Review Article

Assessing the Possible Association between Polymorphism of *C677T MTHFR* with Preeclampsia Risk: A Systematic Review and Bayesian Hierarchical Meta-Analysis

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Article info:
Received: 1 Feb 2023
Revised: 29 Feb 2023
Accepted: 15 Mar 2023

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ABSTRACT

Objectives: Preeclampsia (PE) is a pregnancy-related disorder with an incidence of 2-5% that causes the death of 40,000 women worldwide each year. Among different accepted etiologies, hyperhomocysteinemia has been shown to be a key player in the progression of PE. Considering the solid role of methylenetetrahydrofolate reductase (*MTHFR*) in the metabolism of homocysteine, genetic polymorphism of *MTHFR* that could affect its activity may trigger the risk of PE. This hierarchical Bayesian meta-analysis aimed to assess the possible association between C677T *MTHFR* polymorphism and the risk of PE.

Methods: In this study, PubMed, Scopus, and Web of Science databases were searched from 2000 until 2019 to evaluate the association of *MTHFR C677T* polymorphism with the risk of PE in relevant case-control studies. The relevant studies were included regardless of population ethnicity and geographical limitation. The extracted data were statistically analyzed using a hierarchical Bayesian method and the association strength was estimated by log (OR) with a 95% credible interval.

Results: Thirty-three studies with 3930 cases and 5236 controls met our inclusion criteria. The pooled results indicated no significant effect of *MTHFR C677T (C>T)* on PE risk under allelic (log(OR) = 0.09, 95% CI = -0.02, 0.204), homozygous (log(OR) = 0.173, 95% CI = -0.027, 0.378), heterozygous (log(OR) = -0.009, 95% CI = -0.123, 0.104), dominant (log(OR) = 0.009, 95% CI = -0.109, 0.133), and recessive (log(OR) = 0.173, 95% CI = -0.012, 0.366) models.

Conclusion: It can be concluded that *MTHFR C677T* polymorphism had no significant effect on the risk of PE.

Keywords: Preeclampsia, Polymorphism, Methylenetetrahydrofolate reductase, Bayesian hierarchical meta-analysis

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Citation: Mohassel Y, Asadi S, Mostafaei S, Goodarzi MT. Assessing the Possible Association between Polymorphism of C677T MTHFR with Preeclampsia Risk: A Systematic Review and Bayesian Hierarchical Meta-Analysis. Acta Biochimica Iranica. 2023;1(1):3-11.

https://doi.org/*

Introduction

Preeclampsia (PE) is a pregnancy-related disorder (1) with clinical and paraclinical features including hypertension (systolic blood pressure >140 mmHg and diastolic blood pressure >90 mmHg) and proteinuria (>300 mg/day), which occurs during the second and third trimesters of pregnancy (2-4). The overall incidence of PE has been estimated to be 2-5%, causing the death of 40,000 women worldwide each year. Although no exact etiology for PE has been described, the crucial role of genetic factors in the occurrence of this disorder is undeniable (5). According to previous studies, an increased level of homocysteine (hyperhomocysteinemia) plays an important role in the progression of PE. Thus, any genetic polymorphisms in enzymes involved in homocysteine metabolism could be helpful for better understanding PE pathogenesis and etiology (6, 7). One of the most important enzymes that participates in the metabolism of homocysteine is methylenetetrahydrofolate reductase (*MTHFR*), which is responsible for converting 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate (8, 9). A missense mutation that converts C to T at nucleotide 677 of the *MTHFR* gene reduces *MTHFR* activity and consequently causes hyperhomocysteinemia (10-13). Although there is a theoretical link between the mentioned homocysteine pathway and PE, there is controversy in current data about the role of C677T *MTHFR* polymorphism in the risk of PE (14-16). Taking these into consideration, this study aimed to systematically review and examine available published data on C677T *MTHFR* polymorphism and PE risk using Bayesian hierarchical meta-analysis to find out a clearer picture of the possible association between this polymorphism and PE risk.

Methods

Search Strategies

A comprehensive literature search investigating the association between *MTHFR* C677T polymorphism and PE risk was performed independently by two authors. The PubMed, Scopus, and Web of Science databases were searched from 2000 to 2019. The keywords for the systematic search were "*MTHFR* C677T" and ("polymorphism" or "variants" or "SNP") and "preeclampsia". After scanning the titles, keywords, and abstracts, studies were assessed based on the following inclusion criteria: case-control studies that investigated the effect of *MTHFR* C677T polymorphism on PE, as well as those that provided sufficient data about genotype or allelic frequencies in case and control groups, regardless of population ethnicity and geographical limitations. Only studies on human subjects with full text in English were reviewed in this study. The exclusion criteria for the study were defined as studies that did not provide sufficient data about genotype or allelic frequencies, letters, reviews, hypotheses, commentary, duplicates of previous publications, and non-English articles.

Data Extraction and Quality Assessment

Two authors separately and independently extracted data from each study by considering the name of the first author, year of publication, sample size of cases and controls, allelic and genotype frequencies in each group. Any conflicts regarding the results provided by each of the two authors were assessed and resolved by consulting a third reviewer. The methodology of the studies was evaluated for quality using the Newcastle-Ottawa Scale (NOS). According to this scale, studies were classified as low (scores 0-3), moderate (scores 4-6), and high (scores 7-9) quality (17).

Statistical Methods

An alternative model to classical analysis for evaluating accurate pooled effect, particularly in cases with a small number of studies, is the Bayesian hierarchical meta-analysis (inverse-variance) model that was used in this study (18-20). The heterogeneity between the studies was tested and measured by the tau (τ) parameter with a 95% C.I (18). In this analysis, Bayes factors were used to test pooled log (OR) and tau parameters.

Furthermore, publication bias was examined using Egger's regression asymmetry and the Begg-Mazumdar adjusted rank correlation tests (19). All statistical analyses were conducted using the "bayesmeta" R package and STATA software (ver. 15).

Results

Characteristics of Studies

According to the inclusion and exclusion criteria, 620 records were identified in PubMed, Web of Science, and Scopus databases. After reviewing the titles, 309 articles were excluded (non-original, older than 2000, irrelevant, and duplicated articles). The abstracts of the remaining records were then reviewed, leading to the exclusion of 184 articles. Ultimately, 33 articles with 3930 cases and 5236 controls were included in this meta-analysis (Figure 1). All the included studies were classified as high-quality studies according to NOS criteria (mean NOS score=7.42; range: 6-9). Table 1 provides the main characteristics of the included studies. Supplementary Table 1 (S1) contains information on the inclusion and exclusion criteria, definition of PE in the methodology, types of PE (early/late or both), and quality assessment of all included studies.

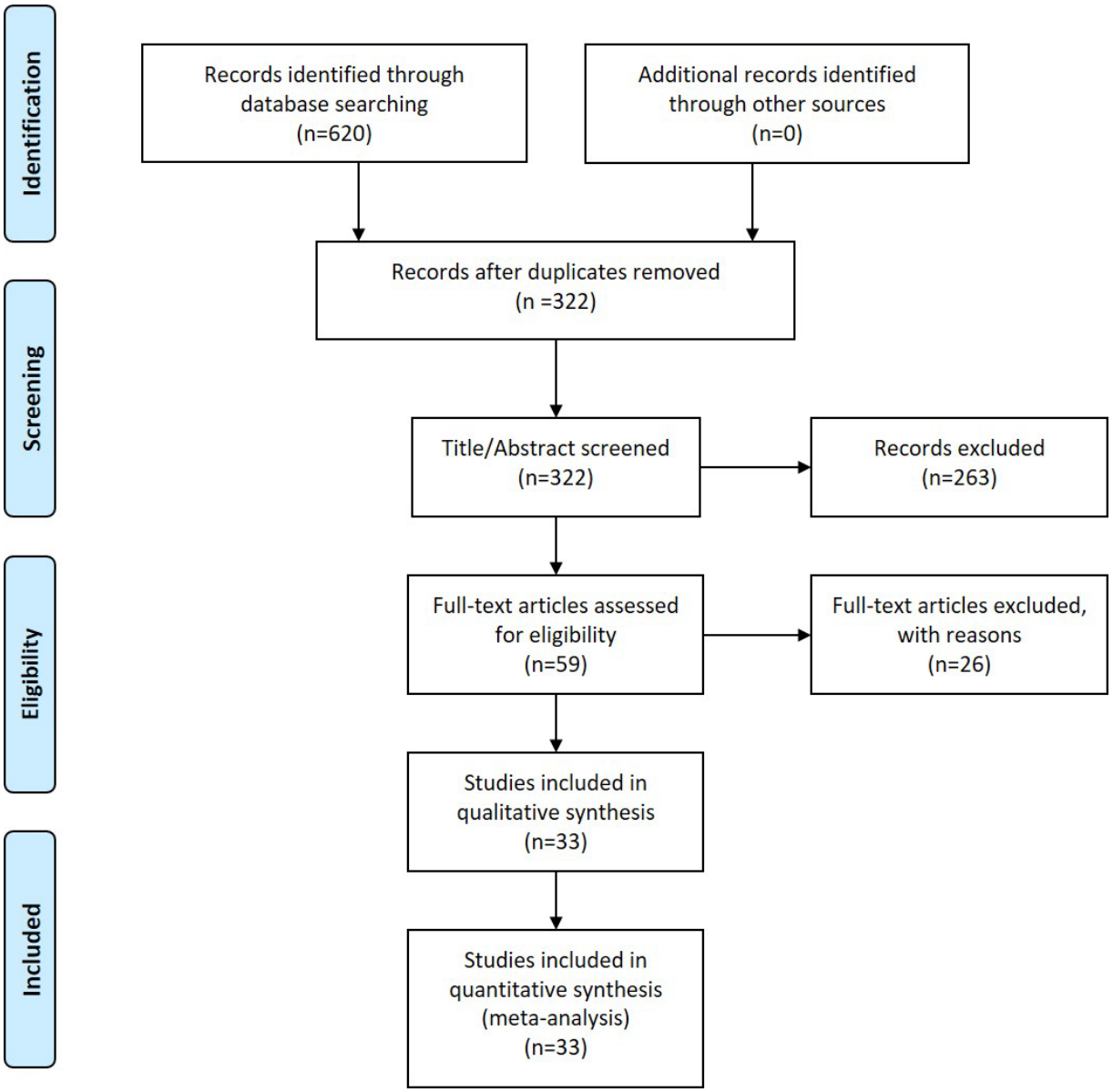

Figure 1: Flowchart of the procedure for the literature search and study selection

Main results of Bayesian hierarchical meta-analysis and sensitivity analysis

After pooling the data, the distribution of genotypes in controls deviated from the Hardy-Weinberg equilibrium (P-value <0.001). The pooled effect size (log(OR)) in the Bayesian hierarchical meta-analysis was calculated as the median of the marginal posterior distribution of the Log(ORs). The results of these models indicated that alleles and genotypes of the *MTHFR C677T (C>T)* polymorphism had no significant associations with the risk of PE in the following models: allelic (log(OR) = 0.09, 95% CI = -0.02, 0.204), homozygous (log(OR) = 0.173, 95% CI = -0.027, 0.378), heterozygous (log(OR) = -0.009, 95% CI = -0.123, 0.104), dominant (log(OR) = 0.009, 95% CI = -0.109, 0.133), and recessive (log(OR) = 0.173, 95% CI = -0.012, 0.366). For instance, a forest plot for the allelic model is shown in Figure 2.

Heterogeneity and publication bias tests

Heterogeneity between studies was estimated with a 95% credible interval (C.I.) by the median of the marginal posterior distribution of the variance parameter. As shown in Figure 3, considerable heterogeneity between studies was observed. In addition, the results of publication bias tests by Egger's and Begg's tests showed that non-significant publication bias was found in all of the models in this study (Table 2).

Discussion

PE is one of the leading causes of maternal and prenatal mortality/morbidity among different populations. It has been shown that both genetic and environmental factors are involved in the pathogenesis of this disorder (1, 5). Among all of the involved factors, hyperhomocysteinemia seems to have a crucial role in the pathogenesis of PE based on previous studies (20-23). Hyperhomocysteinemia can induce vascular and metabolic changes, which consequently lead to placental infarction, recurrent spontaneous abortion, and PE (2, 7). Considering the key role of *MTHFR* in the metabolism of homocysteine, a single nucleotide polymorphism at nucleotide 677 of the *MTHFR* gene (C to T) could affect its activity and lead to hyperhomocysteinemia (5).

Table 1. Main characteristics of the included studies researching the association of *MTHFR C677T* polymorphism with preeclampsia risk.

Authors	Year	Country	Ethnicity	Sample size		Cases			Controls		
				Case	Control	CC	CT	TT	CC	CT	TT
Kim et al. (37)	2001	Korea	Korean	281	360	131	117	133	167	152	41
Kobashi et al. (38)	2000	Japan	Japanese	73	215	25	40	8	83	99	33
Klai et al. (39)	2011	Tunisia	Tunisian	44	100	22	20	2	61	39	0
Yilmaz et al. (40)	2004	Turkey	Turkish	64	47	29	28	7	24	17	6
Yoshida et al. (20)	2008	Japan	Japanese	52	113	17	17	18	48	54	11
Pertegal et al. (41)	2015	Spain	Spanish	53	72	16	24	13	31	29	12
Nagy et al. (42)	2007	Hungary	Hungarian	101	73	49	43	9	32	35	6
Maarten et al. (43)	2001	Netherland	Dutch	167	403	72	74	21	205	162	36
Jafari et al. (44)	2018	Iran	Iranian	129	125	74	38	5	67	50	8
Ibrahim et al. (45)	2011	Egypt	Egyptian	44	44	9	20	15	16	28	0
Vajira et al. (46)	2012	Sri Lanka	Sinhalese	175	171	136	36	3	142	27	2
Jääskeläinen et al. (47)	2006	Finland	Finnish	133	112	78	43	12	64	42	6
Also-Rallo et al. (48)	2005	Spain	Spanish	43	122	11	24	8	38	57	27
Laivouri et al. (49)	2000	Finland	Finnish	113	103	64	45	4	56	40	7
Coral-Vázquez et al. (50)	2013	Mexico	Mexican	230	352	38	109	83	71	166	115
Zhou et al. (51)	2016	China	Chinese	117	286	46	53	18	122	131	33
Pe´rez-Mutul et al. (52)	2004	Mexico	Mexican	148	313	33	66	49	67	159	87
Williams et al. (21)	2004	Peru	Peruvian	125	179	37	61	25	62	85	30
Canto et al. (53)	2008	Mexico	Maya-Mestizo	125	274	36	66	23	61	131	82
Da´valos et al. (54)	2005	Mexico	Mexican	33	62	13	14	6	24	27	11
Rosemary et al. (15)	2009	South Africa	African	271	338	232	38	1	298	38	2
Rahimi et al. (23)	2012	Iran	Iranian	198	101	110	72	16	52	45	4
Mislanova et al. (55)	2011	Austria	Austrian	28	40	12	11	5	21	17	2
Chedraui et al. (56)	2014	Ecuador	Ecuadorian	150	150	59	73	18	47	91	12
Chedraui et al. (57)	2015	Ecuador	Ecuadorian	50	50	15	23	12	20	26	4
De Maat et al. (58)	2004	Netherland	Dutch	157	157	78	59	20	63	75	19
Aggarwal et al. (59)	2011	India	Indian	200	200	160	33	7	134	58	8
Dalmáz et al. (60)	2006	Brazil	Brazilian	75	145	31	27	17	76	51	18
Salimi et al. (22)	2014	Iran	Iranian	192	196	124	60	8	136	51	9
Prasmusinto et al. (9)	2002	Different	Different	81	99	52	25	4	52	35	12
Kaiser et al. (61)	2001	Australia	Australian	156	79	71	66	19	37	31	11
Prasmusinto et al. (62)	2004	Different	Different	82	116	53	25	4	65	39	12
Mishra et al. (63)	2019	India	Indian	40	39	26	10	4	28	10	1

Consequently, polymorphism of the *MTHFR* gene may be important in the risk of PE.

For all of the 3930 cases and 5236 controls who met both inclusion and exclusion criteria and were enrolled in the current study, a Bayesian hierarchical meta-analysis for evaluating the association between 677 of the *MTHFR* gene polymorphism with the risk of PE was conducted. The Bayesian hierarchical meta-analysis has several characteristics such as greater sensitivity and more precise estimation. The results of the Bayesian hierarchical meta-analysis showed that there is no significant association between 677 of the *MTHFR* gene polymorphism with the risk of PE, and our results conflict with those of previous meta-analysis studies. Zhang et al. in their meta-analysis study found that 677 of the *MTHFR* gene polymorphism was associated with the risk of PE (24). Additionally, Wang et al. showed that there was a significant association between 677 of the *MTHFR*

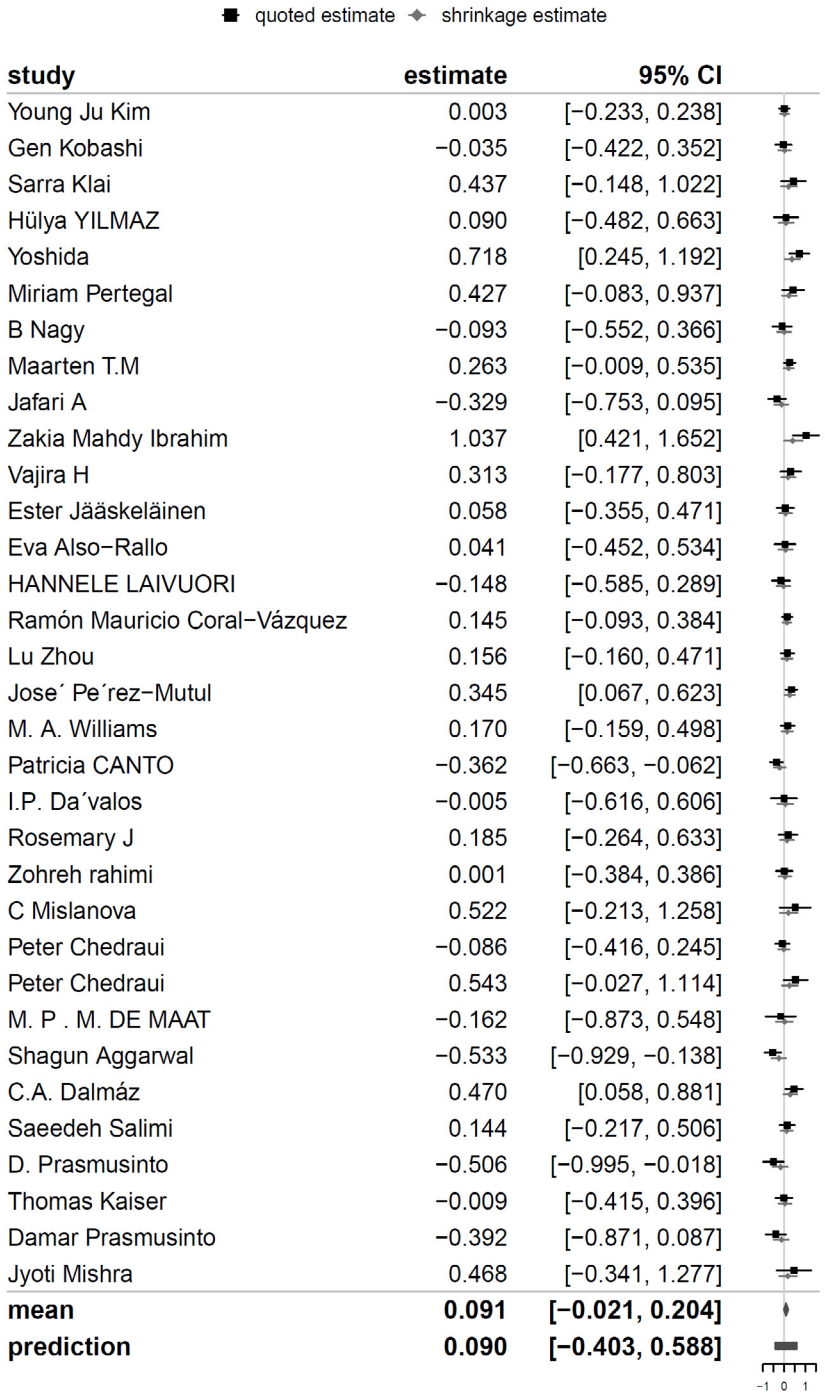

Figure 2: Forest plots estimated Log (OR) and 95% credible interval for both the individual studies and the pooled results of allelic model: C versus T. OR: odds ratio

Table 2. Bayesian hierarchical meta-analysis of the pooled association between *MTHFR C677T* polymorphism and risk of preeclampsia disease.

Variation	Number of Studies	Frequency		Association Test		Heterogeneity Test Tau, (95% Credible Interval)	Publication Bias (Begg's Test, P-value; Egger's test, P-value)	Sensitivity Analysis
		Case	Control	Pooled log(OR)	(95% Credible Interval)			
MTHFR C677T (C>T)								
C	33	5378	7037					
T	33	2454	3431					
CC	33	1959	2470					
CT	33	1460	2097					
TT	33	497	667					
T vs. C	33	-	-	0.0906	(-0.0205, 0.2043)	0.2282, (0.1113, 0.3572)	(P-value=0.08; P-value=0.06)	Robust
TT vs. CC	33	-	-	0.1735	(-0.0268, 0.3784)	0.2867 (0.0001, 0.5278)	(P-value=0.06; P-value=0.06)	Robust
CT vs. CC	33	-	-	-0.0099	(-0.1234, 0.1046)	0.1307 (0.0001, 0.2649)	(P-value=0.45; P-value=0.35)	Robust
TT+CT vs. CC	33	-	-	0.0098	(-0.1098, 0.1331)	0.1949 (0.0216, 0.3413)	(P-value=0.18; P-value=0.09)	Robust
TT vs. CT+CC	33	-	-	0.1734	(-0.0128, 0.3664)	0.2749 (0.0001, 0.4986)	(P-value=0.06; P-value=0.16)	Robust
P-value for HWE in controls <0.001								

Marginal posterior summary, Tau: relative heterogeneity, log (OR): logarithm of odds ratio, HWE: Hardy-Weinberg equilibrium Note. Marginal posterior summary, bold pooled Log (OR) indicated as statistically significant at 0.05 level, I 2: relative heterogeneity. CI: credible interval; HWE: Hardy–Weinberg equilibrium; *MTHFR*: Methylenetetrahydrofolate reductase; OR: odds ratio

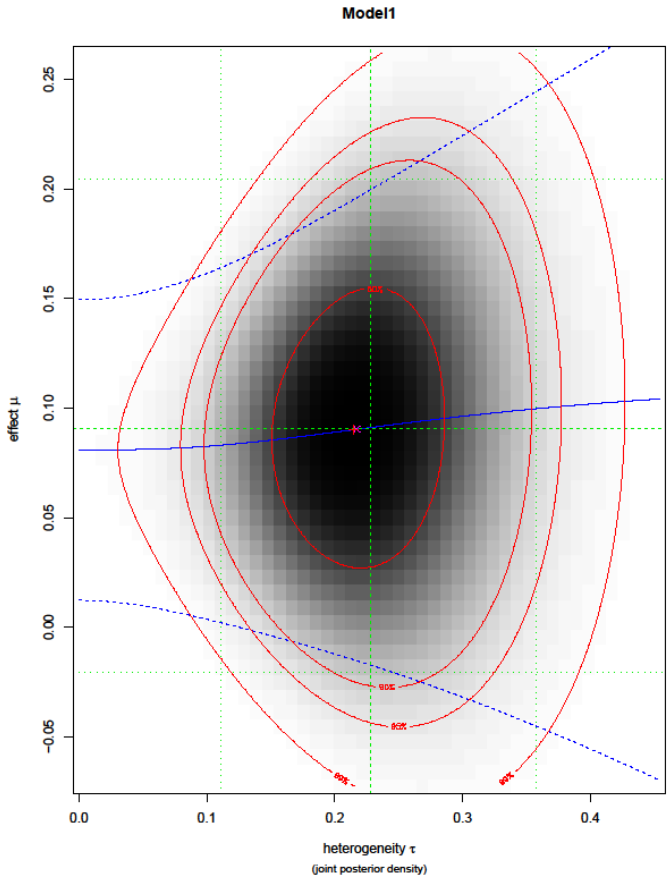

Figure 3: Heterogeneity plot, red lines trace the contours of constant density corresponding to approximate two-dimensional credible regions (based on a $\chi 2$ approximation to the logarithmic posterior density) as labeled. The credible regions are only an approximation based on a "well-behaved," unimodal posterior; contour lines are omitted if the posterior mode is not finite. Blue lines show the conditional mean effect (Log OR) as a function of the heterogeneity τ (solid line) along with conditional 95% confidence bounds (dashed lines). Green lines indicate marginal medians and shortest 95% credible intervals for Log (OR) and τ in allelic model: C versus T. OR: odds ratio.

gene polymorphism and the risk of PE, especially in Caucasian and East Asian ethnic groups (25). Similarly, Yang et al. in their meta-analysis study indicated that 677 of the *MTHFR* gene polymorphism had a significant association with the risk of PE in Caucasian and East Asian ethnic groups (26). Additionally, other studies observed that 677 of the *MTHFR* gene polymorphism elevated the risk of PE in certain ethnicities (24-27). Despite considerable heterogeneity between the included studies, our inadequate number of included studies also prevents subgroup analysis according to ethnicity, unlike previous meta-analyses (24, 26, 27), were not significant so sub-group analysis was not performed in different ethnic groups. In Bayesian hierarchical meta-analysis, the credible interval is slightly wider than that of classical meta-analysis and the results tend to be more conservative against false significant results (28, 29). Therefore, significant results from Bayesian hierarchical meta-analysis are consistent and more reliable compared to classical meta-analysis (30, 31). As well as previous studies indicated that 677 of *MTHFR* gene polymorphism significantly increased the risk of PE in pregnant women, nutritional factors might have effects on this association. For example, vitamin B6 and B12 as well as folate may have a modifier role regarding the association between 677 of *MTHFR* gene polymorphism and the risk of PE (32, 33). There is no additional information about environmental conditions such as family history, BMI, and folate intake, thus the effect of these factors on the incidence of PE cannot be estimated. On the other hand, other genetic factors may participate in the occurrence of PE (34-36). The limitations of this meta-analysis study include not evaluating the effect of MTHFR gene polymorphism on gestational hypertension or eclampsia, not having access to environmental conditions to evaluate gene-environment interactions, and not considering other genetic factors in the incidence and risk of PE.

Finally, this Bayesian hierarchical meta-analysis discloses the possible association of the polymorphisms of MTHFR with PE risk by pooling the available data. The results showed that the polymorphism has no significant effect on the risk of PE.

Conflict of interest

The authors declare no actual or potential conflicts of interest related to this study.

References

1. Lain KY, Roberts JM. Contemporary concepts of the pathogenesis and management of preeclampsia. JAMA. 2002;287(24):3183-6.
2. Kupferminc MJ. Thrombophilia and preeclampsia: the evidence so far. Clin Obstet Gynecol. 2005;48(2):406-15.
3. Rigo Jr J, Rigó J, Nagy B, Fintor L, Tanyi J, Beke A, et al. Maternal and neonatal outcome of preeclamptic pregnancies: the potential roles of factor V Leiden mutation and 5, 10 methylenetetrahydrofolate reductase. Hypertens Pregnancy. 2000;19(2):163-72.
4. Roberts JM, Redman CW. Pre-eclampsia: more than pregnancy-induced hypertension. Lancet. 1993;341(8858):1447-51.
5. Villar J, Say L, Shennan A, Lindheimer M, Duley L, Conde-Agudelo A, et al. Methodological and technical issues related to the diagnosis, screening, prevention, and treatment of pre-eclampsia and eclampsia. Int J Gynecol Obstet. 2004;85:S28-S41.
6. Kupferminc MJ, Eldor A, Steinman N, Many A, Bar-Am A, Jaffa A, et al. Increased frequency of genetic thrombophilia in women with complications of pregnancy. N Engl J Med. 1999;340(1):9-13.
7. Steegers-Theunissen R, Boers GJ, Blom H, Trijbels FM, Eskes TA. Hyperhomocysteinaemia and recurrent spontaneous abortion or abruptio placentae. Lancet. 1992;339(8801):1122-3.
8. Sohda S, Arinami T, Hamada H, Yamada N, Hamaguchi H, Kubo T. Methylenetetrahydrofolate reductase polymorphism and pre-eclampsia. J Med Genet. 1997;34(6):525-6.
9. Prasmusinto D, Skrablin S, Hofstaetter C, Fimmers R, Van Der Ven K. The methylenetetrahydrofolate reductase 677 C→ T polymorphism and preeclampsia in two populations. Obstet Gynecol. 2002;99(6):1085-92.
10. Dávalos I-P, Olivares N, Castillo MT, Cantú J-M, Ibarra B, Sandoval L, et al. The C677T polymorphism of the methylenetetrahydrofolate reductase gene in Mexican mestizo neural-tube defect parents, control mestizo and native populations. Ann Genet. 2000.
11. McColl M, Ellison J, Reid F, Tait R, Walker I, Greer I. Prothrombin 20210 G→ A, MTHFR C677T mutations in women with venous thromboembolism associated with pregnancy. BJOG Int J Obstet Gynaecol. 2000;107(4):565-9.
12. Frosst P, Blom H, 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(1):111.
13. Grandone E, Margaglione M, Colaizzo D, Cappucci G, Paladini D, Martinelli P, et al. Factor V Leiden, C> T MTHFR polymorphism and genetic susceptibility to preeclampsia. Thromb Haemost. 1997;77(06):1052-4.
14. Chikosi A, Moodley J, Pegoraro R, Lanning P, Rom L. 5, 10 methylenetetrahydrofolate reductase polymorphism in black South African women with pre-eclampsia. BJOG Int J Obstet Gynaecol. 1999;106(11):1219-20.
15. Pegoraro RJ, Chikosi A, Rom L, Roberts C, Moodley J. Methylenetetrahydrofolate reductase gene polymorphisms in black South Africans and the association with preeclampsia. Acta Obstet Gynecol Scand. 2004;83(5):449-54.
16. Kaiser T, Brennecke SP, Moses EK. Methylenetetrahydrofolate reductase polymorphisms are not a risk factor for pre-eclampsia/eclampsia in Australian women. Gynecol Obstet Invest. 2000;50(2):100-2.
17. Zeng X, Zhang Y, Kwong JS, Zhang C, Li S, Sun F, et al. The methodological quality assessment tools for preclinical and clinical studies, systematic review and meta-analysis, and clinical practice guideline: a systematic review. J Evid Based Med. 2015;8(1):2-10.
18. Huedo-Medina TB, Sánchez-Meca J, Marín-Martínez F, Botella J. Assessing heterogeneity in meta-analysis: Q statistic or I² index? Psychol Methods. 2006;11(2):193.
19. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315(7109):629-34.
20. Yoshida A, Miura K, Nakayama D, Masuzaki H. Correlation between preeclampsia and prevalence of polymorphism of angiotensinogen, methyleneteterahydrofolate reductase and factor V, prothrombin genes among Japanese women. Acta Med Nagasakiensia. 2008;53(2):37-41.
21. Williams M, Sanchez S, Zhang C, Bazul V. Methylenetetrahydrofolate reductase 677 C→ T polymorphism and plasma folate in relation to pre-eclampsia risk among Peruvian women. J Matern Fetal Neonatal Med. 2004;15(5):337-44.
22. Salimi S, Saravani M, Yaghmaei M, Fazlali Z, Mokhtari M, Naghavi A, et al. The early-onset preeclampsia is associated with MTHFR and FVL polymorphisms. Arch Gynecol Obstet. 2015;291(6):1303-12.
23. Rahimi Z, Malek-Khosravi S, Rahimi Z, Jalilvand F, Parsian A. MTHFR C677T and eNOS G894T variants in preeclamptic women: Contribution to lipid peroxidation and oxidative stress. Clin Biochem. 2013;46(1-2):143-7.
24. Zhang G, Zhao J, Yi J, Luan Y, Wang Q. Association between gene polymorphisms on Chromosome 1 and susceptibility to pre-eclampsia: An updated meta-analysis. Med Sci Monit Int Med J Exp Clin Res. 2016;22:2202.
25. Wang X-m, Wu H-y, Qiu X-j. Methylenetetrahydrofolate reductase (MTHFR) gene C677T polymorphism and risk of preeclampsia: an updated meta-analysis based on 51 studies. Arch Med Res. 2013;44(3):159-68.
26. Yang B, Fan S, Zhi X, Li Y, Liu Y, Wang D, et al. Associations of MTHFR gene polymorphisms with hypertension and hypertension in pregnancy: a meta-analysis from 114 studies with 15411 cases and 21970 controls. PLoS One. 2014;9(2):e87497.
27. Kosmas IP, Tatsioni A, Ioannidis JP. Association of C677T polymorphism in the methylenetetrahydrofolate reductase gene with hypertension in pregnancy and pre-eclampsia: a meta-analysis. J Hypertens. 2004;22(8):1655-62.
28. Mohammadi FS, Aslani S, Mostafaei S, Jamshidi A, Riahi P, Mahmoudi M. Are genetic variations in IL-21–IL-23R–IL-17A cytokine axis involved in a pathogenic pathway of rheumatoid arthritis? Bayesian hierarchical meta-analysis. J Cell Physiol. 2019.
29. Vanaki N, Kavosi H, Aslani S, Mostafaei S, Riahi P, Gharibdoost F, et al. Association between CD247 gene rs2056626 polymorphism and the risk of systemic sclerosis: Evidence from a systematic review and Bayesian hierarchical meta-analysis. Meta Gene. 2019:100613.
30. Lunn D, Barrett J, Sweeting M, Thompson S. Fully Bayesian hierarchical modelling in two stages, with application to meta-analysis. J R Stat Soc Ser C Appl Stat. 2013;62(4):551-72.
31. Wei C, Shouying Z, Ying G, Jie L, ZHANG J. Comparison between Fully Bayesian Hierarchical Meta-analysis and Classical Meta-analysis: A Monte Carlo Study Based on Correlation Coefficient. Metall Min Ind. 2015(9).
32. Leeda M, Riyazi N, de Vries JI, Jakobs C, van Geijn HP, Dekker GA. Effects of folic acid and vitamin B6 supplementation on women with hyperhomocysteinemia and a history of preeclampsia or fetal growth restriction. Am J Obstet Gynecol. 1998;179(1):135-9.
33. Khong T, Hague W. The placenta in maternal hyperhomocysteinaemia. BJOG Int J Obstet Gynaecol. 1999;106(3):273-8.
34. Kosmas IP, Tatsioni A, Ioannidis JP. Association of Leiden mutation in factor V gene with hypertension in

pregnancy and pre-eclampsia: a meta-analysis. J Hypertens. 2003;21(7):1221-8.
35. Roberts J, Cooper DW. Pathogenesis and genetics of pre-eclampsia. Lancet. 2001;357(9249):53-6.
36. Morrison ER, Miedzybrodzka ZH, Campbell DM, Haites NE, Wilson BJ, Watson M, et al. Prothrombotic genotypes are not associated with pre-eclampsia and gestational hypertension: results from a large population-based study and systematic review. Thromb Haemost. 2002;87(05):779-85.
37. Kim YJ, Williamson RA, Murray JC, Andrews J, Pietscher JJ, Peraud PJ, et al. Genetic susceptibility to preeclampsia: Roles of cytosine-to-thymine substitution at nucleotide 677 of the gene for methylenetetrahydrofolate reductase, 68–base pair insertion at nucleotide 844 of the gene for cystathionine β-synthase, and factor V Leiden mutation. Am J Obstet Gynecol. 2001;184(6):1211-7.
38. Kobashi G, Yamada H, Asano T, Nagano S, Hata A, Kishi R, et al. Absence of association between a common mutation in the methylenetetrahydrofolate reductase gene and preeclampsia in Japanese women. Am J Med Genet. 2000;93(2):122-5.
39. Klai S, Fekih-Mrissa N, El Housaini S, Kaabechi N, Nsiri B, Rachdi R, et al. Association of MTHFR A1298C polymorphism (but not of MTHFR C677T) with elevated homocysteine levels and placental vasculopathies. Blood Coagul Fibrinolysis. 2011;22(5):374-8.
40. Yilmaz H, Ünlüçerçi Y, Gürdöl F, Isbilen E, Isbir T. Association of pre-eclampsia with hyperhomocysteinaemia and methylenetetrahydrofolate reductase gene C677T polymorphism in a Turkish population. Aust N Z J Obstet Gynaecol. 2004;44(5):423-7.
41. Pertegal M, Fenoy FJ, Hernández M, Mendiola J, Delgado JL, Bonacasa B, et al. Fetal Val108/158Met catechol-O-methyltransferase (COMT) polymorphism and placental COMT activity are associated with the development of preeclampsia. Fertil Steril. 2016;105(1):134-43.e3.
42. Nagy B, Hupuczi P, Papp Z. High frequency of methylenetetrahydrofolate reductase 677TT genotype in Hungarian HELLP syndrome patients determined by quantitative real-time PCR. J Hum Hypertens. 2007;21(2):154.
43. Raijmakers MT, Zusterzeel PL, Steegers EA, Peters WH. Hyperhomocysteinaemia: a risk factor for preeclampsia? Eur J Obstet Gynecol Reprod Biol. 2001;95(2):226-8.
44. Jafari A, Parchami S, Reiisi S, Miraj S. Association of plasma homocysteine, folic acid levels, and C677T polymorphism in methylene tetra hydrofolate reductase with risk of preeclampsia: a case-control study in Iranian women. Clin Exp Obstet Gynecol. 2018;45(3).
45. Ibrahim ZM, Metawie MAE, El-Baz AM, El-Bahie MA. Methylenetetrahydrofolate C677T polymorphism and pre-eclamptic Egyptian women. Middle East Fertil Soc J. 2012;17(2):105-10.
46. Dissanayake VH, Sirisena ND, Weerasekera LY, Gammulla CG, Seneviratne HR, Jayasekara RW. Candidate gene study of genetic thrombophilic polymorphisms in pre-eclampsia and recurrent pregnancy loss in Sinhalese women. J Obstet Gynaecol Res. 2012;38(9):1168-76.
47. Jääskeläinen E, Keski-Nisula L, Toivonen S, Romppanen EL, Helisalmi S, Punnonen K, et al. MTHFR C677T polymorphism is not associated with placental abruption or preeclampsia in Finnish women. Hypertens Pregnancy. 2006;25(2):73-80.
48. Also-Rallo E, Lopez-Quesada E, Urreizti R, Vilaseca MA, Lailla JM, Balcells S, et al. Polymorphisms of genes involved in homocysteine metabolism in preeclampsia and in uncomplicated pregnancies. Eur J Obstet Gynecol Reprod Biol. 2005;120(1):45-52.
49. Laivuori H, Kaaja R, Ylikorkala O, Hiltunen T, Kontula K. 677 C→ T polymorphism of the methylenetetrahydrofolate reductase gene and preeclampsia. Obstet Gynecol. 2000;96(2):277-80.
50. Coral-Vázquez RM, Arauz JFR, Canizales-Quinteros S, Coronel A, Villalvazo EYV, Rivera JH, et al. Analysis of polymorphisms and haplotypes in genes associated with vascular tone, hypertension and oxidative stress in Mexican-Mestizo women with severe preeclampsia. Clin Biochem. 2013;46(7-8):627-32.
51. Zhou L, Cheng L, He Y, Gu Y, Wang Y, Wang C. Association of gene polymorphisms of FV, FII, MTHFR, SERPINE1, CTLA4, IL10, and TNFalpha with pre-eclampsia in Chinese women. Inflamm Res. 2016;65(9):717-24.
52. Pérez-Mutul J, González-Herrera LZ, Sosa-Cabrera T, Martínez-Olivares R. A mutation in the 5, 10-methylenetetrahydrofolate reductase gene is not associated with preeclampsia in women of southeast Mexico. Arch Med Res. 2004;35(3):231-4.
53. Canto P, Canto-Cetina T, Juárez-Velázquez R, Rosas-Vargas H, Rangel-Villalobos H, Canizales-Quinteros S, et al. Methylenetetrahydrofolate Reductase C677T and Glutathione S− Transferase P1 A313G Are Associated with a Reduced Risk of Preeclampsia in Maya-Mestizo Women. Hypertens Res. 2008;31(5):1015.
54. Davalos I, Moran M, Martinez-Abundis E, Gonzalez-Ortiz M, Flores-Martinez S, Machorro V, et al. Methylenetetrahydrofolate reductase C677T polymorphism and Factor V Leiden variant in Mexican women with preeclampsia/eclampsia. Blood Cells Mol Dis. 2005;35(1):66-9.
55. Mislanova C, Martsenyuk O, Huppertz B, Obolenskaya M. Placental markers of folate-related metabolism in preeclampsia. Reproduction. 2011;142(3):467-76.
56. Chedraui P, Salazar-Pousada D, Villao A, Escobar GS, Ramirez C, Hidalgo L, et al. Polymorphisms of the methylenetetrahydrofolate reductase gene (C677T and A1298C) in nulliparous women complicated with preeclampsia. Gynecol Endocrinol. 2014;30(5):392-6.
57. Chedraui P, Andrade ME, Salazar-Pousada D, Escobar GS, Hidalgo L, Ramirez C, et al. Polymorphisms of the methylenetetrahydrofolate reductase gene (C677T and A1298C) in the placenta of pregnancies complicated with preeclampsia. Gynecol Endocrinol. 2015;31(7):569-72.
58. De Maat M, Jansen M, Hille E, Vos H, Bloemenkamp K, Buitendijk S, et al. Preeclampsia and its interaction with common variants in thrombophilia genes. J Thromb Haemost. 2004;2(9):1588-93.
59. Aggarwal S, Dimri N, Tandon I, Agarwal S. Preeclampsia in North Indian women: the contribution of genetic polymorphisms. J Obstet Gynaecol Res. 2011;37(10):1335-41.
60. Dalmaz C, Santos K, Botton M, Tedoldi C, Roisenberg I. Relationship between polymorphisms in thrombophilic genes and preeclampsia in a Brazilian population. Blood Cells Mol Dis. 2006;37(2):107-10.
61. Kaiser T, Brennecke SP, Moses EK. C677T methylenetetrahydrofolate reductase polymorphism is not a risk factor for pre-eclampsia/eclampsia among Australian women. Hum Hered. 2001;51(1-2):20-2.
62. Prasmusinto D, Skrablin S, Fimmers R, Van Der Ven K. Ethnic differences in the association of factor V Leiden mutation and the C677T methylenetetrahydrofolate reductase gene polymorphism with preeclampsia. Eur J Obstet Gynecol Reprod Biol. 2004;112(2):162-9.
63. Mishra J, Talwar S, Kaur L, Chandiok K, Yadav S, Puri M, et al. Differential global and MTHFR gene specific methylation patterns in preeclampsia and recurrent miscarriages: A case-control study from North India. Gene. 2019;704:68-73.