Association Between Alcohol use in Pregnancy and Preeclampsia or Hypertension in Pregnancy: A Systematic Review

Weiyan Gong

Department of Obstetrics,Shandong Provincial Hospital Affiliated to Shandong First Medical University,Jinan,Shandong,China;OMNI Research Group,Ottawa Hospita Research Institute.

Na Zeng

OMNI Research Group,Ottawa Hospital Research Institute;School of Epidemiology and Public Health,University of Ottawa Faculty of Medicine

Daniel Corsi

OMNI Research Group,Ottawa Hospital Research Institute;Better Outcomes and Registry Network(BORN) Ontario;School of Epidemiology and Public Health,University of Ottawa Faculty of Medicine)

Shi Wu Wen (swwen@ohri.ca)

Ottawa Hospital Research Institute https://orcid.org/0000-0002-7227-0283

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Abstract

Background

To summarize evidence on the association of maternal alcohol consumption during pregnancy with preeclampsia (PE) or hypertensive disorders of pregnancy (HDP).

Methods

We searched PubMed, EMBASE, PsycINFO, and Cochrane Central Register of Controlled Trials databases. We included original studies that presented relative risks, odds ratios, or data to calculate the risks for the association of alcohol consumption during pregnancy with PE or HDP. We used the Newcastle-Ottawa Scale to assess study quality. We conducted a random-effects meta-analysis to calculate the pooled association of gestational alcohol use with PE or HDP.

Results

Thirty-seven articles met the criteria for inclusion. The total study population was 4,434,003 women with 170,481 cases of PE and 467,055 women with 41,708 cases of HDP. For all included studies, there was no significant association between alcohol consumption during pregnancy and incidence of PE (OR=0.93, 95%CI: 0.73-1.20), with statistical significant heterogeneity (I^2=91%, P<0.00001). Among the subgroup of prospective cohort studies, the pooled results showed that alcohol consumption during pregnancy had a protective effect on PE (OR=0.64, 95% CI: 0.54-0.76), and with no statistical heterogeneity (I^2 =0%, P=0.56). The results from the subgroup of retrospective cohort and case-control studies showed that alcohol consumption during pregnancy was not associated with PE, with odds ratios of 1.07 (0.65-1.74) and 1.02 (0.64-1.61), respectively, and with statistically significant heterogeneity. The pooled OR for the association between alcohol consumption during pregnancy and HDP was 0.98 (95% CI: 0.75-1.29), with considerable heterogeneity (I^2=90% P<0.00001).

Conclusion

Overall, there is no apparent association of alcohol consumption during pregnancy with PE or HDP. In prospective cohort studies, an evident protective effect is likely due to residual confounding. Further studies should consider alternative designs such as mendelian randomization, which can overcome some of the limitations of conventional prospective studies.

Background

Preeclampsia (PE), a subclass of hypertensive disorders of pregnancy (HDP), is most commonly defined by new-onset hypertension after 20 weeks of gestation with new-onset proteinuria or end-organ damage [1]. PE and other hypertension disorders account for 14% of maternal deaths worldwide [2]. PE is also the main reason for preterm birth and perinatal mortality. Stillbirth risk pregnancies affected by PE at 34

weeks was seven-fold higher than pregnancies without PE [3]. In the United States, the cost burden of PE within the first year of delivery was $2.18 billion [4]. However, the etiology of PE is still elusive.

Some maternal factors, such as obesity, diabetes mellitus, and renal disease, which also correlated with the risk of cardiovascular disease in women, were associated with PE [5]. Alcohol consumption was associated with an increased risk of developing cardiovascular disease, even at lower levels of use [6]. Further, some intervention studies [7] and Mendelian randomization studies [8] confirmed a robust causal relationship between alcohol intake and hypertension in the non-pregnant population. Moderate-to-heavy drinkers have a higher risk of hypertension [9]. However, there is no consistent conclusion on the relationship between alcohol exposure during pregnancy with PE or HDP.

Because alcohol exposure during pregnancy can cause congenital and neurodevelopmental abnormalities (such as fetal alcohol spectrum disorders), most clinical guidelines recommend abstinence during pregnancy [10, 11]. Still, up to 10 percent of pregnant women drink alcohol in Canada and 15 percent in the United States [12]. In addition to the effects of alcohol on the fetus, there is concern about the effects of alcohol during pregnancy on the mother on developing conditions such as PE and HDP. Therefore, we conducted a systematic review of the literature to summarize available evidence on association of maternal alcohol consumption during pregnancy with PE and HDP.

Methods

A protocol of this systematic review is available from the PROSPERO systematic review register (registration number: CRD42020167063).

Search Strategy And Study Selection

We collaborated with an information specialist to design the search strategy. On January 27, 2020, we searched four databases: Embase (1947 to January 27, 2020), MEDLINE (1946 to January 27, 2020), Cochrane Central Register of Controlled Trials (up to December 2019), and PsycINFO using the follow terms: Preeclampsia, gestational hypertension, and alcohol /ethanol (full search strategy described in Table S1).

No restrictions were applied to the study design (or types of study) and publishing language during the searching step, however we excluded case series and case reports. Conference articles and abstracts were also included if they investigated the association of maternalalcohol consumption during pregnancy with PE or HDP and were not published at a later stage. We also conducted a hand searching for citations and cited references in identified articles, as well as reference lists of reviews.

Original studies which sampled from the general pregnant women population and presented relative risk or odds ratios (or data to calculate these risks) of PE or HDP associated with alcohol consumption during pregnancy were included in this review.

Exposure was any alcohol use during pregnancy. The outcome was PE or HDP.

Exclusion criteria included studying alcohol consumption only before pregnancy, not during pregnancy, and non-clinical diagnosis for PE or HDP .

After imported the references on Covidence which is an online literature screening and data extraction software. W.Y.G and N.Z screened the title and abstracts based on the inclusion criteria separately. If discrepancies arise, we resolve them through conference and review full-text. The unsolved discrepancies were adjudicated by D.J.C.

Data Extraction

W.Y.G and N.Z extracted the data. The following data were extracted: title, last name of the first author, publication date, study design, country/region of study, the period of the study, whether adjusting for confounders, the number of alcohol consumption and non-alcohol consumption during pregnancy, the number of PE in alcohol group and non-alcohol group, how the alcohol consumption was ascertained, the definition of PE or HDP.

Quality Assessment

All included studies were assessed for methodological quality. Non-randomized case-control studies and cohort studies used Newcastle-Ottawa Scale (NOS)[13] which include three domains and eight items of study design and quality of reporting: Selection (4 items), Comparability (1 item), and ascertainment of exposure (3 items). More stars indicate less risk of bias. Agency for Healthcare Research and Quality (AHRQ) methodological checklist was used to assess cross-sectional studies.

We described the risk of bias in the results, and used the total score to assess the quality of the literature, with higher scores indicating better study quality.

Meta-analysis

When analyzing the association of alcohol consumption with PE or HDP, we converted whether have alcohol consumption during pregnancy into a dichotomous variable (yes or no), the outcome of whether PE or HDP, and imported the numbers of exposure and outcome extracted from each study into Revman5 software. Considering the influence of study design on the results, the included studies were divided into prospective cohort, retrospective cohort, and case-control studies. Generic inverse variance methods analyzed the association of alcohol and HDP because some studies just reported the odds ratio. The heterogeneity across studies is assessed by I^2, $I^2 > 50\%$ means high heterogeneity.

We used Revman5 software to make forest plots and funnel plots. Funnel plot asymmetry inspected visually was used to assess the potential for publication bias[14].

Sensitivity analysis was conducted to explore the potential sources of heterogeneity [15]. First, we sequentially excluded one study and recalculated the I^2, the study which was omitted from the meta-analysis to drop I^2 below 25% was the plausible explanation for the heterogeneity. Second, we removed the low quality studies scoring 'less than 4' on the NOS. Third, we excluded studies that had a small sample size (less than 10 participants). Subgroup analysis was also conducted for studies with different designs.

Results

Characteristics Of The Included Studies

A total of 888 non-duplicate works were identified through the literature search, including 12 manually retrieved from systematic reviews and reference lists of identified studies. After title/abstract screening and full-text screening, 37 articles were included for the current systematic review (Fig. 1).

Eleven out of the 37 studies (30%) were conducted in the USA, followed by Ethiopia (11%) and the Netherlands (11%). These included studies were conducted between 1984 and 2019. The sample sizes of these studies varied from 105 [16] to 2,963,888 [17]. The prevalence of alcohol consumption during pregnancy among different samples varied between 0.2% (China) [18] to 73.9% (SCOPE study) [19].

The main outcome of 29 out of the 37 articles was PE. In these 29 studies, 7 were prospective cohort studies, 7 were retrospective cohort studies, and 15 were case-control studies. Eight of the 37 articles were used to analyze the association between alcohol consumption during pregnancy and HDP.

We evaluated the 35 cohort and case-control studies by the NOS (Table 1). Two cross-sectional studies were assessed by an 11-item checklist recommended by Agency for Healthcare Research and Quality (AHRQ). Of these, 5 case-control studies, 6 prospective cohort studies, and 1 cross-sectional study were considered high quality. The main aspect responsible for the lower quality of these cohort studies is comparability as the most of these studies only provide crude odds ratios (OR), without adjustment for confounding factors. The reasons for low quality of case-control studies include the control group were selected from hospitalized population (not community controls), and ascertainment of exposure was not blinded or only based on medical record and self-report.

Table 1
Characteristics of Studies in Systematic Review

Author	study design	exposure ascertainment	country	study year	Quality assessment
PE as outcome					
Bandoli 2018[17]	retrospective population-based cohort	birth certificate and hospital discharge record	USA	2007–2012	6
Bobic 2015[16]	case-control	-	Croatia	2015	6
Bommarito 2019[34]	prospective	At the first visit (median, 10 weeks gestation), women completed detailed questionnaires of demographic information	USA	2006–2008	7
Chedraui 2014[35]	csae control	-	Ecuador	2014	5
Coolman 2012[36]	population-based prospective cohort study	alcohol consumption was assessed by questionnaires in each trimester.	Netherlands	2002–2006	7
Cota 2006[37]	case-contro	medical records postpartum	Brazil	2004	4
Endeshaw 2014[38]	Case-Control	interview after delivery	Ethiopia	2014	6
Eskenazi 1991[39]	case-control	abstracted from medical charts	Northern California(USA)	1984–1985	5
Fang 2009[40]	case-control	a 45- minute in-person interview in which trained research personnel used a structured questionnaire	Thailand	2006–2007	7
Grum 2017[41]	unmatched case control study	using pretested interviewer administered questionnaire	Ethiopia	2015–2016	7
Jhee 2019[42]	retrospective study	retrieved from electronic medical records	Korea	2005–2017	6
Kharkova 2017[43]	retrospective study	alcohol abuse as diagnosed by a doctor based on medical record	Russia	2006–2011	6

Figure 1: Flow-chart of study selection.

Author	study design	exposure ascertainment	country	study year	Quality assessment
Kiondo 2012[44]	case control	the women were interviewed about their socio-demographic characteristics	Uganda	2008–2009	7
KLONOFF-COHEN 1996[45]	case-control	obtained from a standardized telephone interview	USA	1984–1987	7
KURKI 2000[46]	prospective population-based study	by a structured questionnaire at at their first prenatal visit between 8–17 weeks' gestation	Finland	2000	7
Lafaurie 2020[47]	case control	obtained from hospital information systems and medical records	Colombia	2019	4
Laine 2015[48]	nested case-control	based on self report at either baseline or postpartum examination interview.	USA	2004–2007	4
Lardoeyt 2013[22]	case-control study	in-depth interviews were conducted using an instrument designed for the study	Cuba	2007–2009	5
Leemaqz 2016[19]	prospective cohort	dietary and lifestyle questionnaires were recorded at 15 weeks' and 20 weeks' gestation	Australia, New Zealand,Ireland, United Kingdom	2004–2011	8
Meertens 2019[49]	prospective cohort study	by a web-based questionnaire before 16 weeks of gestation (pregnancy questionnaire)	Netherlands	2013–2015	7
Mekie 2020[50]	Age matched case-control study	collected through an interview using a questionnaire	Ethiopia	2018	7
Nobles 2019[51]	retrospective cohort	abstracted from delivery electronic medical records(yes/no)	USA	2002–2010	6
RUDRA 2005[52]	case-control study	an in-person structured interview questionnaire to collect information	USA	1998–2002	5

Figure 1: Flow-chart of study selection.

Author	study design	exposure ascertainment	country	study year	Quality assessment
Salihu 2011[20]	retrospective cohort	Missouri vital record system	USA	1989–2005	6
Sandström 2019[53]	prospectively population-based cohort study	Alcohol consumption at registration are self-reported	Sweden	2008–2013	6
Thompson 2014[54]	prospective cohort study	interview in which trained research personnel used a structured questionnaire before 20 weeks' gestation	USA(Swedish Medical Center)	1996–2008	7
Wang 2015[18]	birth cohort study	in-person interviews at the hospital using a standardized and structured questionnaire after dilivery	China	2010–2012	6
Xiong 2000[55]	retrospective cohort	data were derived from delivery record	Canada	1995–1997	6
Xiong 2009[56]	case–control	obtained during personal interviews	canada	2003–2006	4
HDP as outcome					
Baugh 2016[57]	national population-based survey (retrospective)	contacted by mail and/or telephone to participate 2–4 months after giving birth	USA	2000–2010	6
Chada 2007[58]	case-control	Two midwives administered questionnaires on the day of delivery	Argentina	2007	4
Iwama 2019[59]	prospective birth cohort study	obtained from the two questionnaires, namely, T1(16.5 weeks) and T2（27.9 weeks）	Japan	2011–2014	9
Masho 2015[60]	prospective cohort	contacted by mail and/or telephone to participate 2–4 months after giving birth	USA	2004–2011	5

Figure 1: Flow-chart of study selection.

Author	study design	exposure ascertainment	country	study year	Quality assessment
Mutsaerts 2014[61]	population-based prospective birth-cohort study	Shortly after delivery, the midwife or gynaecologist guiding the pregnancy completed a questionnaire on maternal alcohol use	Netherlands	2006–2007	6
Nugteren 2012[62]	prospective cohort	alcohol consumption was assessed by questionnaires in each trimester.	Netherlands	2002–2006	7
Walle 2019[63]	cross-sectional study	using interviewer administered semi structured questioner	Ethiopia	2017	8
Ye 2014[64]	cross-sectional study	All information was collected on the basis of standardized antenatal, obstetric and neonatal records.	China	2011	7

Figure 1: Flow-chart of study selection.

Alcohol Consumption During Pregnancy And Pe

We analyzed the association between maternal alcohol consumption with PE by using alcohol during pregnancy as a dichotomous variable, regardless of dosage, pattern, and time in the pregnancy. The total study population was 4,434,003 women with 170,481 PE cases in 29 studies. There was no significant association between alcohol consumption during pregnancy and incidence of PE (OR = 0.93, 95% CI: 0.73–1.20), with statistically significant heterogeneity among studies (I^2 = 91%, P < 0.00001) (Fig. 2). Among the subgroup of prospective cohort studies (n = 7), the pooled results showed that alcohol consumption during pregnancy had a protective effect on PE (OR = 0.64, 95% CI: 0.54–0.76), without statistically significant heterogeneity among these studies (I^2 = 0%, P = 0.56). The results from the subsets of retrospective cohort studies (n = 7) and case-control studies, in which alcohol exposure during pregnancy was determined through postpartum interviews or medical records, were consistent with the conclusion that alcohol consumption during pregnancy was not associated with PE, with an odds of 1.07 (0.65–1.74) and 1.02 (0.64–1.61), respectively. By visual inspection of the funnel plot, there was no significant publish bias (Fig. 3)

In the prospective subgroup, sensitivity analysis showed that the pooled results were stable. In the subgroup of retrospective cohort studies, when Salihu's study (2011)[20] was removed, the subtotal OR was changed to 1.47 (1.36–1.58), and the heterogeneity was eliminated (I^2 = 0%, p = 0.45). In case-control

studies subgroup, heterogeneity and pooled OR values did not change even when we removed studies in which the number of cases exposed to alcohol was less than 10 or low quality of the studies.

The literature identified on the dose-response and time-response relationship and quasi-experimental studies between maternal alcohol consumption and PE was limited and insufficient for meta-analysis, so we describe the relevant results as follows.

Regarding the time-response relationship between alcohol consumption, Leemaqz [19] et al reported that alcohol consumption at 15 weeks' gestation has a protective effect for PE with borderline significance 0.72 (0.53–0.99). At 20 weeks' gestation, there was not association with PE in a large prospective cohort study with 5588 nulliparous women (SCOPE).

When it comes to the dose-response relationship, McCarthy[21] reported that alcohol consumption of occasional to binge drinking before 15 weeks' gestation was not associated with the development of PE with an adjusted OR of 0.73 (0.51–1.06) for occasional to low drinking and 0.66 (0.39–1.14) for moderate to heavy alcohol consumption compared with abstinence in pregnancy. However, Salihu [20] used the Missouri maternally-linked cohort data files and the result showed that 1–2 drinks per week had protective effect for PE with an adjusted OR of 0.82 (0.74–0.90). The protective effect disappeared for women consuming three to four drinks per week [OR 0.85 (95% CI: 0.64–1.14)] and more than five drinks per week [OR 1.05 (95% CI: 0.79–1.40)].

Mendelian randomization (MR), and family-based designs are approaches that can be used to improve causal inference. Only one study was family-based design. Lardoeyt et al[22] found a 16-fold increased risk of developing PE (OR 16) when first-degree family history (OR for sister with PE history is 1.61 alone) and alcohol consumption (OR is 4.44 alone) coexisted.

Alcohol Consumption During Pregnancy And Hdp

The 8 studies that had outcome variable of HDP. The total study population was 467,055 women with 41,708 cases of HDP. The pooled estimates OR was 0.98 (95%CI: 0.75–1.29) with significant heterogeneity (I^2 = 90% P < 0.00001) (Fig. 4). The funnel plot of the odds ratios for HDP shows an asymmetrical distribution, which indicates some publish bias (Fig. 5).

Discussion

To our knowledge, this is the first comprehensive systematic review on the effect of maternal alcohol consumption on PE and HDP. Overall, we find no significant association of alcohol consumption during pregnancy with PE or HDP. There was substantial heterogeneity among the included studies. Our review reveals that only a limited number of studies have been conducted on the association between alcohol consumption during pregnancy and the risk of PE or HDP. The quality of most included studies was low and many made no adjustment for potential confounders. Although we performed a meta-analysis to

determine the overall risk, the presence of high heterogeneity suggests that these results must be interpreted cautiously.

Given the nature of alcohol as a risk factor for fetal complications, it is not feasible or ethical to designing and conducting a randomized controlled trial. Therefore we are limited to assessing this association using observational designs which have many problems including lack of adjustment, biases in reporting alcohol intake, sampling biases, etc [23]. These also have many problems which makes the interpretation challenging.

In prospective cohort study, information about alcohol consumption was mostly obtained through questionnaires before 20 weeks' gestation. On the other hand, in the retrospective cohort and case-control studies, alcohol exposure was assessed by questionnaires or retrospective medical records after delivery, which may introduce bias. Recall bias in postnatal reports of alcohol habits has been described [24], and such bias may contribute to heterogeneity in the reported associations in the retrospective cohort and case-control studies.

For the 7 prospective cohort studies, a potential protective effect of alcohol consumption during pregnancy on PE was observed. In a retrospective study by Salihu et al [20], the protective effect of alcohol on PE mainly came from the quite low dose of alcohol (1–2 drinks per weeks). At higher doses, the protective effect disappeared. In non-pregnant women, there was also a J-shaped relationship between alcohol consumption and hypertension, in which the protective effect was observed only in < 5 g/day [25] or < 10 g/day [26]. When women consumed 12–24 g/day, no association with hypertension was observed (RR = 0.94; 0.88–1.01) and when the dose was ≥ 36 g/day a harmful effect was observed (relative risk = 1.42; 1.22–1.66) [27]. But we found no direct biological mechanism that supports the protective effect of alcohol on hypertension in literatures. Intervention studies for the effects of alcohol on blood pressure in non-pregnant women suggest that lower level alcohol has no effect on blood pressure [28]. The protective effect of lower alcohol was due to unmeasured confounders. One example for these confounders is socioeconomic status. Higher household income and highly educated women are more likely to drink alcohol during pregnancy [29]. Low socioeconomic status is a strong risk factor for preeclampsia[30]. The complexity of socioeconomic status makes it difficult to measure accurately.

Poor functioning of the placenta has been recognized as the root cause of PE. In vitro studies have shown that ethanol can induce apoptosis of placental trophoblast cells [31]. Animal experiments showed that exposure to ethanol during pregnancy reduced the invasion and differentiation of placental trophoblast cells and decreased the depth of placental implantation [32], and exposure to alcohol during pregnancy could increase blood pressure in pregnant rats [33]. Because observational studies are prone to bias and because in most included epidemiologic studies, no adjustment for potential confounding was conducted and no dose-response association analysis was performed.

Unmeasured confounders and limitations in the accurate assessment of drinking dose, frequency, mode, time and patterns may be the main reasons for the current inconsistencies in conclusions about the association between alcohol and PE or HDP. So in further studies, an assessment of dose-response could

help to find out if the J-shaped association observed in non-pregnant women with a protective effect at low dose while a harmful effect at high dose, also exists in pregnant women. Novel analytical approaches including mendelian randomization, family-based designs, and natural experiments can improve causal inference and overcome the limitation of confounder such as socioeconomic factors.

Conclusions

Our systematic review of currently available epidemiological studies on the association of alcohol consumption during pregnancy with PE or HDP found no apparent association. Conclusions obtained from different study designs are different. This makes it impossible to draw a firm conclusion. Unmeasured confounders and a lack of quantitative assessment of alcohol exposure may be the main reasons. Further studies should consider alternative designs such as mendelian randomization which can overcome some of the limitations of conventional prospective studies.

Abbreviations

PE
preeclampsia
HDP
hypertensive disorders of pregnancy
PROSPERO
International Prospective Register of Systematic Reviews
OR
odds ratio
RR
risk ratio
NOS
Newcastle-Ottawa Scale
SCOPE
the SCreening for Pregnancy Endpoints study

Declarations

Ethics approval and consent to participate: Not applicable

Consent for publication: Not applicable

Availability of data and materials: All data generated or analyzed during this study are included in this article (and its supplementary files).

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Authors' contributions:

W.Y.G participated in the data collection, analysis, interpretation of data, and drafted the manuscript.

N.Z participated in the Study selection, data extraction, and analysis.

S.W.W coordinated the study and participated in the data analysis and critically revised the different versions of the manuscript.

D.J.C participated in the conception and design of the study, data analysis, and interpretation of data and commented on the manuscript.

All authors read and approved the final manuscript prior to submission.

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Authors' information (optional)

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Figures

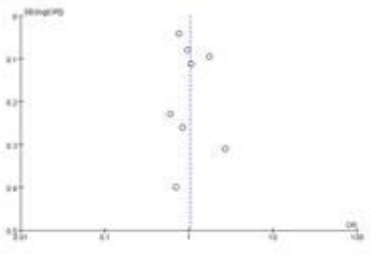

Figure 1

Funnel plot corresponding to the random-effects meta-analysis of the association between alcohol consumption during pregnancy and HDP

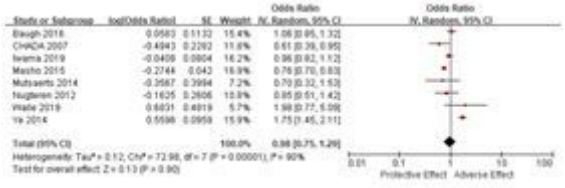

Figure 2

Forest plots (random effect model) of meta-analysis on the association between alcohol consumption during pregnancy and incidence of HDP

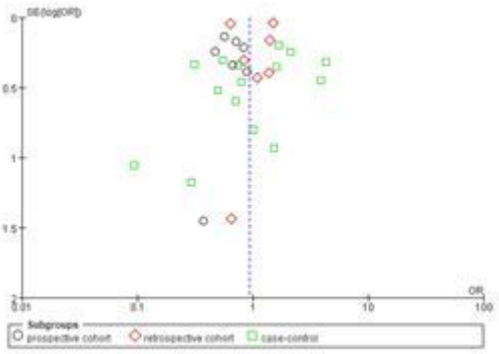

Figure 3

Funnel plot corresponding to the random-effects meta-analysis of the association between alcohol consumption during pregnancy and PE risk.

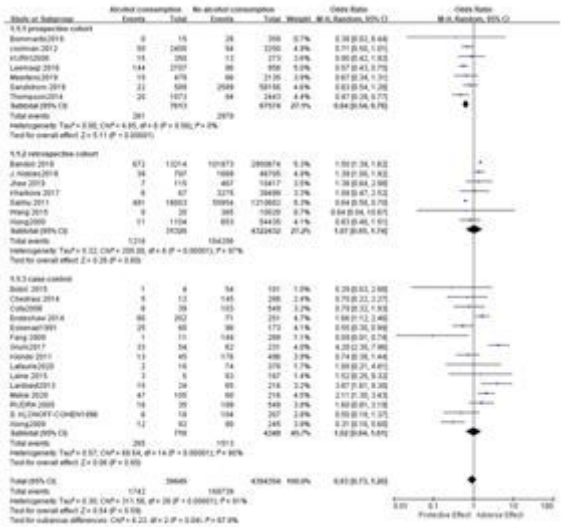

Figure 4

Forest plots (random effect model) of meta-analysis on the association between alcohol consumption during pregnancy and incidence of PE.

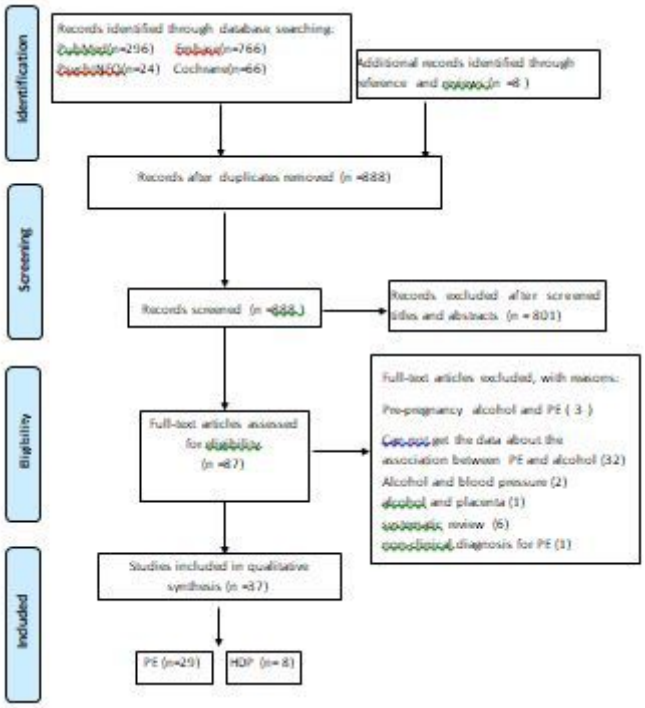

Figure 5

Flow-chart of study selection.

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