Dietary carotenoid intake and risk of developing preeclampsia: a hospital-based case–control study

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Abstract

Background: The effect of carotenoids on the risk of preeclampsia (PE) is uncertain. We aimed to examine the associations between the intake of dietary carotenoids and related compounds by pregnant women in China, and the risk of their developing PE.

Methods: Four hundred and forty PE cases and 440 age- (±3 years), gestational age- (±1 weeks) and gestational diabetes mellitus status- (yes/no) matched healthy controls were recruited from March 2016 to June 2019. Dietary intake of carotenoids was assessed using a 79-item validated food-frequency questionnaire. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using conditional logistic regression.

Results: After adjusting for potential confounders, we found that the intake of total carotenoids, β-carotene, β-cryptoxanthin, lycopene, and lutein and zeaxanthin (lut-zea) were negatively associated with the odds of developing PE. Compared with the lowest quartile intake, the multivariate-adjusted OR (95% CI) of the highest quartile intake was 0.29 (0.16–0.54, \( P_{\text{trend}} < 0.001 \)) for total carotenoids, 0.31 (0.16–0.58, \( P_{\text{trend}} < 0.001 \)) for β-carotene, 0.50 (0.27–0.90, \( P_{\text{trend}} = 0.007 \)) for β-cryptoxanthin, 0.55 (0.30–0.99, \( P_{\text{trend}} = 0.04 \)) for lycopene and 0.32 (0.17–0.61, \( P_{\text{trend}} = 0.001 \)) for lut-zea. However, no significant associations were observed between the risk of developing PE and α-carotene intake (OR = 0.75, 95% CI: 0.41–1.36, \( P_{\text{trend}} = 0.28 \)). Moreover, similar negative associations were found for every one-standard-deviation increase in the intake of total carotenoids, β-carotene, β-cryptoxanthin, lycopene and lut-zea may be associated with a low risk of developing PE.

Conclusion: These results indicate that a high intake of total carotenoids, β-carotene, β-cryptoxanthin, lycopene and lut-zea may be associated with a low risk of developing PE.

Keywords: Preeclampsia, Carotenoids, Chinese, Pregnant women, Case–control study

Background

Preeclampsia (PE) is a major pregnancy complication with a worldwide incidence rate of 2.61%, as reported by the World Health Organization [1]. PE occurs in 4–5% of pregnancies worldwide [2] and leads to 75,000 maternal deaths each year [3]. It is also one of the main causes of maternal, foetal and neonatal deaths in low- and middle-income countries [4]. The main clinical manifestations of PE are hypertension, proteinuria and oedema after 20 weeks of gestation, which in cases of severe PE may be accompanied by systemic multiple organ damage; heart failure; haemolysis, elevated liver enzymes and low platelets syndrome; pulmonary oedema; placental abruption; and systemic small vessel spasm. Furthermore, PE substantially increases the...
risk of adverse pregnancy outcomes, such as foetal growth restriction, premature delivery and stillbirth [5]. There are currently no effective treatments for PE, with premature delivery being almost ineluctable in cases of severe PE. Therefore, identifying risk factors that can help prevent the occurrence of PE is important to reduce morbidity and mortality. The current known risk factors for PE include genetic susceptibility, family history, number of pregnancies, maternal age, maternal smoking, pre-pregnancy body mass index (BMI), the use of assisted reproductive technology and maternal comorbidity condition, such as diabetes, chronic kidney disease and systemic lupus erythematosus [6, 7]. Considering dietary intake can be easily controlled and given, studies on the relationship between dietary factors (energy, nutrients, foods or overall dietary patterns) and PE have attracted more and more attention [8].

The pathophysiology of PE is not clear, but an imbalance between antioxidants and pro-oxidants is known to contribute to the development of the condition [2]. Carotenoids are yellow, orange and red fat-soluble pigments that are widely found in microorganisms, plants, animals and the human body [9]. Carotenoids serve as one of main antioxidant defence systems in the human body [10] and thus play an important role in protection from oxidative stress [11–13]. A recent review noted that the association between carotenoid subclasses and the risk of developing PE has been inconclusive [14]. A meta-analysis of 58 studies, which comprised cohort studies, case–control studies, cross-sectional studies and randomised controlled trials (RCTs), found there was limited and non-definitive evidence that women with PE had low concentrations of carotenoids [15]. Another meta-analysis of RCTs found that oral antioxidant supplements, including lycopene, could not effectively prevent the occurrence of PE [16]. The differences between these meta-analyses’ findings may be partly attributable to differences between the dosages, intervention start times, sample sizes and maternal health status in studies, which demonstrates that more research is required in this field.

Carotenoids can also affect the growth and health of infants, especially their visual and cognitive development [17]. In addition, a recent review recommended that women should consume a diet rich in carotenoids during pregnancy, although there is no current recommendation on carotenoid dietary intake [14]. The few studies that have measured dietary carotenoid intake during pregnancy show that intake varies between study populations [18–20]. There are scarce data from observational studies showing the association between the risk of developing PE and the intake of dietary carotenoids and related compounds, we assessed this relationship in pregnant Chinese women via a hospital-based case–control study.

Materials and methods
Study design and participants
This hospital-based case–control study was conducted in the First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan, China, from March 2016 to June 2019. The inclusion criteria were singleton pregnant women aged ≥18 years and of gestational age ≥ 28 weeks. The case group met the diagnostic criteria of China’s diagnosis and treatment guidelines for hypertensive disorders in pregnancy (2015), which have been detailed in our previous studies [21, 22]. The control group was pregnant women from the same hospital with normal blood pressure and no proteinuria. They were matched with case group based on age (± 3 years), gestational age (± 1 weeks) and gestational diabetes mellitus (GDM) status (yes/no). Women with heart disease, malignant tumours, hyperthyroidism, immune system diseases, chronic renal insufficiency, endocrine diseases, mental disorders or those unable to complete the interviews were excluded.

Assessment of dietary carotenoid intake
A validated semi-quantitative food frequency questionnaire (FFQ) [23] was used to investigate the dietary intake of participants in the 3 months preceding delivery. The FFQ had question in seven categories and regarding a total of 79 food items relevant to Chinese eating habits, including grains, beans and their products, vegetables, fruits, animal foods (meat and poultry, fish and seafood, eggs and dairy), seeds and nuts, and drinks and soups. Participants were asked by trained investigators to report their frequency of consumption of each food item on a daily, weekly or monthly basis during the 3 months preceding delivery. Pre-prepared food pictures were then used to help them estimate the amounts they had consumed. The participants spent 30–40 min recalling their dietary intake with the help of the investigators and these pictures. Their daily intake of energy (kcal/d) and carotenoids (μg/d) was calculated using Chinese Food Composition Tables (2004) [24].

Data collection
Socio-demographic and lifestyle characteristics were recorded using a structured questionnaire. The daily metabolic equivalent (metabolic equivalents task [MET]) was calculated based on the intensity of average daily physical activity. The height, weight and blood pressure of the participants were measured by trained investigators. Height and weight were accurate to 0.1 cm and 0.1kg, respectively. The left-arm blood pressure of the participants was measured at rest at least twice (with an
interval of 10 min). If the difference between the first and second systolic blood pressure (SBP) measurement or diastolic blood pressure (DBP) measurement was more than 3 mmHg, a third measurement was performed. The BMI was calculated as weight (kg)/[height (m)]².

Statistical analysis
Based on previous survey results, we assumed that 25% of the control population consumed more carotenoids and estimated the odds ratio (OR) between higher carotenoid intake and PE to be 0.50 [25]. The minimum sample size of each group was calculated to be 281, based on a statistical power of 90% (β = 0.1) and a two-sided significance level of 5% (α = 0.05). All of the analyses were conducted using SPSS software (v25.0, IBM Corporation) and SAS software (v9.1, SAS Institute Inc.). Two-sided tests were used and P < 0.05 was defined as being statistically significant.

To compare the general characteristics and dietary carotenoid intakes of the case and control groups, a paired sample t-test or Wilcoxon signed rank-sum test was used to analyse quantitative variables and McNemar’s test was used to analyse qualitative variables. To compare the distribution of demographic factors and dietary intake of food groups rich in carotenoids and nutrients according to quartiles of the total carotenoids, ANOVA (P< homogeneity of variance test < 0.05) and Kruskal-Wallis H test (P< homogeneity of variance test > 0.05) and Kruskal-Wallis H test (P< homogeneity of variance test < 0.05) were used to analyse quantitative variables and Chi square test was used to analyse qualitative variables. Data were described as means and standard deviations (SDs), medians and interquartile range (IQRs), numbers and percentages (%) or mean rank.

Based on the intake data of the control group, the quartile method was used to convert the energy-adjusted dietary carotenoid intake (residual method) [26] of the case group into a categorical variable. The energy-adjusted dietary intake was the residual of the regression of the dietary component’s intake on energy intake. A conditional logistic-regression model was used to examine the association between energy-adjusted dietary carotenoid intake and the risk of developing PE. The potential confounding variables were adjusted in the multivariate model, including age (years), gestational age (weeks), pre-pregnancy BMI (kg/m²), gravidity, parity, GDM status (yes/no), family hypertension history (yes/no), physical activity (MET [h/d]), education and income levels and total energy intake (kcal/d). The linear trend was tested by entering the median intake for each quartile of carotenoid intake as a continuous variable into univariate and multivariate logistic regression models. After standardising the energy-adjusted data and entering it into the model, the risk per one SD increase was calculated. A restricted cubic spline (RCS) was used to examine the potentially non-linear relationship between energy-adjusted dietary carotenoid intake and the risk of developing PE (with knots placed on the 20th, 50th and 80th percentiles).

To test the stability of the relationship between the risk of developing PE and the intake of dietary carotenoids and related compounds, a sensitivity analysis was carried out by excluding the GDM participants. Another sensitivity analysis was performed by further adjusted for dietary factors in the logical model on the basis of general confounding factors, including energy-adjusted dietary vegetables, fruits, fat, fibre, vitamin D, vitamin C, vitamin E, and flavonoids intake. In addition, the correlation coefficients between carotenoids and energy intakes were calculated, and the conditional logistic regression using the original data was also performed.

Results
Basic characteristics and dietary intakes of total carotenoids and related compounds of case and control group
Four hundred and forty pairs of pregnant women were matched and assessed to explore the relationship between dietary carotenoid intake and the risk of developing PE. The case and control groups’ basic demographic information and data on their intake of total carotenoids and related compounds are listed in Table 1. No significant differences were observed between those the groups in terms of age, gestational age, district, income level and passive smoking status. Compared with the control group, the SBP, DBP, pre-pregnancy BMI and physical activity level of the case group were higher, whereas its total energy intake was lower. Pregnant women with PE were more likely to have a low educational level and family history of hypertension, to be experiencing their first pregnancy and to gain more weight during pregnancy. Those in the case group consumed fewer total carotenoids, α-carotene, β-carotene, β-cryptoxanthin, lycopene and lutein and zeaxanthin (lut-zea) than those in the control group.

General characteristics and dietary intakes of the participants by quartiles of total carotenoids
The distribution of demographic factors and dietary intake of food groups rich in carotenoids and nutrients according to quartiles of the total carotenoids are listed in Table 2. The results showed that dietary carotenoids intake was related to age, energy-adjusted dietary vegetables, fruits, fat, protein, fibre, vitamin D, vitamin C and flavonoids intake (P < 0.05).
Table 1 Distribution of demographic factors and energy-adjusted dietary carotenoids compounds intake among cases and controls

|                          | Case Group | Control Group | P*         |
|--------------------------|------------|---------------|------------|
|                          | n          | Mean/Median   | SD/IQR     | n          | Mean/Median   | SD/IQR     |
| Age (years) a            | 440        | 30.88         | 5.03       | 440        | 31.03         | 4.85       | 0.11       |
| Pregnant age (weeks) a   | 440        | 34.17         | 2.90       | 440        | 34.24         | 2.67       | 0.07       |
| SBP (mmHg) a             | 440        | 153.78        | 16.71      | 440        | 113.17        | 10.42      | <0.001     |
| DBP (mmHg) a             | 440        | 100.21        | 12.33      | 440        | 72.84         | 8.98       | <0.001     |
| Pre-pregnancy BMI (kg/m²) a | 440  | 23.67         | 3.89       | 440        | 22.35         | 3.35       | <0.001     |
| Physical activity (MET- h/d) b | 440  | 26.17         | 4.47       | 440        | 25.35         | 5.15       | 0.03       |
| Total energy intake (kcal/d) b | 440  | 1747.21       | 622.83     | 440        | 1866.97       | 595.38     | 0.006      |
| District c               | 0.864      |               |            |            |               |            |            |
| Zhengzhou                | 85         | 19.3          |           | 88         | 20.0          |           |            |
| Others                   | 355        | 80.7          |           | 352        | 80.0          |           |            |
| Educational level (%) c  |            |               |            |            |               |            | 0.01       |
| Junior high school and below | 207      | 47.0          |           | 165        | 37.5          |           |            |
| Senior high school       | 75         | 17.0          |           | 83         | 18.9          |           |            |
| Undergraduate and above  | 158        | 36.0          |           | 192        | 43.6          |           |            |
| Income level (yuan/month) (%) c | 0.15 |               |            |            |               |            |            |
| < 3000                   | 185        | 42.0          |           | 166        | 37.7          |           |            |
| 3000–6000                | 194        | 44.1          |           | 193        | 43.9          |           |            |
| > 6000                   | 61         | 13.9          |           | 81         | 18.4          |           |            |
| Family hypertension history (%) c |       |               |            |            |               |            | <0.001     |
| Yes                      | 159        | 36.1          |           | 82         | 18.6          |           |            |
| No                       | 281        | 63.9          |           | 358        | 81.4          |           |            |
| Weight-gain during pregnancy (kg) (%) c |       |               |            |            |               |            | <0.001     |
| < 15                     | 179        | 40.7          |           | 292        | 66.4          |           |            |
| 15–20                    | 142        | 32.3          |           | 122        | 27.7          |           |            |
| > 20                     | 119        | 27.0          |           | 26         | 5.9           |           |            |
| Passive smoking (%) c    | 0.49       |               |            |            |               |            |            |
| Yes                      | 67         | 15.2          |           | 59         | 13.4          |           |            |
| No                       | 373        | 84.8          |           | 381        | 86.6          |           |            |
| Gravidity (%) c          | 0.005      |               |            |            |               |            |            |
| 1                        | 116        | 26.4          |           | 79         | 18.0          |           |            |
| 2                        | 112        | 25.5          |           | 105        | 23.9          |           |            |
| ≥ 3                      | 212        | 48.1          |           | 256        | 58.1          |           |            |
| Parity (%) c             | 0.001      |               |            |            |               |            |            |
| 0                        | 185        | 42.0          |           | 136        | 30.9          |           |            |
| 1–2                      | 249        | 56.6          |           | 286        | 65.0          |           |            |
| ≥ 3                      | 6          | 1.4           |           | 18         | 4.1           |           |            |
| Total carotenoids intake (μg/d) b | 440 | 14,532.38     | 8108.91    | 440        | 17,088.73     | 9849.94    | <0.001     |
| α-carotene intake (μg/d) b | 440 | 815.59        | 750.47     | 440        | 920.02        | 908.30     | 0.006      |
| β-carotene intake (μg/d) b | 440 | 6138.40       | 3474.44    | 440        | 7188.93       | 4422.15    | <0.001     |
| β-cryptoxanthin intake (μg/d) b | 440 | 86.75         | 71.94      | 440        | 101.07        | 102.00     | <0.001     |
| Lycopene intake (μg/d) b  | 440        | 2178.33       | 2377.52    | 440        | 2931.10       | 3566.79    | <0.001     |
| Lut-zea intake (μg/d) b   | 440        | 4418.76       | 3372.54    | 440        | 5069.52       | 3386.23    | <0.001     |

SD Standard deviation, IQR Interquartile range, SBP Systolic blood pressure, DBP Diastolic blood pressure, BMI Body mass index, MET Metabolic equivalent task, Lut-zea Lutein and zeaxanthin

* Described as means and SDs. b Described as medians and IQRs. c Described as numbers and percentages

*Paired sample t-test or Wilcoxon signed-rank sum test was used to analyse quantitative variables and McNemar’s test was used to analyse qualitative variables
### Table 2  Distribution of demographic factors and dietary intake of food groups rich in carotenoids and nutrients according to quartiles of the energy-adjusted consumption of total carotenoids

|                      | Q₁ (< 11.88 mg/d) | Q₂ (11.88–15.98 mg/d) | Q₃ (15.99–20.78 mg/d) | Q₄ (> 20.78 mg/d) | \( P^* \) |
|----------------------|-------------------|------------------------|-----------------------|-------------------|-----------|
| n                    | 220               | 220                    | 220                   | 220               | 0.001     |
| Age (years) a        | 30.2 ± 5.01       | 30.6 ± 4.93            | 30.99 ± 4.95          | 32.04 ± 4.69      | 0.047     |
| Pregnant age (weeks) a| 34.20 ± 2.84      | 34.33 ± 2.77           | 33.96 ± 2.74          | 34.33 ± 2.80      | 0.03      |
| SBP (mmHg) a         | 136.47 ± 24.55    | 135.09 ± 24.43         | 133.18 ± 25.44        | 129.26 ± 23.88    | 0.02      |
| DBP (mmHg) a         | 87.76 ± 16.69     | 87.45 ± 17.32          | 87.15 ± 18.32         | 83.73 ± 17.29     | 0.006     |
| Pre-pregnancy BMI (kg/m²) a | 23.27 ± 3.72 | 22.47 ± 3.53           | 22.18 ± 3.41          | 22.31 ± 3.84      | 0.09      |
| Physical activity (MET·h/d) a | 26.49 ± 4.21 | 26.95 ± 4.30           | 27.00 ± 4.25          | 26.65 ± 4.14      | 0.52      |
| District (%) b       |                  |                        |                       |                   | 0.366     |
| Zhengzhou            | 18.9 ± 4.3        | 18.8 ± 4.3             | 19.0 ± 4.3            | 22.9 ± 4.3        |           |
| Others               | 81.1 ± 1.2        | 81.2 ± 1.2             | 81.0 ± 1.2            | 77.1 ± 1.2        |           |
| Educational level (%) b |         |                        |                       |                   | 0.15      |
| Junior high school and below | 48.2 ± 9.2 | 41.8 ± 8.6             | 39.1 ± 8.3            | 39.5 ± 8.4        |           |
| Senior high school   | 20.5 ± 3.8        | 17.3 ± 3.6             | 16.4 ± 3.6            | 18.2 ± 3.6        |           |
| Undergraduate and above | 31.3 ± 9.0 | 40.9 ± 8.5             | 44.5 ± 8.6            | 42.3 ± 8.6        |           |
| Income level (yuan/month) (%) b |         |                        |                       |                   | 0.34      |
| < 3000               | 43.6 ± 10.3       | 37.7 ± 8.6             | 34.5 ± 8.6            | 36.8 ± 8.6        |           |
| 3000–6000            | 40.9 ± 9.0        | 41.8 ± 8.6             | 41.8 ± 8.6            | 40.9 ± 8.6        |           |
| > 6000               | 15.5 ± 4.7        | 21.4 ± 3.2             | 23.6 ± 3.2            | 22.3 ± 3.2        |           |
| Family hypertension history (%) b |         |                        |                       |                   | 0.57      |
| Yes                  | 27.3 ± 10.3       | 27.7 ± 10.3            | 31.4 ± 10.3           | 25.5 ± 10.3       |           |
| No                   | 72.7 ± 14.7       | 72.3 ± 14.7            | 68.6 ± 14.7           | 74.5 ± 14.7       |           |
| Weight-gain during pregnancy (kg) (%) b |         |                        |                       |                   | 0.09      |
| <15                  | 50.9 ± 10.9       | 49.5 ± 10.9            | 54.5 ± 10.9           | 59.1 ± 10.9       |           |
| 15–20                | 28.2 ± 7.5        | 34.1 ± 7.5             | 27.7 ± 7.5            | 30.0 ± 7.5        |           |
| >20                  | 20.9 ± 7.5        | 16.4 ± 7.5             | 17.7 ± 7.5            | 10.9 ± 7.5        |           |
| Passive smoking (%) b |         |                        |                       |                   | 0.43      |
| Yes                  | 57.3 ± 10.3       | 53.2 ± 10.3            | 50.0 ± 10.3           | 50.9 ± 10.3       |           |
| No                   | 42.7 ± 14.7       | 46.8 ± 14.7            | 50.0 ± 14.7           | 49.1 ± 14.7       |           |
| Gravidity (%) b      |         |                        |                       |                   | 0.09      |
| 1                    | 25.9 ± 5.5        | 25.5 ± 5.5             | 21.8 ± 5.5            | 15.5 ± 5.5        |           |
| 2                    | 22.7 ± 4.8        | 21.8 ± 4.8             | 28.2 ± 4.8            | 25.9 ± 4.8        |           |
| ≥3                   | 51.4 ± 10.3       | 52.7 ± 10.3            | 50.0 ± 10.3           | 58.6 ± 10.3       |           |
| Parity (%) b         |         |                        |                       |                   | 0.32      |
### Table 2 (continued)

| Total carotenoids (mg/d) | Q_1 (< 11.88 mg/d) | Q_2 (11.88–15.98 mg/d) | Q_3 (15.99–20.78 mg/d) | Q_4 (> 20.78 mg/d) |
|-------------------------|---------------------|-------------------------|-------------------------|---------------------|
|                         | n       | Mean/Median | SD/IQR     | n       | Mean/Median | SD/IQR     | n       | Mean/Median | SD/IQR     | n       | Mean/Median | SD/IQR     |
| 0                       | 88      | 40.0        |            | 85      | 38.6        |            | 83      | 37.7        |            | 67      | 35.5        |            |
| 1–2                     | 126     | 57.3        |            | 128     | 58.2        |            | 134     | 60.9        |            | 146     | 66.4        |            |
| ≥ 3                     | 6       | 2.7         |            | 7       | 3.2         |            | 3       | 1.4         |            | 7       | 3.2         |            |
| Total energy intake (kcal/d) |       | 220 464.37  |            | 220     | 430.56      |            | 220     | 408.45      |            | 220     | 458.62      | 0.08       |
| Energy-adjusted dietary vegetables intake (g/d) |       | 220 201.04  |            | 220     | 394.41      |            | 220     | 503.60      |            | 220     | 662.95      | <0.001     |
| Energy-adjusted dietary fruits intake (g/d) |       | 220 390.10  |            | 220     | 392.92      |            | 220     | 439.73      |            | 220     | 539.25      | <0.001     |
| Energy-adjusted dietary carbohydrates intake (g/d) |       | 220 439.67  |            | 220     | 427.81      |            | 220     | 432.39      |            | 220     | 462.14      | 0.50       |
| Energy-adjusted dietary fat intake (g/d) |       | 220 458.84  |            | 220     | 464.85      |            | 220     | 443.82      |            | 220     | 394.49      | 0.02       |
| Energy-adjusted dietary protein intake (g/d) |       | 220 360.03  |            | 220     | 402.76      |            | 220     | 457.04      |            | 220     | 542.17      | <0.001     |
| Energy-adjusted dietary fiber intake (g/d) |       | 220 277.45  |            | 220     | 365.78      |            | 220     | 458.93      |            | 220     | 659.84      | <0.001     |
| Energy-adjusted dietary vitamin D intake (μg/d) |       | 220 395.29  |            | 220     | 410.73      |            | 220     | 465.66      |            | 220     | 490.32      | <0.001     |
| Energy-adjusted dietary vitamin C intake (mg/d) |       | 220 245.01  |            | 220     | 360.40      |            | 220     | 484.50      |            | 220     | 672.09      | <0.001     |
| Energy-adjusted dietary vitamin E intake (mg/d) |       | 220 30.16   | 9.58       | 220     | 31.79       | 9.05      | 220     | 31.05       | 8.44     | 220     | 50.33       | <0.001     |
| Energy-adjusted dietary flavonoids intake (mg/d) |       | 220 392.40  |            | 220     | 417.63      |            | 220     | 445.64      |            | 220     | 506.33      |            |

SD Standard deviation, IQR Interquartile range, SBP Systolic blood pressure, DBP Diastolic blood pressure, BMI Body mass index, MET Metabolic equivalent task, Lut-zea Lutein and zeaxanthin

* Described as means and SDs. ** Described as numbers and percentages. *** Described as mean rank

*ANOVA (P homogeneity of variance test > 0.05) and Kruskal-Wallis H test (P homogeneity of variance test < 0.05) were used to analyse quantitative variables and Chi square test was used to analyse qualitative variables
The results of conditional logistic regression are shown in Table 3. A comparison of the highest and lowest intake quartiles shows that the consumption of total carotenoids, α-carotene, β-carotene, β-cryptoxanthin, lycopene and lut-zea were negatively associated with the risk of developing PE. After adjusting for all of the potential confounders, we found that high intakes of total carotenoids, β-carotene, β-cryptoxanthin, lycopene and lut-zea were associated with a lower risk of developing PE. Compared with the lowest quartile intake, the multivariate-adjusted OR (95% confidence interval [CI]) of the highest quartile intake was 0.29 (0.16–0.54, \( P_{\text{trend}} < 0.001 \)) for total carotenoids, 0.31 (0.16–0.58, \( P_{\text{trend}} < 0.001 \)) for β-carotene, 0.50 (0.27–0.90, \( P_{\text{trend}} = 0.007 \)) for β-cryptoxanthin, 0.55 (0.30–0.99, \( P_{\text{trend}} = 0.04 \)) for lycopene and 0.32 (0.17–0.61, \( P_{\text{trend}} = 0.01 \)) for lut-zea. However, there were no associations observed between PE and α-carotene intake (OR = 0.75, 95% CI: 0.41–1.36, \( P_{\text{trend}} = 0.28 \)). Moreover, the odds of developing PE decreased by 38% (OR = 0.62, 95% CI: 0.48–0.79), 28% (OR = 0.72, 95% CI: 0.58–0.89), 33% (OR = 0.67, 95% CI: 0.47–0.95), 31% (OR = 0.69, 95% CI: 0.53–0.90) and 33% (OR = 0.67, 95% CI: 0.53–0.85) for every one SD increase in consumption of total carotenoids, β-carotene, β-cryptoxanthin, lycopene and lut-zea, respectively.

### Table 3

| Carotenoids          | Quartiles of carotenoid intakes (OR, 95% CI) | \( P_{\text{trend}} \) | Per one-SD increase\(^b\) |
|----------------------|---------------------------------------------|------------------------|---------------------------|
|                      | \( Q_1 \) | \( Q_2 \) | \( Q_3 \) | \( Q_4 \) | \( Q_1 \) | \( Q_2 \) | \( Q_3 \) | \( Q_4 \) |
| Total carotenoids    | 1.0     | 0.76 (0.54, 1.08) | 0.65 (0.45, 0.94)* | 0.41 (0.27, 0.61)** | <0.001 | 0.67 (0.57, 0.78)** |
|                      | 1.0     | 0.55 (0.31, 0.96)* | 0.52 (0.28, 0.97)* | 0.29 (0.16, 0.54)** | <0.001 | 0.62 (0.48, 0.79)** |
| α-carotene           | 1.0     | 1.04 (0.73, 1.48) | 0.96 (0.67, 1.38) | 0.69 (0.45, 0.99)* | 0.03 | 0.88 (0.77, 1.10) |
|                      | 1.0     | 0.88 (0.51, 1.52) | 0.93 (0.52, 1.68) | 0.75 (0.41, 1.36) | 0.28 | 0.95 (0.79, 1.15) |
| β-carotene           | 1.0     | 0.75 (0.52, 1.08) | 0.68 (0.47, 0.99)* | 0.47 (0.32, 0.70)** | <0.001 | 0.74 (0.63, 0.85)** |
|                      | 1.0     | 0.58 (0.33, 1.03) | 0.38 (0.21, 0.71)* | 0.31 (0.16, 0.58)** | <0.001 | 0.72 (0.58, 0.89)* |
| β-cryptoxanthin      | 1.0     | 0.97 (0.68, 1.39) | 0.87 (0.59, 1.29) | 0.70 (0.47, 1.03) | 0.04 | 0.72 (0.58, 0.88)* |
|                      | 1.0     | 1.19 (0.68, 2.09) | 0.94 (0.51, 1.75) | 0.75 (0.27, 0.90)* | 0.007 | 0.67 (0.47, 0.95)* |
| Lycopene             | 1.0     | 0.99 (0.68, 1.44) | 0.74 (0.50, 1.08) | 0.52 (0.35, 0.77)* | <0.001 | 0.64 (0.53, 0.77)** |
|                      | 1.0     | 0.69 (0.39, 1.21) | 0.61 (0.33, 1.12) | 0.55 (0.30, 0.99)* | 0.04 | 0.69 (0.53, 0.90)* |
| Lut-zea              | 1.0     | 0.86 (0.61, 1.23) | 0.65 (0.43, 0.96)* | 0.59 (0.39, 0.87)* | 0.004 | 0.80 (0.69, 0.93)* |

* PE: Preeclampsia, OR: odds ratio, CI: confidence interval, Q: Quartile, SD: Standard deviation, Lut-zea: Lutein and zeaxanthin
* a Tested by entering the median intake of each quartile of carotenoids as a continuous variable into univariate and multivariate logistic regression models. b Performed by standardising the energy-adjusted carotenoid intake data and entering it into the model.

** Adjusted model was adjusted for age (years), gestational age (weeks), pre-pregnancy BMI (kg/m²), gravidity, parity, gestational diabetes mellitus (GDM) status (yes/no), family hypertension history (yes/no), physical activity (MET [h/d]), education and income levels and total energy intake (kcal/d).

\*P < 0.05; \**P < 0.001.
Fig. 1 Multivariable-adjusted spline curve of association between energy-adjusted dietary carotenoid intake and the risk of developing PE. Multivariable-adjusted odds ratios (ORs) (solid lines) and 95% confidence intervals (CIs) (dashed lines) for risk of developing PE based on the dietary intake of total carotenoids (a), α-carotene (b), β-carotene (c), β-cryptoxanthin (d), lycopene (e) and lutein-zeaxanthin (lut-zea) (f). The horizontal dashed line represents an OR of 1. The ORs were adjusted for age (years), gestational age (weeks), pre-pregnancy BMI (kg/m²), total energy intake (kcal/d), gravidity, parity, gestational diabetes mellitus (GDM) status (yes/no), family hypertension history (yes/no), physical activity (MET [h/d]) and education and income level.
β-carotene, 0.379 for β-cryptoxanthin, 0.255 for lycopene, 0.231 for lut-zea and 0.337 for total carotenoids. The conditional logistic regression using the original data was performed, yet similar results were found (Additional file 1).

**Discussion**

To the best of our knowledge, this was the first study to assess the relationship between the risk of developing PE and the intake of dietary carotenoids and related compounds in China. After adjusting for potential confounding...
factors, we found that a high intake of total carotenoids, β-carotene, β-cryptoxanthin, lycopene and lutein was associated with a reduced risk of developing PE. The highest quartile intakes of dietary carotenoids, except that of α-carotene, were associated with a 45% or greater reduction in the risk of developing PE than the other quartiles, which indicated a significant dose-response trend. The carotenoid profiles were considered to be relatively complete in this study, and represented approximately 95% of the carotenoids in the blood [27]. We included six of the most studied categories: α-carotene, β-carotene, β-cryptoxanthin, lycopene, and lutein.

Our results for total carotenoids, α-carotene, β-carotene and lutein were consistent with those of several previous studies that have reported that the total carotenoid concentrations in the sera of patients with mild and severe PE were significantly lower than those in the sera of healthy pregnant women [28, 29]. Our results for β-carotene were similar to those of a case–control study conducted by Yusuf, et al. [30] in Jordan, which used three 24-h dietary records to compare dietary carotenoid intake of a PE and a control groups. It should be noted that only correlation analysis (Chi-square test) was performed in their study, but further correlation strength (OR) analysis was not. In addition, dietary recording may lead to changes in eating behavior in the process of recording food intake, suggesting that bias may exist. In contrast, FFQ covers a longer time span, so it may better reflect habitual intake than dietary record, and may be more suitable for epidemiological studies on the relationship between dietary exposure and chronic diseases. A case–control study conducted in Zimbabwé (n = 173/186) showed that higher concentrations of β-carotene in the blood were inversely associated with the risk of developing PE [25]. Cohen et al. [31] found an inverse association between lycopene, lutein and total carotenoid concentrations and the risk of developing PE, but lutein was the only carotenoid that was significantly associated after adjusting for confounders. Zhang et al. [32] did not find any relationships between plasma α-carotene concentrations and the risk of developing PE.

The current study has some inconsistencies with previous studies on β-cryptoxanthin and lycopene. For example, Zhang et al. [32] did not find any associations between the risk of developing PE and the intake of β-cryptoxanthin and lycopene (n = 125/179). Notably, the blood samples in that study were collected only when the clinical manifestations of PE became obvious. In addition, the gestational age at the time of blood collection from the case and control groups in their study was different (36.0 ± 0.3 weeks vs. 37.3 ± 0.3 weeks, P < 0.05). Similarly, two RCTs [33, 34] that have been conducted in India did not find that lycopene intake reduced the incidence rate of PE (n = 44/54 and 159/159, respectively). However, in the current study, we found that a high lycopene intake had an unambiguously protective effect against the development of PE (lycopene intakes in the case and control groups were 2.18 mg and 2.93 mg, respectively). Our results are similar to those of another RCT (n = 116/135) conducted in India [35], which found that fewer pregnant women developed PE in the intervention group supplemented with 4 mg lycopene per day from 16 to 20 weeks compared to the placebo group (intervention vs. placebo: 8.6% vs. 17.7%, P = 0.04). Subsequently, blood samples from 50 PE pregnant women and 50 healthy pregnant women in this Indian study revealed that those with PE had significantly lower blood concentrations of lycopene than those without PE [36]. Finally, a meta-analysis conducted in 2018 of RCTs of oral antioxidant therapy for the prevention and treatment of PE found that oral lycopene supplementation of 2 mg/d or 4 mg/d from the second trimester to delivery did not prevent the occurrence of PE (relative risk [RR] = 0.67, 95% CI: 0.44–1.04, P = 0.08) [16]. Many factors could be responsible for these differences between study results, such as the study design, the treatment dose, the season, and pregnant women’s ethnicity and health status (high or low PE risk). Previous studies have found that pregnant women who are younger [12], smoking [19], and getting pregnant in the spring and summer [20] consume fewer carotenoids. In view of the results of this current study, future large-scale studies are required on the dietary carotenoid intake of pregnant women with PE.

Although most of the studies only measured blood concentrations and did not collect dietary data, they indirectly confirm our results, as the human body cannot synthesise carotenoids and thus the carotenoids in blood are derived from the diet. The Norwegian Mother and Child Cohort Study (MoBa) found that the plasma carotenoid concentrations of pregnant women were significantly correlated with food consumption, especially of fruits (r = 0.24; p < 0.01) and vegetables (r = 0.32; p < 0.01), which lends validity to our method [37]. In their study, strong correlations between carotenoids and food intake were found between α-carotene and carrots (r = 0.50; p < 0.01) and cooked vegetables (r = 0.39; p < 0.01). A meta-analysis [38] of RCTs on the effect of changes in fruit and vegetable intake on carotenoid blood concentration showed that four common carotenoids (α-carotene, β-carotene, β-cryptoxanthin and lutein) may be used as biomarkers to objectively measure general fruit and vegetable intake.

Currently, the pathogenesis of PE is thought to involve two stages: reduced placental perfusion and secondary maternal multisystem impairment [2]. Placental ischaemia and reperfusion injury caused by insufficient remodelling of the uterine spiral artery is considered to
be a cause of oxidative stress [39–41], which has also been confirmed by animal [42] and in vitro experiments [43]. The injury of vascular endothelial function caused by oxidative stress and inflammatory media leads to the decrease of vasodilators and the increase of vasoconstrictors, thus promoting vasospasm [44, 45]. It is clear that oxidative stress, a basic pathophysiological mediator of PE, plays an important role in the occurrence of PE. In truth, oxidative stress plays a key role in the development of both normal and defective placentas [2, 46]. However, there appears to be an imbalance between antioxidant and pro-oxidant mechanisms in PE. Some studies have confirmed that pregnant women with PE have higher concentrations of markers of oxidative damage and lower concentrations of antioxidants and lower total antioxidant capacity than healthy pregnant women [36, 47, 48]. The human body has various antioxidants, both enzymatic and non-enzymatic, to counter the effects of oxidants. Among non-enzymatic antioxidants, nutrients such as vitamin C, vitamin E and carotenoids play a crucial role in the human antioxidant system [10]. Previous studies have found that the intake of antioxidant nutrients affects oxidative stress [49, 50], with an insufficient intake increasing the risk of higher levels of oxidative stress and leading to poor obstetric outcomes [51, 52]. Two Cochrane reviews evaluated the effectiveness of vitamin C and E alone or in combination in the prevention of PE, but no benefit was found for routine supplementation of vitamin C and/or E [53, 54]. Carotenoids contain many double bonds that can quench singlet oxygen and scavenge free radicals and oxides, which gives them significant antioxidant activity [27]. The demand for micronutrients becomes more sensitive during pregnancy and inadequate intake may affect the mother and foetus [55]. Therefore, it is important to fully understand the role of dietary carotenoids in the occurrence of PE.

In addition to antioxidant nutrients, vitamin D supplementation has been proposed for the prevention of PE, although evidence has been inconsistent [56]. Our previous research observed a negative relationship between dietary VD intake and PE risk [57]. Vitamin D is a regulator of inflammation and may affect the occurrence of PE by regulating maternal immune response and reducing the concentrations of proinflammatory cytokines. Furthermore, Yusuf et al. [30] found a strong positive association exists for the intake of fat and negative association for the vegetables and fruits with PE. A systematic literature review and meta-analysis confirmed that high intake of fruits and vegetables had a protective effect on PE [8]. Brantsæter et al. [58] found that “vegetable dietary pattern” characterized by vegetables, plant-based foods and vegetable oils could reduce the risk of PE, whereas a dietary pattern characterized by a high consumption of processed meat, sweet drinks, and salty snacks increases the likelihood of PE. The possible reason is plant foods are rich in micronutrients (phytochemicals, antioxidants, vitamins and minerals) and dietary fibre. Moreover, a review pointed out that high intake of carotenoids may be related to a healthier diet and lifestyle, which may be beneficial in themselves [14]. Considering the role of these dietary related factors, a sensitivity analysis was performed on the basis of general confounding factors. But the results indicated that a high intake of total carotenoids, β-carotene, β-cryptoxanthin and lutein zeaxanthin was still associated with a reduced risk of developing PE, which may reflect that carotenoids intake can play a role as a predictor in the risk of PE, independent of the effects of other nutritional factors.

Some limitations of the study should be acknowledged. First, the causality of the studied association remained uncertain due to the inherent limitation of the retrospective study design of case–control study. Second, according to the rare disease assumption in the case-control study, OR might not well estimate RR (relative ratio) for the low incidence (but not rare) disease of PE in China (about 3%) [59]. The First Affiliated Hospital of Zhengzhou University is the most authoritative comprehensive hospital in Henan Province and has treated enough PE patients in this area. We recruited almost all incident cases which admitted in the target hospitals on workdays, but some cases admitted on holidays might be missed. For hospital-based case-control studies, it’s really hard to exactly identify the source population of the cases and controls. We compared the distribution of the source of the study population (Zhengzhou and other regions) in the case group and the control group, and found that the proportion of the two groups from Zhengzhou was about 20%, suggesting that the two groups were comparable. Thus, in this case, we believe OR may be an acceptable choice for estimating of the incidence rate ratio. Third, the data on dietary carotenoid intake were based on the recall of the participants, which means that recall bias was unavoidable. To minimise recall bias, we took the following measures: (1) participants’ dietary intakes were assessed in face-to-face interviews with trained investigators; (2) detailed food pictures were used to help the participants recall their eating habits; and (3) we investigated dietary intake in only the 3 months immediately preceding delivery, during which period the diet is relatively stable compared to other periods of pregnancy. This meant that our study may be unable to explain the effect of diet in early pregnancy on the occurrence of PE, but given that it is often less than 3 months from the beginning to delivery of PE patients, we believe that this study reflects the relationship between the risk of developing PE and the intake of dietary carotenoids and related compounds.
to a certain degree. Finally, instead of detecting serum carotenoids, which can be traumatic, low-cooperative and expensive, we investigated dietary carotenoid intake in a non-invasive and low-cost manner using an FFQ. As mentioned above, considering the consistency between dietary and circulating carotenoid levels and the significance of measuring carotenoid levels from dietary sources, this study may guide pregnant women’s dietary behavior and contribute to the prevention of PE.

**Conclusion**

Our results indicate that high intakes of total carotenoids, β-Carotene, β-cryptoxanthin, lycopene and lut-zea may be associated with a reduction in the risk of developing PE. Larger-scale studies are needed to verify this relationship. In the future, we recommend that pregnant women consume carotenoid-rich foods during pregnancy to prevent the occurrence of PE.

**Abbreviations**

PE: Preeclampsia; ORs: Odds ratios; Cis: Confidence intervals; Lut-zea: Lutein and zeaxanthin; RCTs: Randomised controlled trials; GDM: Gestational diabetes mellitus; FFQ: Food frequency questionnaire; MET: Metabolic equivalents task; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; BMI: Body mass index; SD: Standard deviations; IQR: Medians and interquartile range; RCS: Restricted cubic spline.

**Supplementary Information**

The online version contains supplementary material available at https://doi.org/10.1186/s12884-022-04737-5.

**Additional file 1: Table 1** Association between intake of dietary carotenoids and their subclasses and the risk of developing PE.

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**Authors’ contributions**

YHL, XLZ, and DDD designed the study; YC, DDD, WFD and WJF conducted the investigation; TX, XC and XMH analysed the data; TK drafted the manuscript; and YHL, YCB, JL, FFZ, SST and QJL reviewed the manuscript. All of the authors read and approved the final manuscript.

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**Availability of data and materials**

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

**Declarations**

**Ethics approval and consent to participate**

The study was approved by the Ethics Committee of Scientific Research and Clinical Trials of the First Affiliated Hospital of Zhengzhou University (No. Scientific research-2016-LW-34). All of the participants signed a written informed consent form before the study commenced. All of the procedures in the study were carried out in accordance with the Declaration of Helsinki.

**Consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

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**References**

1. Abalos E, Cuesta C, Carroli G, Qureshi Z, Widmer M, Vogel JP, et al. Maternal WHOMo, newborn Health Research: pre-eclampsia, eclampsia and adverse maternal and perinatal outcomes: a secondary analysis of the World Health Organization multicountry survey on maternal and newborn health. BJOG. 2014;121(Suppl 1):14–24.

2. Phipps EA, Thadhani R, Benzing T, Karumanchi SA. Pre-eclampsia: pathogenesis, novel diagnostics and therapies. Nat Rev Nephrol. 2019;15(5):275–89.

3. Duley L. The global impact of pre-eclampsia and eclampsia. Semin Perinatol. 2009;33(3):130–7.

4. Saleem S, McClure EM, Goudar SS, Patel A, Esamai F, Gacesa A, et al. A prospective study of maternal, fetal and neonatal deaths in low- and middle-income countries. Bull World Health Organ. 2014;92(6):605–12.

5. Mol BWJ, Roberts CT, Thangaratnam S, Magee LA, de Groot CJM, Hofmeyr GJ. Pre-eclampsia. Lancet. 2016;387(10022):999–1011.

6. Bartsch E, Medcalf KE, Park AL, Ray JG. High risk of pre-eclampsia identification: clinical risk factors for pre-eclampsia determined in early pregnancy: systematic review and meta-analysis of large cohort studies. BMJ. 2016;353:i1753.

7. Hutcheon JA, Lisonkovova S, Joseph KS. Epidemiology of pre-eclampsia and the other hypertensive disorders of pregnancy. Best Pract Res Clin Obstet Gynaecol. 2011;25(4):391–403.

8. Schoenaker Das-Ms, Mishra GD. The association between dietary factors and gestational hypertension and pre-eclampsia: a systematic review and meta-analysis of observational studies. BMC Med. 2014;22(12):157.

9. Krinsky NI, Johnson EJ. Carotenoid actions and their relation to health and disease. Mol Asp Med. 2005;26(6):459–516.

10. Birben E, Sahiner UM, Sackesen C, Erzurum S, Kalayci O. Oxidative stress and antioxidant defense. World Allergy Organ J. 2012;5(1):9–19.

11. Agarwal A, Aponte-Mellado A, Premkumar BJ, Shaman A, Gupta S. The effects of oxidative stress on female reproduction: a review. Reprod Biol Endocrinol. 2012;10(49).

12. Thorne-Lyman AL, Fawzi WW. Vitamin a and carotenoids during pregnancy and maternal, neonatal and infant health outcomes: a systematic review and meta-analysis. Paediatr Perinat Epidemiol. 2012;26(1):36–54.

13. Zielinska MA, Wesolowska A, Pawlus B, Kuciak O. Carotenoid oxidative stress and antioxidant defense. World Allergy Organ J. 2012;5(1):9–19.

14. Cohen JM, Beddau M, Kramer MS, Platt RW, Basso O, Kahn SR. Maternal antioxidant levels in pregnancy and risk of preeclampsia and small for gestational age birth: a systematic review and Meta-analysis. PLoS One. 2015;10(8):e0135192.
16. Tenorio MB, Ferreira RC, Moura FA, Bueno NB, Goulart MOF, Oliveira ACM. Oral antioxidant therapy for prevention and treatment of preeclampsia: Meta-analysis of randomized controlled trials. Nutr Metab Cardiovasc Dis. 2018;28(9):865–76.

17. Johnson EI. Role of lutein and zeaxanthin in visual and cognitive function throughout the lifespan. Nutr Rev. 2014;72(9):605–12.

18. Hamulka J, Sulich A, Zielinska M, Wawrzyzniak A. assessment of carotenoid intake in a selected group of pregnant women. Probl Hig Epidemiol. 2015;96(4):763–8.

19. Scalife AR, McVeigh G, Campbell DM, Martindale S, Devereux G, Seaton A. Maternal intake of antioxidant vitamins in pregnancy in relation to maternal and fetal plasma levels at delivery. Br J Nutr. 2006;95(4):771–8.

20. Watson PE, McDonald BW. Seasonal variation of nutrient intake in pregnancy: effects on infant measures and possible influences on disease related to season of birth. Eur J Clin Nutr. 2007;61(1):1271–80.

21. Cao Y, Liu Y, Zhao X, Duan D, Dou W, Fu W, et al. Adherence to a dietary pattern that reduces the risk of preeclampsia. J Nutr. 2016;146(3):605–12.

22. Li SN, Liu YH, Luo ZY, Cui YF, Cao Y, Fu WJ, et al. The association between dietary fatty acid intake and the risk of developing preeclampsia: a matched case-control study. Sci Rep. 2021;11(1):4048.

23. Zhang CX, Ho SC. Validity and reproducibility of a food frequency questionnaire among Chinese women in Guangdong province. Asia Pac J Clin Nutr. 2009;18(2):240–50.

24. Yuexin Y, Guangya W, Xingchao P. China food composition. Beijing: Peking University Medical Press; 2004.

25. Williams MA, Woelk GB, King IB, Jenkins K, K M. Plasma carotenoids, retinol, tocopherols, and lipoproteins in preeclamptic and normotensive pregnant Zimbabwean women. Am J Hypertens. 2003;16(8):665–72.

26. Willett WC, Howe GR, LH K. adjustment for total energy intake in epidemiologic studies. Am J Clin Nutr. 1997;65(4 Suppl):1220S–8S.

27. Maiani G, Caston MJ, Catasta G, Toti E, Cambrodon IG, Bysted A, et al. Carotenoids: actual knowledge on food sources, intakes, stability and bioavailability and their protective role in humans. Mol Nutr Food Res. 2009;53(Suppl 2):S194–218.

28. Serdar Z, Guz E, Colak奥hurriy M, Develdoethluo Q, Sarandel O. Lipid and protein oxidation and antioxidant function in women with mild and severe preeclampsia. Arch Gynecol Obstet. 2003;268(1):19–25.

29. Serdar Z, Guz E. O.D: serum iron and copper status and oxidative stress in severe and mild preeclampsia. Cell Biochem Funct. 2006;24(3):209–15.

30. Yusuf H, Subhi HS, Obadat BS, Shargas K. Associations of macro and micronutrients and antioxidants intakes with preeclampsia: a case-control study in Jordanian pregnant women. Nutr Metab Cardiovasc Dis. 2019;29(5):458–66.

31. Maiman G, Caston MJ, Catasta G, Toti E, Cambrodon IG, Bysted A, et al. Carotenoids: actual knowledge on food sources, intakes, stability and bioavailability and their protective role in humans. Mol Nutr Food Res. 2009;53(Suppl 2):S194–218.

32. Roberts JM, Balk JL, Bodnar LM, Belizan JM, Bergel E, Martinez A. Nutrient intake in preeclampsia; a matched case-control study in Jordanian pregnant women. J Nutr. 2003;133(10):3137–40.

33. Roberts JM. Pathophysiology of ischemic placental disease. Semin Perinatol. 2015;114(9):1331–40.

34. Zhou Y, Damsky CH, Fisher SJ. Preeclampsia is associated with failure of human cytotrophoblasts to mimic a vascular adhesion phenotype. One cause of defective endothelial vascular in this syndrome? J Clin Invest. 1997;99(9):2152–64.

35. Burton GF, Woods AW, Jauniaux E, Kingdom JC. Rheological and physiological consequences of conversion of the maternal spiral arteries for uteroplacental blood flow during human pregnancy. Placenta. 2009;30(6):473–82.

36. Roberts JM. Pathophysiology of ischemic placental disease. Semin Perinatol. 2014;38(3):139–45.

37. Sidney VC, Palei AC, Metzger IF, Gomes VA, Cavalli RC, Tanus-Santos JL. Adipocytokines: the role of reactive oxygen species in hypertension produced by reduced uterine perfusion in pregnant rats. Am J Hypertens. 2008;21(10):1152–6.

38. Hung TH, Stepek IN, Burton GF In vitro ischemia-reperfusion injury in term human placenta as a model for oxidative stress in pathological pregnancies. Am J Pathol. 2001;159(3):1031–43.

39. Grimaldi VC, Palei AC, Metzger IF, Gomes VA, Cavalli RC, Tanus-Santos JL. Nitric oxide expression is inversely related to serum levels of antiangiogenic factors soluble fms-like tyrosine kinase-1 and soluble endoglin in preeclampsia. Hypertension. 2008;52(2):402–7.

40. Saleh L, Verdonk KL, Visser V, van den Meiracker AH, Danser AH. The emerging role of endothelin-1 in the pathogenesis of pre-eclampsia. Ther Adv Cardiovasc Dis. 2016;10(5):282–93.

41. Yang X, Guo L, Li H, Chen X, Tong X. Analysis of the original causes of placental oxidative stress in normal pregnancy and pre-eclampsia: a hypothesis. J Matern Fetal Neonat Med. 2012;25(7):884–8.

42. Karacay O, Sepici-Dincel A, Karcaaltincaba D, Sahin D, Yalvac S, Akol M, et al. A quantitative evaluation of total antioxidant status and oxidative stress markers in preeclampsia and gestational diabetic patients in 24–36 weeks of gestation. Diabetes Res Clin Pract. 2010;89(3):231–8.

43. Harsen NK, Braekke K, Staff AC. Augmented oxidative stress as well as antioxidant capacity in maternal circulation in preeclampsia. Eur J Obstet Gynecol Reprod Biol. 2006;128(1–2):209–15.

44. Winklhofer-Roob BM, Rock E, Ribalta J, Shmerling DH, Roob JM. Effects of vitamin E and carotenoid status on oxidative stress in health and disease. Evidence obtained from human intervention studies. Mol Asp Med. 2009;30(6):391–402.

45. Huang HF, Apple JL. Supplementation of diets with alpha-tocopherol reduces serum concentrations of gamma- and delta-tocopherol in humans. J Nutr. 2003;133(10):3137–40.

46. Roberts JM, Balk JL, Bodnar LM, Belizan JM, Bergel E, Martinez A. Nutrient involvement in preeclampsia. J Nutr. 2003;133(Suppl 2):1684S–1692.

47. Fowles ER, Murphy C, Ruiz RJ. Exploring relationships among psychosocial status, dietary quality, and measures of placental development during the first trimester in low-income women. Biol Reprod. 2011;85(1):70–7.

48. Rumbold A, Ota E, Hori H, Miyazaki C, Crowther CA. Vitamin E supplementation in pregnancy: Cochrane Database Syst Rev. 2015;2015(9):CD004069.

49. Rumbold A, Ota E, Nagata C, Shahrook S, Crowther CA. Vitamin C supplementation in pregnancy: Cochrane Database Syst Rev. 2015;2015(9):CD004072.

50. Mate A, Reyes-Goya C, Santana-Garrido A, Vazquez CM. Lifestyle, maternal nutrition and healthy pregnancy. Curr Vasc Pharmacol. 2021;19(2):132–40.

51. Purswani JM, Gala P, Dwarakanath P, Larkin HM, Kurpad A, Mehta S. The role of vitamin D in pre-eclampsia: a systematic review. BMC Pregnancy Childbirth. 2017;17(1):231.

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