

# Evaluation of vascular cell adhesion molecule-1, intracellular cell adhesion molecule-1 and E-selectin levels in preeclampsia: A Systematic Review and Meta-Analysis.

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## Research article

**Keywords:** Vascular cell adhesion molecule-1, Intracellular cell adhesion molecule-1, E-selectin, Meta-Analysis, Preeclampsia

**Posted Date:** January 27th, 2020

**DOI:** <https://doi.org/10.21203/rs.2.21928/v1>

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# Abstract

## Background

Soluble adhesive molecules are potential mediators of endothelial dysfunction in preeclampsia. The purpose of this study was to examine the relationship between pre-eclampsia and maternal circulation vascular cell adhesion molecule-1 (VCAM-1), Intracellular cell adhesion molecule-1 (ICAM-1) and E-selectin.

## Methods

VCAM-1, ICAM-1 and E-selectin studies of maternal circulation in preeclampsia and normal pregnant women were reported by systematic literature search in PubMed (Medline), with 21 eligible reports. The standardized mean difference (MD) and their 95% confidence intervals (CIs) were calculated as random effect analysis of association among studies.

## Results

Preeclampsia is associated with elevated VCAM-1 [mean difference (MD) = 1.17 ng/ml, 95% confidence interval (CI) 0.85-1.50 ng/ml], and E-Selectin (MD = 2.18ng/ml, 95% CI 1.16-3.20ng/ml), but not associated with ICAM-1 (MD= 0.43ng/ml, 95% CI -0.03-0.90ng/ml). In the subgroup analysis of mild and severe preeclampsia, VCAM-1, ICAM-1 and E-selectin all showed increased levels compared with normal pregnancy women.

## Conclusion

The meta-analyses have shown elevated VCAM-1 and E-selectin levels in the circulation of pregnant women with preeclampsia.

## 1. Background

Preeclampsia is a high blood pressure disorder that occurs during pregnancy and affects about 2 to 8% of pregnant women (1). Preeclampsia is significantly associated with maternal and fetal morbidity, including maternal eclampsia and HELLP syndrome, as well as premature birth and intrauterine growth restriction. Moreover, the effects of Preeclampsia on the health and quality of life of women and their offspring after delivery are lifelong (2).

Previous studies have shown that inflammatory mediators such as soluble adhesive molecule may be potential mediators of endothelial dysfunction in preeclampsia (3). Adhesion between leukocytes and endothelial cells is mainly affected by adhesion molecules, including vascular cell adhesion molecule-1 (VCAM-1), Intracellular cell adhesion molecule-1 (ICAM-1) and E-selectin. Inflammation-mediated endothelial injury results in a pro-inflammatory signaling cascade and the expression of VCAM-1, which recruit blood monocytes to the vascular wall so that more cytokines and chemokines are permanently released at the site of injury (4). VCAM-1 can cause endothelial dysfunction by providing an adhesion phenotype to vascular endothelium(5). ICAM-1 is a member of the immunoglobulin superfamily by binding to leukocyte 2-integrin and mediating its functional activity (6). ICAM-1 plays an important role in regulating leukocyte adhesion to endothelial cells and leukocyte migration (7). E-selectin is a member of the selectin family involved in mediating the interaction between white blood cells and endothelial cells, and is expressed only in endothelial cells, while the increased circulating level of e-selectin may indicate the activation and injury of endothelial cells (8).

The soluble form of these molecules can be measured and considered as a biomarker for monitoring endothelial function in preeclampsia (9-11). However, whether there is a systematic increase in cytokine concentrations in preeclampsia remains controversial because of conflicting reports from clinical studies. Some studies have found a significant increase in VCAM-1, ICAM-1 and E-selectin serum levels in women with preeclampsia (12-14), however, there have been some contrary findings that there is no difference or a decline in VCAM-1, ICAM-1 and E-selectin serum levels between preeclampsia and normotensive pregnant women (13, 15-17).

Based on this, the purpose of this meta-analysis was to systematically investigate the circulating levels of VCAM-1, ICAM-1 and E-selectin in pregnant women with and without preeclampsia. It is helpful to understand whether these molecules are involved in the pathological process of preeclampsia, elucidating the state of endothelial function in this disease, and ultimately may help us better understand the process of this disease.

## 2. Methods

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (see additional file 3).

### 2.1 Literature search strategy

Two authors screened for clinical studies in PubMed (Medline) up to August 2019. Searching terms (medical subject headings [MeSH] terms) was: ("Vascular cell adhesion molecule-1" [MeSH] OR "Intracellular cell adhesion molecule-1" [MeSH] OR "E-Selectin" [MeSH]) AND "preeclampsia" [MeSH]. All articles were retrieved into an EndNote library.

### 2.2. Inclusion and exclusion criteria

Only studies assessing the relationship between soluble VCAM-1, ICAM-1 or E-selectin and PE were included. Meeting the following four criteria can be included in the meta-analysis: (1) Original prospective, retrospective, cross-sectional or prospective case controlled design are accepted for soluble adhesive molecule concentration detection studies. (2) PE was diagnosed as hypertension (140/90 mmHg or blood pressure elevation 15 mmHg) with proteinuria (300 mg/24 h or 1+ dipstick 6h apart) without pre-existing hypertension. Women with systolic blood pressure >160 mmHg and/or diastolic blood pressure >110

mmHg, accompanied by proteinuria >5 g in a 24-hr collection or with  $\geq 3+$  on a dipstick, were defined as severe preeclampsia. Mild pre-eclampsia is defined as fulfilling the criteria for pre-eclampsia but not fulfilling the criteria for severe pre-eclampsia. Controls were healthy pregnant women. (3) Maternal peripheral blood was used for concentration detection. (4) Original data should be included in the study and be represented by mean (SD or SE).

Besides, due to the lack of comparability, duplicate publications, review articles, non-English articles, studies in non-pregnant period, studies on the detection of cytokine concentrations in placenta, peripheral blood cytokines and amniotic fluid, or detecting cytokine concentrations after exogenous test stimulation, or studies provided with case-only were excluded.

### 2.3 Data extraction

The following information was extracted from each study: author, publication year, study design, and other essential characteristics. For continuity variables, information was collected including the number of case groups and control groups, the mean concentration and standard difference (SD) of maternal plasma or serum VCAM-1, ICAM-1 and E-selectin. If the data provided by the study is standard error (SE), the SE shall be converted into SD according to the formula ( $SD=SE^*$ ). In addition, ng/ml is the concentration unit of VCAM-1, ICAM-1 and E-selectin for analysis.

### 2.4 Study quality assessment

Two reviewers independently reviewed the titles/abstracts of all possible studies. Since most articles do not show relevant data in their respective abstracts, the most are reviewed in full. In the event of disagreement, the decision is made by the third reviewer.

### 2.5 Statistical processing

For the continuous outcomes, we used an inverse-variance weighted mode(18) to calculate the standardized mean difference (MD) and 95% confidence intervals (CIs). Funnel plot(19) and egger's test (20) was used to evaluate publication bias. If there was no heterogeneity ( $P \geq 0.1, I^2 \leq 50\%$ ), we used the fixed-effects model. If there was a significant heterogeneity ( $P < 0.1, I^2 > 50\%$ ), the random-effects model was adopted to allow for the inherent heterogeneity found between studies. Forest plots of the parametric data were generated using the Stata 15.0 software (Stata Corporation, College Station, TX, USA).

We also performed a subgroup analysis of preeclampsia patients. Subgroup 1, mild preeclampsia (M-PE); Subgroup 2, severe preeclampsia(S-PE).

## 3. Results

### 3.1 Description of the included studies

Using the initial search for VCAM-1, ICAM-1 or E-selectin related literature, there were 144 potentially eligible citations. VCAM-1, ICAM-1 and E-selectin had a total of 85 articles excluded due to title duplication, animal or *in vitro* studies, additional interventions, non-english publication, and other exclusion criteria, respectively. In the remaining literatures, 38 articles did not meet the inclusion criteria, respectively. Finally, 21 articles meet these requirements of VCAM-1, ICAM-1 or E-selectin (Fig. 1).

### 3.2. Basic information

Based on the principle of Cochrane systematic review, 21 published cohort studies (6, 7, 11, 14, 16, 21-36) were included in this meta-analysis according to the inclusion and exclusion criteria of the meta-analysis. In the study of VCAM-1, ICAM-1 and E-selectin, there were 934 cases, 585 cases and 400 cases in the group with preeclampsia and 878 cases, 565 cases and 422 cases in the normal blood pressure group, respectively. Table 1-3 describes the experimental characteristics of these studies in more detail (see Additional file 1).

### 3.3 Vascular cell adhesion molecule-1

A total of 17 studies included 934 women with preeclampsia and 878 women with normal pregnancies. The level of VCAM-1 in peripheral blood of preeclampsia pregnant women was higher than that of normal pregnant women (mean difference (MD) = 1.17 ng/ml, 95% confidence interval (CI) 0.85-1.50 ng/ml, Fig 2). The subgroup analysis of mild and severe preeclampsia included 314 women with preeclampsia (174 with mild and 140 with severe) and 184 women with normal pregnancy. Circulating VCAM-1 levels in women with severe and mild preeclampsia were higher than those in normal pregnancy women, respectively (MD = 1.68ng/ml, 95% CI 1.10-2.26ng/ml and MD = 1.12ng/ml, 95% CI 0.67-1.57ng/ml) (Fig. 2).

### 3.4 Intracellular cell adhesion molecule-1

A total of 585 preeclampsia women and 565 normal pregnant women participated in 11 studies. There was no statistical difference in the level of ICAM-1 in peripheral blood of preeclampsia pregnant women compared with normal pregnant women (MD = 0.43ng/ml, 95% CI -0.03-0.90ng/ml, Fig 3). In the subgroup analysis of mild and severe preeclampsia, the studies including 289 patients with preeclampsia (136 with mild and 153 with severe). ICAM-1 circulating levels were slightly higher in women with severe and mild preeclampsia than in women with normal pregnancy (MD = 0.36ng/ml, 95% CI 0.11-0.62ng/ml and MD = 0.31ng/ml, 95% CI 0.07-0.56ng/ml) (Fig. 3). In addition, in the original study without subgroup information, there was no statistical difference in the two groups (MD = 0.49ng/ml, 95% CI -0.35-1.32ng/ml, Fig. 3).

### 3.5 E-Selectin

A total of 400 women with preeclampsia and 422 women with normal pregnancy were included in the analysis. The level of peripheral blood E-Selectin in preeclampsia pregnant women was higher than that in normal pregnant women (MD = 2.18ng/ml, 95% CI 1.16-3.20ng/ml, Fig 4). At the same time, mild

preeclampsia also had higher peripheral blood E-Selectin levels than normal pregnant women (MD = 0.92ng/ml, 95% CI 0.51-1.33ng/ml), but the E-selectin levels in severe preeclampsia women were comparable with normal control (MD = 1.80ng/ml, 95% CI -0.11-3.72ng/ml, Fig 4).

### 3.6 Egger's test

According to Egger's test, no publication bias was found in the parametric data reporting maternal circulatory VCAM-1, ICAM-1 and E-Selectin levels ( $p=0.710$ ,  $0.409$  and  $0.289$ , respectively).

## 4. Discussion

In this study, we conducted a meta-analysis of the included studies to evaluate the effect of soluble adhesive molecule on preeclampsia. The results showed that compared with the normal pregnancy group, the circulating level of VCAM-1 and E-Selectin was significantly increased in the preeclampsia group. However, there was a slight difference of ICAM-1 level between preeclampsia group and normal pregnancy group.

Under normal non-pregnant physiological conditions, VCAM-1 has a low expression on endothelial cells. In normal pregnant women, white blood cells are activated in peripheral blood of, which is mainly regulated by adhesion molecules expressed on the surface of white blood cells and endothelial cells. However, in pathological conditions such as preeclampsia, VCAM-1 is shed to the cell surface and enters the blood circulation after vascular endothelial cell injury, further causing endothelial cells dysfunction (5). In this analysis, we found that the level of VCAM-1 in the preeclampsia group was higher than that in the normal pregnancy group, and was correlated with the severity of preeclampsia, indicating the importance of endothelial cell injury in the pathogenesis of preeclampsia.

ICAM-1 can induce circulating white blood cells to adhere to activated endothelial cells and migrate to the intima of blood vessels, which is an important process of inflammation(37). In this analysis, no difference was found in the level of ICAM-1 between the preeclampsia pregnancy group and the normal pregnancy group in the original studies without subgroup information. However, there were differences in subgroup analysis. Probably because fibroblasts, white blood cells, endothelial cells, epithelial cells and other cells are activated by various cytokines and then produce many membrane ICAM-1 in the process of inflammation(38). Membrane ICAM-1 rarely falls off into the blood circulation. It could also be due to race or small sample size. Further detection of changes in cell surface adhesion molecules in preeclampsia is needed.

E-selectin is expressed by activated endothelial cells under inflammatory stimulation, such as bacterial endotoxin, IL-1, or TNF- $\alpha$  (8). Our results suggest that the expression of adhesive molecule E-selectin is enhanced in patients with preeclampsia and is associated with the severity of the disease. So E-selectin may exacerbate the early inflammatory state of preeclampsia. Moreover, previous studies have found that E-selectin, which is stimulated by TNF- $\alpha$ , plays a pathological mechanism through the NF- $\kappa$ B and JNK/p38 mitogen-activated protein kinase (p38MAPK) pathways, (39). Therefore, understanding the pathogenesis of TNF- $\alpha$  may contribute to understanding the role of E-selectin in preeclampsia.

At present, the changes of VCAM-1, ICAM-1 and E-selectin in maternal circulation are in the same direction, which emphasizes the importance of meta-analysis of the reported parametric data. Preeclampsia is a heterogeneous disease with multiple clinical symptoms. Soluble adhesive molecule of individuals related to preeclampsia can be affected by various factors. It is not surprising that high heterogeneity was found in the meta-analysis, so we need to carefully interpret the results of the analysis. The sources of heterogeneity may be due to differences in gestational weeks (although most of them are in the third trimester), differences in age and weight, inconsistencies in the treatment and collection methods of specimens, different sensitivity of reagents and other unknown confounding factors, which lead to the inability to find the sources of heterogeneity in this study. It is also possible that we do not know other clinical data, including other specific conditions such as physical fitness or even race at that time, which make it impossible to explain all heterogeneity in this study.

Funnel plot analysis of the parameter data of preeclampsia pregnancy showed that the funnel plot of all three cytokines was asymmetric (data not shown). However, further detection of publication bias found no publication bias among the three cytokines. This indicates that the asymmetry of funnel plot is not caused by publication bias. However, considering the small number of studies included, the results of this meta-analysis may be greatly influenced by the studies excluded from this analysis.

It is noteworthy that the soluble VCAM-1, ICAM-1 and E-selectin levels in serum can reflect the role of endothelial cell injury in preeclampsia. These three adhesive molecules interacting with their receptors at the appropriate time and place can play important roles in the inflammatory response. However, this complex and coordinated interaction may be affected by many regulatory factors. Therefore, there are limitations to the interpretation of elevated serum or plasma VCAM-1, ICAM-1 and E-selectin levels.

## 5. Conclusion

This meta-analysis showed that maternal circulating levels of VCAM-1, ICAM-1 and E-selectin in preeclampsia women were elevated compared with normal pregnant women, and were correlated with the severity of preeclampsia, suggesting that soluble VCAM-1, ICAM-1 and E-selectin levels were associated with endothelial dysfunction in preeclampsia. However, the value of VCAM-1, ICAM-1 and E-selectin in the evaluation of endothelial dysfunction in pre-eclampsia needs to be verified by further well-designed large sample studies.

## Abbreviations

VCAM-1: Vascular cell adhesion molecule-1; ICAM-1: Intracellular cell adhesion molecule-1; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; MD: Mean difference; CIs: Confidence intervals; SD: Standard difference; SE: Standard error; M-PE: Mild preeclampsia; S-PE: Severe preeclampsia

## Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this published article and its supplementary information files.

Competing interests

The authors declare that they have no competing interests.

Funding

Not applicable.

Authors' contributions

XL: Research design, Literature search, Data collection, Data analysis, Manuscript writing; QT: Data collection, Data analysis; SL: Project development, Quality control; YX: Literature search, Data extraction; ML: Data management, Data analysis; CC: Project development, Quality control; LZ: Research design, Data analysis, Manuscript writing. All authors read and approved the final version of the manuscript and participated in revising the paper.

Acknowledgements

Not applicable.

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## Tables

Table 1. Characteristics of included studies of VCAM-1

Author	Year	Plasma/Serum	Subgroup	PE/NP	Preeclampsia		Normotensive		Assay	Supplier	Sensitivity(ng)
					Mean	SD	Mean	SD			
Portelinha et al.	2008	S		58/49	610.3	192.2	605.39	162.4	ELISA	Bender MedSystems	
Tuzcu et al.	2015	S		17/23	8250000	3280000	4040000	1470000	ELISA	eBioscience	
Zubor et al.	2014	S		38/38	1,243	671	651	250	ELISA	Beckman Coulter	
Heyl et al.	2005	S		10/10	851.5	234.9	659.3	215	ELISA	DPC Biermann	
Kim et al.	2004	S	M-PE	33/63	960.71	364.7	570.33	222.56	ELISA	R&D	
			S-PE	82/63	1,376.75	451.5	570.33	222.56			
Carr et al.	2001	P		46/25	491.7	133.7	441.4	75.9	ELISA	R&D	<2
Freeman et al.	2004	P		45/45	289	61	311	88	ELISA	R&D	
Bretelle et al.	2001	P		15/15	995	232	705	192	ELISA	R&D	
Phocas et al.	2000	S	M-PE	19/20	873	130	668	186	ELISA	R&D	
			S-PE	11/20	898	117	668	186			
Madazli et al.	2000	P	M-PE	16/25	353	86	325	102	ELISA	Boehringer Mannheim	
			S-PE	16/25	525	100	325	102			
Daniel et al.	1999	P		10/10	1831	534	1254	386	ELISA	R&D	
Krauss et al.	1998	P		80/112	1201	473	715	170	ELISA	R&D	
Djurovic et al.	1997	P	M-PE	106/76	835.34	106.84	667.62	145.45	ELISA	R&D	
			S-PE	31/76	855.25	203.14	667.62	145.45			
Lyall et al.	1994	S		16/18	841.9	49.7	560.2	47.9	ELISA	British Biotechnology	
Lewis et al.	2010	S		40/40	322.76	79.82	307.9	64.19	ELISA	R&D	
Chavarría et al.	2008	S		75/125	458	76.21	303	116.28	ELISA	R&D	
Vadachkoria et al.	2006	P		170/184	987.7	402.89	720.4	250.95	Enzyme immunoassay	R&D	

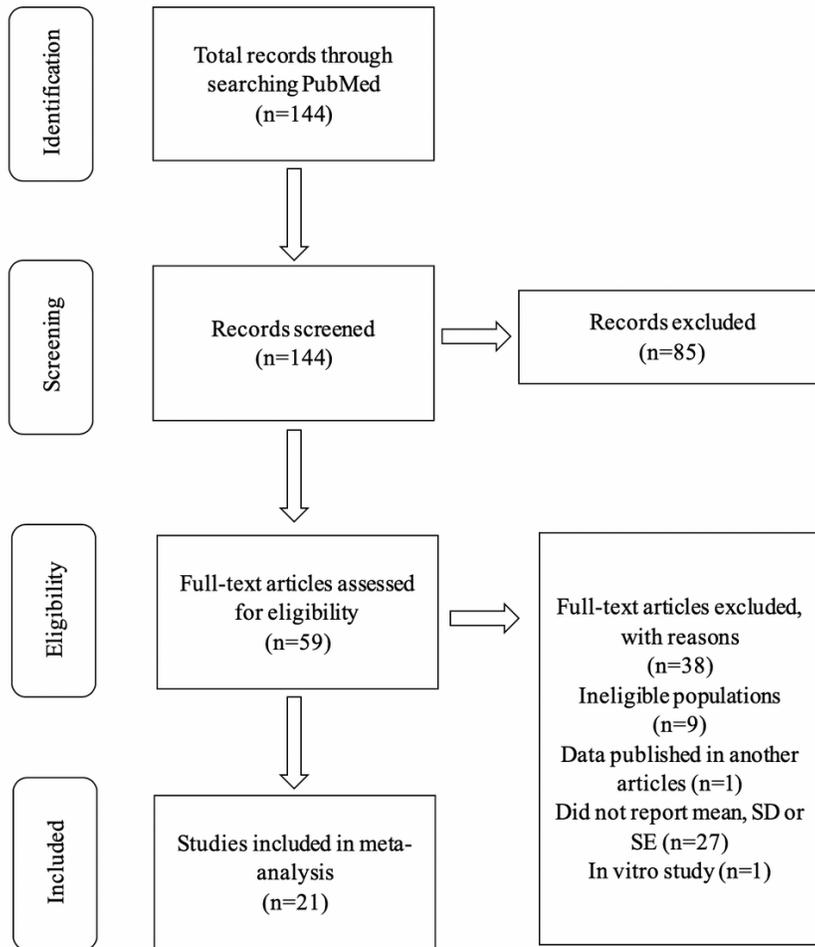
Table 2. Characteristics of included studies of ICAM-1

Author	Year	Plasma/Serum	subgroup	PE/NP	Preeclampsia		Normotensive		Assay	Supplier	Sensitivity(ng)	Interassay variation (%)
					Mean	SD	Mean	SD				
Tuzcu et al.	2015	S		17/21	4940000	1860000	4560000	1750000	ELISA	eBioscience		
Kim et al.	2004	S	M-PE	33/63	282.38	121.14	243.27	57.56	ELISA	R&D		
			S-PE	82/63	291	108.73	243.27	57.56				
Freeman et al.	2004	p		45/45	187	75	187	56	ELISA	R&D		
Bretelle et al.	2001	p		15/15	473	237	240	95	ELISA	R&D		<10
Daniel et al.	1999	p		20/20	303	72	301	66	ELISA	R&D	0.09	<9.3
Krauss et al.	1998	P		80/112	431	233	247	65	ELISA	R&D		
Airoldi et al.	1998	S		25/30	309.8	58	367.3	86.54	ELISA	Bender MedSystem		8
Djurovic et al.	1997	P	M-PE	106/76	246.13	106.84	224.86	50.62	ELISA	R&D		
			S-PE	31/76	248.62	81.36	224.86	50.62				
Lewis et al.	2010	S	S-PE	40/40	174.96	90.76	169.01	42.44	ELISA	R&D		<7
Chavarría et al.	2008	S		75/125	275	63.22	136	49.19	ELISA	R&D		
Lyall et al.	1994	S		16/18	148.8	47.60	187.3	67.03	ELISA	British Biotechnology		

Table 3. Characteristics of included studies of E-selectin

Author	Year	Plasma/Serum	Subgroup	PE/NP	Preeclampsia		Normotensive		Assay	Supplier	Sensitivity(ng)	Interassay variation (%)
					Mean	SD	Mean	SD				
Tuzcu et al.	2015	S		17/23	695000	383000	375000	241000	ELISA	eBioscience		
Cartya et al.	2012	P		49/74	15.1	4.9	12.9	4.5	Multianalyte biochip	Randox		
Papakonstantinou et al.	2011	P	M-PE	5/10	7.51	3.49	4.91	1.79	ELISA	Bender		
			S-PE	7/10	11.74	2.99	4.91	1.79				
Chavarría et al.	2008	S		75/125	65.9	0.8	54.6	0.9	ELISA	R&D		9
Kim et al.	2004	S	M-PE	33/63	52.4	27.42	33.94	16	ELISA	R&D		
			S-PE	82/63	61.94	36.8	33.94	16				
Aydın et al.	2004	P		35/34	6.69	1.82	3.11	0.82	ELISA	Hycult		
Bretelle et al.	2001	P		15/15	59	21	36	16	ELISA	R&D		<10
Krauss et al.	1998	P		66/60	55	28	34	14	ELISA	R&D		
Lyall et al.	1994	S		16/18	49.8	7.2	45.8	46	ELISA	British Biotechnology		

## Figures



PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Figure 1

Flow diagram for the systematic review [PRISMA statement].

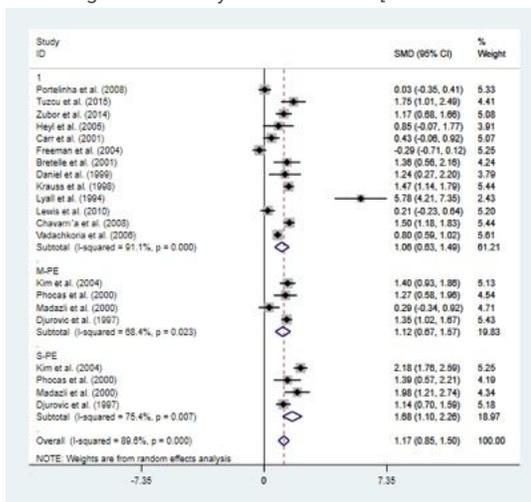


Figure 2

Forrest blot analysis of serum or plasma concentrations of VCAM-1. The subgroup difference test represents the difference between mild and severe preeclampsia.

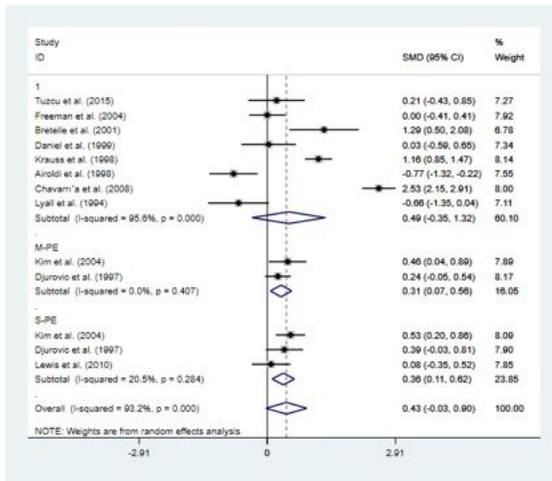


Figure 3

Forrest blot analysis of serum or plasma concentrations of ICAM-1. The subgroup difference test represents the difference between mild and severe pre-eclampsia.

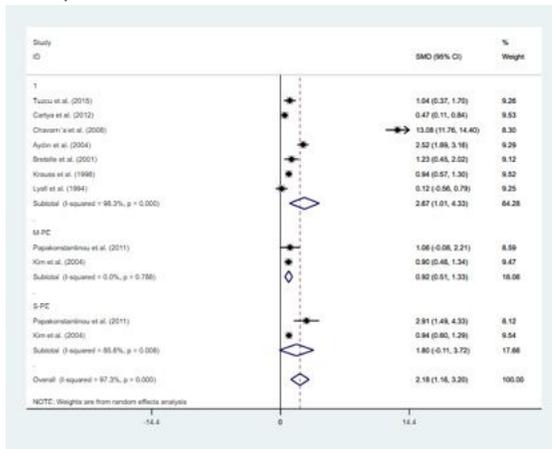


Figure 4

Forrest blot analysis of serum or plasma concentrations of E-selectin. The subgroup difference test represents the difference between mild and severe preeclampsia.