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

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4 1 **Hypertensive Disorders of Pregnancy and Risk of Asthma in Offspring: A**
5 2 **Systematic Review and Meta-Analysis**

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56 22
57 23 Word count: 2168
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4 24 **Abstract**

5 25 **Introduction:** Hypertensive disorders of pregnancy (HDP), as one of the most
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8 26 common obstetrical complications, has been reported to have a controversial
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11 27 relationship with an increased risk of asthma in offspring. No systematic review has
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14 28 been performed on this topic. The aim of this systematic review is to summarize the
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17 29 available evidence examining the association between HDP and the risk of asthma in
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19 30 offspring.

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21 31 **Methods and analysis:** We will follow the Preferred Reporting Items for Systematic
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24 32 Reviews and Meta-Analyses (PRISMA) and Meta-analysis of Observational Studies
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27 33 in Epidemiology (MOOSE) guidelines. A systematic search of the PubMed,
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30 34 EMBASE, Cochrane and Web of Science databases will be performed using a
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33 35 detailed search strategy. Cohort, case-control and cross-sectional studies that report a
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36 36 diagnosis of maternal HDP and asthma in offspring will be included. Studies will be
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39 37 limited to the English language and include only human participants. Two
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42 38 independent reviewers will conduct the study selection, data extraction, and risk of
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45 39 bias assessments using a standardized data extraction form. A meta-analysis will be
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48 40 performed to calculate overall pooled estimates using the generic inverse variance
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51 41 method. The data will be synthesized by either fixed-effect or random effects models
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54 42 according to heterogeneity tests. All analyses will be performed in STATA 14 and
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56
57 43 RevMan5.3. High-quality evidence of the relationship between HDP and the risk of
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60 44 asthma in exposed offspring will be confirmed based on the synthesis of current
45 studies. In addition, the results of subgroup analyses and related secondary outcomes

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4 46 will be reported. The following will be concluded: (i) whether HDP increases the risk
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7 47 of asthma in offspring; (ii) whether HDP affects the severity of asthma in exposed
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10 48 offspring; and (iii) whether possible differences in the risk of asthma among different
11
12 49 HDP subgroups exist.
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16
17 51 **Keywords:** Asthma, Hypertension, Perinatology, Paediatrics, Community child
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20 52 health
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26 27 54 **Ethics and Dissemination** 28

29
30 55 There is no requirement for ethics approval because the meta-analysis and systematic
31
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33 56 review are based on published data. It is anticipated that the dissemination of results
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36 57 will take place at conferences and through publication in a peer-reviewed journal.
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42 43 59 **Strengths and limitations of this study** 44

- 45
46 60 ➤ This will be the first meta-analysis to explore the relationship between HDP and
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49 61 the risk of asthma in exposed offspring.
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51 62 ➤ This protocol was designed following the Preferred Reporting Items for
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54 63 Systematic Reviews and Meta-Analyses (PRISMA) and Meta-analysis of
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57 64 Observational Studies in Epidemiology (MOOSE) guidelines.
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4 65 ➤ Selection, data extraction and risk of bias assessments will be performed by two
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6 66 independent reviewers.
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10 67 ➤ The supporting evidence may promote strengthened surveillance of
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12 68 HDP-exposed infants, leading to early identification and intervention, finally
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14 69 improving lung function and asthma outcomes.
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19 70 ➤ Since the positive results are more prone to be published online, leading
20
21 71 to potential publication bias, the funnel plots will be used to assess
22
23 72 publication bias.
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73 INTRODUCTION

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

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

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4 95 breath, chest tightness and/or cough, and by variable expiratory airflow limitation. It
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6 96 is the most common chronic disease of childhood responsible for school absences,
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9 97 emergency department visits and hospitalizations. Thus, asthma has been regarded as
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12 98 a major public health challenge worldwide, affecting 1-18% of populations in
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14 99 different countries ^{12 13}. The development of asthma has generally been attributed to
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17 100 the interactions of genetics and environmental factors ^{14 15}. Currently, it is widely
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19
20 101 accepted that asthma develops early in life ¹⁶. Recurrent wheezing and other
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22 102 asthma-like symptoms usually begin as early as the first few weeks or months after
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25 103 birth. There is growing evidence that negative events occurring early in life, even in
26
27 104 the perinatal period, significantly increase the risk of asthma and poor lung function
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29
30 105 later in life ^{17 18}. Hence, adverse obstetrical events, such as HDP, may have strong
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32
33 106 effects on fetal airway structure, lung and immune system development during the
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36 107 prenatal period and may significantly increase the susceptibility of offspring to
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38 108 asthma ^{19 20}.

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41 109 Approximately half of individuals with asthma are reported to suffer from
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43 110 asthma-like symptoms during childhood ²¹. Therefore, early recognition and
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46 111 intervention is critical to reduce short- and long-term morbidity and to prevent
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49 112 potential long-term sequelae resulting in impaired lung function. Recent studies have
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52 113 shown that HDP is a potential risk factor for childhood asthma in offspring ^{4 22}.
53
54 114 However, the association between HDP and asthma is controversial ²³. Identifying the
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57 115 relationship between HDP and asthma could help us to understand the pathogenesis of
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60 116 asthma. It also facilitates early asthma recognition and intervention in high-risk

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4 117 populations. Therefore, we aim to perform a systematic review and meta-analysis to
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6 118 summarize the available evidence regarding the relationship between HDP and
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9 119 asthma in offspring.
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13 14 121 **OBJECTIVES**

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17 122 The aim of the present systematic review and meta-analysis is to summarize the
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20 123 available evidence to explore the following:

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23 124 1. Whether HDP increases the risk of asthma in offspring;
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27 125 2. Whether HDP affects the severity of asthma in the exposed offspring;
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31 126 3. Whether differences in the risk of asthma among different HDP subgroups exist.
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33
34 127 The study will be conducted based on the following requirements.
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36 37 128 **Population**

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40 129 Pregnant women and their offspring will be included.
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42 43 130 **Intervention/exposures**

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46 131 HDP, defined as any hypertension (systolic blood pressure (BP) ≥ 140 and/or diastolic
47
48 132 BP ≥ 90 mmHg) during pregnancy, mainly includes the following:

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51 133 (1) Gestational hypertension (GH): any hypertensive disorder that develops at or
52
53 134 after 20 weeks of gestation in the absence of features of preeclampsia (PE);

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56 135 (2) PE: GH accompanied by one or more of the following new-onset conditions at or
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59 136 after 20 weeks of gestation: (i) proteinuria, (ii) other maternal organ dysfunction, such
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4 137 as acute kidney injury, liver involvement, neurological complications, hematological

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7 138 complications, and (iii) uteroplacental dysfunction;

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9 139 (3) Chronic hypertension (essential and secondary): high blood pressure predating

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12 140 pregnancy or recognized at < 20 weeks of gestation;

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14 141 (4) PE superimposed on chronic hypertension: chronic essential hypertension

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17 142 accompanied by any of the above maternal organ dysfunctions consistent with PE.

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20 143 The definitions were developed according to current guidelines, such as the Canadian

21
22 144 Hypertensive Disorders of Pregnancy Working Group ²⁴, Society of Obstetric

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25 145 Medicine of Australia and New Zealand ²⁵, American College of Obstetricians and

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27
28 146 Gynecologists ³, and International Society for the Study of Hypertension in Pregnancy

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31 147 guidelines ²⁶.

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33 148 **Comparison**

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36 149 Normotensive pregnant women will be used as the control group.

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41 151 **Outcomes**

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44 152 1. Primary outcome: asthma.

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47 153 Asthma is defined by a history of respiratory symptoms including wheezing,

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50 154 shortness of breath, chest tightness and cough that vary over time and in intensity

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53 155 together with variable expiratory airflow limitation, according to the Global Initiative

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56 156 for Asthma (GINA) ¹² and International Collaboration in Asthma, Allergy and

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59 157 Immunology (iCAALL)²⁷.

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4 158 2. Secondary outcomes:

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6 159 (1) Wheezing/recurrent wheezing;

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9 160 (2) Lung/pulmonary function (including forced expiratory volume in the first second
10
11 [FEV₁], forced expiratory volume at 0.5 seconds [FEV_{0.5}], forced vital capacity
12
13 [FVC], FEV₁/FVC, 50% of the forced expiratory flow [FEF₅₀] and 75% of the forced
14
15 162 [FEF₇₅], maximal midexpiratory flow [FEF₂₅₋₇₅]), active asthma,
16
17 163 asthma exacerbations and asthma treatment (including hospitalization, systemic
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19 164 corticosteroid use, inhaled β_2 -agonist use, inhaled corticosteroid [ICS] use,
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21 165 combination of inhaled β_2 -agonists and corticosteroid use, leukotriene antagonists
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23 166 use, and other prescriptions for antiasthma medications);
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30 168 3. Serum IgE levels.
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34 35 170 **METHODS**

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38 171 The systematic review and meta-analysis will follow the Preferred Reporting Items
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40 172 for Systematic Reviews and Meta-Analysis (PRISMA)²⁸ and Meta-analysis of
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42 173 Observational Studies in Epidemiology (MOOSE) guidelines²⁹.
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47 48 49 175 **Criteria for considering studies for review**

50 51 176 **Inclusion criteria**

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54 177 (1) Studies with a cohort, case-control or cross-sectional design that report a
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56 178 diagnosis of HDP and asthma in offspring as the outcomes of interest;

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59 179 (2) Studies that estimate the relationship between HDP and asthma and report the
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4 180 estimated risks (odds ratios [ORs] or relative risks [RRs]) with 95% confidence

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7 181 intervals (CIs) or provide sufficient information to calculate these values;

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9 182 (3) Studies published in only the English language;

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12 183 (4) Studies published in any year;

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15 184 (5) Studies that include only humans.

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17 185 **Exclusion criteria**

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20 186 (1) Conference abstracts, letters to editors, reviews and commentary articles;

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22 187 (2) Studies with overlapping data;

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25 188 (3) Studies missing raw data.

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31 190 **Search strategy**

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35 191 A systematic search of the literature will be conducted in the following electronic

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37 192 databases: PubMed, EMBASE, Cochrane and Web of Science. We will search

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40 193 databases such as Google Scholar for gray literature. A three-phase search strategy

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42
43 194 will be applied in this review.

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46 195 1. For HDP, the following combination of search terms will be used: “hypertensive

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48 196 disorders during pregnancy” or “hypertensive disorders in pregnancy” or

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51 197 “hypertensive disorders of pregnancy” or “pregnancy-induced hypertension” or

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54 198 “eclampsia” or “preeclampsia” or “preeclampsia” or “preeclamptic pregnancy” or

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57 199 “chronic hypertension” or “gestational hypertension” or “chronic hypertension with

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4 200 superimposed preeclampsia” or “postpartum hypertension” or “maternal hypertensive
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6 201 disorders”.

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10 202 2. For asthma, the following search terms will be used: “asthma” or “wheeze” or
11
12 203 “wheezing” or “shortness of breath” or “bronchial spasm” or “bronchospasm” or
13
14 204 “bronchoconstriction” or “bronchoconstrict” or “bronchial hyperreactivity” or
15
16 205 “bronchial hyperresponsiveness” or “reactive airway disease” or “obstructive lung
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18 206 disease” or “air low limitation” or “chronic obstructive respiratory disorder” or
19
20 207 “chronic obstructive pulmonary disease”.

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27 208 3. We will combine steps 1 and 2 with “and”.

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30 209 The detailed search strategy is listed in the Supplement 1. We will manually search
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32 210 the reference lists of the included studies to further identify eligible studies.

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38 39 40 212 **Study selection and data extraction**

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44 213 The eligibility of each study will be assessed independently by two investigators (PL
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46 214 and TX) and disagreements will be solved by discussion (with a third author, YH,
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48 215 when necessary). Data from the identified studies will be extracted using a
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50 216 standardized data extraction form listed in the Supplement 2. The titles and abstracts
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52 217 of the studies retrieved from each database will be stored and managed in EndNote
53
54 218 reference manager. For each included study, we will extract the following information:
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56 219 first author’s last name, year of publication, study location, study design, sample size,

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4 220 ascertainment of exposure (HDP and its subgroups), outcome diagnostic criteria,
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6 221 offspring age at diagnosis, adjusted/matched confounding variables and effect
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9 222 estimates (RRs or ORs) with 95% CIs. The eligibility of each study will be assessed
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12 223 independently by two investigators (PL and TX) and disagreements will be solved by
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14 224 discussion (with a third author, YH, when necessary).
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22 226 **Subgroups /subsets**
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25 227 Subgroup analyses will be carried out according to the following: (1) study design
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27 228 (cohort vs. case-control vs. cross-sectional), (2) sample size, (3) location (e.g., Europe
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29 229 vs. United States), (4) income level of the country (low/middle/high), (5) year of
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31 230 publication, (6) study subject selection, (7) study quality (minimal/low vs.
32
33 231 moderate/high), (8) child adjusted factors (e.g., age at diagnosis of asthma, sex, birth
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35 232 weight, gestational age), and (9) maternal adjusted factors (e.g., maternal asthma,
36
37 233 maternal body mass index, gestational weight gain, maternal smoking). Sensitivity
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39 234 analyses will be performed by excluding each study one by one and by calculating a
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41 235 pooled estimate for the remainder of the studies.
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50 236 If any other subgroup/sensitivity analyses are identified during the process of the
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52 237 meta-analysis, these will be clearly labeled as post hoc analyses.
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4 **240 Risk of bias (quality) assessment**
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8 241 The quality of cohort and case-control studies will be assessed using the
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10 242 Newcastle-Ottawa scale (NOS)³⁰, which evaluates the selection (1 star for each term),
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12 243 comparability (up to 2 stars), and exposure or outcome (1 star for each term). A study
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15 244 with a high score indicates a low risk of bias. Additionally, the cross-sectional studies
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17 245 will be assessed using the Agency for Healthcare Research and Quality (AHRQ)
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19 246 recommended eleven items³¹. Furthermore, the Grading of Recommendations
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21 247 Assessment, Development and Evaluation (GRADE) methodology will be used to
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23 248 evaluate the overall likelihood of quality by examining 6 types of bias in each study
24
25 249 (selection, exposure, outcome, analytic, attrition, and confounding)³². GRADE
26
27 250 classifies the quality of studies as low, moderate, and high. The quality assessment of
28
29 251 each study will be independently carried out by two of the authors, and any
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31 252 disagreements will be resolved through discussion (with a third author when
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33 253 necessary). We will use funnel plots to assess the publication bias, and Egger's linear
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35 254 regression will be applied to test for funnel plot asymmetry.
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49 **256 Strategy for data synthesis**
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53 257 The overall pooled estimates for the association between HDP and asthma will be
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55 258 calculated in the meta-analysis. We will use the generic inverse variance method to
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57 259 determine both the crude and adjusted results. A summary OR estimate with a 95% CI
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4 260 will be calculated by using fixed-effect and random effects models. The *I*-squared
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6 261 statistics will be applied to examine heterogeneity. According to the Cochrane
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8 262 Handbook criteria, if the *I*-squared value is less than 50%, the heterogeneity is low,
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10 263 and a fixed-effect model will be used in the analysis. Otherwise, the heterogeneity
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12 264 will be considered high if the *I*-squared value is 50% or more, and a random effects
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14 265 model will be used. Forest plots will be constructed to show the study-specific
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16 266 RR/OR estimates and pooled RR/OR estimates. If a study is eligible for inclusion in
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18 267 the systematic review but does not provide adequate data for inclusion in the
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20 268 meta-analysis, a narrative synthesis will be conducted to summarize and tabulate the
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22 269 results. All analyses will be performed in STATA 14 and RevMan5.3.
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35 271 **Presenting and reporting the results**

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38 272 The study selection procedure will be outlined by a flow diagram according to the
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40 273 PRISMA statement in the meta-analysis. In addition, the reason for excluding studies
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42 274 will be presented. The characteristics of each included study, including the population,
43
44 275 age range of participants, sample size, year range of studies, study design, country,
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46 276 exposure, outcome, measure of effect, unadjusted or adjusted effect (95% CI), and
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48 277 adjustment for covariates, will be tabulated in detail. The heterogeneity of the results
49
50 278 will be listed in another table. Additionally, we will use the forest plots to present the
51
52 279 pooled estimates in the meta-analysis. Eligible studies for which we could not obtain
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4 280 raw data by contacting the corresponding authors will be listed individually in a
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6 281 separate table.
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13 283 **Summary**

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17 284 In the systematic review and meta-analysis, we will assess the association between
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19 285 HDP and asthma in offspring by summarizing the existing literature based on a
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21 286 predesigned protocol. Our results might help to reveal the potential etiology of asthma
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23 287 involving fetal lung and immune system development during the prenatal period.
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25 288 Thus, the supporting evidence may promote strengthened surveillance of
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27 289 HDP-exposed infants, leading to early identification and intervention, finally
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29 290 improving lung function and asthma outcomes.
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42 292 **Ethics and dissemination**

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44 293 There is no requirement for ethics approval because the meta-analysis and systematic
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46 294 review are based on published data. It is anticipated that the dissemination of results
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48 295 will take place at conferences and through publication in a peer-reviewed journal.
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9
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11
12
13 301 school, Derby, UK) on the conception and design of the analysis as well as other
14
15 302 valuable advice to this manuscript.
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18
19 303 **Author Contributions**
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23 304 The study was conceived by PL and TX. PL, TX, and YH developed the eligibility
24
25 305 criteria, search strategy, assessment of methodological quality, data extraction and
26
27
28 306 data summary plan. PL and TX wrote the protocol. TX supervised the work. All
29
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31 307 authors approved the final version.
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33

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48 313 **Competing Interests**
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52 314 None declared.
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59 316 **References**
60

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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
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) 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	

For peer review only

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
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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)

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3	Study records - data	#11c	Describe planned method of extracting data from reports (such as 11-12
4	collection process		piloting forms, done independently, in duplicate), any processes
5			for obtaining and confirming data from investigators
6			
7			
8	Data items	#12	List and define all variables for which data will be sought (such 11-12
9			as PICO items, funding sources), any pre-planned data
10			assumptions and simplifications
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13	Outcomes and	#13	List and define all outcomes for which data will be sought, 8-9
14	prioritization		including prioritization of main and additional outcomes, with
15			rationale
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18	Risk of bias in	#14	Describe anticipated methods for assessing risk of bias of 12-13
19	individual studies		individual studies, including whether this will be done at the
20			outcome or study level, or both; state how this information will
21			be used in data synthesis
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25	Data synthesis	#15a	Describe criteria under which study data will be quantitatively 13-14
26			synthesised
27			
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29	Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe 13-14
30			planned summary measures, methods of handling data and
31			methods of combining data from studies, including any planned
32			exploration of consistency (such as I ² , Kendall's τ)
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36	Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or 12
37			subgroup analyses, meta-regression)
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40	Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of 14
41			summary planned
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43	Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as 13
44			publication bias across studies, selective reporting within studies)
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47	Confidence in	#17	Describe how the strength of the body of evidence will be 14
48	cumulative evidence		assessed (such as GRADE)
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BMJ Open

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

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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
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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4 1 **Hypertensive Disorders of Pregnancy and Risk of Asthma in Offspring: Protocol**
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6 2 **for A Systematic Review and Meta-Analysis**

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For peer review only

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4 **23 Abstract**
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7 **24 Introduction:** Hypertensive disorders of pregnancy (HDP), one of the most common
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10 **25** obstetrical complications, has been reported to have a controversial relationship with
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12 **26** the increased risk of asthma in offspring. No systematic review of this topic has been
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15 **27** performed. The aim of this systematic review will be to summarize the available
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18 **28** evidence examining the association between HDP and the risk of asthma in offspring.
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21 **29 Methods and analysis:** We will follow the Preferred Reporting Items for Systematic
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23 **30** Reviews and Meta-Analyses (PRISMA) and Meta-analysis of Observational Studies in
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26 **31** Epidemiology (MOOSE) guidelines. A systematic search of the PubMed, EMBASE,
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29 **32** Cochrane and Web of Science databases will be performed using a detailed search
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32 **33** strategy from database inception through Dec. 31, 2019. Cohort, case-control and cross-
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35 **34** sectional studies that report a diagnosis of maternal HDP and asthma in offspring will
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38 **35** be included. Studies will be limited to the English language and include only human
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41 **36** participants. Two independent reviewers will conduct the study selection, data
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44 **37** extraction, and risk of bias assessments using a standardized data extraction form. A
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47 **38** meta-analysis will be performed to calculate overall pooled estimates using the generic
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50 **39** inverse variance method. The data will be synthesized by either fixed-effect or random
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53 **40** effects models according to heterogeneity tests. All analyses will be performed in
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56 **41** STATA 14 and RevMan 5.3. High-quality evidence of the relationship between HDP
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59 **42** and the risk of asthma in exposed offspring will be identified through the synthesis of
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43 current studies. In addition, the results of subgroup analyses and related secondary

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4 44 outcomes will be reported. The following will be concluded: (i) whether HDP increases
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6 45 the risk of asthma in offspring; (ii) whether HDP affects the severity of asthma in
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9 46 exposed offspring; and (iii) whether possible differences in the risk of asthma among
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12 47 different HDP subgroups exist.
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19 **Keywords:** Asthma, Hypertension, Perinatology, Pediatrics, Community child health
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51 **Ethics and dissemination**

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

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

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4 62 ➤ Since there may be some potential confounding factors, we will perform detailed
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6 63 subgroup analyses to reduce the effects of confounding factors.
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10 64 ➤ Since positive results are more prone to be published online, funnel plots will be
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12 65 used to assess publication bias.
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16 66 ➤ Selection bias will be considered because the pooled data will be obtained from
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18 67 observational studies.
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68 INTRODUCTION

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

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4 88 Asthma, a common lung disease associated with abnormal inflammation and
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7 89 immune response, is characterized by variable symptoms of wheezing, shortness of
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10 90 breath, chest tightness and/or cough, and variable expiratory airflow limitation. It is a
11
12 91 chronic disease of childhood and is responsible for the majority school absences,
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14 92 emergency department visits and hospitalizations. Thus, asthma has been regarded as a
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16
17 93 major public health challenge worldwide, affecting 1-18% of populations in different
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19
20 94 countries^{12 13}. The development of asthma has generally been attributed to the
21
22 95 interactions between genetics and environmental factors^{14 15}. Currently, it is widely
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24
25 96 accepted that asthma develops early in life¹⁶. Recurrent wheezing and other asthma-
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28 97 like symptoms usually begin within the first few weeks or months after birth. There is
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31 98 increasing evidence to suggest that negative events occurring early in life, even in the
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34 99 perinatal period, significantly increase the risk of asthma and poor lung function later
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36 100 in life^{17 18}. Hence, adverse obstetrical events, such as HDP, may have strong effects on
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38
39 101 fetal airway structure and lung and immune system development during the prenatal
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41 102 period and may significantly increase the susceptibility of offspring to asthma^{19 20}.

44 103 Approximately half of individuals with asthma are reported to have suffered from
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47 104 asthma-like symptoms during childhood²¹. Therefore, early recognition and
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50 105 intervention are critical to reduce short- and long-term morbidity and to prevent
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53 106 potential long-term sequelae resulting in impaired lung function. Recent studies have
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56 107 shown that HDP is a potential risk factor for childhood asthma in offspring^{4 22}.
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58 108 However, the association between HDP and asthma is controversial²³. Identifying the

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4 109 relationship between HDP and asthma could help us to understand the pathogenesis of
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6 110 asthma. It also facilitates early asthma recognition and intervention in high-risk
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9 111 populations. Therefore, we aim to perform a systematic review and meta-analysis to
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12 112 summarize the available evidence regarding the relationship between HDP and asthma
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15 113 in offspring.

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19 20 21 115 **OBJECTIVES**

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25 116 The aim of the present systematic review and meta-analysis is to summarize the
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27 117 available evidence to explore the following:

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31 118 1. Whether HDP increases the risk of asthma in offspring;
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35 119 2. Whether HDP affects the severity of asthma in exposed offspring; and
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38 120 3. Whether differences in the risk of asthma among different HDP subgroups exist.

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42 121 The study will be conducted based on the following requirements.

43 44 45 122 **Population**

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49 123 Pregnant women and their offspring at any age (both child offspring and adult
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51 124 offspring) will be included.

52 53 54 55 125 **Intervention/exposures**

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4 126 HDP, defined as any hypertension (systolic blood pressure (BP) ≥ 140 and/or diastolic
5
6 127 BP ≥ 90 mmHg) during pregnancy, mainly includes the following:

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10 128 (1) GH: any hypertensive disorder that develops at or after 20 weeks of gestation in
11
12 129 the absence of features of preeclampsia (PE);

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16 130 (2) PE: GH accompanied by one or more of the following new-onset conditions at or
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18 131 after 20 weeks of gestation: (i) proteinuria, (ii) maternal organ dysfunction, such as
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20 132 acute kidney injury, liver complications, neurological complications, or hematological
21
22 133 complications, and (iii) uteroplacental dysfunction;

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27 134 (3) Chronic hypertension (essential and secondary): high blood pressure predating
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29 135 pregnancy or recognized at < 20 weeks of gestation; and

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33 136 (4) PE superimposed on chronic hypertension: chronic essential hypertension
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35 137 accompanied by any of the above maternal organ dysfunctions consistent with PE.

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40 138 The definitions were developed according to current guidelines, such as the Canadian
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42 139 Hypertensive Disorders of Pregnancy Working Group²⁴, Society of Obstetric Medicine
43
44 140 of Australia and New Zealand²⁵, American College of Obstetricians and Gynecologists
45
46 141³, and International Society for the Study of Hypertension in Pregnancy guidelines²⁶.

47 48 49 50 51 142 **Comparison**

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54 143 Normotensive pregnant women will be used as the control group.

55 56 57 58 144 **Outcomes**

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4 145 1. Primary outcome: asthma.
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7 146 Asthma is defined by a history of respiratory symptoms, including wheezing, shortness
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9
10 147 of breath, chest tightness and cough, that vary over time and in intensity in addition to
11
12 148 variable expiratory airflow limitation according to the Global Initiative for Asthma
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14
15 149 (GINA)¹² and International Collaboration in Asthma, Allergy and Immunology
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18 150 (iCAALL)²⁷.
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21 151 2. Secondary outcomes:
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25 152 (1) Wheezing/recurrent wheezing;
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28 153 (2) Lung/pulmonary function (including forced expiratory volume in one second
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30 154 [FEV₁], forced expiratory volume at 0.5 seconds [FEV_{0.5}], forced vital capacity [FVC],
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32 155 FEV₁/FVC, 50% of the forced expiratory flow [FEF₅₀] and 75% of the forced expiratory
33
34 156 flow [FEF₇₅], maximal midexpiratory flow [FEF₂₅₋₇₅]), active asthma, asthma
35
36 157 exacerbations and asthma treatment (including hospitalization, systemic corticosteroid
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39 158 use, inhaled β_2 -agonist use, inhaled corticosteroid [ICS] use, combination of inhaled
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42 159 β_2 -agonists and corticosteroid use, leukotriene antagonist use, and other antiasthma
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45 160 medication use); and
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50 161 3. Serum IgE levels.
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57 163 **METHODS**
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4 164 The systematic review and meta-analysis will follow the Preferred Reporting Items for
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6 165 Systematic Reviews and Meta-Analysis (PRISMA) ²⁸ and Meta-analysis of
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9 166 Observational Studies in Epidemiology (MOOSE) guidelines ²⁹.
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16 168 **Criteria for considering studies for review**

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20 169 **Inclusion criteria**

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23 170 (1) Studies with cohort, case-control and cross-sectional designs that report a
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26 171 diagnosis of HDP and asthma in offspring as the outcome of interest;

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29 172 (2) Studies that estimate the relationship between HDP and asthma and report the
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32 173 estimated risks (odds ratios [ORs] or relative risks [RRs]) with 95% confidence
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35 174 intervals (CIs) or provide sufficient information to calculate these values;

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38 175 (3) Studies published in only the English language;

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41 176 (4) Studies published in any year; and

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45 177 (5) Studies that include only humans.

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48 178 **Exclusion criteria**

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52 179 (1) Conference abstracts, letters to the editor, reviews and commentary articles;

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55 180 (2) Studies with overlapping data; or
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4 181 (3) Studies missing raw data.
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11 183 **Search strategy**
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14 184 A systematic search of the literature will be conducted in the PubMed, EMBASE,
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16 185 Cochrane and Web of Science databases from database inception through Dec. 31, 2019.
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18 186 We will search databases such as Google Scholar for gray literature. A three-phase
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20 187 search strategy will be applied in this review.
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26 188 1. For HDP, the following combination of search terms will be used: “hypertensive
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28 189 disorders during pregnancy” or “hypertensive disorders in pregnancy” or “hypertensive
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30 190 disorders of pregnancy” or “pregnancy-induced hypertension” or “eclampsia” or
31
32 191 “preeclampsia” or “preeclampsia” or “preeclamptic pregnancy” or “chronic
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34 192 hypertension” or “gestational hypertension” or “chronic hypertension with
35
36 193 superimposed preeclampsia” or “postpartum hypertension” or “maternal hypertensive
37
38 194 disorders”.
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45 195 2. For asthma, the following search terms will be used: “asthma” or “wheeze” or
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47 196 “wheezing” or “shortness of breath” or “bronchial spasm” or “bronchospasm” or
48
49 197 “bronchoconstriction” or “bronchoconstrict” or “bronchial hyperreactivity” or
50
51 198 “bronchial hyperresponsiveness” or “reactive airway disease” or “obstructive lung
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4 199 disease” or “air low limitation” or “chronic obstructive respiratory disorder” or “chronic
5
6 200 obstructive pulmonary disease”.

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10 201 3. We will combine steps 1 and 2 with “and”.

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14 202 The detailed search strategy is listed in Supplement table 1. We will manually search
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16 203 the reference lists of the included studies to further identify eligible studies.

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24 205 **Study selection and data extraction**

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27 206 The eligibility of each study will be assessed independently by two investigators (PL
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29 207 and TX), and disagreements will be solved by discussion (with a third author, YH, when
30
31 208 necessary). Data from the identified studies will be extracted using the standardized
32
33 209 data extraction form listed in Supplement table 2. The titles and abstracts of the studies
34
35 210 retrieved from each database will be stored and managed in the EndNote reference
36
37 211 manager. For each included study, we will extract the following information: first
38
39 212 author’s last name, year of publication, study location, study design, sample size,
40
41 213 ascertainment of exposure (HDP and its subgroups), outcome diagnostic criteria,
42
43 214 offspring age at diagnosis, adjusted/matched confounding variables and effects
44
45 215 estimates (RRs or ORs) with 95% CIs. The eligibility of each study will be assessed
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47 216 independently by two investigators (PL and TX), and disagreements will be solved by
48
49 217 discussion (with a third author, YH, when necessary).

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8 219 **Subgroups/subsets**
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11 220 Subgroup analyses will be carried out according to the following: (1) study design
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13 221 (cohort vs. case-control vs. cross-sectional), (2) sample size, (3) location (e.g., Europe
14
15 222 vs. United States), (4) income level of the country (low/middle/high), (5) year of
16
17 223 publication, (6) study subject selection, (7) study quality (minimal/low vs.
18
19 224 moderate/high), (8) adjusted offspring factors (e.g., age at diagnosis of asthma, sex,
20
21 225 birth weight, gestational age), and (9) adjusted maternal factors (e.g., maternal asthma,
22
23 226 maternal body mass index, gestational weight gain, maternal smoking). Sensitivity
24
25 227 analyses will be performed by excluding each study one by one and calculating a pooled
26
27 228 estimate for the remainder of the studies.
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36 229 If any other subgroup/sensitivity analyses are identified during the process of the meta-
37
38 230 analysis, these will be clearly labeled as post hoc analyses.
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47 232 **Risk of bias (quality) assessment**
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49 233 The quality of cohort and case-control studies will be assessed using the Newcastle-
50
51 234 Ottawa Scale (NOS)³⁰, which evaluates the selection of study groups (1 star for each
52
53 235 term), comparability (up to 2 stars), and exposure or outcome (1 star for each term)
54
55 236 (Supplemental table 3). A high score indicates a low risk of bias. Additionally, cross-
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4 237 sectional studies will be assessed using the Agency for Healthcare Research and Quality
5
6 238 (AHRQ)-recommended eleven items scale (Supplemental table 4)³¹. Furthermore, the
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9 239 Grading of Recommendations Assessment, Development and Evaluation (GRADE)
10
11
12 240 methodology will be used to evaluate the overall likelihood of quality by examining 6
13
14
15 241 types of bias in each study (selection, exposure, outcome, analytic, attrition, and
16
17 242 confounding) (Supplemental table 5)³². The GRADE classifies the quality of studies
18
19
20 243 as low, moderate, and high. The quality assessment of each study will be independently
21
22
23 244 carried out by two authors, and any disagreements will be resolved through discussion
24
25 245 (with a third author when necessary). We will use funnel plots to assess publication bias,
26
27
28 246 and Egger's linear regression will be applied to test for funnel plot asymmetry.
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35 248 **Strategy for data synthesis**

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39 249 The overall pooled estimates for the association between HDP and asthma will be
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41 250 calculated in the meta-analysis. We will use the generic inverse variance method to
42
43
44 251 determine both the crude and adjusted results. A summary OR estimate with a 95% CI
45
46
47 252 will be calculated by using fixed-effect and random effects models. The *I*-squared
48
49 253 statistic will be applied to examine heterogeneity. According to the Cochrane
50
51
52 254 Handbook criteria, if the *I*-squared value is less than 50%, heterogeneity is low, and a
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55 255 fixed-effect model will be used in the analysis. Otherwise, the heterogeneity will be
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57 256 considered high if the *I*-squared value is 50% or more, and a random effects model will
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4 257 be used. Forest plots will be constructed to show the study-specific RR/OR estimates
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6 258 and pooled RR/OR estimates. If a study is eligible for inclusion in the systematic review
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8
9 259 but does not provide adequate data for inclusion in the meta-analysis, a narrative
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11
12 260 synthesis will be conducted to summarize and tabulate the results. All analyses will be
13
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15 261 performed in STATA 14 and RevMan 5.3.
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21 263 **Presenting and reporting the results**

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25 264 The study selection procedure will be outlined by a flow diagram according to the
26
27
28 265 PRISMA statement in the meta-analysis (Supplemental figure 1). In addition, the
29
30
31 266 reason for excluding studies will be presented. The characteristics of each included
32
33
34 267 study, including the population, age range of participants, sample size, year range of
35
36
37 268 studies, study design, country, exposure, outcome, measure of effect, unadjusted or
38
39 269 adjusted effects (95% CI), and adjustment for covariates, will be tabulated in detail.
40
41
42 270 The heterogeneity of the results will be listed in another table. Additionally, we will use
43
44
45 271 forest plots to present the pooled estimates in the meta-analysis. Eligible studies for
46
47
48 272 which we could not obtain raw data by contacting the corresponding authors will be
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50
51 273 listed individually in a separate table.
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53 274 **Patient and public involvement**

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4 275 This systematic review and meta-analysis will be based on published studies; therefore,
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6 276 primary patient data will not be collected. Patients and the public will not be involved
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8
9 277 in the study design, recruitment and data analysis.
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16 279 **Summary**

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20 280 In this systematic review and meta-analysis, we will assess the association between
21
22 281 HDP and asthma in offspring by summarizing the existing literature based on a
23
24 282 predesigned protocol. Our results might help reveal the potential etiology of asthma
25
26 283 involving fetal lung and immune system development during the prenatal period. Thus,
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28 284 the supporting evidence may promote strengthened surveillance of HDP-exposed
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30 285 infants, leading to early identification and intervention and improved lung function and
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32 286 asthma outcomes.
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44 288 **Ethics and dissemination**

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47 289 There is no requirement for ethics approval because the meta-analysis and systematic
48
49 290 review will be based on published data. It is anticipated that the dissemination of results
50
51 291 will take place at conferences and through publication in a peer-reviewed journal.
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4 293 **Acknowledgments**
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8
9
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11
12
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14
15
16 297 other valuable advice regarding this manuscript.
17

18
19 298 **Author contributions**
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23 299 The study was conceived by PL and TX. PL, TX, and YH developed the eligibility
24
25 300 criteria, search strategy, assessment of methodological quality, data extraction methods
26
27
28 301 and data summary plan. PL and TX wrote the protocol. TX supervised the work. All
29
30
31 302 authors approved the final version.
32

33
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35

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42
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44
45
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47

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49 308 **Competing interests**
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53 309 None declared.
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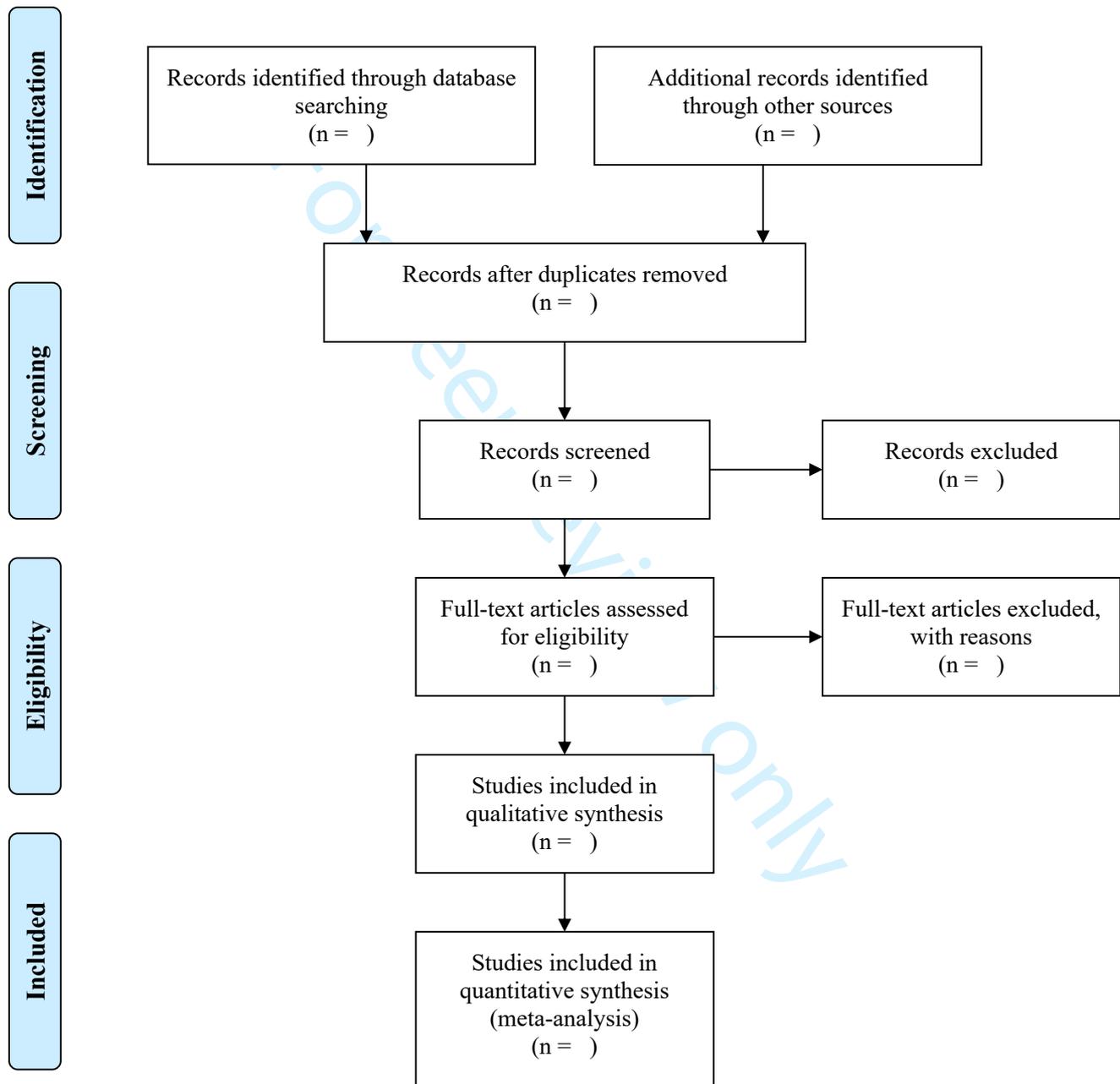
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For peer review only

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). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: 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 <input type="checkbox"/> exclude <input type="checkbox"/>
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							
	Representativeness 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

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4 **Supplemental table 4. Agency for Healthcare Research and Quality**

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7 **(AHQR) scale for cross-sectional study**

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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
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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)

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3	Study records - data	#11c	Describe planned method of extracting data from reports (such as 11-12
4	collection process		piloting forms, done independently, in duplicate), any processes
5			for obtaining and confirming data from investigators
6			
7			
8	Data items	#12	List and define all variables for which data will be sought (such 11-12
9			as PICO items, funding sources), any pre-planned data
10			assumptions and simplifications
11			
12			
13	Outcomes and	#13	List and define all outcomes for which data will be sought, 8-9
14	prioritization		including prioritization of main and additional outcomes, with
15			rationale
16			
17			
18	Risk of bias in	#14	Describe anticipated methods for assessing risk of bias of 12-13
19	individual studies		individual studies, including whether this will be done at the
20			outcome or study level, or both; state how this information will
21			be used in data synthesis
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25	Data synthesis	#15a	Describe criteria under which study data will be quantitatively 13-14
26			synthesised
27			
28			
29	Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe 13-14
30			planned summary measures, methods of handling data and
31			methods of combining data from studies, including any planned
32			exploration of consistency (such as I ² , Kendall's τ)
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36	Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or 12
37			subgroup analyses, meta-regression)
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40	Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of 14
41			summary planned
42			
43	Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as 13
44			publication bias across studies, selective reporting within studies)
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47	Confidence in	#17	Describe how the strength of the body of evidence will be 14
48	cumulative evidence		assessed (such as GRADE)
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BMJ Open

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

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Date Submitted by the Author:	21-Mar-2020
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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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4 1 **Hypertensive Disorders of Pregnancy and Risk of Asthma in Offspring: Protocol**
5 2 **for A Systematic Review and Meta-Analysis**

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7 3 Ping Li, MD,^{1,2} Tao Xiong*, MD PhD^{1,2,3} Yong Hu, MD^{1,2}
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54 22 Word count: 2290
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4 23 **ABSTRACT**

5 24 **Introduction:** Hypertensive disorders of pregnancy (HDP), one of the most common
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8 25 obstetrical complications, has been reported to have a controversial relationship with
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11 26 the increased risk of asthma in offspring. No systematic review of this topic has been
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14 27 performed. The aim of this systematic review will be to summarize the available
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16 28 evidence examining the association between HDP and the risk of asthma in offspring.

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19 29 **Methods and analysis:** We will follow the Preferred Reporting Items for Systematic
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21 30 Reviews and Meta-Analyses (PRISMA) and Meta-analysis of Observational Studies in
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24 31 Epidemiology (MOOSE) guidelines. A systematic search of the PubMed, EMBASE,
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27 32 Cochrane and Web of Science databases will be performed using a detailed search
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30 33 strategy from database inception through Dec. 31, 2019. Cohort, case-control and cross-
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32 34 sectional studies that report a diagnosis of maternal HDP and asthma in offspring will
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35 35 be included. Studies will be limited to the English language and include only human
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38 36 participants. Two independent reviewers will conduct the study selection, data
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41 37 extraction, and risk of bias assessments using a standardized data extraction form. A
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44 38 meta-analysis will be performed to calculate overall pooled estimates using the generic
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47 39 inverse variance method. The data will be synthesized by either fixed-effect or random
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50 40 effects models according to heterogeneity tests. All analyses will be performed in
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53 41 STATA 14 and RevMan 5.3. High-quality evidence of the relationship between HDP
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56 42 and the risk of asthma in exposed offspring will be identified through the synthesis of
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59 43 current studies. In addition, the results of subgroup analyses and related secondary
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44 outcomes will be reported. The following will be concluded: (i) whether HDP increases

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4 45 the risk of asthma in offspring; (ii) whether HDP affects the severity of asthma in
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6 46 exposed offspring; and (iii) whether possible differences in the risk of asthma among
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9 47 different HDP subgroups exist.
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14 49 **Keywords:** Asthma, Hypertension, Perinatology, Pediatrics, Community child health
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21 51 **Ethics and dissemination**

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25 52 There is no requirement for ethics approval because the meta-analysis and systematic
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28 53 review will be based on published data. It is anticipated that the dissemination of results
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31 54 will take place at conferences and through publication in a peer-reviewed journal.
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36 37 38 56 **Strengths and limitations of this study**

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41 57 ➤ This will be the first meta-analysis to explore the relationship between HDP and
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43 58 the risk of asthma in exposed offspring.
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46 59 ➤ This protocol was designed following the Preferred Reporting Items for
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49 60 Systematic Reviews and Meta-Analyses (PRISMA) and Meta-analysis of
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51 61 Observational Studies in Epidemiology (MOOSE) guidelines.
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55 62 ➤ Since there may be some potential confounding factors, we will perform detailed
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58 63 subgroup analyses to reduce the effects of confounding factors.
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4 64 ➤ Since positive results are more prone to be published
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7 65 online, funnel plots will be used to assess publication bias.
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10 66 ➤ Selection bias will be considered because the pooled data will be obtained from
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68 INTRODUCTION

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

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

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4 90 breath, chest tightness and/or cough, and variable expiratory airflow limitation. It is a
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7 91 chronic disease of childhood and is responsible for the majority school absences,
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10 92 emergency department visits and hospitalizations. Thus, asthma has been regarded as a
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12 93 major public health challenge worldwide, affecting 1-18% of populations in different
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14 94 countries ^{12 13}. The development of asthma has generally been attributed to the
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17 95 interactions between genetics and environmental factors ^{14 15}. Currently, it is widely
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20 96 accepted that asthma develops early in life ¹⁶. Recurrent wheezing and other asthma-
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22 97 like symptoms usually begin within the first few weeks or months after birth. There is
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25 98 increasing evidence to suggest that negative events occurring early in life, even in the
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28 99 perinatal period, significantly increase the risk of asthma and poor lung function later
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30 100 in life ^{17 18}. Hence, adverse obstetrical events, such as HDP, may have strong effects on
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33 101 fetal airway structure and lung and immune system development during the prenatal
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36 102 period and may significantly increase the susceptibility of offspring to asthma ^{19 20}.

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38 103 Approximately half of individuals with asthma are reported to have suffered from
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41 104 asthma-like symptoms during childhood ²¹. Therefore, early recognition and
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44 105 intervention are critical to reduce short- and long-term morbidity and to prevent
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47 106 potential long-term sequelae resulting in impaired lung function. Recent studies have
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49 107 shown that HDP is a potential risk factor for childhood asthma in offspring ^{4 22}.
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52 108 However, the association between HDP and asthma is controversial ²³. Identifying the
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55 109 relationship between HDP and asthma could help us to understand the pathogenesis of
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57 110 asthma. It also facilitates early asthma recognition and intervention in high-risk
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59 111 populations. Therefore, we aim to perform a systematic review and meta-analysis to
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4 112 summarize the available evidence regarding the relationship between HDP and asthma
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6 113 in offspring.
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11 115 **OBJECTIVES**

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14 116 The aim of the present systematic review and meta-analysis is to summarize the
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17 117 available evidence to explore the following:

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20 118 1. Whether HDP increases the risk of asthma in offspring;
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23 119 2. Whether HDP affects the severity of asthma in exposed offspring; and
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28 120 3. Whether differences in the risk of asthma among different HDP subgroups exist.

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31 121 The study will be conducted based on the following requirements.

32 122 **Population**

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35 123 Pregnant women and their offspring at any age (both child offspring and adult
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38 124 offspring) will be included.

39 125 **Intervention/exposures**

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43 126 HDP, defined as any hypertension (systolic blood pressure (BP) ≥ 140 and/or diastolic
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46 127 BP ≥ 90 mmHg) during pregnancy, mainly includes the following:

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49 128 (1) GH: any hypertensive disorder that develops at or after 20 weeks of gestation in
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52 129 the absence of features of preeclampsia (PE);

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55 130 (2) PE: GH accompanied by one or more of the following new-onset conditions at or
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58 131 after 20 weeks of gestation: (i) proteinuria, (ii) maternal organ dysfunction, such as

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4 132 acute kidney injury, liver complications, neurological complications, or hematological

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7 133 complications, and (iii) uteroplacental dysfunction;

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9 134 (3) Chronic hypertension (essential and secondary): high blood pressure predating

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12 135 pregnancy or recognized at < 20 weeks of gestation; and

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14 136 (4) PE superimposed on chronic hypertension: chronic essential hypertension

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17 137 accompanied by any of the above maternal organ dysfunctions consistent with PE.

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20 138 The definitions were developed according to current guidelines, such as the Canadian

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22 139 Hypertensive Disorders of Pregnancy Working Group²⁴, Society of Obstetric Medicine

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25 140 of Australia and New Zealand²⁵, American College of Obstetricians and Gynecologists

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27
28 141³, and International Society for the Study of Hypertension in Pregnancy guidelines²⁶.

29
30 142 **Comparison**

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33 143 Normotensive pregnant women will be used as the control group.

34
35 144 **Outcomes**

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39 145 1. Primary outcome: asthma.

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41
42 146 Asthma is defined by a history of respiratory symptoms, including wheezing, shortness

43
44
45 147 of breath, chest tightness and cough, that vary over time and in intensity in addition to

46
47
48 148 variable expiratory airflow limitation according to the Global Initiative for Asthma

49
50 149 (GINA)¹² and International Collaboration in Asthma, Allergy and Immunology

51
52 150 (iCAALL)²⁷.

53
54
55 151 2. Secondary outcomes:

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57
58 152 (1) Wheezing/recurrent wheezing;

59
60

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4 153 (2) Lung/pulmonary function (including forced expiratory volume in one second
5
6 154 [FEV₁], forced expiratory volume at 0.5 seconds [FEV_{0.5}], forced vital capacity [FVC],
7
8
9 155 FEV₁/FVC, 50% of the forced expiratory flow [FEF₅₀] and 75% of the forced expiratory
10
11 156 flow [FEF₇₅], maximal midexpiratory flow [FEF₂₅₋₇₅]), active asthma, asthma
12
13 157 exacerbations and asthma treatment (including hospitalization, systemic corticosteroid
14
15 158 use, inhaled β_2 -agonist use, inhaled corticosteroid [ICS] use, combination of inhaled
16
17 159 β_2 -agonists and corticosteroid use, leukotriene antagonist use, and other antiasthma
18
19 160 medication use); and
20
21 161 3. Serum IgE levels.
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32 163 **METHOD**

33 164 The systematic review and meta-analysis will follow the Preferred Reporting Items for
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35 165 Systematic Reviews and Meta-Analysis (PRISMA) ²⁸ and Meta-analysis of
36
37 166 Observational Studies in Epidemiology (MOOSE) guidelines ²⁹.
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42 168 **Criteria for considering studies for review**

43 169 **Inclusion criteria**

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47 170 (1) Studies with cohort, case-control and cross-sectional designs that report a
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49 171 diagnosis of HDP and asthma in offspring as the outcome of interest;
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52
53 172 (2) Studies that estimate the relationship between HDP and asthma and report the
54
55 173 estimated risks (odds ratios [ORs] or relative risks [RRs]) with 95% confidence
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57 174 intervals (CIs) or provide sufficient information to calculate these values;
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59
60

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4 175 (3) Studies published in only the English language;
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6 176 (4) Studies published in any year; and
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9 177 (5) Studies that include only humans.
10

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12 178 **Exclusion criteria**
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14 179 (1) Conference abstracts, letters to the editor, reviews and commentary articles;
15

16
17 180 (2) Studies with overlapping data; or
18

19 181 (3) Studies missing raw data.
20
21

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26 183 **Search strategy**
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29 184 A systematic search of the literature will be conducted in the PubMed, EMBASE,
30

31
32 185 Cochrane and Web of Science databases from database inception through Dec. 31, 2019.
33

34
35 186 We will search databases such as Google Scholar for gray literature. A three-phase
36

37 187 search strategy will be applied in this review.
38
39

40
41 188 1. For HDP, the following combination of search terms will be used: “hypertensive
42

43 189 disorders during pregnancy” or “hypertensive disorders in pregnancy” or “hypertensive
44

45 190 disorders of pregnancy” or “pregnancy-induced hypertension” or “eclampsia” or
46

47 191 “preeclampsia” or “preeclampsia” or “preeclamptic pregnancy” or “chronic
48

49 192 hypertension” or “gestational hypertension” or “chronic hypertension with
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51 193 superimposed preeclampsia” or “postpartum hypertension” or “maternal hypertensive
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53 194 disorders”.
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4 195 2. For asthma, the following search terms will be used: “asthma” or “wheeze” or
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6 196 “wheezing” or “shortness of breath” or “bronchial spasm” or “bronchospasm” or
7
8
9 197 “bronchoconstriction” or “bronchoconstrict” or “bronchial hyperreactivity” or
10
11
12 198 “bronchial hyperresponsiveness” or “reactive airway disease” or “obstructive lung
13
14
15 199 disease” or “air low limitation” or “chronic obstructive respiratory disorder” or “chronic
16
17 200 obstructive pulmonary disease”.

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19
20
21 201 3. We will combine steps 1 and 2 with “and”.

22
23
24 202 The detailed search strategy is listed in Supplement table 1. We will manually search
25
26
27 203 the reference lists of the included studies to further identify eligible studies.
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29

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31 204

32 33 34 205 **Study selection and data extraction**

35
36
37
38 206 The eligibility of each study will be assessed independently by two investigators (PL
39
40 207 and TX), and disagreements will be solved by discussion (with a third author, YH, when
41
42
43 208 necessary). Data from the identified studies will be extracted using the standardized
44
45
46 209 data extraction form listed in Supplement table 2. The titles and abstracts of the studies
47
48
49 210 retrieved from each database will be stored and managed in the EndNote reference
50
51 211 manager. For each included study, we will extract the following information: first
52
53
54 212 author’s last name, year of publication, study location, study design, sample size,
55
56
57 213 ascertainment of exposure (HDP and its subgroups), outcome diagnostic criteria,
58
59 214 offspring age at diagnosis, adjusted/matched confounding variables and effects

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4 215 estimates (RRs or ORs) with 95% CIs. The eligibility of each study will be assessed
5
6 216 independently by two investigators (PL and TX), and disagreements will be solved by
7
8
9 217 discussion (with a third author, YH, when necessary).
10
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12

13 218

16 219 **Subgroups/subsets**

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20 220 Subgroup analyses will be carried out according to the following: (1) study design
21
22 221 (cohort vs. case-control vs. cross-sectional), (2) sample size, (3) location (e.g., Europe
23
24 222 vs. United States), (4) income level of the country (low/middle/high), (5) year of
25
26 223 publication, (6) study subject selection, (7) study quality (minimal/low vs.
27
28 224 moderate/high), (8) adjusted offspring factors (e.g., age at diagnosis of asthma, sex,
29
30 225 birth weight, gestational age), and (9) adjusted maternal factors (e.g., maternal asthma,
31
32 226 maternal body mass index, gestational weight gain, maternal smoking). Sensitivity
33
34 227 analyses will be performed by excluding each study one by one and calculating a pooled
35
36 228 estimate for the remainder of the studies.
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45 229 If any other subgroup/sensitivity analyses are identified during the process of the meta-
46
47 230 analysis, these will be clearly labeled as post hoc analyses.
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54 232 **Risk of bias (quality) assessment**

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4 233 The quality of cohort and case-control studies will be assessed using the Newcastle-
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6 234 Ottawa Scale (NOS)³⁰, which evaluates the selection of study groups (1 star for each
7
8
9 235 term), comparability (up to 2 stars), and exposure or outcome (1 star for each term)
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11
12 236 (Supplemental table 3). A high score indicates a low risk of bias. Additionally, cross-
13
14 237 sectional studies will be assessed using the Agency for Healthcare Research and Quality
15
16
17 238 (AHRQ)-recommended eleven items scale (Supplemental table 4)³¹. Furthermore, the
18
19 239 Grading of Recommendations Assessment, Development and Evaluation (GRADE)
20
21
22 240 methodology will be used to evaluate the overall likelihood of quality by examining 6
23
24 241 types of bias in each study (selection, exposure, outcome, analytic, attrition, and
25
26
27 242 confounding) (Supplemental table 5)³². The GRADE classifies the quality of studies
28
29 243 as low, moderate, and high. The quality assessment of each study will be independently
30
31
32 244 carried out by two authors, and any disagreements will be resolved through discussion
33
34
35 245 (with a third author when necessary). We will use funnel plots to assess publication bias,
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37
38 246 and Egger's linear regression will be applied to test for funnel plot asymmetry.
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248 **Strategy for data synthesis**

49 249 The overall pooled estimates for the association between HDP and asthma will be
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51
52 250 calculated in the meta-analysis. We will use the generic inverse variance method to
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54
55 251 determine both the crude and adjusted results. A summary OR estimate with a 95% CI
56
57
58 252 will be calculated by using fixed-effect and random effects models. The *I*-squared
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60 253 statistic will be applied to examine heterogeneity. According to the Cochrane

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4 254 Handbook criteria, if the *I*-squared value is less than 50%, heterogeneity is low, and a
5
6 255 fixed-effect model will be used in the analysis. Otherwise, the heterogeneity will be
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8
9 256 considered high if the *I*-squared value is 50% or more, and a random effects model will
10
11
12 257 be used. Forest plots will be constructed to show the study-specific RR/OR estimates
13
14 258 and pooled RR/OR estimates. If a study is eligible for inclusion in the systematic review
15
16
17 259 but does not provide adequate data for inclusion in the meta-analysis, a narrative
18
19
20 260 synthesis will be conducted to summarize and tabulate the results. All analyses will be
21
22 261 performed in STATA 14 and RevMan 5.3.
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26 262
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30 263 **Presenting and reporting the results**
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33 264 The study selection procedure will be outlined by a flow diagram according to the
34
35 265 PRISMA statement in the meta-analysis (Supplemental figure 1). In addition, the
36
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38 266 reason for excluding studies will be presented. The characteristics of each included
39
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41 267 study, including the population, age range of participants, sample size, year range of
42
43
44 268 studies, study design, country, exposure, outcome, measure of effect, unadjusted or
45
46 269 adjusted effects (95% CI), and adjustment for covariates, will be tabulated in detail.
47
48
49 270 The heterogeneity of the results will be listed in another table. Additionally, we will use
50
51
52 271 forest plots to present the pooled estimates in the meta-analysis. Eligible studies for
53
54
55 272 which we could not obtain raw data by contacting the corresponding authors will be
56
57 273 listed individually in a separate table.
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4 **274 Patient and public involvement**
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8 275 This systematic review and meta-analysis will be based on published studies; therefore,
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10 276 primary patient data will not be collected. Patients and the public will not be involved
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12
13 277 in the study design, recruitment and data analysis.
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20 279 **Summary**
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24 280 In this systematic review and meta-analysis, we will assess the association between
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26 281 HDP and asthma in offspring by summarizing the existing literature based on a
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28
29 282 predesigned protocol. Our results might help reveal the potential etiology of asthma
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31 283 involving fetal lung and immune system development during the prenatal period. Thus,
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34 284 the supporting evidence may promote strengthened surveillance of HDP-exposed
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37 285 infants, leading to early identification and intervention and improved lung function and
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40 286 asthma outcomes.
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47 288 **Acknowledgments**
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50
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52
53 290 Health and Editor in Chief of BMJ Paeds Open, University of Nottingham, the
54
55
56 291 Medical School, Derby, UK) on the conception and design of the analysis as well as
57
58
59 292 other valuable advice regarding this manuscript.
60

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4 293 **Author contributions**
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6

7 294 The study was conceived by PL and TX. PL, TX, and YH developed the eligibility
8
9 295 criteria, search strategy, assessment of methodological quality, data extraction methods
10
11
12 296 and data summary plan. PL and TX wrote the protocol. TX supervised the work. All
13
14
15 297 authors approved the final version.
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18
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21

22
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26
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28
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33 303 **Competing interests**
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37 304 None declared.
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4 399 **Figure legends**

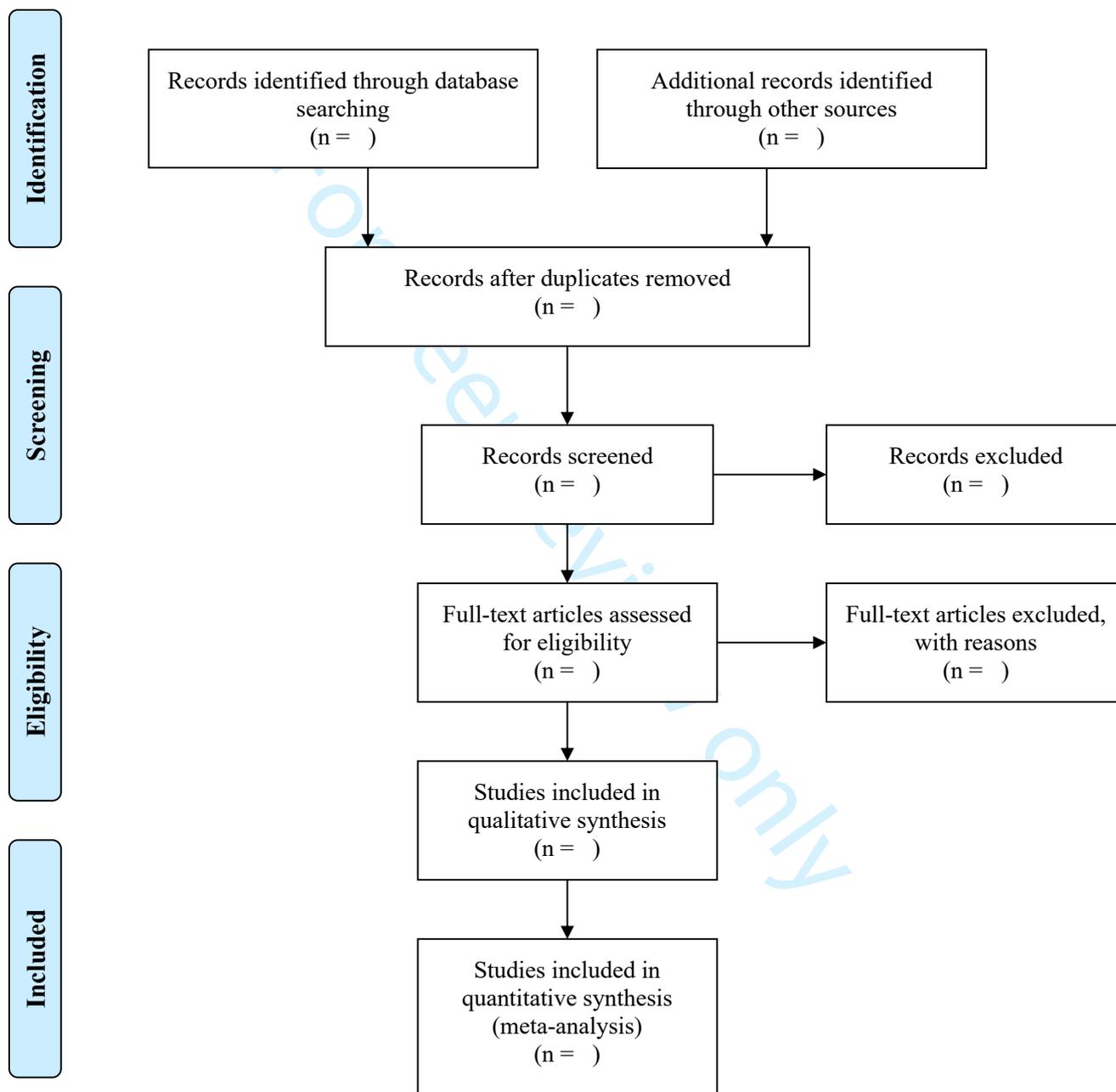
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6 400 **Supplemental figure 1.** Flow Diagram of Studies Selected for Inclusion in the Systematic

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9 401 Review (PRISMA 2009 Flow Diagram)

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For peer review only

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). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: 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 <input type="checkbox"/> exclude <input type="checkbox"/>
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							
	Representativeness 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

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4 **Supplemental table 4. Agency for Healthcare Research and Quality**

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7 **(AHQR) scale for cross-sectional study**

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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
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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)

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3	Study records - data	#11c	Describe planned method of extracting data from reports (such as 11-12
4	collection process		piloting forms, done independently, in duplicate), any processes
5			for obtaining and confirming data from investigators
6			
7			
8	Data items	#12	List and define all variables for which data will be sought (such 11-12
9			as PICO items, funding sources), any pre-planned data
10			assumptions and simplifications
11			
12			
13	Outcomes and	#13	List and define all outcomes for which data will be sought, 8-9
14	prioritization		including prioritization of main and additional outcomes, with
15			rationale
16			
17			
18	Risk of bias in	#14	Describe anticipated methods for assessing risk of bias of 12-13
19	individual studies		individual studies, including whether this will be done at the
20			outcome or study level, or both; state how this information will
21			be used in data synthesis
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25	Data synthesis	#15a	Describe criteria under which study data will be quantitatively 13-14
26			synthesised
27			
28			
29	Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe 13-14
30			planned summary measures, methods of handling data and
31			methods of combining data from studies, including any planned
32			exploration of consistency (such as I ² , Kendall's τ)
33			
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36	Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or 12
37			subgroup analyses, meta-regression)
38			
39			
40	Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of 14
41			summary planned
42			
43	Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as 13
44			publication bias across studies, selective reporting within studies)
45			
46			
47	Confidence in	#17	Describe how the strength of the body of evidence will be 14
48	cumulative evidence		assessed (such as GRADE)
49			
50			

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