofolate reductase gene 677C > T polymorphism with hypertension in older women in a population of Buenos Aires City. Clin Exp Hypertens 2013;35:159–66.
[57] Muncer S, Taylor S, Craigie M. Power dressing and meta-analysis: incorporating power analysis into meta-analysis. J Adv Nurs 2002;38:274–80.
[58] Xi B, Zhao X, Chandak GR, Shen Y, Cheng H, Hou D, et al. Influence of obesity on association between genetic variants identified by genome-wide association studies and hypertension risk in Chinese children. Am J Hypertens 2013; 26:990–6.
[59] Sen U, Tyagi SC. Homocysteine and hypertension in diabetes: does PPARgamma have a regulatory role? PPAR Res 2010; 2010:806538.
[60] Xi B, Shen Y, Reilly KH, Wang X, Mi J. Recapitulation of four hypertension susceptibility genes (CSK, CYP17A1, MTHFR, and FGF5) in East Asians. Metabolism 2013;62:196–203.