Systematic Review and Meta-Analysis

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# Risk of future cardiovascular diseases in different years postpartum after hypertensive disorders of pregnancy

## A systematic review and meta-analysis

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**Abstract**

**Objective:** There are limited data on the optimal timing and frequency of postpartum follow-up visits after hypertensive disorders of pregnancy (HDP) for primary prevention and early detection of cardiovascular diseases (CVDs) in high-risk women. We aimed to evaluate the risk of cardiovascular outcomes later in life in women with prior HDP in different years postpartum and in preeclamptic women with severe features, or early onset of preeclampsia.

**Methods:** We searched MEDLINE, Cochrane Library, Web of Science, and Scopus without language restriction for relevant articles published from inception to March 16, 2022. We included prospective and retrospective cohort studies assessing hypertension, ischemic heart disease, heart failure, venous thromboembolism, peripheral vascular disease, stroke, dementia, composite cardiovascular and/or cerebrovascular diseases, and mortality after 6 weeks postpartum, in women with prior HDP compared with controls. Two authors independently selected and appraised the studies. Article quality was independently assessed using the Newcastle-Ottawa Scale (NOS). Random-effect models were used for meta-analysis. Stratified analyses based on years postpartum, severity, and onset of preeclampsia were performed.

**Results:** We included 59 studies for qualitative review, of which 56 were included in quantitative meta-analysis, involving 1,262,726 women with prior HDP and 14,711,054 controls. Women with prior HDP had increased risks of hypertension (relative risk [RR] 3.46, 95% confidence interval [CI]: 2.67–4.49), ischemic heart disease (RR 2.06, 95% CI: 1.38–3.08), and heart failure (RR 2.53, 95% CI: 1.28–5.00) later in life, compared with those with normotensive pregnancies. The risk of hypertension was highest during 5 years postpartum (RR 5.34, 95% CI: 2.74–10.39). Compared with normotensive pregnancies, the risk of future CVDs significantly increased in preeclamptic women.

**Discussion:** A history of HDP is associated with approximately 2- to 4-fold increase in the risk of CVDs. Screening for CVDs and their risk factors in women with prior HDP since delivery, especially the first 5 years after delivery is suggested for early detection and appropriate management. Evidence on the risks of CVDs in preeclampsia with severe features and early onset of preeclampsia is limited due to having few studies and high heterogeneity.

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**Abbreviations:** ACOG = American College of Obstetricians and Gynecologists, CI = confidence interval, CVD = cardiovascular diseases, HDP = hypertensive disorders of pregnancy, MOOSE = Meta-Analyses and Systematic Reviews of Observational Studies, NOS = Newcastle-Ottawa Scale, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analysis, RR = relative risk.

**Key Words:** cardiovascular diseases, hypertension, hypertension disorders of pregnancy, preeclampsia

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## 1. Introduction

Cardiovascular diseases (CVDs) are a group of conditions affecting the heart and/or blood vessels, such as ischemic heart disease, venous thromboembolism, peripheral artery disease, and stroke.[1] In 2019, CVDs accounted for 17.9 million deaths globally, of which 80% occurred in low- and middle-income countries.[2] CVDs have also become a leading cause of death in Thailand for decades.[3] Well-known risk factors for CVDs include older age, family history of CVDs, smoking, hypertension, diabetes mellitus, and dyslipidemia.[4] However, there are several risk factors that are specific for women and one of them is hypertensive disorders of pregnancy (HDP).[5]

HDP are the most common medical complications in pregnancy and roughly affect 5% to 8% of all pregnant women.[6] Among HDP, preeclampsia (hypertension plus proteinuria) is the largest contributor to maternal and neonatal morbidity.[7,8] Adverse maternal and neonatal outcomes are more likely to occur in women with eclampsia, preeclampsia superimposed on chronic hypertension, preeclampsia with severe features (severe hypertension and/or significant end-organ injury),[8,9] and early-onset preeclampsia (developed before 34 completed weeks of gestation).[10] Women with prior preeclampsia are also associated with an approximately 2- to 4-fold increased risk for developing hypertension and CVDs later on in life in 4 previous systematic reviews.[11–14] Although the association between future CVDs and HDP is well-established, previous studies have not focused on the severity of HDP or risks in different years after index pregnancy. This is important as there are the changes of cardiovascular risks in different years after HDP.[15]

According to immediate postpartum care, women with pregnancy complicated by HDP are usually advised to measure blood pressure at 3 to 10 days postpartum and to visit routine postpartum care at 6 weeks postpartum.[16–18] National guidelines from the United States, United Kingdom, Norway, and Netherlands recommend the monitoring of blood pressure after HDP.[5,16–20] These guidelines advise counseling women about the higher risk of CVDs later in life, as well as in regards to a healthy life style including exercise, smoking cessation, balanced diet, and optimal weight. Nevertheless, the timing of the postpartum follow-up visit varies from 3 to 5 months postpartum up to screening at the age of 50 and most guidelines do not differentiate between follow-up durations on the basis of the severity and onset of preeclampsia.[5,16,18,19]

To date, there is insufficient information on the progression after HDP to future CVDs. The optimal timing and frequency of postpartum follow-up visits in women with prior HDP are still unknown. A systematic review evaluating the risk of future CVDs in different years postpartum can provide information on the natural history and is useful for the development of CVDs screening guidelines in women with prior HDP. Moreover, identifying women at risk of future CVDs is beneficial for promoting primary prevention and early detection of CVDs in these women. This systematic review aimed to evaluate the risk of cardiovascular outcomes later in life in women with prior HDP, in regards to different postpartum years, preeclampsia with severe features, and early onset of preeclampsia.

## 2. Methods

### 2.1. Search strategy

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) and Meta-Analyses and Systematic Reviews of Observational Studies (MOOSE).[21,22] The review protocol was registered in the PROSPERO International Prospective Register of Systematic Reviews (CRD42020191550).

We searched articles published in any language in MEDLINE, Cochrane Library, Web of Science, and Scopus from inception to March 16, 2022. Detailed search strategies are provided in Supplemental Digital Content, http://links.lww.com/MD/G949. For those articles which full texts were not available, authors were contacted to ask for the full texts.[23,24] Articles in languages other than English were translated using Google Translate. Duplicated articles were identified and removed using Zotero software before assessing the remaining articles.

### 2.2. Study selection

We included retrospective and prospective cohort studies assessing cardiovascular outcomes after 6 weeks postpartum in women with prior HDP compared with controls. HDP was classified and defined in regard to American College of Obstetricians and Gynecologists (ACOG) guidelines.[25] Women with prior HDP, as the exposure, included gestational hypertension and preeclampsia, not chronic hypertension. Gestational hypertension is defined as "*a systolic blood pressure of 140 mm Hg or more or a diastolic blood pressure of 90 mm Hg or more, or both detected after 20 weeks of gestation in a woman with a previously normal blood pressure*." Preeclampsia is defined as gestational hypertension with proteinuria that severe features include systolic blood pressure of 160 mm Hg or more, or diastolic blood pressure of 110 mm Hg or more, thrombocytopenia, impaired liver function, renal insufficiency, pulmonary edema, new-onset headache unresponsive to medication, and visual disturbances. Controls were defined as women with prior normotensive pregnancies, preeclampsia without severe features, or late-onset preeclampsia (developed after 34 completed weeks of gestation) depending on individual included studies. Case-control studies were excluded due to selection and recall biases. There was no restriction based on the severity of preeclampsia or duration of follow-up.

Cardiovascular outcomes in this review included hypertension (blood pressure ≥ 140/90 mm Hg), ischemic heart disease, heart failure, venous thromboembolism, peripheral vascular disease, stroke, dementia, cardiovascular and/or cerebrovascular diseases, cardiovascular mortality, and all-cause mortality. Ischemic heart disease included coronary heart disease, myocardial infarction, angina pectoris, coronary artery bypass grafting, coronary angioplasty, and balloon dilatation or stent placement. Venous thromboembolism included deep venous thrombosis and pulmonary embolism. Stroke included both hemorrhagic and ischemic cerebrovascular accidents. Composite cardiovascular and/or cerebrovascular diseases included any cardiovascular and cerebrovascular diseases. If there were multiple publications based on the same cohort, data from the study with the most comprehensive information and largest sample size, in descending priority order, were selected and extracted to avoid overlapping in data.

Two authors (JS and TL) independently screened the title and abstract of all search results in Rayyan software. Full texts of potentially relevant articles were further retrieved and assessed for eligibility by the same authors. Disagreements were resolved through discussion between 2 authors. The number of included and excluded articles was reported using the PRISMA flow diagram.

### 2.3. Data extraction and methodological assessment

Data were extracted by 2 authors independently. Extracted data included year of publication, country, study design and setting, inclusion and exclusion criteria, ascertainment of exposures and outcomes, outcomes per group, sample size of each group, follow-up duration, baseline characteristics of participants (age, parity, family history of HDP and CVDs, underlying diseases,

smoking status, and body mass index), and covariates used for adjustment or matching.

Two authors assessed the quality of included articles independently using the Newcastle-Ottawa Scale (NOS).[26] The NOS consisted of 8 items in 3 key domains with a maximum score of 9 stars: selection of study groups (four stars), comparability of groups (two stars), and ascertainment of outcomes (three stars). The detailed criteria for the NOS are provided in Supplemental Digital Content, http://links.lww.com/MD/G949. Studies with NOS scores of 0 to 3, 4 to 6, and 7 to 9 were classified as having low, moderate and high quality, respectively. Grading of Recommendations Assessment, Development and Evaluation (GRADE) methods were carried out based on 5 domains, namely risk of bias, imprecision, inconsistency, indirectness, and publication bias.[27] The quality of evidence for each outcome was then presented as very low, low, moderate or high certainty in the summary of findings table.

### 2.4. Statistical analysis

We used an inverse variance method to calculate the effect size in terms of pooled relative risk (RR) at a 95% confidence interval (CI). A random-effect model was chosen as a substantial variation in study population and methodology was expected. A continuity correction of 0.1 was added to the number of events in studies with zero events. Meta-analyses of each cardiovascular outcome were stratified to assess the associations among: (1) women with prior HDP pregnancy, (2) women with preeclampsia with severe features only, (3) women with preeclampsia without severe features only, and (4) women with early-onset preeclampsia only, in comparison with women with prior normotensive pregnancies. Additional stratified analyses based on different years postpartum at ≤ 5 years, 6 to 10 years, 11–15 years, and > 15 years after index pregnancy were performed. Due to no standard years postpartum recommended for following up women with prior HDP for future risk of cardiovascular diseases, we used the 25th percentiles of known average years from the included studies, accounted for 5 years for stratification.

Heterogeneity was assessed using $I^2$ test, where $I^2$ values more than 50% was considered as having substantial heterogeneity.[28] If there was a substantial heterogeneity, a sensitivity analysis was performed considering the outlier and influence studies.[29] Possible publication bias was estimated by funnel plot visualization and the arcsine-Thompson test when there were at least ten studies included.[30] A $P$ value of <.05 was

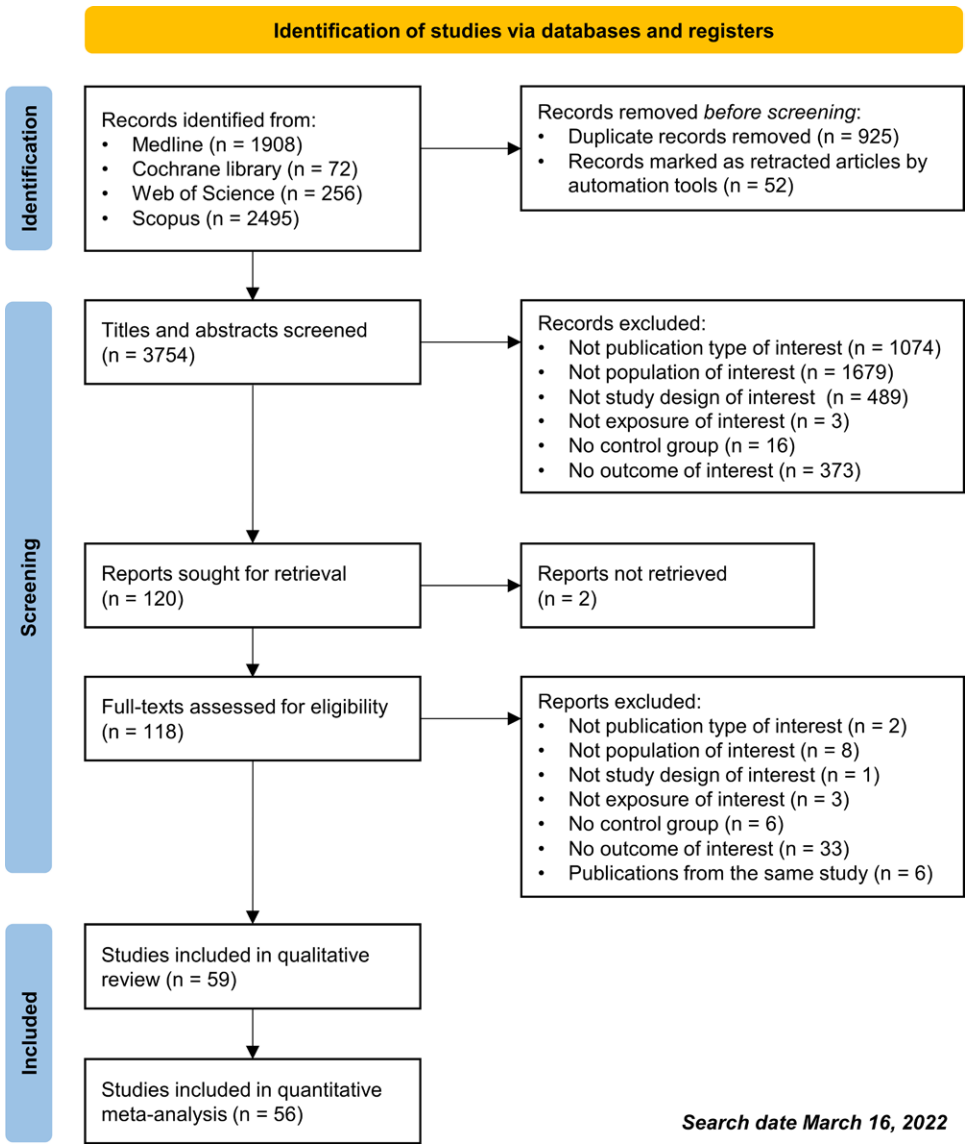


**Figure 1.** PRISMA flow diagram.

**Table 1**

**Characteristics of included studies.**

| Author, year | Country | Study design | Exposure | No. of exposed | No. of control | Average duration (y) | Outcome |
|---|---|---|---|---|---|---|---|
| Kestenbaum, 2003[34] | United States | Retrospective cohort | Gestational hypertension, mild preeclampsia, severe preeclampsia | 31,239 | 92,902 | 7.8 (mean) | Myocardial infarction, venous thromboembolism |
| Lykke, 2009*[35] | Denmark | Retrospective cohort | Gestational hypertension, mild preeclampsia, severe preeclampsia | 41,275 | 741,012 | 14.6 (median) | **Hypertension, myocardial infarction**, heart failure, **venous thromboembolism, stroke** |
| Edlow, 2009[36] | United States | Prospective cohort | Preeclampsia | 74 | 127 | 0.6 (mean) | Hypertension |
| Garovic, 2010[37] | United States | Retrospective cohort | Hypertensive pregnancy, preeclampsia | 643 | 3421 | NS | Hypertension, myocardial infarction, stroke |
| Mongraw-Chaffin, 2010[38] | United States | Retrospective cohort | Preeclampsia | 481 | 13,922 | 37 (median) | Cardiovascular disease death |
| Melchiorre, 2011[39] | United Kingdom | Prospective cohort | Preeclampsia | 64 | 78 | NS | Hypertension |
| Drost, 2012[40] | Netherlands | Prospective cohort | Early-onset preeclampsia | 339 | 332 | 9.9 (mean) | Hypertension |
| Zhao, 2012[41] | China | Retrospective cohort | Hypertensive pregnancy | 581 | 3278 | 15.3 (mean) | Myocardial infarction, ischemic stroke, hemorrhagic stroke |
| Collen, 2013[42] | Sweden | Prospective cohort | Hypertensive pregnancy | 50 | 55 | NS | Hypertension |
| Callaway, 2013[43] | Australia | Prospective cohort | Hypertensive pregnancy | 191 | 1926 | NS | Hypertension |
| Shalom, 2013[44] | Israel | Retrospective cohort | Preeclampsia | 2072 | 20,742 | NS | Hypertension |
| Östlund, 2013[45] | Sweden | Prospective cohort | Severe preeclampsia | 15 | 16 | 11.2 (mean) | Hypertension |
| Kvehaugen, 2014†[46] | Norway | Retrospective cohort | Preeclampsia | 934 | 2011 | 15.1 (mean) | **Hypertension**, cardiovascular disease |
| Zhou, 2014[47] | China | Prospective cohort | Preeclampsia | 651 | 2684 | 3.1 (mean) | Hypertension |
| Ghossein-Doha, 2014[48] | Netherlands | Prospective cohort | Preeclampsia | 20 | 8 | NS | Hypertension |
| Yeh, 2014‡[49] | Taiwan | Retrospective cohort | Hypertensive pregnancy | 1260 | 5040 | 5.8 (median) | Hypertension, **cardiovascular disease** |
| Breetveld, 2014[50] | Netherlands | Prospective cohort | Preeclampsia | 115 | 50 | 6.2 (median) | Hypertension, cardiovascular disease |
| Ehrenthal, 2015[51] | United States | Prospective cohort | Hypertensive pregnancy | 31 | 40 | NS | Hypertension |
| Behrens, 2016*[52] | Denmark | Retrospective cohort | Gestational hypertension, mild preeclampsia, severe preeclampsia | 51,992 | 1,023,771 | 17.9 (mean) | **Cardiomyopathy, heart failure** |
| Cain, 2016[53] | United States | Retrospective cohort | Gestational hypertension, preeclampsia | 24,221 | 265,973 | 4.8 (median) | Cardiovascular disease |
| Nelander, 2016[54] | Sweden | Retrospective cohort | Gestational hypertension, preeclampsia | 382 | 2646 | NS | Dementia, cardiovascular disease, stroke |
| Pérez-Adan, 2016[55] | Spain | Retrospective cohort | Hypertensive pregnancy | 134 | 145 | 13.1 (mean) | Hypertension, stroke |
| Grandi, 2017§[56] | United Kingdom | Retrospective cohort | Hypertensive pregnancy | 5399 | 141,349 | 4.7 (median) | Cardiovascular disease, **hypertension** |
| Timpka, 2017[57] | Netherlands | Prospective cohort | Hypertensive pregnancy | 5520 | 49,068 | NS | Hypertension |
| Dunietz, 2017[58] | United States | Prospective cohort | Hypertensive pregnancy | 78 | 190 | 11.0 (median) | Hypertension |
| Best, 2017[59] | United States | Prospective cohort | Preeclampsia | 130 | 288 | 13.1 (mean) | Hypertension |
| Ghossein-Doha, 2017[60] | Netherlands | Prospective cohort | Preeclampsia | 107 | 41 | 5.6 (median) | Hypertension |
| Bokslag, 2018[61] | Netherlands | Prospective cohort | Early-onset preeclampsia | 131 | 56 | 13.4 (mean) | Hypertension |
| Li, 2018[62] | Singapore | Prospective cohort | Hypertensive pregnancy | 23 | 253 | NS | Hypertension |
| Chen, 2018[63] | Taiwan | Retrospective cohort | Hypertensive pregnancy | 29,186 | 116,744 | 5.7 (mean) | Heart failure |
| Bergen, 2018[64] | Netherlands | Retrospective cohort | Gestational hypertension, preeclampsia | 300 | 4612 | 6 (median) | Hypertension |
| Theilen, 2018[65] | United States | Retrospective cohort | Hypertensive pregnancy | 57,384 | 114,768 | NS | All-cause mortality |
| Basit, 2018*[66] | Denmark | Retrospective cohort | Preeclampsia | 58,410 | 1,119,595 | 21.1 (median) | **Dementia** |
| Kuo, 2018‡[67] | Taiwan | Retrospective cohort | Preeclampsia | 1295 | 5180 | 9.8 (median) | Hypertension, **myocardial infarction, peripheral vascular disease**, heart failure, stroke |
| Egeland, 2018[68] | Norway | Retrospective cohort | Gestational hypertension, preeclampsia | 3381 | 56,646 | 7.1 (mean) | Hypertension |
| Haas, 2019[69] | United States | Prospective cohort | Hypertensive pregnancy, preeclampsia | 581 | 3355 | 3.0 (mean) | Hypertension |
| Haug, 2019†[70] | Norway | Retrospective cohort | Hypertensive pregnancy, gestational hypertension, preeclampsia | 2119 | 21,766 | 18.0 (median) | **Cardiovascular disease, myocardial infarction, heart failure, stroke** |
| Amiri, 2019[71] | Iran | Retrospective cohort | Preeclampsia | 355 | 2667 | 3.3 (median) | Hypertension |
| Smith, 2019[72] | Canada | Retrospective cohort | Hypertensive pregnancy, preeclampsia | 375 | 130 | NS | Hypertension |
| Honigberg, 2019[73] | United Kingdom | Prospective cohort | Hypertensive pregnancy | 2808 | 217,216 | 7 (median) | Hypertension, myocardial infarction, heart failure, venous thromboembolism, peripheral artery disease, ischemic stroke |
| Ernawati, 2019[74] | Indonesia | Retrospective cohort | Early-onset preeclampsia | 17 | 25‖ | 5.4 (mean) | Hypertension |
| Osoti, 2019[75] | Kenya | Prospective cohort | Hypertensive pregnancy | 63 | 131 | NS | Hypertension |
| Leon, 2019§[76] | United Kingdom | Retrospective cohort | Preeclampsia | 25,554 | 1,277,811 | 9.2 (median) | **Cardiovascular disease** |

(*Continued*)

**Table 1**

**(*Continued*)**

| Author, year | Country | Study design | Exposure | No. of exposed | No. of control | Average duration (y) | Outcome |
|---|---|---|---|---|---|---|---|
| Arnaout, 2019[77] | United States | Retrospective cohort | Gestational hypertension, preeclampsia | 99,492 | 1,539,445 | 2.7 (median) | Myocardial infarction, heart failure, stroke |
| Huang, 2020‡[78] | Taiwan | Retrospective cohort | Hypertensive pregnancy | 41,870 | 125,610 | 4.9¶ | **Hypertension, heart disease, stroke** |
| Scheres, 2020[79] | Netherlands | Retrospective cohort | Hypertensive pregnancy, preeclampsia | 264,135 | 1,624,849 | 13.7 (median) | Venous thromboembolism |
| Wagata, 2020[80] | Japan | Retrospective cohort | Hypertensive pregnancy | 1585 | 31,827 | NS | Hypertension |
| Garovic, 2020[81] | United States | Retrospective cohort | Hypertensive pregnancy | 571 | 1142 | 35.9 (median) | Myocardial infarction, heart failure, stroke, dementia, hypertension |
| Bergman, 2020[82] | Sweden | Retrospective cohort | Preeclampsia | 34,923 | 857,502 | NS | Cardiovascular disease |
| Moe, 2020[83] | Norway | Prospective cohort | Gestational hypertension, early- and late-onset preeclampsia | 116 | 94 | 1.1 (median) | Hypertension |
| Sharma, 2021[84] | Sweden | Prospective cohort | Preeclampsia | 115 | 2319 | 49.9 (median) | Cardiovascular diseases |
| Mooij, 2021[85] | Tanzania | Retrospective cohort | Severe preeclampsia, eclampsia | 24 | 72 | NS | Hypertension |
| Ntlemo, 2021[86] | South Africa | Prospective cohort | Preeclampsia | 150 | 163 | NS | Hypertension |
| Nuckols, 2021[87] | United States | Retrospective cohort | Preeclampsia | 23 | 38 | 1.5 (mean) | Hypertension |
| Oliver-Williams, 2022[88] | United Kingdom | Retrospective cohort | Gestational hypertension, preeclampsia | 159,819 | 2,199,567 | NS | Cardiovascular diseases, stroke, myocardial infarction, heart failure, cardiomyopathy, cardiac arrhythmia |
| Park, 2022[89] | Korea | Retrospective cohort | Gestational hypertension, preeclampsia or eclampsia | 37,297 | 1,998,387 | NS | Cardiac arrhythmia |
| Hung, 2022‡[90] | Taiwan | Retrospective cohort | Hypertensive pregnancy | 13,617 | 54,468 | NS | **Stroke** |
| Kennedy, 2022[91] | Australia | Prospective cohort | Gestational hypertension, preeclampsia | 15 | 34 | NS | Hypertension |
| van Baar, 2022[92] | Netherlands | Retrospective cohort | Gestational hypertension, preeclampsia | 258,994 | 963,467 | 11.8 (mean) | Cardiovascular disease death |

* Participants in these 3 studies were drawn from Denmark National Patient Register (NPR). Outcomes extracted from each study were given in boldface.

† Participants in these 2 studies were drawn from Norway Nord-Trøndelag Health (HUNT) Study. Outcomes extracted from each study were given in boldface.

‡ Participants in these 4 studies were drawn from Taiwan National Health Insurance Research Database (NHIRD). Outcomes extracted from each study were given in boldface.

§ Participants in these 2 studies were drawn from United Kingdom's Clinical Practice Research Datalink (CPRD). Outcomes extracted from each study were given in boldface.

|| Controls were women with late-onset preeclampsia.

¶ Calculated from the total number of women years.

NS = Not specified; y = years.

considered as statistical significance for all pooled estimates. Statistical analyses were performed with R version 4.0.4 (2020 The R Foundation for Statistical Computing, Vienna, Austria)[31] using the "meta"[32] and "dmetar"[33] packages.

## 3. Results

### 3.1. Study identification and study characteristics

Study identification and selection processes in the PRISMA diagram are shown in Figure 1. The initial searches result in 3754 titles and abstracts. After screening based on eligibility criteria, 59 included studies were qualitatively reviewed, and 56 of them were quantitatively reviewed in the meta-analysis. Table 1 presents the characteristics of the studies included. There were 59 studies involving 1,262,726 women with prior HDP and 14,711,054 controls. These studies were conducted in Europe (27 studies),[35,39,40,42,45,46,48,50,52,54–57,60,61,64,66,68,70,73,76,79,82–84,88,92] North America (14 studies),[34,36–38,51,53,58,59,65,69,72,77,81,87] Asia (12 studies),[41,47,49,62,63,67,71,74,78,80,89,90] and other regions of the world.[43,44,75,85,86,91] The study design of the studies included was the retrospective cohort for 36 of them[34,35,37,38,41,44,46,49,52–56,63–68,70–72,74,76–82,85,87–90,92] and the prospective cohort for the remaining 23 studies.[36,39,40,42,43,45,47,48,50,51,57–62,69,73,75,83,84,86,91] In 23 studies, only women with preeclampsia were included[36,38–40,44–48,50,59–61,66,67,71,74,76,82,84–87] and the other 36 studies included women with gestational hypertension and preeclampsia.[34,35,37,41–43,49,51–58,62–65,68–70,72,73,75,77–81,83,88–92] The control subjects in all studies were women with prior normotensive pregnancies, except 1 study that compared women who had early-onset preeclampsia to those with late-onset preeclampsia[74] which was not quantitatively analyzed in this meta-analysis. Mean or median follow-up duration was reported in 39 studies, and its weighted average was 11.6 years postpartum.

### 3.2. Study quality and risk of bias assessment

Assessments of study quality and risk of bias are demonstrated in Tables S1 and S2, Supplemental Digital Content, http://links.lww.com/MD/G949. Using the NOS, 40 studies were considered as high quality[34,35,37,38,41,43,45,48,49,51–53,55,56,59,61,63–70,73–79,81–84,88–92] and the rest were identified as moderate quality.[36,39,40,42,44,46,47,50,54,57,58,60,62,71,72,80,85–87] In 55 out of the 59 studies, women with HDP, served as the representative exposed participants, were selected from national databases or hospital medical record systems. Controls in all but 1 study were drawn from the same source as exposed women.[72] Self-report or interview was used in 5 studies for measuring exposure[57,62,71,73,80] and in 4 studies for measuring outcome.[36,37,46,57] Definition of study outcome (hypertension) was not reported in 4 studies.[39,42,45,50] Nine studies did not clearly state outcomes of interest in the methods of the studies.[36,39,40,42,54,55,58,72,80] Only 21 studies clearly showed the adjustment for both key confounding factors (age, smoking, and body mass index) and other factors,[37,38,43,45,51,53,54,56,57,59,61,64,68,69,73,77,81,84,88,89,91] while 8 studies did not adjust for any factors.[44,50,60,71,85–87,92] Adequate follow-up duration was reported in 27 studies. Data regarding completeness of follow-up were unavailable in 25

studies[37,38,43,44,46,49–51,53,54,56,57,59,60,63,65–68,72,76,78,88,90,91] and 7 of them had follow-up rates that were <80%.[36,40,47,48,58,69,74] The summary of findings table of each outcome is presented in Table S3, Supplemental Digital Content, http://links.lww.com/MD/G949.

### 3.3. Risk of hypertension later in life

***3.3.1. Women with prior HDP versus normotensive pregnancies.*** Of 56 studies included in the meta-analysis, 37 evaluated the risk of hypertension, later in life, in women with prior HDP in comparison to women with normotensive pregnancies involving 16 studies including only women with preeclampsia and 21 studies including women with gestational hypertension and preeclampsia (Fig. 2).[35–37,39,40,42–48,50,51,55–62,64,68,69,71–73,75,78,80,81,83,85–87,91] Substantial heterogeneity was found in total meta-analysis ($I^2$ = 99%). When stratified analyses based on different years postpartum were considered, substantial heterogeneities existed, except in the group with 15 years or more postpartum years. The findings of random-effect models showed that women with prior HDP had significantly higher risk of hypertension (RR 3.46, 95% CI: 2.67–4.49; $I^2$ = 99%; 37 studies; 1,517,583 women; low certainty of evidence), compared to women without prior HDP, of which the RRs at different years postpartum at ≤ 5 years, 6 to 10 years, 11–15 years, and > 15 years were accounted for 5.34 (95% CI: 2.74–10.39; $I^2$ = 98%; 7 studies; 321,971 women; very low certainty of evidence), 4.22 (95% CI: 2.19–8.10; $I^2$ = 98%; 6 studies; 285,947 women; very low certainty of evidence), 3.27 (95% CI: 2.02–5.30; $I^2$ = 97%; 7 studies; 786,479 women; low certainty of evidence), and 1.79 (95% CI: 1.22–2.61; $I^2$ = 0%; 2 studies; 4535 women; low certainty of evidence), respectively. Similar findings were observed when a sensitivity analysis was performed.

***3.3.2. Women with prior preeclampsia in different severity and onset versus normotensive pregnancies.*** The risk of hypertension later in life in women with prior preeclampsia based on severity and onset in comparison to women with prior normotensive pregnancies is presented in Figure 3. Four studies evaluated the risk of hypertension later on in the life of women with prior preeclampsia that has severe features[35,45,47,88] and 2 studies evaluated the same but for those without severe features,[35,47] respectively. Women with prior preeclampsia with severe features had a greater risk of hypertension (RR 6.67, 95% CI: 1.51–29.40, $I^2$ = 91%; 4 studies; 751,128 women; very low certainty of evidence) compared with normotensive pregnancies. Wide CI of the risk of hypertension in women without severe features was found. In 2 studies, the risk of hypertension in later life of women with prior early-onset preeclampsia was 2.53 (95% CI: 1.93–3.32, $I^2$ = 0%; 2 studies; 858 women; low certainty of evidence).[40,61]

## 4. Risk of Cardiovascular Disease Later in Life

### 4.1. Women with prior HDP versus normotensive pregnancies

The risk of 4 CVDs later in life including ischemic heart disease, heart failure, venous thromboembolism, and peripheral vascular disease is presented in Figure 4A–D. There were ten studies evaluating the risk of ischemic heart disease later in life for women with prior HDP compared with women with normotensive pregnancies (Fig. 4A).[34,35,37,41,67,70,73,77,81,88] Women with prior HDP had approximately a twofold increase in risk (RR 2.06, 95% CI: 1.38–3.08, $I^2$ = 83%; 10 studies; 5,168,215 women; low certainty of evidence). Substantial heterogeneity and similar results were also observed after we performed a sensitivity analysis. In 7 studies evaluating the risk of heart failure later in life, women with prior HDP were found to have significantly greater risk compared with women that have prior normotensive pregnancies (RR 2.53, 95% CI: 1.28–5.00, $I^2$ = 97%; 7 studies; 5,469,345 women; very low certainty of evidence) as shown in Figure 4B.[52,63,70,73,77,81,88] Sensitivity analysis did not change the heterogeneity and findings.

The risk of venous thromboembolism later in life in women with prior HDP was not significantly higher than in women with normotensive pregnancies in 4 studies (Fig. 4C) with RR of 1.34 (95% CI: 0.84–2.24, $I^2$ = 69%; 4 studies; 3,015,436 women; very low certainty of evidence).[34,35,73,79] In sensitivity analysis, the heterogeneity was not substantial and found that the risk of venous thromboembolism probably increased for women with prior HDP (RR 1.47, 95% CI: 1.20–1.80, $I^2$ = 46%; 3 studies; 2,795,412 women; low certainty of evidence). Three studies evaluated the risk of peripheral vascular disease later in life in regards to women with prior HDP (Fig. 4D).[67,73,88] The risk of peripheral vascular disease for women with prior HDP and normotensive pregnancies was not statistically different and a wide CI was also observed. The risks of ischemic heart disease, heart failure, and venous thromboembolism at different years postpartum showed high heterogeneity and a very low to low certainty of evidence.

### 4.2. Women with prior preeclampsia in different severity versus normotensive pregnancies

Two studies evaluated the risks of ischemic heart disease (Fig. 5A) and venous thromboembolism (Fig. 5B) later in life for women with different severity of preeclampsia compared with women with prior normotensive pregnancies.[34,35] Compared with women with prior normotensive pregnancies, the RRs of developing ischemic heart disease and venous thromboembolism in women with prior preeclampsia with severe features were 2.11 (95% CI: 0.04–113.97, $I^2$ = 73%; 2 studies; 845,974 women; very low certainty of evidence) and 2.00 (95% CI: 0.41–9.78, $I^2$ = 0%; 2 studies; 845,974 women; very low certainty of evidence), respectively. Women with prior preeclampsia without severe features had a slightly higher risk of developing ischemic heart disease (RR 1.92, 95% CI: 1.09–3.38, $I^2$ = 0%; 2 studies; 876,232 women; low certainty of evidence) and venous thromboembolism (RR 1.64, 95% CI: 1.55–1.73, $I^2$ = 0%; 2 studies; 876,232 women; low certainty of evidence) compared with women with prior normotensive pregnancies.

### 4.3. Risk of cerebrovascular disease later in life

The risks of stroke and dementia later in life in women with prior HDP compared with women with normotensive pregnancies are demonstrated in Figure 6A and B, respectively. In regards to twelve studies evaluating the risk of stroke later in life, women with prior HDP had a greater risk compared with women with prior normotensive pregnancies (RR 1.59, 95% CI: 1.08–2.33, $I^2$ = 91%; 12 studies; 5,276,478 women; low certainty of evidence).[35,37,41,54,55,70,73,77,78,81,88,90] Furthermore, the risks of stroke at different years postpartum showed high heterogeneity and low certainty of evidence. Similar findings were detected when performing a sensitivity analysis. In 3 studies, the risk of dementia later in life in women with prior HDP in comparison to women with normotensive pregnancies was 1.37 (95% CI: 0.70–2.71, $I^2$ = 44%; 3 studies; 1,182,746 women; very low certainty of evidence).[54,66,81]

### 4.4. Risk of composite cardiovascular and/or cerebrovascular diseases later in life

In 8 studies, the risks of composite cardiovascular and/or cerebrovascular diseases later on in life for women with prior HDP

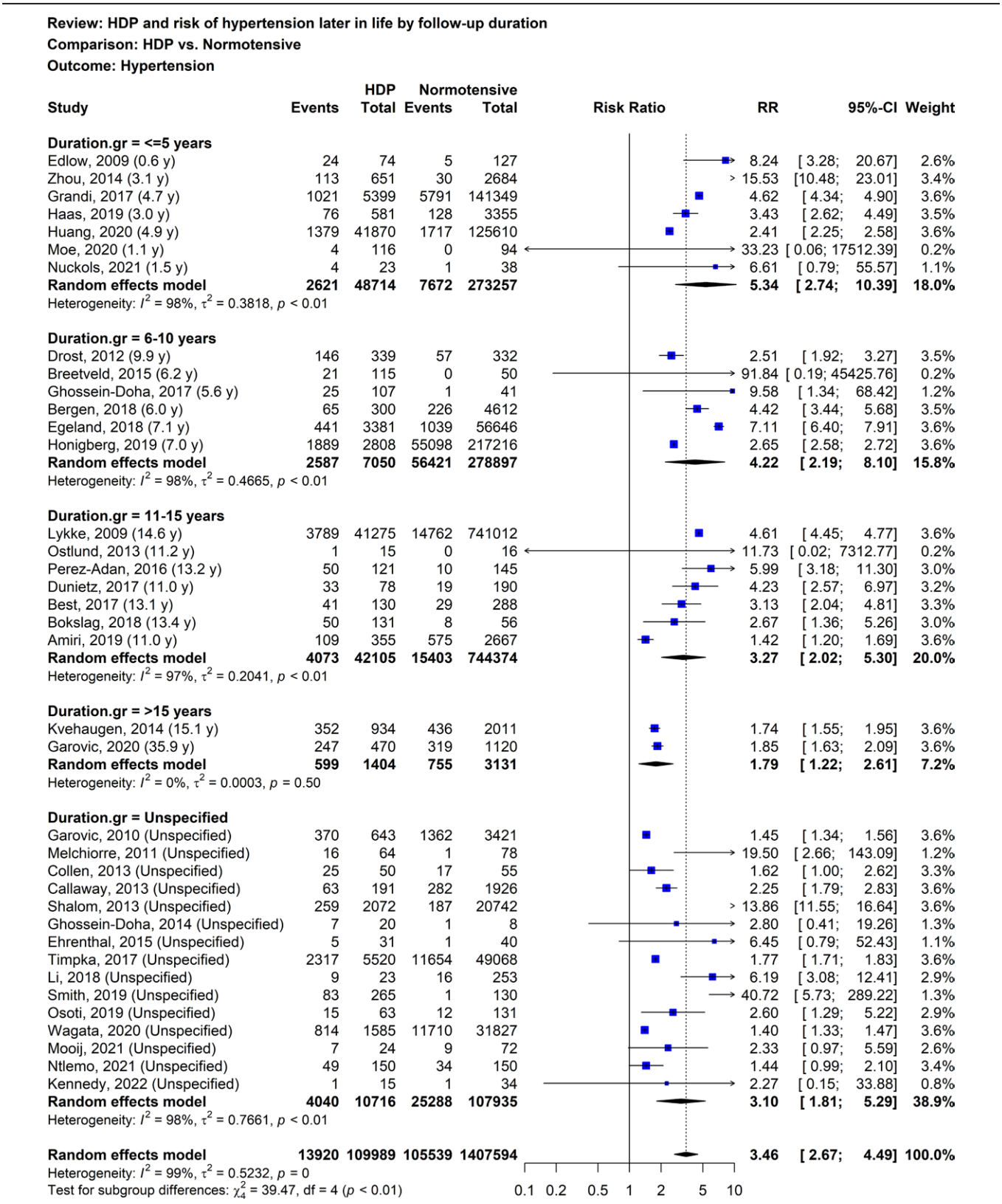


**Figure 2.** Forest plot of HDP and risk of hypertension later in life by follow-up duration. HDP = hypertensive disorder of pregnancy.

compared with women that had normotensive pregnancies are shown in Figure S1, Supplemental Digital Content, http://links.lww.com/MD/G949.[41,49,53,70,76,82,84,88] We found that women with prior HDP had a higher risk of composite cardiovascular and/or cerebrovascular diseases (RR 1.91, 95% CI: 1.18–3.09, $I^2$ = 97%; studies; 4,885,556 women; very low certainty of evidence). The risks of composite cardiovascular and/or cerebrovascular diseases at 6 to 10 years increased by 2.09 (95% CI: 1.19–3.66, 3 studies, $I^2$ = 97.2%; studies; women; very low certainty of evidence). The estimated effects in each group were significantly different. When performing a sensitivity analysis, substantial heterogeneity and similar results were observed.

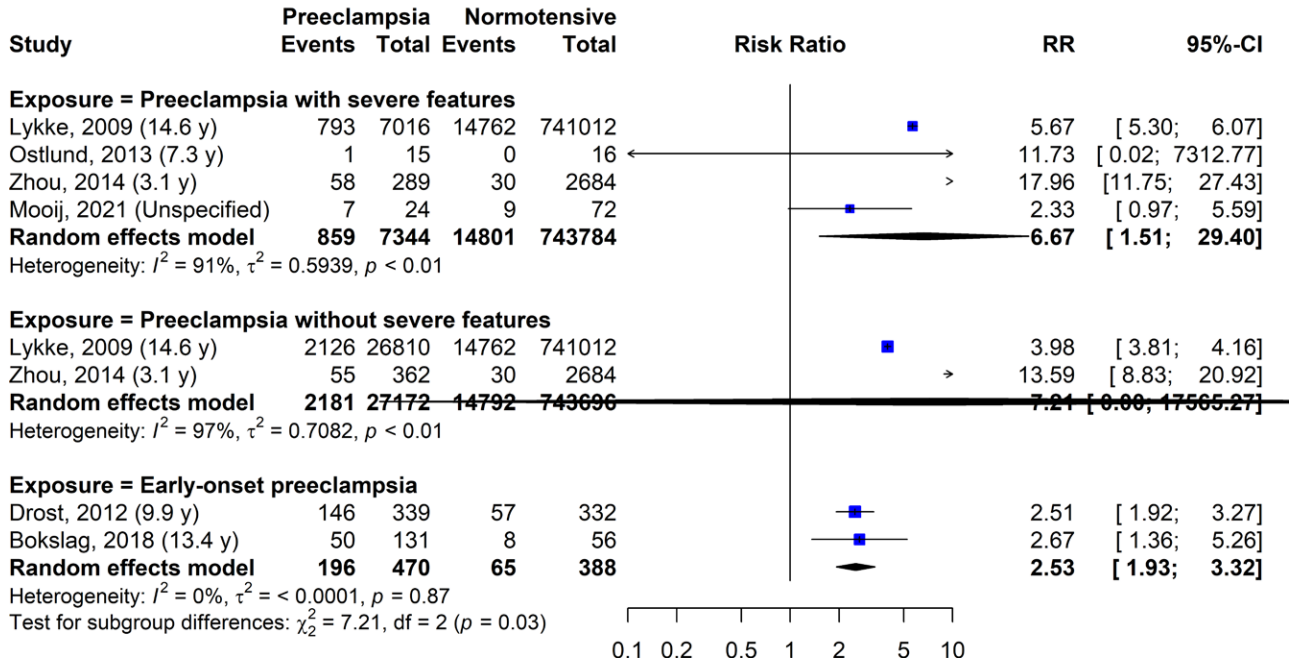


**Figure 3.** Forest plot of preeclampsia and risk of hypertension later in life by severity and onset of disease.

### *4.5. Risk of mortality later in life*

Only 3 studies evaluated the risk of mortality later on in life for women with prior HDP compared with women that had normotensive pregnancies: 2 for cardiovascular-specific mortality and another for all-cause mortality. The pooled RR for cardiovascular-specific mortality in women with prior HDP was 2.81 (95% CI: 2.55–3.09, 2 studies, $I^2$ = 0%; 2 studies; women; low certainty of evidence)[38,92] and the RR for all-cause mortality reported in a study was 1.32 (95% CI: 1.27–1.36)[65] comparing with normotensive pregnancies (Figure S2, Supplemental Digital Content, http://links.lww.com/MD/G949).

## 5. Discussion

Women with HDP had elevated risks of hypertension, ischemic heart disease, and heart failure later in life throughout postpartum years. Only hypertension had sufficient number of studies to stratify the analysis on its risk later in life for women with prior HDP in different periods of postpartum years. A history of HDP makes little or no difference regarding the risks of future venous thromboembolism, peripheral vascular disease, and dementia. Regardless of severity, women with prior preeclampsia had higher risks of hypertension, ischemic heart disease, and venous thromboembolism than what women with prior normotensive pregnancies had. These findings were based on studies of moderate and high quality. Nonetheless, substantial heterogeneity was found in most outcomes.

The findings of an increasing risk of hypertension later on in life for women with prior HDP in our review were consistent with previous systematic reviews only involving women with prior preeclampsia.[11,14] This may suggest that HDP, regardless of gestational hypertension or preeclampsia, independently affects the risk of hypertension later in life.[93] The highest effect of HDP on the risk of hypertension was during the first 5 years after pregnancy, then it decreased over time. A potential explanation is that hypertension prevalence increases with age[94] that may be more dominant than a HDP history. Furthermore, the risk of hypertension after HDP still existed after performing a sensitivity analysis by excluding the predominated outcome effects studies. However, publication bias in the hypertensive outcome was indicated by an asymmetrical funnel plot (Figure S3, Supplemental Digital Content, http://links.lww.com/MD/G949) with a statistical significance in regards to the arcsine-Thompson test,[30] suggesting that any interpretation should be done with caution. A strong association between a history of preeclampsia with severe features and the risk of future hypertension found in our review could be explained by the synergistic effect of the severity and onset of preeclampsia. However, the wide CI of effects may be due to the variations in women's race and age at follow-up visit among included studies in our systematic review.[35,45]

The increasing risk of ischemic heart disease and heart failure later on in life for women with prior HDP in our systematic review was supported by the findings of previous systematic reviews.[11–13] We also found that the risk of heart failure was higher than ischemic heart disease, which might be confounded by unmeasured CVD risk factors since only 1 included study adjusted for all identified factors including age, smoking, family history of CVDs, BMI, hypertension, diabetes mellitus, and dyslipidemia.[56] The mechanistic association between HDP and future CVDs remains undetermined[95,96]; however, it may be hypothesized that HDP and CVDs generally share common risk factors. In addition, HDP may exaggerate prepregnancy risk factors or cause de novo endothelial injury and metabolic abnormalities possibly resulting in left ventricular hypertrophy,[97] as an independent predictor of CVDs and mortality.[98,99] The interpretation of risks of future ischemic heart disease and venous thromboembolism in women with or without severe features should be done with caution because of the small number of studies in each group and the wide CI in preeclampsia with severe features. We did not find a statistical difference in the risk of peripheral vascular disease for women with prior HDP and normotensive pregnancies. This was consistent with the result

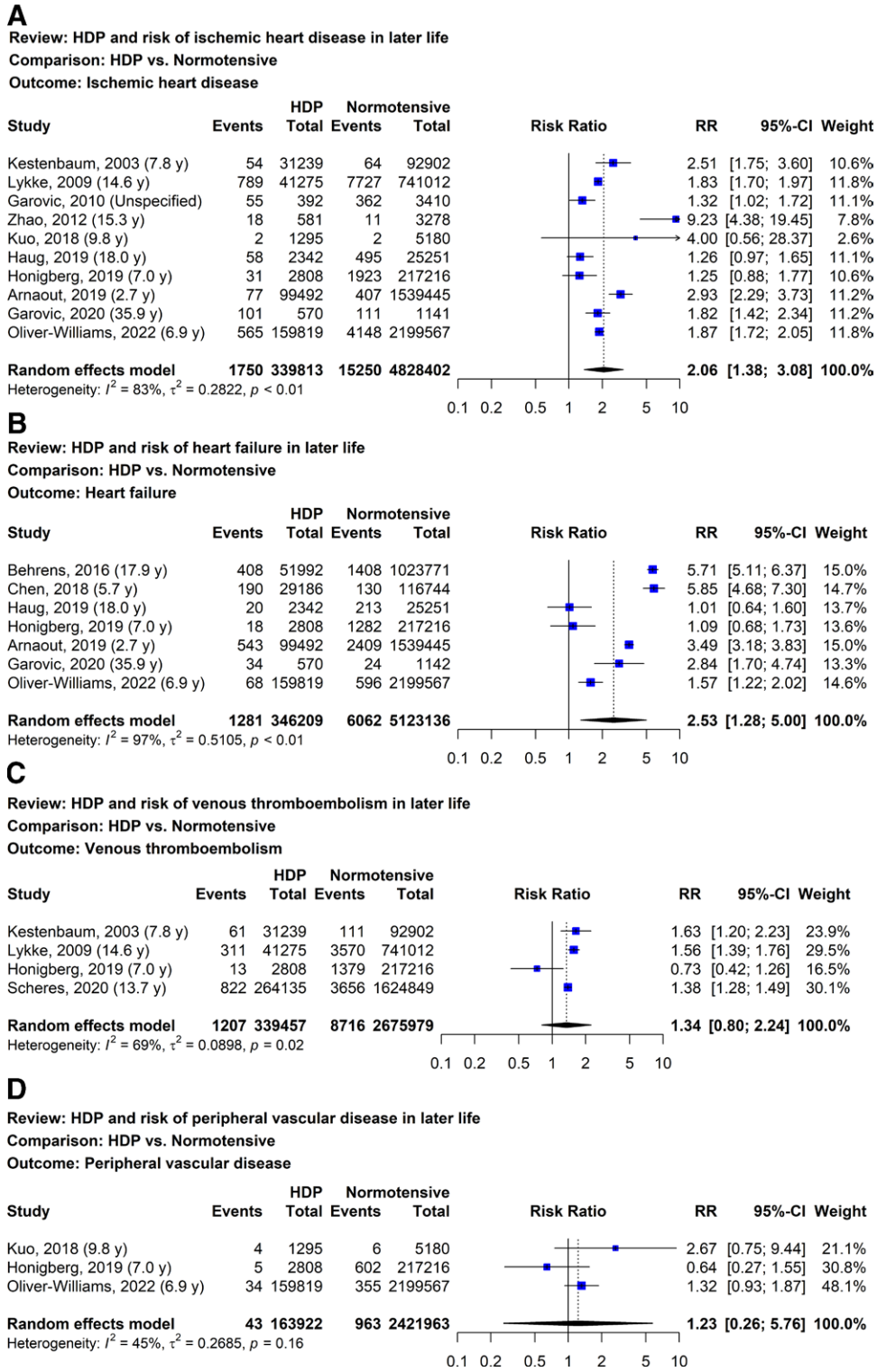


**Figure 4.** Forest plot of HDP and risk of ischemic heart disease (A), heart failure (B), venous thromboembolism (C), and peripheral vascular disease (D) later in life. HDP = hypertensive disorder of pregnancy.

of a previous systematic review,[12] but the estimated effect was imprecise since we could only include 2 studies for this outcome.

The RR of future stroke in women with prior HDP in our systematic review was similar to what was previously reported.[11,13] Substantial heterogeneity between studies might be due to variation in research methodology. For example, 2 studies ascertained exposure status via interview,[37,54] 1 study only explored the risk of ischemic cerebrovascular accident,[73] and 1 study did not include all stroke-related International Classification of Diseases (ICD) codes regarding outcome.[78] We also observed a positive association between history of HDP and the risk of dementia later in life, which was not assessed in the previous review. Nevertheless, the effects of HDP varied and it was possible that they made little or no difference to the risks of future stroke and dementia. Findings on the risk of composite cardiovascular and/or cerebrovascular diseases were consistent with

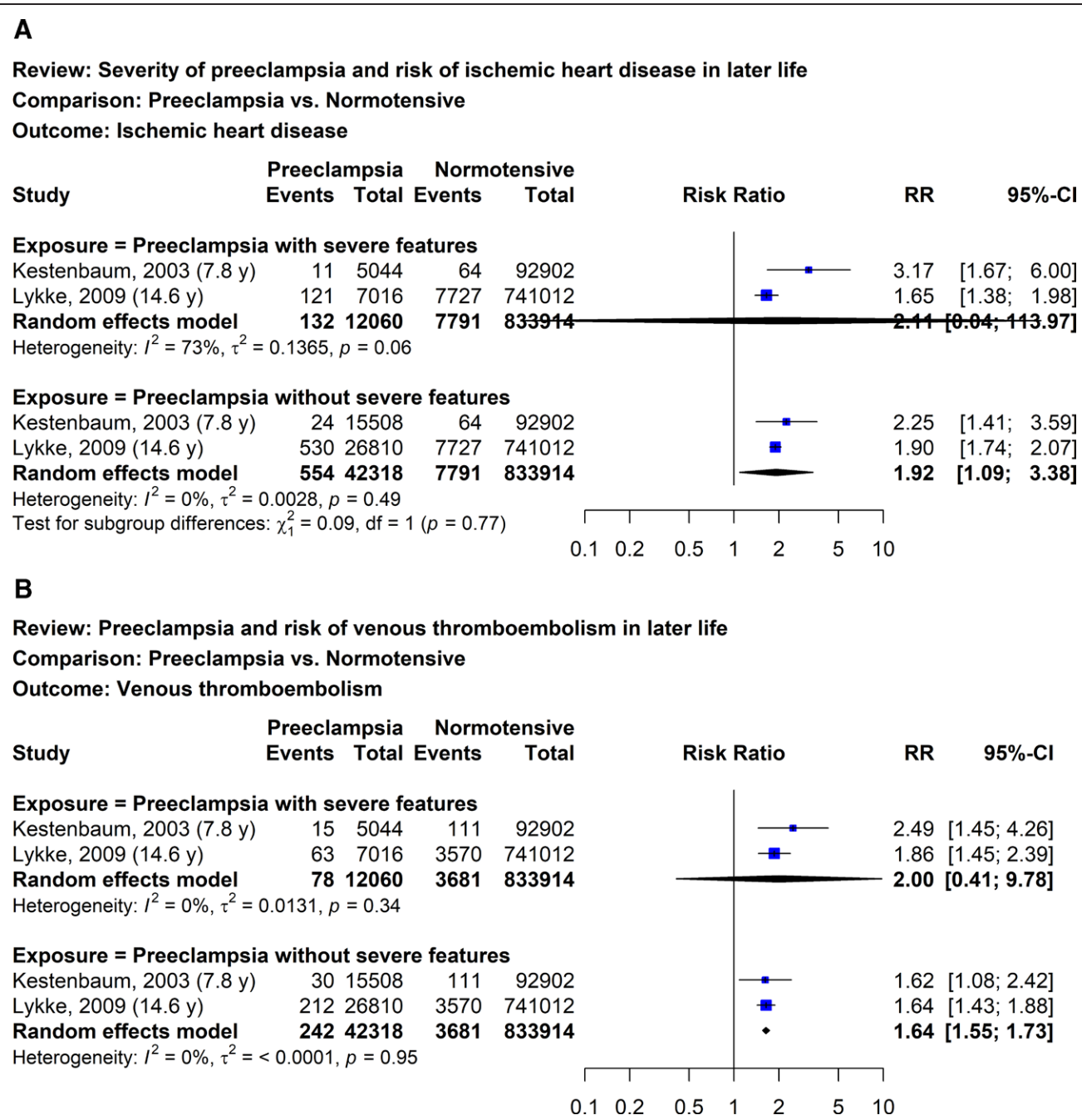


**Figure 5.** Forest plot of preeclampsia and risk of ischemic heart disease (A) and venous thromboembolism (B) later in life by disease severity.

the risks of specifically defined cardiovascular and cerebrovascular diseases in women with prior HDP.

To date, there have been limited data in regards to the risk of CVDs in women and the critical point of disease development after HDP, which may have different pathophysiology and effect of cardiovascular outcomes from preeclampsia. Our systematic review included more than 50 studies involving over 10 million women to assess various cardiovascular outcomes after HDP in different postpartum years. Moreover, potential risk of CVDs identified mostly during the first 5 years after HDP, preeclamptic women with severe features or early-onset of preeclampsia is an essential component for a strategy aiming to target high-risk women with appropriate policy of follow-up periods.

There are some limitations to our systematic review. First, the heterogeneity of effects was high in almost all outcomes. We found that sensitivity analysis based on the study quality score of the NOS was not suitable for the meta-analysis of observational studies due to questionable validity and reliability of the tool.[100,101] Hence, we conducted a sensitivity analysis using outlier and influence diagnostics, which mostly contributed to similar results. This high heterogeneity may be due to different women's characteristics across studies. There were a variation in race/ethnicity,[43,44,75] study setting,[41,57] as well as obstetric characteristics.[53,56,69,77] Second, this systematic review used aggregate data for which not all potential confounding factors could be adjusted. Meta-analysis of individual participant data from studies with available data may successfully mitigate the heterogeneity and confounder issues. Third, the evaluation of publication bias was limited in scope as only the bias in hypertensive outcomes could be assessed. Fourth, the number of studies was too small to perform

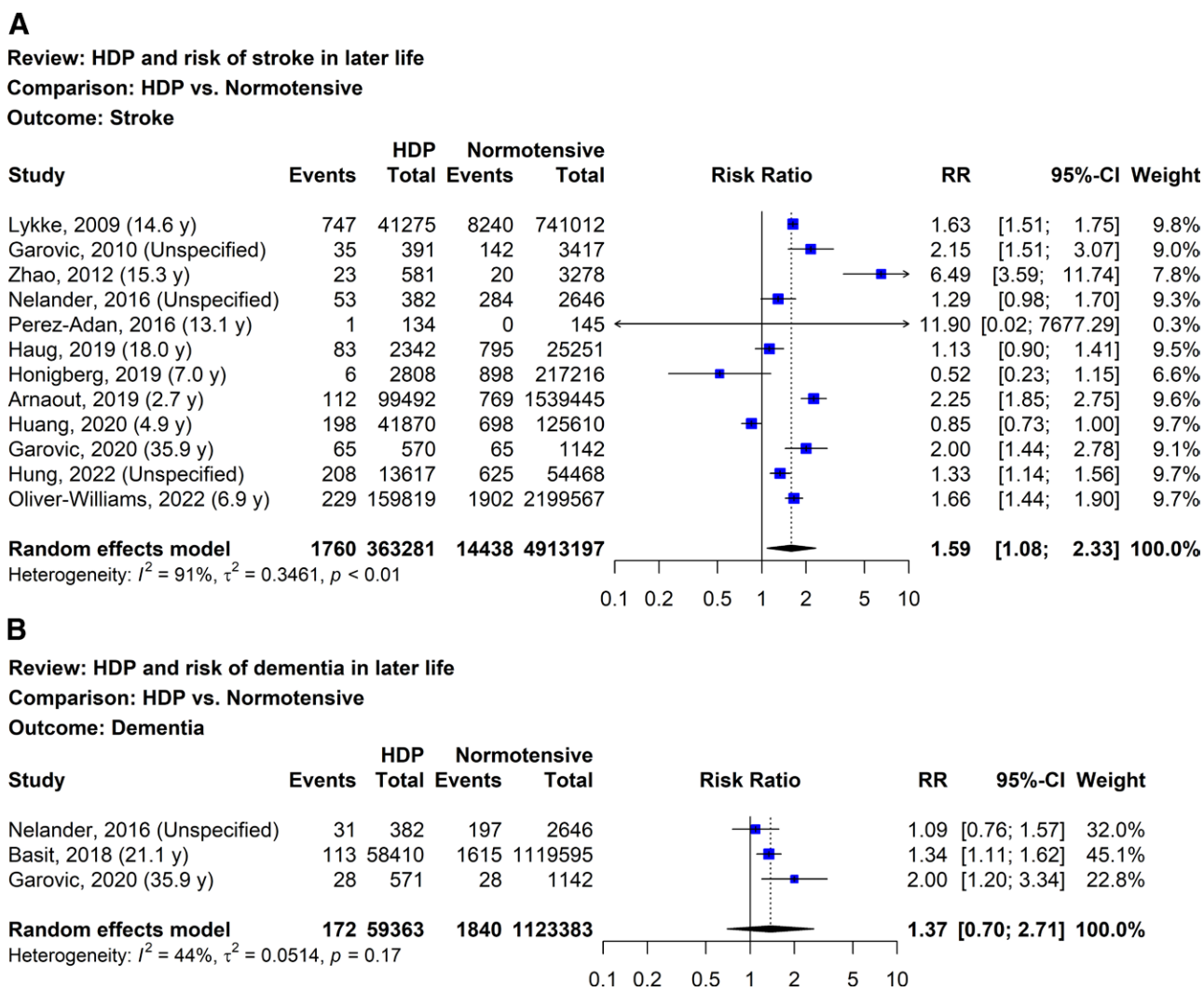


**Figure 6.** Forest plot of HDP and risk of stroke (A) and dementia (B) later in life. HDP = hypertensive disorder of pregnancy.

stratified analysis by severity and onset of preeclampsia in every cardiovascular outcome. Fifth, only 1 study comparing early- with late-onset preeclampsia on risk of future cardiovascular diseases which was not included in this meta-analysis and no study directly compared between preeclampsia with and without severe features. Finally, only available search databases, namely MEDLINE, Cochrane Library, Web of Science, and Scopus, were used which unpublished studies and some studies may not be retrieved.

## 6. Conclusion

Women with prior HDP had approximately a 2- to 4-fold increased risk for hypertension, ischemic heart disease, heart failure later in life, and cardiovascular mortality compared with those with normotensive pregnancies. The risk of future hypertension was highest during the first 5 years after delivery. However, the certainty of most evidence was very low and low due to limitation of study design, inconsistency, and imprecision. Influences of different severity and onset of preeclampsia are still inconclusive. Our findings emphasize the significance of CVD risks after HDP especially in women with preeclampsia with severe features, requiring proper screening after delivery for the early detection of subclinical CVDs, particularly during the 5 years after index HDP.

## Author contributions

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Methodology: Jarawee Sukmanee, Tippawan Liabsuetrakul.
Supervision: Tippawan Liabsuetrakul.
Validation: Jarawee Sukmanee, Tippawan Liabsuetrakul.
Visualization: Jarawee Sukmanee.
Writing—original draft: Jarawee Sukmanee, Tippawan Liabsuetrakul.
Writing—review and editing: Jarawee Sukmanee, Tippawan Liabsuetrakul.

## References

[1] Mendis S, Puska P, Norrving B; World Health Organization, World Heart Federation, World Stroke Organization. Global atlas on cardiovascular disease prevention and control. Geneva: World Health Organization, 2011.
[2] GBD 2017 Risk Factor Collaborators. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990-2017: a systematic analysis for the global burden of disease study 2017. Lancet Lond Engl. 2018;392:1923–94.

[3] Porapakkham Y, Rao C, Pattaraarchachai J, et al. Estimated causes of death in Thailand, 2005: implications for health policy. Popul Health Metr 2010;8:14.
[4] Eaton CB. Traditional and emerging risk factors for cardiovascular disease. Prim Care Clin Off Pract. 2005;32:963–76.
[5] Mosca L, Benjamin EJ, Berra K, et al. Effectiveness-based guidelines for the prevention of cardiovascular disease in women—2011 update. J Am Coll Cardiol. 2011;57:1404–23.
[6] Umesawa M, Kobashi G. Epidemiology of hypertensive disorders in pregnancy: prevalence, risk factors, predictors and prognosis. Hypertens Res Off J Jpn Soc Hypertens. 2017;40:213–20.
[7] Villar K, Say L, Gulmezoglu A, et al. Eclampsia and pre-eclampsia: a health problem for 2000 years. In: Critchly H, MacLean A, Poston L, Walker J, eds. Preeclampsia: RCOG Press; 2003;189–207.
[8] Kongwattanakul K, Saksiriwuttho P, Chaiyarach S, et al. Incidence, characteristics, maternal complications, and perinatal outcomes associated with preeclampsia with severe features and HELLP syndrome. Int J Womens Health. 2018;10:371–7.
[9] Ye C, Ruan Y, Zou L, et al. The 2011 survey on hypertensive disorders of pregnancy (HDP) in China: prevalence, risk factors, complications, pregnancy and perinatal outcomes. PLoS One. 2014;9:e100180.
[10] Lisonkova S, Joseph KS. Incidence of preeclampsia: risk factors and outcomes associated with early- versus late-onset disease. Am J Obstet Gynecol. 2013;209:544.e1–544.e12.
[11] Bellamy L, Casas JP, Hingorani AD, et al. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. BMJ 2007;335:974.
[12] McDonald SD, Malinowski A, Zhou Q, et al. Cardiovascular sequelae of preeclampsia/eclampsia: a systematic review and meta-analyses. Am Heart J. 2008;156:918–30.
[13] Wu P, Haththotuwa R, Kwok CS, et al. Preeclampsia and future cardiovascular health: a systematic review and meta-analysis. Circ Cardiovasc Qual Outcomes. 2017;10:e003497.
[14] Alonso-Ventura V, Li Y, Pasupuleti V, et al. Effects of preeclampsia and eclampsia on maternal metabolic and biochemical outcomes in later life: a systematic review and meta-analysis. Metabolism 2020;102:154012.
[15] Stuart JJ, Tanz LJ, Missmer SA, et al. Hypertensive disorders of pregnancy and maternal cardiovascular disease risk factor development: an observational cohort Study. Ann Intern Med. 2018;169:224–32.
[16] National Institute for Health and Care Excellence. Hypertension in pregnancy: diagnosis and management. NICE guidelines. Published June 25, 2019. Available at: https://www.nice.org.uk/guidance/ng133. [Access date May 30, 2020].
[17] Committee Opinion ACOG. 736: optimizing postpartum care. Obstet Gynecol. 2018;131:e140–50.
[18] Magee LA, Pels A, Helewa M, et al. Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy. Pregnancy Hypertens Int J Womens Cardiovasc Health.2014;4:105-145.
[19] Heida KY, Bots ML, de Groot CJ, et al. Cardiovascular risk management after reproductive and pregnancy-related disorders: a Dutch multidisciplinary evidence-based guideline. Eur J Prev Cardiol. 2016;23:1863–79.
[20] Staff AC, Andersgaard AB, Henriksen T, et al. Chapter 28 hypertensive disorders of pregnancy and eclampsia. Eur J Obstet Gynecol Reprod Biol. 2016;201:171–8.
[21] Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71.
[22] Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA. 2000;283:2008–12.
[23] Forrester TE, Grell GA, Bennett F, et al. Persistence of high leucocyte sodium and blood pressure after pre-eclampsia. J Hum Hypertens. 1990;4:25–30.
[24] Drost J, Arpad G, Eyck J, et al. Hypertension in pregnancy: important predictor of cardiovascular risk. Hart Bull. 2010;41:47–9.
[25] American College of Obstetricians and Gynecologists. Gestational hypertension and preeclampsia: ACOG practice bulletin, number 222. Obstet Gynecol. 2020;135:e237–60.
[26] Wells G, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Updated July 2000. Published 2000. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. [Access date May 29, 2020].
[27] Schünemann H, Brożek J, Guyatt G, et al. GRADE handbook. GRADE handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach. Updated October 2013. Published 2013. Available at: https://gdt.gradepro.org/app/handbook/handbook.html. [Access date November 5, 2021].
[28] Deeks JJ, Higgins JP, Altman DG (eds). Chapter 10: analysing data and undertaking meta-analyses. Cochrane handbook for systematic reviews of interventions version 6.2s. Published February 2021. Available at: http://www.training.cochrane.org/handbook. [Access date June 13, 2021].
[29] Viechtbauer W, Cheung MWL. Outlier and influence diagnostics for meta-analysis. Res Synth Methods 2010;1:112–25.
[30] Jin ZC, Wu C, Zhou XH, et al. A modified regression method to test publication bias in meta-analyses with binary outcomes. BMC Med Res Methodol. 2014;14:132.
[31] R Core Team. R: a language and environment for statistical computing. R Foundation for Statistical Computing. 2021. Available at: https://www.R-project.org/.
[32] Balduzzi S, Rücker G, Schwarzer G. How to perform a meta-analysis with R: a practical tutorial. Evid Based Ment Health. 2019;22:153–60.
[33] Harrer M, Cuijpers P, Furukawa T, et al. Dmetar: companion R package for the guide "Doing Meta-Analysis in R". 2019. Available at: http://dmetar.protectlab.org/.
[34] Kestenbaum B, Seliger SL, Easterling TR, et al. Cardiovascular and thromboembolic events following hypertensive pregnancy. Am J Kidney Dis. 2003;42:982–9.
[35] Lykke JA, Langhoff-Roos J, Sibai BM, et al. Hypertensive pregnancy disorders and subsequent cardiovascular morbidity and type 2 diabetes mellitus in the mother. Hypertension. 2009;53:944–51.
[36] Edlow AG, Srinivas SK, Elovitz MA. Investigating the risk of hypertension shortly after pregnancies complicated by preeclampsia. Am J Obstet Gynecol. 2009;200:e60–62.
[37] Garovic VD, Bailey KR, Boerwinkle E, et al. Hypertension in pregnancy as a risk factor for cardiovascular disease later in life. J Hypertens. 2010;28:826–33.
[38] Mongraw-Chaffin ML, Cirillo PM, Cohn BA. Preeclampsia and cardiovascular disease death: prospective evidence from the child health and development studies cohort. Hypertens Dallas Tex 1979. 2010;56:166–71.
[39] Melchiorre K, Sutherland GR, Liberati M, et al. Preeclampsia is associated with persistent postpartum cardiovascular impairment. Hypertens Dallas Tex 1979. 2011;58:709–15.
[40] Drost JT, Arpaci G, Ottervanger JP, et al. Cardiovascular risk factors in women 10 years post early preeclampsia: risk evaluation the Preeclampsia in females study (PREVFEM). Eur J Prev Cardiol. 2012;19:1138–44.
[41] Zhao HY, Chen XW, Niu JQ, et al. History of pregnancy induced hypertension is linked with increased risk of cardio-cerebral vascular events. Zhonghua Xin Xue Guan Bing Za Zhi. 2012;40:645–651.
[42] Collén AC, Hellgren M, Gustafsson H, et al. Cardiovascular and metabolic characteristics 40 years after hypertensive pregnancies: a long-term follow-up study of mothers. J Hypertens. 2013;31:758–65.
[43] Callaway LK, Mamun A, McIntyre HD, et al. Does a history of hypertensive disorders of pregnancy help predict future essential hypertension? Findings from a prospective pregnancy cohort study. J Hum Hypertens. 2013;27:309–14.
[44] Shalom G, Shoham-Vardi I, Sergienko R, et al. Is preeclampsia a significant risk factor for long-term hospitalizations and morbidity? J Matern Fetal Neonatal Med. 2013;26:13–5.
[45] Östlund E, Al-Nashi M, Hamad RR, et al. Normalized endothelial function but sustained cardiovascular risk profile 11 years following a pregnancy complicated by preeclampsia. Hypertens Res. 2013;36:1081–1087.
[46] Kvehaugen AS, Melien O, Holmen OL, et al. Hypertension after preeclampsia and relation to the C1114G polymorphism (rs4606) in RGS2: data from the Norwegian HUNT2 study. BMC Med Genet. 2014;15:28.
[47] Zhou Y, Niu J, Duan D, et al. Incident and related risk factors of hypertension in women with a history of preeclampsia. Zhonghua Xin Xue Guan Bing Za Zhi. 2014;42:603–8.
[48] Ghossein-Doha C, Spaanderman M, van Kuijk SMJ, et al. Long-term risk to develop hypertension in women with former preeclampsia: a longitudinal pilot study. Reprod Sci. 2014;21:846–53.
[49] Yeh JS, Cheng H, Hsu P, et al. Synergistic effect of gestational hypertension and postpartum incident hypertension on cardiovascular health: a nationwide population study. J Am Heart Assoc. 2014;3:e001008.
[50] Breetveld N, Ghossein-Doha C, van Kuijk S, et al. Cardiovascular disease risk is only elevated in hypertensive, formerly preeclamptic women. BJOG Int J Obstet Gynaecol. 2015;122:1092–100.
[51] Ehrenthal DB, Rogers S, Goldstein ND, et al. Cardiovascular risk factors one year after a hypertensive disorder of pregnancy. J Womens Health. 2015;24:23–9.
[52] Behrens I, Basit S, Lykke JA, et al. Association between hypertensive disorders of pregnancy and later risk of cardiomyopathy. JAMA. 2016;315:1026.

[53] Cain MA, Salemi JL, Tanner JP, et al. Pregnancy as a window to future health: maternal placental syndromes and short-term cardiovascular outcomes. Am J Obstet Gynecol. 2016;215:484.e1–484.e14.
[54] Nelander M, Cnattingius S, Åkerud H, et al. Pregnancy hypertensive disease and risk of dementia and cardiovascular disease in women aged 65 years or older: a cohort study. BMJ Open 2016;6:e009880.
[55] Pérez-Adan M, Vázquez-Rodríguez M, Álvarez-Silvares M, et al. Risk factors for cardiovascular disease in patients with hypertensive disorders during pregnancy. Experience of 10 years. Ginecol Obstet Mex. 2016;84:573–85.
[56] Grandi SM, Vallée-Pouliot K, Reynier P, et al. Hypertensive disorders in pregnancy and the risk of subsequent cardiovascular disease. Paediatr Perinat Epidemiol. 2017;31:412–21.
[57] Timpka S, Stuart JJ, Tanz LJ, et al. Lifestyle in progression from hypertensive disorders of pregnancy to chronic hypertension in Nurses' Health Study II: observational cohort study. BMJ. 2017;358:j3024.
[58] Dunietz G, Strutz K, Holzman C, et al. Moderately elevated blood pressure during pregnancy and odds of hypertension later in life: the POUCHmoms longitudinal study. BJOG Int J Obstet Gynaecol. 2017;124:1606–13.
[59] Best LG, Lunday L, Webster E, et al. Pre-eclampsia and risk of subsequent hypertension: in an American Indian population. Hypertens Pregnancy 2017;36:131–7.
[60] Ghossein-Doha C, van Neer J, Wissink B, et al. Pre-eclampsia: an important risk factor for asymptomatic heart failure. Ultrasound Obstet Gynecol. 2017;49:143–9.
[61] Bokslag A, Franssen C, Alma LJ, et al. Early-onset preeclampsia predisposes to preclinical diastolic left ventricular dysfunction in the fifth decade of life: an observational study. Cavarretta E, ed. PLoS One. 2018;13:e0198908.
[62] Li LJ, Aris IM, Su LL, et al. Effect of gestational diabetes and hypertensive disorders of pregnancy on postpartum cardiometabolic risk. Endocr Connect. 2018;7:433–42.
[63] Chen SN, Cheng CC, Tsui KH, et al. Hypertensive disorders of pregnancy and future heart failure risk: a nationwide population-based retrospective cohort study. Pregnancy Hypertens. 2018;13:110–5.
[64] Bergen NE, Schalekamp-Timmermans S, Roos-Hesselink J, et al. Hypertensive disorders of pregnancy and subsequent maternal cardiovascular health. Eur J Epidemiol. 2018;33:763–71.
[65] Theilen LH, Meeks H, Fraser A, et al. Long-term mortality risk and life expectancy following recurrent hypertensive disease of pregnancy. Am J Obstet Gynecol. 2018;219:107.e1–6.
[66] Basit S, Wohlfahrt J, Boyd HA. Pre-eclampsia and risk of dementia later in life: nationwide cohort study. BMJ. 2018;363:k4109.
[67] Kuo YL, Chan TF, Wu CY, et al. Preeclampsia-eclampsia and future cardiovascular risk among women in Taiwan. Taiwan J Obstet Gynecol. 2018;57:364–9.
[68] Egeland GM, Skurtveit S, Staff AC, et al. Pregnancy related risk factors are associated with a significant burden of treated hypertension within 10 years of delivery: findings from a population-based Norwegian cohort. J Am Heart Assoc. 2018;7:e008318.
[69] Haas DM, Parker CB, Marsh DJ, et al. Association of adverse pregnancy outcomes with hypertension 2 to 7 years postpartum. J Am Heart Assoc. 2019;8:e013092.
[70] Haug EB, Horn J, Markovitz AR, et al. Association of conventional cardiovascular risk factors with cardiovascular disease after hypertensive disorders of pregnancy: analysis of the Nord-Trøndelag Health Study. JAMA Cardiol 2019;4:628.
[71] Amiri M, Ramezani Tehrani F, Rahmati M, et al. Changes over-time in blood pressure of women with preeclampsia compared to those with normotensive pregnancies: a 15 year population-based cohort study. Pregnancy Hypertens. 2019;17:94–9.
[72] Smith GN, Pudwell J, Saade GR. Impact of the new American hypertension guidelines on the prevalence of postpartum hypertension. Am J Perinatol. 2019;36:440–2.
[73] Honigberg MC, Zekavat SM, Aragam K, et al. Long-term cardiovascular risk in women with hypertension during pregnancy. J Am Coll Cardiol. 2019;74:2743–54.
[74] Ernawati, Joewono HT, Akbar MIA, et al. Maternal cardiovascular risk in early and late onset of preeclampsia patients five years after labor: a comparative study. Biochem Cell Arch. 2019;19:4721–8.
[75] Osoti AO, Page ST, Richardson BA, et al. Postpartum metabolic syndrome after gestational hypertension and preeclampsia, a prospective cohort study. Pregnancy Hypertens 2019;18:35–41.
[76] Leon LJ, McCarthy FP, Direk K, et al. Preeclampsia and cardiovascular disease in a large UK pregnancy cohort of linked electronic health records: a CALIBER study. Circulation. 2019;140:1050–60.
[77] Arnaout R, Nah G, Marcus G, et al. Pregnancy complications and premature cardiovascular events among 1.6 million california pregnancies. Open Heart. 2019;6:e000927.
[78] Huang CC, Huang CC, Lin SY, et al. Association between hypertensive pregnancy disorders and future risk of stroke in Taiwan: a nationwide population-based retrospective case-control study. BMC Pregnancy Childbirth. 2020;20:217.
[79] Scheres LJJ, Lijfering WM, Groenewegen NFM, et al. Hypertensive complications of pregnancy and risk of venous thromboembolism. Hypertension. 2020;75:781–7.
[80] Wagata M, Kogure M, Nakaya N, et al. Hypertensive disorders of pregnancy, obesity, and hypertension in later life by age group: a cross-sectional analysis. Hypertens Res. 2020;43:1277–83.
[81] Garovic VD, White WM, Vaughan L, et al. Incidence and long-term outcomes of hypertensive disorders of pregnancy. J Am Coll Cardiol. 2020;75:2323–34.
[82] Bergman L, Nordlöf-Callbo P, Wikström AK, et al. Multi-fetal pregnancy, preeclampsia, and long-term cardiovascular disease. Hypertension. 2020;76:167–75.
[83] Moe K, Sugulle M, Dechend R, et al. Risk prediction of maternal cardiovascular disease one year after hypertensive pregnancy complications or gestational diabetes mellitus. Eur J Prev Cardiol. 2020;27:1273–83.
[84] Sharma S, Skog J, Timpka S, et al. Preeclampsia and high blood pressure in early pregnancy as risk factors of severe maternal cardiovascular disease during 50-years of follow-up. Pregnancy Hypertens. 2021;26:79–85.
[85] Mooij R, Kapanga RR, Mwampagatwa IH, et al. Beyond severe acute maternal morbidity: a mixed-methods study on the long-term consequences of (severe pre-) eclampsia in rural Tanzania. Trop Med Int Health. 2021;26:33–44.
[86] Ntlemo P, Cronje T, Soma-Pillay P. Metabolic syndrome at 6 weeks after delivery in a cohort of pre-eclamptic and normotensive women. S Afr Med J. 2021;111:350–4.
[87] Nuckols VR, Stroud AK, Hueser JF, et al. Twenty-four-hour blood pressure variability is associated with lower cognitive performance in young women with a recent history of preeclampsia. Am J Hypertens. 2021;34:1291–9.
[88] Oliver-Williams C, Stevens D, Payne RA, et al. Smith GCS, Wood A. Association between hypertensive disorders of pregnancy and later risk of cardiovascular outcomes. BMC Med. 2022;20:19.
[89] Park Y, Cho GJ, Roh SY, et al. Increased cardiac arrhythmia after pregnancy-induced hypertension: a South Korean nationwide database study. J Am Heart Assoc. 2022;11:e023013.
[90] Hung SK, Lee MS, Lin HY, et al. Impact of hypertensive disorders of pregnancy on the risk of stroke stratified by subtypes and follow-up time. Stroke. 2022;53:338–44.
[91] Kennedy R, Roberts L, Davis G, et al. The P4 study: subsequent pregnancy maternal physiology after hypertensive and normotensive pregnancies. Pregnancy Hypertens. 2022;27:29–34.
[92] van Baar PM, Welters SM, Ravelli ACJ, et al. Cardiovascular mortality risk a decade after twin and singleton pregnancies complicated by hypertensive disorders of pregnancy. Pregnancy Hypertens. 2022;28:9–14.
[93] Mannisto T, Mendola P, Vaarasmaki M, et al. Elevated blood pressure in pregnancy and subsequent chronic disease risk. Circulation. 2013;127:681–90.
[94] Vasan RS, Larson MG, Leip EP, et al. Assessment of frequency of progression to hypertension in non-hypertensive participants in the framingham heart study: a cohort study. Lancet Lond Engl. 2001;358:1682–6.
[95] Staff AC, Redman CWG, Williams D, et al. Pregnancy and long-term maternal cardiovascular health: progress through harmonization of research cohorts and biobanks. Hypertension. 2016;67:251–60.
[96] Rodie VA, Freeman DJ, Sattar N, et al. Pre-eclampsia and cardiovascular disease: metabolic syndrome of pregnancy? Atherosclerosis. 2004;175:189–202.
[97] Scantlebury DC, Kane GC, Wiste HJ, et al. Left ventricular hypertrophy after hypertensive pregnancy disorders. Heart Br Card Soc. 2015;101:1584–90.
[98] Levy D, Garrison RJ, Savage DD, et al. Prognostic implications of echocardiographically determined left ventricular mass in the framingham heart Study. N Engl J Med. 1990;322:1561–6.
[99] Gardin JM, McClelland R, Kitzman D, et al. M-mode echocardiographic predictors of six- to seven-year incidence of coronary heart disease, stroke, congestive heart failure, and mortality in an elderly cohort (the Cardiovascular Health Study). Am J Cardiol. 2001;87:1051–7.
[100] Stang A. Critical evaluation of the newcastle-ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol. 2010;25:603–5.
[101] Hartling L, Milne A, Hamm MP, et al. Testing the Newcastle Ottawa scale showed low reliability between individual reviewers. J Clin Epidemiol. 2013;66:982–93.