CEOG Clinical and Experimental Obstetrics & Gynecology

Non-association of MMP-9 -1562C/T polymorphism with preeclampsia risk: evidence from a meta-analysis

C.M. Wang[1], S.L. Zhang[2]

[1] *Department of Gynecology and Obstetrics, The Second Affiliated Hospital of the Southeast University, Nanjing*
[2] *Department of General Surgery, Zhongda Hospital, Medical College of Southeast University, Nanjing (China)*

Summary

Individual genetic association studies examining the relationship between the MMP-9 -1562C/T polymorphism (rs3918242) and preeclampsia risk have yielded inconsistent results. *Objective:* This study aims to evaluate the association between the MMP-9 -1562C/T polymorphism and preeclampsia risk using meta-analysis. *Materials and Methods:* Relevant studies were identified by searching PubMed database. Data were extracted and statistical analysis was performed using STATA 12.0 software. A total of six publications involving 871 cases and 845 controls were included in this meta-analysis. *Results:* Combined analysis revealed no association between the MMP-9 -1562C/T polymorphism and preeclampsia risk (allelic model: OR = 1.10, 95% CI 0.86 - 1.41, $P_{heterogeneity}$= 0.07; recessive model: OR = 0.38, 95% CI 0.14-1.01, $P_{heterogeneity}$= 0.64; dominant model: OR = 1.09, 95% CI 0.70 - 1.69, $P_{heterogeneity}$= 0.01; homozygous model: OR = 0.41, 95% CI 0.15 - 1.09, $P_{heterogeneity}$ = 0.67; heterozygous model: OR = 1.36, 95% CI 0.80 - 2.29, $P_{heterogeneity}$ = 0.01). Similarly, subgroup analysis by ethnicity showed that MMP-9 -1562C/T polymorphism was not associated with preeclampsia risk in Brazilian (allelic model: OR = 1.37, 95% CI 0.92 - 2.05, $P_{heterogeneity}$= 0.61; recessive model: OR = 0.80, 95% CI 0.18 - 3.57, $P_{heterogeneity}$= 0.58; dominant model: OR = 1.12, 95%CI 0.60-2.10, $P_{heterogeneity}$= 0.03; homozygous model: OR = 0.87, 95%CI 0.19-3.94, $P_{heterogeneity}$ = 0.62; heterozygous model: OR = 1.55, 95% CI 0.99 - 1.75, $P_{heterogeneity}$ = 0.32). *Conclusion:* This meta-analysis indicated that MMP-9 -1562C/T polymorphism was not associated with preeclampsia risk. However, large well-designed, multi-center epidemiological studies should be carried out in these and other ethnic populations to confirm our findings.

Key words: MMP-9; Polymorphism; Preeclampsia; Meta-analysis.

Introduction

Preeclampsia is a leading cause of maternal mortality and morbidity worldwide. It is characterized by the new onset of hypertension and proteinuria after the 20th week of gestation and occurs in about 3% to 7% of all pregnancies [1-4]. The pathogenesis of preeclampsia has not been completely elucidated. However, previous studies have suggested that preeclampsia development is multifactorial, resulting from endothelial cell dysfunction, excessive vasoconstriction, inflammation, immunological disorder, etc [5, 6]. Among them, a genetic component in preeclampsia cannot be neglected.

It is well known that abnormal placentation, impairing trophoblast invasion, may play a vital role in the pathophysiology of preeclampsia. MMP-9 is a member of the MMP family which plays a crucial role in restructuring the extracellular matrix, and possesses proteolytic activity against type IV collagen, a major component of the basement membrane. It has been reported that cytotrophoblast MMP-9 activity is increased in human placental tissue [7]. In addition, the inability to produce sufficient matrix metalloproteinases may be an early manifestation of abnormal placentation such as in preeclampsia [8]. Therefore, abnormal MMP-9 expression may be related to preeclampsia development.

The MMP-9 gene, localized to chromosome 20q13.2, encodes zinc-dependent enzyme that breaks down extracellular matrix and promotes cell invasion. MMP-9 gene expression is known to be influenced by functional SNP-1562C/T (rs3918242) in the promoter region [9, 10]. Many epidemiological investigations have investigated the role of MMP-9 -1562C/T polymorphism (rs3918242) in preeclampsia risk. However, the results of these studies remain inconclusive. Therefore, the authors performed a comprehensive meta-analysis to derive a more precise estimation of the relationship between MMP-9 - 1562C/T polymorphism and the risk of preeclampsia.

Materials and Methods

Publication search and inclusion criteria: A literature search of the PubMed database was carried out (updated to May 1, 2014) using the following keywords: "polymorphism", "preeclampsia", and "MMP-9". In addition, studies were identified by a manual search of the reference lists of reviews and retrieved studies. Studies were eligible if they met the following criteria: (a) investigating the association between the MMP-9 -1562C/T polymorphism

Revised manuscript accepted for publication July 7, 2014

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

First author [Ref]	Year	Country	Case/Control	Case			Control		
				TT	TC	CC	TT	TC	CC
Rahimi Z. [13]	2013	Iran	160/112	0	38	122	4	14	94
Luison M.R. [14]	2012	Brazil	82/79	1	20	61	2	10	67
Palei A.C. [15]	2010	Brazil	154/176	2	34	118	2	31	143
Fraser R. [16]	2008	UK	117/146	1	34	82	4	28	114
Coolman M. [9]	2007	Netherlands	145/151	1	16	128	2	31	118
Palei A.C. [17]	2012	Brazil	213/181	47		166	55		126

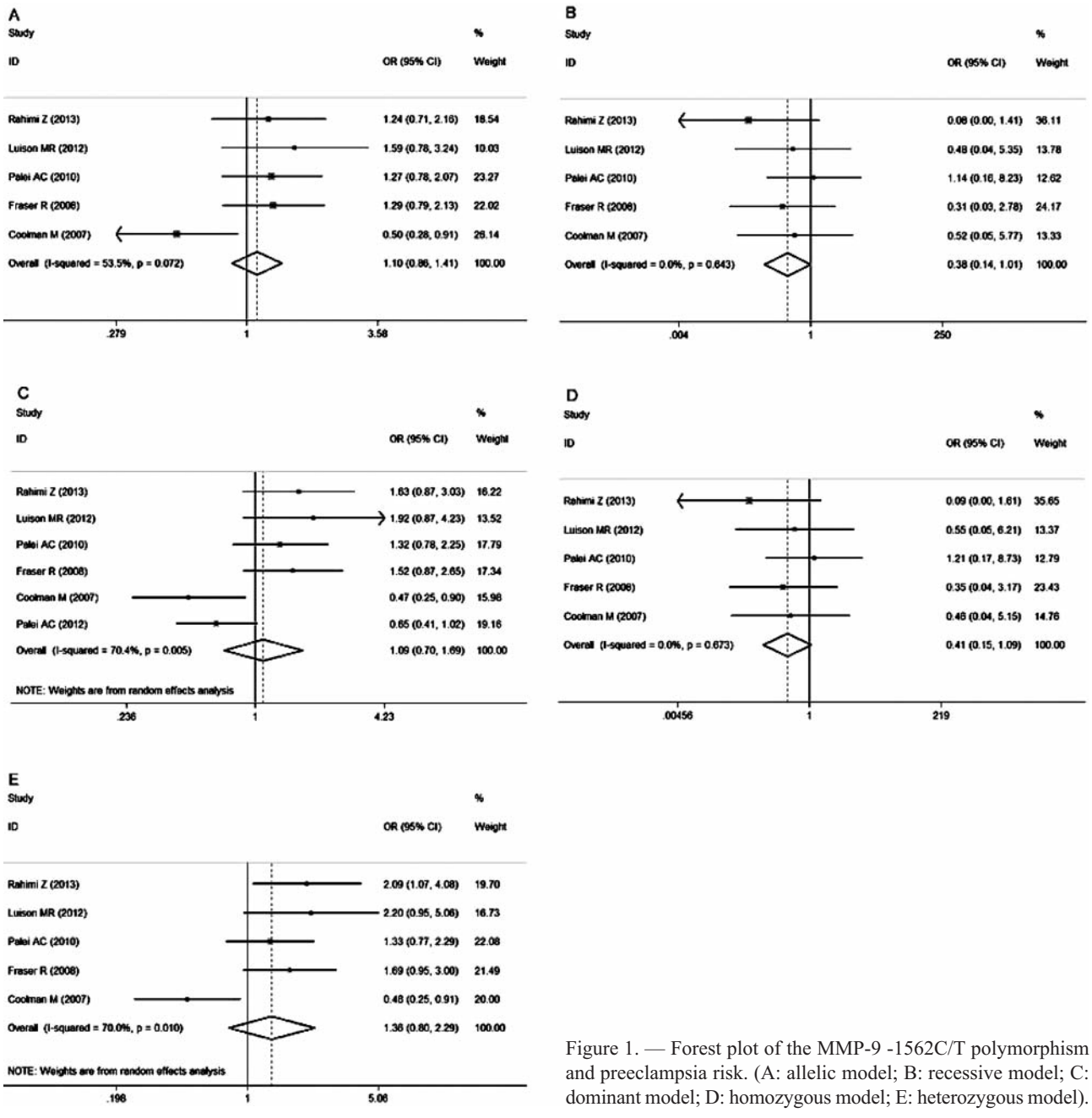

Figure 1. — Forest plot of the MMP-9 -1562C/T polymorphism and preeclampsia risk. (A: allelic model; B: recessive model; C: dominant model; D: homozygous model; E: heterozygous model).

and preeclampsia risk, (b) case-control studies, and (c) genotype data for estimating of odds ratio (OR) and 95% confidence interval (CI). Accordingly, the following exclusion criteria were applied: (a) review, abstracts, case reports, and editorials; and (b) studies that reported duplicated results.

Data extraction: The two present reviewers (Wang and Zhang) independently extracted data from included studies. The following data were extracted: the name of the first author, year of publication, country of origin, sample size, and the genotype frequencies in the preeclampsia cases and controls. Disagreements between authors were resolved by consensus.

Statistical analyses: Five genetic models were used, including allelic (T allele *vs.* C allele), recessive (TT *vs.* TC+CC), dominant (TT+TC *vs.* CC), homozygous (TT *vs.* CC), and heterozygous (TC *vs.* CC) models. The ORs and their corresponding 95% CIs were used to compare the association between MMP-9 -1562C/T polymorphism and preeclampsia risk. Chi-square-based Q-tests were used to calculate the heterogeneity between the individual studies with significance set at the $p < 0.05$ level [11]. The random-effect model was used to assess the pooled OR if there was heterogeneity among the individual studies [12]. Otherwise, the fixed-effect model was used. The pooled OR was determined through Z test with significance set at the $p < 0.05$ level. Then, sensitivity analysis was conducted by excluding each study, one at a time, and recalculating the OR and 95% CI to assess the effects of each study on the pooled risk of preeclampsia. Finally, funnel plot was performed to assess the publication bias of the literatures. All of the statistical tests were performed using STATA version 12.0.

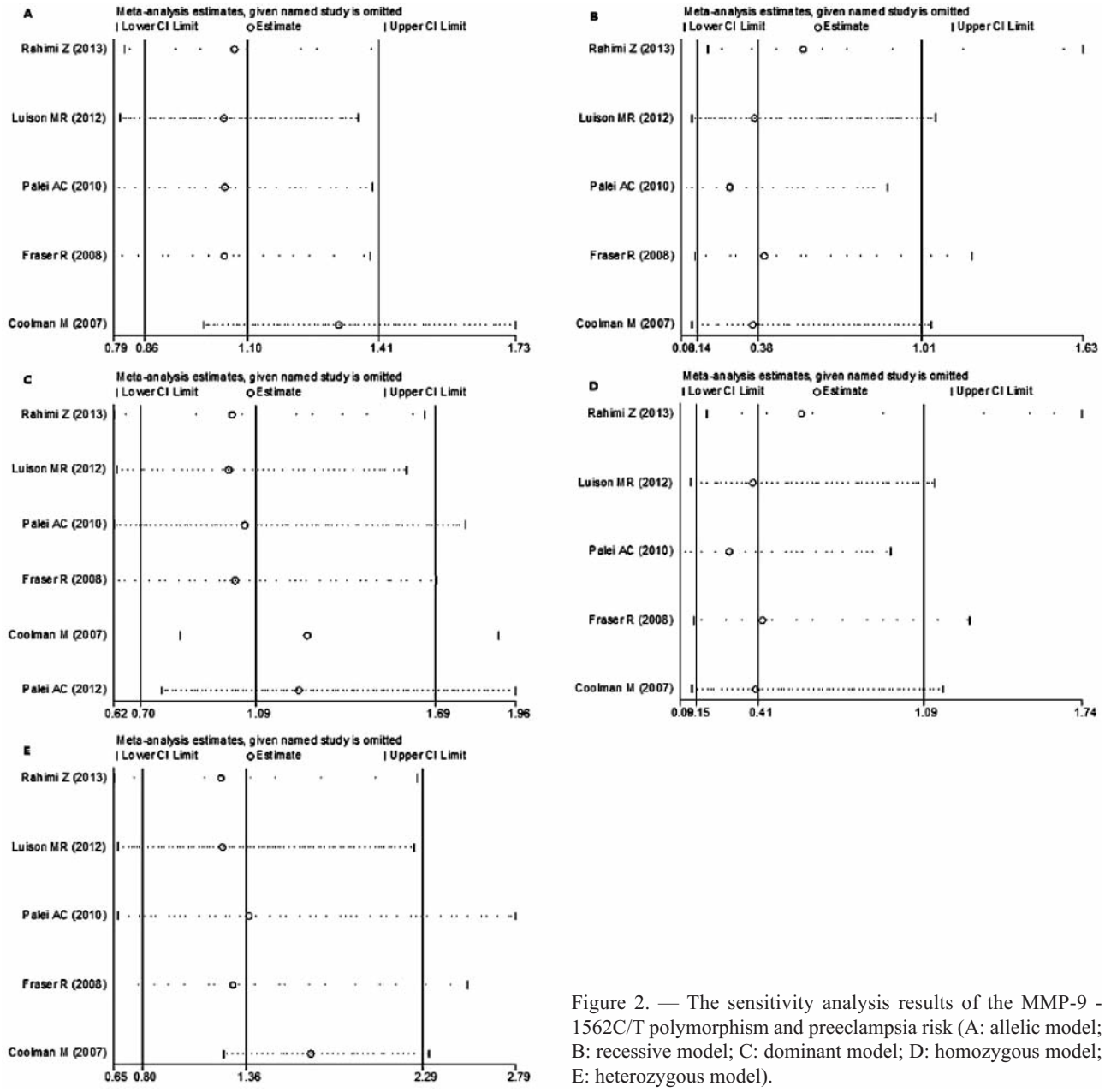

Figure 2. — The sensitivity analysis results of the MMP-9 -1562C/T polymorphism and preeclampsia risk (A: allelic model; B: recessive model; C: dominant model; D: homozygous model; E: heterozygous model).

Table 2. — *Meta-analysis of the association between the MMP-9 -1562C/T polymorphism and preeclampsia.*

Poly-morphism	Country	Test of association			Test of heterogeneity	
		OR	95%CI	*p*-value	Model	*p*-value
T *vs.* C	Overall	1.10	0.86-1.41	0.43	Fixed	0.07
	Brazil	1.37	0.92-2.05	0.12	Fixed	0.61
TT *vs.* TC+CC	Overall	0.38	0.14-1.01	0.05	Fixed	0.64
	Brazil	0.80	0.18-3.57	0.77	Fixed	0.58
TT+TC *vs.* CC	Overall	1.09	0.70-1.69	0.70	Random	0.01
	Brazil	1.12	0.60-2.10	0.73	Random	0.03
TT *vs.* CC	Overall	0.41	0.15-1.09	0.07	Fixed	0.67
	Brazil	0.87	0.19-3.94	0.86	Fixed	0.62
TC *vs.* CC	Overall	1.36	0.80-2.29	0.26	Random	0.01
	Brazil	1.55	0.99-1.75	0.06	Fixed	0.32

Results

According to the searching strategy, eight papers were found. The authors reviewed the titles, abstracts and the full texts of all retrieved articles through defined criteria. Finally, six eligible studies concerning the MMP-9 -1562C/T polymorphism and preeclampsia risk were included in the meta-analysis. Among all included studies with 871 cases and 845 controls, three studies were conducted in Brazil, one conducted in Italy, one conducted in UK, and one performed in Netherlands (Table 1).

Table 2 shows the main results of this meta-analysis. Overall, no significant association between the MMP-9 -

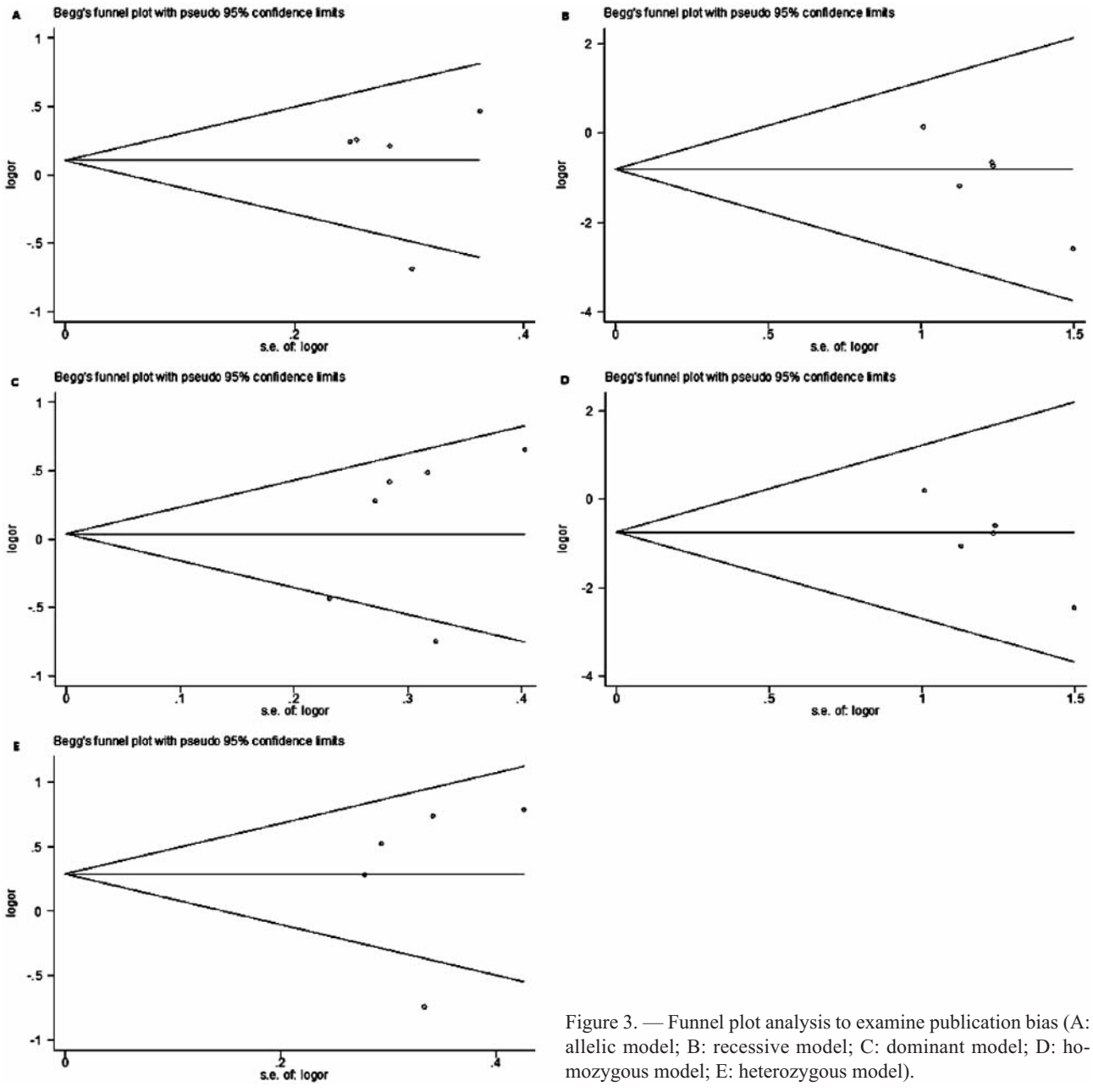

Figure 3. — Funnel plot analysis to examine publication bias (A: allelic model; B: recessive model; C: dominant model; D: homozygous model; E: heterozygous model).

1562C/T polymorphism and preeclampsia risk was observed (allelic model: OR = 1.10, 95% CI 0.86 - 1.41, $P_{heterogeneity}$= 0.07; recessive model: OR = 0.38, 95% CI 0.14 - 1.01, $P_{heterogeneity}$= 0.64; dominant model: OR = 1.09, 95% CI 0.70 - 1.69, $P_{heterogeneity}$= 0.01; homozygous model: OR = 0.41, 95% CI 0.15 - 1.09, $P_{heterogeneity}$ = 0.67; heterozygous model: OR = 1.36, 95% CI 0.80 - 2.29, $P_{heterogeneity}$ = 0.01) (Figure 1). Then, the authors performed subgroup analysis by ethnicity. Similarly, no obvious associations were found for all genetic models (allelic model: OR = 1.37, 95% CI 0.92 - 2.05, $P_{heterogeneity}$= 0.61; recessive model: OR = 0.80, 95% CI 0.18 - 3.57, $P_{heterogeneity}$= 0.58; dominant model: OR = 1.12, 95% CI 0.60 - 2.10, $P_{heterogeneity}$= 0.03; homozygous model: OR = 0.87, 95% CI 0.19 - 3.94, $P_{heterogeneity}$ = 0.62; heterozygous model: OR = 1.55, 95% CI 0.99 - 1.75, $P_{heterogeneity}$ = 0.32).

Sensitivity analysis was performed to explore the influence of an individual study on the pooled results by deleting a single study each time from the pooled analysis. The results showed that no individual study significantly affected the pooled OR (Figure 2). Funnel plot was performed to assess the publication bias of the literatures. Symmetrical funnel plots were obtained in the polymorphism tested in all of the models (Figure 3).

Discussion

Accumulating number of genetic association studies have focused on the association between gene polymorphisms and preeclampsia risk. However, the findings are generally inconsistent, probably due to some limitation in these studies such as small sample size. Meta-analysis is considered a powerful tool for summarizing the contradicting results from different studies with more statistical power, so that it can obtain more reliable results than a single study [18]. To the best of the present authors' knowledge, this was the first meta-analysis providing comprehensive insights into the effects of MMP-9 -1562C/T polymorphism on the risk of preeclampsia. The main findings of this meta-analysis are the lack of any significant association between MMP-9 -1562C/T polymorphism and preeclampsia risk in overall populations. Similar results were also found in stratified analysis based on ethnicity.

Despite the present authors' efforts in performing a comprehensive analysis, some limitations exist in this meta-analysis. Firstly, they pooled the data using unadjusted information, whereas a more precise analysis could be conducted if detailed information of original data is available. Secondly, gene-environment interactions should be considered in further studies if individual data of environmental exposure are available. Finally, the pooled sample size was relatively limited in this meta-analysis. Therefore, this meta-analysis could only preliminarily appraise the association of MMP-9 -1562C/T polymorphism with preeclampsia risk.

In conclusion, the present results suggest that MMP-9 -1562C/T polymorphism is not associated with preeclampsia risk. However, large well-designed, multi-center epidemiological studies should be carried out in these and other ethnic populations to confirm the present findings.

Acknowledgements

This work was granted by Health Department of Preventive Medical Science Foundation Project of Jiangsu Province (No.Y2012074) and the Medical Fund Project of Nanjing Health Bureau (No.YKK12119).

References

[1] Stillman I.E., Karumanchi S.A.: "The glomerular injury of preeclampsia". *J. Am. Soc. Nephrol.*, 2007, *18*, 2281.
[2] Saftlas A.F., Olson D.R., Franks A.L., Atrash H.K., Pokras R.: "Epidemiology of preeclampsia and eclampsia in the United States, 1979-1986". *Am. J. Obstet. Gynecol*., 1990, *163*, 460.
[3] Sibai B.M., Gordon T., Thom E., Caritis S.N., Klebanoff M., McNellis D., et al.: "Risk factors for preeclampsia in healthy nulliparous women: a prospective multicenter study. The National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units". *Am. J. Obstet. Gynecol.*, 1995, *172*, 642.
[4] Zhang J., Meikle S., Trumble A.: "Severe maternal morbidity associated with hypertensive disorders in pregnancy in the United States". *Hypertens. Pregnancy*, 2003, *22*, 203.
[5] Roberts J.M., Gammill H.S.: "Preeclampsia: recent insights". *Hypertension*, 2005, *46*, 1243.
[6] Hubel C.A., Wallukat G., Wolf M., Herse F., Rajakumar A., Roberts J.M., *et al.*: "History of preeclampsia agonistic angiotensin II type 1 receptor autoantibodies in postpartum women with a preeclampsia history". *Hypertension*, 2007, *49*, 612.
[7] Shimonovitz S., Hurwitz A., Dushnik M., Anteby E., Geva-Eldar T., Yagel S.: "Developmental regulation of the expression of 72 and 92 kd type IV collagenases in human trophoblasts: a possible mechanism for control of trophoblast invasion". *Am. J. Obstet. Gynecol.*, 1994, *171*, 832.
[8] Merchant S.J., Davidge S.T.: "The role of matrix metalloproteinases in vascular function: implications for normal pregnancy and preeclampsia". *Br. J. Gynaecol.*, 2004, *111*, 931.
[9] Coolman M., de Maat M., Van Heerde W.L., Felida L., Schoormans S., Steegers E.A., et al.: "Matrix metalloproteinase-9 gene -1562C/T polymorphism mitigates preeclampsia". *Placenta*, 2007, *28*, 709.
[10] Palei A.C., Sandrim V.C., Cavalli R.C., Tanus-Santos J.E.: "Comparative assessment of matrix metalloproteinase (MMP)-2 and MMP-9, and their inhibitors, tissue inhibitors of metalloproteinase (TIMP)-1 and TIMP-2 in preeclampsia and gestational hypertension". *Clin. Biochem.*, 2008, *41*, 875.
[11] Cochran W.G.: "The effectiveness of adjustment by subclassification in removing bias in observational studies". *Biometrics*, 1968, *24*, 295.
[12] Mantel N., Haensze W.: "Statistical aspects of the analysis of data from retrospective studies of disease". *J. Natl. Cancer. Inst.*, 1959, *22*, 719.
[13] Rahimi Z., Rahimi Z., Shahsavandi M.O., Bidoki K., Rezaei M.: "MMP-9 (-1562 C:T) polymorphism as a biomarker of susceptibility to severe pre-eclampsia". *Biomark. Med.*, 2013, *7*, 93.
[14] Luizon M.R., Sandrim V.C., Palei A.C., Lacchini R., Cavalli R.C., Duarte G., *et al.*: "Epistasis among eNOS, MMP-9 and VEGF maternal genotypes in hypertensive disorders of pregnancy". *Hypertens. Res.*, 2012, *35*, 917.

[15] Palei A.C., Sandrim V.C., Duarte G., Cavalli R.C., Gerlach R.F., Tanus-Santos J.E.: "Matrix metalloproteinase (MMP)-9 genotypes and haplotypes in preeclampsia and gestational hypertension". *Clin. Chim. Acta*, 2010, *411*, 874.

[16] Fraser R., Walker J.J., Ekbote U.V., Martin K.L., McShane P., Orsi N.M.: "Interleukin-4 -590 (C>T), toll-like receptor-2 +2258 (G>A) and matrix metalloproteinase-9 -1562 (C>T) polymorphisms in pre-ecla"mpsia. *BJOG*, 2008, *115*, 1052.

[17] Palei A.C., Sandrim V.C., Amaral L.M., Machado J.S., Cavalli R.C., Lacchini R., *et al.*: "Matrix metalloproteinase-9 polymorphisms affect plasma MMP-9 levels and antihypertensive therapy responsiveness in hypertensive disorders of pregnancy". *Pharmacogenomics J.*, 2012, *12*, 489.

[18] Munafo M.R., Flint J.: "Meta-analysis of genetic association studies". *Trends. Genet.*, 2004, *20*, 439.

Address reprint requests to:
C.M. WANG, M.D.
Department of Gynecology and Obstetrics
The Second Affiliated Hospital of the
Southeast University
11 Bengfu Road
Nanjing, Jiangsu (China)
e-mail: wcmwcmlove@163.com