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CORRESPONDENCE

The association between methylenetetrahydrofolate reductase C677T polymorphism and pre-eclampsia risk: appraisal of a recent meta-analysis

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We read with great interest the article entitled 'Meta-analysis of the methylenetetrahydrofolate reductase C677T polymorphism and susceptibility to pre-eclampsia',[1] which was published in *Hypertension Research* in 2012. Xia *et al.*[1] found methylenetetrahydrofolate reductase (*MTHFR*) 677T increased the risk of pre-eclampsia in Asians, but not in the Caucasian ethnicity. However, we have several concerns related to the article.

First, failure in obtaining/including all published reports should be considered. Limiting to the same search deadline (March 2012), we located five additional reports on *MTHFR* C677T and pre-eclampsia risk published between 2006–2011,[2–6] which have not been included in the meta-analysis, even though they satisfied the inclusion criteria. In addition, another two papers are available to date.[7,8] Careful analysis of these seven studies on the basis of validated Newcastle–Ottawa scale (NOS) (recommended by the Cochrane Non-Randomized Studies Methods Working Group) revealed that these studies were of moderate to high quality (Table 1). Missing these studies would obviously affect the accuracy of the results.

In addition, Xia *et al.*[1] included four studies published in Chinese, which were obtained from Chinese Biomedical Database and the China National Knowledge Infrastructure. Although these four studies demonstrated a significant positive association between 677T and pre-eclampsia risk, the NOS evaluations suggested that they were poor in quality, therefore, including these studies may exaggerate the strength of the association between *MTHFR* C677T and pre-eclampsia in Asians.

Second, there are some issues with the Hardy–Weinberg equilibrium (HWE). In the results, Xia *et al.*[1] stated that 'Among the 40 eligible articles, four studies were excluded because the genotype distribution in the control population deviated significantly from the HWE'. We assessed the HWE by the same online calculator mentioned in the methods (http://ihg.gsf.de/cgi-bin/hw/hwa1.pl). However, the genotype distributions among the control populations in two[9,10] of the excluded studies were in agreement with HWE ($P>0.05$) (Table 1). Thus, these papers did meet the inclusion criteria and should have been included in the meta-analysis.

Third, Xia *et al.*[1] identified the population in Aggarwal's study as Asian ethnicity. However, according to the original statement 'All patients were Indian nationals from Lucknow and the surrounding countryside, and belonged to the same linguistic group (Indo-European speakers)'; therefore, the population should be clarified as Caucasian ethnicity.

Finally, there are two mistakes in the article. The data extracted from the investigation of Grandone *et al.*[11] seemed not to be in line with the raw data. Grandone *et al.*[11] reported the distribution of *MTHFR* C677T in cases and controls as CC (25), CT (41), TT (28); CC (41), CT (64), TT (24), respectively. Nevertheless, there was a printing mistake in Table 1 of Xia's meta-analysis, the numbers of carriers of TT and CC genotypes were reversed. The correct order should be 'CC, CT, TT'.

Taking into account these methodological considerations, we put all studies into a new meta-analysis including 38 eligible studies, and observed that the *MTHFR* 677T carriers were 1.12 times more likely to develop pre-eclampsia (95%CI, 1.03-1.21) compared with 677CC homozygous individuals. Similar results were obtained under other genetic comparisons (Table 2). Moreover, subgroup analysis showed *MTHFR* 677T was associated with increased pre-eclampsia risk, not only in Asians but also in populations of Caucasian ethnicity (Table 2).

Table1 Characteristics of included studies of *MTHFR* C677T and pre-eclampsia

First author[ref.]	*Country*	*Ethnicity*	P-*value of HWE*	*NOS score*
Grandone[11]	Italy	Caucasian	0.02	7
Rigo[9]	Hungary	Caucasian	0.07	8
Livingston[10]	USA	Mixed	0.13	5
Demir[2]	Turkey	Unknown	1.00	5
Stonek[3]	Austria	Caucasian	0.06	7
Yoshida[4]	Japan	Asian	0.53	5
Kahn[5]	Canada	Unknown	0.10	9
Mislanova[6]	Ukraine	Caucasian	0.70	5
Lykke[8]	Denmark	Caucasian	0.10	7
Dissanayake[7]	Sri Lanka	Asian	0.63	8

Abbreviation: *MTHFR*, methylenetetrahydrofolate reductase gene.

Table2 Subgroup analysis of ORs and 95% CI of *MTHFR* C677T and pre-eclampsia risk

Analysis model	*Population (study no.)*	*Heterogeneity P-value*	I^2*(%)*[a]	*OR*	*95% CI*	*Egger's test*
Recessive model (TT vs CC + CT)	Total (38)	0.00	43.40	1.18[b]	0.98–1.41	0.54
	Asian (6)	0.04	56.00	1.97[b]	1.08–3.61	
	Caucasian (23)	0.10	28.80	1.17[b]	0.95–1.43	
Dominant model (CT + TT vs CC)	Total (38)	0.54	0.00	1.12	1.03–1.21	0.87
	Asian (6)	0.96	0.00	1.42	1.11–1.81	
	Caucasian (24)	0.29	12.20	1.09	0.98–1.20	
TT vs CC	Total (38)	0.03	31.60	1.23[b]	1.03–1.46	0.56
	Asian (6)	0.17	36.30	2.17[b]	1.27–3.70	
	Caucasian (23)	0.43	2.20	1.24[b]	1.04–1.48	
CT vs CC	Total (38)	0.64	0.00	1.09	1.00–1.19	0.99
	Asian (6)	0.92	0.00	1.24	0.96–1.61	
	Caucasian (23)	0.14	25.10	1.05	0.94–1.17	
Allele-frequency (T vs C allele)	Total (38)	0.01	38.90	1.11[b]	1.02–1.21	0.98
	Asian (6)	0.28	20.70	1.44[b]	1.17–1.77	
	Caucasian (23)	0.07	31.70	1.08[b]	0.98–1.19	

Abbreviations: CI, confidence interval; *MTHFR*, methylenetetrahydrofolate reductase gene; OR, odds ratio.
[a]Quantification of the heterogeneity, ranging from 0 to 100%.
[b]Random-effects model.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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1 Xia XP, Chang WW, Cao YX. Meta-analysis of the methylenetetrahydrofolate reductase C677T polymorphism and susceptibility to pre-eclampsia. *Hypertens Res* 2012; **35**: 1129–1134.
2 Demir SC, Evruke C, Ozgunen T, Kadayifci O, Altintas U, Kokangul S. The relationship between pregnancy induced hypertension and congenital thrombophilia. *Saudi Med J* 2006; **27**: 1161–1166.
3 Stonek F, Hafner E, Philipp K, Hefler LA, Bentz EK, Tempfer CB. Methylenetetrahydrofolate reductase C677T polymorphism and pregnancy complications. *Obstet Gynecol* 2007; **110**(Part 1): 363–368.
4 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 Nagasaki* 2008; **53**: 37–41.
5 Kahn SR, Platt R, McNamara H, Rozen R, Chen MF, Genest Jr J, Goulet L, Lydon J, Seguin L, Dassa C, Masse A, Asselin G, Benjamin A, Miner L, Ghanem A, Kramer MS. Inherited thrombophilia and preeclampsia within a multicenter cohort: the montreal preeclampsia study. *Obstet Gynecol Surv* 2009; **64**: 366–368.
6 Mislanova C, Martsenyuk O, Huppertz B, Obolenskaya M. Placental markers of folate-related metabolism in preeclampsia. *Reproduction* 2011; **142**: 467–476.
7 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**: 1168–1176.
8 Lykke JA, Bare LA, Olsen J, Lagier R, Arellano AR, Tong C, Paidas MJ, Langhoff-Roos J. Thrombophilias and adverse pregnancy outcomes: results from the Danish National Birth Cohort. *J Thromb Haemost* 2012; **10**: 1320–1325.
9 Rigo Jr. J, Nagy B, Fintor L, Tanyi J, Beke A, Karadi I, Papp Z. Maternal and neonatal outcome of preeclamptic pregnancies: the potential roles of factor V Leiden mutation and 5,10 methylenetetrahydrofolate reductase. *Hypertens Pregnancy* 2000; **19**: 163–172.
10 Livingston JC, Barton JR, Park V, Haddad B, Phillips O, Sibai BM. Maternal and fetal inherited thrombophilias are not related to the development of severe preeclampsia. *Am J Obstet Gynecol* 2001; **185**: 153–157.
11 Grandone E, Margaglione M, Colaizzo D, Cappucci G, Paladini D, Martinelli P, Montanaro S, Pavone G, Di Minno G. Factor V Leiden, C>T MTHFR polymorphism and genetic susceptibility to preeclampsia. *Thromb Haemost* 1997; **77**: 1052–1054.