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GENETICS

Folate metabolism gene polymorphisms *MTHFR* C677T and A1298C and risk for preeclampsia: a meta-analysis

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Abstract
Objectives *MTHFR* C677T and A1298C have been associated with the risk of preeclampsia (PE), but with conflicting results. We performed this meta-analysis to derive a more precise estimation of the association between *MTHFR* polymorphisms and PE.
Study design An electronic search of PubMed and Chinese Biomedicine database was conducted to select studies for meta-analysis. 54 case controlled studies containing *MTHFR* C677T and A1298C gene polymorphisms were chosen, and odds ratio (OR) with confidence interval (CI) was used to assess the strength of this association.
Result These studies evaluated 7398 cases and 11230 controls for *MTHFR* C677T. The overall results suggested that *MTHFR* C677T was associated with the risk of PE. (T vs. C: OR = 1.157, 95 % CI: 1.057-1.266, p=0.002; TT+CT vs. CC: OR=1.165, 95 % CI 1.049-1.293, $P = 0.004$; TT vs. CT + CC: OR = 1.371, 95 % CI: 1.153-1.63, $p < 0.001$). We also evaluated 1103 cases and 988 controls for MTHFR A1298C but could not demonstrate an increased risk of PE for this polymorphism (p=0.667). A symmetric funnel plot, the Egger's test ($p = 0.819$) suggested a lack of publication bias.
Conclusion This meta-analysis supports the idea that *MTHFR* C677T genotype is associated with increased risk for PE, especially in the case of Asians and Caucasians.

Keywords *MTHFR* C677T · A1298C · Polymorphism · Preeclampsia · Meta-analysis

Capsule This meta-analysis showed that *MTHFR* C677T genotype had increased risk of preeclampsia.

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Introduction

Preeclampsia (PE), characterized by the presence of a triad of signs involving high blood pressure, proteinuria and oedema after the 20th week of pregnancy, is one of the commonest and most serious complications of pregnancy [1]. This disease can progress to eclampsia (characterized by seizures as a sign of affection of the cerebral vessels), HELLP syndrome (hemolysis, elevated liver enzyme, low platelets) or disseminated intravascular coagulation. PE affects about 5–8 % of pregnancies, and it is still responsible for 10 to 15 % of maternal mortality [2, 3]. Although preeclampsia remains a significant source of maternal and perinatal mortality and morbidity, its etiology is not yet elucidated.

Nowadays, an association between hyperhomocysteinemia and preeclamptic patients has been reported [4–7]. Hyperhomocysteinemia lead to vascular and metabolic changes which have been associated as an established risk factor for endothelial disorders, such as arteriosclerosis and coronary artery disease, however, the underlying mechanisms remain unknown [8]. In previous studies, homocysteine concentration is increased in preeclampsia and it weakly and negatively correlates with plasma folate concentration [9, 10]. The increasing of homocysteine concentration in preeclampsia may be due to a C677T polymorphism in the *MTHFR* results in a

reduced MTHFR enzyme activity, and subsequently elevated homocysteine levels.

The human *MTHFR* gene contains 11 exons, located on chromosome 1p36.3, and encodes methylenetetrahydrofolate reductase (MTHFR) key enzyme in folate and homocysteine metabolism. MTHFR catalyzes the biologically irreversible reduction of 5, 10-methylenetetrahydrofolate to 5-methyltetrahydrofolate. Folate is important as the substrate for 5-methyltetrahy, which acts as a methyl donor for the B12-dependent remethylation of homocysteine to methionine via the methionine synthase reaction. In the MTHFR enzyme, several single nucleotide polymorphisms including the two most important C677T and A1298C can affect folate and total homocysteine (tHcy) status.

Women with the *MTHFR* C677T and A1298C mutations displayed higher plasma HCy levels as compared to controls with normal genotype [11–13]. The *MTHFR* C677T, which involves a cytosine (C) to a thymine (T) substitution at position 677, changes an alanine to a valine in the enzyme. The C677T substitution increases thermolability of MTHFR and causes impaired folate binding and reduced activity of the MTHFR enzyme [14]. *MTHFR* C677T results in an increased requirement for folic acid to maintain normal homocysteine remethylation to methionine. *MTHFR* C677T is associated with decreased concentrations of folate in serum, plasma, and red blood cells , and mildly increased plasma total homocysteine (tHcy) concentration [15].

Because of the mild hyperhomocysteinaemia found in women with preeclampsia [9, 10], the *MTHFR* C677T polymorphism could be a genetic factor contributing to the pathophysiology preeclampsia. In preeclampsia, a strong heritable component has been demonstrated: women born of a preeclamptic pregnancy are themselves at increased risk of preeclampsia in their own pregnancies; men born of a preeclamptic pregnancy have an increased risk of fathering a preeclamptic pregnancy [16]. Genetic predisposition plays an important role in the development of preeclampsia, but attempts to show associations between *MTHFR* C677T and preeclampsia have produced widely divergent results [6, 13, 17–41]. Thus in the present study, we conducted a meta-analysis to quantitatively assess the associations between the *MTHFR* polymorphisms and preeclampsia.

Materials and methods

Publication search

We searched the PubMed and Chinese biomedicine databases for all articles on the association between *MTHFR* C677T/A1298C and preeclampsia risk(last search update,July 7, 2014). The following key words were used :'MTHFR ' , 'C677T', 'A1298C ', 'polymorphism' and 'preeclampsia' or 'pre-eclampsia '. Case–control studies containing available genotype frequencies of C677T were chosen. Preeclampsia was defined as the development of hypertension and proteinuria (>300 mg urinary protein in 24 h) in women with no baseline proteinuria. Hypertension was defined as blood pressure≥140/90 mmHg. Maternal age ranged from18 to 44 years. The control group comprised women with uncomplicated pregnancy admitted for natural childbirth or caesarean section, with normal-length pregnancy, blood pressure ≤120/80 mmHg, and without proteinuria. Of the studies with overlapping data published by the same author, only the most recent or complete study was included in this meta-analysis.

Statistic analysis

The genotype distribution of the control group was evaluated for agreement with the hardy-Weinberg equilibrium (HWE) using the $\chi 2$ test with a significant level of 0.05. Odds ratios (OR) with 95 % CIs were used to determine the strength of association between the *MTHFR* polymorphisms and PE risk. The pooled ORs for the risk associated with the *MTHFR* C677T genotype, additive genetic model (T vs. C), dominant model (TT+CT vs. CC), and recessive model (TT vs. CT+CC) respectively. For *MTHFR* A1298C, the pooled ORs were performed for additive genetic model (C vs. A), dominant model (CC+CA vs. AA), and recessive model (CC vs. CA+AA) respectively. Subgroup analyses were done by ethnicity. Heterogeneity assumption was evaluated by a chi-square based Q-test. A p value greater than 0.05 for the Q test indicated a lack of heterogeneity among the studies. Thus, the pooled OR estimate of each study was calculated by the fixed-effects model. Otherwise, the random-effects model was used [42, 43]. An estimate of the potential publication bias was examined by a Begg's test (funnel plot method) and Egger's linear regression test ($P<0.05$ considered representative of statistical significance) [44]. All analyses were performed using Stata software (version 8.2; Stata Corporation, College Station, TX).

Result

Eligible studies

In this meta-analysis, we identified 54 studies on the association between MTHFR gene polymorphisms and preeclampsia (Fig. 1), including 7398/11222 cases/controls for *MTHFR* C677T (Table 1) and 1103 /988 cases/controls for *MTHFR* A1298C (Table 3, Table 4). The distribution of genotypes in the controls of the studies was in agreement with Hardy–Weinberg equilibrium, except for four studies [11, 33, 45, 46]. The search results were combined and duplicates were removed.

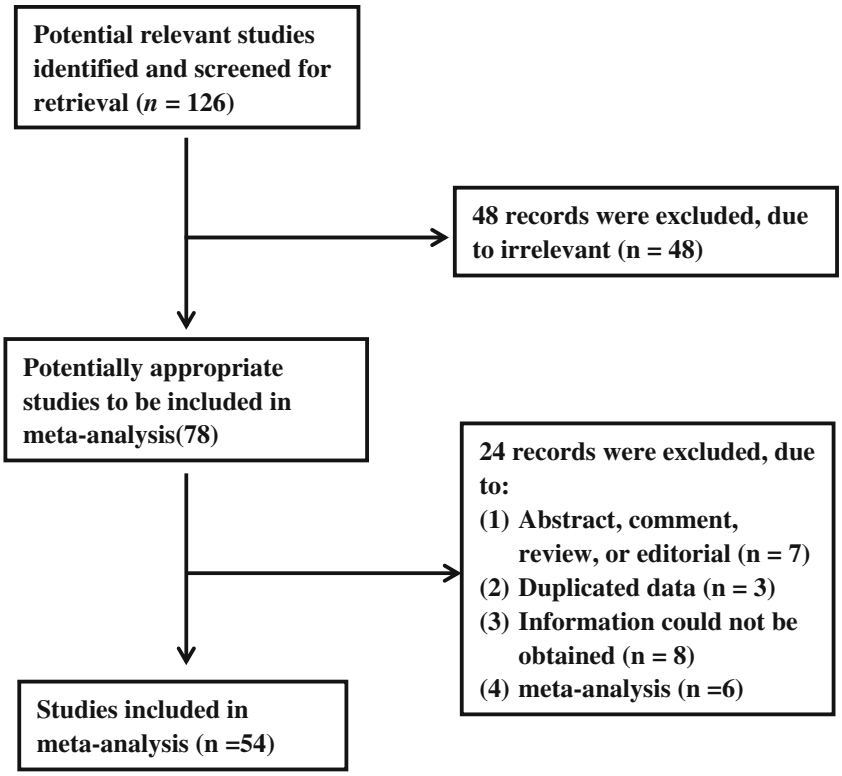


Fig. 1 Flow chart of the literature search and article selection

Meta-analysis

Differences in allelic distribution by ethnicity could be partially responsible for the observed differences in the association between *MTHFR* C677T and preeclampsia. The results of the association between the *MTHFR* C677T polymorphism and preeclampsia and the heterogeneity test are shown in Table 2. The association was most pronounced for *MTHFR* C677T (Additive model: OR = 1.157, 95 % CI: 1.057–1.266, p=0.002; dominant model:OR = 1.165 95 % CI 1.049-1.293, p=0.004 ; Recessive model: OR = 1.371,95 % CI: 1.153-1.63, $p < 0.001$). The positive association was driven by a Caucasian recessive model (OR = 0.282, 95 % CI: 1.048-1.567,p = 0.015) and an Asian recessive model (OR = 2.078, 95 % CI: 1.368-3.157, p=0.001, Fig. 2). For *MTHFR* A1298C gene polymorphism and its association with increased the risk for preeclampsia, the additive (p = 0.667), dominant (p = 0.844) and recessive models (p = 0.264) for *MTHFR* A1298C produced no significant associations overall.

Publication bias

Funnel plot and Egger's test were performed to quantitatively evaluate the publication bias of literatures on PE. The results of Egger's test provided statistical evidence for funnel plot symmetry (P=0.819) in overall results, suggesting the absence of publication bias.

Discussion

In this study, we investigated that *MTHFR* C677T polymorphism is positively related to PE risk. The frequency of *MTHFR* C677T was 1.371 times higher in case patients than in control patients. The association appeared to be stronger in Caucasian and Asian patients. However, the correlation was not found between *MTHFR* A1298C and PE. We speculated that *MTHFR* C677T might be an early marker for PE diagnosis.

The mechanism of PE is still relatively unclear. Some maternal metabolic disorders like diabetes and chronic hypertension probably contribute to the aberrant endothelial function observed in preeclampsia. On the other hand, some clinical studies have documented a familial tendency toward development of preeclampsia, suggesting a genetic factors could predispose women to develop it [47]. Hyperhomocysteinemia has also been described as a risk factor for PE and a promoter of endothelial dysfunction in preeclampsia [10, 48].

The meta-analysis examined the MTHFR gene polymorphisms C677T and A1298C and their relationship to the risk of PE. The frequency of T-carriers genotypes was found significantly higher among the women with PE than the control groups indicated that *MTHFR* C677T polymorphism would be expected to play a major role to bring about PE. Some studies reported significantly increased prevalence of *MTHFR* C677T among cases [22–24, 49]. In contrast, other

Table 1 The distribution of the MTHFR C677T genotypes for cases and controls

Author	Publication year	Country	Ethnicity	Case			Control			P[a]
				CC	CT	TT	CC	CT	TT	
Chedraui, P.[11]	2014	Ecuador	Caucasian	59	73	18	47	91	12	0
Coral-Vazquez, R. M.[56]	2013	Mexico	Latino	38	109	83	71	166	115	0.43
Lykke, J. A[60]	2012	Denmark	Caucasian	113	118	31	906	793	143	0.09
Dissanayake, V. H.[61]	2012	Sri Lanka	Asian	136	36	3	142	27	2	0.58
Klai, S.[45]	2011	Tunisia	Caucasian	22	20	2	61	39	0	0.02
Mislanova, C.[12]	2011	Austria	Caucasian	12	11	5	21	17	2	0.54
Aggarwal, S.[62]	2011	India	Asian	160	33	7	134	58	8	0.59
Sun [55]	2011	China	Asian	32	22	22	331	154	28	0.08
Stiefel, P.[63]	2009	Spain	Caucasian	157[a]	–	27	113	–	21	–
Shen, X.N[31]	2009	China	Asian	12	35	14	30	21	9	0.12
Wang, S.M[46]	2008	China	Asian	6	19	17	13	40	11	0.04
Zhang, X.Y[64]	2008	China	Asian	22	21	7	29	8	3	0.05
Muetze, S.[65]	2008	German	Caucasian	30	34	7	35	29	15	0.06
Canto, P.[18]	2008	Mexico	Latino	36	66	23	61	131	82	0.53
Stonek, F.[66]	2007	Austria	Caucasian	9	14	2	669	573	155	0.06
Nagy, B.[67]	2007	Hungary	Caucasian	71	68	25	32	35	5	0.27
Zhang, Z.H[54]	2007	China	Asian	12	21	20	10	30	9	0.12
Dusse, L. M.[68]	2007	Brazil	Latino	16	12	2	46	31	6	0.81
Jaaskelainen, E.[69]	2006	Finland	Caucasian	78	43	12	64	42	6	0.79
Demir, S. C.[70]	2006	German	Caucasian	19	29	8	43	47	12	0.88
Dalmaz, C. A.[19]	2006	Brazil	Latino	31	27	17	76	51	18	0.05
Mello, G.[71]	2005	Italy	Caucasian	729[a]	–	79	793	–	15	–
Driul, L.[72]	2005	Italy	Caucasian	34 [a]	–	5	57	–	7	–
Davalos, I. P.[20]	2005	Mexico	Latino	13	14	6	24	27	11	0.48
Also-Rallo, E.[26]	2005	Spain	Caucasian	78	59	20	63	75	19	0.64
Yilmaz, H.[73]	2004	Turkey	Caucasian	29	28	7	24	17	6	0.30
Williams, M. A[74]	2004	Peru	Latino	37	61	25	62	85	30	0.92
Perez-Mutul, J.[75]	2004	Mexico	Latino	33	66	49	36	80	61	0.30
Pegoraro, R. J.[36]	2004	South Africa	Asian	464	76	2	298	38	2	0.52
De Maat, M. P.[41]	2004	Netherlands	Caucasian	78	59	20	63	75	19	0.64
Fabbro, D.[76]	2003	Italy	Caucasian	44 [a]	–	8	68	–	12	–
Prasmusinto, D.[22]	2002	German	Caucasian	7	7	1	12	15	7	0.57
Prasmusinto, D.[22]	2002	Croatian	Caucasian	11	12	2	18	15	5	0.51
Prasmusinto, D.[22]	2002	Indonesian	Asian	34	6	1	22	5	0	0.60
Morrison, E. R.[29]	2002	Scotland	Caucasian	169	193	42	81	66	17	0.52
D'Elia, A. V.[77]	2002	Italy	Caucasian	52 [a]	–	6	65	–	9	–
Watanabe, H.[78]	2001	Japan	Asian	40	59	34	89	103	32	0.80
Raijmakers, M. T.[30]	2001	Scotland	Caucasian	72	74	21	205	162	36	0.62
Livingston, J. C.[37]	2001	USA	Caucasian	66	34	10	61	27	7	0.12
Lachmeijer, A. M.[13]	2001	Netherlands	Caucasian	66	94	14	58	51	11	0.96
Kim, Y. J.[31]	2001	USA	Caucasian	131	117	33	167	152	41	0.47
Kaiser, T.[54]	2001	Australia	Caucasian	71	66	19	37	31	11	0.29
Alfirevic, Z.[64]	2001	UK	Caucasian	56 [a]	–	7	42	–	2	–
Rigo, J., Jr.[33]	2000	Hungary	Caucasian	46	66	8	42	53	6	0.04
Rajkovic, A.[79]	2000	USA	Caucasian	142	28	1	151	32	0	0.19
Li, K.[80]	2000	China	Asian	9	30	18	5	16	3	0.09
Laivuori, H.[81]	2000	Finland	Caucasian	64	45	4	56	40	7	0.97

Table 1 (continued)

Author	Publication year	Country	Ethnicity	Case			Control			P[a]
				CC	CT	TT	CC	CT	TT	
Kupferminc, M. J.[82]	2000	Israel	Caucasian	48 [a]	–	15	114	–	12	–
Kobashi, G.[23]	2000	Japan	Asian	25	40	8	83	99	33	0.7
Kaiser, T.[83]	2000	Australia	Caucasian	65	68	14	46	49	14	0.87
Powers, R. W.[84]	1999	USA	Caucasian	35	49	15	54	46	14	0.39
O'Shaughnessy, K. M.[35]	1999	UK	Caucasian	138	114	31	51	37	12	0.2
Kupferminc, M. J.[23]	1999	Israel	Caucasian	27 [a]	–	7	101	–	9	–
Chikosi, A. B.[85]	1999	South Africa.	Asian	86	18	1	97	13	0	0.51
Sohda, S.[5]	1997	Japan	Asian	19	32	16	38	49	11	0.42
Grandone, E.[6]	1997	Italy	Caucasian	66 [a]	–	28	105	–	24	–

[a] CC+CT

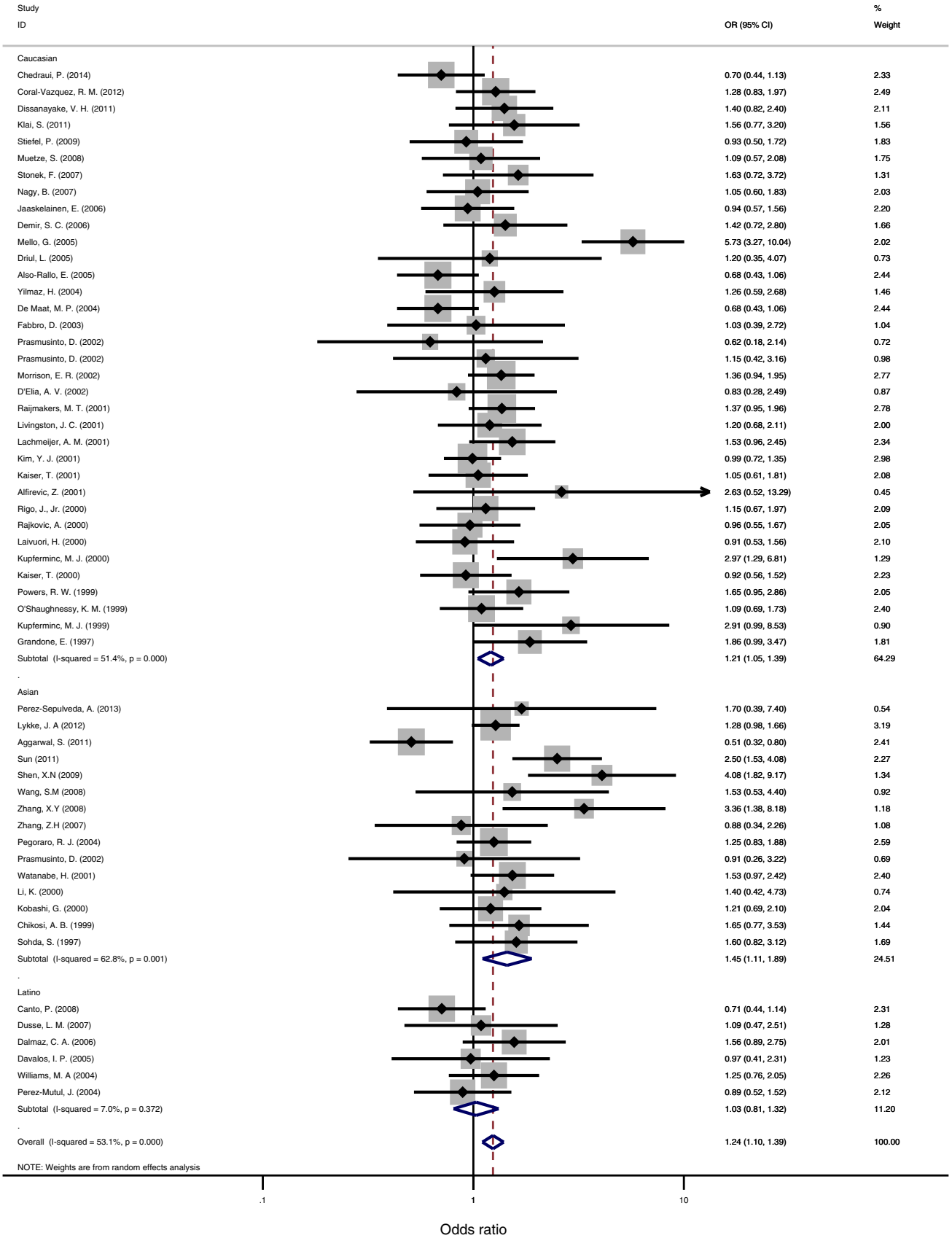
studies reported an insignificant association between the *MTHFR* C677T and PE [19, 20, 25, 32, 36, 39, 50]. For MTHFR A1298C polymorphism, much more contradictory reports have been presented. The differences in ethnicity may be a major reason for the controversy.

Table 2 ORs and 95 % CI for PE and the MTHFR C677T polymorphism under different genetic models

genetice model	population	pooled OR [95 % CI] p	Heterogeneity *p*-value	Publication Bias	
				p-value Begg	*p*-value Egger
Additive	Caucasian	1.07[0.993–1.152]0.075	0.752	0.547	0.502
(T vs. C)	Asian	1.477[1.175–1.857]0.001	*P*<0.001	0.826	0.74
	Latino	1.026[0.797–1.32]0.844	0.038	0.188	0.53
	Overall	1.157[1.057–1.266]0.002	*P*<0.001	0.569	0.885
Dominant	Caucasian	1.099[0.995-1.213]0.063	0.41*P*<0.001	0.378	0.921
(T-carriers vs.CC)	Asian	1.465[1.086-1.977]0.013	p<0.001	0.956	0.414
	Latino	1.081[0.876-1.333]0.469	0.411	0.881	0.947
	Overall	1.165[1.049-1.293]0.004	*p*=0.004 *P*<0.001	0.441	0.819
Recessive	Caucasian	1.282[1.048-1.567]0.015	0.002	0.865	0.553
(TT vs. C-carriers)	Asian	2.078[1.368-3.157]0.001	*P*=0.001	0.547	0.394
	Latino	1.033[0.755-1.414]0.837	0.093	0.881	0.888
	Overall	1.371[1.153-1.63]p<0.001	P<0.001	1.000	0.383

Table 3 The distribution of the MTHFR A1298C variant for cases and controls

Author	Publication year	Country	Ethnicity	Case			Control			P[a]
				AA	AC	CC	AA	AC	CC	
Chedraui, P.[11]	2014	Ecuador	Caucasian	100	27	23	110	39	1	
Dissanayake, V. H.[61]	2012	SriLanka	Asian	71	89	13	76	83	12	
Klai, S.[45]	2011	Tunisia	Caucasian	40	0	4	61	39	0	
Pegoraro, R. J.[36]	2004	South Africa	Asian	426	110	6	263	67	8	
Lachmeijer, A. M.[13]	2001	Netherlands	Caucasian	18	22	7	45	64	11	
Kaiser, T.[83]	2000	Australia	Caucasian	53	81	13	44	53	12	


Study
ID
OR (95% CI)
%
Weight
Caucasian
Chedraui, P. (2014) 0.70 (0.44, 1.13) 2.33
Coral-Vazquez, R. M. (2012) 1.28 (0.83, 1.97) 2.49
Dissanayake, V. H. (2011) 1.40 (0.82, 2.40) 2.11
Klai, S. (2011) 1.56 (0.77, 3.20) 1.56
Stiefel, P. (2009) 0.93 (0.50, 1.72) 1.83
Muetze, S. (2008) 1.09 (0.57, 2.08) 1.75
Stonek, F. (2007) 1.63 (0.72, 3.72) 1.31
Nagy, B. (2007) 1.05 (0.60, 1.83) 2.03
Jaaskelainen, E. (2006) 0.94 (0.57, 1.56) 2.20
Demir, S. C. (2006) 1.42 (0.72, 2.80) 1.66
Mello, G. (2005) 5.73 (3.27, 10.04) 2.02
Driul, L. (2005) 1.20 (0.35, 4.07) 0.73
Also-Rallo, E. (2005) 0.68 (0.43, 1.06) 2.44
Yilmaz, H. (2004) 1.26 (0.59, 2.68) 1.46
De Maat, M. P. (2004) 0.68 (0.43, 1.06) 2.44
Fabbro, D. (2003) 1.03 (0.39, 2.72) 1.04
Prasmusinto, D. (2002) 0.62 (0.18, 2.14) 0.72
Prasmusinto, D. (2002) 1.15 (0.42, 3.16) 0.98
Morrison, E. R. (2002) 1.36 (0.94, 1.95) 2.77
D'Elia, A. V. (2002) 0.83 (0.28, 2.49) 0.87
Raijmakers, M. T. (2001) 1.37 (0.95, 1.96) 2.78
Livingston, J. C. (2001) 1.20 (0.68, 2.11) 2.00
Lachmeijer, A. M. (2001) 1.53 (0.96, 2.45) 2.34
Kim, Y. J. (2001) 0.99 (0.72, 1.35) 2.98
Kaiser, T. (2001) 1.05 (0.61, 1.81) 2.08
Alfirevic, Z. (2001) 2.63 (0.52, 13.29) 0.45
Rigo, J., Jr. (2000) 1.15 (0.67, 1.97) 2.09
Rajkovic, A. (2000) 0.96 (0.55, 1.67) 2.05
Laivuori, H. (2000) 0.91 (0.53, 1.56) 2.10
Kupferminc, M. J. (2000) 2.97 (1.29, 6.81) 1.29
Kaiser, T. (2000) 0.92 (0.56, 1.52) 2.23
Powers, R. W. (1999) 1.65 (0.95, 2.86) 2.05
O'Shaughnessy, K. M. (1999) 1.09 (0.69, 1.73) 2.40
Kupferminc, M. J. (1999) 2.91 (0.99, 8.53) 0.90
Grandone, E. (1997) 1.86 (0.99, 3.47) 1.81
Subtotal (I-squared = 51.4%, p = 0.000) 1.21 (1.05, 1.39) 64.29
.
Asian
Perez-Sepulveda, A. (2013) 1.70 (0.39, 7.40) 0.54
Lykke, J. A (2012) 1.28 (0.98, 1.66) 3.19
Aggarwal, S. (2011) 0.51 (0.32, 0.80) 2.41
Sun (2011) 2.50 (1.53, 4.08) 2.27
Shen, X.N (2009) 4.08 (1.82, 9.17) 1.34
Wang, S.M (2008) 1.53 (0.53, 4.40) 0.92
Zhang, X.Y (2008) 3.36 (1.38, 8.18) 1.18
Zhang, Z.H (2007) 0.88 (0.34, 2.26) 1.08
Pegoraro, R. J. (2004) 1.25 (0.83, 1.88) 2.59
Prasmusinto, D. (2002) 0.91 (0.26, 3.22) 0.69
Watanabe, H. (2001) 1.53 (0.97, 2.42) 2.40
Li, K. (2000) 1.40 (0.42, 4.73) 0.74
Kobashi, G. (2000) 1.21 (0.69, 2.10) 2.04
Chikosi, A. B. (1999) 1.65 (0.77, 3.53) 1.44
Sohda, S. (1997) 1.60 (0.82, 3.12) 1.69
Subtotal (I-squared = 62.8%, p = 0.001) 1.45 (1.11, 1.89) 24.51
.
Latino
Canto, P. (2008) 0.71 (0.44, 1.14) 2.31
Dusse, L. M. (2007) 1.09 (0.47, 2.51) 1.28
Dalmaz, C. A. (2006) 1.56 (0.89, 2.75) 2.01
Davalos, I. P. (2005) 0.97 (0.41, 2.31) 1.23
Williams, M. A (2004) 1.25 (0.76, 2.05) 2.26
Perez-Mutul, J. (2004) 0.89 (0.52, 1.52) 2.12
Subtotal (I-squared = 7.0%, p = 0.372) 1.03 (0.81, 1.32) 11.20
.
Overall (I-squared = 53.1%, p = 0.000) 1.24 (1.10, 1.39) 100.00
NOTE: Weights are from random effects analysis
.1
1
10
Odds ratio

◀ **Fig. 2** Forest plot of ORs of PE for T-carriers allele (TT+CT) when compared to the CC genotype. The squares and horizontal lines correspond to the study-specific OR and 95 % CI. The area of the squares reflects the study-specific weight. The diamond represents the pooled OR and 95 % CI

Three meta-analysis summarizing studies on association between the *MTHFR* C677T polymorphism and the risk of PE until August 2012 have been performed [51–53], however, their meta-analysis did not perform analyses on association between the *MTHFR* A1298C and the risk of PE. Six studies with 1103 /988 cases /controls for *MTHFR* A1298C were chosen. We found that the previous meta-analysis did not include at least 5 studies in the last updated meta-analysis [4, 36, 41, 54, 55]. In addition, two new studies have been published since July 2014 [11, 56]. We excluded two studies in the previous meta-analyses after evaluating the articles.

The summary OR from our meta-analyses evidenced the importance of the ethnical origin when approaching the issue, as we have observed a correlation between *MTHFR* C677T and preeclampsia in Caucasian (p=0.015) and Asian (p=0.001). When the *MTHFR* A1298C was considered, we failed to find any association with the risk for preeclampsia.

The C677T polymorphism in *MTHFR* gene was associated with elevated plasma homocysteine level, increased risk of arterial stiffness [57]. Women with elevated total homocysteine concentrations showed a significant association with cellular fibronectin concentration,a marker of endothelial dysfunction [10]. Cellular fibronectin (cFN), an isoform of fibronectin synthesized locally by endothelial cells in response to tissue injury, has been reported in several studies to be elevated in women with preeclampsia [58, 59]. It is also possible that the association of the *MTHFR* 677TT genotype with PE, independent of hyperhomocysteinemia, was due to interference with red blood cell folate metabolism.

There are limitations that are present in this analysis, which mainly relate to the lack of other risk factors between the subjects in the available studies. In these cases, few investigators reported results from subgroup analysis for other risk factors, such as maternal age, dietary parameters, and behavioral factors and so on. Therefore, the association in these factors could not be assessed. There is a need for larger and wider case–control studies to explore the role of other factors that are likely to cause PE.

This is a meta-analysis with sufficient individual data to stratify results by ethnicity. In the stratified analysis, individuals with the TT genotype in the recessive model had increased risk of PE (OR=0.282, 95 % CI: 1.048-1.567, p=0.015) in Caucasian subjects and in Asian subjects (OR=2.078, 95 % CI: 1.368-3.157, p=0.001). In conclusion, the overall result of the present meta-analysis demonstrated that the *MTHFR* T677T genotype had increased risk of PE. Our finding, showing *MTHFR* 677TT polymorphism is associated with PE,may provide a clue toward a better understanding of the correlation between *MTHFR* 677 TT genotype and the pathogenesis of PE in human.

Table 4 ORs and 95 % CI for PE and the MTHFR A1298C polymorphism under different genetic models

genetice model	population	pooled OR [95 % CI] p	Heterogeneity *p*-value	Publication Bias	
				p-value Begg	*p*-value Egger
Additive (C vs. A)	Caucasian	1.074[0.642–1.798]0.785	0.004	0.497	0.374
	Asian	0.988[0.795–1.229]0.917	0.399	0.317	–
	Overall	1.067[0.795–1.431]0.667	0.009	0.748	0.256
Dominant (C-carriers vs.AA)	Caucasian	0.821[0.417–1.619]0.57	0.004	0.042	0.037
	Asian	1.023[0.788–1.327]0.865	0.5	0.317	–
	Overall	0.965[0.679–1.371]0.844	0.02	0.108	0
Recessive (CC vs. A-carriers)	Caucasian	3.755[0.748–18.852]0.10-8	0.001	0.174	0.068
	Asian	0.759[0.335–1.717]0.507	0.217	0.317	–
	Overall	1.729[0.662–4.52]0.264	0.001	0.335	0

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