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Complete List of Authors:	Li, Ping; West China Second University Hospital, Sichuan University, Department of Pediatrics; Key Laboratory of Birth Defects and Related Diseases of Women and Children (Sichuan University) Ministry of Education Xiong, tao; West China Second University Hospital, Sichuan University, Department of Pediatrics; Key Laboratory of Birth Defects and Related Diseases of Women and Children (Sichuan University) Ministry of Education Hu, Yong; West China Second University Hospital, Sichuan University, Department of Pediatrics; Key Laboratory of Birth Defects and Related Diseases of Women and Children (Sichuan University) Ministry of Education
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Hypertensive Disorders of Pregnancy and Risk of Asthma in Offspring: A Systematic Review and Meta-Analysis

Ping Li, MD,[1,2] Tao Xiong*, MD PhD [1,2,3] Yong Hu, MD [1,2]

[1] Department of Pediatrics, West China Second University Hospital, Sichuan University, Chengdu, China

[2] Key Laboratory of Birth Defects and Related Diseases of Women and Children (Sichuan University) Ministry of Education

[3] Deep Underground Space Medical Center, West China Hospital, Sichuan University, Chengdu, China

Ping Li: liping_371986@163.com

Yong Hu: huyong1003@163.com

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***Correspondence**

Dr. Tao Xiong No. 20, Section Three, South Renmin Road, Chengdu, China

Tel: 1-5126616986

Email: tao_xiong@126.com

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Abstract

Introduction: Hypertensive disorders of pregnancy (HDP), as one of the most common obstetrical complications, has been reported to have a controversial relationship with an increased risk of asthma in offspring. No systematic review has been performed on this topic. The aim of this systematic review is to summarize the available evidence examining the association between HDP and the risk of asthma in offspring.

Methods and analysis: We will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines. A systematic search of the PubMed, EMBASE, Cochrane and Web of Science databases will be performed using a detailed search strategy. Cohort, case-control and cross-sectional studies that report a diagnosis of maternal HDP and asthma in offspring will be included. Studies will be limited to the English language and include only human participants. Two independent reviewers will conduct the study selection, data extraction, and risk of bias assessments using a standardized data extraction form. A meta-analysis will be performed to calculate overall pooled estimates using the generic inverse variance method. The data will be synthesized by either fixed-effect or random effects models according to heterogeneity tests. All analyses will be performed in STATA 14 and RevMan5.3. High-quality evidence of the relationship between HDP and the risk of asthma in exposed offspring will be confirmed based on the synthesis of current studies. In addition, the results of subgroup analyses and related secondary outcomes

will be reported. The following will be concluded: (i) whether HDP increases the risk of asthma in offspring; (ii) whether HDP affects the severity of asthma in exposed offspring; and (iii) whether possible differences in the risk of asthma among different HDP subgroups exist.

Keywords: Asthma, Hypertension, Perinatology, Paediatrics, Community child health

Ethics and Dissemination

There is no requirement for ethics approval because the meta-analysis and systematic review are based on published data. It is anticipated that the dissemination of results will take place at conferences and through publication in a peer-reviewed journal.

Strengths and limitations of this study

- This will be the first meta-analysis to explore the relationship between HDP and the risk of asthma in exposed offspring.
- This protocol was designed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines.

- Selection, data extraction and risk of bias assessments will be performed by two independent reviewers.
- The supporting evidence may promote strengthened surveillance of HDP-exposed infants, leading to early identification and intervention, finally improving lung function and asthma outcomes.
- Since the positive results are more prone to be published online, leading to potential publication bias, the funnel plots will be used to assess publication bias.

INTRODUCTION

Hypertensive disorders of pregnancy (HDP) is estimated to affect 5% to 15% of all pregnancies and is recognized as one of the most common obstetrical complications [1] [2]. HDP includes any hypertensive condition before gestation or with manifestation before 20 weeks and hypertension starting at or after 20 weeks; types of hypertension include gestational hypertension (GH), preeclampsia (PE), chronic hypertension, and PE superimposed on chronic hypertension, according to the International Society for the Study of Hypertension in Pregnancy [3]. Recent research has reported that HDP is closely associated with an increased risk of diseases in offspring, including asthma, allergy, eczema [4], high blood pressure [5], congenital heart defects [6], obesity [7], autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD), low cognitive function, anxiety/depression, and other neurodevelopmental disorders [8 9]. The "Developmental Origins of Health and Disease (DOHaD)" hypothesis, which has been widely proven, has revealed that fetuses exposed to adverse uterine environments are prone to develop chronic noncommunicable diseases later in life, owing to the perpetual alteration of the fetal vasculature, cardiac structure, pancreas, adipose tissue and brain structure [10 11]. In addition, HDP induces a detrimental in utero environment, with systemic inflammation and oxidative stress experienced by the fetus, thus impairing vulnerable fetal lung development and disturbing immune function, which may persist throughout life in offspring.

Asthma, a common lung disease associated with abnormal inflammation and immune response, is characterized by variable symptoms of wheezing, shortness of

breath, chest tightness and/or cough, and by variable expiratory airflow limitation. It is the most common chronic disease of childhood responsible for school absences, emergency department visits and hospitalizations. Thus, asthma has been regarded as a major public health challenge worldwide, affecting 1-18% of populations in different countries [12 13]. The development of asthma has generally been attributed to the interactions of genetics and environmental factors [14 15]. Currently, it is widely accepted that asthma develops early in life [16]. Recurrent wheezing and other asthma-like symptoms usually begin as early as the first few weeks or months after birth. There is growing evidence that negative events occurring early in life, even in the perinatal period, significantly increase the risk of asthma and poor lung function later in life [17 18]. Hence, adverse obstetrical events, such as HDP, may have strong effects on fetal airway structure, lung and immune system development during the prenatal period and may significantly increase the susceptibility of offspring to asthma [19 20].

Approximately half of individuals with asthma are reported to suffer from asthma-like symptoms during childhood [21]. Therefore, early recognition and intervention is critical to reduce short- and long-term morbidity and to prevent potential long-term sequelae resulting in impaired lung function. Recent studies have shown that HDP is a potential risk factor for childhood asthma in offspring [4 22]. However, the association between HDP and asthma is controversial [23]. Identifying the relationship between HDP and asthma could help us to understand the pathogenesis of asthma. It also facilitates early asthma recognition and intervention in high-risk

populations. Therefore, we aim to perform a systematic review and meta-analysis to summarize the available evidence regarding the relationship between HDP and asthma in offspring.

OBJECTIVES

The aim of the present systematic review and meta-analysis is to summarize the available evidence to explore the following:

1. Whether HDP increases the risk of asthma in offspring;

2. Whether HDP affects the severity of asthma in the exposed offspring;

3. Whether differences in the risk of asthma among different HDP subgroups exist.

The study will be conducted based on the following requirements.

Population

Pregnant women and their offspring will be included.

Intervention/exposures

HDP, defined as any hypertension (systolic blood pressure (BP) ≥140 and/or diastolic BP ≥90 mmHg) during pregnancy, mainly includes the following:

(1) Gestational hypertension (GH): any hypertensive disorder that develops at or after 20 weeks of gestation in the absence of features of preeclampsia (PE);

(2) PE: GH accompanied by one or more of the following new-onset conditions at or after 20 weeks of gestation: (i) proteinuria, (ii) other maternal organ dysfunction, such

as acute kidney injury, liver involvement, neurological complications, hematological complications, and (iii) uteroplacental dysfunction;

(3) Chronic hypertension (essential and secondary): high blood pressure predating pregnancy or recognized at < 20 weeks of gestation;

(4) PE superimposed on chronic hypertension: chronic essential hypertension accompanied by any of the above maternal organ dysfunctions consistent with PE.

The definitions were developed according to current guidelines, such as the Canadian Hypertensive Disorders of Pregnancy Working Group [24], Society of Obstetric Medicine of Australia and New Zealand [25], American College of Obstetricians and Gynecologists [3], and International Society for the Study of Hypertension in Pregnancy guidelines [26].

Comparison

Normotensive pregnant women will be used as the control group.

Outcomes

1. Primary outcome: asthma.

Asthma is defined by a history of respiratory symptoms including wheezing, shortness of breath, chest tightness and cough that vary over time and in intensity together with variable expiratory airflow limitation, according to the Global Initiative for Asthma (GINA) [12] and International Collaboration in Asthma, Allergy and Immunology (iCAALL)[27].

2. Secondary outcomes:

(1) Wheezing/recurrent wheezing;

(2) Lung/pulmonary function (including forced expiratory volume in the first second [FEV_1], forced expiratory volume at 0.5 seconds [$FEV_{0.5}$], forced vital capacity [FVC], FEV_1/FVC, 50% of the forced expiratory flow [FEF_{50}] and 75% of the forced expiratory flow [FEF_{75}], maximal midexpiratory flow [FEF_{25-75}]), active asthma, asthma exacerbations and asthma treatment (including hospitalization, systemic corticosteroid use, inhaled β_2-agonist use, inhaled corticosteroid [ICS] use, combination of inhaled β_2-agonists and corticosteroid use, leukotriene antagonists use, and other prescriptions for antiasthma medications);

3. Serum IgE levels.

METHODS

The systematic review and meta-analysis will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [28]and Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines [29].

Criteria for considering studies for review

Inclusion criteria

(1) Studies with a cohort, case-control or cross-sectional design that report a diagnosis of HDP and asthma in offspring as the outcomes of interest;

(2) Studies that estimate the relationship between HDP and asthma and report the

estimated risks (odds ratios [ORs] or relative risks [RRs]) with 95% confidence intervals (CIs) or provide sufficient information to calculate these values;

(3) Studies published in only the English language;

(4) Studies published in any year;

(5) Studies that include only humans.

Exclusion criteria

(1) Conference abstracts, letters to editors, reviews and commentary articles;

(2) Studies with overlapping data;

(3) Studies missing raw data.

Search strategy

A systematic search of the literature will be conducted in the following electronic databases: PubMed, EMBASE, Cochrane and Web of Science. We will search databases such as Google Scholar for gray literature. A three-phase search strategy will be applied in this review.

1. For HDP, the following combination of search terms will be used: “hypertensive disorders during pregnancy” or “hypertensive disorders in pregnancy” or “hypertensive disorders of pregnancy” or “pregnancy-induced hypertension” or “eclampsia” or “preeclampsia” or “preeclampsia” or “preeclamptic pregnancy” or “chronic hypertension” or ”gestational hypertension” or “chronic hypertension with

superimposed preeclampsia" or "postpartum hypertension" or "maternal hypertensive disorders".

2. For asthma, the following search terms will be used: "asthma" or "wheeze" or "wheezing" or "shortness of breath" or "bronchial spasm" or "bronchospasm" or "bronchoconstriction" or "bronchoconstrict" or "bronchial hyperreactivity" or "bronchial hyperresponsiveness" or "reactive airway disease" or "obstructive lung disease" or "air low limitation" or "chronic obstructive respiratory disorder" or "chronic obstructive pulmonary disease".

3. We will combine steps 1 and 2 with "and".

The detailed search strategy is listed in the Supplement 1. We will manually search the reference lists of the included studies to further identify eligible studies.

Study selection and data extraction

The eligibility of each study will be assessed independently by two investigators (PL and TX) and disagreements will be solved by discussion (with a third author, YH, when necessary). Data from the identified studies will be extracted using a standardized data extraction form listed in the Supplement 2. The titles and abstracts of the studies retrieved from each database will be stored and managed in EndNote reference manager. For each included study, we will extract the following information: first author's last name, year of publication, study location, study design, sample size,

ascertainment of exposure (HDP and its subgroups), outcome diagnostic criteria, offspring age at diagnosis, adjusted/matched confounding variables and effect estimates (RRs or ORs) with 95% CIs. The eligibility of each study will be assessed independently by two investigators (PL and TX) and disagreements will be solved by discussion (with a third author, YH, when necessary).

Subgroups /subsets

Subgroup analyses will be carried out according to the following: (1) study design (cohort vs. case-control vs. cross-sectional), (2) sample size, (3) location (e.g., Europe vs. United States), (4) income level of the country (low/middle/high), (5) year of publication, (6) study subject selection, (7) study quality (minimal/low vs. moderate/high), (8) child adjusted factors (e.g., age at diagnosis of asthma, sex, birth weight, gestational age), and (9) maternal adjusted factors (e.g., maternal asthma, maternal body mass index, gestational weight gain, maternal smoking). Sensitivity analyses will be performed by excluding each study one by one and by calculating a pooled estimate for the remainder of the studies.

If any other subgroup/sensitivity analyses are identified during the process of the meta-analysis, these will be clearly labeled as post hoc analyses.

Risk of bias (quality) assessment

The quality of cohort and case-control studies will be assessed using the Newcastle-Ottawa scale (NOS) [30], which evaluates the selection (1 star for each term), comparability (up to 2 stars), and exposure or outcome (1 star for each term). A study with a high score indicates a low risk of bias. Additionally, the cross-sectional studies will be assessed using the Agency for Healthcare Research and Quality (AHRQ) recommended eleven items [31]. Furthermore, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology will be used to evaluate the overall likelihood of quality by examining 6 types of bias in each study (selection, exposure, outcome, analytic, attrition, and confounding) [32]. GRADE classifies the quality of studies as low, moderate, and high. The quality assessment of each study will be independently carried out by two of the authors, and any disagreements will be resolved through discussion (with a third author when necessary). We will use funnel plots to assess the publication bias, and Egger's linear regression will be applied to test for funnel plot asymmetry.

Strategy for data synthesis

The overall pooled estimates for the association between HDP and asthma will be calculated in the meta-analysis. We will use the generic inverse variance method to determine both the crude and adjusted results. A summary OR estimate with a 95% CI

will be calculated by using fixed-effect and random effects models. The *I*-squared statistics will be applied to examine heterogeneity. According to the Cochrane Handbook criteria, if the *I*-squared value is less than 50%, the heterogeneity is low, and a fixed-effect model will be used in the analysis. Otherwise, the heterogeneity will be considered high if the *I*-squared value is 50% or more, and a random effects model will be used. Forest plots will be constructed to show the study-specific RR/OR estimates and pooled RR/OR estimates. If a study is eligible for inclusion in the systematic review but does not provide adequate data for inclusion in the meta-analysis, a narrative synthesis will be conducted to summarize and tabulate the results. All analyses will be performed in STATA 14 and RevMan5.3.

Presenting and reporting the results

The study selection procedure will be outlined by a flow diagram according to the PRISMA statement in the meta-analysis. In addition, the reason for excluding studies will be presented. The characteristics of each included study, including the population, age range of participants, sample size, year range of studies, study design, country, exposure, outcome, measure of effect, unadjusted or adjusted effect (95% CI), and adjustment for covariates, will be tabulated in detail. The heterogeneity of the results will be listed in another table. Additionally, we will use the forest plots to present the pooled estimates in the meta-analysis. Eligible studies for which we could not obtain

raw data by contacting the corresponding authors will be listed individually in a separate table.

Summary

In the systematic review and meta-analysis, we will assess the association between HDP and asthma in offspring by summarizing the existing literature based on a predesigned protocol. Our results might help to reveal the potential etiology of asthma involving fetal lung and immune system development during the prenatal period. Thus, the supporting evidence may promote strengthened surveillance of HDP-exposed infants, leading to early identification and intervention, finally improving lung function and asthma outcomes.

Ethics and dissemination

There is no requirement for ethics approval because the meta-analysis and systematic review are based on published data. It is anticipated that the dissemination of results will take place at conferences and through publication in a peer-reviewed journal.

Acknowledgments

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Author Contributions

The study was conceived by PL and TX. PL, TX, and YH developed the eligibility criteria, search strategy, assessment of methodological quality, 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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Competing Interests

None declared.

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Table 1

Search strategy
(for each electronic database to be searched)

#1	Search terms	No of records returned
1	hypertensive disorders during pregnancy	
2	hypertensive disorders in pregnancy	
3	hypertensive disorders of pregnancy	
4	pregnancy-induced hypertension	
5	eclampsia	
6	pre-eclampsia	
7	preeclampsia	
8	preeclamptic pregnancy	
9	chronic hypertension	
10	gestational hypertension	
11	chronic hypertension with superimposed preeclampsia	
12	postpartum hypertension	
13	gravid hypertension	
14	maternal hypertensive disorders	
15	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14)	
16	asthma	
17	wheeze	
18	wheezing	
19	shortness of breath	
20	bronchial spasm	
21	bronchospasm	
22	bronchoconstriction	
23	bronchoconstrict	
24	bronchial hyperreactivity	

25	bronchial hyperresponsiveness	
26	reactive airway disease	
27	obstructive lung disease	
28	air low limitation	
29	chronic obstructive respiratory disorder	
30	chronic obstructive pulmonary disease	
31	(#16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30)	
32	(#15 AND #31)	
33	limit #32 to English language	
34	limit #33 to humans	

Table 2. Data Extraction Form for Review and meta-analysis

Study Details	
General information	
• First author	
• Year of publication	
• Study location	
• Study duration	
Study eligibility	
• Study design (case-control, cohort)	
• Participants	
exposed group	
unexposed group	
• Inclusion criteria	
• Exclusion criteria	
• Ascertainment of exposure	
• Outcome diagnostic criteria	
• Confounding variables	
• Matching factors	
Include or exclude	Include exclude
Reason for exclusion	
Characteristics of included studies	
• Sample size	
exposed group (including subgroups)	
unexposed group	
• Data source	
• Race	
• Income level of country	
• Maternal adjusted factors	
Maternal age, yrs	
Educational level	
Maternal asthma	
Maternal body mass index, kg/m^2	
Gestational weight gain, kg	

Parity	
Maternal smoking	
Others	
• Children`s adjusted factors	
Gender (M/F)	
Birth weight, kg	
Gestational age, w	
Offspring age at diagnosis, yrs	
Others	
Main outcome	
Effect estimates (RR or OR) with 95% CI	
Mean difference	
Other findings	

Risk of Bias assessment (For cohort studies**)**

Domain	Item	Score
election	1) Representativeness of the exposed cohort	a) truly representative of the average ___ (describe) in the community ✸ b) somewhat representative of the average____ in the community c) selected group of users eg nurses, volunteers ✸ d) no description of the derivation of the cohort
	2) Representativeness of the non-exposed cohort	a) drawn from the same community as the exposed cohort ✸ b) drawn from a different source c) no description of the derivation of the non exposed cohort
	3) Ascertainment of exposure	a) secure record (eg surgical records) ✸ b) structured interview ✸ c) written self report d) no description
	4) Demonstration the outcome of interest was not present at start of study	a) yes ✸ b) no
Comparability	1) Comparability of cohort on the basis of the design or analysis	a) study controls for ___ (select the most important factor) ✸ b) study controls for any additional factor ✸ (This criteria could be modified to indicate specific control for a second important factor.)
Outcome	1) Assessment of outcome	a) independent blind assessment ✸ b) record linkage ✸ c) self report d) no description
	2) Was follow-up long enough for outcomes to occur	a) yes (select an adequate follow up period for outcome of interest) ✸ b) no
	3) Adequacy of follow up of cohort	a) complete follow up - all subjects accounted for ✸ b) subjects lost to follow up unlikely to introduce bias - small number lost - > ___ % (select an adequate %) follow up, or description provided of those lost) ✸ c) follow up rate < ___% (select an adequate %) and no description of those lost d) no statement
Quality scores		

Risk of Bias assessment (For case control studies)

Domain	Item	Score
Selection	1) Is the case definition adequate	a) yes, with independent validation✸ b) yes, eg record linkage or based on self reports c) no description
	2) Representativeness of the cases	a) consecutive or obviously representative series of cases✸ b) potential for selection biases or not stated
	3) Selection of Controls	a) community controls ✸ b) hospital controls c) no description
	4) Definition of Controls	a) no history of disease (endpoint) ✸ b) no description of source
Comparability	1) Comparability of cases and controls on the basis of the design or analysis	a) study controls for ____ (Select the most important factor.)✸ b) study controls for any additional factor ✸ (This criteria could be modified to indicate specific control for a second important factor.)
Exposure	1) Ascertainment of exposure	a) secure record (eg surgical records) ✸ b) structured interview where blind to case/control status ✸ c) interview not blinded to case/control status d) written self report or medical record only e) no description
	2) Same method of ascertainment for cases and controls	a) yes ✸ b) no
	3) Non-Response rate	a) same rate for both groups ✸ b) non respondents described c) rate different and no designation
Quality scores		

Other information

	Description as stated in report/paper
Key conclusions	
Study funding sources	
Conflicts of interest	
References to other relevant studies	
Correspondence required for further study information	

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

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		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	2
Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	n/a under review
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	16

Amendments			
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	2
Support			
Sources	#5a	Indicate sources of financial or other support for the review	1
Sponsor	#5b	Provide name for the review funder and / or sponsor	1
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	1
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is already known	5-6
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	7
Methods			
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	11-12
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	10-11
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	10-11
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	11
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review	11-12

		(that is, screening, eligibility and inclusion in meta-analysis)	
Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	11-12
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	11-12
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	8-9
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	12-13
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	13-14
Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	13-14
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	12
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	14
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	13
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	14

BMJ Open

Hypertensive Disorders of Pregnancy and Risk of Asthma in Offspring: Protocol for A Systematic Review and Meta-Analysis

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Hypertensive Disorders of Pregnancy and Risk of Asthma in Offspring: Protocol for A Systematic Review and Meta-Analysis

Ping Li, MD,[1,2] Tao Xiong*, MD PhD [1,2,3] Yong Hu, MD [1,2]

[1] Department of Pediatrics, West China Second University Hospital, Sichuan University, Chengdu, China

[2] Key Laboratory of Birth Defects and Related Diseases of Women and Children (Sichuan University), Ministry of Education

[3] Deep Underground Space Medical Center, West China Hospital, Sichuan University, Chengdu, China

Ping Li: liping_371986@163.com

Yong Hu: huyong1003@163.com

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***Correspondence**

Dr. Tao Xiong

No. 20, Section Three, South Renmin Road, Chengdu, China

Tel: 86 13730652940

Email: tao_xiong@126.com

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Abstract

Introduction: Hypertensive disorders of pregnancy (HDP), one of the most common obstetrical complications, has been reported to have a controversial relationship with the increased risk of asthma in offspring. No systematic review of this topic has been performed. The aim of this systematic review will be to summarize the available evidence examining the association between HDP and the risk of asthma in offspring.

Methods and analysis: We will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines. A systematic search of the PubMed, EMBASE, Cochrane and Web of Science databases will be performed using a detailed search strategy from database inception through Dec. 31, 2019. Cohort, case-control and cross-sectional studies that report a diagnosis of maternal HDP and asthma in offspring will be included. Studies will be limited to the English language and include only human participants. Two independent reviewers will conduct the study selection, data extraction, and risk of bias assessments using a standardized data extraction form. A meta-analysis will be performed to calculate overall pooled estimates using the generic inverse variance method. The data will be synthesized by either fixed-effect or random effects models according to heterogeneity tests. All analyses will be performed in STATA 14 and RevMan 5.3. High-quality evidence of the relationship between HDP and the risk of asthma in exposed offspring will be identified through the synthesis of current studies. In addition, the results of subgroup analyses and related secondary

outcomes will be reported. The following will be concluded: (i) whether HDP increases the risk of asthma in offspring; (ii) whether HDP affects the severity of asthma in exposed offspring; and (iii) whether possible differences in the risk of asthma among different HDP subgroups exist.

Keywords: Asthma, Hypertension, Perinatology, Pediatrics, Community child health

Ethics and dissemination

There is no requirement for ethics approval because the meta-analysis and systematic review will be based on published data. It is anticipated that the dissemination of results will take place at conferences and through publication in a peer-reviewed journal.

Strengths and limitations of this study

- This will be the first meta-analysis to explore the relationship between HDP and the risk of asthma in exposed offspring.
- This protocol was designed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines.

- Since there may be some potential confounding factors, we will perform detailed subgroup analyses to reduce the effects of confounding factors.
- Since positive results are more prone to be published online, funnel plots will be used to assess publication bias.
- Selection bias will be considered because the pooled data will be obtained from observational studies.

INTRODUCTION

Hypertensive disorders of pregnancy (HDP) is estimated to affect 5% to 15% of all pregnancies and is recognized as one of the most common obstetrical complications [1] [2]. HDP includes any hypertensive condition before gestation or manifested before 20 weeks and hypertension starting at or after 20 weeks; types of hypertension include gestational hypertension (GH), preeclampsia (PE), chronic hypertension, and PE superimposed on chronic hypertension according to the International Society for the Study of Hypertension in Pregnancy [3]. Recent studies have reported that HDP is closely associated with an increased risk of diseases in offspring, including asthma, allergy, eczema [4], high blood pressure [5], congenital heart defects [6], obesity [7], autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD), low cognitive function, anxiety/depression, and other neurodevelopmental disorders [8] [9]. The "Developmental Origins of Health and Disease (DOHaD)" hypothesis, which has been widely confirmed, suggests that fetuses exposed to adverse uterine environments are prone to develop chronic noncommunicable diseases later in life owing to perpetual alterations in the fetal vasculature, cardiac structure, pancreas, adipose tissue and brain structure [10] [11]. In addition, HDP induces a detrimental in utero environment, with systemic inflammation and oxidative stress experienced by the fetus, thus impairing vulnerable fetal lung development and disturbing immune function, which may persist throughout life in the offspring.

Asthma, a common lung disease associated with abnormal inflammation and immune response, is characterized by variable symptoms of wheezing, shortness of breath, chest tightness and/or cough, and variable expiratory airflow limitation. It is a chronic disease of childhood and is responsible for the majority school absences, emergency department visits and hospitalizations. Thus, asthma has been regarded as a major public health challenge worldwide, affecting 1-18% of populations in different countries [12 13]. The development of asthma has generally been attributed to the interactions between genetics and environmental factors [14 15]. Currently, it is widely accepted that asthma develops early in life [16]. Recurrent wheezing and other asthma-like symptoms usually begin within the first few weeks or months after birth. There is increasing evidence to suggest that negative events occurring early in life, even in the perinatal period, significantly increase the risk of asthma and poor lung function later in life [17 18]. Hence, adverse obstetrical events, such as HDP, may have strong effects on fetal airway structure and lung and immune system development during the prenatal period and may significantly increase the susceptibility of offspring to asthma [19 20].

Approximately half of individuals with asthma are reported to have suffered from asthma-like symptoms during childhood [21]. Therefore, early recognition and intervention are critical to reduce short- and long-term morbidity and to prevent potential long-term sequelae resulting in impaired lung function. Recent studies have shown that HDP is a potential risk factor for childhood asthma in offspring [4 22]. However, the association between HDP and asthma is controversial [23]. Identifying the

relationship between HDP and asthma could help us to understand the pathogenesis of asthma. It also facilitates early asthma recognition and intervention in high-risk populations. Therefore, we aim to perform a systematic review and meta-analysis to summarize the available evidence regarding the relationship between HDP and asthma in offspring.

OBJECTIVES

The aim of the present systematic review and meta-analysis is to summarize the available evidence to explore the following:

1. Whether HDP increases the risk of asthma in offspring;

2. Whether HDP affects the severity of asthma in exposed offspring; and

3. Whether differences in the risk of asthma among different HDP subgroups exist.

The study will be conducted based on the following requirements.

Population

Pregnant women and their offspring at any age (both child offspring and adult offspring) will be included.

Intervention/exposures

HDP, defined as any hypertension (systolic blood pressure (BP) ≥140 and/or diastolic BP ≥90 mmHg) during pregnancy, mainly includes the following:

(1) GH: any hypertensive disorder that develops at or after 20 weeks of gestation in the absence of features of preeclampsia (PE);

(2) PE: GH accompanied by one or more of the following new-onset conditions at or after 20 weeks of gestation: (i) proteinuria, (ii) maternal organ dysfunction, such as acute kidney injury, liver complications, neurological complications, or hematological complications, and (iii) uteroplacental dysfunction;

(3) Chronic hypertension (essential and secondary): high blood pressure predating pregnancy or recognized at < 20 weeks of gestation; and

(4) PE superimposed on chronic hypertension: chronic essential hypertension accompanied by any of the above maternal organ dysfunctions consistent with PE.

The definitions were developed according to current guidelines, such as the Canadian Hypertensive Disorders of Pregnancy Working Group [24], Society of Obstetric Medicine of Australia and New Zealand [25], American College of Obstetricians and Gynecologists [3], and International Society for the Study of Hypertension in Pregnancy guidelines [26].

Comparison

Normotensive pregnant women will be used as the control group.

Outcomes

1. Primary outcome: asthma.

Asthma is defined by a history of respiratory symptoms, including wheezing, shortness of breath, chest tightness and cough, that vary over time and in intensity in addition to variable expiratory airflow limitation according to the Global Initiative for Asthma (GINA) [12] and International Collaboration in Asthma, Allergy and Immunology (iCAALL)[27].

2. Secondary outcomes:

(1) Wheezing/recurrent wheezing;

(2) Lung/pulmonary function (including forced expiratory volume in one second [FEV_1], forced expiratory volume at 0.5 seconds [$FEV_{0.5}$], forced vital capacity [FVC], FEV_1/FVC, 50% of the forced expiratory flow [FEF_{50}] and 75% of the forced expiratory flow [FEF_{75}], maximal midexpiratory flow [FEF_{25-75}]), active asthma, asthma exacerbations and asthma treatment (including hospitalization, systemic corticosteroid use, inhaled β_2-agonist use, inhaled corticosteroid [ICS] use, combination of inhaled β_2-agonists and corticosteroid use, leukotriene antagonist use, and other antiasthma medication use); and

3. Serum IgE levels.

METHODS

The systematic review and meta-analysis will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [28] and Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines [29].

Criteria for considering studies for review

Inclusion criteria

(1) Studies with cohort, case-control and cross-sectional designs that report a diagnosis of HDP and asthma in offspring as the outcome of interest;

(2) Studies that estimate the relationship between HDP and asthma and report the estimated risks (odds ratios [ORs] or relative risks [RRs]) with 95% confidence intervals (CIs) or provide sufficient information to calculate these values;

(3) Studies published in only the English language;

(4) Studies published in any year; and

(5) Studies that include only humans.

Exclusion criteria

(1) Conference abstracts, letters to the editor, reviews and commentary articles;

(2) Studies with overlapping data; or

(3) Studies missing raw data.

Search strategy

A systematic search of the literature will be conducted in the PubMed, EMBASE, Cochrane and Web of Science databases from database inception through Dec. 31, 2019. We will search databases such as Google Scholar for gray literature. A three-phase search strategy will be applied in this review.

1. For HDP, the following combination of search terms will be used: “hypertensive disorders during pregnancy” or “hypertensive disorders in pregnancy” or “hypertensive disorders of pregnancy” or “pregnancy-induced hypertension” or “eclampsia” or “preeclampsia” or “preeclampsia” or “preeclamptic pregnancy” or “chronic hypertension” or ”gestational hypertension” or “chronic hypertension with superimposed preeclampsia” or “postpartum hypertension” or “maternal hypertensive disorders”.

2. For asthma, the following search terms will be used: “asthma” or “wheeze” or “wheezing” or “shortness of breath” or “bronchial spasm” or “bronchospasm” or “bronchoconstriction” or “bronchoconstrict” or “bronchial hyperreactivity” or “bronchial hyperresponsiveness” or “reactive airway disease” or “obstructive lung

disease" or "air low limitation" or "chronic obstructive respiratory disorder" or "chronic obstructive pulmonary disease".

3. We will combine steps 1 and 2 with "and".

The detailed search strategy is listed in Supplement table 1. We will manually search the reference lists of the included studies to further identify eligible studies.

Study selection and data extraction

The eligibility of each study will be assessed independently by two investigators (PL and TX), and disagreements will be solved by discussion (with a third author, YH, when necessary). Data from the identified studies will be extracted using the standardized data extraction form listed in Supplement table 2. The titles and abstracts of the studies retrieved from each database will be stored and managed in the EndNote reference manager. For each included study, we will extract the following information: first author's last name, year of publication, study location, study design, sample size, ascertainment of exposure (HDP and its subgroups), outcome diagnostic criteria, offspring age at diagnosis, adjusted/matched confounding variables and effects estimates (RRs or ORs) with 95% CIs. The eligibility of each study will be assessed independently by two investigators (PL and TX), and disagreements will be solved by discussion (with a third author, YH, when necessary).

Subgroups/subsets

Subgroup analyses will be carried out according to the following: (1) study design (cohort vs. case-control vs. cross-sectional), (2) sample size, (3) location (e.g., Europe vs. United States), (4) income level of the country (low/middle/high), (5) year of publication, (6) study subject selection, (7) study quality (minimal/low vs. moderate/high), (8) adjusted offspring factors (e.g., age at diagnosis of asthma, sex, birth weight, gestational age), and (9) adjusted maternal factors (e.g., maternal asthma, maternal body mass index, gestational weight gain, maternal smoking). Sensitivity analyses will be performed by excluding each study one by one and calculating a pooled estimate for the remainder of the studies.

If any other subgroup/sensitivity analyses are identified during the process of the meta-analysis, these will be clearly labeled as post hoc analyses.

Risk of bias (quality) assessment

The quality of cohort and case-control studies will be assessed using the Newcastle-Ottawa Scale (NOS) [30], which evaluates the selection of study groups (1 star for each term), comparability (up to 2 stars), and exposure or outcome (1 star for each term) (Supplemental table 3). A high score indicates a low risk of bias. Additionally, cross-

sectional studies will be assessed using the Agency for Healthcare Research and Quality (AHRQ)-recommended eleven items scale (Supplemental table 4) [31]. Furthermore, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology will be used to evaluate the overall likelihood of quality by examining 6 types of bias in each study (selection, exposure, outcome, analytic, attrition, and confounding) (Supplemental table 5) [32]. The GRADE classifies the quality of studies as low, moderate, and high. The quality assessment of each study will be independently carried out by two authors, and any disagreements will be resolved through discussion (with a third author when necessary). We will use funnel plots to assess publication bias, and Egger's linear regression will be applied to test for funnel plot asymmetry.

Strategy for data synthesis

The overall pooled estimates for the association between HDP and asthma will be calculated in the meta-analysis. We will use the generic inverse variance method to determine both the crude and adjusted results. A summary OR estimate with a 95% CI will be calculated by using fixed-effect and random effects models. The *I*-squared statistic will be applied to examine heterogeneity. According to the Cochrane Handbook criteria, if the *I*-squared value is less than 50%, heterogeneity is low, and a fixed-effect model will be used in the analysis. Otherwise, the heterogeneity will be considered high if the *I*-squared value is 50% or more, and a random effects model will

be used. Forest plots will be constructed to show the study-specific RR/OR estimates and pooled RR/OR estimates. If a study is eligible for inclusion in the systematic review but does not provide adequate data for inclusion in the meta-analysis, a narrative synthesis will be conducted to summarize and tabulate the results. All analyses will be performed in STATA 14 and RevMan 5.3.

Presenting and reporting the results

The study selection procedure will be outlined by a flow diagram according to the PRISMA statement in the meta-analysis (Supplemental figure 1). In addition, the reason for excluding studies will be presented. The characteristics of each included study, including the population, age range of participants, sample size, year range of studies, study design, country, exposure, outcome, measure of effect, unadjusted or adjusted effects (95% CI), and adjustment for covariates, will be tabulated in detail. The heterogeneity of the results will be listed in another table. Additionally, we will use forest plots to present the pooled estimates in the meta-analysis. Eligible studies for which we could not obtain raw data by contacting the corresponding authors will be listed individually in a separate table.

Patient and public involvement

This systematic review and meta-analysis will be based on published studies; therefore, primary patient data will not be collected. Patients and the public will not be involved in the study design, recruitment and data analysis.

Summary

In this systematic review and meta-analysis, we will assess the association between HDP and asthma in offspring by summarizing the existing literature based on a predesigned protocol. Our results might help reveal the potential etiology of asthma involving fetal lung and immune system development during the prenatal period. Thus, the supporting evidence may promote strengthened surveillance of HDP-exposed infants, leading to early identification and intervention and improved lung function and asthma outcomes.

Ethics and dissemination

There is no requirement for ethics approval because the meta-analysis and systematic review will be based on published data. It is anticipated that the dissemination of results will take place at conferences and through publication in a peer-reviewed journal.

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Author contributions

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

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Competing interests

None declared.

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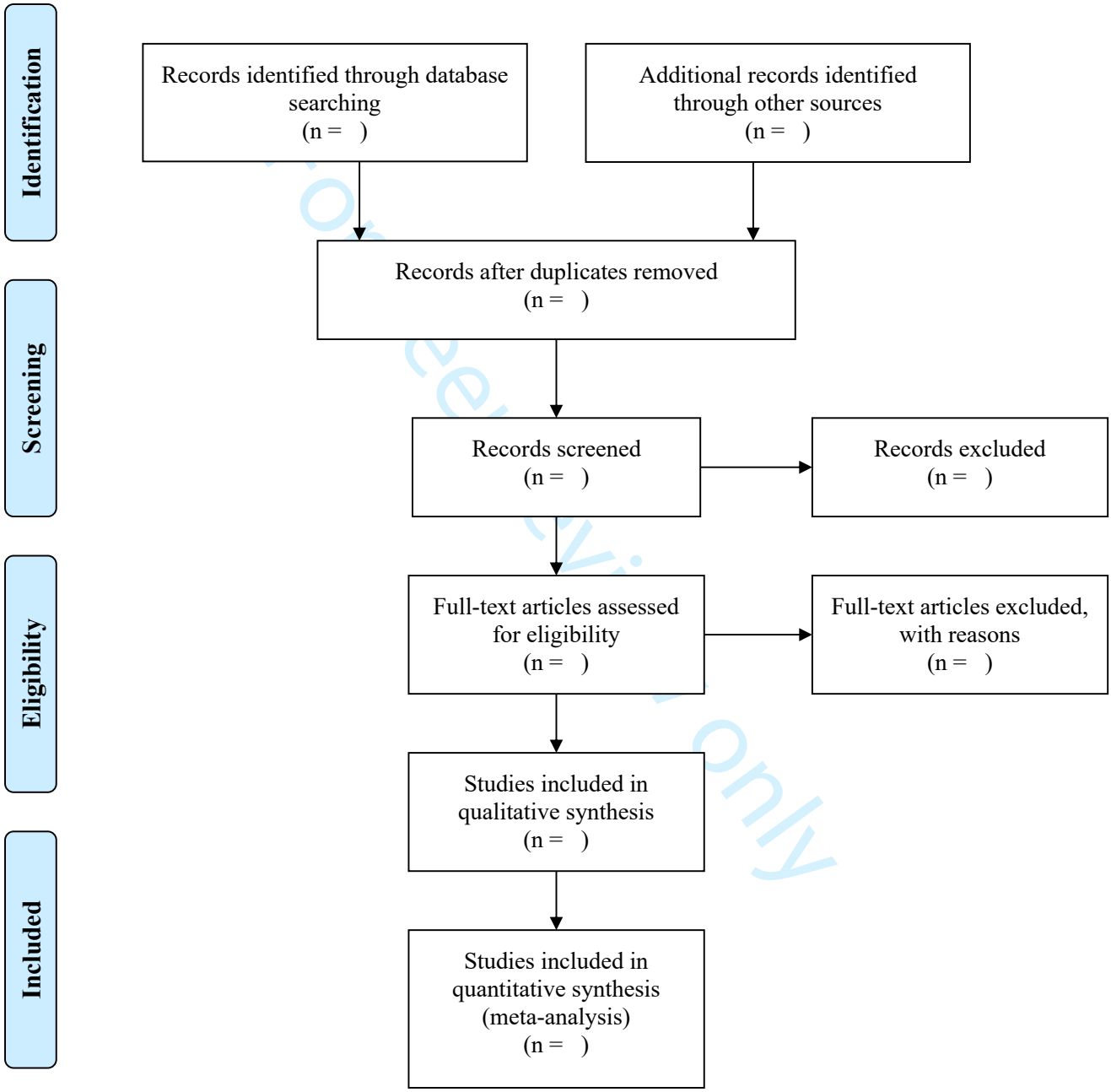
Supplemental figure 1. Flow Diagram of Studies Selected for Inclusion in the Systematic Review (PRISMA 2009 Flow Diagram)



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

Supplemental table 1. Search strategy (for each electronic database to be searched)

#1	Search terms	No of records returned
1	hypertensive disorders during pregnancy	
2	hypertensive disorders in pregnancy	
3	hypertensive disorders of pregnancy	
4	pregnancy-induced hypertension	
5	eclampsia	
6	pre-eclampsia	
7	preeclampsia	
8	preeclamptic pregnancy	
9	chronic hypertension	
10	gestational hypertension	
11	chronic hypertension with superimposed preeclampsia	
12	postpartum hypertension	
13	gravid hypertension	
14	maternal hypertensive disorders	
15	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14)	
16	asthma	
17	wheeze	
18	wheezing	
19	shortness of breath	
20	bronchial spasm	
21	bronchospasm	
22	bronchoconstriction	
23	bronchoconstrict	
24	bronchial hyperreactivity	
25	bronchial hyperresponsiveness	

26	reactive airway disease	
27	obstructive lung disease	
28	air low limitation	
29	chronic obstructive respiratory disorder	
30	chronic obstructive pulmonary disease	
31	(#16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30)	
32	(#15 AND #31)	
33	limit #32 to English language	
34	limit #33 to humans	

Supplemental table 2. Data Extraction Form for Review and meta-analysis

Study Details	
General information	
• First author	
• Year of publication	
• Study location	
• Study duration	
Study eligibility	
• Study design (case-control, cohort)	
• Participants	
exposed group	
unexposed group	
• Inclusion criteria	
• Exclusion criteria	
• Ascertainment of exposure	
• Outcome diagnostic criteria	
• Confounding variables	
• Matching factors	
Include or exclude	Include ☐ exclude ☐
Reason for exclusion	
Characteristics of included studies	
• Sample size	
exposed group (including subgroups)	
unexposed group	
• Data source	
• Race	
• Income level of country	
• Maternal adjusted factors	
Maternal age, yrs	

Educational level	
Maternal asthma	
Maternal body mass index, kg/m^2	
Gestational weight gain, kg	
Parity	
Maternal smoking	
Others	
• Children`s adjusted factors	
Gender (M/F)	
Birth weight, kg	
Gestational age, w	
Offspring age at diagnosis, yrs	
Others	
Main outcome	
Effect estimates (RR or OR) with 95% CI	
Mean difference	
Other findings	

Other information

	Description as stated in report/paper
Key conclusions	
Study funding sources	
Conflicts of interest	
References to other relevant studies	
Correspondence required for further study information	

Supplemental table 3. Newcastle-Ottawa scale (NOS)

Supplemental table 3.1 Newcastle-Ottawa Scale (NOS) – for cohort study

Study	Item & score							
	Representiveness of the exposed cohort（1）	Selection of the non-exposed cohort（1）	Ascertainment of exposure（1）	Demonstration that outcome of interest was not present at start of study（1）	Compare ability of cohorts on the basis of the design or analysis（2）	Assessment of outcome（1）	Was follow up long enough for outcomes to occur（1）	Adequacy of follow up of cohorts（1）

Supplemental table 3.2 Newcastle-Ottawa Scale (NOS) – for case-control study

Study	Item & score							
	Is the case definition adequate?（1）	Representativeness of the cases（1）	Selection of Controls（1）	Definition of Controls（1）	Comparability of cases and controls on the basis of the design or analysis（2）	Ascertainment of exposure（1）	Same method of ascertainment for cases and controls（1）	Non-Response rate（1）

Supplemental 3.3 NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE COHORT STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

1) Representativeness of the exposed cohort
   a) truly representative of the average _____ (describe) in the community ✸
   b) somewhat representative of the average _____ in the community ✸
   c) selected group of users eg nurses, volunteers
   d) no description of the derivation of the cohort

2) Selection of the non exposed cohort
   a) drawn from the same community as the exposed cohort ✸
   b) drawn from a different source
   c) no description of the derivation of the non exposed cohort

3) Ascertainment of exposure
   a) secure record (eg surgical records) ✸
   b) structured interview ✸
   c) written self report
   d) no description

4) Demonstration that outcome of interest was not present at start of study
   a) yes ✸
   b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis
   a) study controls for _____ (select the most important factor) ✸
   b) study controls for any additional factor ✸ (This criteria could be modified to indicate specific control for a second important factor.)

Outcome

1) Assessment of outcome
   a) independent blind assessment ✸
   b) record linkage ✸
   c) self report
   d) no description

2) Was follow-up long enough for outcomes to occur
   a) yes (select an adequate follow up period for outcome of interest) ✸
   b) no

3) Adequacy of follow up of cohorts
   a) complete follow up - all subjects accounted for ✸
   b) subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow up, or description provided of those lost) ✸
   c) follow up rate < ____% (select an adequate %) and no description of those lost
   d) no statement

Supplemental 3.4 NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE CASE CONTROL STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

Selection

1) Is the case definition adequate?
   a) yes, with independent validation ✸
   b) yes, eg record linkage or based on self reports
   c) no description

2) Representativeness of the cases
   a) consecutive or obviously representative series of cases ✸
   b) potential for selection biases or not stated

3) Selection of Controls
   a) community controls ✸
   b) hospital controls
   c) no description

4) Definition of Controls
   a) no history of disease (endpoint) ✸
   b) no description of source

Comparability

1) Comparability of cases and controls on the basis of the design or analysis
   a) study controls for _____ (Select the most important factor.) ✸
   b) study controls for any additional factor ✸ (This criteria could be modified to indicate specific control for a second important factor.)

Exposure

1) Ascertainment of exposure
   a) secure record (eg surgical records) ✸
   b) structured interview where blind to case/control status ✸
   c) interview not blinded to case/control status
   d) written self report or medical record only
   e) no description

2) Same method of ascertainment for cases and controls
   a) yes ✸
   b) no

3) Non-Response rate
   a) same rate for both groups ✸
   b) non respondents described
   c) rate different and no designation

Supplemental table 4. Agency for Healthcare Research and Quality (AHQR) scale for cross-sectional study

Item	Yes	No	Unclear
1) Define the source of information (survey, record review)			
2) List inclusion and exclusion criteria for exposed and unexposed subjects (cases and controls) or refer to previous publications			
3) Indicate time period used for identifying patients			
4) Indicate whether or not subjects were consecutive if not population-based			
5) Indicate if evaluators of subjective components of study were masked to other aspects of the status of the participants			
6) Describe any assessments undertaken for quality assurance purposes (e.g., test/retest of primary outcome measurements)			
7) Explain any patient exclusions from analysis			
8) Describe how confounding was assessed and/or controlled			
9) If applicable, explain how missing data were handled in the analysis			
10) Summarize patient response rates and completeness of data collection			
11) Clarify what follow-up, if any, was expected and the percentage of patients for which incomplete data or follow-up was obtained			

Supplemental table 5. GRADE assessment

Supplemental table 5.1 The Summary of Findings Tables

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Overall results

Supplemental table 5.2 GRADE Evidence Profile

Quality assessment							No. of patients		Effect	Quality
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HDP	Controls	Relative (95% CI)	
Outcome 1										
Outcome 2										
Outcome 3										

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	2
Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	n/a under review
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	16

Amendments			
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	2
Support			
Sources	#5a	Indicate sources of financial or other support for the review	1
Sponsor	#5b	Provide name for the review funder and / or sponsor	1
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	1
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is already known	5-6
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	7
Methods			
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	11-12
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	10-11
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	10-11
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	11
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review	11-12

		(that is, screening, eligibility and inclusion in meta-analysis)	
Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	11-12
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	11-12
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	8-9
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	12-13
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	13-14
Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	13-14
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	12
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	14
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	13
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	14

BMJ Open

Hypertensive Disorders of Pregnancy and Risk of Asthma in Offspring: Protocol for A Systematic Review and Meta-Analysis

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Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	Research methods, Obstetrics and gynaecology, Paediatrics
Keywords:	Asthma < THORACIC MEDICINE, Hypertension < CARDIOLOGY, PERINATOLOGY, PAEDIATRICS, Community child health < PAEDIATRICS

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Hypertensive Disorders of Pregnancy and Risk of Asthma in Offspring: Protocol for A Systematic Review and Meta-Analysis

Ping Li, MD,[1,2] Tao Xiong*, MD PhD [1,2,3] Yong Hu, MD [1,2]

[1] Department of Pediatrics, West China Second University Hospital, Sichuan University, Chengdu, China

[2] Key Laboratory of Birth Defects and Related Diseases of Women and Children (Sichuan University), Ministry of Education

[3] Deep Underground Space Medical Center, West China Hospital, Sichuan University, Chengdu, China

Ping Li: liping_371986@163.com

Yong Hu: huyong1003@163.com

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***Correspondence**

Dr. Tao Xiong

No. 20, Section Three, South Renmin Road, Chengdu, China

Tel: 86 13730652940

Email: tao_xiong@126.com

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ABSTRACT

Introduction: Hypertensive disorders of pregnancy (HDP), one of the most common obstetrical complications, has been reported to have a controversial relationship with the increased risk of asthma in offspring. No systematic review of this topic has been performed. The aim of this systematic review will be to summarize the available evidence examining the association between HDP and the risk of asthma in offspring.

Methods and analysis: We will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines. A systematic search of the PubMed, EMBASE, Cochrane and Web of Science databases will be performed using a detailed search strategy from database inception through Dec. 31, 2019. Cohort, case-control and cross-sectional studies that report a diagnosis of maternal HDP and asthma in offspring will be included. Studies will be limited to the English language and include only human participants. Two independent reviewers will conduct the study selection, data extraction, and risk of bias assessments using a standardized data extraction form. A meta-analysis will be performed to calculate overall pooled estimates using the generic inverse variance method. The data will be synthesized by either fixed-effect or random effects models according to heterogeneity tests. All analyses will be performed in STATA 14 and RevMan 5.3. High-quality evidence of the relationship between HDP and the risk of asthma in exposed offspring will be identified through the synthesis of current studies. In addition, the results of subgroup analyses and related secondary outcomes will be reported. The following will be concluded: (i) whether HDP increases

the risk of asthma in offspring; (ii) whether HDP affects the severity of asthma in exposed offspring; and (iii) whether possible differences in the risk of asthma among different HDP subgroups exist.

Keywords: Asthma, Hypertension, Perinatology, Pediatrics, Community child health

Ethics and dissemination

There is no requirement for ethics approval because the meta-analysis and systematic review will be based on published data. It is anticipated that the dissemination of results will take place at conferences and through publication in a peer-reviewed journal.

Strengths and limitations of this study

- This will be the first meta-analysis to explore the relationship between HDP and the risk of asthma in exposed offspring.
- This protocol was designed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines.
- Since there may be some potential confounding factors, we will perform detailed subgroup analyses to reduce the effects of confounding factors.

- Since positive results are more prone to be published online, funnel plots will be used to assess publication bias.
- Selection bias will be considered because the pooled data will be obtained from observational studies.

INTRODUCTION

Hypertensive disorders of pregnancy (HDP) is estimated to affect 5% to 15% of all pregnancies and is recognized as one of the most common obstetrical complications [1] [2]. HDP includes any hypertensive condition before gestation or manifested before 20 weeks and hypertension starting at or after 20 weeks; types of hypertension include gestational hypertension (GH), preeclampsia (PE), chronic hypertension, and PE superimposed on chronic hypertension according to the International Society for the Study of Hypertension in Pregnancy [3]. Recent studies have reported that HDP is closely associated with an increased risk of diseases in offspring, including asthma, allergy, eczema [4], high blood pressure [5], congenital heart defects [6], obesity [7], autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD), low cognitive function, anxiety/depression, and other neurodevelopmental disorders [8] [9]. The "Developmental Origins of Health and Disease (DOHaD)" hypothesis, which has been widely confirmed, suggests that fetuses exposed to adverse uterine environments are prone to develop chronic noncommunicable diseases later in life owing to perpetual alterations in the fetal vasculature, cardiac structure, pancreas, adipose tissue and brain structure [10] [11]. In addition, HDP induces a detrimental in utero environment, with systemic inflammation and oxidative stress experienced by the fetus, thus impairing vulnerable fetal lung development and disturbing immune function, which may persist throughout life in the offspring.

Asthma, a common lung disease associated with abnormal inflammation and immune response, is characterized by variable symptoms of wheezing, shortness of

breath, chest tightness and/or cough, and variable expiratory airflow limitation. It is a chronic disease of childhood and is responsible for the majority school absences, emergency department visits and hospitalizations. Thus, asthma has been regarded as a major public health challenge worldwide, affecting 1-18% of populations in different countries [12 13]. The development of asthma has generally been attributed to the interactions between genetics and environmental factors [14 15]. Currently, it is widely accepted that asthma develops early in life [16]. Recurrent wheezing and other asthma-like symptoms usually begin within the first few weeks or months after birth. There is increasing evidence to suggest that negative events occurring early in life, even in the perinatal period, significantly increase the risk of asthma and poor lung function later in life [17 18]. Hence, adverse obstetrical events, such as HDP, may have strong effects on fetal airway structure and lung and immune system development during the prenatal period and may significantly increase the susceptibility of offspring to asthma [19 20].

Approximately half of individuals with asthma are reported to have suffered from asthma-like symptoms during childhood [21]. Therefore, early recognition and intervention are critical to reduce short- and long-term morbidity and to prevent potential long-term sequelae resulting in impaired lung function. Recent studies have shown that HDP is a potential risk factor for childhood asthma in offspring [4 22]. However, the association between HDP and asthma is controversial [23]. Identifying the relationship between HDP and asthma could help us to understand the pathogenesis of asthma. It also facilitates early asthma recognition and intervention in high-risk populations. Therefore, we aim to perform a systematic review and meta-analysis to

summarize the available evidence regarding the relationship between HDP and asthma in offspring.

OBJECTIVES

The aim of the present systematic review and meta-analysis is to summarize the available evidence to explore the following:

1. Whether HDP increases the risk of asthma in offspring;

2. Whether HDP affects the severity of asthma in exposed offspring; and

3. Whether differences in the risk of asthma among different HDP subgroups exist.

The study will be conducted based on the following requirements.

Population

Pregnant women and their offspring at any age (both child offspring and adult offspring) will be included.

Intervention/exposures

HDP, defined as any hypertension (systolic blood pressure (BP) ≥140 and/or diastolic BP ≥90 mmHg) during pregnancy, mainly includes the following:

(1) GH: any hypertensive disorder that develops at or after 20 weeks of gestation in the absence of features of preeclampsia (PE);

(2) PE: GH accompanied by one or more of the following new-onset conditions at or after 20 weeks of gestation: (i) proteinuria, (ii) maternal organ dysfunction, such as

acute kidney injury, liver complications, neurological complications, or hematological complications, and (iii) uteroplacental dysfunction;

(3) Chronic hypertension (essential and secondary): high blood pressure predating pregnancy or recognized at < 20 weeks of gestation; and

(4) PE superimposed on chronic hypertension: chronic essential hypertension accompanied by any of the above maternal organ dysfunctions consistent with PE.

The definitions were developed according to current guidelines, such as the Canadian Hypertensive Disorders of Pregnancy Working Group [24], Society of Obstetric Medicine of Australia and New Zealand [25], American College of Obstetricians and Gynecologists [3], and International Society for the Study of Hypertension in Pregnancy guidelines [26].

Comparison

Normotensive pregnant women will be used as the control group.

Outcomes

1. Primary outcome: asthma.

Asthma is defined by a history of respiratory symptoms, including wheezing, shortness of breath, chest tightness and cough, that vary over time and in intensity in addition to variable expiratory airflow limitation according to the Global Initiative for Asthma (GINA) [12] and International Collaboration in Asthma, Allergy and Immunology (iCAALL)[27].

2. Secondary outcomes:

(1) Wheezing/recurrent wheezing;

(2) Lung/pulmonary function (including forced expiratory volume in one second [FEV_1], forced expiratory volume at 0.5 seconds [$FEV_{0.5}$], forced vital capacity [FVC], FEV_1/FVC, 50% of the forced expiratory flow [FEF_{50}] and 75% of the forced expiratory flow [FEF_{75}], maximal midexpiratory flow [FEF_{25-75}]), active asthma, asthma exacerbations and asthma treatment (including hospitalization, systemic corticosteroid use, inhaled β_2-agonist use, inhaled corticosteroid [ICS] use, combination of inhaled β_2-agonists and corticosteroid use, leukotriene antagonist use, and other antiasthma medication use); and

3. Serum IgE levels.

METHOD

The systematic review and meta-analysis will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [28] and Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines [29].

Criteria for considering studies for review

Inclusion criteria

(1) Studies with cohort, case-control and cross-sectional designs that report a diagnosis of HDP and asthma in offspring as the outcome of interest;

(2) Studies that estimate the relationship between HDP and asthma and report the estimated risks (odds ratios [ORs] or relative risks [RRs]) with 95% confidence intervals (CIs) or provide sufficient information to calculate these values;

(3) Studies published in only the English language;

(4) Studies published in any year; and

(5) Studies that include only humans.

Exclusion criteria

(1) Conference abstracts, letters to the editor, reviews and commentary articles;

(2) Studies with overlapping data; or

(3) Studies missing raw data.

Search strategy

A systematic search of the literature will be conducted in the PubMed, EMBASE, Cochrane and Web of Science databases from database inception through Dec. 31, 2019. We will search databases such as Google Scholar for gray literature. A three-phase search strategy will be applied in this review.

1. For HDP, the following combination of search terms will be used: “hypertensive disorders during pregnancy” or “hypertensive disorders in pregnancy” or “hypertensive disorders of pregnancy” or “pregnancy-induced hypertension” or “eclampsia” or “preeclampsia” or “preeclampsia” or “preeclamptic pregnancy” or “chronic hypertension” or ”gestational hypertension” or “chronic hypertension with superimposed preeclampsia” or “postpartum hypertension” or “maternal hypertensive disorders”.

2. For asthma, the following search terms will be used: “asthma” or “wheeze” or “wheezing” or “shortness of breath” or “bronchial spasm” or “bronchospasm” or “bronchoconstriction” or “bronchoconstrict” or “bronchial hyperreactivity” or “bronchial hyperresponsiveness” or “reactive airway disease” or “obstructive lung disease” or “air low limitation” or “chronic obstructive respiratory disorder” or “chronic obstructive pulmonary disease”.

3. We will combine steps 1 and 2 with “and”.

The detailed search strategy is listed in Supplement table 1. We will manually search the reference lists of the included studies to further identify eligible studies.

Study selection and data extraction

The eligibility of each study will be assessed independently by two investigators (PL and TX), and disagreements will be solved by discussion (with a third author, YH, when necessary). Data from the identified studies will be extracted using the standardized data extraction form listed in Supplement table 2. The titles and abstracts of the studies retrieved from each database will be stored and managed in the EndNote reference manager. For each included study, we will extract the following information: first author’s last name, year of publication, study location, study design, sample size, ascertainment of exposure (HDP and its subgroups), outcome diagnostic criteria, offspring age at diagnosis, adjusted/matched confounding variables and effects

estimates (RRs or ORs) with 95% CIs. The eligibility of each study will be assessed independently by two investigators (PL and TX), and disagreements will be solved by discussion (with a third author, YH, when necessary).

Subgroups/subsets

Subgroup analyses will be carried out according to the following: (1) study design (cohort vs. case-control vs. cross-sectional), (2) sample size, (3) location (e.g., Europe vs. United States), (4) income level of the country (low/middle/high), (5) year of publication, (6) study subject selection, (7) study quality (minimal/low vs. moderate/high), (8) adjusted offspring factors (e.g., age at diagnosis of asthma, sex, birth weight, gestational age), and (9) adjusted maternal factors (e.g., maternal asthma, maternal body mass index, gestational weight gain, maternal smoking). Sensitivity analyses will be performed by excluding each study one by one and calculating a pooled estimate for the remainder of the studies.

If any other subgroup/sensitivity analyses are identified during the process of the meta-analysis, these will be clearly labeled as post hoc analyses.

Risk of bias (quality) assessment

The quality of cohort and case-control studies will be assessed using the Newcastle-Ottawa Scale (NOS) [30], which evaluates the selection of study groups (1 star for each term), comparability (up to 2 stars), and exposure or outcome (1 star for each term) (Supplemental table 3). A high score indicates a low risk of bias. Additionally, cross-sectional studies will be assessed using the Agency for Healthcare Research and Quality (AHRQ)-recommended eleven items scale (Supplemental table 4) [31]. Furthermore, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology will be used to evaluate the overall likelihood of quality by examining 6 types of bias in each study (selection, exposure, outcome, analytic, attrition, and confounding) (Supplemental table 5) [32]. The GRADE classifies the quality of studies as low, moderate, and high. The quality assessment of each study will be independently carried out by two authors, and any disagreements will be resolved through discussion (with a third author when necessary). We will use funnel plots to assess publication bias, and Egger's linear regression will be applied to test for funnel plot asymmetry.

Strategy for data synthesis

The overall pooled estimates for the association between HDP and asthma will be calculated in the meta-analysis. We will use the generic inverse variance method to determine both the crude and adjusted results. A summary OR estimate with a 95% CI will be calculated by using fixed-effect and random effects models. The *I*-squared statistic will be applied to examine heterogeneity. According to the Cochrane

Handbook criteria, if the *I*-squared value is less than 50%, heterogeneity is low, and a fixed-effect model will be used in the analysis. Otherwise, the heterogeneity will be considered high if the *I*-squared value is 50% or more, and a random effects model will be used. Forest plots will be constructed to show the study-specific RR/OR estimates and pooled RR/OR estimates. If a study is eligible for inclusion in the systematic review but does not provide adequate data for inclusion in the meta-analysis, a narrative synthesis will be conducted to summarize and tabulate the results. All analyses will be performed in STATA 14 and RevMan 5.3.

Presenting and reporting the results

The study selection procedure will be outlined by a flow diagram according to the PRISMA statement in the meta-analysis (Supplemental figure 1). In addition, the reason for excluding studies will be presented. The characteristics of each included study, including the population, age range of participants, sample size, year range of studies, study design, country, exposure, outcome, measure of effect, unadjusted or adjusted effects (95% CI), and adjustment for covariates, will be tabulated in detail. The heterogeneity of the results will be listed in another table. Additionally, we will use forest plots to present the pooled estimates in the meta-analysis. Eligible studies for which we could not obtain raw data by contacting the corresponding authors will be listed individually in a separate table.

Patient and public involvement

This systematic review and meta-analysis will be based on published studies; therefore, primary patient data will not be collected. Patients and the public will not be involved in the study design, recruitment and data analysis.

Summary

In this systematic review and meta-analysis, we will assess the association between HDP and asthma in offspring by summarizing the existing literature based on a predesigned protocol. Our results might help reveal the potential etiology of asthma involving fetal lung and immune system development during the prenatal period. Thus, the supporting evidence may promote strengthened surveillance of HDP-exposed infants, leading to early identification and intervention and improved lung function and asthma outcomes.

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Author contributions

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

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Competing interests

None declared.

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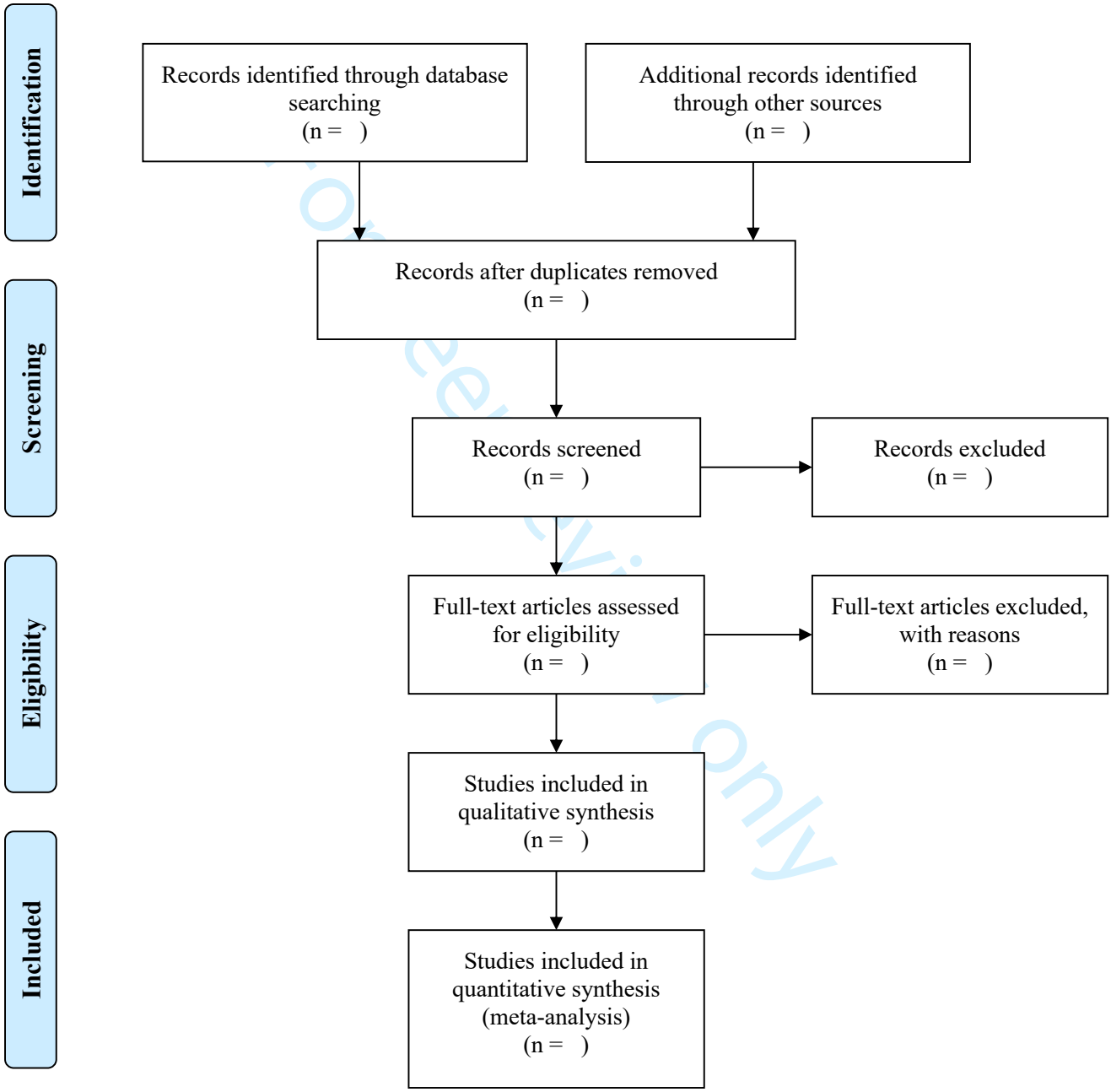
Figure legends

Supplemental figure 1. Flow Diagram of Studies Selected for Inclusion in the Systematic Review (PRISMA 2009 Flow Diagram)

Supplemental figure 1. Flow Diagram of Studies Selected for Inclusion in the Systematic Review (PRISMA 2009 Flow Diagram)



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

Supplemental table 1. Search strategy (for each electronic database to be searched)

#1	Search terms	No of records returned
1	hypertensive disorders during pregnancy	
2	hypertensive disorders in pregnancy	
3	hypertensive disorders of pregnancy	
4	pregnancy-induced hypertension	
5	eclampsia	
6	pre-eclampsia	
7	preeclampsia	
8	preeclamptic pregnancy	
9	chronic hypertension	
10	gestational hypertension	
11	chronic hypertension with superimposed preeclampsia	
12	postpartum hypertension	
13	gravid hypertension	
14	maternal hypertensive disorders	
15	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14)	
16	asthma	
17	wheeze	
18	wheezing	
19	shortness of breath	
20	bronchial spasm	
21	bronchospasm	
22	bronchoconstriction	
23	bronchoconstrict	
24	bronchial hyperreactivity	
25	bronchial hyperresponsiveness	

26	reactive airway disease	
27	obstructive lung disease	
28	air low limitation	
29	chronic obstructive respiratory disorder	
30	chronic obstructive pulmonary disease	
31	(#16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30)	
32	(#15 AND #31)	
33	limit #32 to English language	
34	limit #33 to humans	

Supplemental table 2. Data Extraction Form for Review and meta-analysis

Study Details	
General information	
• First author	
• Year of publication	
• Study location	
• Study duration	
Study eligibility	
• Study design (case-control, cohort)	
• Participants	
exposed group	
unexposed group	
• Inclusion criteria	
• Exclusion criteria	
• Ascertainment of exposure	
• Outcome diagnostic criteria	
• Confounding variables	
• Matching factors	
Include or exclude	Include ☐ exclude ☐
Reason for exclusion	
Characteristics of included studies	
• Sample size	
exposed group (including subgroups)	
unexposed group	
• Data source	
• Race	
• Income level of country	
• Maternal adjusted factors	
Maternal age, yrs	

Educational level	
Maternal asthma	
Maternal body mass index, kg/m^2	
Gestational weight gain, kg	
Parity	
Maternal smoking	
Others	
• Children`s adjusted factors	
Gender (M/F)	
Birth weight, kg	
Gestational age, w	
Offspring age at diagnosis, yrs	
Others	
Main outcome	
Effect estimates (RR or OR) with 95% CI	
Mean difference	
Other findings	

Other information

	Description as stated in report/paper
Key conclusions	
Study funding sources	
Conflicts of interest	
References to other relevant studies	
Correspondence required for further study information	

Supplemental table 3. Newcastle-Ottawa scale (NOS)

Supplemental table 3.1 Newcastle-Ottawa Scale (NOS) – for cohort study

Study	Item & score							
	Representiveness of the exposed cohort（1）	Selection of the non-exposed cohort（1）	Ascertainment of exposure（1）	Demonstration that outcome of interest was not present at start of study（1）	Compare ability of cohorts on the basis of the design or analysis（2）	Assessment of outcome（1）	Was follow up long enough for outcomes to occur（1）	Adequacy of follow up of cohorts（1）

Supplemental table 3.2 Newcastle-Ottawa Scale (NOS) – for case-control study

Study	Item & score							
	Is the case definition adequate?（1）	Representativeness of the cases（1）	Selection of Controls（1）	Definition of Controls（1）	Comparability of cases and controls on the basis of the design or analysis（2）	Ascertainment of exposure（1）	Same method of ascertainment for cases and controls（1）	Non-Response rate（1）

Supplemental 3.3 NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE COHORT STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

1) Representativeness of the exposed cohort
   a) truly representative of the average _____ (describe) in the community ✸
   b) somewhat representative of the average _____ in the community ✸
   c) selected group of users eg nurses, volunteers
   d) no description of the derivation of the cohort

2) Selection of the non exposed cohort
   a) drawn from the same community as the exposed cohort ✸
   b) drawn from a different source
   c) no description of the derivation of the non exposed cohort

3) Ascertainment of exposure
   a) secure record (eg surgical records) ✸
   b) structured interview ✸
   c) written self report
   d) no description

4) Demonstration that outcome of interest was not present at start of study
   a) yes ✸
   b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis
   a) study controls for _____ (select the most important factor) ✸
   b) study controls for any additional factor ✸ (This criteria could be modified to indicate specific control for a second important factor.)

Outcome

1) Assessment of outcome
   a) independent blind assessment ✸
   b) record linkage ✸
   c) self report
   d) no description

2) Was follow-up long enough for outcomes to occur
   a) yes (select an adequate follow up period for outcome of interest) ✸
   b) no

3) Adequacy of follow up of cohorts
   a) complete follow up - all subjects accounted for ✸
   b) subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow up, or description provided of those lost) ✸
   c) follow up rate < ____% (select an adequate %) and no description of those lost
   d) no statement

Supplemental 3.4 NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE CASE CONTROL STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

Selection

1) Is the case definition adequate?
   a) yes, with independent validation ✸
   b) yes, eg record linkage or based on self reports
   c) no description

2) Representativeness of the cases
   a) consecutive or obviously representative series of cases ✸
   b) potential for selection biases or not stated

3) Selection of Controls
   a) community controls ✸
   b) hospital controls
   c) no description

4) Definition of Controls
   a) no history of disease (endpoint) ✸
   b) no description of source

Comparability

1) Comparability of cases and controls on the basis of the design or analysis
   a) study controls for _____ (Select the most important factor.) ✸
   b) study controls for any additional factor ✸ (This criteria could be modified to indicate specific control for a second important factor.)

Exposure

1) Ascertainment of exposure
   a) secure record (eg surgical records) ✸
   b) structured interview where blind to case/control status ✸
   c) interview not blinded to case/control status
   d) written self report or medical record only
   e) no description

2) Same method of ascertainment for cases and controls
   a) yes ✸
   b) no

3) Non-Response rate
   a) same rate for both groups ✸
   b) non respondents described
   c) rate different and no designation

Supplemental table 4. Agency for Healthcare Research and Quality (AHQR) scale for cross-sectional study

Item	Yes	No	Unclear
1) Define the source of information (survey, record review)			
2) List inclusion and exclusion criteria for exposed and unexposed subjects (cases and controls) or refer to previous publications			
3) Indicate time period used for identifying patients			
4) Indicate whether or not subjects were consecutive if not population-based			
5) Indicate if evaluators of subjective components of study were masked to other aspects of the status of the participants			
6) Describe any assessments undertaken for quality assurance purposes (e.g., test/retest of primary outcome measurements)			
7) Explain any patient exclusions from analysis			
8) Describe how confounding was assessed and/or controlled			
9) If applicable, explain how missing data were handled in the analysis			
10) Summarize patient response rates and completeness of data collection			
11) Clarify what follow-up, if any, was expected and the percentage of patients for which incomplete data or follow-up was obtained			

Supplemental table 5. GRADE assessment

Supplemental table 5.1 The Summary of Findings Tables

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Overall results

Supplemental table 5.2 GRADE Evidence Profile

Quality assessment							No. of patients		Effect	Quality
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HDP	Controls	Relative (95% CI)	
Outcome 1										
Outcome 2										
Outcome 3										

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-Preporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	2
Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	n/a under review
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	16

Amendments			
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	2
Support			
Sources	#5a	Indicate sources of financial or other support for the review	1
Sponsor	#5b	Provide name for the review funder and / or sponsor	1
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	1
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is already known	5-6
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	7
Methods			
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	11-12
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	10-11
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	10-11
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	11
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review	11-12

		(that is, screening, eligibility and inclusion in meta-analysis)	
Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	11-12
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	11-12
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	8-9
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	12-13
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	13-14
Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	13-14
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	12
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	14
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	13
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	14