META-ANALYSIS

Association between hypertensive disorders during pregnancy and elevated blood pressure in offspring: A systematic review and meta-analysis

Huan Yu MD1 | Wei Li MD1 | Zhengxia Mao MD1 | Lijuan Luo MD1 | Na He MD1 | Wenbin Dong MD1 | Xiaoping Lei MD, PhD1,2,3

1Division of Neonatology, Department of Pediatrics, Affiliated Hospital of Southwest Medical University, Luzhou, Sichuan, China
2Birth Defects Clinical Medical Research Center of Sichuan Province, Sichuan, China
3Department of Perinatology, Southwest Medical University, Luzhou, Sichuan, China

Correspondence
Xiaoping Lei, Division of Neonatology, Department of Pediatrics, Affiliated Hospital of Southwest Medical University, 25 Taiping Road, Luzhou, Sichuan 646000, China. Email: leixiaopingde@126.com

Abstract
Hypertensive disorders during pregnancy (HDP) are associated with cardiovascular disease among mothers and offspring. This meta-analysis was conducted to further explore the associations between maternal HDP and offspring blood pressure (BP). The authors performed a search strategy in PubMed, Embase, Web of Science, and Cochrane library from database inception to January 2022. Twenty-four studies regarding HDP were included, with pregnancy-associated hypertension (PAH), preeclampsia (PE), gestational hypertension (GH), and chronic hypertension included in 12, 16, 6, and 3 studies, respectively. Offspring who were exposed to HDP and PAH in utero had higher systolic BP (2.46 mm Hg, 95% CI: 1.88–3.03 mm Hg; 2.70 mm Hg 95% CI: 1.89–3.51 mm Hg) and diastolic BP (1.38 mm Hg 95% CI: 0.94–1.83 mm Hg; 1.39 mm Hg 95% CI: 0.71–2.06 mm Hg) than those birthed to normotensive mothers. The offspring exposure to PE, GH, and chronic hypertension had higher systolic BP by 1.90 mm Hg (95% CI: 1.39–2.40 mm Hg), 2.47 mm Hg (95% CI: 1.59–3.35 mm Hg), and 7.85 mm Hg (95% CI: 4.10–11.61 mm Hg), respectively, and higher diastolic BP by 0.99 mm Hg (95% CI: 0.50–1.49 mm Hg), 1.04 mm Hg (95% CI: 0.60–1.47 mm Hg), and 2.92 mm Hg (95% CI: 0.98–4.86 mm Hg), respectively. An Egger test and funnel plot confirmed no significant publication bias. In conclusion, offspring exposure to all subtypes of HDP in utero led to higher BP than no exposure. It is necessary to investigate the potential mechanisms to clarify the roles of genetic and environmental factors in these associations, which could provide insight on preventing hypertension and related cardiovascular disease.

KEYWORDS
blood pressure, hypertensive disorders during pregnancy, offspring, the developmental origins of health and disease

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INTRODUCTION

Hypertension is a complex multifactor disorder, and its incidence is rapidly increasing worldwide. It is a major cause of cardiovascular deaths, affecting more than one billion people around the world, and it is associated with more than nine million deaths annually. According to "the developmental origins of health and disease (DOHaD)" hypothesis, the gestation period is regarded as a critical window for the developmental origin of hypertension.

Hypertensive disorders during pregnancy (HDP), affecting up to 10% of pregnant women worldwide, constitute a risk factor for maternal-fetal morbidity and mortality. HDP are divided into hypertension known before pregnancy or present in the first 20 weeks, including chronic hypertension, white-coat hypertension, and masked hypertension, and hypertension arising de novo at or after 20 weeks, including gestational hypertension (GH), preeclampsia (PE) de novo or superimposed on chronic hypertension, and transient GH. Previous studies have confirmed that women who develop HDP have an increased risk of cardiovascular disease later in life, while there have been studies demonstrating that offspring exposure to HDP in utero is associated with metabolic syndrome, mental and behavioral disorders, asthma, and other conditions. Several reviews have shown that offspring born to mothers with HDP have higher blood pressure (BP). However, a recent systematic review that did not perform a pooled estimate among offspring aged 2–18 years but focused on pregnancies with PE and GH drew conflicting conclusions from the previous systematic reviews.

Previous studies have revealed structural changes in cardiovascular organs among offspring exposed to HDP. In addition, as a genetic-environmental interaction disorder, the role of genetic factors might be considered to explain the true associations between offspring BP and HDP. Evidence has shown that although subtypes of HDP have clear overlap, they also have distinct differences; different pathophysiological pathways are involved in the development and clinical course of the different HDP phenotypes. Thus, different subtypes of HDP may be differently associated with offspring BP. Therefore, we performed a systematic review and meta-analysis for the pooled estimates of the specific effects on the offspring BP in each subtype of HDP.

METHOD

2.1 Search strategy and selection criteria

This meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Table S1), and the supporting data can be found at the PROSPERO website (https://www.crd.york.ac.uk/prospero/) with registration number CRD 42018110872. The detailed protocol has been previously published, and approval was not required because the data are anonymous in peer-reviewed review papers. We performed a detailed search strategy in PubMed, Embase, Web of Science, and Cochrane library from database inception to January 2022 (sText).

2.2 Data extraction and evidence evaluation

The data extraction was independently conducted by two authors (H.Y. and (Z.M. or W.L.)). For each study, based on a standardized data collection form, we extracted the relevant information such as title, population description, offspring age, BP measurement, HDP definitions, sample size, adjusted factors, and BP. If the studies provided the outcome of interest without using mean difference (MD) and standard deviation, the RevMan Calculator (https://training.cochrane.org/resource/revman-calculator) was used. In addition, when a key message was not obtained, we contacted the authors at least twice (except when not found). All primary results obtained from the authors were preferentially used in the meta-analysis. In addition, the assessment of the risk of bias conducted using the ROBINS-I (Risk Of Bias In Nonrandomized Studies-of Interventions) tool.

2.3 Data analyses

The meta-analysis was conducted with Review Manager software (version 5.3) and Stata software, version 16 (Stata Corp, College Station, TX, USA), based on an inverse variance method. As there is greater chance of random error in observational studies, the pooled MDs and 95% confidence intervals (CIs) in BP between the offspring of mothers with HDP and normotensive mothers were calculated using a random-effect model. We also performed the overall pooled MD of BP based on the outcome with and without adjustment for confounders.
Heterogeneity was initially assessed by studying the forest plot generated for the outcomes. To explore sources of heterogeneity, the meta-regression analysis was used to investigate the potential effects of several confounders; subgroup analysis was subsequently performed. The Egger test was used to evaluate publication bias in all of the groups, and the funnel plots were reported for publication bias when more than nine studies were analyzed. In addition, sensitivity analysis was used to assess the stability of the results. An overall grading of the evidence was performed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach. \(^3^9\)

3 RESULTS

The characteristics of the included studies are summarized in Table S2. In total, data from 3839 offspring exposed HDP in utero and 57977 offspring from normotensive mothers were analyzed. Compared to the normotensive group, the HDP group had higher systolic BP (MD 2.46 mm Hg, 95% CI: 1.88–3.03 mm Hg) and diastolic BP (MD 1.38 mm Hg, 95% CI: 0.94–1.83 mm Hg) (Figure 1). The pooled MDs in systolic and diastolic BP between the offspring of mothers with chronic hypertension and normotensive ones (Figure 4).
In the meta-regression analysis, we found that offspring age accounted for some heterogeneity in the pooled estimates (Table S3). Compared to the offspring < 18 years old, the older offspring of mothers with HDP had higher systolic BP (MD 3.49 mm Hg, 95% CI: 1.74–5.24 mm Hg vs. MD 2.24 mm Hg, 95% CI: 1.69–2.79 mm Hg, P < 0.0001) and diastolic BP (MD 2.76 mm Hg, 95% CI: 2.01–3.51 mm Hg vs. MD 1.06 mm Hg, 95% CI: 0.76–1.37 mm Hg, P < 0.0001), respectively (Figure S3). In the four studies with adjusted results, the pooled MDs between the HDP and the normotensive groups were 2.29 mm Hg (95% CI: 1.20–3.39 mm Hg) in systolic BP and 1.15 mm Hg (95% CI: 0.01–2.30 mm Hg) in diastolic BP, respectively (Figure S5), adjusting for factors such as age, weight/BMI, birthweight, and sex. The adjusted significant MDs in BP between the PE and the normotensive groups were also computed (Figure S6).

**(A)**

| Study or Subgroup | Preeclampsia Mean (SD) | Control Mean (SD) | Mean Difference IV, Random. 95% CI |
|-------------------|------------------------|-------------------|----------------------------------|
| Birukov 2020      | 102.3 (8.3) 114 100.8 | 6.9 1498 10.4 % | 1.50 [-0.06, 3.06] |
| Fraser 2013       | 118.4 (8.3) 82 116.1 | 9.8 3644 7.6 % | 2.30 [0.48, 4.12] |
| Henley 2016       | 119.0 (9.1) 17 116.0 | 11.0 528 1.3 % | 3.00 [-1.43, 7.43] |
| Hoodby 2021       | 109.2 (8.6) 80 107.3 | 7.1 80 4.3 % | 1.90 [-0.54, 4.34] |
| Kaye 2012         | 108.0 (9.0) 48 110.0 | 11.0 90 2.2 % | -2.00 [-5.41, 1.41] |
| Khehaghian 2011   | 98.6 (6.7) 26 98.2 | 5.7 15 1.7 % | 1.60 [-2.27, 5.47] |
| Langford 1980     | 102.1 (12.4) 115 100.2 | 12.3 298 3.6 % | 1.90 [-0.76, 5.56] |
| Plummer 2021      | 111.8 (12.7) 38 112.0 | 12.5 129 1.2 % | -0.20 [-4.78, 4.38] |
| Randhir 2020      | 96.6 (7.1) 194 95.0 | 6.8 420 17.9 % | 1.60 [0.41, 2.79] |
| Seidman 2003      | 116.4 (8.8) 39 113.2 | 8.9 60 2.5 % | 3.20 [0.02, 6.38] |
| Tripathi 2018     | 108.0 (9.0) 48 110.0 | 11.0 90 2.2 % | 0.60 [-2.65, 3.85] |
| Vatten 2003       | 122.4 (10.2) 220 119.5 | 10.5 347 13.1 % | 2.90 [1.51, 4.29] |
| Washburn 2015     | 106.4 (10.0) 48 106.0 | 9.8 111 2.3 % | 0.40 [-2.94, 3.74] |
| Yu 2016           | 95.1 (13.1) 108 95.5 | 11.7 104 2.3 % | -0.40 [-3.74, 2.94] |
| Øgland 2009       | 115.3 (9.8) 181 113.5 | 8.5 356 9.0 % | 1.80 [0.12, 3.48] |

| Total (95% CI)    | 1792 | 32192 100.0% | 1.90 [1.39, 2.40] |

**FIGURE 2** Mean difference in BP in mm Hg between offspring exposure to preeclampsia in utero and controls. (A) systolic BP; (B) diastolic BP

In the meta-regression analysis, we found that offspring age accounted for some heterogeneity in the pooled estimates (Table S3). Compared to the offspring < 18 years old, the older offspring of mothers with HDP had higher systolic BP (MD 3.49 mm Hg, 95% CI: 1.74–5.24 mm Hg vs. MD 2.24 mm Hg, 95% CI: 1.69–2.79 mm Hg, P < 0.0001) and diastolic BP (MD 2.76 mm Hg, 95% CI: 2.01–3.51 mm Hg vs. MD 1.06 mm Hg, 95% CI: 0.76–1.37 mm Hg, P < 0.0001), respectively (Figure S3). In the four studies with adjusted results, the pooled MDs between the HDP and the normotensive groups were 2.29 mm Hg (95% CI: 1.20–3.39 mm Hg) in systolic BP and 1.15 mm Hg (95% CI: 0.01–2.30 mm Hg) in diastolic BP, respectively (Figure S5), adjusting for factors such as age, weight/BMI, birthweight, and sex. The adjusted significant MDs in BP between the PE and the normotensive groups were also computed (Figure S6).

Using the ROBINS-I, seven studies were evaluated to have a low risk of bias, with fourteen for moderate and two for serious (Figure S7). Further, the GRADE quality of evidence was moderate for systolic BP in PE/GH groups, very low for BP in the chronic hypertension group, and low for other groups (Table S4). There was no evidence of publication bias among the studies assessed by the Egger test with the funnel plot reported in the HDP/PAH/PE groups (Figure S8). The sensitivity analysis demonstrated the stability of the pooled values.

**4 DISCUSSION**

The present systematic review and meta-analysis first reported that the offspring exposed to all subtypes of HDP had higher BP than those with no exposure.
Many studies exploring the health outcomes of offspring exposure to HDP have been conducted and have demonstrated that exposure to PE and GH in utero is associated with higher BP in offspring.15–17,19,20,27–30 Offspring from PAH pregnancies had higher BP compared to those from normotensive pregnancies.40 PE offspring also had higher BP than normotensive offspring.41 However, without the pooled estimate, a recent systematic review drew a conflicting conclusion on the associations between PE and offspring BP.10 In the present meta-analysis, in line with most of the previous meta-analyses, the findings showed that offspring exposed to any subtype of HDP had higher BP than normotensive offspring. According to the DOHaD hypothesis,3,4 exposure to any adverse environment in utero during the specific critical windows of fetal development could induce short- and long-term changes in tissues and organs. Furthermore, in
previous studies, some epigenetic changes have been observed in the offspring of mothers with HDP, including DNA methylation in cord blood cells and alterations of the vasculature and cardiac structure. These changes could partly explain the associations between exposure to HDP in utero and BP in offspring. Notably, our findings also showed that the offspring in the chronic hypertension group with a longer duration of exposure had a greater elevation in BP than those in the PE/GH groups.

It is believed that the development of hypertension is the combined effect of environmental and genetic factors. The main question is whether the major contributor to the elevations regarding offspring exposure to HDP was genetic factors or the adverse intrauterine environment. Although environmental factors contribute to hypertension, genetic pathways are still involved in its pathogenesis. In general, people with a family history have obviously higher risks of hypertension than those with no family history. In family-based studies, parental genes could be transmitted to offspring and cause a higher risk of PE in their daughters. Thus, mothers with HDP and their offspring might be more likely to have chronic hypertension than normotensive mothers. In addition, some evidence supports that GH, PE and chronic hypertension are caused by similar genes, and pregnant women suffering from PE/GH are prone to chronic hypertension later in life. Sibling studies have also confirmed that, possibly with the same genetic resources, no BP differences were observed between offspring exposed to PE/GH and their nonexposed siblings in utero. Thus, the higher elevation of BP in the offspring of mothers with PE/GH could also be explained by weaker heredity compared to that in the offspring of chronic hypertension mothers. While minor heterogeneity of the pooled estimates was observed in the PE/GH/chronic hypertension group, moderate or significant heterogeneity was observed in the PAH/HDP group, perhaps due to inconsistent exposure.

It was shown that the heterogeneity came from the offspring age in the meta-regression analysis. This phenomenon may be interpreted by gene-environment interactions; as offspring with susceptibility genes of hypertension age, the effects from lifestyle and other environmental factors become stronger, and the effect of exposure to HDP in utero becomes less obvious.

In the pooled analysis, the study by Hosaka and coworkers was excluded because BP was measured not by medical staff but mother’s report at home, which can be affected by various possible factors. Meanwhile, compared to those in other studies, the offspring in this study were from Japanese districts, with unique perinatal exposures to methylmercury and persistent organic pollutants. Long exposures to toxic substances could be confounders for offspring BP, accompanied by other unknown biological variations.

4.1 Strengths and limitations

In this meta-analysis, we first investigate the associations between different types of HDP and offspring BP, but there are still several limitations that could not be addressed. The major limitation is that BP monitors in the included studies have not been validated for pediatric populations according to the STRIDE BP website (https://stridebp.org/bp-monitors), possibly affecting the results. Although the versions of BP monitors have not been mentioned, the brands of BP monitors (36%) have been validated in adults and most studies used their own standard measurement protocols. In addition, the included observational studies might be more prone to publication bias than randomized clinical trials. Thus, the funnel plot and Egger test were used to assess publication bias, with the sensitivity analysis identifying the stability of the results. Due to the strict criteria used, there was still the possibility of misidentified cases or nonconformity in meeting the current diagnostic criteria. Meanwhile, there were some different confounders adjusted for in different studies, but the pooled estimates with the adjusted data were similar to the whole pooled estimates. BP was higher in offspring exposed to different HDP than in normotensive offspring, but the potential genetic mechanism and the effects of intrauterine exposure remain unclear. Thus, more studies are needed to confirm and investigate these similar associations.

5 CONCLUSION

In summary, to our knowledge, this meta-analysis is the first to demonstrate that offspring exposed to all subtypes of HDP in utero have higher BP than those with no exposure. Additionally, genetic factors might be a relatively more important pathogenesis than intrauterine environmental factors.

AUTHOR CONTRIBUTIONS

The study sponsor (Huan Yu) designed the study and was involved in the analysis, including search strategy, selection criteria, data extraction, and evidence evaluation, and data analysis, and wrote the first draft of the manuscript. Wei Li participated in the revision and the secondary search, selection studies, data extraction, and evidence evaluation. Zhengxia Mao was involved in search strategy, selection criteria, data extraction, and manuscript revisions. Xiaoping Lei designed the study, critically revised the manuscript, and approved the manuscript for publication. Lijuan Luo, Na He, and Wenbin Dong revised the manuscript.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

ORCID

Huan Yu MD https://orcid.org/0000-0001-9078-4563
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SUPPORTING INFORMATION
Additional supporting information can be found online in the Supporting Information section at the end of this article.

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