The association between caffeine exposure during pregnancy and risk of gestational hypertension/preeclampsia: a meta-analysis and systematical review

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Abstract

The potential effect of caffeine exposure during pregnancy on gestational hypertension (GH)/preeclampsia has attracted attention but remains unclear. A systematic literature search of PubMed, Embase, and Cochrane Library databases was performed until March 2022. Observational studies assessing the association between caffeine exposure during pregnancy and the risk of GH/preeclampsia were included. The study protocol was registered in PROSPERO: CRD42022322387. Ten studies involving 114984 pregnant women (2548 diagnosed with GH and 2473 diagnosed with preeclampsia) were included. Comparing caffeine exposure with non-caffeine exposure, no significant association was found between caffeine exposure during pregnancy and the risk of GH (OR = 0.99, 95% CI: 0.90–1.08, p = 0.800) and preeclampsia (OR = 1.13, 95% CI: 0.97–1.31, p = 0.114). Subgroup analyses comparing low to moderate doses with no/lowest doses showed that caffeine exposure during pregnancy was not significantly associated with GH (OR = 1.00, 95% CI: 0.90–1.08) or preeclampsia (OR = 1.03, p = 0.648). Besides, subgroup analyses comparing high doses with no/lowest doses showed that caffeine exposure during pregnancy was not significantly associated with GH (OR = 1.06, p = 0.623) or preeclampsia (OR = 1.18, p = 0.192). This study found that caffeine exposure during pregnancy was not significantly associated with the risk of GH/preeclampsia.

Introduction

Hypertensive disorders of pregnancy (HDP) are one of the leading causes of maternal and perinatal morbidity and mortality worldwide, especially in low-income and middle-income countries(1). Gestational hypertension (GH) and preeclampsia are two types of HDP, accounting for 6–7% and 2–5% of diagnoses in pregnant women respectively(2, 3). GH is defined as new-onset hypertension with blood pressure ≥ 140/90mmHg on 2 occasions at least 4 hours apart after 20 weeks’ gestation(4). Preeclampsia is defined as hypertension with proteinuria or other end-organ dysfunction after 20 weeks of gestation(5). Furthermore, it is estimated that the latter complicates the pregnancy for about 3–5% of the women who give birth(5). The etiology and predictors of GH/preeclampsia remain unclear(6, 7).

Important dietary sources of caffeine include coffee, tea, caffeinated soda (cola), energy drinks and other soft drinks(8, 9). Epidemiological evidence supports the benefits of caffeine for some chronic diseases, stating that moderate caffeine consumption is safe, but noting that excessive consumption can have negative effects on children and pregnant women(10, 11). WHO recommends that pregnant women consume no more than 300mg caffeine per day(12). Additionally, a review of caffeine consumption recommends that pregnant women consume no more than 2 cups of coffee or 4 cups of tea per day(10).

Caffeine consumption is more common among women aged 20–50 years old(13), raising concerns about its potential effects on GH/preeclampsia. Nevertheless, observational studies on caffeine intake during pregnancy and the risk of GH/preeclampsia have yielded mixed results. Some papers displayed no relationship between caffeine intake during pregnancy and the risk of GH/preeclampsia(14, 15). Conversely, a nationwide birth cohort study by Kawanishi et al.(16) reported that high dose of caffeine intake during pregnancy could increase the risk of GH/preeclampsia. Therefore, we conducted a meta-analysis to discover the potential association between caffeine exposure during pregnancy and the risk of GH/preeclampsia.

Methods

Search strategy

We performed a systematic search on PubMed, Embase, and Cochrane Library databases from inception to 11 March 2022. The search items included (1,3,7-trimethylxanthine OR caffeine OR tea OR coffee OR cola OR chocolate OR soft drink OR cocoa) AND (pregnant woman OR woman, pregnant OR pregnancy OR pregnancy OR pregnancies OR maternity OR maternal OR maternally OR prenatal OR perinatal) AND (‘pre-eclampsia’ [Mesh] OR ‘hypertension, pregnancy-induced’ [Mesh] OR ‘hypertension’ [Mesh] OR pre-eclampsia OR hypertension, pregnancy induced OR pregnancy-induced hypertension OR induced hypertension, pregnancy OR gestational hypertension OR hypertension, gestational). Moreover, the references of the included articles were manually checked for additional sources. The entire review process was mapped using the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram and the study protocol was registered in PROSPERO: CRD42022322387.

Eligible criteria

The meta-analysis included studies with the following criteria, which: (1) were observational studies (cohort, cross-sectional, or case-control studies); (2) assigned participants consumed caffeinated beverages to the exposure group, and participants consumed no or the lowest dose of caffeinated beverages to the non-exposure group; (3) reported risk estimates for the association between caffeine exposure during pregnancy and the risk of GH/preeclampsia; (4) were published in English.

The exclusion criteria were as follows: (1) pregnant women with a medical history of hypertension and/or renal disease, history of HDP in previous pregnancies, and history of diabetes mellitus and gestational diabetes mellitus were included. (2) The articles were designed to investigate the association between caffeine exposure before pregnancy and the risk of GH/preeclampsia. (3) No exactable data was available. (4) When more than one paper was published by the same author or institution, the paper with the highest quality was selected.

Quality assessment and data extraction

Two researchers independently evaluated the eligibility of each study and exploited the desired information from it. Disagreements were arbitrated by a third researcher. The Newcastle-Ottawa Quality Assessment Scale (NOS) was used to assess the methodological quality of the included observational studies. Additionally, the following data were extracted: author, year of publication, country, study design, number of participants, time to recruit participants, pregnancy stage, outcome, caffeine intake sources, dietary assessment tool, and adjusted variables.
Statistical analysis

All statistical analyses were performed using Stata software version 12.0, with p<0.05 estimated as significant. OR and 95% CIs were applied as the effect sizes of caffeine exposure during pregnancy on the risk of GH/preeclampsia. As the dose and source of caffeine intake differed, a random effects model was used to combine effect sizes. Moreover, statistical heterogeneity among studies was assessed based on $I^2$ statistics. The values $I^2$ of 25-50%, 50-75%, and >75% were considered as low, moderate, and high heterogeneity, respectively(17). Subgroup analysis was established to identify sources of heterogeneity. When more than 10 articles are included in the meta-analysis, relevant calculation of publication bias and sensitivity analysis will be carried out.

Results

Characteristics of eligible research

The flow chart of study selection is summarized in Fig. 1. An initial search from various electronic databases found 701 relevant studies. After excluding unrelated papers, 10 studies eventually met the inclusion criteria(14–16, 18–24). The basic characteristics of selected studies are described in Table 1. One cross-sectional study(24), two case-control studies(19, 22), and seven cohort studies(14–16, 18, 20, 21, 23) were imported into meta-analysis. All studies were published between 1997 and 2021, and these were conducted in Norway, USA, Canada, Netherlands, Ethiopia, Japan, and Brazil. A total of 114984 pregnant women participated, including 2548 diagnosed with GH and 2473 diagnosed with preeclampsia. Dietary assessment of pregnant women was based on the food frequency questionnaire and interviews. In addition, caffeine sources for pregnant women included coffee, tea, chocolate, soft drinks, and energy drinks. Nine studies controlled the variables, except one that was not adjusted. Common variables adjusted for included studies were age, body mass index (BMI), education, smoking and alcohol consumption.
| Author   | Year | Country | Study design | Time to recruit patients | Patients number | Outcome | Dietary assessment tool | Caffeine intake sources | Trimester considered |
|----------|------|---------|--------------|--------------------------|----------------|---------|------------------------|-----------------------|---------------------|
| Wergeland | 1997 | Norway  | Cross-sectional | 1989.10-1989.11          | 5292           | Preeclampsia | Questionnaire          | Coffee (cups/day)     | Throughout pregnancy |
| Triche   | 2008 | USA     | Cohort       | 1996.9-2000.1            | 1681           | Preeclampsia | Structured interview   | Chocolate (servings/week) | First and third      |
| Wei      | 2009 | Canada  | Case-control | 2003.1-2006.3           | 245            | Preeclampsia | In-person interview and structured questionnaire | Tea (cups/week)       | Throughout pregnancy |
| Saftlas  | 2010 | USA     | Cohort       | 1988.4-1991.12           | 2325           | Preeclampsia | Interview and FFQ      | Chocolate (servings/week) | First and third      |
| Bakker   | 2011 | Netherlands | Cohort     | 2001-2005                | 7771           | Preeclampsia | FFQ                    | Coffee and tea (units/day) | Throughout pregnancy |
| Borgen   | 2012 | Norway  | Cohort       | 1999-2008                | 31230          | Preeclampsia | FFQ                    | Sugar-sweetened soft beverages, carbonated (ml/day) | First and second     |

NA, not applicable; GH, gestational hypertension; FFQ, food frequency questionnaire; BMI, body mass index.
| Author       | Year | Country    | Study design | Time to recruit patients | Patients number | Outcome     | Dietary assessment tool | Caffeine intake sources | Trimester considered |
|--------------|------|------------|--------------|---------------------------|-----------------|-------------|-------------------------|------------------------|----------------------|
| Endeshaw     | 2015 | Ethiopia   | Case-control | 2014.9                    | 302             | Preeclampsia | In-person interview and questionnaire | Coffee (cups/day)      | Throughout pregnancy |
| Hinkle       | 2021 | USA        | Cohort       | 2009–2013                 | 2719            | Preeclampsia | FFQ                     | Coffee, tea, soda and energy drink (mg/day) | First and second      |
| Kawanishi    | 2021 | Japan      | Cohort       | 2011.1–2014.3             | 56300           | GH          | FFQ                     | Coffee, tea (cups/day) | Throughout pregnancy |
| Barbosa      | 2021 | Brazil     | Cohort       | 2010.1–2011.6             | 2750            | GH          | Structured questionnaire | Soft drink (times/week) | Second               |

NA, not applicable; GH, gestational hypertension; FFQ, food frequency questionnaire; BMI, body mass index.

**Quality Assessment**

The NOS consists of eight items and is divided into three dimensions, according to selectivity, comparability and the study type-outcome (cohort study) or exposure (case-control study) (25). The NOS was performed to evaluate the quality of observational studies, and only high-quality studies with an overall score ≥ 7 were included in the final analysis. Details of the quality assessment are displayed in Supplementary Table 1.

**Prognostic Analysis**

**Gestational hypertension**

Three studies have been reported in GH comparing caffeine intake with no caffeine intake during pregnancy. The results revealed that caffeine intake during pregnancy was not significantly associated with the risk of GH (OR = 0.99, 95% CI: 0.90–1.08, I² = 51.0%, p = 0.800) (Fig. 2).

Subgroup analysis of doses was performed to compare low to moderate dose with no/lowest dose and high dose with no/lowest dose respectively. The results illustrated that the dose of caffeine consumption had no significant correlation with the incidence of GH (low/moderate dose: OR = 1.00, p = 0.987; high dose: OR = 1.06, p = 0.623, respectively) (Table 2).
Table 2: Subgroup analysis of the effects of caffeine intake on gestational hypertension and preeclampsia.

|                      | No. of Studies | OR   | 95% CI       | p        | Heterogeneity (I²) (%) |
|----------------------|----------------|------|--------------|----------|------------------------|
| **Gestational hypertension** |                |      |              |          |                        |
| Low to moderate vs. no/lowest | 4              | 1.00 | 0.93–1.08    | 0.987    | 24.9                   |
| High vs. no/lowest     | 5              | 1.06 | 0.84–1.33    | 0.623    | 64.7                   |
| **Preeclampsia**       |                |      |              |          |                        |
| Yes vs. no             |                |      |              |          |                        |
| Coffee                | 2              | 1.78 | 1.15–2.74    | 0.009    | 0.0                    |
| Soft drink            | 2              | 1.10 | 1.00–1.21    | 0.056    | 14.2                   |
| Low to moderate vs. no/lowest | 6              | 1.03 | 0.91–1.17    | 0.648    | 15.0                   |
| Chocolate             | 2              | 0.63 | 0.36–1.09    | 0.098    | 0.0                    |
| Soft drink            | 2              | 1.07 | 0.95–1.20    | 0.280    | 9.6                    |
| High vs. no/lowest     | 6              | 1.18 | 0.92–1.50    | 0.192    | 35.0                   |
| Coffee                | 2              | 1.24 | 0.70–2.19    | 0.456    | 65.8                   |
| Chocolate             | 2              | 0.66 | 0.37–1.17    | 0.153    | 0.0                    |
| Soft drink            | 2              | 1.40 | 0.79–2.47    | 0.246    | 48.9                   |

**Preeclampsia**

Five studies referred to preeclampsia and compared caffeine intake with no caffeine intake during pregnancy. The pooled results depicted no significant association between caffeine exposure during pregnancy and the risk of preeclampsia (OR = 1.13, 95% CI: 0.97–1.31, I² = 50.8%, p = 0.114) (Fig. 3). Besides, the sources of caffeine intake were analyzed by subgroup. The pooled results depicted that coffee (OR = 1.78, p = 0.009) and soft drink (OR = 1.10, p = 0.056) consumption during pregnancy was associated with an increased risk of preeclampsia, although the latter was not statistically significant (Table 2).

Subgroup analysis was performed on the doses and sources of caffeine intake. The pooled results of low to medium dose versus no/lowest dose showed no significant association between caffeine consumption during pregnancy and the risk of preeclampsia (OR = 1.03, p = 0.648). Moreover, pooled results of further subgroup analyses showed that consumption of chocolate (OR = 0.63, p = 0.098) and soft drinks (OR = 1.07, p = 0.280) during pregnancy was not significantly associated with the risk of preeclampsia (Table 2).

Similarly, the pooled results showed no significant correlation between caffeine consumption and the risk of preeclampsia (OR = 1.18, p = 0.192) at high doses versus no/lowest doses. Additionally, pooled results of further subgroup analyses showed that consumption of coffee (OR = 1.24, p = 0.456), chocolate (OR = 0.66, p = 0.153) and soft drinks (OR = 1.40, p = 0.246) during pregnancy was not significantly associated with the risk of preeclampsia (Table 2).

**Discussion**

Caffeine is the most widely consumed psychoactive substance worldwide(26, 27). It is estimated that approximately 70% of women in the USA consume caffeine continuously during pregnancy(28). Although a large body of reviews investigated that caffeine consumption in adults was associated with a reduced risk of several chronic diseases and cancers, it has also been indicated that caffeine consumption during pregnancy may increase the risk of pregnancy complications(11, 27, 29). The relationship between caffeine consumption and HDP is therefore of concern, but remains controversial.

Our meta-analysis aimed to investigate the association between caffeine exposure during pregnancy and the risk of GH/preeclampsia. The results demonstrated that caffeine exposure during pregnancy was not significantly associated with GH/preeclampsia. For preeclampsia, the results of subgroup analyses comparing caffeine exposure with non-caffeine exposure revealed that coffee and soft drink intake during pregnancy may increase the risk of preeclampsia, although there were only two studies in each subgroup analysis. Moreover, other subgroup analyses showed no association between caffeine intake during pregnancy and the risk of preeclampsia.

In parallel to our findings, a meta-analysis indicated that coffee consumption had no significant effect on hypertension(30). Furthermore, one review detected no clear connection between coffee exposure and the risk of hypertension(31). Nevertheless, dose-response meta-analysis by Xie et al.(32) and Grosso et al. (33) both demonstrated that coffee consumption was inversely associated with risk of hypertension in a dose-response manner. Besides, a meta-analysis proved a significant connection between soda consumption and the risk of hypertension(34). Additionally, a case-crossover study of 286 women(35) detected
a strong inverse association of caffeine consumption with preeclampsia. Based on the above, the mechanism between caffeine intake during pregnancy and GH/preeclampsia remains unclear.

These discrepancies can be explained by a number of underlying reasons. First of all, the limited number of studies covered is probably the main reason. Then, the respective effects of different sources of caffeine may interact, obscuring the actual correlation between caffeine exposure during pregnancy and the risk of GH/preeclampsia. In addition, the classification of caffeine dose levels varied between studies. Consequently, the lack of standardization in caffeine measurement cannot be ignored. Finally, guidelines from the American College of Obstetricians and Gynecologists (ACOG) recommended that pregnant women consume up to two cups of moderate-strength coffee per day(36). Pregnant women have been shown to significantly reduce their caffeine intake, especially coffee during pregnancy(37–40). Therefore, one possible explanation for our results is the low caffeine intake of pregnant women in the included studies, leading to a lower proportion of pregnant women consuming moderate to high doses (14, 15, 41).

Caffeine and its metabolites belong to methylxanthines, which are non-selective adenosine receptor antagonists and have diuretic and natriuretic effects(42). Caffeine and its metabolites play a natriuretic role through adenosine A1 receptor blockade, resulting in reduced proximal tubular sodium reabsorption(43–45). This may be one reason why heavy coffee consumption is associated with lower blood pressure.

The renin-angiotensin aldosterone system (RAAS) is a key regulator of physiological homeostasis(46). Historically, the role of the RAAS has been considered an important cause of proteinuria leading to preeclampsia(47). The compensatory alterations in the RAAS, characterized by an increase in almost all components of RAAS, benefit the maintenance of salt-water balance and adequate placental perfusion to ensure maternal and fetal health during normal pregnancy. However, preeclampsia disrupts homeostasis, leading to disruption of the delicate equilibrium of RAAS in the circulatory and uteroplacental units(48), presenting with increased sensitivity to Ang II. Further, Ang II sensitivity continues to increase, increasing salt sensitivity and altering renal hemodynamics(49). Diuretic effects of caffeine on renal tubules or caffeine-induced epinephrine release may increase renin release(50, 51), thereby activating RAAS and further raising blood pressure.

Molecular mechanisms of action of caffeine on cellular signaling is primarily through competitive inhibition of G-protein coupled adenosine receptors, reducing intracellular inositol triphosphate, diacylglycerol, and calcium signaling(52, 53). There are studies and reviews that have proved a beneficial effect of coffee on renal function(54, 55). This phenomenon may be due to caffeine inhibiting vasoconstriction of afferent arterioles by type-1 adenosine receptors and increasing glomerular filtration rate (GFR)(56). Adenosine modulators have been implicated in several pathophysiology of preeclampsia. The mechanism may be related to placental ischemia and hypoxia in preeclampsia(57, 58). However, the association between caffeine intake and renal impairment in preeclampsia is still being investigated.

Caffeine beverages contain ingredients other than caffeine that may have different effects on GH and preeclampsia. For example, coffee contains several compounds such as kahweol, cafestol, chlorogenic acid, and trigonelline. These compounds have bidirectional effects on blood pressure regulation(59). Furthermore, these ingredients also have antioxidant, anti-inflammatory, anticarcinogenic, and antifibrotic effects(56, 60). It seems that the benefits of caffeine on GH/preeclampsia may be due to these substances. Collectively, the mechanisms of caffeine intake during pregnancy and GH/preeclampsia are intricate.

The strengths of this article are that, to our knowledge, no meta-analysis has examined the association between caffeine exposure during pregnancy and the risk of GH/preeclampsia. In addition, comprehensive subgroup analyses were established to explore the heterogeneity and compare the potential differences between different subgroups.

However, there are also some limitations. First, the number of articles included in this meta-analysis was limited. Second, there was no standardization of caffeine in estimating caffeine consumption, which could lead to measurement bias. Third, all eligible articles were observational studies that had certain biases, such as recall bias and selection bias. Fourth, some studies did not control for covariates or ignored some potential residual confusions. Taking race as an example, although a large prospective cohort study has noted significant racial differences in HDP(61), only two studies in this meta-analysis adjusted for race as a variable. Finally, the exclusion of non-English articles may introduce publication bias.

Conclusion

The results of this meta-analysis showed that caffeine exposure during pregnancy is not significantly associated with the risk of GH/preeclampsia, regardless of the dose or source of caffeine intake. Moreover, more appropriately designed, larger-scale studies are needed to explore the impact of caffeine exposure during pregnancy on the risk of GH/preeclampsia.

Abbreviations

HDP, hypertensive disorders of pregnancy; GH, gestational hypertension; OR, odds ratio, CI, confidence interval; NOS, Newcastle-Ottawa Quality Assessment Scale; RAAS, renin-angiotensin aldosterone system.

Declarations

Conflicts of Interest

The authors declare there was no conflict of interest.
Ethics approval
Not applicable.

Consent to participate
Not applicable.

Consent for publication
Not applicable.

Availability of data and material
Data supporting findings reported in this study are available in the supplementary materials.

Acknowledgments
Not applicable.

Author Contributions
Each author contributed significantly to concept and development of the present paper. Lihu Gu and Mengting Zhang designed the research process. Yujing He and Yuexiu Si searched the database for corresponding articles and extracted useful information from the articles above. Yetan Shi and Ke Jiang used statistical software for analysis. Jingyi Shen and Jiaze Hong drafted the meta-analysis. All authors had read and approved the manuscript and ensured that this was the case.

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**Supplementary Table 1**

Supplementary Table 1 is not available with this version.

**Figures**

**Figure 1**

A schematic flow for the selection of articles included in this meta-analysis.

**Figure 2**

Forest plot of the association between caffeine exposure vs. non-caffeine exposure during pregnancy and the risk of gestational hypertension (GH) (p=0.800).

**Figure 3**

Forest plot of the association between caffeine exposure vs. non-caffeine exposure during pregnancy and the risk of preeclampsia (p=0.114).