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## OBSTETRICS

# Time to onset of cardiovascular and cerebrovascular outcomes after hypertensive disorders of pregnancy: a nationwide, population-based retrospective cohort study

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**BACKGROUND:** The increased maternal cardiocerebrovascular risk after a pregnancy complicated by hypertensive disorders of pregnancy, is well documented in the literature. Recent evidence has suggested a shorter timeframe for the development of these postnatal outcomes, which could have major clinical implications.

**OBJECTIVE:** This study aimed to determine the risk of and time to onset of maternal cardiovascular and cerebrovascular outcomes after a pregnancy complicated by hypertensive disorders of pregnancy.

**STUDY DESIGN:** This study included 2,227,711 women, without preexisting chronic hypertension, who delivered during the period 2008 to 2010: 37,043 (1.66%) were diagnosed with preeclampsia, 34,220 (1.54%) were diagnosed with gestational hypertension, and 2,156,448 had normotensive pregnancies. Hospitalizations for chronic hypertension, heart failure, coronary heart disease, cerebrovascular disease, and peripheral arterial disease were studied. A classical Cox regression was performed to estimate the average effect of hypertensive disorders of pregnancy over 10 years compared with normotensive pregnancy; moreover, an extended Cox regression was performed with a step function model to estimate the effect of the exposure variable in different time intervals: <1, 1 to 3, 3 to 5, and 5 to 10 years of follow-up.

**RESULTS:** The risk of chronic hypertension after a pregnancy complicated by preeclampsia was 18 times higher in the first year (adjusted hazard ratio, 18.531; 95% confidence interval, 16.520–20.787) to only 5 times higher at 5 to 10 years after birth (adjusted hazard ratio, 4.921; 95% confidence interval, 4.640–5.218). The corresponding risks of women with gestational hypertension were 12 times higher (adjusted hazard ratio, 11.727; 95% confidence interval, 10.257–13.409) and 6 times higher

(adjusted hazard ratio, 5.854; 95% confidence interval, 5.550–6.176), respectively. For other cardiovascular and cerebrovascular outcomes, there was also a significant effect with preeclampsia (heart failure: adjusted hazard ratio, 6.662 [95% confidence interval, 4.547–9.762]; coronary heart disease: adjusted hazard ratio, 3.083 [95% confidence interval, 1.626–5.844]; cerebrovascular disease: adjusted hazard ratio, 3.567 [95% confidence interval, 2.600–4.893]; peripheral arterial disease: adjusted hazard ratio, 4.802 [95% confidence interval, 2.072–11.132]) compared with gestational hypertension in the first year of follow-up. A dose-response effect was evident for the severity of preeclampsia with the averaged 10-year adjusted hazard ratios for developing chronic hypertension after early, preterm, and late preeclampsia being 10, 7, and 6 times higher, respectively.

**CONCLUSION:** The risks of cardiovascular and cerebrovascular outcomes were the highest in the first year after a birth complicated by hypertensive disorders of pregnancy. We found a significant relationship with both the severity of hypertensive disorders of pregnancy and the gestational age of onset suggesting a possible dose-response relationship for the development of cardiovascular and cerebrovascular outcomes. These findings call for an urgent focus on research into effective postnatal screening and cardiocerebrovascular risk prevention for women with hypertensive disorders of pregnancy.

**Key words:** cardiovascular complications, cerebrovascular complications, chronic hypertension, gestational hypertension, hazard ratio, hypertensive disorders, medicoadministrative database, preeclampsia, pregnancy

## Introduction

Although hypertensive disorders of pregnancy (HDP) are common complications,

their pathophysiology is still poorly understood, especially concerning preeclampsia (PE). For decades, the main hypothesis was that of defective trophoblastic invasion of the myometrial spiral arteries in early pregnancy leading to the characteristic signs and symptoms we recognize as the syndrome of PE.<sup>1</sup> More recently, several studies have put forward the hypothesis of maternal cardiovascular dysfunction relative to the increased hemodynamic load of pregnancy as the primary etiology, leading to secondary placental dysfunction.<sup>2</sup> The increase in long-term cardiovascular and cerebrovascular events after a pregnancy complicated

by PE would be consistent with such a mechanism. This increase in cardiovascular or cerebrovascular morbidity after a pregnancy complicated by PE is reported in several publications and meta-analyses.<sup>3–21</sup> To date, most of these studies evaluated the prevalence of chronic hypertension and its cardiovascular or cerebrovascular complications over several decades after birth. Therefore, there is a paucity of evidence regarding the risk and time course for the development of both cardiovascular and cerebrovascular events immediately after a birth complicated by PE. Some studies suggest that these outcomes occur as early as the first year after

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## AJOG at a Glance

**Why was this study conducted?**

The increased maternal cardiocerebrovascular risk after a pregnancy complicated by hypertensive disorders of pregnancy (HDP) is well documented in the literature. Recent evidence has suggested a shorter timeframe for the development of these postnatal outcomes, which could have major clinical implications.

**Key findings**

For both cardiovascular and cerebrovascular risks, the risk was the highest in the first year (chronic hypertension risks were 20 times more in patients with preeclampsia and 12 times more in patients with gestational hypertension) and progressively decreases thereafter. The average risk within 10 years of delivery for a maternal composite adverse outcome was similar to that of diabetes mellitus or personal cardiovascular history and greater than that of heavy smoking.

**What does this add to what is known?**

Given the magnitude of these immediate postpartum cardiocerebrovascular risks, there has been an urgent need to develop effective screening programs and initiation of cardiocerebrovascular prevention measures shortly after a birth complicated by hypertensive disorders of pregnancy.

delivery; however, data from other studies do not support this finding.<sup>5,10,12,17,21–23</sup>

Such knowledge is essential for planning screening, diagnostic, and cardio-preventive measures to mitigate the clinical effect of maternal cardiovascular and cerebrovascular outcomes. In this French nationwide study, we aimed to better characterize the risk of and time to onset of chronic hypertension and its cardiovascular and cerebrovascular complications after a pregnancy complicated by hypertensive disorders within 10 years after giving birth.

**Methods****Database**

To analyze the effect of HDP on cardiovascular outcomes after a pregnancy with 10 years of follow-up, we used a national observational cohort created from all hospitalizations in France. The French national Programme de Médicalisation des Systèmes d'Information (PMSI), a medicoadministrative database, collects the discharge abstracts from all French hospitals, both public and private. As for the American diagnosis-related group model, the information in the PMSI abstracts is anonymous. The unique anonymous identification number generated for each patient makes it possible to link all

hospitalizations of the same person, thus allowing for longitudinal studies.

The use of this database for the allocation of hospital budgets encourages improvement in data quality in terms of coherence, accuracy, and exhaustiveness, because of internal and external validations of its quality. Therefore, these hospital data have been used in medical research for many years,<sup>24–32</sup> and their quality has been confirmed in recent perinatal studies.<sup>33–42</sup> Almost all births (out-of-hospital deliveries represent only 0.4% of births) are recorded, which enables us to cover the entire set of deliveries within a specified timeframe.

Diagnoses identified during the hospital stay are coded according to the International Classification of Diseases, Tenth Revision (ICD-10), and procedures are coded according to the French Classification of Medical Procedures (CCMP).

**Population**

All women who gave birth between January 1, 2008, and December 31, 2010, were included. ICD-10 code Z37 was used to determine delivery associated with different procedures. We excluded women with preexisting chronic hypertension (ICD-10 codes O10–11,

I10–13, and I15) to avoid attributing to PE a cardiovascular outcome that would be associated with chronic hypertension and avoid potential bias. In addition, we excluded those noted with unspecified hypertension before pregnancy (ICD-10 code O16). Women whose maternal age was <12 and >57 years (to retain women of childbearing age) and women who died during the inclusion delivery stay were excluded.

We separated the remaining women into 3 groups: those who had PE (ICD-10 codes O14–15), those with a diagnosis of gestational hypertension (GH; ICD-10 code O13), and those with normotensive pregnancy.

**Outcomes**

Our outcomes of interest were hospitalizations because of chronic hypertension and cardiovascular diseases (CVDs): heart failure; coronary heart disease, including angina pectoris, myocardial infarction, and coronary revascularization; cerebrovascular disease, including both hemorrhagic and ischemic strokes and transient ischemic attacks; carotid revascularization; peripheral arterial disease; and arterial revascularization. The ICD-10 codes for the aforementioned outcomes that were used are presented in [Supplemental Table 1](#). All these cardiovascular outcomes were counted from the inclusion delivery until December 2020 to allow 10 years of follow-up for each woman. If a woman was hospitalized for the same condition more than once during follow-up, only the first event was considered. Moreover, we used a composite outcome, which included all such cardiovascular events and was defined by the first occurrence of at least 1 of the aforementioned conditions.

**Variables**

Our exposure variable was HDP (both PE and GH). Moreover, we included other variables in the models to adjust for risk factors for CVD that were available in our dataset: maternal age (<20, 20–29, 30–39, and ≥40), gestational diabetes mellitus (ICD-10 code O24), dyslipidemia (ICD-10 code E78), body mass index (BMI) of ≥40 kg/m<sup>2</sup>

(ICD-10 codes E6601–02, E6606–07, E6611–12, E6616–17, E6621–22, E6626–27, E6681–82, E6686–87, E6691–92, and E6696–97), heavy smoking (ICD-10 code F17, except F170, T652, and Z720) or alcohol intake (ICD-10 code F10, except F100, G621, G721, I426, K292, K852, K860, and K70), family (ICD-10 code Z824) and personal history (ICD-10 codes Z867 and I69) of CVD, and parity when it was available (only for vaginal deliveries in our database). These variables were extracted for each woman during the entire pregnancy (before the inclusion delivery), noting whether it was a single or multiple pregnancy.

### Statistical analysis

Individual characteristics and occurrence of cardiovascular outcomes are presented as proportions. Moreover, maternal age is presented as mean  $\pm$  standard deviation (SD) and as median and interquartile range (IQR). To compare women with PE, women with GH, and women without HDP, we used the chi-square test.

The main analysis was to investigate the effect of PE and GH on the risk of cardiovascular outcomes during 10 years of follow-up. To count each woman only once, only the first pregnancy of the inclusion period and the associated delivery were included in the main analysis, and the exposure variable was defined according to information collected during this first pregnancy. It was performed using the classical Cox regression model for survival data, adjusting for all variables listed above. Patients who died during follow-up were censored, if this death was not related to one of the cardiovascular events.

We checked whether the 2 underlying assumptions of the Cox model are respected. First, we accounted for a possible non-log-linear effect of the exposure variable (HDP, with 3 modalities) by using disjunctive variables: a first indicator variable for women with PE and a second indicator variable for women with GH. For each of these variables, the reference was women who did not have hypertensive disorders during the inclusion of pregnancy. Second, we

checked the proportional hazard assumption. For this aim, we introduced an interaction of the effect with time in the Cox model.<sup>43</sup> Moreover, we used the extended Cox regression with a step function model<sup>44,45</sup> to test the interaction of the effect of the exposure variable with time. In case the proportional hazard assumption is rejected, it is possible with this step function model to estimate the effect of the exposure variable in different time intervals (chosen for their clinical significance).

In addition, we performed a sub-analysis where we separated early PE (gestational age of <34 weeks of amenorrhea), preterm PE (gestational age between 34 and 37 weeks of amenorrhea), and late PE (gestational age of  $\geq$ 37 weeks of amenorrhea).<sup>46</sup> In this sub-analysis, based on the same models, we only included women whose inclusion delivery was in 2010, as it is the year that gestational ages became systematically collected and reliable.

We performed several sensitivity analyses. In the first sensitivity analysis, we removed chronic hypertension from the composite outcome. In the second analysis, we included unspecified hypertension in our population, where the unspecified hypertension was considered as being related to GH. To limit the effect of the potential underrecording of the smoking variable, we performed a third sensitivity analysis in which we stratified on tobacco status (heavy smoking or nonheavy smoking) by applying Cox multivariate analyses only on women who were coded as heavy smokers. In the fourth sensitivity analysis, we considered only vaginal deliveries to include parity in the adjustment. In the fifth sensitivity analysis, we excluded women who had CVD or diabetes mellitus before pregnancy. In the sixth sensitivity analysis, if women had PE or GH during one of the pregnancies corresponding to the inclusion period, and not only for the first pregnancy, the exposure variable was reclassified as PE or GH accordingly. This means that we have taken into account all pregnancies in the inclusion period to construct this new exposure variable. Finally, we also conducted sensitivity

analyses with different subsets of covariates to estimate the total effects of secondary covariates (gestational diabetes mellitus and personal history of CVD), as recommended by Westreich and Greenland.<sup>47</sup>

To interpret the results, we used the hazard ratio (HR) and 95% confidence interval (CI) given by models. Statistical significance was set at a *P* value of .05 for all analyses. SAS software (version 9.4; SAS Institute Inc, Cary, NC) was used for analyses, and the parametric proportional hazards regression procedure was used for Cox regression models.

### Ethics approval

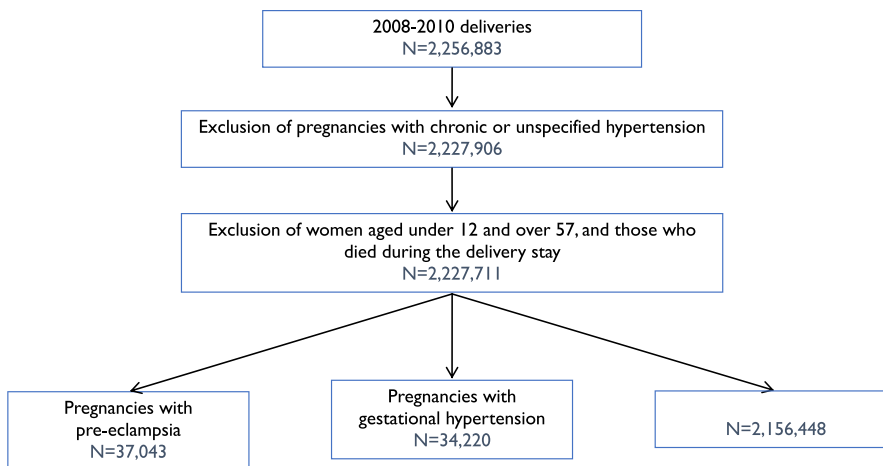
This study was approved by the French National Committee for Data Protection (declaration of conformity to the methodology of reference 05 obtained on July 8, 2018, under the number 2204633 v0).

Written consent was not needed for this study because this was a retrospective study and the national data used, were anonymous.

### Results

The French hospital database recorded 2,256,883 deliveries between 2008 and 2010. After excluding 28,977 women (1.28%) who had chronic or unspecified hypertension before pregnancy, women aged <12 and >57 years, and women who died during pregnancy (*n*=195), the final cohort for analysis was 2,227,711 women. Among these women, 37,043 (1.66%) had a diagnosis of PE, 34,220 (1.54%) had a diagnosis of GH, and 2,156,448 remained normotensive throughout pregnancy (Figure 1). The characteristics of the 3 groups of women are presented in Table 1. Gestational diabetes mellitus, dyslipidemia, and multiple pregnancy were significantly more frequent in pregnancies with PE or GH compared with those that remained normotensive (*P*<.05 for all).

The prevalence of each cardiovascular outcome was at least twice as frequent in the 10 years after birth after PE or GH than in those without HDP (Table 2). Almost 8 and 9 times more chronic hypertension was observed in patients with PE or GH than in normotensive patients. Heart failure, coronary heart disease,

**FIGURE 1**  
**Flowchart of the population**

Simon. Time to onset of cardiocerebrovascular outcomes after hypertensive disorders of pregnancy. *Am J Obstet Gynecol* 2023.

and peripheral arterial disease were 3 times more frequent in women with HDP, and cerebrovascular disease was 2 times more frequent.

Before and after adjustments on gestational diabetes mellitus, personal history, maternal age, multiple pregnancy, dyslipidemia, obesity, heavy smoking, alcohol intake, and family history, we found that the average risk over 10 years of developing each cardiovascular outcome was always at least 2 times higher for women with HDP compared with normotensive women (Table 3). In particular, in adjusted models, we found that for chronic hypertension, the average risk was almost 7 times higher for women with HDP (adjusted hazard ratio [aHR], 6.718 [95% CI, 6.451–6.995] for PE and 6.946 [95% CI, 6.679–7.225] for GH). Similarly, for heart failure, the average risks were 3 times higher (aHR, 3.161; 95% CI, 2.649–3.771) for women who had PE and 2 times higher (aHR, 1.854; 95% CI, 1.480–2.323) after a pregnancy complicated by GH. For coronary heart, cerebrovascular, and peripheral arterial diseases, the average risk was 2 to 3 times higher for women with HDP.

The average risk over 10 years of developing any one of the cardiovascular outcomes (composite outcome) for women who had PE or GH was 5 times higher than

women without HDP (aHR, 4.974 [95% CI, 4.790–5.165] for PE and 5.086 [95% CI, 4.901–5.277] for GH). These risks were similar to the risk of gestational diabetes mellitus (aHR, 5.576) or strong personal history of CVD (aHR, 4.564) for the development of a composite adverse outcome (Table 4). In addition, these risks were greater than that for heavy smoking (aHR, 2.868). As the interaction of our exposure variable with time was found to be significant for the classical Cox model, we used the extended Cox step function model to estimate the effect of the exposure variable in different time intervals: during the first year, 1 to 3 years, 3 to 5 years, and 5 to 10 years of follow-up. We found that for all cardiovascular events, the effects of PE and GH were significantly ( $P < 0.05$  for all) more pronounced in the first year of follow-up and decreased over time (Figure 2 and Table 5). For women with PE compared with those that were normotensive, the risk of chronic hypertension was almost 20 times higher in the first year (aHR, 18.531; 95% CI, 16.520–20.787), but only 5 times higher at 5 to 10 years after birth (aHR, 4.921; 95% CI, 4.640–5.218). The corresponding risks for women with GH were 12 times higher (aHR, 11.727; 95% CI, 10.257–13.409) and 6 times higher (aHR, 5.854; 95% CI, 5.550–6.176), respectively. For other cardiovascular and cerebrovascular outcomes,

there was also a significant effect with PE (heart failure: aHR, 6.662 [95% CI, 4.547–9.762]; coronary heart disease: aHR, 3.083 [95% CI, 1.626–5.844]; cerebrovascular disease: aHR, 3.567 [95% CI, 2.600–4.893]; peripheral arterial disease: aHR, 4.802 [95% CI, 2.072–11.132]) compared with GH in the first year of follow-up (Table 5). As expected, although we found the highest incident risk in the first year, cumulative prevalence continues to increase over time, thus reaching higher levels after 5 years, as shown in the Supplemental Figure S2.

The subanalysis by gestational age demonstrated that the average risk of most cardiovascular outcomes was more pronounced for women with early PE than for those with preterm PE and those with late PE (Supplemental Tables S3–5). It seems that the earlier the PE occurs in the pregnancy, the greater the risk of cardiovascular consequences. For example, the average risks of developing chronic hypertension were 10 times higher for women with early PE (aHR, 9.514; 95% CI, 8.358–10.829), only 7 times higher for women with preterm PE (aHR, 6.896; 95% CI, 6.042–7.869), and 6 times higher for those with late PE (aHR, 5.627; 95% CI, 5.078–6.235) (Supplemental Table S4). The difference between early, preterm, and late PE was still significant ( $P < .05$ ) but less marked for other outcomes and nonsignificant for cerebrovascular and peripheral arterial diseases.

Regarding the first sensitivity analysis (Supplemental Table S6), the magnitude of the risk of the new composite outcome (excluding chronic hypertension) was lower than that of the previous composite outcome (including chronic hypertension), but the risks remained higher in the first year of first delivery, both for PE (aHR, 4.412; 95% CI, 3.541–5.498) and for GH (aHR, 2.899; 95% CI, 2.220–3.787).

All other sensitivity analyses yielded results that were similar to the main analysis (Supplemental Tables S7–14).

## Discussion

### Principal findings

The original information provided by this nationwide, population-based study was the description of the burden and



TABLE 1

## Characteristics of the women who gave birth in France between 2008 and 2010 by hypertensive disorders of pregnancy

Characteristics	PE		GH		Normotensive		P value (PE vs normotensive) <sup>a</sup>	P value (GH vs normotensive) <sup>a</sup>
	n	%	n	%	n	%		
	37,043	1.66	34,220	1.54	2,156,448	96.8		
Maternal age								
Mean (SD)	29.72 (5.87)		30.23 (5.87)		29.50 (5.39)			
Median (IQR)	29 (26–34)		30 (26–35)		29 (26–33)			
<20 y	1173	3.17	829	2.42	60,807	2.82	<.0001	<.0001
between 20 and 29 y	17,681	47.73	15,520	45.35	1,042,487	48.34		
between 30 and 39 y	16,174	43.66	15,688	45.84	980,870	45.49		
>40 y	2015	5.44	2183	6.38	72,284	3.35		
Multiple pregnancy	2633	7.11	1043	3.05	33,502	1.55	<.0001	<.0001
Gestational diabetes mellitus	1692	4.57	2019	5.9	37,908	1.76	<.0001	<.0001
Dyslipidemia	15	0.04	23	0.07	406	0.02	.0028	<.0001
Obesity (BMI ≥ 40 kg/m <sup>2</sup> )	356	0.96	373	1.09	3144	0.15	<.0001	<.0001
Heavy smoking	537	1.45	617	1.8	25,480	1.18	<.0001	<.0001
Alcohol intake	11	0.03	17	0.05	499	0.02	.4119	.0015
Personal history of CVD	32	0.09	47	0.14	1211	0.06	.0154	<.0001
Family history of CVD	36	0.1	32	0.09	634	0.03	<.0001	<.0001

BMI, body mass index; CVD, cardiovascular disease; GH, gestational hypertension; PE, preeclampsia.

<sup>a</sup> The chi-square test was used.

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TABLE 2

## Prevalence of cardiovascular events by hypertensive disorders in the 10 years after delivery in 2008–2010 in France

Characteristics	PE		GH		Normotensive		P value (PE vs normotensive) <sup>a</sup>	P value (GH vs normotensive) <sup>a</sup>
	n	%	n	%	n	%		
Composite outcome	3035	8.19	3206	9.37	31,984	1.48	<.0001	<.0001
Chronic hypertension	2742	7.4	2969	8.68	20,826	0.97	<.0001	<.0001
Heart failure	135	0.36	80	0.23	2093	0.1	<.0001	<.0001
Coronary heart disease	145	0.39	148	0.43	2776	0.13	<.0001	<.0001
Cerebrovascular disease	287	0.77	244	0.71	7911	0.37	<.0001	<.0001
Peripheral arterial disease	68	0.18	45	0.13	942	0.04	<.0001	<.0001
Carotid revascularization	6	0.02	3	0.01	33	0.00	<.0001	0.0185

GH, gestational hypertension; PE, preeclampsia.

<sup>a</sup> The chi-square test was used.

Simon. Time to onset of cardiocerebrovascular outcomes after hypertensive disorders of pregnancy. *Am J Obstet Gynecol* 2023.

immediate postnatal time course of the cardiovascular and cerebrovascular outcomes after HDP and the need to develop strategies for their prevention.<sup>48,49</sup>

The findings of this nationwide population-based study are that the risks of cardiovascular and cerebrovascular outcomes are the highest in the first year after birth with a diagnosis of HDP compared with risks in the following decade. The risks are higher for hypertension and heart failure than other outcomes, increased after a pregnancy complicated by PE compared with a pregnancy complicated by GH, and the highest for early PE before 34 weeks of gestation.

### Results in the context of what is known

The data confirm that the cardiovascular and cerebrovascular risks, in general, are greater after a pregnancy complicated by PE compared with a pregnancy complicated by GH, and the greatest for early PE before 34 weeks of gestation. In the first year after delivery, the risks of hypertension were 19 times higher with PE and 12 times higher after a pregnancy complicated by GH. The equivalent risks for heart failure in the first year after pregnancies complicated by PE and GH were 7 and 4 times higher than after normotensive pregnancy, respectively.

Moreover, the risks of coronary heart disease and peripheral arterial disease were higher in pregnancies complicated by PE or GH than in normotensive pregnancies, but the magnitudes of the risk were similar for pregnancies complicated by PE and GH. The risks of all cardiovascular and cerebrovascular adverse events decreased progressively with time over the following decade. The incident risk of a composite adverse outcome for both PE and GH decreased gradually from 7 times between 1 and 3 years to 4 times between 5 and 10 years after a pregnancy complicated by HDP.

The observed progressive decrease in incident risk over time is not typical for cardiovascular and cerebrovascular risks (of course, cumulative prevalence continues to increase over time), recalling that pregnancy is a specific cause of vascular events mainly for cerebrovascular events in young women.<sup>49</sup> Outside perinatal medicine, the probability of a deleterious event increases gradually over time. With pregnancies complicated by HDP, the cardiovascular incident risk is maximal after delivery and gradually decreases and seems to stabilize a decade after birth. This phenomenon has not been described for most cardiovascular and cerebrovascular outcomes evaluated in this study other than for chronic hypertension after pregnancies complicated by HDP.<sup>15</sup> Very

few studies report cardiovascular or cerebrovascular risks at 1 year after birth complicated by HDP.<sup>5,12,15,17,22,23</sup> The latter are limited by the binary analysis of variables, uncensored data, and low event rates that adjusted odd ratios exhibited very wide CIs.<sup>17</sup> For chronic hypertension, our results are consistent with those of Behrens et al<sup>15</sup> and another French study,<sup>22</sup> both of which differed from the current study by the inclusion of out-of-hospital data, such as antihypertensive medication use. In our study, we also performed a sensitivity analysis by excluding chronic hypertension from the composite outcome, seeing as chronic hypertension is a known risk factor rather than a cardiovascular complication per se. The sensitivity analysis performed after excluding chronic hypertension showed that HDP remains a major risk factor for the occurrence of a cardiovascular complication (aHR at 1 year, 4.412 [95% CI, 3.541–5.498] for PE and 2.899 [95% CI, 2.220–3.787] for GH). However, the complete composite outcome (including chronic hypertension) remains important in our view because it allows us to measure the global cardiovascular effect, insofar as chronic hypertension alone contributes to approximately 60% to 80% of the long-term risk of CVD.<sup>19</sup>

Of note, 1 previous study assessed specific emergency admissions for heart

TABLE 3

**Average adjusted effects<sup>a</sup> of hypertensive disorders of pregnancy on cardiovascular events over 10 years in women who gave birth in 2008–2010 (determined using a multivariate Cox model)**

Variable	Model 1: composite outcome	Model 2: chronic hypertension	Model 3: heart failure	Model 4: coronary heart disease	Model 5: cerebrovascular disease	Model 6: peripheral arterial disease	Model 7: carotid revascularization
	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)
Preeclampsia <sup>b</sup>	4.974 (4.790–5.165)	6.718 (6.451–6.995)	3.161 (2.649–3.771)	2.509 (2.120–2.970)	1.976 (1.755–2.224)	3.349 (2.610–4.297)	10.149 (4.208–24.479)
Gestational hypertension <sup>b</sup>	5.086 (4.901–5.277)	6.946 (6.679–7.225)	1.854 (1.480–2.323)	2.413 (2.041–2.852)	1.702 (1.498–1.935)	2.038 (1.506–2.757)	5.084 (1.550–16.682)

aHR, adjusted hazard ratio; CI, confidence interval.

<sup>a</sup> Adjusted for maternal age, multiple pregnancy, gestational diabetes mellitus, dyslipidemia, obesity, heavy smoking, alcohol intake, personal history, and family history; <sup>b</sup> Normotensive pregnancies were used as reference. *Simon. Time to onset of cardio-cerebrovascular outcomes after hypertensive disorders of pregnancy. Am J Obstet Gynecol 2023.*

failure at 1, 3, and 5 years after delivery, producing aHRs that were lower than seen with the current data.<sup>23</sup> The latter study had a higher-than-expected prevalence of HDP (15.7%) despite a younger population and the exclusion of multiple pregnancies or women with comorbidities that predispose them to heart failure. Moreover, the authors used BMI as a quantitative variable rather than a qualitative one and did not distinguish between a pregnancy complicated by PE and a pregnancy complicated by GH. The design of the current study with all women included at the same period (within 2 years) and followed during 10 years limits the biases related to the variation in population characteristics and comorbidities with time and to potential changes in the diagnostic criteria or clinical protocols. However, despite these differences, the most likely reason for lower aHRs in the latter study is that the authors only considered emergency department admissions for heart failure, whereas the current study included both elective and emergency hospital admissions. Furthermore, the 1-year cerebrovascular risk is consistent with that observed in 2 other studies,<sup>12,17</sup> and the stroke risk is higher than previously reported,<sup>5</sup> but the latter was evaluated at 6 months and not at 1 year.

### Clinical implications

Tight blood pressure (BP) control in the early postpartum period aided by home BP monitoring and self-management of antihypertensive medications is associated with improved BP up to 3 years after delivery even after stopping antihypertensive treatment at 6 months.<sup>50,51</sup> The finding of this study that the risk of hypertension and related cardiovascular complications is the highest in the first year after a birth complicated by HDP necessitates consideration of early postpartum screening and initiation of cardioprotective measures in the year after the delivery to at least 5 years postnatally. In previous studies, the authors excluded cardiovascular events occurring in the immediate postpartum period up to 90 days,<sup>2,9</sup> on the basis that these events are due to the pregnancy and unlikely to be



TABLE 4

**Average effects of hypertensive disorders of pregnancy and risk factors on the composite outcomes over 10 years in women who gave birth in 2008–2010 (determined using a multivariate Cox model)**

Variables	aHR (95% CI)
Preeclampsia <sup>a</sup>	4.974 (4.790–5.165)
Gestational hypertension <sup>a</sup>	5.086 (4.901–5.277)
Maternal age of <20 y (reference = 20–29)	0.412 (0.371–0.458)
Maternal age of 30–39 y (reference = 20–29)	1.714 (1.677–1.752)
Maternal age of ≥40 y (reference = 20–29)	2.985 (2.874–3.1)
Multiple pregnancy	0.846 (0.788–0.91)
Gestational diabetes mellitus	5.576 (5.398–5.759)
Dyslipidemia	1.548 (1.233–1.942)
Obesity (BMI ≥40 kg/m <sup>2</sup> )	2.619 (2.415–2.84)
Heavy smoking	2.868 (2.726–3.017)
Alcohol intake	2.177 (1.724–2.75)
Personal history	4.564 (4.002–5.205)
Family history	2.945 (2.369–3.66)

aHR, adjusted hazard ratio; BMI, body mass index; CI, confidence interval.

<sup>a</sup> Normotensive pregnancies were used as reference.

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related to long-term complications. However, the data show that the risks were the highest in the first year, indicating that the cardiovascular effect of PE is immediate, if not continuous from pregnancy. Furthermore, the magnitude of the averaged risk of the composite outcome (of which chronic hypertension represents the most frequent outcome) after either PE or GH pregnancy is approximately 5 times higher—similar to the risk conferred by gestational diabetes mellitus and a strong personal history of CVD (Table 4). This risk is higher than that of heavy smoking, even though smoking is one of the best-known cardiovascular risk factors. The importance of a pregnancy complicated by HDP as a risk factor for CVD is known; however, the magnitude of this risk being equivalent to gestational diabetes mellitus or greater than that of heavy smoking is not typically acknowledged by clinicians or population screening programs. Thus, our work has given additional weight to

current considerations<sup>52</sup> regarding the need for postpartum CVD screening with very specific guidelines. Some recently published work suggests that screening should be based on maternal factors (age and BMI), BP during pregnancy, and ultrasound data.<sup>53</sup>

### Research implications

This study highlights the importance of an early screening program and follow-up of women after a birth complicated by HDP. There should be a focus on improving our ability to effectively screen and distinguish at postnatal discharge women who are likely to develop new-onset chronic hypertension.<sup>53</sup> Postnatal BP monitoring after a birth complicated by HDP is infrequently performed and not constantly recommended in national protocols. The use of postpartum home BP monitoring to detect and assist with tailored antihypertensive treatment should be further investigated in this subset of women. Finally, the use of

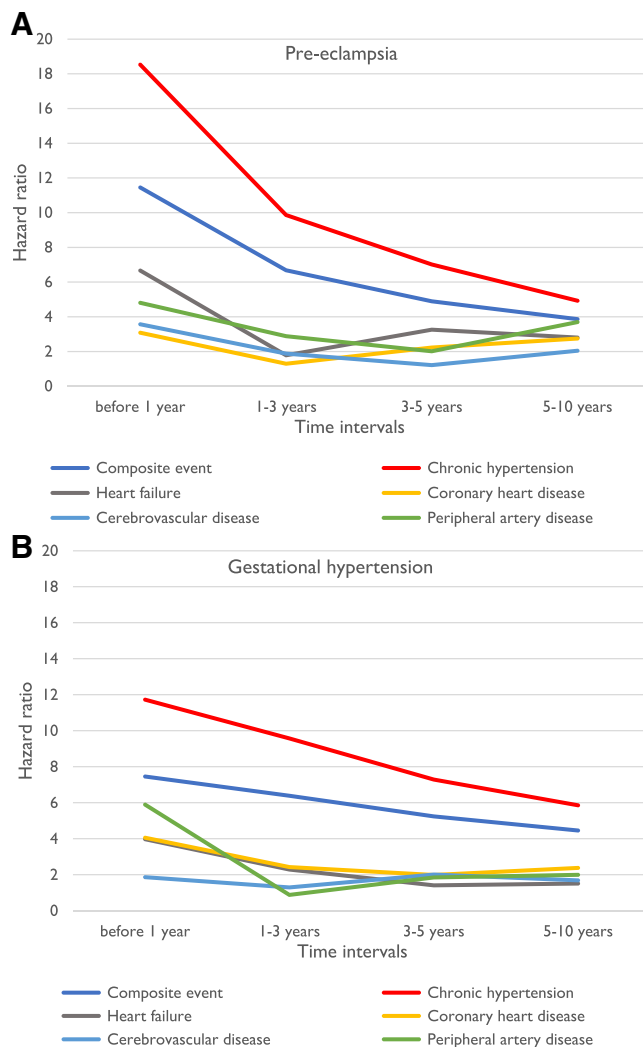
antihypertensive medication is well understood, but there is only limited research on the value of postpartum lifestyle modification and quality improvement initiatives, although with promising results in improving maternal cardiometabolic risk.<sup>54,55</sup> The 19-fold elevation in the risk of developing chronic hypertension in the first year after a birth complicated by PE is a notable finding. Bradford Hill's first criterion for disease causation states that the larger an association between exposure and disease, the more likely it is to be causal.<sup>56</sup> The magnitude of the cardiovascular and cerebrovascular risks after a birth complicated by HDP supports the emerging hypothesis for the cardiovascular etiology of HDP.<sup>2,57</sup>

### Strengths and limitations

The data were derived from a validated national dataset (PMSI) containing more than 2 million pregnancies with follow-up for at least 10 years after birth. The PMSI data are used for the evaluation of perinatal care and allocation of hospital budgets, encouraging data quality and justifying its use in several domains.<sup>36,58,59</sup> As coding practices may vary from 1 institution to another, there is still potential for coding errors; however, a previous validation study<sup>60</sup> confirmed the quality and the exhaustiveness of PMSI data. However, comorbidities and risk factors are not always fully documented in the PMSI database. For example, smoking is only noted in cases of heavy smoking, explaining the very low percentage recorded and providing the rationale for a stratified analysis of smoking in this study. This sensitivity analysis showed that the effect of HDP remained the same, and it is unlikely that smoking would be a major confounding factor in the relationship between HDP and CVD.<sup>23</sup>

In the main analysis, we excluded women with preexisting chronic or unexplained hypertension to avoid incorrectly attributing a postnatal cardiovascular event to HDP. As this exclusion may have removed women with GH from the data, we performed

**FIGURE 2**  
Time interval effects of HDP on different outcomes



**A**, Preeclampsia. **B**, Gestational hypertension. An extended Cox regression with a step function model was used to determine the effect of HDP on the different outcomes.

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another sensitivity analysis by including unspecified hypertension in our population and classifying these women as having HDP. This allowed us to obtain an estimate of the effect of HDP under the assumptions of maximum and minimum biases, and both estimates were very similar. In addition, when we presented the effects of all adjustment variables, it should be noted that only the effect of PE and GH is considered as the total effect on the risk of cardiovascular events. The others are considered direct effects. In addition, we performed sensitivity

analyses with different subsets of covariates to estimate the total effects of secondary covariates (gestational diabetes mellitus and personal history of CVD), as recommended by Westreich and Greenland.<sup>47</sup>

Finally, as we did not have access to out-of-hospital data, we could not necessarily identify all women who had chronic hypertension, especially women who may not have been hospitalized. Moreover, we were unable to assess the potential effect of aspirin prescription in women at risk of PE. Therefore, further studies are needed to assess the effect of

aspirin prophylaxis in early pregnancy on subsequent cardiovascular events, if possible using a clinical trial design.

The main strength of the analysis is the investigation of the evolution of the postnatal effect of HDP over time using an extended Cox regression with a step function model.<sup>23</sup> This method of modeling can provide an estimate in disjointed time intervals, allowing estimates of the effect in each interval separately taking into account the deviation from proportionality, which would not have been possible using the classical proportional hazard Cox model. In addition, the former method allows us to gain power as these estimates are obtained in a single model. This robust approach allowed outputs for all cardiovascular and cerebrovascular outcomes and allowed us to distinguish the independent risks of GH, early PE, preterm PE, and late PE for these outcomes.

## Conclusion

The incident risks of maternal cardiovascular and cerebrovascular outcomes were extremely high and were the highest in the first year after a birth complicated by HDP. As expected, although we found the highest incident risk in the first year, cumulative prevalence continues to increase over time, thus reaching higher levels after 5 years. We found a significant relationship with the severity of HDP (PE confers higher risks than GH, and risks are increased with earlier onset of PE), suggesting a possible dose-response relationship. The magnitude of these risks was similar to those for gestational diabetes mellitus and a strong personal history of CVD and greater than that of heavy smoking. These findings call for an urgent focus on research into effective postnatal screening and cardiovascular and cerebrovascular risk prevention for women whose pregnancies are complicated by HDP. ■

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TABLE 5

Time intervals<sup>a</sup> and adjusted effects<sup>b</sup> of hypertensive disorders of pregnancy on cardiovascular events over 10 years in women who gave birth in 2008–2010 (determined using a multivariate step function model)

Variables	Model 1: composite outcome		Model 2: chronic hypertension		Model 3: heart failure		Model 4: coronary heart disease		Model 5: cerebrovascular disease		Model 6: peripheral arterial disease			
	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)			
Preeclampsia (n=37,043) <sup>c</sup>	Before	11.452 (10.344–12.678)	18.531 (16.520–20.787)	6.662 (4.547–9.762)	3.083 (1.626–5.844)	3.567 (2.600–4.893)	4.802 (2.072–11.132)	1–3 y	6.679 (6.137–7.269)	9.863 (9.004–10.804)	1.784 (0.949–3.355)	1.298 (0.669–2.517)	1.874 (1.387–2.531)	2.883 (1.469–5.658)
	1 y	4.889 (4.487–5.327)	7.017 (6.410–7.682)	3.254 (2.169–4.884)	2.229 (1.438–3.456)	1.218 (0.871–1.703)	2.011 (0.942–4.290)	3–5 y	3.861 (3.655–4.078)	4.921 (4.640–5.218)	2.806 (2.201–3.577)	2.749 (2.255–3.352)	2.047 (1.753–2.391)	3.694 (2.728–5.001)
	5–10 y	7.455 (6.612–8.405)	11.727 (10.257–13.409)	3.971 (2.455–6.423)	4.058 (2.350–7.006)	1.866 (1.208–2.883)	5.894 (2.813–12.350)	Gestational hypertension	6.386 (5.867–6.952)	9.573 (6.069–10.476)	2.286 (1.310–3.990)	2.422 (1.506–3.893)	1.297 (0.903–1.864)	0.880 (0.280–2.761)
Before	5.240 (4.829–5.686)	7.286 (6.679–7.948)	1.411 (0.774–2.572)	1.987 (0.912–4.327)	2.006 (1.540–2.614)	1.845 (0.865–3.938)	1–3 y	4.452 (4.232–4.684)	5.854 (5.550–6.176)	1.511 (1.092–2.090)	2.377 (1.218–4.640)	1.688 (1.423–2.003)	1.996 (1.354–2.944)	
1 y							3–5 y							
5–10 y														

aHR, adjusted hazard ratio; CI, confidence interval.

<sup>a</sup> An extended Cox regression with a step function multivariate model was used; <sup>b</sup> Adjusted for maternal age, multiple pregnancy, gestational diabetes mellitus, dyslipidemia, obesity, heavy smoking, alcohol intake, personal history, and family history; <sup>c</sup> Normotensive pregnancies were used as reference.

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For this study, we used the French National Programme de Médicalisation des Systèmes d'Information (PMSI), a national medicoadministrative database that collects the discharge abstracts from all French hospitals, both public and private. The use of these data by our department was approved by the National Committee for Data Protection. We are not allowed to transmit these data.

PMSI data are available for researchers who meet the criteria for access to these French individual and anonymous data (this access is submitted to the approval of the National Committee for Data Protection) from the national agency for the management of hospitalization (Agence Technique de l'Information sur l'Hospitalisation).

The authors report no conflict of interest.

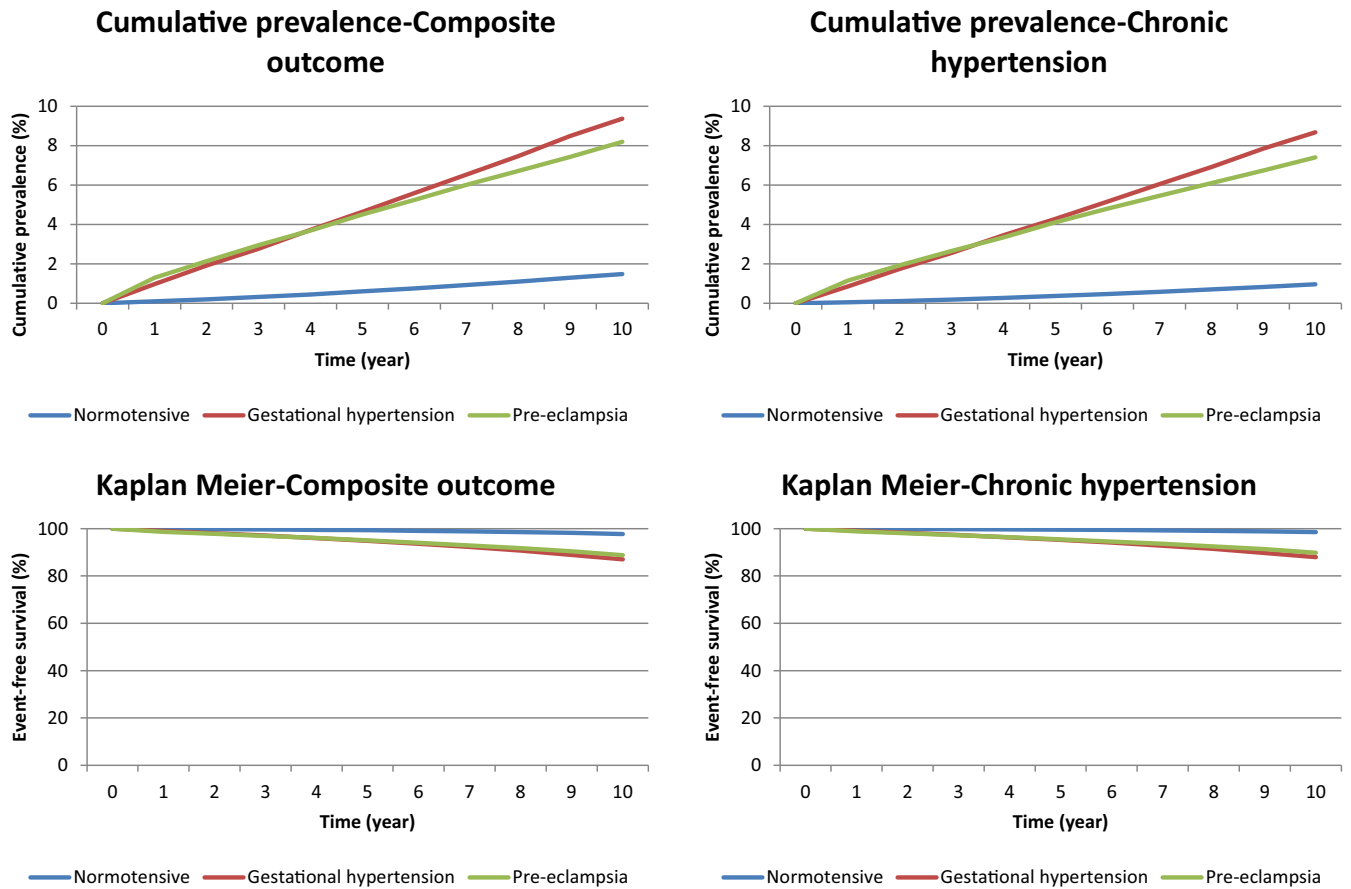
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## SUPPLEMENTARY FIGURE S2

## Cumulative prevalence and Kaplan Meier curves for the composite outcome and chronic hypertension



Simon. Time to onset of cardiocerebrovascular outcomes after hypertensive disorders of pregnancy. *Am J Obstet Gynecol* 2023.

## SUPPLEMENTARY TABLE S1

## Codes of cardiovascular events

Cardiovascular events	ICD-10 & CCMP codes
Coronary heart disease	
Angina pectoris	I20
Myocardial infarction	I21-I23
Coronary revascularization	DDAF001 DDAF006 DDAF004 DDAF003 DDAF010 DDAF008 DDAF007 DDAF009 DDMA025 DDMA015 DDMA023 DDMA017 DDMA032 DDMA011 DDMA029 DDMA018 DDMA038 DDMA021 DDMA026 DDMA020 DDMA031 DDMA006 DDMA033 DDMA008 DDMA022 DDMA005 DDMA034 DDMA009 DDMA030 DDMA003 DDMA035 DDMA013 DDMA036 DDMA012 DDMA028 DDMA007 DDMA024 DDMA019 DDMA027 DDMA016 DDMA037 DDMA004 DDPF002 DDF002 DDF001 DDAA002
Cerebrovascular disease	
Ischemic and haemorrhagic stroke	I60-I61 I62.9 I63-I64
Transient cerebral ischemic attacks and vascular syndromes of brain in cerebrovascular disease	G45 except G454 G46
Peripheral arterial disease	
Peripheral arterial disease	I702 I708-709 I743-I744

Simon. Time to onset of cardiocerebrovascular outcomes after hypertensive disorders of pregnancy. *Am J Obstet Gynecol* 2023. (continued)

## SUPPLEMENTARY TABLE S1

## Codes of cardiovascular events (continued)

Cardiovascular events	ICD-10 & CCMP codes
Arterial revascularization	EDAF002 EDAF003 DGPF001 DGPF002 EDPF008 EDPF009 EDPF006 DGFA010 DGFA004 DGFA012 DGFA009 DGFA003 DGFA007 DGFA008 EDFA006 EDFA003 EDFA007 DGCA019 DGCC859 DGCA009 DGCC822 DGCA026 DGCC857 DGCA022 DGCC862 DGCA010 DGCC825 DGCA004 DGCC846 DGCA030 DGCC810 DGCA020 DGCC872 DGCA029 DGCC835 EDCA003 EEAF003 EEAF004 EEAF005 EEAF002 EEAF001 EEAF006 EENF002 EENF001 EEPF002 EEPF001 EEJF001 EEFA004 EEFA002 EEFA001 EEFA003 EECA007 EECA006 EDCA005 EDCA004 EECA002 EECA001 EECA003 EECA008 EECA010 EECA005 EECA012 EEGA001 EEGA002 EEAA002 ENAF002 ENAF001 ENNF001 ENFF001 ENFA006 ENFA001 ENFA004 ENFA005 DGLF002 DGLF001 DGLF005IF if ICD-10 codes I702 I743 I745
Carotid revascularization	EBFA005 EBFA003 EBFA010 EBKA017 EBKA001 EBKA003 EBFA021 EBFA012 EBFA006 EBFA016 EBFA002 EBFA008 EBFA015 EBKA004 EBFA019 EBFA014 EBFA009 EBKA002 EBFA013
Heart failure	I50
Chronic hypertension	I10-I13 I15

Simon. Time to onset of cardiocerebrovascular outcomes after hypertensive disorders of pregnancy. *Am J Obstet Gynecol* 2023.

**SUPPLEMENTARY TABLE S3**

**Average effects of hypertensive disorders (early, preterm and late PE and GH) and risk factors on the composite outcome, over 10-years, in women who gave birth in 2010, multivariate Cox model**

	aHR [95% CI]
<b>Early pre-eclampsia*</b>	6.596 [5.822-7.473]
<b>Preterm pre-eclampsia*</b>	5.070 [4.473-5.745]
<b>Late pre-eclampsia*</b>	4.243 [3.858-4.666]
<b>Gestational hypertension*</b>	4.882 [4.565-5.221]
<b>Maternal age &lt;20 (ref = 20-29)</b>	0.428 [0.356-0.514]
<b>Maternal age 30-39 (ref = 20-29)</b>	1.685 [1.618-1.754]
<b>Maternal age ≥ 40 (ref = 20-29)</b>	2.807 [2.620-3.008]
<b>Multiple pregnancy</b>	0.769 [0.672-0.880]
<b>Gestational Diabetes</b>	5.571 [5.254-5.908]
<b>Dyslipidemia</b>	1.477 [0.993-2.198]
<b>Obesity (BMI ≥40 kg/m<sup>2</sup>)</b>	3.112 [2.763-3.506]
<b>Heavy smoking</b>	2.911 [2.661-3.183]
<b>Alcohol intake</b>	2.112 [1.416-3.148]
<b>Personal history</b>	5.413 [4.357-6.725]
<b>Family history</b>	3.623 [2.494-5.262]

aHR, adjusted hazard ratio; CI, confidence interval.

\* taking normotensive pregnancies as reference.

Simon. Time to onset of cardiocerebrovascular outcomes after hypertensive disorders of pregnancy. *Am J Obstet Gynecol* 2023.

## SUPPLEMENTARY TABLE S4

**Average adjusted\*\* effects of hypertensive disorders (early, preterm and late PE and GH) on cardiovascular events, over 10-years, in women who gave birth in 2010, multivariate Cox model**

	<u>Model 1 : Composite outcome</u>	<u>Model 2 : Chronic hypertension</u>	<u>Model 3 : Heart failure</u>	<u>Model 4 : Coronary heart disease</u>	<u>Model 5 : Cerebrovascular disease</u>	<u>Model 6 : Peripheral arterial disease</u>
	aHR [95% CI]	aHR [95% CI]	aHR [95% CI]	aHR [95% CI]	aHR [95% CI]	aHR [95% CI]
<b>Early pre-eclampsia*</b>	6.596 [5.822-7.473]	9.514 [8.358-10.829]	4.129 [2.326-7.329]	2.502 [1.338-4.677]	2.235 [1.453-3.436]	1.486 [0.369-5.982]
<b>Preterm pre-eclampsia*</b>	5.070 [4.473-5.745]	6.896 [6.042-7.869]	3.455 [2.017-5.919]	2.416 [1.389-4.201]	1.354 [0.827-2.219]	2.819 [1.154-6.884]
<b>Late pre-eclampsia*</b>	4.243 [3.858-4.666]	5.627 [5.078-6.235]	2.135 [1.299-3.510]	1.735 [1.073-2.806]	2.147 [1.643-2.806]	3.576 [2.005-6.376]
<b>Gestational hypertension*</b>	4.882 [4.565-5.221]	6.646 [6.185-7.141]	2.207 [1.541-3.160]	2.339 [1.733-3.158]	1.779 [1.422-2.226]	2.187 [1.293-3.698]

aHR, adjusted hazard ratio; CI, confidence interval.

\*\* adjusted on maternal age, multiple pregnancy, gestational diabetes, dyslipidemia, obesity, heavy smoking, alcohol intake, personal and family history; \* taking normotensive pregnancies as reference.

Simon. Time to onset of cardiocerebrovascular outcomes after hypertensive disorders of pregnancy. *Am J Obstet Gynecol* 2023.



## SUPPLEMENTARY TABLE S5

Time intervals<sup>§</sup> adjusted\*\* effects of hypertensive disorders (early, preterm and late PE and GH) on cardiovascular events, over 10 years, in women who gave birth in 2010, multivariate step function model

		Model 1 : Composite outcome	Model 2 : Chronic hypertension	Model 5 : Cerebrovascular disease
		aHR [95% CI]	aHR [95% CI]	aHR [95% CI]
<b>Early pre-eclampsia*</b> N = 2 353	<b>before 1 year</b>	18.589 [13.939-24.789]	31.253 [23.026-42.419]	1.312 [0.184-9.360]
	<b>1-3 years</b>	9.360 [7.164-12.228]	14.305 [10.836-18.886]	1.998 [0.641-6.224]
	<b>3-5 years</b>	6.394 [4.784-8.544]	9.201 [6.782-12.484]	2.957 [1.322-6.615]
	<b>5-10 years</b>	4.532 [3.728-5.510]	6.395 [5.234-7.812]	2.156 [1.190-3.906]
<b>Preterm pre-eclampsia*</b> N = 2 945	<b>before 1 year</b>	10.216 [7.358-14.185]	15.079 [10.485-21.686]	3.143 [1.005-9.831]
	<b>1-3 years</b>	7.852 [6.108-10.095]	11.986 [9.254-15.525]	1.058 [0.264-4.250]
	<b>3-5 years</b>	4.587 [3.410-6.170]	6.708 [1.950-23.072]	1.571 [0.587-4.206]
	<b>5-10 years</b>	3.813 [3.157-4.605]	4.843 [1.439-16.302]	1.089 [0.517-2.292]
<b>Late pre-eclampsia*</b> N = 6 878	<b>before 1 year</b>	6.272 [4.648-8.463]	9.286 [6.640-12.987]	2.363 [0.973-5.740]
	<b>1-3 years</b>	5.526 [4.475-6.823]	8.225 [6.581-10.279]	1.672 [0.792-3.530]
	<b>3-5 years</b>	4.730 [3.851-5.809]	6.720 [5.401-8.360]	1.072 [0.479-2.397]
	<b>5-10 years</b>	3.495 [3.048-4.008]	4.310 [3.711-5.006]	2.696 [1.944-3.739]
<b>Gestational hypertension*</b> N = 11 000	<b>before 1 year</b>	5.984 [4.763-7.518]	8.732 [6.747-11.301]	1.349 [0.555-3.279]
	<b>1-3 years</b>	6.058 [5.210-7.044]	9.021 [7.686-10.589]	1.632 [0.918-2.899]
	<b>3-5 years</b>	4.865 [4.185-5.655]	6.806 [5.793-7.995]	1.933 [1.222-3.058]
	<b>5-10 years</b>	4.442 [4.053-4.869]	5.828 [5.287-6.424]	1.827 [1.352-2.469]

aHR, adjusted hazard ratio; CI, confidence interval.

<sup>§</sup> extended Cox regression with Step Function multivariate model; \*\* adjusted on maternal age, multiple pregnancy, gestational diabetes, dyslipidemia, obesity, heavy smoking, alcohol intake, personal and family history; \* taking normotensive pregnancies as reference.

Simon. Time to onset of cardiocerebrovascular outcomes after hypertensive disorders of pregnancy. *Am J Obstet Gynecol* 2023.

**SUPPLEMENTARY TABLE S6**

**Sensitivity analysis 1 : time intervals<sup>§</sup> and average<sup>μ</sup> adjusted\*\* effects of hypertensive disorders on the composite outcome excluding chronic hypertension, over 10 years, in women who gave birth in 2008-2010**

aHR [95% CI]		
<b>Average <sup>μ</sup> effects</b>		
<b>Pre-eclampsia*</b>		2.296 [2.111-2.498]
<b>Gestational hypertension*</b>		1.892 [1.726-2.074]
<b>Time intervals<sup>§</sup> effects</b>		
<b>Pre-eclampsia*</b>	<b>before 1 year</b>	4.412 [3.541-5.498]
	<b>1-3 years</b>	1.869 [1.475-2.369]
	<b>3-5 years</b>	1.760 [1.416-2.189]
	<b>5-10 years</b>	2.300 [2.061-2.567]
<b>Gestational hypertension*</b>	<b>before 1 year</b>	2.899 [2.220-3.787]
	<b>1-3 years</b>	1.483 [1.140-1.930]
	<b>3-5 years</b>	1.819 [1.470-2.251]
	<b>5-10 years</b>	1.888 [1.674-2.128]

aHR, adjusted hazard ratio; CI, confidence interval.

<sup>§</sup> extended Cox regression with Step Function multivariate model; <sup>μ</sup> multivariate Cox model; \*\* adjusted on maternal age, multiple pregnancy, gestational diabetes, dyslipidemia, obesity, heavy smoking, alcohol intake, personal and family history; \* taking normotensive pregnancies as reference.

Simon. Time to onset of cardiocerebrovascular outcomes after hypertensive disorders of pregnancy. *Am J Obstet Gynecol* 2023.

**SUPPLEMENTARY TABLE S7**

**Sensitivity analysis 2: average effects of hypertensive disorders and risk factors on the composite outcome, over 10-years, in women who gave birth in 2008-2010, including unspecified hypertension as gestational hypertension, multivariate Cox model**

	aHR [95% CI]
<b>Pre-eclampsia*</b>	5.125 [4.942-5.316]
<b>Gestational hypertension*</b>	5.237 [5.070-5.409]
<b>Maternal age &lt;20 (ref = 20-29)</b>	0.414 [0.373-0.460]
<b>Maternal age 30-39 (ref = 20-29)</b>	1.718 [1.682-1.756]
<b>Maternal age ≥ 40 (ref = 20-29)</b>	2.952 [2.845-3.064]
<b>Multiple pregnancy</b>	0.840 [0.783-0.901]
<b>Gestational Diabetes</b>	5.505 [5.334-5.681]
<b>Dyslipidemia</b>	1.584 [1.268-1.980]
<b>Obesity (BMI ≥40 kg/m<sup>2</sup>)</b>	2.538 [2.347-2.744]
<b>Heavy smoking</b>	2.853 [2.714-2.999]
<b>Alcohol intake</b>	1.991 [1.581-2.506]
<b>Personal history</b>	4.373 [3.839-4.982]
<b>Family history</b>	2.916 [2.349-3.619]

aHR, adjusted hazard ratio; CI, confidence interval.

\* taking normotensive pregnancies as reference.

Simon. Time to onset of cardiocerebrovascular outcomes after hypertensive disorders of pregnancy. *Am J Obstet Gynecol* 2023.

**SUPPLEMENTARY TABLE S9**  
**Sensitivity analysis 3: stratification in women who gave birth in 2008-2010 and coded as heavy smokers, average effects of hypertensive disorders and risk factors on the composite outcome, over 10-years, multivariate Cox model**

	aHR [95% CI]
<b>Pre-eclampsia*</b>	4.320 [3.620-5.155]
<b>Gestational hypertension*</b>	4.085 [3.458-4.824]
<b>Maternal age &lt;20 (ref = 20-29)</b>	0.471 [0.326-0.679]
<b>Maternal age 30-39 (ref = 20-29)</b>	3.190 [2.871-3.544]
<b>Maternal age ≥ 40 (ref = 20-29)</b>	7.257 [6.127-8.595]
<b>Multiple pregnancy</b>	0.933 [0.666-1.307]
<b>Gestational Diabetes</b>	1.283 [1.117-1.473]
<b>Dyslipidemia</b>	1.238 [0.659-2.323]
<b>Obesity (BMI ≥40 kg/m<sup>2</sup>)</b>	1.609 [1.222-2.117]
<b>Alcohol intake</b>	1.175 [0.866-1.594]
<b>Personal history</b>	2.028 [1.394-2.949]
<b>Family history</b>	2.570 [1.332-4.957]

aHR, adjusted hazard ratio; CI, confidence interval.

\* Taking normotensive pregnancies as reference.

Simon. Time to onset of cardiocerebrovascular outcomes after hypertensive disorders of pregnancy. *Am J Obstet Gynecol* 2023.

**SUPPLEMENTARY TABLE S8**

**Sensitivity analysis 2: average adjusted\*\* effects of hypertensive disorders on cardiovascular events, over 10-years, in women who gave birth in 2008-2010, including unspecified hypertension as gestational hypertension, multivariate Cox model**

	<u>Model 1 : Composite outcome</u> aHR [95% CI]	<u>Model 2 : Chronic hypertension</u> aHR [95% CI]	<u>Model 3 : Heart failure</u> aHR [95% CI]	<u>Model 4 : Coronary heart disease</u> aHR [95% CI]	<u>Model 5 : Cerebrovascular disease</u> aHR [95% CI]	<u>Model 6 : Peripheral arterial disease</u> aHR [95% CI]
<b>Pre-eclampsia*</b>	5.125 [4.942-5.316]	6.936 [6.669-7.213]	3.276 [2.763-3.884]	2.585 [2.197-3.041]	2.011 [1.793-2.256]	3.459 [2.721-4.396]
<b>Gestational hypertension*</b>	5.237 [5.070-5.409]	7.208 [6.963-7.461]	2.035 [1.683-2.461]	2.367 [2.040-2.745]	1.659 [1.481-1.858]	2.124 [1.637-2.756]

aHR, adjusted hazard ratio; CI, confidence interval.

\*\* adjusted on maternal age, multiple pregnancy, gestational diabetes, dyslipidemia, obesity, heavy smoking, alcohol intake, personal and family history; \* taking normotensive pregnancies as reference.

Simon. Time to onset of cardiocerebrovascular outcomes after hypertensive disorders of pregnancy. *Am J Obstet Gynecol* 2023.

## SUPPLEMENTARY TABLE S10

**Sensitivity analysis 3: stratification in women who gave birth in 2008-2010 and coded as heavy smokers, average adjusted\*\* effects of hypertensive disorders on cardiovascular events, over 10-years, multivariate Cox model**

	Model 1 : Composite outcome aHR [95% CI]	Model 2 : Chronic hypertension aHR [95% CI]	Model 3 : Heart failure aHR [95% CI]	Model 4 : Coronary heart disease aHR [95% CI]	Model 5 : Cerebrovascular disease aHR [95% CI]	Model 6 : Peripheral arterial disease aHR [95% CI]
<b>Pre-eclampsia*</b>	4.320 [3.620-5.155]	5.899 [4.862-7.157]	1.136 [0.415-3.104]	3.416 [2.191-5.328]	3.129 [2.057-4.760]	3.605 [1.866-6.964]
<b>Gestational hypertension*</b>	4.085 [3.458-4.824]	5.517 [4.592-6.629]	2.193 [1.105-4.351]	2.234 [1.377-3.627]	2.061 [1.291-3.290]	1.354 [0.548-3.346]

aHR, adjusted hazard ratio; CI, confidence interval.

\*\* adjusted on maternal age, multiple pregnancy, gestational diabetes, dyslipidemia, obesity, heavy smoking, alcohol intake, personal and family history; \* taking normotensive pregnancies as reference.

Simon. *Time to onset of cardiocerebrovascular outcomes after hypertensive disorders of pregnancy. Am J Obstet Gynecol* 2023.

## SUPPLEMENTARY TABLE S11

**Sensitivity analysis 4: stratification on vaginal deliveries, average adjusted\*\* effects of hypertensive disorders on the composite outcome, over 10-years, in women who gave birth in 2008-2010**

	aHR [95% CI]
<b>Pre-eclampsia*</b>	4.875 [4.573-5.196]
<b>Gestational hypertension*</b>	5.411 [5.160-5.676]

\*\* adjusted on parity, maternal age, multiple pregnancy, gestational diabetes, dyslipidemia, obesity, heavy smoking, alcohol intake, personal and family history; \* taking normotensive pregnancies as reference.

Simon. *Time to onset of cardiocerebrovascular outcomes after hypertensive disorders of pregnancy. Am J Obstet Gynecol* 2023.

## SUPPLEMENTARY TABLE S12

**Sensitivity analysis 5: Exclusion of women with pre-existing diabetes or CVD before pregnancy, average adjusted\*\* effects of hypertensive disorders on the composite outcome, over 10-years, in women who gave birth in 2008-2010**

	aHR [95% CI]
<b>Pre-eclampsia*</b>	5.067 [4.875-5.266]
<b>Gestational hypertension*</b>	5.212 [5.020-5.411]

\*\* adjusted on parity, maternal age, multiple pregnancy, gestational diabetes, dyslipidemia, obesity, heavy smoking, alcohol intake, personal and family history; \* taking normotensive pregnancies as reference.

Simon. *Time to onset of cardiocerebrovascular outcomes after hypertensive disorders of pregnancy. Am J Obstet Gynecol* 2023.

## SUPPLEMENTARY TABLE S13

**Sensitivity analysis 6: reclassification of the exposure variable according the maximum bias assumption<sup>μ</sup>, average adjusted\*\* effects of hypertensive disorders on the composite outcome, over 10-years, in women who gave birth in 2008-2010**

	aHR [95% CI]
<b>Pre-eclampsia*</b>	5.026 [4.842-5.217]
<b>Gestational hypertension*</b>	5.150 [4.966-5.342]

<sup>μ</sup> if women had PE or GH during one of the pregnancies corresponding to the inclusion period, and not only for the first pregnancy, the exposure variable was reclassified as PE or GH accordingly; \*\* adjusted on parity, maternal age, multiple pregnancy, gestational diabetes, dyslipidemia, obesity, heavy smoking, alcohol intake, personal and family history; \* taking normotensive pregnancies as reference.

Simon. *Time to onset of cardiocerebrovascular outcomes after hypertensive disorders of pregnancy. Am J Obstet Gynecol* 2023.

## SUPPLEMENTARY TABLE S14

**Sensitivity analysis 7: total effects of hypertensive disorders, gestational diabetes and personal history of cardiovascular disease on the composite outcome, over 10-years, in women who gave birth in 2008-2010, multivariate Cox model**

	aHR [95% CI]
<b>Pre-eclampsia**<sup>a</sup></b>	4.974 [4.79-5.165]
<b>Gestational hypertension**<sup>a</sup></b>	5.086 [4.901-5.277]
<b>Gestational diabetes<sup>b</sup></b>	6.544 [6.338-6.757]
<b>Personal history<sup>c</sup></b>	6.111 [5.354-6.975]

aHR, adjusted hazard ratio; CI, confidence interval.

\* taking normotensive pregnancies as reference; <sup>a</sup> adjusted on gestational diabetes, personal history, maternal age, multiple pregnancy, dyslipidemia, obesity, heavy smoking, alcohol intake and family history; <sup>b</sup> adjusted on personal history, maternal age, multiple pregnancy, dyslipidemia, obesity, heavy smoking, alcohol intake and family history; <sup>c</sup> adjusted on maternal age, multiple pregnancy, dyslipidemia, obesity, heavy smoking, alcohol intake and family history.

Simon. Time to onset of cardiocerebrovascular outcomes after hypertensive disorders of pregnancy. *Am J Obstet Gynecol* 2023.