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Review Article

Vitamins supplementation affects the onset of preeclampsia

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Preeclampsia may affect between 2–8% of all pregnancies. It seriously affects maternal health after pregnancy. This meta-analysis was performed to define the efficacy of vitamins supplementation on the risk of preeclampsia. Potential articles were systematically searched on the databases of Pubmed, Embase and Web of Science up to May 2016. Relative risk (RR) and 95% confidence intervals (95%CIs) were used to analyze the relationship of vitamins supplementation with risk of preeclampsia. Cochran Q test was used to test inter-study heterogeneity. Begg's funnel plot was adopted to assess the potential publication bias. 28 eligible studies were selected. Pooled results indicated that vitamins supplementation could reduce the risk of preeclampsia (RR = 0.74, 95%CI = 0.64–0.86). The studies with non-randomized controlled trial (RCT) analysis also suggested the significant relationship of vitamins supplementation with risk of preeclampsia (RR = 0.60, 95%CI = 0.42–0.85). However, negative results were observed in studies with RCT analysis. Subgroup analysis by vitamin type was performed among the studies with RCT analysis. The results indicated that vitamin D supplementation could significantly reduce the risk of preeclampsia (RR = 0.41, 95%CI = 0.22–0.78). Similar results were observed in the studies with multivitamins supplementation (RR = 0.69, 95% CI = 0.51–0.93). Vitamins supplementation could reduce the onset of preeclampsia.

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Introduction

Preeclampsia is a main cause of perinatal and maternal mortality worldwide, which is tightly related with hypertension, proteinuria, and end-organ disease. It has been demonstrated that preeclampsia may affect between 2–8% of all pregnancies.[1,2] It seriously affects maternal health after pregnancy.[3] Zhang et al. suggested that women with preeclampsia and eclampsia showed 3- to 25-fold increased risk of thrombocytopenia, abruption placentae, pulmonary edema, disseminated intravascular coagulation, and aspiration pneumonia.[4] Oxidative stress has been regarded as a pathogenic mechanism of this disease.[5,6] Therefore, it was hypothesized that antioxidants supplementation might blunt the diseases' severity or prevent the disorder.

Oxidative stress is commonly brought about by the increased level of reactive oxygen species (ROS) or lack of antioxidants. It has been demonstrated that lack of antioxidants may be related with the onset of preeclampsia.[7,8] Antioxidant vitamins contribute to stabilizing reactive free radicals, which behave as the first defense line against free radicals and lipid peroxidation.[9] Vitamin C and vitamin E are common powerful antioxidants.[9] Vitamin E, an important lipid-soluble antioxidant, is responsible for protecting cells against inflammatory response and lipid peroxidation,[10] which shows regulatory effects on the blood pressure. It is commonly thought that vitamin C could inhibit the constrictor response of those resistance arteries to various stimuli. Chappel et al. reported that supplementation with vitamins C and E may be beneficial in the prevention of preeclampsia.[11] In addition, vitamin D supplementation was in early pregnancy demonstrated to lower the risk of preeclampsia of pregnant women.[12] Meanwhile, Wen et al. suggested that supplementation of mulitivitamins containing folic acid in the second trimester is associated with reduced risk of preeclampsia.[13] These evidences indicate the crucial role of vitamin supplementation in the pathogenesis of preeclampsia.

Therefore, this meta-analysis was initiated to extract a conclusion about the definitive role of vitamins supplementation in the pathogenesis of preeclampsia.

Methods

Data sources

This meta-analysis was performed according to the PRISMA statement. Systematic search was performed on the databases of Pubmed, Embase and Web of Science for studies investigating the relationship of vitamin supplement with risk of preeclampsia. Data were collected up to May 2016. The used terms were preeclampsia OR pre-eclampsia OR hypertension AND vitamin OR antioxidants. Only the articles in English were considered. The references of obtained articles were checked for possible studies.

Inclusion criteria

The relevant studies were reviewed to assess the eligibility according to the following inclusion criteria: a. Pregnant women was provided with vitamins; b. Relationship of vitamins supplementation with onset of preeclampsia was investigated; c. Preeclampsia of pregnancy was defined as primary outcome.

Exclusion criteria were as follows: a. Case report; b. Review articles; c. Articles with unavailable data.

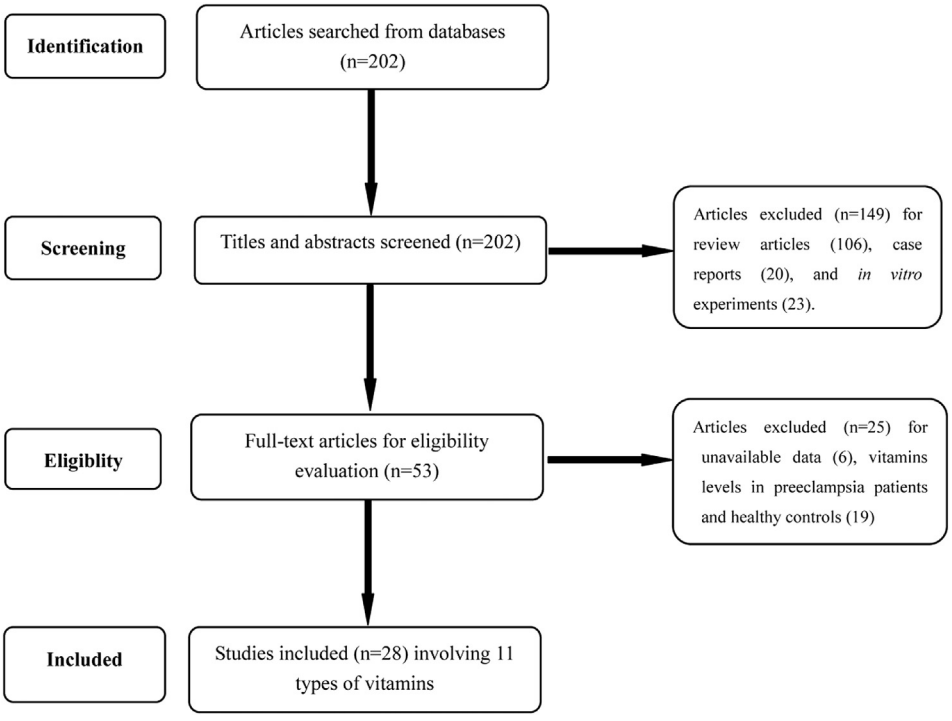

Figure 1 Flow chart about article selection.

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Data extraction

Two authors independently extracted data on the dosage and duration, study design, populations, entry criteria, the definition of pre-eclampsia, sample size and outcome measures. There were no disagreements between authors.

Statistical analysis

The data were analyzed with Stata 12.0 software. Relative risk (RR) and 95% confidence intervals (95%CIs) were calculated to analyze the effects of vitamin supplement on the occurrence of preeclampsia. The primary outcome was the incidence of preeclampsia in treated women and placebo groups. The Cochran Q test was used to test heterogeneity. Funnel plot was used to indicate the potential publication bias. Sensitivity analysis was performed to test the robustness of pooled results.

Results

Article selection

28 relevant articles were selected according to inclusion and exclusion criteria.[11,13–39] A total of 202 potential articles were obtained for evaluation about the eligibility. Then, the authors reviewed the title and abstract and 149 articles were excluded. The reasons were review articles (n = 106), case reports (n = 20), and *in vitro* experiments (n = 23). The remaining 53 full-text articles were evaluated further. 25 articles were excluded for unavailable data (n = 6), vitamins levels in preeclampsia patients and healthy controls (n = 19). The selection process was shown in Fig. 1. Basic information of selected studies was listed in Table 1. The involved vitamin mainly included vitamin C, E, D, and folic acid. Other vitamins included vitamin A, B1, B2, B3, B5, B6, B6 and B12.

Table 1 Main information of selected studies.

Author	Year	Country	Design	Supplementation vs. Placebo	Vitamins	Dosage/day
Kiondo	2014	Uganda	RCT	415 vs. 418	C	1000 mg
Naghshineh	2014	Iran	RCT	68 vs. 70	D	600IU
Vadillo-Ortega	2011	USA	RCT	222 vs. 222	Complex[a]	—
Bastani	2011	Iran	RCT	104 vs. 168	E	400IU
Villar	2009	UK	RCT	687 vs. 678	C and E	1000 mg vitamin C and 400IU vitamin E
Wen	2016	Canada	Non-RCT	7220 vs. 404	Complex[b]	—
Rumiris	2006	Indonesia	RCT	29 vs. 31	Complex[c]	1000IU vitamin A, 2.2 mg B6, 2.2 μg B12, 200 mg vitamin C, 400IU vitamin E, 400 μg folic acid
Abramovici	2015	UK	RCT	4993 vs. 4976	C and E	1000 mg vitamin C and 400IU vitamin E
Wang	2015	China	Non-RCT	556 vs. 150	Complex[d]	—
Romero	2006	USA	RCT	1196 vs. 1205	C and E	1000 mg vitamin C and 400IU vitamin E
Wen	2008	Canada	Non-RCT	2713 vs. 238	Complex[e]	—
Karamali	2015	Iran	RCT	30 vs. 30	D	50000IU
Kalpdev	2010	India	RCT	22 vs. 22	C and E	1000 mg vitamin C and 400IU vitamin E
Chappell	1999	UK	RCT	141 vs. 142	C and E	1000 mg vitamin C and 400IU vitamin E
Kim	2014	Canada	Non-RCT	134 vs. 81	Folic acid	—
Spinnato II	2007	USA	RCT	371 vs. 368	C and E	1000 mg vitamin C and 400IU vitamin E
Cardoso	2016	India	RCT	100 vs. 100	C and E	500 mg vitamin C and 400IU vitamin E
Haugen	2009	Norway	Non-RCT	18,695 vs. 1798	D	—
Qian	2015	China	RCT	30 vs. 30	D	2000IU
Asemi	2015	Iran	RCT	23 vs. 23	D	400IU
Johnston	2015	UK	RCT	27 vs. 30	C and E	1000 mg vitamin C and 400IU vitamin E
Li	2013	China	Non-RCT	92,731 vs. 100,823	Folic acid	—
McCance	2010	UK	RCT	375 vs. 374	C and E	1000 mg vitamin C and 400IU vitamin E
Poston	2006	UK	RCT	1196 vs. 1199	C and E	1000 mg vitamin C and 400IU vitamin E
Samimi	2015	Iran	RCT	30 vs. 30	D	50000IU
Vanderlelie	2014	Australia	Non-RCT	719 vs. 1066	Complex[f]	—
Xu	2010	Canada	RCT	1167 vs. 1196	C and E	1000 mg vitamin C and 400IU vitamin E
Beazley	2005	USA	RCT	52 vs. 48	C and E	1000 mg vitamin C and 400IU vitamin E

Note.
[a] Multi- vitamins included vitamin C, E, B6 and B12.
[b] Did not report the types of vitamin in addition of folic acid.
[c] Multi- vitamins included vitamin A, B6, B12, C, E and folic acid.
[d] Multi- vitamins included did not provide information about types of vitamin.
[e] Multi- vitamins included vitamin A, C, B1, B2, B3, B5, B6, B12, D, E and Biotin.
[f] Multi- vitamins included vitamin B1, B2, B3, B5, B6, B12, C, D3, E and folic acid.

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Vitamins supplementation and reduced risk of preeclampsia

Overall results indicated that vitamins supplementation could reduce the risk of preeclampsia (RR = 0.74, 95% CI = 0.64—0.86). These selected studies were performed with RCT or cohort analysis, thus, we performed subgroup analysis based on study design. We found that vitamins supplementation was still related with reduced risk of preeclampsia in studies with non-RCT analysis (RR = 0.60, 95%CI = 0.42—0.85) (Fig. 2). However, we did not observe positive result in those studies with RCT analysis.

Meanwhile, subgroup analysis by vitamin type was performed among the studies with RCT analysis (Fig. 3). The results indicated that vitamin D supplementation could significantly reduce the risk of preeclampsia (RR = 0.41, 95%CI = 0.22—0.78). Similar results were observed in the studies with multivitamins supplementation (RR = 0.69, 95%CI = 0.51—0.93). However, joint supplementation of vitamin C and E had no obvious influences on the risk of preeclampsia.

Sensitivity analysis

The pooled results were tested by sensitivity analysis, which suggested that the pooled results were robust.

Publication bias detection

Begg's funnel plot seemed to be symmetrical (Fig. 4), which indicated that there was no significant publication bias.

Discussion

Abnormal placentation is regarded as underlying cause of preeclampsia, which is featured by invasion of trophoblast cells and remodeling of the uterine vasculature.[40] It also

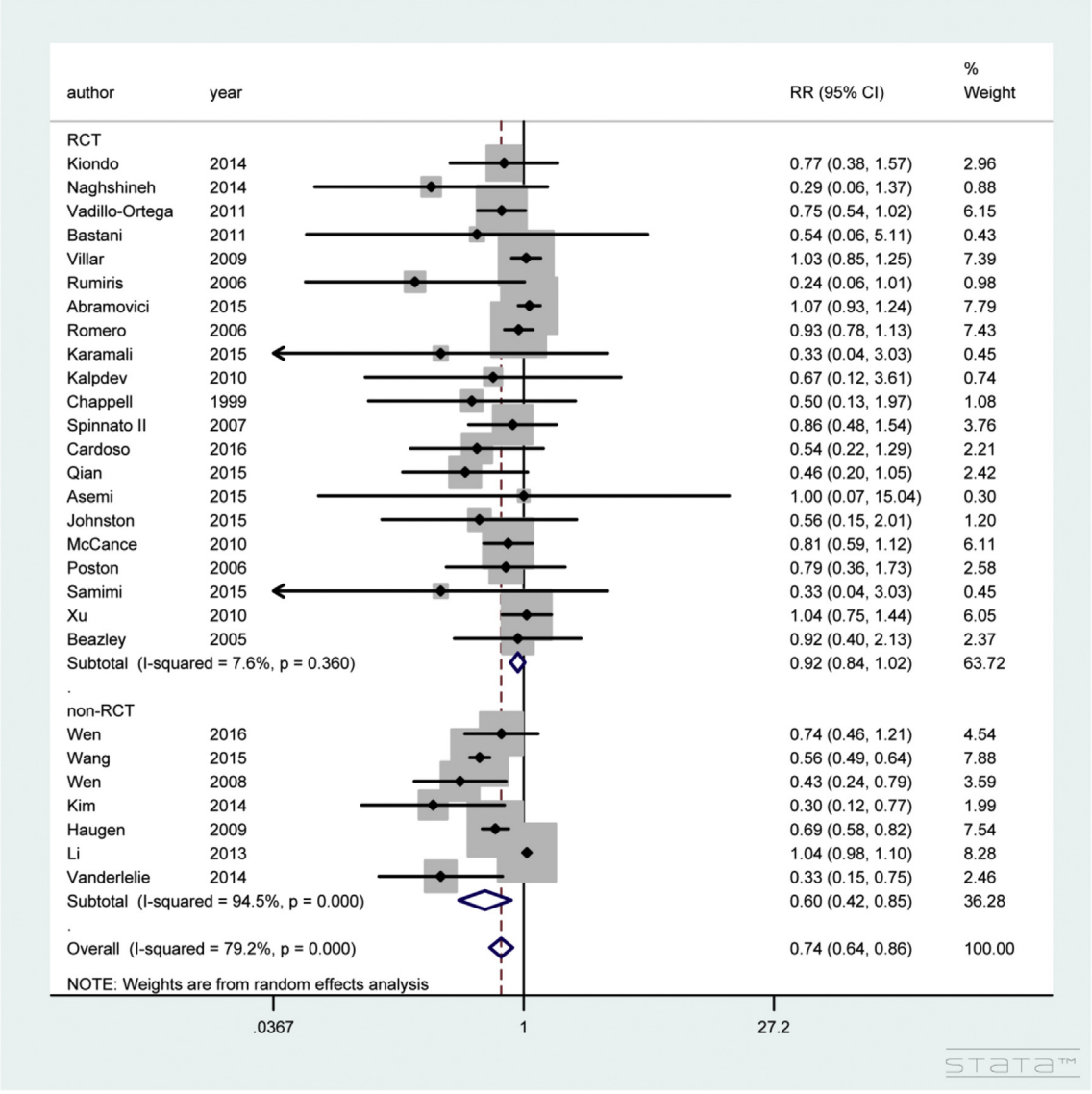

Figure 2 Subgroup analysis by study design.

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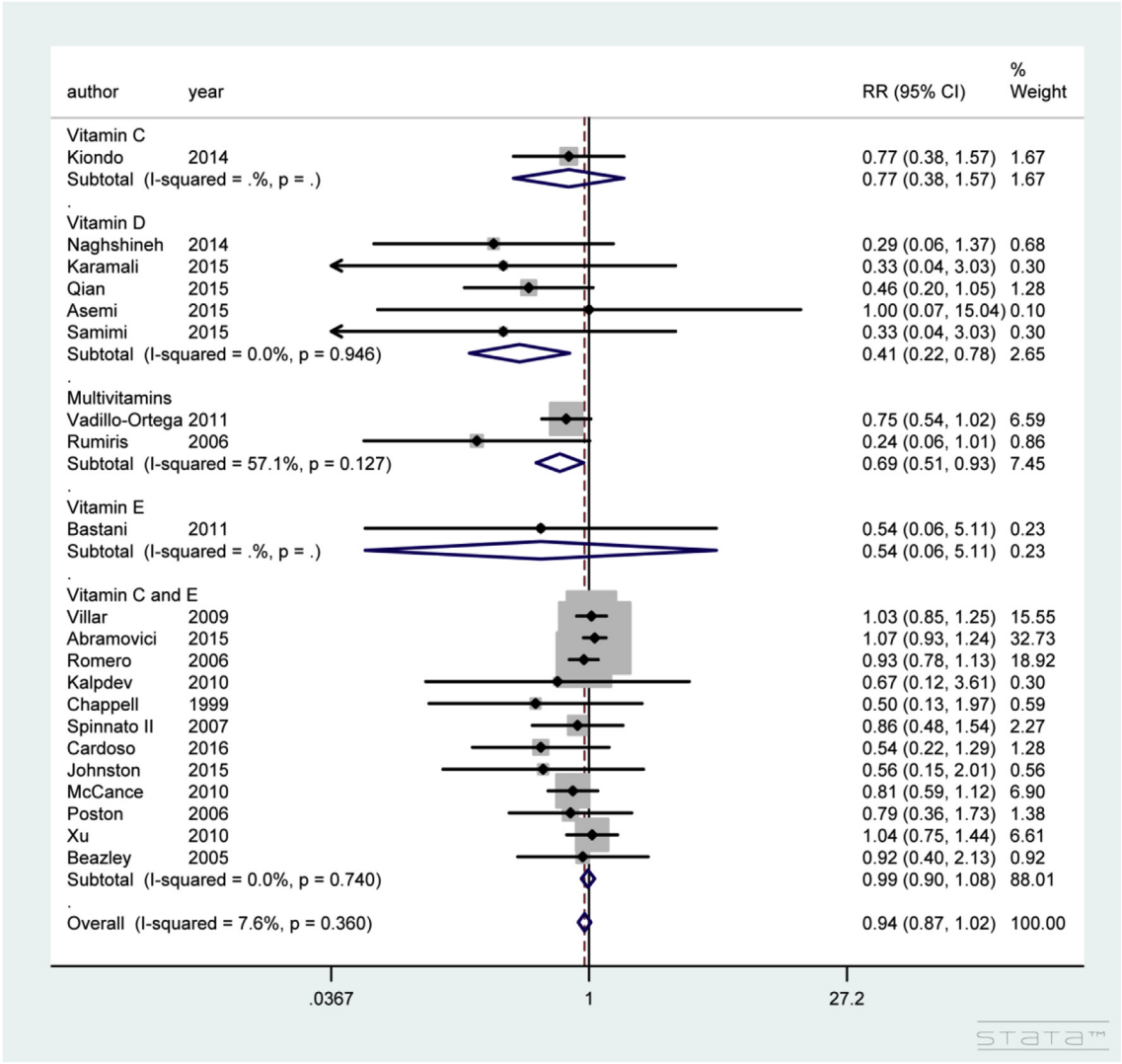

Figure 3 Subgroup analysis by vitamins type among RCT studies.

results in reduced utero-placental perfusion that could activate the mechanisms regarding to promoting maternal vasoconstriction and damage or activation of endothelial cells. Damage could be aggravated by ROS.[41] Women with preeclampsia usually show increased oxidative stress,[42] increased level of 8-iso-prostaglandin$F_{2\alpha}$ (markers of oxidative stress), and low levels of antioxidants in plasma and placenta.[43,44] Oxidative stress plus exaggerated inflammatory response may bring about the release of the maternal factors that were related with endothelial dysfunction.[45] The dysfunction of endothelial cells contributes to causing the clinical signs of preeclampsia, such as hypertension and proteinuria. Genetic predisposition, immune mal-adaptation,[46] availability of low density lipoproteins, and deficiency of antioxidants determine the response to oxidative stress. Antioxidants supplementation may regulate the response to oxidative stress of pregnant women and thus reduce the utero-placental endothelial damage in preeclampsia.

Nutritional supplementation during pregnancy may prevent complications by the following two mechanisms.[47] One mechanism is that nutritional supplementation show pharmacological effects in well-nourished women.[48] Another is that nutritional supplementation may achieve benefit via correcting the deficiency.[49] In recent years, vitamins supplementation was extensively studied. Our meta-analysis focused on the preventative role of vitamins supplementation for preeclampsia since debatable opinions on it. The results suggested that vitamins supplementation was related with reduced risk of preeclampsia.

In the analysis, we found that vitamin D supplementation could significantly reduce the risk of preeclampsia. Different from our conclusion, Naghshineh et al. found no significant association between vitamin D supplementation and preeclampsia.[15] The study of Karamali et al. extracted same conclusion.[24] Pérez-López et al. conducted a meta-analysis based on randomized controlled trials (RCTs) to analyze the effects of vitamin D supplementation during pregnancy on obstetric outcomes and concluded that incidence of preeclampsia, low birth weight and cesarean section were not influenced by vitamin D supplementation.[50] Meanwhile, we found that multivitamins

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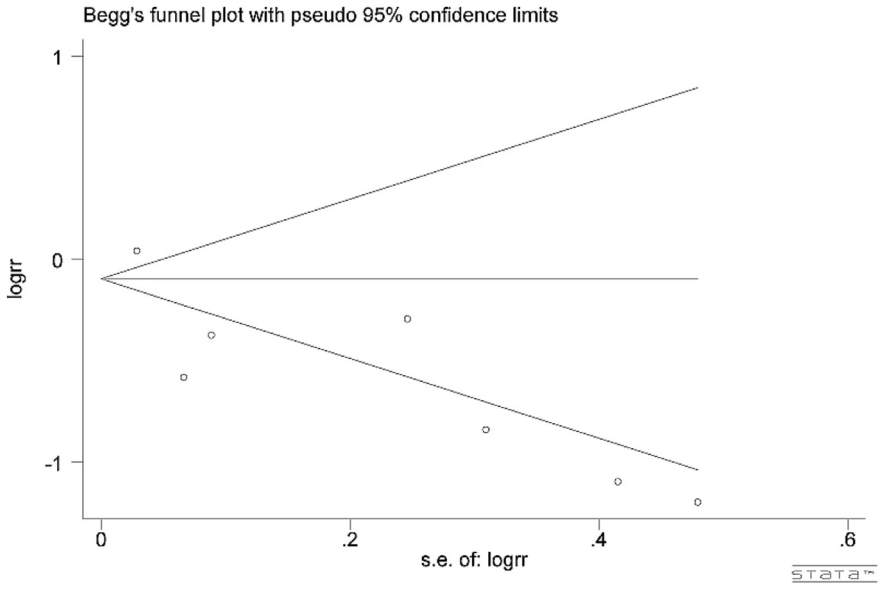

Figure 4 Begg's funnel plot.

supplementation was also related with reduced risk of preeclampsia. Likewise, Wen et al. reported that the rate of preeclampsia was lower in the supplementation group than in the no supplementation group, and the difference was statistically significant.[19] However, joint supplementation of vitamin C and E had no obvious influences on the risk of preeclampsia. Rahimi et al. also found that combined vitamin C and E supplementation have no benefit in reduce the risk of preeclampsia in pregnant women.[51]

Our analysis were based on 28 eligible articles involving 249, 975 women. The involved countries included Uganda, Iran, USA, UK, Canada, China, India, Norway and Australia. Moreover, the processes of articles search and selection, data extraction and analysis were all performed by two independent authors, which may avoid the subjective mistakes. Therefore, our results were credible and reliable. However, preeclampsia is only one of common events in pregnant women and other threatening events were not analyzed. Moreover, if the studies were all conducted with RCTs, the results would be much more credible.

In conclusion, vitamins supplementation is related with reduced risk of preeclampsia. Both of vitamin D and multivitamin supplementations could decrease the risk of preeclampsia. Combined vitamin C and E supplementation has no influences on the occurrence of preeclampsia.

Conflicts of interests statements

We declare that we have no conflict of interest.

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References

1. Brantsaeter AL, Myhre R, Haugen M, Myking S, Sengpiel V, Magnus P, et al. Intake of probiotic food and risk of preeclampsia in primiparous women the Norwegian mother and child cohort study. *Am J Epidemiol* 2011;**174**:807–15.
2. Sibai B, Dekker G, Kupferminc M. Pre-eclampsia. *Lancet* 2005; **365**:785–99.
3. Carty DM, Delles C, Dominiczak AF. Preeclampsia and future maternal health. *J Hypertens* 2010;**28**:1349–55.
4. Zhang J, Meikle S, Trumble A. Severe maternal morbidity associated with hypertensive disorders in pregnancy in the United States. *Hypertens Pregnancy* 2003;**22**:203–12.
5. Roberts JM, Speer P. Antioxidant therapy to prevent preeclampsia. *Semin Nephrol* 2004;**24**:557–64.
6. Mignini LE, Latthe PM, Villar J, Kilby MD, Carroli G, Khan KS. Mapping the theories of preeclampsia: the role of homocysteine. *Obstet Gynecol* 2005;**105**:411–25.
7. Hubel CA, Kozlov AV, Kagan VE, Evans RW, Davidge ST, McLaughlin MK, et al. Decreased transferrin and increased transferrin saturation in sera of women with preeclampsia: implications for oxidative stress. *Am J Obstet Gynecol* 1996; **175**:692–700.
8. Ehrenkranz RA. Vitamin E and the neonate. *Am J Dis Child* 1980;**134**:1157–66.
9. Czernichow S, Hercberg S. International studies concerning the role of antioxidant vitamins in cardiovascular diseases: a review. *J Nutr Health Aging* 2001;**5**:188–95.
10. Raijmakers MT, Dechend R, Poston L. Oxidative stress and preeclampsia: rationale for antioxidant clinical trials. *Hypertension* 2004;**44**:374–80.
11. Chappell LC, Seed PT, Briley AL, Kelly FJ, Lee R, Hunt BJ. Effect of antioxidants on the occurrence of pre-eclampsia in women at increased risk: a randomised trial. *Lancet* 1999;**354**: 810–6.
12. Hyppönen E, Cavadino A, Williams D, Vereczkey A, Fraser WD, Bánhidy F, et al. Vitamin D and pre-eclampsia: original data, systematic review and meta-analysis. *Ann Nutr Metab* 2013; **63**:331–40.
13. Wen SW, Chen XK, Rodger M, White RR, Yang Q, Smith GN, et al. Folic acid supplementation in early second trimester and the risk of preeclampsia. *Am J Obstet Gynecol* 2008;**198**:e1–7.

14. Kiondo P, Wamuyu-Maina G, Wandabwa J, Bimenya GS, Tumwesigye NM, Okong P. The effects of vitamin C supplementation on pre-eclampsia in Mulago Hospital, Kampala, Uganda: a randomized placebo controlled clinical trial. *BMC Pregnancy Childbirth* 2004;**14**:283.
15. Naghshineh E, Sheikhaliyan S. Effect of vitamin D supplementation in the reduce risk of preeclampsia in nulliparous women. *Adv Biomed Res* 2016;**5**:7.
16. Vadillo-Ortega F, Perichart-Perera O, Espino S, Avila-Vergara MA, Ibarra I, Ahued R, et al. Effect of supplementation during pregnancy with L-arginine and antioxidant vitamins in medical food on pre-eclampsia in high risk population: randomised controlled trial. *BMJ* 2011;**342**:d2901.
17. Bastani P, Hamdi K, Abasalizadeh F, Navali N. Effects of vitamin E supplementation on some pregnancy health indices: a randomized clinical trial. *Int J Gen Med* 2011;**4**:461—4.
18. Villar J, Purwar M, Merialdi M, Zavaleta N, Thi NNN, Anthony J, et al. World Health Organisation multicentre randomised trial of supplementation with vitamins C and E among pregnant women at high risk for pre-eclampsia in populations of low nutritional status from developing countries. *BJOG* 2009;**116**:780—8.
19. Wen SW, Guo YF, Rodger M, White RR, Yang QY, Smith GN, et al. Folic acid supplementation in pregnancy and the risk of pre-eclampsia—a cohort study. *PLoS One* 2016;**11**, e0149818.
20. Rumiris D, Purwosunu Y, Wibowo N, Farina A, Sekizawa A. Lower rate of preeclampsia after antioxidant supplementation in pregnant women with low antioxidant status. *Hypertens Pregnancy* 2006;**25**:241—53.
21. Abramovici A, Gandley RE, Clifton RG, Leveno KJ, Myatt L, Wapner RJ, et al. Prenatal vitamin C and E supplementation in smokers is associated with reduced placental abruption and preterm birth: a Secondary Analysis. *BJOG* 2015;**122**:1740—7.
22. Wang Y, Zhao N, Qiu J, He X, Zhou M, Cui H, et al. Folic acid supplementation and dietary folate intake, and risk of pre-eclampsia. *Eur J Clin Nutr* 2015;**69**:1145—50.
23. Romero R, Garite TJ. Unexpected results of an important trial of vitamins C and E administration to prevent preeclampsia. *Am J Obstet Gynecol* 2006;**194**:1213—4.
24. Karamali M, Beihaghi E, Mohammadi AA, Asemi Z. Effects of high-dose vitamin D supplementation on metabolic status and pregnancy outcomes in pregnant women at risk for pre-eclampsia. *Horm Metab Res* 2015;**47**:867—72.
25. Kalpdev A, Saha SC, Dhawan V. Vitamin C and E supplementation does not reduce the risk of superimposed PE in pregnancy. *Hypertens Pregnancy* 2011;**30**:447—56.
26. Samimi M, Kashi M, Foroozanfard F, Karamali M, Bahmani F, Asemi Z, et al. The effects of vitamin D plus calcium supplementation on metabolic profiles, biomarkers of inflammation, oxidative stress and pregnancy outcomes in pregnant women at risk for pre-eclampsia. *J Hum Nutr Diet* 2016;**29**:505—15.
27. Kim MW, Ahn KH, Ryu KJ, Hong SC, Lee JS, Nava-Ocampo AA, et al. Preventive effects of folic acid supplementation on adverse maternal and fetal outcomes. *PLoS One* 2014;**9**, e97273.
28. Spinnato 2nd JA, Freire S, Pinto ESJL, Cunha RMV, Martins-Costa S, Koch MA, et al. Antioxidant therapy to prevent pre-eclampsia A randomized controlled trial. *Obstet Gynecol* 2007;**110**:1311—8.
29. Cardoso PM, Surve S. The effect of vitamin E and vitamin C on the prevention of preeclampsia and newborn outcome: a case—control study. *J Obstet Gynaecol India* 2016;**66**:271—8.
30. Haugen M, Brantsaeter AL, Trogstad L, Alexander J, Roth C, Magnus P, et al. Vitamin D supplementation and reduced risk of preeclampsia in nulliparous women. *Epidemiology* 2009;**20**:720—6.
31. Qian L, Wang H, Wu F, Li M, Chen W, Lv L. Vitamin D3 alters Toll-like receptor 4 signaling in monocytes of pregnant women at risk for preeclampsia. *Int J Clin Exp Med* 2015;**8**:18041—9.
32. Asemi Z, Esmaillzadeh A. The Effect of multi mineral vitamin D supplementation on pregnancy outcomes in pregnant women at risk for preeclampsia. *Int J Prev Med* 2015;**6**:62.
33. Johnston PC, McCance DR, Holmes VA, Holmesb VA, Youngb IS, McGintyb A. Placental antioxidant enzyme status and lipid peroxidation in pregnant women with type 1 diabetes: the effect of vitamin C and E supplementation. *J Diabetes Complicat* 2016;**30**:109—14.
34. Li Z, Ye R, Zhang L, Li H, Liu J, Ren A, et al. Folic acid supplementation during early pregnancy and the risk of gestational hypertension and preeclampsia. *Hypertension* 2013;**61**:873—9.
35. McCance DR, Holmes VA, Maresh MJ, Patterson CC, Walker JD, Pearson DWM, et al. Vitamins C and E for prevention of pre-eclampsia in women with type 1 diabetes (DAPIT): a randomised placebo-controlled trial. *Lancet* 2010;**376**:259—66.
36. Poston L, Briley AL, Seed PT, Kelly FJ, Shennan AH. Vitamin C and vitamin E in pregnant women at risk for pre-eclampsia (VIP trial): randomised placebo-controlled trial. *Lancet* 2006;**367**:1145—54.
37. Vanderlelie J, Scott R, Shibl R, Lewkowicz J, Perkins A, Scuffham PA. First trimester multivitamin/mineral use is associated with reduced risk of pre-eclampsia among overweight and obese women. *Matern Child Nutr* 2016;**12**:339—48.
38. Xu H, Perez-Cuevas R, Xiong X, Reyes H, Roy C, Julien P, et al. An international trial of antioxidants in the prevention of preeclampsia (INTAPP). *Am J Obstet Gynecol* 2010;**202**:239.e1-239.e10.
39. Beazley D, Ahokas R, Livingston J, Griggs M, Sibai BM. Vitamin C and E supplementation in women at high risk for preeclampsia: a double-blind, placebo-controlled trial. *Am J Obstet Gynecol* 2005;**192**:520—1.
40. Mignini LE, Villar J, Khan KS. Mapping the theories of pre-eclampsia: the need for systematic reviews of mechanisms of the disease. *Am J Obstet Gynecol* 2006;**194**:317—21.
41. Davidge ST. Oxidative stress and altered endothelial cell function in pre-eclampsia. *Semin Reprod Endocrinol* 1998;**16**:65—73.
42. Poston L, Raijmakers MT. Trophoblast oxidative stress, antioxidants and pregnancy outcome—a review. *Placenta* 2004;**25**:S72—8.
43. Agarwal A, Gupta S, Sharma R. Oxidative stress and its implications in female infertility - a clinician's perspective. *Reprod Biomed Online* 2005;**11**:641—50.
44. Kiondo P, Tumwesigye NM, Wandabwa J, Wamuyumaina G, Bimenya GS, Okong P. Plasma vitamin C assay in women of reproductive age in Kampala, Uganda using a colorimetric method. *Trop Med Int Health* 2012;**17**:191—6.
45. Roberts JM, Gammill HS. Preeclampsia: recent insights. *Hypertension* 2005;**46**:1243—9.
46. Hiby SE, Walker JJ, O'shaughnessy KM, Redman CWG, Carrington M, Trowsdale J, et al. Combinations of maternal KIR and fetal HLA-C genes influence the risk of preeclampsia and reproductive success. *J Exp Med* 2004;**200**:957—65.
47. Villar J, Belizán JM. Same nutrient, different hypotheses: disparities in trials of calcium supplementation during pregnancy. *Am J Clin Nutr* 2000;**71**(2000):1375S—9S.
48. Rumbold AR, Crowther CA, Haslam RR, Dekker GA, Robinson JS. Vitamins C and E and the risks of preeclampsia and perinatal complications. *N Engl J Med* 2006;**354**:1796—806.
49. Villar J, Abdel-Aleem H, Merialdi M, Mathai M, Ali MM, Zavaleta N, et al. World Health Organization randomized trial of calcium supplementation among low calcium intake pregnant women. *Am J Obstet Gynecol* 2006;**194**:639—49.

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50. Pérez-López FR, Pasupuleti V, Mezones-Holguin E, Benites-Zapata VA, Thota P, Deshpande A, et al. Effect of vitamin D supplementation during pregnancy on maternal and neonatal outcomes: a systematic review and meta-analysis of randomized controlled trials. *Fertil Steril* 2015;**103**:1278—88.

51. Rahimi R, Nikfar S, Rezaie A, Abdollahi M. A meta-analysis on the efficacy and safety of combined vitamin C and E supplementation in preeclamptic women. *Hypertens Pregnancy* 2009; **28**:417—34.

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