Hypertensive Disorders of Pregnancy and Risk of Cardiovascular Disease-Related Morbidity and Mortality: A Systematic Review and Meta-Analysis

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Keywords

Hypertensive disorders of pregnancy · Gestational hypertension · Preeclampsia · Cardiovascular disease · Hypertension · Death

Abstract

Introduction: Several studies have demonstrated that there is a higher risk of cardiovascular disease (CVD) in women with a history of hypertensive disorders of pregnancy (HDP). However, effect sizes varied greatly between these studies, and a complete overview of the existing data in the literature is lacking. We aimed to evaluate the association between HDP and the risk of CVD-related morbidity and mortality. **Methods:** Systematic literature searches were conducted in several electronic databases from inception to July 2019. Exposure of interest was any type of HDP. Outcomes of interest included any CVD, CVD-related mortality, and hypertension. **Results:** Sixty-six cohort and 7 case-control studies involving >13 million women were included. The overall combined relative risks (RRs) for women with a history of HDP compared with the reference group were 1.80 (95% confidence interval [CI] 1.67–1.94) for any CVD, 1.66 (1.49–1.84) for coronary artery heart disease, 2.87 (2.14–3.85) for heart failure, 1.60 (1.29–2.00) for peripheral vascular disease, 1.72 (1.50–

1.97) for stroke, 1.78 (1.58–2.00) for CVD-related mortality, and 3.16 (2.74–3.64) for hypertension. Significant heterogeneity was partially explained by all or part of the variables including type of exposure, follow-up time, geographic region, and sample source. **Conclusions:** Women with a history of HDP are at an increased risk of future CVD-related morbidity and mortality. Our study highlights the importance of life-long monitoring of cardiovascular risk factors in women with a history of HDP.

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Introduction

Approximately 15% of parous women have at least 1 pregnancy complicated by a hypertensive disorder [1]. As reported, hypertensive disorders of pregnancy (HDP) are associated with maternal and fetal complications [2–7]. Given that approximately 30,000 maternal and 500,000 perinatal deaths annually can be attributed to HDP, these disorders have been regarded as one of the major contributors to maternal and fetal mortality and morbidity globally [8–10].

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Historically, HDP were considered to be self-limiting and have little long-term effect on health since the blood pressure of most of the women affected would return to normal within 12 weeks after delivery [11]. However, residual anomalies and increased cardiovascular disease (CVD) risk factors (e.g., hypertension and diabetes) in women with a history of HDP are likely to render these people becoming increasingly at risk of developing CVD [12, 13]. Interest in testing this hypothesis has grown rapidly in the past years. However, no consensus has been reached even today. Several studies have reported a significantly higher risk of composite cardiovascular events in women with a history of HDP compared with a reference group [14, 15], but others have not found a significant association between HDP and a long-term risk of developing CVD [16, 17]. Notably, even in studies providing a supportive evidence, effect sizes varied greatly. Given the increasing prevalence of HDP, it is necessary to summarize the existing evidence of the association of HDP with long-term CVD-related morbidity and mortality through integrated approaches.

To this end, our objective here was to perform an updated meta-analysis regarding the association between HDP and the risk of developing CVD-related morbidity and mortality. Our results may lead to a better understanding of CVD risk in women with HDP, which will help to guide future management and contribute to guidelines for clinicians.

Methods

Search Strategy

This systematic review was conducted following the proposed Systematic Reviews and Meta-Analyses (PRISMA) [18] and the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) [19] reporting guidelines.

Two authors independently identified observational studies published in English prior to 8 July 2019 and reported data on cardiovascular outcomes in women with and without HDP. PubMed, Embase, and Web of Science were systematically searched. The search terms used in combination were: (1) pregnancy, pregnant, gestational, gestation, hypertensive, hypertension, pre-eclampsia (PE), preeclampsia, eclampsia, edema-proteinuria-hypertension gestosis, toxemia of pregnancy, and hemolysis-elevated liver enzymes-low platelets (HELLP) syndrome; and (2) cardiovascular diseases, CVD, coronary disease, coronary thrombosis, coronary stenosis, coronary restenosis, coronary artery disease, coronary heart disease, acute coronary syndrome, ischemic heart disease, myocardial ischemia, myocardial infarction; heart failure, cardiac failure, left ventricular systolic dysfunction, cardiomyopathy, peripheral vascular disease, pulmonary embolism, venous thromboembolism, deep vein thrombosis, cerebrovascular disorders, cerebrovascular disease, cerebrovascular accident, stroke, death, and

mortality. In addition, the reviewers manually searched the reference lists of the articles selected to identify any relevant studies missed in the initial search.

Exposure and Outcomes

The exposure of interest was any type of HDP, including gestational hypertension (GH), PE, eclampsia, HELLP syndrome, and chronic hypertension with superimposed PE. Primary outcomes included any type of CVD and CVD-related mortality. CVD was defined as any of the following events: coronary artery heart disease, heart failure, peripheral vascular disease, and stroke. Coronary artery heart disease included coronary heart disease, ischemic heart disease, myocardial infarction, and coronary artery disease. Peripheral vascular disease was defined as peripheral arterial disease, deep vein thrombosis, and any thromboembolic events. Stroke was defined as any composite stroke, stroke unspecified, and stroke/transient ischemic attack. The outcome CVD-related mortality was defined as death due to any CVD. Although hypertension is outside the range of CVD, we included hypertension as the secondary outcome given its importance as a risk factor for CVD.

Study Selection

At the title and abstract screening stage, we purposely broadened the inclusion criteria to obtain all relevant studies. Studies were considered for inclusion if they were published in English and reported on CVD, CVD-related mortality, and hypertension among women with HDP. The full texts of all selected studies were then reviewed. Studies were included if they (1) were original articles, (2) included at least 2 groups (1 with HDP and 1 without HDP), (3) provided sufficient information to allow for accurate risk estimates to be calculated, and (4) the full-length article was available. Conversely, studies were excluded if they (1) were review papers, conference abstracts, case reports, experimental studies, or qualitative studies, (2) had incomplete or unclear data, or (3) were duplicate publications. There was no restriction based on cohort type, study design, or duration of follow-up. When there was >1 study that involved the same population of HDP patients, only the most recent published or comprehensive one was included.

Data Extraction

Two reviewers independently extracted and evaluated the data for each included article using a self-designed data abstraction form. Disagreements were resolved through discussion or consultation with a third reviewer when consensus could not be achieved. The following data were extracted: first author, year of publication, geographic region, study period, sample source (population- or hospital-based), type of exposure (HDP, GH, PE, eclampsia, HELLP syndrome, or chronic hypertension with superimposed PE), any adjustments or matches made, sample size, mean age, reported outcomes, and risk estimates with 95% confidence intervals (CIs; the adjusted ones were collected when available). In cohort studies, the duration of follow-up was also extracted.

Study Quality Assessments

The methodological quality of studies was assessed using the Newcastle-Ottawa Scale (NOS) for quality assessment of cohort and case-control studies by 2 researchers (R.W. and T.W.) independently. The NOS was composed of 8 items. It ranged from 1–9 stars and assessed the quality of each study based on 3 modules:

Fig. 1. Flow chart of study selection.

selection, comparability, and outcome (cohort studies) or exposure (case-control studies). A final median score of ≥ 6 was regarded as high quality.

Statistical Analyses

The risk ratio (RR) was used as the measure of the association between the history of HDP and a risk of any CVD, coronary artery heart disease, heart failure, peripheral vascular disease, stroke, CVD-related mortality, and hypertension. The hazard ratios (HRs) and odds ratios (ORs) were directly considered as RRs.

RevMan v5.3 (Nordic Cochrane Center) and Comprehensive Meta-Analysis v2.2 were used to perform all analyses in this study. The Cochran Q test and the I^2 statistic were used to assess the heterogeneity of RRs across studies. The Cochran Q test was used to evaluate whether the variation across studies was compatible with chance, and $p < 0.1$ was considered to indicate significant heterogeneity. The I^2 statistic was a quantitative indicator used to evaluate the percentage of total variance in risk estimates due to statistical heterogeneity rather than chance, or sampling error ($I^2 > 75\%$, high heterogeneity; 51–75%, substantial heterogeneity; 26–50%, moderate heterogeneity; $\leq 25\%$, low heterogeneity). The pooled RRs and 95% CIs were calculated using random-effects meta-analyses. To explore possible sources of heterogeneity, subgroup analyses were performed according to geographic region (Asia vs. Europe vs. North America), sample source (hospital-based vs. popu-

lation-based), type of exposure (GH vs. PE), whether the confounders were adjusted (adjusted vs. unadjusted), and median/mean follow-up time (≤ 10 vs. 10–20 vs. ≥ 20 years). Then, a Q test for heterogeneity was used to compare the subgroup differences under the random-effects model (here, Q would be distributed as χ^2 with $df = 1$ and $p < 0.05$ indicating statistically significant differences) [20].

Sensitivity analysis was conducted to examine the influence of individual studies on the overall RRs by repeating the meta-analysis after the exclusion of each included study. Sensitivity analyses were also performed to examine the influence of case-control studies on the overall RRs. Publication bias was evaluated using Begg's test ($p < 0.05$ indicated statistically significant differences).

Results

Identification and Characteristics of Studies

In total, 24,395 unique citations were identified after an initial search. Of these, 24,290 were excluded after screening titles and abstracts, mainly because they were duplications, reviews, or not related to our study (Fig. 1). Then, the full texts of 105 articles were reviewed; a total

Table 1. Selected characteristics of 66 cohort studies of HDP and CVD, CVD-related mortality, and hypertension

Study	Geographic region	Study period	Sample source	Type of exposure	Follow-up duration, years	Mean age at follow-up, years	Controlled confounders	HDP group, <i>n</i>	Control group, <i>n</i>	Reported outcomes
Rise et al. [77], 2019	Norway, Europe	1994–2009	population-based	HDP	median 11.4	median HDP: 37.1; control: 37.2	BMI, smoking, hypertension, diabetes, serum glucose and lipid levels	1,246	18,829	coronary heart disease, acute MI/acute cerebral stroke
Haug et al. [78], 2019	Norway, Europe	1984–2015	population-based	HDP	median 18	median HDP: 50; control: 48	age, highest obtained educational level, ever smoked daily, parity at younger than 40 years, maternal birth year, and family history of coronary heart disease	2,117	21,752	CVD, MI, HF, cerebrovascular disease
Grandi et al. [83], 2018	UK, Europe	1999–2015	population-based	HDP	median early-onset HDP: 5.3; late-onset HDP: 4.8; control: 4.7	mean early-onset HDP: 29.5; late-onset HDP: 29.8; control: 29.2	age, smoking, BMI, excessive alcohol use, year of cohort entry, region of residence, multiple gestation at first pregnancy, depression, dyslipidemia, venous thromboembolism, polycystic ovary syndrome, gestational diabetes, diabetes mellitus, renal disease, migraines, family history of hypertension and family history of CVD, any time before cohort entry, number of distinct drug classes prescribed, use of statins, aspirin and antidepressants in the year prior to pregnancy	5,399	141,349	CVD, hypertension
Kuo et al. [82], 2018	Taiwan, China, Asia	1996–2010	population-based	PE, E	median 9.8; IQR 5.1–12.7 years	mean age at first delivery HDP: 29.7; control: 29.6	age and date of delivery	1,295	5,180	hypertension, congestive HF, stroke
Mito et al. [81], 2018	Japan, Asia	2003–2005	hospital-based	HDP	5	mean age at delivery HDP: 35.3; control: 33.9	age, BMI, family history of hypertension and salt intake	25	746	hypertension
Bergen et al. [84], 2018	The Netherlands, Europe	n.r.	population-based	GH, PE	6	age at admission: GH: 30.7; PE: 29.6; control: 30.3	maternal age, ethnicity, educational level, smoking, subsequent pregnancies between index and follow-up, child's sex, and BMI	300	4,612	hypertension
Stuart et al. [85], 2018	USA, North America	1989–2013	population-based	GH, PE	mean 25–32	mean age in 1989: GH: 34.5; PE: 34.6; control: 35.2	age, race/ethnicity, years of parental education, strenuous physical activity, pre-pregnancy smoking status, pre-pregnancy BMI, pre-pregnancy alcohol consumption, quintile of pre-pregnancy Alternative Healthy Eating Index score, pre-pregnancy oral contraceptive use, family history of chronic hypertension and type 2 diabetes mellitus	5,386	53,285	hypertension
Auger et al. [87], 2017	Canada, North America	1989–2014	hospital-based	PE	mean HDP: 10.8–14.6; control: 14.6; maximum: 25.2	majority: age at first delivery: 25–29	age, preexisting disease, socioeconomic deprivation, and period	64,358	1,044,223	hypertension, HF, cerebrovascular disease
Ghossein-Doha et al. [88], 2017	The Netherlands, Europe	n.r.	hospital-based	PE	4–10	PE: 36; control: 40	unadjusted	107	41	HF
McDonald et al. [24], 2016	Canada, North America	2009–2013	hospital-based	GH, PE	n.r.	median GH: 48; PE: 47.5; control: 50	age, race, obesity, hypertension, diabetes, dyslipidemia, and smoking	76	166	MI
Canoy et al. [21], 2016	UK, Europe	1996–2001	population-based	HDP	mean 11.6	mean GH: 55.9; control: 56.0	unadjusted	290,00	815,560	coronary heart disease, cerebrovascular disease, death from coronary heart and cerebrovascular disease
Behrens et al. [23], 2016	Denmark, Europe	1978–2012	population-based	GH, PE	mean 17.9	majority 25–29	maternal age, maternal birth year, parity, multiple pregnancy, and stillbirth	51,992	1,023,771	cardiomyopathy
Toohar et al. [22], 2016	Australia, Oceania	1980–1989	population-based	HDP	n.r.	age at death: HDP: 46; control: 48	unadjusted	4,387	27,262	CVD death
Weisserger et al. [25], 2016	Serbia, Europe	n.r.	population-based	HDP	n.r.	56	BMI and diabetes	252	353	hypertension, coronary heart disease, stroke
Kessous et al. [28], 2015	Israel, Asia	1988–2012	population-based	PE	mean 11.2	PE: 28.3; control: 28.8	maternal age, parity, diabetes mellitus and obesity	7,284	88,546	cardiovascular hospitalization
Savitz et al. [30], 2014	USA, North America	1995–2004	hospital-based	GH, PE	1	n.r.	maternal age, maternal race/ethnicity, health insurance, gestational diabetes, parity, maternal education, prenatal smoking, prenatal care, and prepregnancy weight	HDP and control: 849,639	n.r.	HF, intracranial hemorrhage, stroke, coronary heart disease, deep vein thrombosis
Weisserger et al. [31], 2013	USA, North America	1996–2004	population-based	HDP	n.r.	HDP: 59; control: 61	race, age, height, heart rate, education, log BMI, ever smoking, hypertension, diabetes, dyslipidemia, family history of hypertension and coronary heart disease	281	1,272	peripheral arterial disease

Table 1 (continued)

Study	Geographic region	Study period	Sample source	Type of exposure	Follow-up duration, years	Mean age at follow-up, years	Controlled confounders	HDP group, <i>n</i>	Control group, <i>n</i>	Reported outcomes
Männistö et al. [16], 2013	Finland, Europe	1966–2006	population-based	GH, PE/E	mean 39.4	mean age at birth GH: 27.8; PE/E: 26.7; control: 26.6	BMI, smoking before pregnancy, parity, and diabetes mellitus before/during pregnancy and socioeconomic status	782	4,283	total CVD, IHD, MI and MI deaths, HF, ischemic cerebrovascular disease, and arterial hypertension
Bhattacharya et al. [35], 2012	UK, Europe	1950–2008	population-based	GH, PE/E	at least 10 years	mean age at 1st delivery GH: 24.34; PE/E: 24.57; Control: 24.25	year of birth, social class, and smoking	10,917	23,937	hypertension, IHD; cerebrovascular disease; death of CVD
Drost et al. [36], 2012	The Netherlands, Europe	1991–2007	population-based	PE	10	PE: 38.9; control: 39.3	age, years post index partus and current smoking	339	332	hypertension
Skjaerven et al. [34], 2012	Norway, Europe	1967–2002	population-based	PE	median 25	n.r.	maternal education, maternal age at first birth, and year of first birth	34,824	801,323	cardiovascular deaths
Lin et al. [41], 2011	Taiwan, China, Asia	1999–2003	population-based	PE/E	at least 3 years	n.r.	age, years of education, marital status, multiple gestations, infant sex, birth weight, parity, long-term hypertension, pregnancy-related hypertension, anemia, diabetes, antepartum hemorrhage, postpartum hemorrhage, and systemic lupus erythematosus	HDP and control: 1,132,064	n.r.	major CVD, MI, HF, stroke, major adverse cardiovascular event-related death
Mongraw-Chaffin et al. [44], 2010	USA, North America	1959–1972	population-based	GH, PE	median: 37	median age at enrollment was 26 years, and median age at death from CVD was 65 years	pre-existing hypertension, pre-existing diabetes mellitus, and having a baby with intrauterine growth retardation	PE: 481	13,922	CVD death
Lykke et al. [14], 2009	Denmark, Europe	1978–2007	population-based	GH, PE	median 12.88	42.6	preterm delivery, small for gestational age, placental abruption, and stillbirth, and the development of type 2 diabetes mellitus	41,275	741,012	hypertension, IHD, congestive heart failure, thromboembolic event, stroke, death from cardiovascular causes
Garovic et al. [42], 2010	USA, North America	2000–2004	population-based	HDP	n.r.	estimated at 70 years	race, family history of CVD, smoking, dyslipidemia, and diabetes mellitus	643	3,421	hypertension, coronary heart disease, and stroke
Haukkanen et al. [48], 2009	Finland, Europe	2000–2001	population-based	GH, PE	n.r.	range 45–74	unadjusted	96	489	coronary artery disease, hypertension
Cassidy-Bushrow et al. [49], 2009	USA, North America	2000–2005	population-based	HDP	5	median HDP 61.0; control 63.2	age, BMI, waist-to-hip ratio, blood pressure, ln (SCR), ln (UACR), diabetes status, menopause status, and BP-lowering medication use	52	446	coronary artery calcification
Wikström et al. [63], 2005	Sweden, Europe	1973–1982	population-based	GH, PE	mean 15	median 48; range 33–75	maternal age, socioeconomic level and category of hospital in which the first child was born	20,469	383,081	IHD
Funai et al. [65], 2005	Israel, Asia	1964–1976	population-based	PE	median 30; range 24.5–36.5	median 53	age, insulin-dependent diabetes, gestational diabetes, birth of infant(s) weighing, education, social class, and year of baseline birth	1,055	36,858	CVD death
Arnadottir et al. [64], 2005	Iceland, Europe	1931–1996	hospital-based	HDP	40	n.r.	parity and age	325	629	CVD death
Wilson et al. [68], 2003	UK, Europe	1951–1999	population-based	GH, PE/E	n.r.	GH: 61.7; PE: 60.4; control: 59.9	age, BMI, social class, and smoking habit, age at delivery	1,017	295	hypertension, stroke, angina, MI, deep vein thrombosis, cerebrovascular disease death, IHD death
Smith et al. [71], 2001	UK, Europe	1981–1999	population-based	PE	15–19	median 38.5	maternal age, maternal height, socioeconomic deprivation category, essential hypertension, lowest birthweight quintile, preterm delivery	22,781	106,509	death due to IHD, and any IHD event
Nelander et al. [12], 2016	Sweden, Europe	1998–2010	population-based	HDP	11	71	BMI, education and smoking	419	2,646	CVD, stroke
Kurabayashi et al. [32], 2013	Japan, Asia	2001–2007	population-based	GH/PE	n.r.	≥45	age, BMI, smoking, alcohol consumption	1,285	9,171	hypertension
Andersgaard et al. [37], 2012	Norway, Europe	1994–1995	population-based	PE	PE: 25.4; control: 24.0	PE: 48.8; control: 47.4	unadjusted	901	7,187	CVD
Gordin et al. [59], 2007	Finland, Europe	1988–1996	hospital-based	GH, PE	mean 10.6	GH: 39.5; PE: 37.9; control: 41.7	unadjusted	75	105	coronary heart disease, MI

Table 1 (continued)

Study	Geographic region	Study period	Sample source	Type of exposure	Follow-up duration, years	Mean age at follow-up, years	Controlled confounders	HDP group, <i>n</i>	Control group, <i>n</i>	Reported outcomes
Hovsepian et al. [15], 2014	USA, North America	2005–2011	population-based	PE, E	6–12 weeks postdelivery	28.3	age, ethnicity, insurance status, PE, eclampsia, peripartum hemorrhage, peripartum infection, pregnancy-related hematologic disorders, hypertension, diabetes mellitus, congestive heart failure, chronic kidney disease, coronary heart disease, peripheral vascular disease, atrial fibrillation, tobacco use and alcohol abuse	165,656	1,900,574	acute cerebrovascular disease, stroke
Kaaja et al. [62], 2005	Finland, Europe	2002	population-based	PE	n.r.	mean PE: 48; control range 25–64	unadjusted	397	3,162	cardiac insufficiency, coronary artery disease, hypertension
Melchiorre et al. [39], 2011	UK, Europe	2008–2011	hospital-based	PE	2	mean PE: 33; controls 34	age, gestational age and ethnicity	64	78	stage B HF, hypertension
Nijdam et al. [17], 2009	The Netherlands, Europe	2000–2007	population-based	PE	mean PE: 2.9; control: 2.5	mean age at index pregnancy: 32.3	unadjusted	35	150	CVD/cerebrovascular disease
Berends et al. [56], 2008	The Netherlands, Europe	1983–2004	population-based	PE	mean PE: 7; control: 13	mean PE: 36; controls 39 at time of study	unadjusted	45	106	hypertension
Portelinha et al. [43], 2010	Portugal, Europe	n.r.	hospital-based	PE	mean 6; range: 4–9	mean 34	unadjusted	90	60	hypertension
Hannaford et al. [74], 1997	UK, Europe	1968–1995	population-based	PE	up to 26 years	mean 29 at recruitment	unadjusted	3,000	18,451	hypertension, total IHD, total cerebrovascular disease, total peripheral vascular disease, total venous thromboembolism
Best et al. [86], 2017	USA, North America	1995–2012	hospital-based	PE	PE: 13.5; controls: 12.9	PE: 36.1; controls: 35.9	age, BMI, and blood pressure	130	228	hypertension
Valdés et al. [51], 2009	Chile, South America	2006–2007	hospital-based	HDP	n.r.	60.9	age, smoking, diabetes mellitus, BMI, and familial premature CVD	71	146	coronary artery disease
Marin et al. [73], 2000	Spain, Europe	1973–1996	hospital-based	HDP	HDP: 13.6; control: 16.2	mean HDP: 43; controls: 42	unadjusted	273	86	hypertension, cardiovascular morbidity
Blauw et al. [61], 2006	The Netherlands, Europe	2003–2004	hospital-based	PE	range 3–13 months	31	age, BMI and smoking	22	22	hypertension
Canit et al. [46], 2010	Brazil, South America	n.r.	hospital-based	PE	mean PE: 15.9; controls: 14.6	mean PE: 39; controls: 37	unadjusted	40	14	hypertension
Kharazmi et al. [57], 2007	Finland, Europe	2000–2001	population-based	PE	n.r.	range 30–99	unadjusted	131	2,834	isolated systolic hypertension
Spaan et al. [53], 2009	The Netherlands, Europe	2001–2008	hospital-based	PE	mean 23; range 20–28	49	BMI, age, and date of birth	22	29	hypertension
Gaugler-Senden et al. [55], 2008	The Netherlands, Europe	1993–2003	hospital-based	PE	mean 5.5; range 4–10 years	median PE: 39; controls: 38	age, parity, race and year of delivery	20	20	hypertension
Shahbazian et al. [40], 2011	Iran, Asia	2001–2003	hospital-based	PE/E	mean 5.7; range 5.2–7.3	mean PE/E: 25; controls: 25.8	year of delivery and age	35	35	hypertension
Manien et al. [58], 2007	The Netherlands, Europe	n.r.	hospital-based	PE	mean PE: 9.8 months; controls: 5.8 months	mean PE: 31; controls: 33	unadjusted	256	53	hypertension
Diehl et al. [54], 2008	USA, North America	1960–1979	hospital-based	PE/E	median PE: 24.5; controls: 27.3	mean PE/E: 54; controls: 56	time-matched	103	100	hypertension
Hübel et al. [72], 2000	Iceland, Europe	1931–1996	hospital-based	E	mean PE: 32.6; controls: 32.7	range: 50–67 mean PE: 57; controls: 56	date of birth, age at pregnancy and parity	30	30	hypertension
Sattar et al. [69], 2003	UK, Europe	n.r.	hospital-based	PE	median 20; range 15–25 years	median PE: 43; control: 44	time of index pregnancy, smoking, and current BMI	40	40	hypertension
Edlow et al. [50], 2009	USA, North America	2005–2007	hospital-based	PE	range 6–13 months	mean PE: 26; controls: 28	race, BMI, and parity	79	140	hypertension

Table 1 (continued)

Study	Geographic region	Study period	Sample source	Type of exposure	Follow-up duration, years	Mean age at follow-up, years	Controlled confounders	HDP group, <i>n</i>	Control group, <i>n</i>	Reported outcomes
Magnussen et al. [52], 2009	Norway, Europe	1995–1997	population-based	PE	mean 16	40	BMI	943	14,122	hypertension
Leon et al. [79], 2019	UK, Europe	1997–2016	population-based	PE	20	maternal age at delivery, mean PE: 28.61; controls: 28.47	maternal ethnicity, maternal age, pre-pregnancy diabetes, pre-pregnancy hypertension, index of multiple deprivation, and a cluster term to account for correlation within patients	25,554	1,277,811	all CVD, any stroke, cardiac atherosclerotic events (MI, etc.), all peripheral events, HF, cardiovascular deaths, chronic hypertension
Heida et al. [26], 2015	The Netherlands, Europe	1993–1997	population-based	HDP	15	mean age at enrolment HDP: 54.1; controls: 53.7	age, BMI, current smoking, and current alcohol consumption at study enrollment, total cholesterol/ high density lipoprotein ratio, prevalent hypertension at study enrollment, and type 2 diabetes	6,157	15,560	CVD, IHD, stroke, hypertension
Kestenbaum et al. [70], 2003	USA, North America	1987–1998	population-based	GH, PE	mean 7.8	mean maternal age at the time of a first cardiovascular event was 36.1	age, parity, and calendar year of delivery	31,239	92,902	cardiovascular events, thromboembolic events
Iversen et al. [47], 2010	UK, Europe	1968–2005	population-based	PE	median PE: 7.25; controls 8.71	mean age at recruitment 29	age group, social class, number of cigarettes/day parity	2,865	11,460	CVD death
Jónsdóttir et al. [75], 1995	Iceland, Europe	1956–1990	population-based	HDP	mean 41.9; range 1–60	age at index pregnancy 28.9	unadjusted	374	n.r.	IHD death
Ray et al. [66], 2005	Canada, North America	1990–2004	population-based	GH, PE	median 8.7	age at the index delivery 28.2	maternal age, multiple gestation, length of stay, income quintile, rural residence, drug dependence, and gestational diabetes mellitus in index delivery, and hypertension, any diabetes mellitus, obesity, dyslipidemia, tobacco use, renal disease, migraine headache, and systemic lupus erythematosus up to 24 months before index delivery	57,924	950,885	CVD
Shalom et al. [33], 2013	Israel, Asia	1988–1998	population-based	PE	at least 10 years	n.r.	unadjusted	2,072	20,742	CVD at least 1 hospitalization
Park et al. [80], 2018	Korea, Asia	2010–2012	population-based	PE	1	cases: 31.08; controls: 30.76	age, gestational diabetes mellitus, placenta previa, placental abruption, postpartum hemorrhage, etc.	25,698	1,049,363	cerebrovascular disease

HDP, hypertensive disorders of pregnancy; MI, myocardial infarction; CVD, cardiovascular disease; IHD, ischemic heart disease; HF, heart failure; GH, gestational hypertension; PE, preeclampsia; E, eclampsia; n.r., not reported; BMI, body mass index.

of 73 studies [12, 14–17, 21–88] were considered eligible and were included in this meta-analysis.

Of the 73 observational studies included, 66 were cohort studies and 7 were case-control studies. The characteristics of the 66 cohort studies with a total sample size >13 million are shown in Table 1. There was a large variance in sample sizes (40–2,066,230). The year of publication was between 1995 and 2019, within which nearly 57.6% (38/66 studies) were published in 2010–2019. Forty studies (60.6%) were conducted in Europe, 14 (21.2%) in North America, 9 (13.6%) in Asia, 2 (3.0%) in South America, and 1 (1.5%) in Oceania. Studies reported a mean or median age of participants in the range of 25–75 years, whereas median or mean follow-ups ranged from 0 to 42 years. For sample sources, 44 studies (66.7%) were population-based, and 22 (33.3%) were hospital-based. Seventeen studies (25.8%) did not adjust for any confounder when estimating the risk of CVD associated with HDP, but the remainder (74.2%) adjusted or matched for age, smoking, or other potential confounders.

The characteristics of the 7 case-control studies with sample sizes ranging from 158 to 3,678 women and published between 2004 and 2019, are shown in Table 2. Study populations were selected from Europe ($n = 3$), North America ($n = 3$), and Asia ($n = 1$). The age of the participants ranged from 15 to 66 years. For sample sources, 2 studies were population-based and 5 were hospital-based. Adjustments and matches were made in 6 studies.

The quality of the 73 studies included here was evaluated using the NOS as shown in online supplementary Tables 1 and 2 (for all online suppl. material, see www.karger.com/doi/10.1159/000508036). The quality was generally good, as 66 studies (90.4%) got 6–9 stars. The long-term outcomes reported in the 73 studies were: 43 cases of any CVD, 25 of coronary artery heart disease, 10 of heart failure, 8 of peripheral vascular disease, 14 of stroke, 17 of CVD-related mortality, and 36 of hypertension. Several studies reported more than 1 outcome of interest.

HDP and Risk of Cardiovascular Outcomes

The risk estimate of any CVD associated with HDP is summarized in Figure 2. The RRs for the association reported by included studies ranged from 0.88 to 13.18. Meta-analytic pooling of these risk estimates yielded a summary RR of 1.80 (95% CI 1.67–1.94), with substantial heterogeneity ($I^2 = 92\%$, $p < 0.001$). Begg's test did not indicate a potential publication bias ($Z = 0.283$, $p = 0.778$).

The relationships between HDP and coronary artery heart disease, heart failure, peripheral vascular disease, and stroke are summarized in online supplementary Figures 1–4. The overall RR in relation to HDP was 1.66 (95% CI 1.49–1.84; $I^2 = 86\%$, $p < 0.001$) for coronary artery heart disease, 2.87 (95% CI 2.14–3.85; $I^2 = 90\%$, $p < 0.001$) for heart failure, 1.60 (95% CI 1.29–2.00; $I^2 = 76\%$, $p < 0.001$) for peripheral vascular disease, and 1.72 (95% CI 1.50–1.97; $I^2 = 81\%$, $p < 0.001$) for stroke. No evidence of publication bias was detected by using Begg's test (coronary artery heart disease: $Z = 0.701$, $p = 0.484$; heart failure: $Z = 0.626$, $p = 0.531$; peripheral vascular disease: $Z = 1.485$, $p = 0.138$; stroke: $Z = 1.478$, $p = 0.139$).

Subgroup analyses for risk of any CVD, coronary artery heart disease, heart failure, peripheral vascular disease, and stroke are shown in online supplementary Table 3. After these analyses were conducted, the variables including geographic region, sample source, type of exposure, and median/mean follow-up time were identified as the relevant heterogeneity moderators for any CVD (χ^2 range: 6.79–22.12; all $p < 0.05$). Notably, in hospital-based studies, the risk estimate of any CVD (2.54, 95% CI 2.16–2.99) was higher than in studies targeted at the general population (1.66, 95% CI 1.54–1.78). When stratified according to the type of exposure, the pooled risk estimate of any CVD in women with a history with GH (1.64, 95% CI 1.43–1.89) was lower than that in women with a history of PE (2.07, 95% CI 1.86–2.30). The risk of developing any CVD associated with a history of HDP was higher in studies with a follow-up time ≤ 10 years (2.64, 95% CI 2.15–3.25) than in studies with a follow-up time of 10–20 years (1.59, 95% CI 1.43–1.75) or a follow-up time ≥ 20 years (1.68, 95% CI 1.62–1.75). For coronary artery heart disease, variables including geographic region, type of exposure, and median/mean follow-up time partially explained the between-study heterogeneity (χ^2 range: 7.00–23.38; all $p < 0.05$). The 2 variables geographic region and median/mean follow-up time also partially explained the between-study heterogeneity for heart failure and stroke (χ^2 range: 13.13–34.62; all $p < 0.001$). Only the sample source was identified as the heterogeneity moderator for peripheral vascular disease ($\chi^2 = 9.38$, $p = 0.002$).

HDP and Risk of CVD-Related Mortality

The risk estimate of CVD-related mortality associated with HDP is summarized in Figure 3. The RR for the association reported in the included studies was in the range of 1.28–5.04. Meta-analytic pooling of these risk estimates yielded a summary RR of 1.78 (95% CI 1.58–2.00)

Fig. 2. Risk of any cardiovascular disease associated with hypertensive disorders of pregnancy. CI, confidence interval; IV, inverse variance; SE, standard error.

with substantial heterogeneity ($I^2 = 77\%$, $p < 0.001$). Begg's test did not indicate a potential publication bias ($Z = 0.659$, $p = 0.510$).

Subgroup analyses of risk of CVD-related mortality appear in online supplementary Table 3. After these analyses, only geographic region was identified as the relevant heterogeneity moderator for CVD-related mortality ($\chi^2 = 5.61$; $p = 0.018$). The risk estimate of CVD-related mortality was higher in studies conducted in Asia (2.63, 95% CI

1.90–3.65) than in those conducted in Europe (1.72, 95% CI 1.51–1.96).

HDP and Risk of Hypertension

Online supplementary Figure 5 shows the result from the random-effects model combining the RRs for hypertension in women with a history of HDP. The RRs for the association varied from 1.32 to 23.74. Overall, women with a history of HDP compared to the reference group

Table 2. Selected characteristics of 7 case-control studies of HDP and CVD, and CVD-related mortality

Study	Geographic region	Study period	Sample source	Type of exposure	Mean age, years	Controlled confounders	Case group, <i>n</i>	Control group, <i>n</i>	Reported outcomes
Sia et al. [76], 2019	Canada, North America	2005–2009	hospital-based	GH, PE	cases: 66.3 controls: 65.8	1:1 age-matched within 5 years of cases participants	244	246	coronary artery disease
Schoemaker et al. [27], 2015	The Netherlands, Europe	2008–2010	hospital-based	HDP	cases: 49.5–51.5 controls: 47.8	age-matched	83	75	cerebrovascular disease, CVD
Brown et al. [60], 2006	USA, North America	1992–2003	population-based	PE	range 15–44	age, race, education, and number of pregnancies, smoking, BMI, diabetes, elevated cholesterol, angina-MI, hypertension	261	421	stroke
Haukkanen et al. [67], 2004	Finland, Europe	1996–2000	hospital-based	PE	cases: 55 controls: 52	age, BMI, smoking, hypertension, current hormone replacement therapy, hypercholesterolemia, type 2 diabetes mellitus	141	99	coronary artery disease
Ben-Ami et al. [45], 2010	Israel, Asia	1995–2004	hospital-based	GH, PE	cases: 43.3 controls: 41.9	age and BMI	101	101	atherothrombotic occlusive vascular disease
Soh et al. [29], 2015	Sweden, Europe	1973–2011	population-based	HDP	cases: 41 controls: 38	year of first delivery plus number of inpatient admissions and cardiovascular risk factors (renal disease, hypertension, and diabetes mellitus)	44	3,634	died of primarily cardiovascular causes
Borna et al. [38], 2012	Iran, Asia	2009–2010	hospital-based	GH, PE	cases: 58.1 controls: 55.98	unadjusted	345	345	coronary artery disease

HDP, hypertensive disorders of pregnancy; CVD, cardiovascular disease; MI, myocardial infarction; GH, gestational hypertension; PE, preeclampsia; BMI, body mass index.

had a significantly higher risk of developing hypertension (RR 3.16 [95% CI 2.74–3.64]). There was high heterogeneity across studies ($I^2 = 98\%$, $p < 0.001$). Begg's test also did not indicate a potential publication bias ($Z = 1.716$, $p = 0.086$). After subgroup analyses, the variables including sample source and median/mean follow-up time were identified as the relevant heterogeneity moderators for hypertension ($\chi^2 = 9.37$, 12.68; all $p = 0.002$; online suppl. Table 3).

Sensitivity Analyses

Sensitivity analyses were performed to examine the influence of individual studies on the overall risk estimate for CVD, CVD-related mortality, and hypertension associated with HDP (online suppl. Table 4). Exclusion of any single study did not materially alter the overall combined RR, which ranged from 1.76 (95% CI 1.64–1.89) to 1.85 (1.69–2.03) for any CVD, 1.60 (1.44–1.77) to 1.71 (1.53–1.90) for coronary artery heart disease, 2.59 (1.95–3.44) to 3.16 (2.29–4.37) for heart failure, 1.48 (1.24–1.77) to 1.72 (1.44–2.06) for peripheral vascular disease, 1.60 (1.41–1.81) to 1.87 (1.54–2.28) for stroke, 1.72 (1.54–1.92) to 1.83 (1.62–2.08) for CVD-related mortality, and 3.05 (2.64–3.52) to 3.26 (2.82–3.77) for hypertension. Furthermore, sensitivity analyses were conducted to examine the influence of case-control studies on overall RR (online suppl. Table 5). Results showed that exclusion of case-control studies did not alter the risk estimates for CVD and CVD-related mortality.

Discussion

In this systematic review and meta-analysis, 73 studies involving >13 million women were included. We showed an association of HDP with the long-term risk of developing CVD, CVD-related mortality, and hypertension. The mean risk estimates were 1.80 for CVD, 1.66 for coronary artery heart disease, 2.87 for heart failure, 1.60 for peripheral vascular disease, 1.72 for stroke, 1.78 for CVD-related mortality, and 3.16 for hypertension, when compared with participants without a history of HDP. To the best of our knowledge, this is the most comprehensive meta-analysis to assess the association between HDP and risk of CVD. Our findings supply helpful information to both clinicians and women with HDP and can contribute to the guidelines for the clinical management of HDP in the future.

Five systematic reviews and meta-analysis [89–93] have been previously performed to investigate the asso-

Fig. 3. Risk of cardiovascular-related mortality associated with hypertensive disorders of pregnancy. CI, confidence interval; IV, inverse variance; SE, standard error.

ciation between PE and future CVD, death due to CVD, and hypertension. A recent review, performed by Grandi et al. [94], examined the risk of CVD associated with GH and PE. Although the results of our current meta-analysis are generally in line with these previous reviews, we also provide a contemporary synthesis of the evidence for all HDP with a rigorous assessment of study quality. Given that different types of specific CVD may have different etiologies, it may be conceivable that the risk of developing each specific CVD is inconsistent. Therefore, we combined the risk of specific CVDs in women with HDP, such as coronary artery heart disease, heart failure, etc. Moreover, we synthesized the literature on peripheral vascular disease, which has not been previously performed. By comparison, our risk estimates of CVD associated with PE were slightly lower than those in a meta-analysis published in 2017 [91], possibly due to the inconsistencies in the included studies. The meta-analysis published in 2017 included 1 study [95] which was not included in our meta-analysis due to the overlap of the study population. Notably, after considering the effects of hypertension in the future coronary heart disease outcome, the link between preeclampsia and future coronary heart disease was no longer statistically significant in 2017. However, the abovementioned meta-analysis was published earlier than 9 large cohort studies from Norway [77, 78], the UK

[21, 79, 83], Denmark [23], the USA [85], Canada [87], and Australia [22], all of which were included in our study.

In our study, the increased risk for all CVD and hypertension was greater at ≤ 10 years compared with at > 10 years postpartum. This may be because of a higher absolute risk in the control group during longer follow-up periods (i.e., > 10 years). Therefore, the reduction in the RR may be a product of the higher baseline risk. Furthermore, the effect is exacerbated by the small sample size and number of events in the control group reported [39, 73, 88]. Historically, it was thought that GH is a milder form of PE; our study showed that the risk of developing any CVD in GH was lower than that in PE. However, it is only significantly lower in the outcome of any CVD and coronary artery heart disease. Among other outcomes such as heart failure, stroke, hypertension, and so on, the difference was not statistically significant in the GH and PE groups.

The strength of this study is the large sample size; it consisted of contemporary studies on > 13 million study participants. This helps to enhance statistical power providing more reliable and precise risk estimates. At the beginning of the study, a comprehensive search strategy was used to identify relevant studies. Moreover, the process including literature retrieval and screening, and data ex-

traction were performed by 2 reviewers independently. Finally, most of the studies were designed to examine future CVDs as their main outcome ($n = 43$).

One potential limitation of this meta-analysis was the significant heterogeneity across studies for the association between HDP and the risk of developing CVD. This is not surprising, given the different study designs and characteristics of study populations. Fortunately, our subgroup analyses identified several variables associated with the between-study heterogeneity, including geographic region, sample source, type of exposure, and follow-up time. In addition, the variability and complexity of HDP might have contributed to the heterogeneity, given the underlying mechanisms involved in the association between HDP and CVD. However, we were unable to obtain adequate information to test the hypothesis. A second limitation was that significant unmeasured confounding factors may have contributed to the observed association between HDP and CVD. Although most of the studies included here attempted to control for some potential confounding factors, only a few adequately controlled all the conventional cardiovascular risk factors reported in previous studies, such as age, body mass index, gestational diabetes, blood pressure, cholesterol, and family history of CVD. Finally, the duration of follow-up in several of the included studies may not have been sufficient to capture all cardiovascular-related events of interest [15, 30, 50, 61]. Last, but not least, according to the previously published studies [91, 93], we used both HRs and ORs to approximate the RRs. Given the lack of information on incidence rates from case-control studies, however, we could not determine the RR from the pooled data. From individual cohort studies, it was suggested that the risk of CVD incidence was low [77–78].

This study demonstrated that all women who present with any of the HDP subtypes are at significant risk of future CVD, CVD-related mortality, and hypertension, when compared with women who remain normotensive during their pregnancy. In view of the burden and impact of CVDs on women in our society, we recommend a detailed cost-benefit analysis to determine the postnatal timing for a screening program in this high-risk population.

Conclusions

Our meta-analysis reports an increased risk of CVD, CVD-related mortality, and hypertension in women with HDP compared with the reference population. In keeping

with current recommendations, our findings highlight the importance of education and lifestyle modifications to reduce risks. Regular monitoring of cardiovascular risk factors in women with a history of HDP is also strongly advised.

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Statement of Ethics

This systematic review was conducted following the proposed Systematic Reviews and Meta-Analyses (PRISMA) [18] and the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) [19] reporting guidelines.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

L.C., R.W., and T.W. contributed to the conception or design of the work. R.W., T.W., R.G., C.Y., Y.C., X.L., and D.X. contributed to the acquisition, analysis, or interpretation of data for the work. R.W. and T.W. drafted the manuscript. L.C. critically revised the manuscript. All authors gave their final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

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