Hypertensive disorders in pregnancy and risk of asthma in offspring: a systematic review and meta-analysis

Ping Li, Tao Xiong, Yong Hu

ABSTRACT

Objectives The association between hypertensive disorders in pregnancy (HDP) and an increased risk of asthma in offspring remains controversial. No systematic review of this topic has been performed. The aim of this systematic review was to summarise the available evidence regarding the association between HDP and the risk of asthma in offspring.

Design Systematic review and meta-analysis.

Methods On the basis of a prepared protocol, a systematic search of PubMed, EMBASE, the Cochrane Library and Web of Science was performed using a detailed search strategy from the database inception to 17 January 2020. Cohort, case–control and cross-sectional studies published in English reporting the diagnoses of maternal HDP and asthma in offspring were included. The Meta-analysis of Observational Studies in Epidemiology guidelines were followed throughout the study. The estimated pooled ORs of HDP and asthma in offspring were calculated from the studies, and the meta-analysis was performed using random-effects models.

Results Ten cohort studies involving a total of 6 270 420 participants were included. According to the Newcastle-Ottawa Scale, the overall methodological quality was good since 8 studies were of high quality and 2 studies were of moderate quality. After controlling for potential confounders, HDP was associated with a possible increased risk of asthma in offspring, with a pooled adjusted OR (aOR) of 1.19 (95% CI 1.12 to 1.26). The subgroup analyses according to HDP subgroups, sibling design, study quality, study location, offspring ages, singleton status, exposure assessment, outcome assessment and adjusted factors showed similar results.

Conclusions Exposure to HDP may be associated with an increased risk of asthma in offspring. Further research is needed to verify the results and determine whether the observed relationship is causal.

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INTRODUCTION

Hypertensive disorders in pregnancy (HDP), which are estimated to affect 5% to 15% of all pregnancies, are recognised as among the most common obstetrical complications. HDP are defined as any hypertension condition (systolic blood pressure (BP) ≥140 mmHg and/or diastolic BP ≥90 mmHg) that manifests before gestation or before 20 weeks and hypertension starting at or after 20 weeks. There are mainly four subtypes of HDP, including pre-eclampsia–eclampsia, chronic hypertension, chronic hypertension with superimposed pre-eclampsia, and gestational hypertension. All HDP subtypes pose serious threats to the health of the offspring. Recent studies have confirmed that HDP are closely associated with a risk of offspring diseases, including lung disease, high blood pressure, congenital heart defects, obesity, autism spectrum disorder, attention-deficit/hyperactivity disorder, low cognitive function, anxiety/depression and other neurodevelopmental disorders.

Theoretically, HDP induce a detrimental in utero environment, causing systemic inflammation and oxidative stress in the vulnerable fetal lung. Therefore, the development of the fetal lung may be disturbed by abnormal inflammation and immune function. These disturbances may persist through late life in offspring, leading to subsequent respiratory diseases. HDP may have great impacts on the fetal airway structure and respiratory and immune system development during the prenatal period, significantly increasing the susceptibility of offspring to asthma.

Strengths and limitations of this study

- The studies included in this meta-analysis adopted a prospective cohort design, and 10 studies were of high quality, which could eliminate various confounding factors.
- An extremely large sample size of more than 6 million participants was included; thus, our findings are potentially more robust than those of any individual study.
- This study was based on a pre-prepared protocol and followed meta-analysis guidelines and the Meta-analysis of Observational Studies in Epidemiology guidelines.
- The diagnostic criteria for hypertensive disorders in pregnancy and asthma varied among the included studies, which may increase clinical heterogeneity.
Asthma, which affects 1%–18% of the population, is the most common lung disease associated with abnormal inflammation and immune function. Asthma is characterised by variable symptoms, such as wheezing, shortness of breath, chest tightness and/or cough, and variable expiratory airflow limitation. Since asthma can cause recurrent school absences, emergency department visits and hospitalisations, it has been regarded as a major public health challenge worldwide.

The aetiology of asthma is not completely clear. In addition to genetic and environmental factors, it is widely accepted that asthma originates early in life. Negative events during the perinatal period increase the risk of asthma and impair lung function later in life. Asthma symptoms beginning in adulthood may have originated in childhood. Recurrent wheezing and other asthma-like symptoms usually begin as early as the first few weeks or months after birth, highlighting the need for the early recognition of and interventions for the risk factors of asthma to minimise the development of asthma and its potential long-term sequelae. Recent epidemiological studies have reported that maternal HDP may be a potential risk factor for asthma in offspring. However, evidence of the association between maternal HDP and asthma in offspring is inconsistent. Hence, clarifying the magnitude of this association is extremely important. Therefore, we performed the current systematic review and meta-analysis to synthesise the available evidence regarding the relationship between HDP and asthma in offspring.

**METHODS**

**Search strategy**

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, and a prepared protocol registered in the international prospective register of systematic reviews and published in *BMJ Open*. Two reviewers (PL and TX) independently conducted a systematic search of the literature in PubMed, EMBASE, the Cochrane Library and Web of Science from database inception to 17 January 2020. Search terms related to HDP and asthma were combined according to the principles of Boolean logic (using AND, OR or NOT). The full search strategy is included in online supplemental table 1. In addition, the reference lists of the included studies were manually searched to further identify eligible studies. The authors further requested the full text or research data of articles with only abstracts or unpublished articles. The authors of three studies were contacted for additional information. The searches were limited to human studies published in English. No restrictions were placed on the publication date, location of the study or the age of the participants.

**Study selection**

Two investigators (PL and YH) independently inspected the titles and abstracts of the citations and obtained the full texts. When consensus regarding eligibility could not be reached, a third reviewer (TX) was involved in the discussion. The eligibility criteria for inclusion in the systematic review included the following: (1) cohort, case-control or cross-sectional studies in which a diagnosis of HDP was reported, asthma was the primary outcome of interest, and the secondary outcomes consisted of recurrent wheezing/wheezing, lung/pulmonary function, the severity of asthma (active asthma or asthma exacerbations) or asthma treatment; (2) studies in which the association between HDP and asthma was a main objective of the study; (3) studies that contained original data and confirmed HDP through medical records and/or physician-diagnosed self-reporting; (4) peer-reviewed published studies. The exclusion criteria were as follows: (1) case series, case reports, conference abstracts, letters to the editor, reviews and commentary articles; (2) studies with overlapping data (same data from the same population in two or more studies); (3) studies without raw data (no data were provided for the meta-analysis).

**Data extraction**

Two reviewers (PL and YH) independently extracted the data from the eligible studies using a standardised data extraction form. The titles and abstracts were retrieved from each article, stored and managed using EndNote reference manager. From each included study, we extracted the following information: first author's last name, year of publication, study location, study design, sample size, exposure (HDP and its subgroups), outcome diagnostic criteria, offspring age at diagnosis, adjusted/matched confounding variables and effect estimates (risk ratios (RRs) or ORs) with the 95% CIs. Any discrepancies were resolved by consensus with a third reviewer (TX).

**Bias and quality assessment**

The quality assessments of the included studies were conducted by two reviewers (PL and YH) independently, and any discrepancies were resolved by a third reviewer (TX). The quality assessment followed our published protocol. The quality of the cohort studies was assessed using the Newcastle-Ottawa Scale (NOS). The study quality was classified into the following three categories: high quality (scores 7–9), moderate quality (scores 4–6) and low quality (scores 0–3).

**Statistical analysis**

The data were analysed using Stata V14.0 (StataCorp, College Station, Texas, USA). The ORs and 95% CIs were used as a measure of the association between HDP and the risk of asthma in offspring among the studies. We computed a summary OR and its 95% CIs using the study-specific most-adjusted OR or RR (maternal HDP exposure compared with maternal non-HDP exposure) and its 95% CIs. We used a random-effects model to
calculate the pooled ORs. The $I^2$ statistic (significance level, $>50\%$) was applied to examine heterogeneity. Forest plots were constructed to show the study-specific OR estimates and the pooled OR estimate. A protocol-based subgroup analysis was performed.\textsuperscript{31} Since some potential confounding factors may exist, we performed detailed subgroup analyses to reduce the effects of confounding factors. Because the family situation and genetic factors are similar in siblings, we performed a subgroup analysis of sibling-design studies. Finally, subgroups analyses stratified by HDP subgroups, sibling design, study quality, study location, offspring ages, singleton status, exposure assessment, outcome assessment and adjusted factors were performed. The sensitivity analysis was performed by omitting one study at a time to evaluate the changes in the pooled OR. The potential risk of publication bias was estimated by inspection of a funnel plot. Publication bias was further assessed by Egger’s test and Begg’s test (significance level, $p<0.05$) and the ‘trim-and-fill’ procedure.

**Patient and public involvement**

Patients or the public were not involved.

**RESULTS**

**Literature search and selection**

The original search produced 1247 unique results after the removal of duplicates. Of these articles, 29 full-text articles were reviewed after screening the titles and abstracts. Of these articles, 19 articles were excluded because they did not meet the inclusion criteria. Finally, 10 studies\textsuperscript{23–28 33–36} were included in this study. The reasons for exclusion are outlined in figure 1.

**Study characteristics**

The characteristics of the 10 included studies are shown in table 1. The studies were published between 2003 and 2019. All selected studies\textsuperscript{23–28 33–36} were cohort studies, and there was a total of 6270 430 participants. The sample sizes of the studies ranged from 580 to 1 698 638, and four studies\textsuperscript{23 24 33 35} had sample sizes of more than 1 million. Nine studies\textsuperscript{23 24 26–28 33–36} were performed in Europe, and one study\textsuperscript{35} was performed in the USA. Four studies\textsuperscript{28 33 34 36} included children aged 6–7 years, and two studies\textsuperscript{26 27} included children aged 10–12 years. In two cohort studies,\textsuperscript{23 36} the authors used a sibling analysis in which children with the same mother were included to control for shared genetic and social confounders. According to the NOS, the overall methodological quality was good since eight studies\textsuperscript{23 24 26–28 33 34 36} were of high quality and two studies\textsuperscript{25 35} were of moderate quality (online supplemental table 2). The confounders that were adjusted in the studies are shown in online supplemental table 3.

**Results of the meta-analyses**

**Primary outcome: HDP and risk of asthma in offspring**

Ten studies\textsuperscript{23–28 33–36} in which a diagnosis of HDP was reported and asthma was the outcome of interest were identified. Seven studies\textsuperscript{24–28 33 36} described that the incidence of HDP ranged from 2.0% to 14.0% (mean, 6.7%; median, 5.6%; IQR, 3.3%–10.0%), and an average of
<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Study design</th>
<th>Country</th>
<th>Data source</th>
<th>Sample size</th>
<th>Ascertainment of HDP</th>
<th>Ascertainment of asthma</th>
<th>Offspring age at diagnosis (years)</th>
<th>Study quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mirzakhani et al (2019)</td>
<td>Cohort</td>
<td>USA</td>
<td>VDAART</td>
<td>67 (mothers with pre-eclampsia) 739 (mothers with pre-eclampsia) 28 (mothers with asthma and pre-eclampsia) 254 (mothers with asthma without pre-eclampsia)</td>
<td>Medical records (ACOG)</td>
<td>Maternal-reported (physician-diagnosed)</td>
<td>3 (6.8–12)</td>
<td>M</td>
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<tr>
<td>Wilmink et al (2018)</td>
<td>Cohort</td>
<td>Netherlands</td>
<td>Generation R study</td>
<td>206 (mothers with GH) 91 (mothers with pre-eclampsia or HELLP syndrome) 4783 (control)</td>
<td>Medical records (ISSHP, ACOG)</td>
<td>Maternal-reported (physician-diagnosed)</td>
<td>10</td>
<td>H</td>
</tr>
<tr>
<td>Stokholm et al (2017)</td>
<td>Cohort</td>
<td>Denmark</td>
<td>Registry-based cohort</td>
<td>62,728 (mothers with pre-eclampsia) 1635910 (mothers without pre-eclampsia) 20 (mothers with asthma and pre-eclampsia) 317 (mothers with asthma without pre-eclampsia)</td>
<td>Medical records (ICD-8, ICD-10)</td>
<td>Medical records (ICD-10)</td>
<td>0–15</td>
<td>H</td>
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<tr>
<td>Shaheen et al (2016)</td>
<td>Cohort</td>
<td>UK</td>
<td>ALSPAC</td>
<td>161 (mothers with pre-eclampsia) 1140 (mothers with GH) 308 (mothers with HbP) 6486 (normotensive)</td>
<td>Medical records (ISSHP criteria14)</td>
<td>Maternal-reported (doctor-diagnosed)</td>
<td>7</td>
<td>H</td>
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<tr>
<td>Magnus et al (2016)</td>
<td>Cohort</td>
<td>Norway</td>
<td>Registry-based study</td>
<td>16329 (mothers with pre-eclampsia) 390578 (control)</td>
<td>Medical records</td>
<td>Medical records</td>
<td>7</td>
<td>H</td>
</tr>
<tr>
<td>Liu et al (2015)</td>
<td>Cohort</td>
<td>Denmark</td>
<td>DMBR</td>
<td>Nested case-control study: 30767 (mothers with pre-eclampsia) 1239965 (mothers without pre-eclampsia) case–sibling study: 3608 (mothers with pre-eclampsia) 143704 (mothers without pre-eclampsia)</td>
<td>Medical records (ICD-8, ICD-10)</td>
<td>Medical records (ICD-10)</td>
<td>3–7</td>
<td>H</td>
</tr>
<tr>
<td>Byberg et al (2014)</td>
<td>Cohort</td>
<td>Norway</td>
<td>Stavanger study</td>
<td>FU1 (F: 10.8 years, M: 11.8 years): 214 (mothers with pre-eclampsia) 366 (mothers without pre-eclampsia) FU2 (F: 12.8 years): 169 (mothers with pre-eclampsia) 279 (mothers without pre-eclampsia)</td>
<td>Medical records</td>
<td>FU1: maternal-reported (physician-diagnosed) FU2: self-reported (ISAAC)</td>
<td>10–12</td>
<td>H</td>
</tr>
<tr>
<td>Aapberg et al (2010)</td>
<td>Cohort</td>
<td>Switzerland</td>
<td>Registry-based study</td>
<td>41389 (mothers with pre-eclampsia) 1299693 (control)</td>
<td>Medical records</td>
<td>Medical records</td>
<td>2–15</td>
<td>M</td>
</tr>
<tr>
<td>Rusconi et al (2007)</td>
<td>Cohort</td>
<td>Italy</td>
<td>SIDRIA</td>
<td>862 (mothers with hypertension or pre-eclampsia) 14729 (control)</td>
<td>Medical records</td>
<td>Medical records</td>
<td>6–7</td>
<td>H</td>
</tr>
<tr>
<td>Nafstad et al (2003)</td>
<td>Cohort</td>
<td>Norway</td>
<td>Registry-based study</td>
<td>98188 (mothers with pre-eclampsia) 1428341 (control)</td>
<td>Medical records (ICD-8)</td>
<td>Derived from NIAR (doctor-diagnosed, ICD-7, ICD-9)</td>
<td>7.5–25.5</td>
<td>H</td>
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</table>

ACOG, American College of Obstetricians and Gynaecologists; ALSPAC, Avon Longitudinal Study of Parents and Children; COPSAC, Copenhagen Prospective Studies on Asthma in Childhood; HELLP, hemolysis, elevated liver enzymes and low platelets; ISAAC, International Study of Asthma and Allergies in Childhood; ISSHP, International Society for the Study of Hypertension in Pregnancy; M, median quality (scores 4–6); MBRN, Medical Birth Registry of Norway; NIAR, National Insurance Administration Register; SIDRIA, Italian Studies of Respiratory Disorders in Childhood and the Environment; VDRRT, Vitamin D Antenatal Asthma Reduction Trial.
4.6% mothers had pre-eclampsia (IQR, 2.3%–6.9%). The incidence of asthma ranged from 4.9% to 25.5% (mean, 14.7%; median, 12.5%; IQR, 6.5%–23.4%) in the offspring of mothers diagnosed with HDP and 3.6%–17.5% (mean, 8.9%; median, 8.6%; IQR, 4.8%–13.3%) in the controls.23–28 34–36 Fourteen estimates from 10 unique studies included adjusted estimates and were included in the meta-analysis. Figure 2 displays the adjusted estimates, producing a pooled adjusted OR (aOR) of 1.19 (95% CI 1.12 to 1.26), suggesting an increased risk of asthma among the offspring of mothers with HDP. Statistically significant heterogeneity was found across the studies (I²=72.5%).

**Secondary outcomes**

Only a few included studies reported secondary outcomes, including recurrent wheezing/wheezing, active asthma, asthma exacerbations or asthma treatment. Only two studies reported the physiological parameters of lung function. One study reported a decreased forced expiratory volume in 1 s, and another study reported a reduced forced expiratory flow between 25% and 75% in offspring of mothers with pre-eclampsia.26 28

**Subgroup and sensitivity analyses**

We performed subgroup analyses to explore heterogeneity according to subgroups of HDP, study quality, study location, offspring ages, singleton births, exposure assessment, outcome assessment and adjusted factors.

The results of the subgroup analyses are outlined in table 2. The subgroup analysis examining the associations between subtypes of HDP and asthma in offspring resulted in aORs of 1.18 (95% CI 1.11 to 1.25) for pre-eclampsia and 1.26 (95% CI 0.98 to 1.61) for other HDP (online supplemental figure 1). The sibling analysis failed to reveal a relationship between pre-eclampsia and asthma in offspring, with a pooled aOR of 1.06 (95% CI 0.99 to 1.14). The high quality studies yielded a significant aOR of 1.17 (95% CI 1.09 to 1.25). In addition, significant aORs were observed in studies conducted in both Europe and the USA. Regarding the offspring ages, the aORs in three age groups were significant, but not among the offspring aged 10–12 years. The aOR in the singleton subgroup was slightly higher than that in the non-singleton subgroup, with decreased heterogeneity of I²=47.2%. The aORs of any type of exposure assessment (HDP from self-reports or medical records) and any type of outcome assessment (asthma from maternal reports or medical records) were all significant. In the subgroup analyses by adjusted factors, the aORs were generally significant after adjusting for maternal smoking during pregnancy (aOR 1.23; 95% CI 1.17 to 1.28) and maternal asthma (aOR 1.22; 95% CI 1.12 to 1.33). Meanwhile, the
heterogeneity obviously decreased after adjusting for maternal smoking during pregnancy ($I^2=30.7\%$) and maternal asthma ($I^2=50.4\%$).

The sensitivity analysis, which was performed by omitting one study at a time, showed that the overall pooled adjusted ORs did not substantially vary (online supplemental table 4).

**Publication bias**
A visual inspection of the funnel plot revealed potential publication bias (online supplemental figure 2), although both Egger’s test and Begg’s test were not statistically significant (Egger’s test, $p=0.709$, 95% CI $-1.26$ to $1.80$; Begg’s test, $z=0.770$ (continuity corrected), $Pr> |z|=0.443$ (continuity corrected)). Therefore, we further applied the trim-and-fill method to adjust for the funnel plot asymmetry,$^{37}$ but the results showed that no trimming was performed, and the data were unchanged (‘no trimming performed, data unchanged’). There was no indication of publication bias using Duval’s trim-and-fill method (no new studies added).

**DISCUSSION**
In this systematic review and meta-analysis based on 10 observational studies involving 6270430 participants, we...
found that maternal HDP exposure was associated with approximately 20% increased odds of asthma in offspring compared with non-exposure. Most subgroup analyses showed that offspring have a slightly increased asthma risk after maternal HDP exposure. The results of the subgroup analysis examining the association between pre-eclampsia and asthma in offspring provided a significant aOR of 1.18.23–28 33 35 36

High heterogeneity was detected in this meta-analysis. Therefore, we performed subgroup analyses to explore the cause of the heterogeneity. Notably, we found that the heterogeneity significantly decreased when studies that considered only singletons and maternal smoking during pregnancy as a confounding factor were included, revealing that the number of offspring and maternal smoking during pregnancy may have contributed to the heterogeneity. Another explanation for the observed heterogeneity may be due to variability in the incidence of asthma in the offspring among the included studies. The incidence of asthma ranged from 4.9% to 25.5% in the offspring of mothers diagnosed with HDP and 3.6%–17.5% in the controls.

The genetic susceptibility of offspring to asthma was evaluated through three analyses in this study. First, since the family situation and genetic factors are similar in siblings, we performed a subgroup analysis of two-sibling-design studies23 36 and found that there was a borderline significant relationship between pre-eclampsia and asthma in the offspring (aOR 1.06; 95% CI 0.99 to 1.14). Second, a positive relationship (aOR 1.22; 95% CI 1.12 to 1.33) was observed between HDP and asthma in offspring after adjusting for maternal asthma.25 26 28 36 The discrepancy between the two analyses may be due to the limited sample size or other unadjusted factors. The fundamental role of genetics should be noted in future studies evaluating maternal HDP and asthma in offspring.

**Strengths and limitations**

This systematic review has several strengths. First, this study had an extremely large sample size involving more than 6 million participants. Second, all 10 studies adopted prospective cohort designs, and 8 of the 10 studies were of high quality. Five studies included birth registry-based cohorts.23 24 33 35 36 Third, the estimates in the original studies were carefully adjusted for potential confounders. Fourth, our study was based on a pre-prepared protocol and followed the PRISMA guidelines and MOOSE guidelines.29–31 Thus, our meta-analysis provided reliable evidence showing a significantly increased risk of asthma in offspring exposed to maternal HDP. However, there are several potential limitations in this review. First, the included studies were limited to the English language, and potential non-English-language studies may have been missed. Second, the generalisability of the results worldwide should be performed cautiously because of the geographical restriction of the included studies, which mostly involved participants from Europe or the USA. Future clinical investigations performed in other regions are needed. Third, the different assessments of HDP and asthma used among the studies may potentially introduce misclassification bias. The diagnostic criteria for HDP and asthma varied among the included studies, which may increase clinical heterogeneity.36 Several studies33 33 35 36 followed the diagnosis of asthma according to the National Insurance Administration Register or National Prescribed Drug Register, which might exclude offspring with mild asthma. Fourth, important confounding factors were not fully adjusted in the included studies. Therefore, although a significant association exists between HDP and asthma in offspring, future research is needed to identify a comprehensive set of confounders to assess whether this association is causal or attributable to residual or unmeasured confounding. Although there was a significant influence of HDP on asthma in offspring, the effects of HDP on the physiological parameters of lung function, asthma exacerbations or asthma treatment need further consideration in future studies.

Exposure to maternal HDP in early life may be associated with an increased risk of developing asthma later in life. HDP appears to be an interesting predictor of asthma in offspring. This finding provides important evidence of the long-term consequences of exposure to maternal HDP on offspring. Furthermore, this study supports the fetal origin hypothesis of the development of asthma. Because maternal HDP is a common risk factor for multiple poor outcomes in offspring, early surveillance and interventions are warranted for high-risk children of mothers with HDP. HDP increase the risk of offspring diseases, which start from the fetus (such as preterm delivery and stillbirth) and may last to adulthood (multiorgan diseases, such as cardiovascular, endocrine and neurodevelopmental functions). Early surveillance from the fetus stage to adulthood should be comprehensive. In addition, assessing whether maternal HDP was present when evaluating infants for asthma could be important. For future asthma studies, maternal HDP should be considered a potential risk factor.

**CONCLUSION**

Our study found a mild increased risk of asthma in offspring of mothers with HDP; this reliable result was derived from a large population and mostly high-quality studies. Additional robust research is needed to address the key limitations in the literature, use the gold standard for disease diagnosis, verify the results and determine whether the observed relationship is causal. We advocate for improved paediatric surveillance of infants exposed to maternal HDP as increased surveillance may be beneficial for the early diagnosis of and interventions for asthma.

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Contributors This study was conceived by PL and TX. TX and YH developed the eligibility criteria, search strategy, methodological quality assessment, data extraction and data summary plan. PL and TX wrote the protocol. TX supervised the work. All authors approved the final version.

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