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The determinants of pre-eclampsia/eclampsia: A meta-analysis

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***Abstract*---** The aim of this study is to assess determinants of pre-eclampsia/eclampsia among pregnant women. This article was a systematic review and meta-analysis study conducted by searching of primary articles from online databases including EMBASE, PubMed, and Google Scholar. The inclusion criteria for this study were full articles using a case-control and cohort study, with the publication year until 2022. The analysis of data in this study using Review Manager (RevMan) 5.3 software. A random-effect model was used when heterogeneity was observed to pool the studies, and the results were reported via adjusted odds ratio and corresponding 95% confidence interval (CI). Results: A total of 13 articles reviewed in the meta-analysis (consisted 6, 4, and 7 articles in each variables) showed that pregnant women with chronic hypertension and nulliparous had higher risk of experiencing pre-eclampsia/ eclampsia (AOR= 3.13; 95% CI= (0.27- 36.51; p= 0.36); (AOR= 2.15; 95% CI= 1.47-3.13; p< 0.00001). Meanwhile smoke during pregnancy could decrease the risk of pre-eclampsia/ eclampsia (AOR= 0.81; 95% CI= 0.51 to 1.29; p= 0.37). Conclusion: chronic hypertension and nulliparity is risk factors of pre-eclampsia/ eclampsia.

***Keywords*---**determinants, pre-eclampsia/ eclampsia, predictors.

Introduction

According to the World Health Organization (WHO), secondary analysis of multi-country survey on maternal and newborn health, incidences of preeclampsia and eclampsia cases were 2.16% and 0.28%, respectively. Maternal near-miss cases were eight times more frequent in women with preeclampsia, and this can be increased by far to up to 60-fold higher frequency in women with eclampsia[1]. Since pre-eclampsia's etiology remains unknown[2], investigation and identification of the most important risk factors is vital for policy and clinical purposes

including prioritization of interventions, resource allocation, identification of high-risk pregnant women for more intensive observation and care, and development or improvement of risk management strategies[3]. Women with pre-eclampsia/eclampsia are at higher risk of obstetric complications like abruptio placenta and intra-uterine growth restriction as compared to normotensive women. They also have a higher risk of developing chronic hypertension in the future (14.8% versus. 5.6%), and this risk increases markedly on long-term follow up (to 51% versus 14%)[4]. Therefofe, the objective of the study was to evaluate the factors associated with pre-eclampsia/eclampsia among patients.

Method

Data sources and search strategy

This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) guidelines [5]. An electronic search of Embase, PubMed/ Medline, and Science-Direct was conducted from their inception to 31th May 2022 with only English language-based literature using the search string: (pre-eclampsia OR eclampsia) AND (predictors OR factors OR determinants). In addition, we manually screened the cited articles of previous meta-analyses, case-control, cohort studies, and review articles to identify any relevant studies.

Study selection

All studies were included if they met the following eligibility criteria: (a) articles on determinants of pre-eclampsia or eclampsia; (b) independent variables influencing pre-eclampsia or eclampsia, we only concludes three variables, including smoking status, nulliparity, and history or present chronic hypertension; (c) associations measured by an adjusted odds ratio; and (d) respondents were pregnant women. Furthermore, the strategy for research was PECOS: 1) P (population): pregnant women; 2) E (exposure): active smoker during pregnant, nulliparous, and have history or present chronic hypertension; 3) C (control): non smoker, multiparous, and do not have history or present chronic hypertension; 4) O (outcome): pre-eclampsia/ eclampsia; 5) S (Studies): case-control and cohort studies published in English only. Case series, case reports, human-based randomized controlled trials, literature reviews, editorials, and studies not meeting the inclusion criteria were excluded.

Data extraction and quality assessment of studies

Two reviewers independently searched the electronic databases. Studies that were searched were exported to EndNote Reference Library software version 20.0.1 (Clarivate Analytics), and duplicates were screened and removed. Data extraction and quality assessment of included studies was performed simultaneously and independently by two reviewers. The National Heart, Lung, and Blood Institute scale 2014 was used to assess the quality of the cohort and case-control studies. (Details of scoring are provided in Table 1 and 2).

Table 1
Quality assessment of cohort studies using the National Heart, Lung, and Blood Institute scale 2014

Questions	Das et al., 2019	Esakoff et al., 2015	Lewa-dowska et al., 2020	Li et al., 2021	Morikawa et al., 2012	Ngwenya et al., 2021	Yang et al., 2005
1. Was the research question or objective in this paper clearly stated?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Was the study population clearly specified and defined?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3. Was the participation rate of eligible persons at least 50%?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study pre-specified and applied uniformly to all participants?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5. Was a sample size justification, power description, or variance and effect estimates provided?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the	Yes	Yes	Yes	Yes	Yes	Yes	Yes

outcome (e.g., categories of exposure, or exposure measured as continuous variable)?							
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
10. Was the exposure(s) assessed more than once over time?	No	No	No	No	No	No	No
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
12. Were the outcome assessors blinded to the exposure status of participants?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
13. Was loss to follow-up after baseline 20% or less?	No	No	No	No	No	No	No
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Table 2
Quality assessment of case-control studies using the National Heart, Lung, and Blood Institute scale 2014

Questions	Coghill et al., 2019	Condea-gudelo et al., 1997	Fikadu et al., 2020	Kumar et al., 2010	Logan et al., 2020	Njelita et al., 2021
1. Was the research question or objective in this paper clearly stated and appropriate?	Yes	Yes	Yes	Yes	Yes	Yes
2. Was the study population clearly specified and defined?	Yes	Yes	Yes	Yes	Yes	Yes
3. Did the authors include a sample size justification?	Yes	Yes	Yes	Yes	Yes	Yes

4. Were controls selected or recruited from the same or similar population that gave rise to the cases (including the same timeframe)?	Yes	Yes	Yes	Yes	Yes	Yes
5. Were the definitions, inclusion and exclusion criteria, algorithms or processes used to identify or select cases and controls valid, reliable, and implemented consistently across all study participants?	Yes	Yes	Yes	Yes	Yes	Yes
6. Were the cases clearly defined and differentiated from controls?	Yes	Yes	Yes	Yes	Yes	Yes
7. If less than 100 percent of eligible cases and/or controls were selected for the study, were the cases and/or controls randomly selected from those eligible?	Yes	Yes	Yes	Yes	Yes	Yes
8. Was there use of concurrent controls?	Yes	Yes	Yes	Yes	Yes	Yes
9. Were the investigators able to confirm that the exposure/risk occurred prior to the development of the condition or event that defined a participant as a case?	Yes	Yes	Yes	Yes	Yes	Yes
10. Were the measures of exposure/risk clearly defined, valid, reliable, and implemented consistently (including the same time period) across all study participants?	Yes	Yes	Yes	Yes	Yes	Yes
11. Were the assessors of exposure/risk blinded to the case or control status of participants?	Yes	Yes	Yes	Yes	Yes	Yes
12. Were key potential confounding variables measured and adjusted statistically in the analyses? If matching was used, did the investigators account for matching during study analysis?	Yes	Yes	Yes	Yes	Yes	Yes

Statistical analysis

Review Manager (version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) was used for all statistical analyses. The data from studies were pooled using a random-effects model. Analysis of results was performed using the adjusted odds ratio (AOR) with respective 95% confidence intervals (CI). As per Higgins et al., the scale for heterogeneity was considered as follows: I^2 = 25–60% – moderate; 50–90% – substantial; 75–100% – considerable

heterogeneity, and p< 0.1 – significant heterogeneity [6]. A p< 0.05 was considered significant for all analyses.

Results

Literature search results

The initial search of the three electronic databases yielded 5380 potential studies. After exclusions based on titles and abstracts, the full texts of 85 studies were read for possible inclusion. A total of 6 studies remained for quantitative analysis. Figure 1 summarizes the results of our literature search

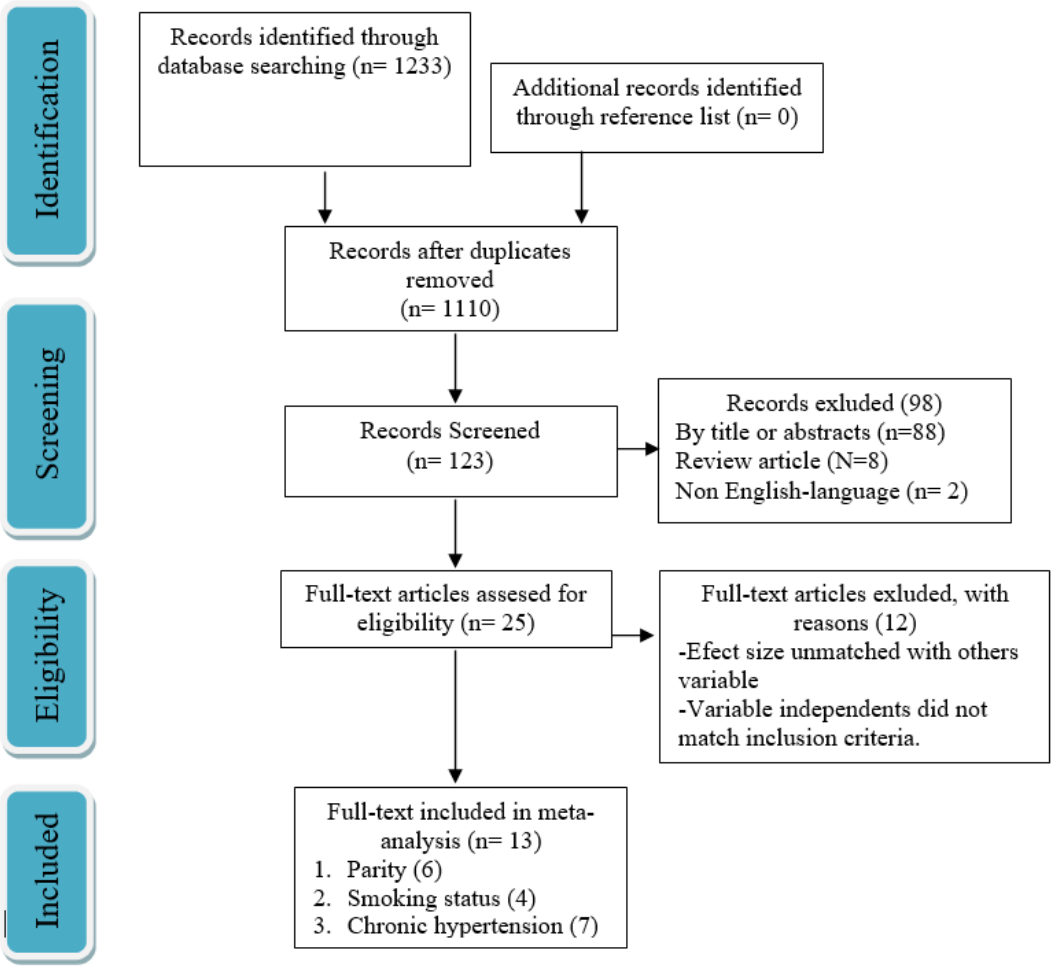

Figure1. PRISMA flow diagram for systematic reviews and meta-analysis which included searches of databases

Study characteristics

Table 3 provides the basic characteristics of the included studies. Our analysis included 13 published studies[7–19]. Six studies were case-control and 7 studies were cohort. In total, 3,541,769 respondents were involved in this analysis. Three studies was from USA; Ethiopia, Colombia, Nepal, India, Poland, China, Japan, Kenya, Nigeria, and Zimbabwe each had one study. There were four, six, and seven studies each in examining the association between smoking status, parity, and chronic hypertension with pre-eclampsia/ eclampsia, respectfuly.

Table 3
Basic characteristics of selected studies

No	Study (year)	Country	Study Design	Total Sample	Exposure	AOR Extracted (CI 95%)
1.	Coghill et al., 2019	USA	Population-based case-control study	Cases = 781 Controls = 3124	Nulliparity; Smoking during pregnancy; Chronic hypertension	3.04 (2.20–4.19); 0.53 (0.35–0.79); 2.06 (0.72–5.87)
2.	Condeagudelo et al., 1997	Colombia	Case-control	Cases = 24 Controls = 101	History of chronic hypertension	2.4 (0.43-12.08)
3.	Das et al., 2019	Nepal	A retrospective study	Cases = 85 Controls = 4735	Chronic hypertension	13.64 (4.45–41.81)
4.	Esakoff et al., 2015	USA	Retrospective cohort	74,242	Nulliparity; Chronic hypertension	1.34 (1.20-1.49); 0.07 (0.04-0.12)
5.	Fikadu et al., 2020	Ethiopia	Case-control	Cases = 167 Controls = 352	Smoking during pregnancy	4.25 (1.15-15.7)
6.	Kumar et al., 2010	India	Case-control	Cases = 100 Controls = 100	History of chronic hypertension	6.69 (1.37-32.75)
7.	Lewandowska et al., 2020	Poland	Cohort	Cases = 24 Controls = 775	Smoking during pregnancy	0.91 (0.29–2.88)
8.	Li et al., 2021	China	A multicentre retrospective cohort study	Cases = 24 Controls = 775	Nulliparity; Chronic hypertension	1.48 (1.09–2.02); 35.03 (25.40–48.31)
9.	Logan et al., 2020	Kenya	Case-control	Cases = 88 Controls = 264	Nulliparity	4.8 (1.0-22.4)
10.	Morikawa et al., 2012	Japan	A retrospective observational study	301,735	Nulliparity	2.61 (1.87-3.65)

11.	Ngwenya et al., 2021	Zimbabwe	Cohort	179	Nulliparity	2.76 (1.48- 5.15)
12.	Njelita et al., 2021	South East Nigeria	A retrospective case-control	Cases = 50 Controls = 100	Chronic hypertension	2.73 (0.45–16.59)
13.	Yang et al., 2005	USA	Cohort	3,153,944	Smoking during pregnancy	0.75 (0.70–0.81)

Publication bias and quality assessment

As the studies included less than 10 articles, publication bias could not be assessed. All studies met the criteria of suitable articles according quality assesment scale.

Results of the meta-analysis

There were 7 studies included in the analysis of chronic hypertension. Based on the forest plot (Figure 2), pregnant women with chronic hypertension have 3.13 higher risk of experiencing pre-eclampsia/ eclampsia compared to pregnant women with no chronic hypertension condition (AOR= 3.13; 95% CI= (0.27-36.51). This result proves statistically insignificant (p = 0.36). The heterogeneity of the article (I^2) shows the figure of 98% (p< 0.00001), so the authors use random effect data for the analysis.

The random analysis of pooled AOR from 6 studies suggests there is a substantial association between nulliparity and pre-eclampsia/ eclampsia. Nulliparous women have 2.15 higher risk of experiencing pre-eclampsia/ eclampsia compared to multiparous women (AOR= 2.15; 95% CI= 1.47-3.13; p< 0.00001). The heterogeneity (I^2) showed a substantial category with a value of 87% and it was significant p< 0.0001 (Figure 3).

A detailed forest plot (Figure 4), outlining the association between smoking status and pre-eclampsia/ eclampsia. Four studies were used to conduct the subgroup analysis based on study design. The random analysis of pooled AOR suggests that active smoking during pregnancy could decrease the risk of pre-eclampsia/ eclampsia (AOR= 0.81; 95% CI= 0.51 to 1.29; p= 0.37). The heterogeneity (I^2)showed a moderate category with a value of 69% and it was significant p< 0.02.

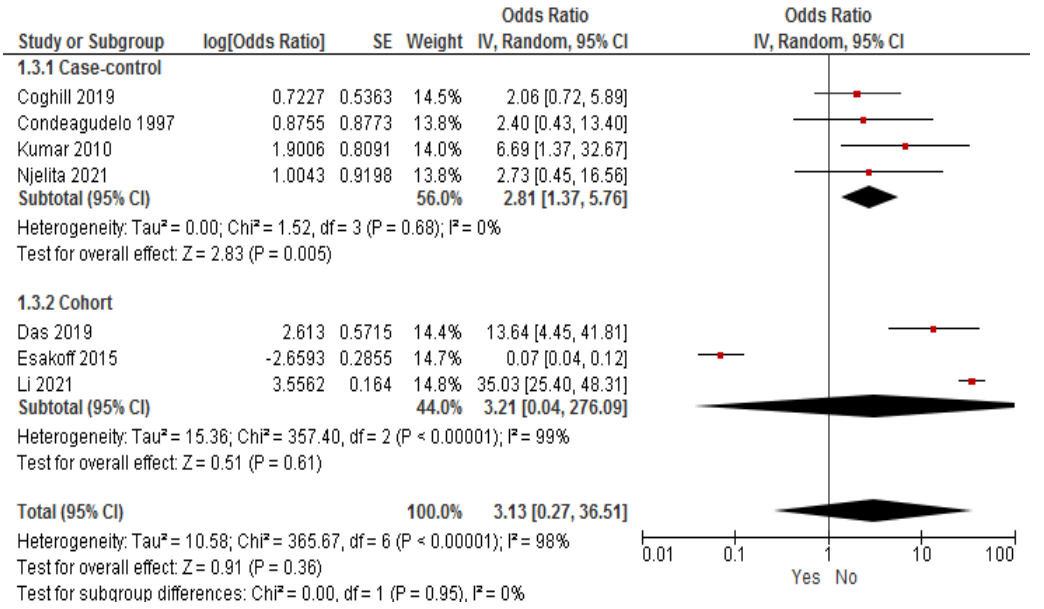

Figure2. Forest plot showing association between chronic hypertension and pre-eclampsia/ eclampsia

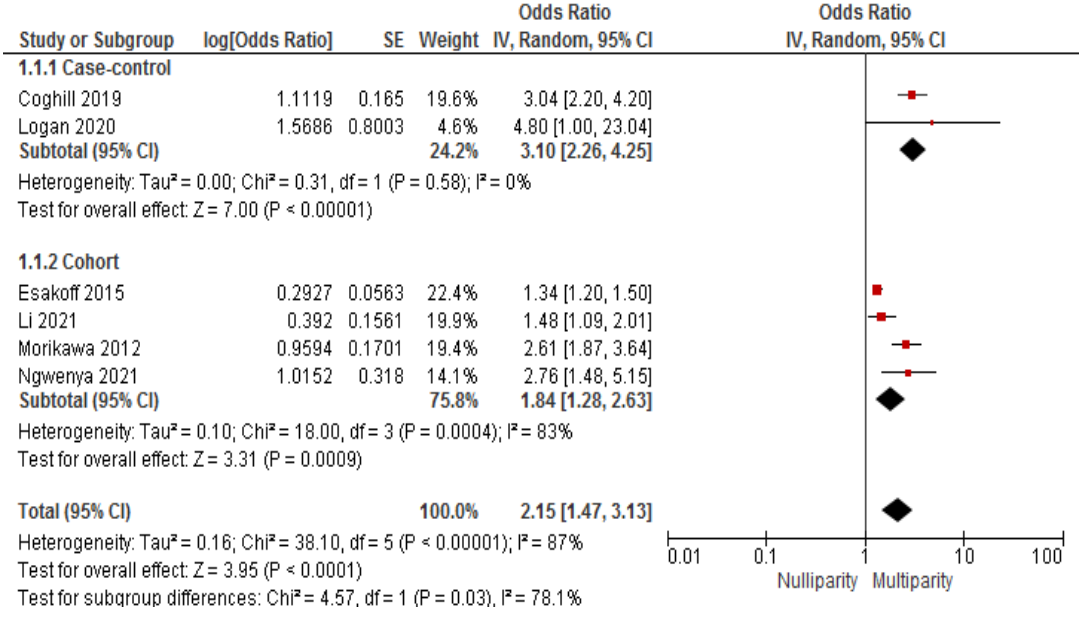

Figure3. Forest plot showing association between nulliparity and pre-eclampsia/ eclampsia

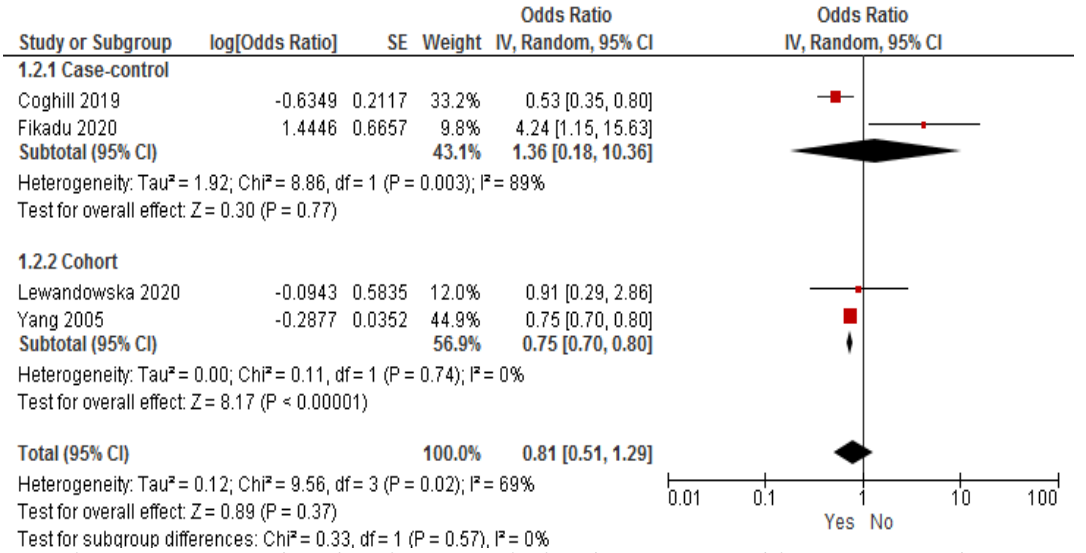

Figure4. Forest plot showing association between smoking status and pre-eclampsia/ eclampsia

Discussion

In absolute terms this makes chronic hypertension the strongest risk factor for preeclampsia. Conversely, it is also the risk factor least well studied; a result of the fact that several different underlying conditions contribute to a diagnosis of prepregnancy hypertension, which may independently contribute to the risk of preeclampsia through different underlying mechanisms. The analysis of this study resulted in association between chronic hypertension with pre-eclampsia/ eclampsia[20]. It was supported of study by Reiter et al., 1994 that stated women who develop recurrent second trimester severe pre-eclampsia or eclampsia are more likely to have an underlying renal disease and tend to have a high risk of developing chronic hypertension on follow up[21].

Nulliparity is the largest population attributable risk factor for preeclampsia [4] and several theories have suggested causal links, many of which relate to an immunological mechanism[22,23]. The relation between nulliparity and pre-eclampsia/ eclampsia might be explain by the conclusion of study by Bdolah et al., 2013, that nulliparous pregnancies had higher circulating sFlt1 levels and sFlt1/PlGF ratios than multiparous pregnancies, suggesting an association with an angiogenic imbalance. Taken together with the pathogenic role of anti-angiogenic factors in preeclampsia, our data may be one explanation for the epidemiological observation that nulliparity is a risk factor for the development of preeclampsia[24].

Our study suggested that smoking during pregnancy could reduce pre-eclampsia or eclampsia. This was supported by Wikström et al that suggest that smoking during pregnancy, but not the use of smokeless tobacco, is associated with lower preeclampsia risk[25]. The protective role of smoking is most likely to be explained through the biological effects of CO that is formed during smoking. CO may act by inhibiting placental production of anti-angiogenic proteins such as sFlt1 and by

inhibiting placental apoptosis and necrosis. Although smoking during pregnancy may lead to many adverse effects such as fetal growth restriction, placental abruption, stillbirth, and preterm labor, smoking is the only environmental exposure known consistently to reduce the risk of preeclampsia and gestational hypertension[26].

The clinical phenotype of preeclampsia may be mediated by a circulating anti-angiogenic state largely due to placental overproduction of soluble fms-like tyrosine kinase 1 (sFlt1 or sVEGFR1), an endogenous vascular endothelial growth factor signaling inhibitor, and soluble endoglin (sEng), a transforming growth factor beta signaling inhibitor[27]. Smoking during pregnancy has been associated with lower circulating concentrations of the anti-angiogenic proteins – sFlt1 and sEng and higher concentrations of the pro-angiogenic protein – placental growth factor[28,29]. Among tobacco combustion products, nitric oxide, which promotes vascular relaxation, is a possible mediator of protection against preeclampsia. However, smokers have been noted to have decreased, not increased circulating levels of nitric oxide metabolites; therefore, nitric oxide is unlikely to mediate the protective effect. On the other hand, recent data suggest that carbon monoxide (CO) may be the critical mediator. CO is a vascular protective agent in a number of vascular disorders such as ischemia/reperfusion injuries. Cigarette smoking may also directly upregulate HO expression in placental trophoblasts, which in turn may stimulate endogenous CO production. It is also likely that carbon monoxide may inhibit placental apoptosis and necrosis directly, thus reducing the release of placentally derived toxic factors. Other evidence to support the hypothesis that the HO pathway may play a important role in the pathogenesis of preeclampsia comes from human studies which have demonstrated decreased HO gene expression in placental villous tissue during first trimester among pregnant women destined to develop preeclampsia and decreased exhaled CO among women with preeclampsia[26,30–33].

Cnattingius et al and Broughton Pipkin have both reported that although smoking reduces the incidence of preeclampsia, it worsens pregnancy outcomes in smokers who develop preeclampsia[34,35].

Limitation

This present study should be evaluated with caution due to the evidence of heterogeneity. The number of primary studies included in this meta-analysis was still limited. In addition, the literature search was carried out only over three databases, and the included studies were only in the English language, potentially missing relevant information. Future studies should allow for more quantity of primary studies from more relevant online databases and also, conduct more criteria of subgroup analysis.

Conclusion

To our knowledge, this is the first paper that explored the relatioship between chronic hypertension, nulliparity, and smoking status with pre-eclampsia and eclamsia, and the results of the meta-analysis suggested that pregnant women with positive condition of chronic hypertension and nulliparous had higher risk of experiencing pre-eclampsia/ eclampsia. Meanwhile, smoking during pregnancy could reduce the risk of pre-eclampsia/ eclampsia. The evaluation of the

eligibility of the identified studies was based on predefined criteria and done independently by the two researchers, who examined in detail the quality of those studies. This study highlighted the factors that we need to consider while developing health promotion activities. Further, health literacy, counseling and education program need to be develop in both clinical and community settings.

Conflict of Interest Statement
No competing interests are declared by the authors of this article.

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Ethical Approval

Not needed.

Author Contribution
First and second author contributed on screening, reviewing, and analyzing the study.

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