Heart Failure in Women with Hypertensive Disorders of Pregnancy:

Insights from the Cardiovascular Disease in Norway Project

Short Title: Heart Failure After Hypertension in Pregnancy

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Abstract

Hypertensive disorders of pregnancy (HDP) have been associated with heart failure (HF). It is unknown whether concurrent pregnancy complications (small-for-gestational age [SGA] or preterm delivery) or recurrent HDP modify HDP-associated HF risk. In this cohort study, we included Norwegian women with a first birth between 1980-2004. Follow-up occurred through 2009. Cox models examined gestational hypertension (GH) and preeclampsia in the first pregnancy as predictors of a composite of HF-related hospitalization or HF-related death, with assessment of effect modification by concurrent SGA and/or preterm delivery. Additional models were stratified by final parity (1 vs. ≥2 births) and tested associations with recurrent HDP. Among 508,422 women, 565 experienced incident HF over a median 11.8 years of follow-up. After multivariable adjustment, GH in the first birth was not significantly associated with HF (hazard ratio [HR] 1.41, 95% CI 0.84-2.35, P=0.19), whereas preeclampsia was associated with an HR of 2.00 (95% CI 1.50-2.68, P<0.001). Among women with HDP, risks were not modified by concurrent SGA and/or preterm delivery ($P_{interaction}$ = 0.42). Largest hazards of HF were observed in women whose only lifetime birth was complicated by preeclampsia and women with recurrent preeclampsia. HF risks were similar after excluding women with coronary artery disease. In summary, women with preeclampsia, especially those with one lifetime birth and those with recurrent preeclampsia, experienced increased HF risk compared to women without HDP. Further research is needed to clarify causal mechanisms.

Introduction

Hypertensive disorders of pregnancy (HDP, i.e., gestational hypertension [GH]; preeclampsia; eclampsia; and hemolysis, elevated liver enzymes, and low platelet [HELLP] syndrome) affect 5-10% of pregnancies worldwide.[1,2] HDP are associated with a roughly two-fold increase in future maternal cardiovascular disease risk.[3-6] Cardiovascular risks associated with HDP are best described for atherosclerotic cardiovascular disease (ASCVD, e.g., coronary artery disease [CAD] and ischemic stroke) but extend beyond ASCVD to include heart failure (HF) and cardiomyopathy.[5,7-9] Although HDP are associated with peripartum cardiomyopathy,[10] HDP may also be associated with long-term HF risk separate from peripartum cardiomyopathy.[9]

Other pregnancy complications, such as small-for-gestational age (SGA) and preterm delivery, are independently associated with increased future maternal ASCVD disease risk[11-13] and modify ASCVD risk when they accompany HDP.[13] In addition, ASCVD risks associated with recurrent HDP are greater than those associated with single-episode HDP.[13,14] However, whether concurrent pregnancy complications (SGA and preterm delivery) or recurrent HDP also modify HF risk among women with HDP remains unclear. Understanding the contribution of concurrent pregnancy complications to the HDP-associated HF risk distribution may help with clinical risk stratification and may yield insights regarding mechanisms of HDP-associated HF.

To better characterize HF risk in women with GH and preeclampsia, we studied HF incidence in a large nationwide cohort of Norwegian women. We hypothesized (1) that HDP would be associated with long-term HF risk, (2) that concurrent SGA and/or preterm delivery would further increase risk compared with HDP alone, and (3) that recurrent HDP would be associated with greater HF risk than single-episode HDP.

Methods

Study cohort

Researchers may apply for permission to analyze data from the Cardiovascular Disease in Norway Project (CVDNOR) at www.cvdnor.no. Women with a first birth between 1980-2004 recorded in the Medical Birth Registry of Norway (MBRN) who were 16-49 years old at the first birth and had ≤5 pregnancies prior to 2010 were considered for inclusion. The MBRN is a nationwide Norwegian registry with mandatory reporting, capturing all pregnancies since 1967 lasting 16 weeks' gestation or more.[15] To ascertain incident cardiovascular diagnoses, MBRN records were linked to the CVDNOR, a database containing inpatient diagnosis codes from all hospitalizations in Norway from 1994 onward, and to the Norwegian Cause of Death Registry. The Norwegian Regional Committee for Medical and Health Research Ethics and the Partners HealthCare institutional review board approved these analyses.

Women with pre-gestational chronic hypertension registered in the MBRN or with established cardiovascular disease (defined as *International Classification of Diseases* [ICD]-10 codes I00-I99, ICD-9 450-454 and 456-459, and ICD-8 390-448) identified in CVDNOR prior to the first birth were excluded, as were women with extreme birthweight outliers (*Z*-score >4 or <-4) in the first birth, multiple gestation in the first birth, missing data on gestational duration or birth weight in the first birth, and births occurring prior to 20 weeks' gestation. To capture each woman's full reproductive career, women with a first birth after 2004 were excluded, and follow-up began at the last birth; we therefore also excluded women who developed HF prior to the last birth. Women who emigrated during follow-up were excluded.

Exposures

GH and preeclampsia in the first pregnancy constituted the primary exposures, with assessment of effect modification by concurrent SGA and/or preterm delivery. (Most HDP cases occur in the first pregnancy.[16]) In primary analyses, women without HDP in the first pregnancy served as the reference group. In analyses of recurrent HDP, women with ≥2 lifetime births and normotension in all pregnancies constituted the reference group.

The MBRN defines GH as newly elevated blood pressure after 20 weeks' gestation with systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg, without proteinuria. The MBRN defines preeclampsia as newly elevated blood pressure, using the same blood pressure criteria, accompanied by proteinuria >0.3 g/24 h or >1+ on urine dipstick, with high positive predictive value demonstrated in validation studies.[17,18] Preterm delivery was defined as delivery occurring before 37 weeks' gestation. SGA was defined as fetal weight below the 10th percentile of the Norwegian birth weight curve.[19]

CAD was incorporated as an exclusion in sensitivity analyses. CAD was defined as hospitalization or death from CAD as indicated by ICD-9 codes 410-414 and ICD-10 codes I20-I25, as in previous CVDNOR analyses.[13]

Outcome

The study outcome was a composite of HF-related hospitalization or death with HF as an underlying, contributing, or associated cause. HF cases were identified in CVDNOR[20,21] and in the Norwegian Cause of Death Registry using ICD-9 codes 425.4 and 428.0-428.9 and using ICD-10 codes I42.0, I42.8, I42.9, I50.1-I50.4, and I50.9, encompassing both HF with reduced ejection fraction and HF with preserved ejection fraction.

Statistical analysis

The population attributable risk percent (i.e., the percent of HF cases in the cohort attributable to HDP) was calculated as the difference in absolute HF incidence in the overall study cohort vs. women without HDP divided by overall HF incidence. The attributable proportion of HF risk in women with HDP was calculated as the difference in absolute HF risk in women with vs. without HDP divided by absolute risk in women with HDP.

Cox proportional hazard models tested the association of HDP with incident HF. Follow-up began at the last birth in all models. Censoring occurred at the first HF hospitalization, death, or the end of the study period (December 31, 2009), whichever occurred first. Primary models were adjusted for maternal birth year (to capture period effects), maternal age at first birth, maternal age at last birth, chronic diabetes status at the time of the last birth, and final parity. To calculate associations with overall HDP and with HDP subtypes, separate models were run for all HDP vs. no HDP (reference) and for gestational hypertension vs. preeclampsia vs. no HDP (reference). To test effect modification by concurrent SGA and/or preterm delivery, models incorporated an interaction term between SGA and/or preterm delivery and HDP status. In addition, because prior data suggested HDP-associated cardiovascular mortality risk is highest among women with only one life-time birth ("one-child mothers"),[22] we also stratified models by a final parity of 1 vs. ≥2 births; in stratified models, women with multiple normotensive pregnancies served as the reference group.

To assess HF risk with respect to a woman's entire reproductive career, we grouped women into 10 categories according to HDP status in the first birth (no HDP, GH, or preeclampsia) and HDP status in the second and all later births (all normotensive, HDP in at least one birth, or no later births), adapting the approach used by Tanz et al.[11] Additional Cox models tested associations of recurrent HDP and recurrent preeclampsia with HF.

CAD is known to be associated with both HDP and HF. To test whether HDP is associated with HF independent of CAD risk, sensitivity analyses excluded women who developed CAD during the study period.

The proportional hazards assumption was tested using Schoenfeld residuals. Two-sided P-values <0.05 were considered statistically significant. Analyses were performed using Stata version 16.0 (StataCorp, LLC, College Station, TX).

Results

Study cohort

After exclusions, the final study cohort included 508,422 women (**Figure 1**). There were no missing data in the final cohort. Participant counts by the number of lifetime episodes of GH and preeclampsia are summarized in **Table S1**.

A total of 46,084 women (9.1%) experienced HDP in any pregnancy, of whom 8,827 women (1.7% of the overall cohort) experienced GH in the first birth and 24,326 (4.8% of the overall cohort) experienced preeclampsia in the first birth (**Table 1**). Women with GH and especially those with preeclampsia were more likely than women without HDP to experience SGA and/or preterm delivery in the first birth (**Table 1**).

Hypertension in the first pregnancy and incident heart failure

We first assessed whether HDP in the first pregnancy associated with incident HF in our cohort. The primary endpoint of HF-related hospitalization or HF-related death occurred in 565 women (**Table 1**) over a median follow-up of 11.8 (interquartile range 6.4-17.8) years. The primary endpoint occurred in 499 women without HDP in the first pregnancy (0.10%, incidence rate 8.48/10,000 woman-years of follow-up [95% CI 7.77-9.24/10,000 woman-years]), 15

women with GH in the first pregnancy (0.17%, incidence rate 13.05/10,000 woman-years of follow-up [95% CI 7.96-20.44/10,000 woman-years], incidence rate difference +4.57/10,000 woman-years vs. women without HDP, P=0.06), and 51 women with preeclampsia in the first pregnancy (0.21%, incidence rate 17.90/10,000 woman-years [95% CI 13.63-23.13/10,000 woman-years], incidence rate difference +9.42/10,000 woman-years vs. women without HDP, P<0.001). Of incident HF diagnoses, 540 (95.6%) occurred >6 months after the last birth. Of 565 incident HF cases, 100 (17.7%) occurred in women with HDP, and the population risk attributable to HDP was 9.5%. Among women with HDP, the proportion of incident HF risk attributable to HDP was 53.7%.

In time-to-event models comparing women with vs. without any HDP in the first pregnancy and adjusted only for maternal age at the last birth, HDP in the first pregnancy was associated with 1.92-fold risk of incident HF (95% CI 1.49-2.48, P<0.001) (**Table 2**). In fully adjusted models, HDP remained significantly associated with HF (HR 1.83, 95% CI 1.41-2.36, P<0.001). GH was associated with an HR of 1.41 (95% CI 0.84-2.35, P=0.19) and preeclampsia with an HR of 2.00 (95% CI 1.50-2.68, P<0.001) (**Figure 2**). In multivariable models additionally incorporating SGA and preterm delivery as predictors in addition to HDP status, SGA delivery was independently associated with incident HF (HR 1.35, 95% CI 1.09-1.67, P=0.006) whereas preterm delivery was not (HR 1.26, 95% CI 0.93-1.70, P=0.13).

Having demonstrated an association between HDP and incident HF, we next tested whether concurrent pregnancy complications modified HF risk. HF risk after HDP in the first birth was not significantly modified by concurrent SGA and/or preterm delivery ($P_{interaction}$ = 0.42). There was no significant interaction of GH ($P_{interaction}$ = 0.81) or preeclampsia ($P_{interaction}$ = 0.80) with SGA and/or preterm delivery for incident HF in fully adjusted models (**Table 2**).

Coronary artery disease and incident heart failure risk

To test whether CAD explained the observed associations between HDP and HF, we conducted a sensitivity analyses that excluded women with CAD. Among 565 women with incident HF during the study period, 155 (27.4%) also developed CAD. After excluding 2,428 women from the overall cohort with incident CAD, observed hazards for incident HF were similar to the primary analysis (for GH, HR 1.32, 95% CI 0.70-2.48, P=0.39; for preeclampsia, HR 1.89, 95% CI 1.33-2.70, P<0.001).

Differential heart failure risk in women with 1 vs. multiple children

We next compared HF risks associated with HDP in women with 1 vs. ≥2 children. Compared to women with ≥2 births and normotension in all pregnancies, women with 1 lifetime birth had increased risk of HF irrespective of HDP status but especially if they experienced HDP. Among women with HDP, risk of HF was greater among women with 1 lifetime birth vs. ≥2 lifetime births (**Table S2**). Women with HDP in the first birth who subsequently experienced only normotensive pregnancies had attenuated HF risk compared to other subgroups of women with HDP (**Table 3**). Notably, elevated HF risks were observed among women with HDP in a second and/or later birth even when the first birth was normotensive (for GH in a second and/or later birth, HR 3.15, 95% CI 1.77-5.61, P<0.001; for preeclampsia in a second and/or later birth, HR 2.92, 95% CI 1.89-4.50, P<0.001).

Heart failure risk in women with recurrent hypertension in pregnancy

Finally, we compared HF risks among women with recurrent HDP, women with one lifetime birth, and multiparous women with normotension in all pregnancies. Women with preeclampsia in the first birth and HDP in a subsequent birth had similarly elevated HF risk compared to women with 1 lifetime birth complicated by preeclampsia (**Table 3**). HF risk

associated with recurrent HDP was driven predominantly by recurrent preeclampsia (**Figure 3, Table S3**), with a progressive increase in HF incidence rate was observed with increasing number of preeclampsia episodes (P_{trend} <0.001). Compared to women without preeclampsia (irrespective of GH status), single-episode preeclampsia was associated with an HR of 1.93 (95% CI 1.47-2.55, P<0.001), and recurrent preeclampsia was associated with an HR of 4.36 (95% CI 2.71-7.02, P<0.001) for HF (**Table S4**). After excluding 2,428 women with incident CAD during the study period, these associations with HF were only mildly attenuated (for single-episode preeclampsia, HR 1.55, 95% CI 1.08-2.22, P=0.02; for recurrent preeclampsia, HR 3.82, 95% CI 2.09-6.99, P<0.001).

Discussion

In a large, nationwide study of Norwegian women followed for a median 12 years after the last birth, we observed a two-fold risk of incident HF in women with a history of preeclampsia. Contrary to our hypothesis, concurrent SGA and/or preterm delivery did not appear to modify HF risks among women with HDP. However, women with preeclampsia in their only lifetime birth, as well as women with more than 1 birth who experienced recurrent preeclampsia, demonstrated further increases in HF risk. Although HDP is associated with incident CAD and CAD is in turn associated with HF, HF risks associated with HDP in our cohort appeared largely independent of CAD. In this relatively young cohort of women, absolute risks of HF were expectedly low, but a disproportionate number of incident HF cases (17.7%) occurred in the 9.1% of women with prior HDP.

The results of the present study align with prior evidence that preeclampsia-associated risk of cardiovascular mortality is highest among women who bear only 1 child[22] and extend this

finding to HF. A similar pattern of risk concentration among one-child mothers has also been

shown with respect to ASCVD risk after preterm delivery.[11] Although greater parity, especially

extreme parity, has been associated with elevated cardiovascular disease risk,[23] studies have

suggested a J-shaped relationship between parity and cardiovascular risk.[24-26] The causes of

HDP-associated risk concentration among women whose only birth is hypertensive are currently

unknown but may reflect avoidance of additional pregnancies and/or impaired fertility related to

accelerated development of comorbidities in women with more severe HDP, as well as

unmeasured socioeconomic factors; further research to clarify mechanisms is needed.

Among women with ≥2 lifetime births, we observed greater HF risk among women with

HDP in a second and/or later birth compared to women who experienced HDP only in a first

birth and normotension in subsequent pregnancies. HDP occurring in a second or subsequent

birth—a relatively rare occurrence, observed in only 4.7% of women in our cohort with ≥2

lifetime births—may serve as an especially important cardiovascular risk signal and warrants

assessment across other cardiovascular conditions and in other cohorts.

Beyond strengthening evidence of an association between HDP and HF, this study's

findings may have other implications for understanding long-term cardiovascular risk after HDP.

First, among women with preeclampsia, we did not observe evidence of effect modification for

HF risk by concurrent SGA and/or preterm delivery, despite the fact that SGA was an

independent predictor of HF. Similarly, a prior analysis observed similar hazards for HF in

women with term and preterm preeclampsia.[9] By contrast, further elevation in ASCVD risk

among women with HDP and SGA and/or preterm delivery has now been well described.[4,6,13,27]

This discrepancy suggests that the mechanisms underlying ASCVD and HF after HDP may be

different, at least among women in early midlife. Additionally, our results replicate the important

finding from Behrens et al.[9] that a significant portion of HF following HDP is non-ischemic, even though HDP is also associated with development of CAD. In a previous study of women followed prospectively from midlife (mean age 57 years), those with a history of HDP had persistently elevated risk of incident HF, and HDP-associated HF risk appeared additive to CAD-associated HF risk.[7] It is likely that the relative contribution of ischemic heart disease to HF risk increases in women with HDP with increasing age as ASCVD risk increases with age in the population overall. In our younger cohort, however, only one-quarter of women with incident HF also had CAD, and exclusion of women with CAD did not meaningfully change the observed risks of HF. Further, most HF after HDP (>95%) occurred >6 months after the first birth, reinforcing that the vast majority of HF in this population is not peripartum cardiomyopathy.[10]

Second, our results support and extend the limited prior literature on cardiovascular disease risk after recurrent HDP[27,28] by demonstrating greater HF risk following recurrent preeclampsia compared with single-episode preeclampsia. Prior work suggested further increase in HF risk after recurrent vs. single-episode preeclampsia,[28] but this analysis only tested risk differences among women with multiple births and did not test the influence of comorbid CAD. In the present analysis, we observed these associations even among women without CAD, despite the dose-dependent relationship shown previously between recurrent preeclampsia and CAD.[6,13,14] Taken together with prior literature, our findings identify women with recurrent preeclampsia and women with a single lifetime birth complicated by preeclampsia as highest-risk for both ASCVD and non-ASCVD cardiovascular disease within the spectrum of HDP-associated risk. Further investigation is needed to disentangle whether HF risk associated with recurrent preeclampsia reflects stronger shared upstream predisposition to both conditions such

as a shared genetic risk,[29] enduring and additive cardiovascular damage imparted by each preeclampsia episode, or both.

GH in the first pregnancy was not significantly associated with incident HF in this analysis, in contrast to findings reported by Behrens et al., who observed similar HF risks associated with GH and moderate preeclampsia.[9] Although they did not meet the threshold for statistical significance in primary models, the hazards associated with GH plus SGA and/or preterm delivery, as well as the hazards associated with GH among one-child mothers, were similar to those associated with preeclampsia in the overall cohort. Given low absolute HF case counts (N=15) among women with GH in the first birth, low power may have hindered our ability to detect significant associations between GH and HF.

Our findings should be interpreted in the context of study design. First, although the CVDNOR Project captures nationwide Norwegian data, diagnoses are ascertained based on inpatient codes and the national death registry; thus, HF cases that were evaluated and managed exclusively in the outpatient setting (i.e., milder HF presentations) may not be captured. Prior work suggests that administrative codes yield high specificity but limited sensitivity for HF.[30] Second, due to low absolute risks and low overall HF case counts in our relatively young cohort, we were unable to test effect modification by preterm delivery and SGA delivery separately due to insufficient power and therefore assessed SGA and/or preterm delivery as a lumped effect-modifier. Third, we were unable to ascertain development of cardiometabolic risk factors in the interval between the last birth and development of HF. Fourth, given lack of racial/ethnic diversity, whether findings in this white northern European cohort extend to non-white populations requires further study. However, the study also has several strengths, most notably a

very large, nationwide cohort with detailed pregnancy phenotyping and complete, long-term

follow-up.

Perspectives

Women with preeclampsia experienced two-fold risk of HF, without evidence of effect modification by concurrent SGA and/or preterm delivery. Risks increased further in women with preeclampsia and only one lifetime birth and in women with recurrent preeclampsia. These risks were largely independent of HDP's association with CAD. Further research is needed to elucidate underlying mechanisms and define optimal cardiovascular disease prevention and treatment in affected women.

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Novelty and Significance

What Is New?

- Compared to women without hypertensive disorders of pregnancy (HDP), women with preeclampsia had two-fold risk of future heart failure. Risk of heart failure was not modified by concurrent small-for-gestational age and/or preterm birth.

- Women with a single lifetime birth complicated by preeclampsia and women with recurrent preeclampsia demonstrated further elevation in heart failure risk.

- Heart failure risks were largely independent of HDP's association with coronary artery disease.

What Is Relevant?

- The hypertensive disorders of pregnancy (e.g., gestational hypertension, preeclampsia) are strongly associated with development of chronic hypertension and diverse cardiovascular disease.

Summary

- Women with preeclampsia experienced two-fold risk of HF, without evidence of effect modification by concurrent SGA and/or preterm delivery. Risks increased further in women whose only lifetime birth was complicated by preeclampsia and in women with recurrent preeclampsia.

Figure Legends.

Figure 1. Creation of the study cohort.

Figure 2. Kaplan-Meier curves for heart failure-free survival by hypertensive disorder of pregnancy status in the first birth.

HDP = hypertensive disorder of pregnancy; GH = gestational hypertension; PE = preeclampsia

Mean (SD) maternal age at the start of follow-up is 30.3 (4.8) years for women with no HDP, 30.8 (4.7) years for women with gestational hypertension, and 30.3 (4.8) years for preeclampsia in the first pregnancy

Figure 3. Kaplan-Meier curves for heart failure-free survival (A) by hypertensive disorder of pregnancy status among one-child mothers and (B) by recurrent hypertensive disorder of pregnancy status among women with ≥2 lifetime births.

HDP = hypertensive disorder of pregnancy; GH = gestational hypertension; PE = preeclampsia

Mean (SD) maternal age at the start of follow-up is 27.6 (5.8) years for one-child mothers with no HDP, 29.0 (5.9) years for one-child mothers with GH, 28.1 (5.9) years for one-child mothers with PE, 30.8 (4.4) years in women with ≥2 births and no HDP, 31.5 (4.4) years in women with GH in ≥1 birth and no PE, 31.1 (4.4) years in women with ≥2 births and 1 PE episode, and 31.5 (4.4) years in women with PE in ≥2 births

Table 1. Baseline characteristics and outcomes of study subjects by hypertensive disorder of pregnancy status in the first birth.

Characteristic	No hypertensive disorder of pregnancy (n = 475,269)	Gestational hypertension (n = 8,827)	Preeclampsia (n = 24,326)
Maternal age at first birth, y	25.5 (4.7)	26.3 (4.8)	25.7 (4.8)
Married/co-habitant during first pregnancy	393,084 (82.7%)	7,646 (86.6%)	20,645 (84.9%)
Chronic diabetes diagnosis prior to first birth	1,495 (0.3%)	62 (0.7%)	369 (1.5%)
Preterm delivery in first birth	25,996 (5.5%)	609 (6.9%)	4,910 (20.2%)
Small-for-gestational age delivery in first birth	57,601 (12.1%)	1,471 (16.7%)	5,846 (24.0%)
Final parity during the study period, median (IQR)	2 (2,3)	2 (2,3)	2 (2,3)
Among participants with ≥2 pregnancies,	12,931 / 395,122 (3.3%)	1,760 / 7,155 (24.6%)	5,252 / 19,545 (26.9%)

HDP in second or subsequent pregnancy, n/N (%)			
Maternal age at last birth, y	30.3 (4.8)	30.7 (4.7)	30.3 (4.8)
Time from last birth to censoring, y	12.4 (7.2)	13.0 (7.6)	11.7 (7.1)
Chronic diabetes diagnosed prior to last birth	2,269 (0.5%)	101 (1.1%)	463 (1.9%)
Chronic hypertension diagnosed prior to last birth	1,108 (0.2%)	266 (3.0%)	439 (1.8%)
Incident coronary artery disease during follow-up	2,128 (0.5%)	78 (0.9%)	221 (0.9%)
Heart failure-related hospitalization or death during follow-up	499 (0.1%)	15 (0.2%)	51 (0.2%)
Among women with heart failure, incident coronary artery	133 / 499 (26.7%)	5 / 15 (33.3%)	17 / 51 (33.3%)

disease during follow-up			

Table 2. Hazard ratios for heart failure* by pregnancy complications in the first birth.

Complications in the first birth	Number of women	Number of events / women-years at risk	Age-adjusted models[†]	Fully adjusted models[‡]
			Hazard ratio (95% confidence interval)	Hazard ratio (95% confidence interval)
By hypertensive disorder of pregnancy status only				
No HDP	475,269	499 / 5,883,782	*Reference*	*Reference*
HDP[§]	33,153	66 / 399,858	1.92 (1.49-2.48)**	1.83 (1.41-2.36)**
Gestational hypertension	8,827	15 / 114,919	1.38 (0.82-2.30)	1.41 (0.84-2.35)
Preeclampsia	24,326	51 / 284,939	2.17 (1.63-2.90)**	2.00 (1.50-2.68)**
By hypertensive disorder of pregnancy, small-for-gestational age delivery, and preterm delivery status				
No HDP	475,269	499 / 5,883,782	*Reference*	*Reference*
HDP alone[§]	22,585	42 / 273,255	1.78 (1.30-2.44)**	1.72 (1.26-2.36)[#]

			2.22	2.04
HDP with preterm and/or SGA delivery[§]	10,568	24 / 126,603	2.22 (1.48-3.35)**	2.04 (1.35-3.08)#
Gestational hypertension alone	6,948	10 / 89,863	1.19 (0.63-2.22)	1.21 (0.65-2.27)
Gestational hypertension with SGA and/or preterm birth	1,879	5 / 25,056	2.02 (0.84-4.88)	2.06 (0.85-4.98)
Preeclampsia alone	15,637	32 / 183,393	2.11 (1.48-3.02)**	1.99 (1.39-2.84)**
Preeclampsia with SGA and/or preterm birth	8,689	19 / 101,547	2.28 (1.44-3.61)**	2.04 (1.28-3.23)#

*Heart failure endpoint is a composite of heart-failure related hospitalization and heart failure-related death

[†]Age-adjusted models are adjusted only for maternal age at the last birth

[‡]Fully adjusted models are adjusted for maternal birth year, maternal age at first birth, maternal age at last birth, chronic diabetes diagnosis prior to last birth, and final party

[§]HDP includes both gestational hypertension and preeclampsia

[‖]P<0.05, [#]P<0.01, **P<0.001

Table 3. Hazard ratios (95% confidence intervals) for heart failure* by hypertensive disorder of pregnancy status in the first and subsequent births.

HDP status in first birth	HDP status in second and/or subsequent births	Number of women	Events / women-years at risk	Age-adjusted models[†]	Fully adjusted models[‡]
				Hazard ratio (95% CI)	Hazard ratio (95% CI)
No HDP	No HDP	382,191	333 / 4,474,400	*Reference*	*Reference*
No HDP	No later births	80,147	132 / 1,273,070	1.12 (0.91-1.38)	1.64 (1.26-2.12)[**]
No HDP	Gestational hypertension but no preeclampsia in later births	4,405	12 / 45,790	3.39 (1.91-6.03)[**]	3.15 (1.77-5.61)[**]
No HDP	Preeclampsia in later births	8,526	22 / 90,522	3.33 (2.16-5.14)[**]	2.92 (1.89-4.50)[**]
Gestational	No HDP	5,395	7 / 66,242	1.32	1.34

hypertension				(0.62-2.78)	(0.64-2.84)
Gestational hypertension	No later births	1,672	5 / 27,200	1.68 (0.69-4.08)	2.58 (1.05-6.34)[‖]
Gestational hypertension	HDP in second and/or later births	1,760	3 / 21,477	1.70 (0.55-5.31)	1.66 (0.53-5.18)
Preeclampsia	No HDP	14,293	17 / 156,015	1.55 (0.95-2.53)	1.46 (0.90-2.39)
Preeclampsia	No later births	4,781	18 / 71,854	2.75 (1.70-4.43)^{**}	3.63 (2.19-6.01)^{**}
Preeclampsia	HDP in second and/or later births	5,252	16 / 57,070	3.83 (2.32-6.32)^{**}	3.47 (2.10-5.75)^{**}

*Heart failure endpoint is a composite of heart-failure related hospitalization and heart failure-related death

†Age-adjusted models are adjusted only for maternal age at the last birth

‡Fully adjusted models are adjusted for maternal birth year, maternal age at first birth, maternal age at last birth, and chronic diabetes diagnosis prior to last birth

‖P<0.05, #P<0.01, **P<0.001

708,614 women aged 16-49 years at first birth occurring between 1980-2009 with final parity ≤5

Excluded (n = 200,192):
- First birth after 2004 (n = 114,391)
- Missing gestational length in first pregnancy (n = 38,580)
- Emigrated during follow-up (n = 29,657)
- Multiple gestation first pregnancy (e.g., twins) (n = 9,507)
- Cardiovascular disease prior to the first pregnancy (n = 4,196)
- Pre-pregnancy chronic hypertension before first pregnancy (n = 2,191)
- Extreme birth weight ($Z>4$ or $Z<-4$) in first pregnancy (n = 1,640)
- Heart failure diagnosis before last birth (n = 27)
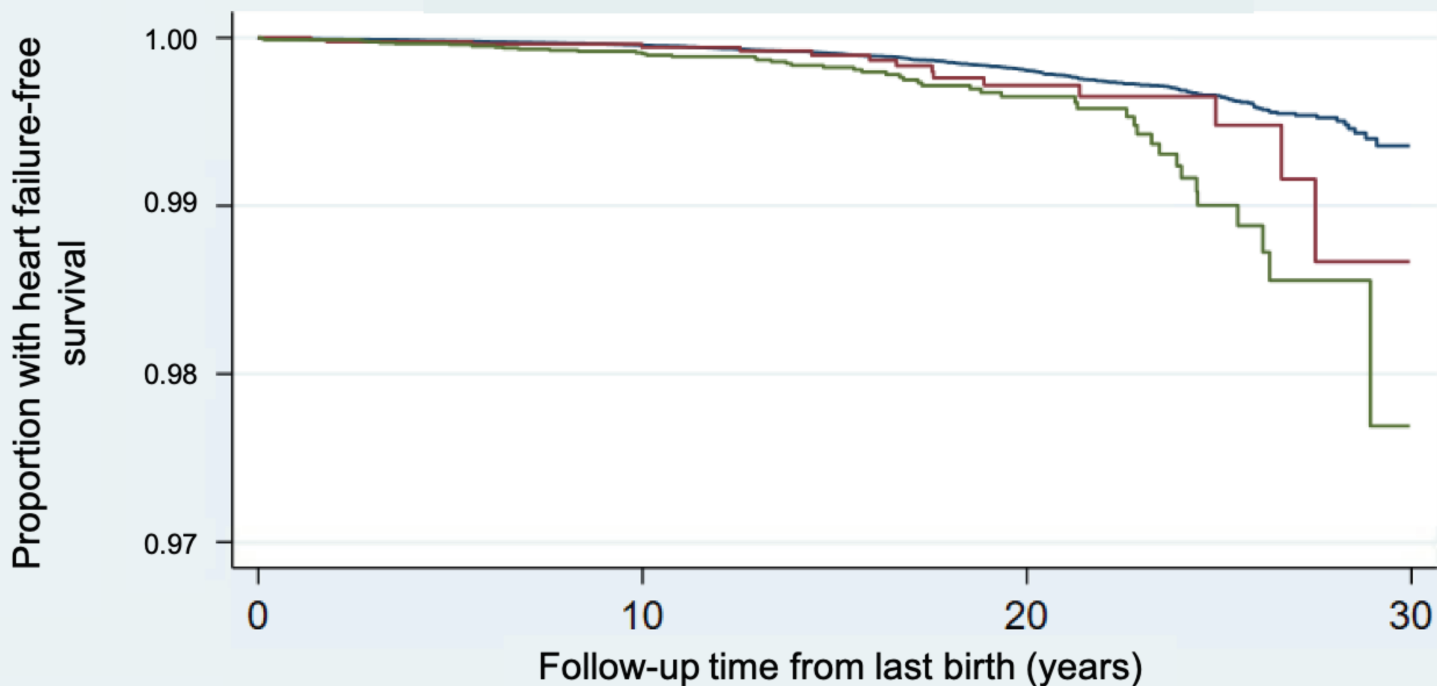- First delivery before 20 weeks' gestation (n = 3)

Study cohort

508,422 women aged 16-49 years at first birth occurring between 1980-2004 with final parity ≤5

475,269 women with no hypertensive disorder of pregnancy in the first birth

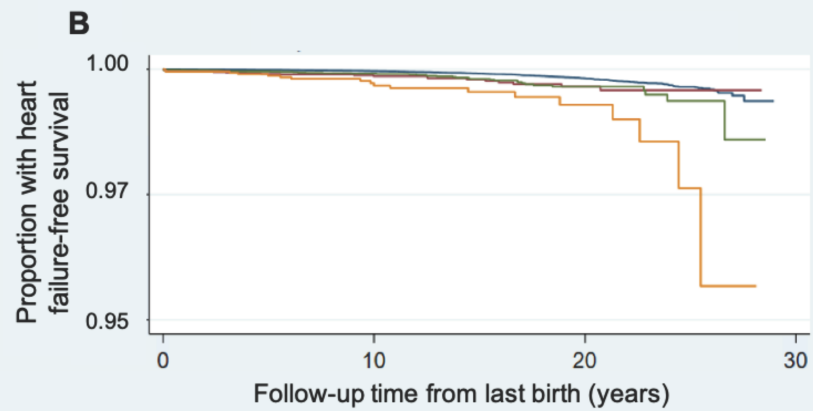8,827 women with gestational hypertension in the first birth

24,326 women with preeclampsia in the first birth

Number at risk

No HDP in first birth	475,269	276,282	82,061	0
GH in first birth	8,827	5,282	1,897	0
PE in first birth	24,326	13,053	3,680	0

No HDP   Gestational hypertension

Preeclampsia

A

Proportion with heart failure-free survival

Follow-up time from last birth (years)
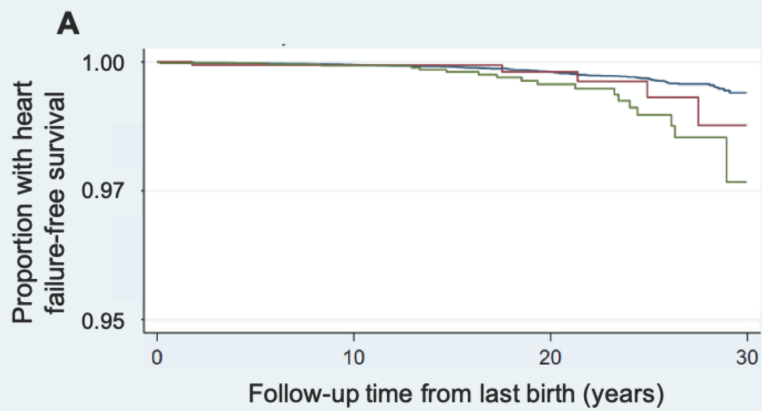
Number at risk

No HDP	80,147	57,536	25,416	0
GH	1,672	1,125	623	0
PE	4,781	3,196	1,340	0

— No HDP   — Gestational hypertension
— Preeclampsia

B

Proportion with heart failure-free survival

Follow-up time from last birth (years)

Number at risk

No HDP in any birth	382,191	212,564	55,245	0
GH in ≥1 birth, no PE	10,687	5,637	1,664	0
PE in 1 birth	24,356	12,410	2,850	0
PE in ≥2 births	4,408	2,134	493	0

— No HDP in any birth   — GH in ≥1 birth, no PE
— PE in 1 birth   — PE in ≥2 births