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Review Article

Association between asymmetric dimethylarginine level and preeclampsia: a meta-analysis

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Abstract: Inconsistent results existed between the circulating asymmetric dimethylarginine (ADMA) concentration and preeclampsia. This meta-analysis aimed to compare the circulating ADMA concentration in patients with preeclampsia and healthy pregnant women. A systematic literature search was performed in PubMed, Embase, CNKI, VIP, and Wanfang database up to May 30, 2016. Case-control studies reporting the circulating ADMA concentration in preeclampsia patients and healthy pregnant women were selected. The pooled standard mean difference (SMD) with 95% confidence interval (CI) were used to estimate the relationship between circulating ADMA concentration and preeclampsia. Eighteen studies involving 879 preeclampsia patients and 994 healthy pregnant women were identified and analyzed. The pooled estimates from 11 studies showed that preeclampsia patients had an increased circulating ADMA concentration as compared with healthy pregnant women (SMD=1.15; 95% CI=0.75-1.55). Subgroup analysis indicated that the association was more pronounced in severe preeclampsia patients (SMD=2.41; 95% CI=1.43-3.39) than in the mild preeclampsia patients (SMD=1.62; 95% CI=0.52-2.71). The meta-analysis suggests that higher circulating ADMA concentration was observed to be higher in women with preeclampsia than that in the healthy pregnant controls. Elevated ADMA concentration is positively correlated to the severity of disease.

Keywords: Asymmetric dimethylarginine, preeclampsia, meta-analysis

Introduction

Preeclampsia is characterized by hypertension and proteinuria occurring 20 weeks of gestation, affecting 2%-8% of all pregnancies [1]. Preeclampsia is a leading cause of fetal growth restriction and preterm birth [2] and contributes to maternal and perinatal morbidity and mortality worldwide [3]. However, biomarkers that help for early predicting pregnant women at risk of developing preeclampsia are challenging [4].

Despite the exact pathogenesis of preeclampsia remains unclear, endothelial dysfunction has been suggested to involve in preeclampsia [5]. Asymmetric dimethylarginine (ADMA) is a mediator of endothelial dysfunction and vascular malfunction [6]. The emerging evidences have showed that circulating ADMA concentration tented to higher in patients with preeclampsia than that of healthy pregnant women [7]. These data reveal that elevated circulating ADMA concentration in pregnant women may be identified as a potential biomarker of preeclampsia. However, inconsistent findings of decreased [8] or unchanged [9-12] circulating ADMA concentration in women with preeclampsia remain exist. These conflicting results may be due to differences in study designs, laboratory methods, time of sample collection, and severity of disease. Furthermore, whether ADMA concentration was correlated with the severity of disease remains questionable [13, 14].

In order to clarify these issues, we performed this meta-analysis to evaluate the relationship of circulating ADMA concentration in patients with preeclampsia as compared with healthy pregnant women.

Materials and methods

Literature search

Ethical approval and informed consent from the patients was not required because it because it

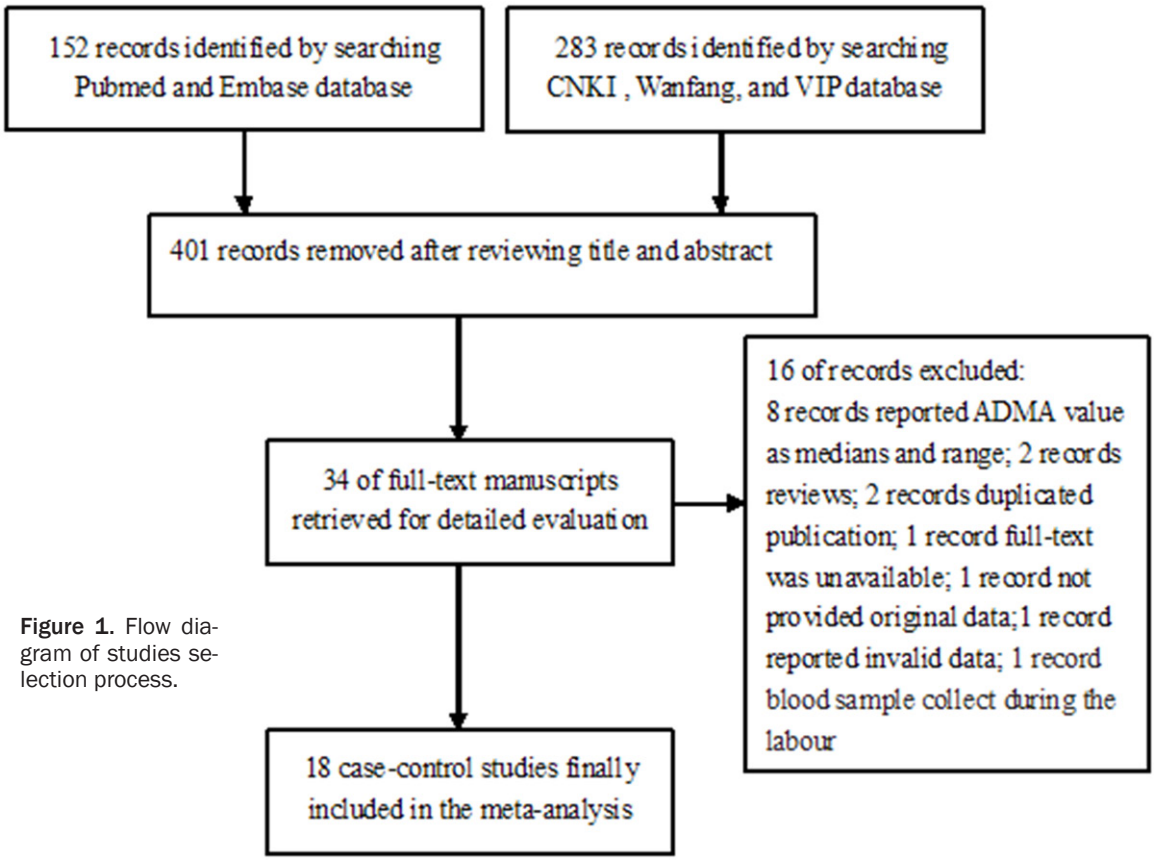

Figure 1. Flow diagram of studies selection process.

evaluated published studies. Two authors independently performed electronic literature searches in PubMed, Embase, CNKI, VIP, and Wanfang database from their inception to May 30, 2016. The following search keywords were used: "ADMA" OR "asymmetric dimethylarginine" AND "preeclampsia" OR "pre-eclampsia". References list in included studies and reviews were manually scanned to identify additional new articles.

Study selection

Studies were eligible for inclusion if they fulfilled the following: 1) case-control or cohort design; 2) studied population was pregnant women; 3) circulating ADMA concentration in preeclampsia women and healthy pregnant women was available and presented as continuous value. The diagnosis of preeclampsia was in accordance with the guideline of the recommended clinical practice [15]. Mild preeclampsia was defined by systolic blood pressure (BP) ≥140 mmHg or diastolic BP ≥90 mmHg on 2 occasions at least 4 h apart concomitant with new onset of ≥300 mg protein in a 24 h urine specimen or 1+ protein on a dipstick occurring after 20th week of pregnancy in women. Severe preeclampsia was defined by systolic blood pressure ≥160 mmHg or diastolic ≥110 mmHg and proteinuria ≥2000 mg/24 h [16] or one of following clinical features: thrombocytopenia, impaired liver function, pulmonary edema, cerebral or visual disturbances, or progressive renal insufficiency were present. Studies reported the ADMA concentration as medians and range (minimum and maximum) values were excluded. Moreover, women with a history of chronic hypertension, preexisting renal disease or any evidence of previous medical illness were also excluded.

Data extraction and quality assessment

The following data were extracted by two independent authors: first author's surname, year of publication, country of origin, study design, numbers of preeclampsia women and controls, severity of preeclampsia, sample type, detecting method of ADMA, circulating ADMA value (mean ± standard deviation [SD]). Discrepancies were resolved by consensus with a third author.

Table 1. Summary characteristic of the included studies

Study/Year	Country	Design	Severity of PE	Sample type	Sample time	Assay method	Preeclampsia			Controls			Overall NOS
							N	Age (Years)	ADMA (μmol/L)	N	Age (Years)	ADMA (μmol/L)	
								Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD	
Pettersson et al 1998 [21]	Sweden	Case-control	Severe	Plasma	Third trimester	HPLC	12	29.1 ± 1.2	0.55 ± 0.07	12	30.3 ± 1.1	0.36 ± 0.03	5
Holden et al 1998 [22]	UK	Case-control	Any	Plasma	Third trimester	HPLC	18	29.4 ± 6.1	1.17 ± 0.42	44	27.9 ± 5.3	0.56 ± 0.22	6
Speer et al 2008 [23]	USA	Prospective nested case-control	Any	Plasma	Delivery	HPLC	15	25.1 ± 5.8	0.55 ± 0.07	31	21.9 ± 4.7	0.49 ± 0.08	6
Huang et al 2009 [24]	China	Case-control	Any	Plasma	NP	HPLC	30	28.2 ± 1.5	1.8 ± 0.72	10	26.8 ± 1.2	1.03 ± 0.17	7
Sandrim et al 2010 [25]	Brazil	Case-control	Any	Plasma	clinic attendance	ELISA	47	27.7 ± 7.3	2.20 ± 0.14	47	24.6 ± 5.4	2.11 ± 0.07	8
Mao et al 2010 [26]	China	Case-control	Mild	Plasma	Third trimester	LC-MS/MS	24	NP	0.97 ± 0.14	30	NP	0.82 ± 0.11	7
			Severe				38		1.46 ± 0.22				
Anderssohn et al 2012 [27]	Germany	Case-control	Any	Plasma	Third trimester	LC-MS/MS	18	31.9 ± 6.2	0.51 ± 0.15	28	31.7 ± 5.3	0.42 ± 0.07	7
Rizos et al 2012 [28]	Greece	Prospective case-control	Any	Serum	Second trimester	ELISA	10	34.0 ± 3.7	0.63 ± 0.14	41	32.6 ± 3.9	0.52 ± 0.13	6
Ehsanipoor et al 2012 [9]	USA	Prospective nested case-control	Any	Plasma	34-42 weeks	ELISA	12	29.8 ± 9.1	1.88 ± 0.19	17	28.2 ± 6.7	2.14 ± 0.33	6
Laskowska et al 2013 [29]	Poland	Case-control	Any	Serum	NP	ELISA	51	29.64 ± 6.26	0.58 ± 0.15	65	29.2 ± 4.42	0.49 ± 0.11	6
Laskowska et al 2013 [30]	Poland	Case-control	Severe	Serum	Third trimester	ELISA	115	29.8 ± 5.4	0.57 ± 0.16	65	29.2 ± 4.4	0.49 ± 0.11	8
Liu et al 2014 [31]	China	Case-control	Any	Plasma	NP	ELISA	91	19-37	0.63 ± 0.19	80	20-38	0.52 ± 0.11	8
López-Alarcón et al 2015 [32]	Mexico	Cohort study	Any	Plasma	Third trimester	HPLC	49	NP	0.82 ± 0.36	179	NP	0.42 ± 0.21	8
Bian et al 2015 [33]	China	Prospective nested case-control	Any	Serum	First trimester	ELISA	44	28.6 ± 2.8	0.86 ± 0.16	100	29.3 ± 2.4	0.68 ± 0.20	7
Zhang et al 2015 [34]	China	Case-control	Mild	Serum	NP	ELISA	44	23.9 ± 4.1	2.9 ± 4.7	50	24.6 ± 3.3	1.9 ± 3.1	6
			Severe				49	24.4 ± 3.9	5.0 ± 3.3				
Lu et al 2016 [35]	China	Case-control	Mild	Plasma	NP	HPLC	20	NP	1.06 ± 0.15	20	NP	0.62 ± 0.12	7
			Severe				20	NP	1.42 ± 0.21				
Dai et al 2016 [36]	China	Case-control	Mild	Serum	NP	ELISA	55	NP	2.88 ± 0.42	100	NP	1.68 ± 0.69	7
			Severe				45	NP	3.59 ± 0.30				
Zheng et al 2016 [37]	China	Case-control	Severe	Serum	28-40 weeks	ELISA	62	29.1 ± 5.7	0.74 ± 0.28	75	28.9 ± 4.4	0.49 ± 0.16	6

Abbreviations: PE, preeclampsia; ADMA, asymmetric dimethylarginine; HPLC, high-pressure liquid chromatography; ELISA, enzyme immunoassays; LC-MS/MS, liquid chromatography/tandem mass spectrometry; SD, standard deviation; NP, not provide; NOS, Newcastle-Ottawa Scale.

The Newcastle-Ottawa Scale (NOS) was used to assess the methodological quality of the included studies [17]. Study with a score more than seven was considered as high quality in this meta-analysis.

Statistical analysis

Circulating ADMA level was presented as mean ± SD. If the standard error (SE) of ADMA level was reported, we calculated SD by the following formula: $SD = SE \times \sqrt{N}$. Standardized mean difference (SMD) with 95% confidence intervals (CI) was used to estimate the circulating ADMA level between the patients with preeclampsia and healthy pregnant controls. Heterogeneity of the SMD across studies was assessed by the Cochran's Q test (P<0.05 as an indicator of significant heterogeneity) and I^2 statistic (≥50% indicating significant heterogeneity). A random effect model was used to pool SMD in the presence of significant heterogeneity. Otherwise, a fixed-effect model was selected. Begg's rank correlation [18] and Egger linear regression test [19] at a 0.1 level of significance were used to explore for publication bias. Subgroup analysis was performed by sample sizes of participants, origin of study conducted, blood type, severity of preeclampsia, and assay method. All statistical analyses were carried out using STATA software (version 12.0; Stata Corp LP, College Station).

Results

Description of the included studies

The flow diagram of studies selection process is illustrated in **Figure 1**. Briefly, our initial literature search produced 435 potentially relevant records. No additional records were identified by other sources. Thirty-four records were kept for detailed evaluation after screening the titles and abstracts. Fifteen of the remaining 34 potentially relevant studies were further removed after reviewing the full-text manuscript. Finally, a total of 18 studies [8, 20-36] were included in this meta-analysis.

The characteristics of the included studies are shown in **Table 1**. A total of 879 preeclampsia patients and 994 healthy pregnant women were identified from the 18 studies. The included studies were published from 1998 to 2016. One [31] was a cohort study, 3 were prospective nested case-control studies [8, 22, 32], and the remaining were case-control studies. Six of the studies [20, 21, 26-29] were performed in Europe, another four studies [8, 22, 24, 31] were performed in America, and the remaining studies were performed in China. Eleven studies [8, 21-24, 26-28, 30-32] reported the results for any preeclampsia, 4 studies [25, 33-35] reported the results for mild preeclampsia and severe preeclampsia, and 3 studies [20, 29, 36] only reported the results for severe preeclampsia. Circulating ADMA concentration was measured by high-pressure liquid chromatography (HPLC) in 5 studies [20-23, 34], liquid chromatography/tandem mass spectrometry (LC-MS/MS) in 2 studies [25, 26], and enzyme immunoassays (ELISA) in 8 studies [8, 24, 27-30, 32, 33, 35, 36]. The overall NOS stars of the individual studies varied from 5 to 8.

Circulating ADMA concentration and preeclampsia

Eleven [8, 21-24, 26-28, 30-32] of the included studies reported the data for any preeclampsia. As shown in **Figure 2**, significant heterogeneity (I^2=90.9%, P<0.001) across the studies was observed. The pooled results showed that patients with preeclampsia had higher circulating ADMA concentration as compared with healthy pregnant controls women (SMD 1.15; 95% CI 0.75-1.55) in a random effect model. Begg's test (P=0.488) and Egger's test (P=0.946) showed no evidence of significant publication bias.

Subgroup and sensitivity analysis

Subgroup analyses based on the severity showed that, compared with healthy pregnant controls women, the pooled SMD was 1.62 (95% CI=0.52-2.71) for mild preeclampsia in 4 studies, and 2.41 (95% CI 1.43-3.39) for severe preeclampsia in 7 studies (**Figure 3**). Moreover, statistically significant differences in the pooled SMD of the circulating ADMA concentration were consistently shown in the varied subgroups stratified by the origin of study conducted, blood type, ADMA assay method, or sample sizes. The detailed results of subgroup analyses are shown in **Table 2**. Sensitivity analysis indicated that there was no significant change in the pooled SMD (ranged 0.66 to 1.66) of any preeclampsia when removing any of the studies (**Figure 4**).

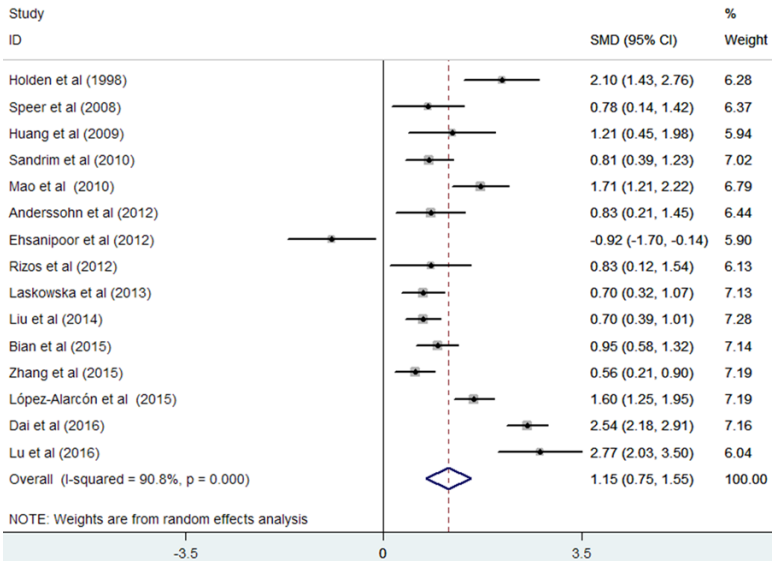

Figure 2. Forest plots showing SMD with corresponding 95% CI of studies on circulating asymmetric dimethylarginine concentration in patients with preeclampsia and healthy pregnant women.

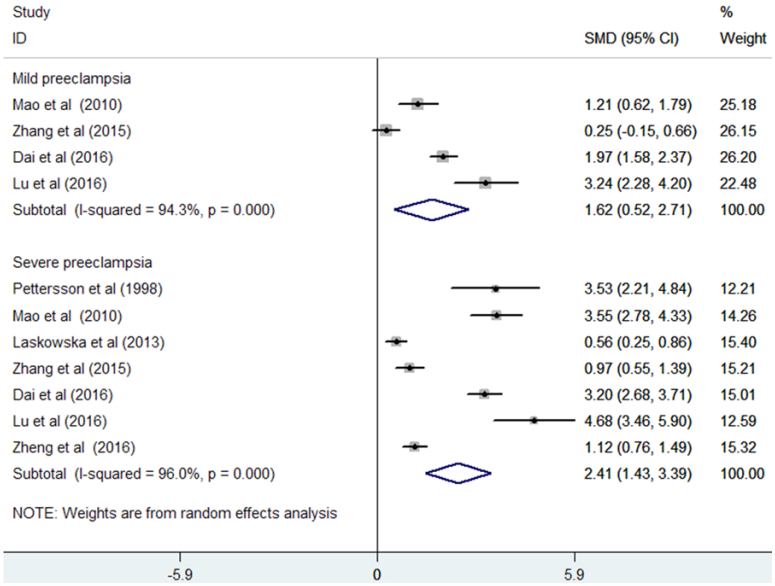

Figure 3. Forest plots showing SMD with corresponding 95% CI of studies on circulating asymmetric dimethylarginine concentration in patients with mild or severe preeclampsia and healthy pregnant women.

Discussion

To the best of our knowledge, this is the first meta-analysis to investigate the association between circulating ADMA concentration and preeclampsia. This meta-analysis suggested that circulating ADMA concentration was significantly higher in patients with preeclampsia as compared with healthy pregnant controls. Subgroup analyses showed that this association was not affected by the type of blood sample, different ADMA analysis methods or geographic location.

Currently, no single biomarker used for preeclampsia has gained widespread acceptance into clinical practice [37]. In addition, there is no definite biomarker to be considered as a sensitive parameter of the disease severity. This meta-analysis also found that the pooled SMD of circulating ADMA concentration was particularly higher in patients with severe preeclampsia (SMD=2.41) than those in mild preeclampsia (SMD=1.62). These findings revealed that ADMA concentration may be a potential biomarker of the severity of preeclampsia.

Despite the exact mechanisms of preeclampsia have not been fully elucidated, there is evidence to indicate that endothelial dysfunction of pregnant women may have a detrimental effect on the development of preeclampsia [38]. ADMA is an endogenous inhibitor of nitric oxide synthases [39]. Plasma ADMA concentration was lower in uncomplicated pregnancies compared to normotensive patients with preeclampsia [21], suggesting endothelial dysfunction is at least partially responsible for the preeclampsia. Increased ADMA concentrations may precede clinical manifestations of preeclampsia. The findings of our meta-analysis are consistent with the conclusion of a previous meta-analysis [40] that endothelial dysfunction may contribute to the pathophysiology of preeclampsia.

By contrast, three studies [9-12] did not observe significant difference in plasma ADMA concentration among women with preeclampsia compared to normotensive controls. In Eh-

Table 2. Subgroup analyses of ADMA level

Subgroups	Number of studies	Pooled SMD	95% CI	Heterogeneity across studies
Sample size				
>100	6	1.15	1.01-1.29	P<0.001; I^2=94.3%
≤100	9	1.14	0.94-1.34	P<0.001; I^2=87.5%
Origin of study				
China	7	1.27	1.11-1.42	P<0.001; I^2=93.9%
America	4	1.01	0.77-1.25	P<0.001; I^2=91.7%
Europe	4	0.97	0.70-1.24	P=0.004; I^2=77.6%
Blood type				
Plasma	10	1.14	0.98-1.29	P<0.001; I^2=88.4%
Serum	5	1.16	0.98-1.34	P<0.001; I^2=94.6%
ADMA assay method				
HPLC	5	1.64	1.39-1.88	P=0.001; I^2=79.0%
ELISA	8	0.96	0.81-1.10	P<0.001; I^2=93.3%
LC-MS/MS	2	1.36	0.97-1.75	P=0.030; I^2=78.7%
Severity of disease				
Mild	4	1.62	0.52-2.71	P<0.001; I^2=94.3%
Severe	7	2.41	1.43-3.39	P<0.001; I^2=96.0%

Abbreviations: ADMA, asymmetric dimethylarginine; HPLC, high-pressure liquid chromatography; ELISA, enzyme immunoassays; LC-MS/MS, liquid chromatography/tandem mass spectrometry; SMD, standard mean difference; CI, confidence interval.

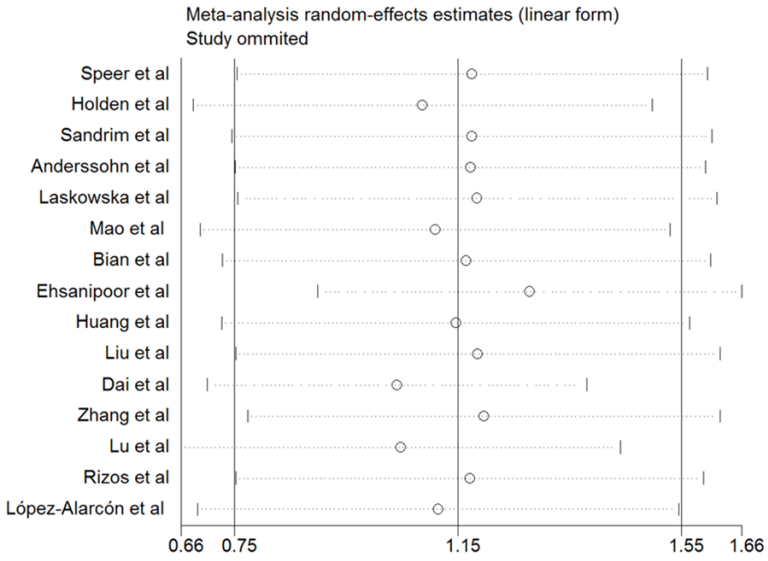

Figure 4. Sensitivity analysis of any preeclampsia by omitting individual study at each turn.

sanipoor et al's study, plasma ADMA concentration was lower in preeclamptic women than normotensive controls [8]. These conflicting results might be partly explained by the methods of ADMA detection, timing of sample collection or time in the possible degradation of the enzymes in the frozen specimens [8].

There are several limitations in this meta-analysis. First, this meta-analysis cannot determine increased ADMA concentration is a cause or a consequence of the preeclamptic state. Second, significant heterogeneity was found in the main pooled analysis (I^2=90.9%, P<0.001); however, the heterogeneity remains difficult to explain by the available subgroup. Third, removal of studies with ADMA concentration as medians and range values may have produced the selection bias. Finally, although Begg's and Egger's test did not show evidences of publication bias, potential publication bias cannot be excluded due to only studies published in English and Chinese included and articles published in other languages may have missed.

This meta-analysis demonstrated that higher circulating ADMA concentration was observed in women with preeclampsia, particularly in severe preeclampsia, than the healthy pregnant controls. The increased circulating levels of ADMA are positively correlated with the severity of the disease. Future well-designed prospective studies are needed to confirm the role of circulating ADMA as a diagnostic tool for the early identification of women at risk of developing preeclampsia.

Disclosure of conflict of interest

None.

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