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Heterogeneity in the risk of cardiovascular disease mortality after the hypertensive disorders of pregnancy across mothers' lifetime reproductive history

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A commentary based on this manuscript appears on pages 238-240.

Abstract

Background: Prior studies on maternal cardiovascular disease (CVD) mortality and hypertensive disorders of pregnancy (HDP) have focused only on a woman's first birth and have not accounted for successive affected pregnancies.

Objectives: The objective of this study is to identify mothers' risk of CVD mortality considering lifetime reproductive history.

Methods: We used data from the Medical Birth Registry of Norway, the Norwegian Cause of Death Registry, and the Norwegian National Population Register to identify all mothers who gave birth from 1967 to 2020. Our outcome was mothers' CVD death before age 70. The primary exposure was the lifetime history of HDP. The secondary exposure was the order of HDP and gestational age at delivery of pregnancies with HDP. We used Cox regression models to estimate hazard ratio (HR) and 95% confidence interval (CI), adjusting for education, mother's age, and year of last birth. These models were stratified by the lifetime number of births.

Results: Among 987,378 mothers, 86,294 had HDP in at least one birth. The highest CVD mortality, relative to mothers without HDP, was among those with a pre-term HDP in their first two births, although this represented 1.0% of mothers with HDP (HR 5.12, 95% CI 2.66, 9.86). Multiparous mothers with term HDP in their first birth only had no increased risk of CVD relative to mothers without HDP (36.9% of all mothers with HDP; HR 1.12, 95% CI 0.95, 1.32). All other mothers with HDP had a 1.5- to 4-fold increased risk of CVD mortality.

Conclusions: This study identified heterogeneity in the risk of CVD mortality among mothers with a history of HDP. A third of these mothers are not at higher risk compared to women without HDP, while some less common patterns of HDP history are associated with severe risk of CVD mortality.

KEYWORDS
cardiovascular disease, gestational hypertension, life-course, lifetime reproductive history, Norway, preeclampsia

1 | BACKGROUND

Hypertensive disorders of pregnancy (HDP) are a spectrum of diseases including gestational hypertension and preeclampsia, superimposed preeclampsia, eclampsia, or the HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets).[2] They can lead to either mild symptoms or severe morbidity and death both in mother and child. While delivery of the placenta is thought to resolve the clinical symptoms of preeclampsia, there is evidence to support long-term maternal health implications, especially for cardiovascular disease (CVD) mortality.[2,3]

Both severe and mild forms of HDP are associated with long-term maternal CVD mortality, with higher risk estimated to be 1.5- to 3-fold[4] compared to mothers without HDP. Long-term CVD and HDP share similar risk factors such as obesity, metabolic disease, and endothelial dysfunction, and pregnancy may function as a stress test for cardiovascular function and future health.[4–6] Preventing premature CVD mortality (before age 70) remains a public health priority, and reproductive health has been increasingly recognised as an important female-specific risk factor.[7,8]

Previous studies found long-term maternal CVD mortality to be especially high among mothers with additional risk factors, such as HDP with pre-term delivery, recurrent HDP, and HDP in mothers with only one lifetime birth.[8,9] While these mothers have a very high relative risk for long-term CVD death compared to mothers without HDP, they represent only a small proportion of the total population of mothers with a history of HDP. Meanwhile, there is some evidence that, in multiparous mothers, a history of HDP only in the first birth, which is most common,[10] may have a lower risk of CVD death.[8,9] Earlier studies have inconsistently defined exposure to preeclampsia as exposure in the first birth, at any point in the reproductive history, or treated each birth as a new exposure. These definitions are problematic for studying long-term maternal health since they do not effectively account for the lifetime number of births of mothers.

Recent findings from Norway[11] found that the risk of CVD mortality increased with an increasing number of births complicated with either preeclampsia, placental abruption, low birth weight, stillbirth, or pre-term birth. This study, however, did not focus on the order of affected pregnancies or account for the subtypes of HDP. We describe the future risk of CVD death associated with different patterns and subtypes of HDP throughout a mother's lifetime reproductive history.

Synopsis

Study question

How is lifetime reproductive history of hypertensive disorders of pregnancy associated with long-term maternal cardiovascular disease (CVD) mortality?

What's already known

Hypertensive disorders of pregnancy are associated with an increased risk of maternal CVD. Current estimates are 1.5- to 3-fold increased risk for a mother with a history of hypertensive disorders of pregnancy.

What this study adds

In contrast to previous studies that have focused on the first pregnancy, we analysed a mother's risk of CVD death by their lifetime reproductive history of hypertensive disorders of pregnancy, including birth order, lifetime number, and gestational age at delivery of births with hypertensive disorders. We found that one-third of mothers with hypertensive disorders of pregnancy are not at the increased risk of CVD death, while others have much higher risk than previously estimated.

2 | METHODS

We conducted a cohort study using the Medical Birth Registry of Norway (MBRN), a population-based national registry of all births in Norway since 1967. Recorded information includes maternal demographics, maternal diseases before and during pregnancy, pregnancy complications, complications and interventions during delivery, and characteristics of the newborn. Registration is compulsory for all live births, stillbirths, and late spontaneous abortions from 16 weeks of gestation, currently including over 3 million births and over 1.5 million mothers. Until 1999, the birth notification form was based on free text, coded using the International Classification of Diseases (ICD), 8th version. In December 1998, the form was changed, checkboxes were introduced, in addition to free text, and ICD-10 codes were used.[12]

2.1 | Cohort selection

The population for this study consisted of mothers, defined as individuals whose first birth was registered in the MBRN from 1967 to 2013. Exclusion criteria were used to ensure all mothers included in the study had data on their lifetime reproductive history. We included only births delivered after 20 weeks of gestation, as HDP is diagnosed after 20 weeks of gestation. We retrieved MBRN data until June 2020, and 95% of Norwegian mothers have their second birth within 7 years after their first. Mothers whose first births were after 2013 were excluded. This allowed for a reasonable follow-up time to capture subsequent births. Mothers whose first birth was not listed in the registry, who had missing information on gestational age for first or second birth, who had more than eight births, and who died within 1 year of their last birth were excluded. Mothers with twin and other multifetal births were also excluded, as HDP may have different underlying

physiology and relationship to CVD mortality in these mothers.[13] A flow chart of our cohort selection is shown in Figure S1.

2.2 | Exposure

The exposure was defined as a lifetime reproductive history of HDP, registered in the MBRN as either preeclampsia, gestational hypertension, eclampsia, or HELLP syndrome. We stratified HDP in the first and second births by gestational age at delivery: term (≥37 weeks of gestation) or preterm HDP (<37 weeks). Given information on first, second, and all later births, we identified 33 categories of reproductive history as the main exposure. The diagnostic criterion for gestational hypertension is elevated blood pressure after 20 weeks' gestation (at least 140/90 mmHg) without proteinuria. The core diagnostic criteria for preeclampsia have been elevated blood pressure after 20 weeks' gestation (at least 140/90 mmHg) and ≥0.3 g/L/24 h proteinuria or reading of +1 on a dip-stick.[1] Eclampsia is further defined as a rare but severe complication of preeclampsia characterised by general convulsions in the mother not due to other causes, and the HELLP syndrome is defined by hemolysis, elevated liver enzymes, and low platelet count.[14]

2.3 | Outcome

The primary outcome was premature maternal death from CVD. These included deaths from ischaemic heart disease, cerebrovascular disease, or peripheral arterial disease in mothers up to and including 69 years of age. We used the national identification number given to every Norwegian resident to link data from the MBRN and data from the Norwegian Cause of Death Registry. The following codes from the ICD 7th, 8th, 9th and 10th revisions were used for CVD: ischemic heart disease: I20–I25 (ICD-10), 410–414 (ICD 7, 8 and 9); cerebrovascular disease: I60-I69 (ICD-10), 430–438 (ICD 7, 8 and 9); and peripheral arterial disease: I70–I72, I74 (ICD-10), 440–444 (ICD 7, 8 and 9).

2.4 | Statistical analyses

We used Cox proportional hazard models to estimate the mortality rates (deaths per 100,000 person-years) and the risk of CVD mortality up to age 70. We chose to study maternal death below age 70 aligning with the World Health definition of premature mortality.[15] Follow-up time was measured as years from last birth until the outcome of CVD death, emigration, censorship at age 69, or the end of the study period. The reference group was mothers without HDP in any birth, within subgroups of mothers with the same lifetime number of births. In a summary table, we combined broader groups with similar reproductive patterns and CVD mortality, highlighting the main findings of the study into four groups of mothers.

Covariates in the adjusted analyses included time period of last recorded birth (1967–1980, 1981–1990, 1991–2000, 2001–2013 and 2013–2020), maternal age at first birth (<20, 20–30 and ≥31 years), and mothers' highest achieved level of education (less than high school, high school, or college/university). All analyses were stratified by the lifetime number of births (1, 2 or 3 or more). We performed secondary analyses on detailed reproductive experiences of the group having the lowest risk, mothers with term HDP in the first birth and no HDP in later births. While the main analyses could provide evidence supporting the conclusion that these mothers are not at increased risk of long-term CVD death, we applied secondary analyses to explore if these women could still be at increased risk of CVD death if they had other risk factors in their lifetime reproductive history, such as long or short inter-pregnancy interval[16] and other pregnancy complications, including stillbirth, small for gestational age (SGA: <10th percentile of birthweight for gestational age and infant sex),[17] placental abruption, gestational diabetes and pre-term in the non-HDP births.[4,18,19] We also examined each HDP condition separately (gestational hypertension, preeclampsia and combined eclampsia or HELLP syndrome).

2.5 | Missing data

Missing data was limited in the study sample. Due to the importance of gestational age to our main exposure, we excluded any mothers who had missing information on gestational age in their first (n = 48,207, 3.2%) or second births (n = 35,620, 2.4%). No mothers had missing data on HDP or other pregnancy complications as all records without any specified pregnancy complication on the form, either as free text or by check boxes, are defined as "no complication." A small proportion of mothers had no reported information on their educational level (2.1%), which was treated as a separate category in analyses adjusting for maternal education.

2.6 | Ethics approval

This project was approved by the Regional Committee for Medical and Health Research Ethics (REK VEST 2015/1728 and REK VEST 13818). Informed consent was not required as data were de-identified, and the researchers did not have any contact with participants.

3 | RESULTS

3.1 | Population characteristics

Among 981,253 mothers included in the study, 84,760 (8.7%) had HDP at any point during their reproductive history. Mothers who died of CVD were followed for 23,648,258 person-years, with 55,383 deaths occurring during the study period. The characteristics of mothers who had HDP at any point during their lifetime reproductive history compared to mothers with no history of HDP is contrasted in Table 1. A greater proportion of mothers with HDP gave

birth after 2000 and were older at their first birth. They also had more lifetime births than mothers with no history of HDP. The majority of mothers with HDP had term delivery at 37 or more weeks of gestation (78.7%).

3.2 | Lifetime reproductive history

The absolute mortality rate for the mothers without a history of HDP was 22 per 100,000 person years, while the absolute mortality for mothers with HDP in any birth was 35 per 100,000 person years. Using definitions for exposure more common in the literature, mothers with HDP in their first birth had an increased risk of CVD mortality (HR 1.63, 95% CI 1.47, 1.79) compared to mothers with no HDP in their first birth. Similarly, women with HDP in any birth had a higher risk of CVD mortality (HR 1.82, 95% CI 1.68, 1.97) compared to mothers without a history of HDP.

TABLE 1 Maternal demographic factors by the hypertensive disorders of pregnancy (HDP) across lifetime reproductive history in mothers delivering their first birth in Norway, 1967–2013.

	No HDP ever	Any history of HDP
	Number (%)	Number (%)
Total	895,493 (91.3)	85,760 (8.7)
Year of mother's last birth		
1967–1979	167,571 (18.7)	12,034 (14.0)
1980–1989	167,667 (18.7)	15,727 (18.3)
1990–1999	191,225 (21.4)	18,067 (21.1)
2000–2013	262,284 (29.3)	29,190 (34.0)
Mother's age at first birth (years)		
<20	106,746 (11.9)	10,742 (12.5)
20–30	102,660 (11.5)	8931 (10.4)
≥31	624,598 (69.7)	59,298 (69.1)
Education		
Less than High School	168,235 (18.8)	17,531 (20.4)
High School	167,822 (18.9)	15,793 (18.5)
University/College	342,710 (38.7)	33,412 (39.2)
Lifetime number of births		
1	375,781 (42.4)	36,028 (42.3)
2	163,290 (18.2)	12,669 (14.8)
≥3	442,210 (49.4)	40,832 (47.6)
History of pre-term birth		
No	289,993 (32.4)	32,259 (37.6)
Yes	810,901 (90.6)	67,519 (78.7)
History of other complications[a]		
No	84,592 (9.4)	18,241 (21.3)
Yes	711,587 (79.5)	57,445 (67.0)

[a]Complications include stillbirth, small for gestational age, placental abruption or gestational diabetes.

CVD risk varied by lifetime number of births, even among mothers without HDP, 30 per 100,000 person-years for mothers with one lifetime birth, 19 per 100,000 person-years for mothers with two lifetime births, and 20 per 100,000 person-years for mothers with three or more lifetime births.

Figure 1 shows CVD mortality first for mothers with one-lifetime birth, adjusted for year of first birth, age at first birth, and education level. The risk of CVD mortality increased both for mothers with term HDP and pre-term HDP, with a higher risk for pre-term HDP. Figure 1 also shows adjusted CVD mortality for mothers with two lifetime births according to their complete reproductive history of HDP. CVD mortality differed by order, number, and gestational age at delivery of HDP births. Mothers at highest risk had pre-term HDP in both births (HR 6.30, 95% CI 2.99, 13.24), with an almost three times greater risk than that of mothers who had pre-term HDP only in the first birth (HR 2.38, 95% CI 1.48, 3.84) and higher risk if the pre-term HDP was only in the second birth (HR 3.83, 95% CI 2.26, 6.48). Mothers with term HDP in the first birth and a subsequent birth without HDP (23.6% of all mothers with a history of HDP and 49.5% of mothers with two lifetime births and a history of HDP) did not have an increased risk of CVD death (HR 1.07, 95% CI 0.86, 1.32).

Figure 2 shows CVD mortality for mothers with three or more lifetime births according to their lifetime reproductive history, adjusted for the year of first birth, age at first birth, and education. The CVD mortality was 20 per 100,000 person-years for the reference group, mothers with three or more births, all without HDP. Mothers with term HDP in the first birth and no HDP in any later birth made 13.3% of all mothers with HDP and 35.4% of mother with 3 or more lifetime births and a history of HDP. While this group had low risk of CVD death in the subgroup of mothers with HDP, they did have an increased risk compared to the reference group of mothers without HDP (HR 1.38, 95% CI 1.07, 1.79). The group with the highest risk was mothers with two pre-term HDP births and later births without HDP (HR 9.90, 95% CI 2.47, 39.66). There were no cases of CVD death among mothers with two pre-term HDP births and later HDP births.

In Table 2, we present a summary of the overall associations (depicted in Figures 1 and 2). Mothers with term HDP in the first birth and later births without HDP make up an especially low-risk group (pooled HR 1.12) and constitute 37% of mothers with a lifetime history of HDP. Mothers with pre-term HDP in both of their first two births have an especially high risk (pooled HR 5.12), but only account for approximately 1% of mothers with HDP. The remainder of mothers with HDP had parity-specific relative risks of between 1.5 to 4.0 (pooled HR 2.16) compared to mothers without HDP, similar or higher to what was previously found for the overall HDP.

3.3 | Secondary analysis

In Table S1, we stratified the group of mothers we found to have little to no risk of CVD (those with term HDP in their first birth and later births without HDP) by other factors in their lifetime

1st Birth	2nd Birth	N (Percent of mothers with HDP)	Mortality Rate	Unadjusted HR (95%CI)	Adjusted HR (95%CI)
No HDP		163,290	29.9 (28.3, 31.5)	1.00 (Reference)	1.00 (Reference)
Term HDP		10,149 (80.1%)	49.0 (40.9, 58.3)	1.75 (1.46, 2.10)	1.63 (1.36, 1.96)
Preterm HDP		2520 (19.9%)	78.9 (57.5, 105.5)	3.48 (2.58, 4.68)	3.44 (2.55, 4.64)
No HDP	No HDP	442,210	19.1 (18.2, 19.9)	1.00 (Reference)	1.00 (Reference)
	Term HDP	9506 (23.3%)	38.3 (30.7, 47.3)	2.16 (1.74, 2.68)	2.13 (1.72, 2.64)
	Preterm HDP	1367 (3.3%)	51.2 (28.0, 85.9)	3.73 (2.20, 6.31)	3.83 (2.26, 6.48)
Term HDP	No HDP	20,232 (49.5%)	18.5 (14.8, 22.9)	1.06 (0.85, 1.32)	1.07 (0.86, 1.33)
	Term HDP	4669 (11.4%)	31.3 (21.7, 43.7)	1.83 (1.31, 2.57)	1.83 (1.30, 2.57)
	Preterm HDP	593 (1.5%)	33.3 (9.1, 85.3)	2.54 (0.95, 6.78)	2.64 (0.99, 7.05)
Preterm HDP	No HDP	2892 (7.1%)	30.9 (18.0, 49.4)	2.24 (1.39, 3.61)	2.38 (1.48, 3.84)
	Term HDP	970 (2.4%)	25.8 (8.4, 60.3)	1.93 (0.80, 4.64)	1.99 (0.83, 4.80)
	Preterm HDP	603 (1.5%)	64.1 (25.8, 132.1)	5.82 (2.77, 12.22)	6.30 (2.99, 13.24)

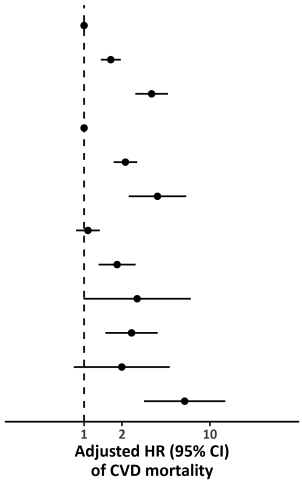

FIGURE 1 Cardiovascular disease (CVD) mortality by the history of hypertensive disorders of pregnancy (HDP) in mothers with one or two lifetime births delivering their first birth in Norway from 1967 to 2013 and followed up to 2020. Results are adjusted for year of first birth, age at first birth and education level. The mortality rate is reported as deaths per 100,000 person-years. Percentages are presented for mothers with one and two lifetime births separately, calculated based on the proportion of mothers with HDP (483,042 for mothers with two lifetime births, 175,959 for mothers with one lifetime birth).

1st birth	2nd birth	Later births	N (Percent of mothers with HDP)	Death per 100,000 person-years	Unadjusted HR (95%CI)	Adjusted HR (95%CI)
No HDP	No HDP	No Later HDP	289,993	20.4 (19.4, 21.6)	1.00 (Reference)	1.00 (Reference)
		Later HDP	8448 (26.2%)	48.3 (39.1, 59.2)	2.47 (2.01, 3.05)	2.37 (1.92, 2.92)
	Term HDP	No Later HDP	3710 (11.5%)	30.0 (19.4, 44.3)	1.51 (1.02, 2.24)	1.52 (1.02, 2.25)
		Later HDP	1189 (3.7%)	48.3 (25.7, 82.6)	2.47 (1.43, 4.26)	2.46 (1.42, 4.24)
	Preterm HDP	No Later HDP	442 (1.4%)	23.8 (2.9, 86.0)	1.44 (0.36, 5.75)	1.41 (0.35, 5.66)
		Later HDP	176 (0.5%)	59.1 (7.2, 213.6)	3.91 (0.98, 15.66)	4.08 (1.02, 16.36)
Term HDP	No HDP	No Later HDP	11,421 (35.4%)	25.6 (19.6, 32.9)	1.36 (1.06, 1.76)	1.38 (1.07, 1.79)
		Later HDP	1859 (5.8%)	32.2 (17.1, 55.1)	1.77 (1.03, 3.06)	1.78 (1.03, 3.08)
	Term HDP	No Later HDP	1371 (4.2%)	41.4 (21.4, 72.4)	2.28 (1.29, 4.03)	2.42 (1.37, 4.28)
		Later HDP	890 (2.8%)	43.1 (18.6, 84.9)	2.49 (1.24, 4.98)	2.67 (1.33, 5.34)
	Preterm HDP	No Later HDP	93 (0.3%)	62.3 (1.6, 347.4)	3.90 (0.55, 27.68)	3.97 (0.56, 28.22)
		Later HDP	110 (0.3%)	0	NA	NA
Preterm HDP	No HDP	No Later HDP	1510 (4.7%)	41.8 (21.6, 72.9)	2.38 (1.35, 4.19)	2.37 (1.34, 4.18)
		Later HDP	319 (1.0%)	64.6 (17.6, 165.4)	4.05 (1.52, 10.80)	4.20 (1.57, 11.22)
	Term HDP	No Later HDP	261 (0.8%)	42.4 (5.1, 153.3)	2.77 (0.69, 11.07)	3.66 (0.91, 14.66)
		Later HDP	249 (0.8%)	40.3 (4.9, 145.4)	2.50 (0.62, 10.01)	2.51 (0.63, 10.05)
	Preterm HDP	No Later HDP	91 (0.3%)	121.5 (14.7, 438.9)	8.65 (2.16, 34.65)	9.90 (2.47, 39.66)
		Later HDP	120 (0.4%)	0	NA	NA

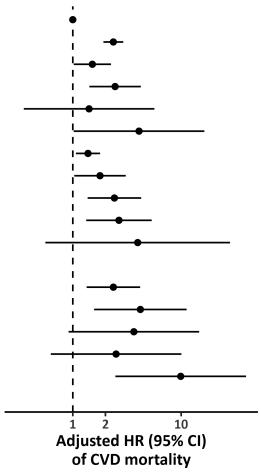

FIGURE 2 CVD mortality by history hypertensive disorders of pregnancy (HDP) in mothers with 3 or more lifetime births delivering their first birth in Norway from 1967 to 2013 and followed to 2020. Results are adjusted for year of first birth, age at first birth, and education level. The mortality rate is reported as deaths per 100,000 person-years. Percentages are calculated based on the proportion of mothers with HDP ($n = 322,262$).

reproductive history. Compared to mothers with two or more lifetime births without HDP, these mothers had increased risk of CVD death if they had other complications in addition to HDP (HR 2.03, 95% CI 1.59, 2.60), a pre-term delivery in their second normotensive birth (HR 2.43, 95% CI 1.38, 4.28), or a short interpregnancy interval (<2 years) before their last birth (HR 2.02, 95% CI 1.25, 3.27). Specifically for mothers with three or more lifetime births, mothers with term HDP in the first birth only had the lowest observed risk of CVD death if they had an interpregnancy interval of 2–5 years between their last two births (HR 0.86, 95% CI 0.51, 1.43).

4 | COMMENT

4.1 | Principal findings

Mothers with HDP had a 1.5- to 4-fold increased risk of CVD death compared to mothers with no HDP ever. Factors associated with higher risk of CVD death were consistent with previous literature, including pre-term delivery, recurrent HDP, and one lifetime birth. We also found that over a third of mothers with any history of HDP in the first birth have no difference in CVD mortality compared to

TABLE 2 Summary table of mothers in the Norwegian population by reproductive history, showing the relationship between different patterns of HDP history and later CVD mortality.

HDP history	Number of mothers (% of all mothers with HDP)	Parity-specific relative risk estimates from Figures 1 and 2	Pooled risk aHR (95% CI)	Plain language summary
No hypertensive disorders of pregnancy	895,504	Reference	Reference	Reference
Term hypertensive disorders in the first birth followed by more births without hypertensive disorders	31,653 (36.9%)	<1.5-fold	1.12 (0.95, 1.32)	Little to no increased risk
Other history of hypertensive disorders of pregnancy	53,292 (62.1%)	1.5 to 4-fold	2.16 (1.97, 2.37)	Moderately increased risk
Pre-term hypertensive disorders in the first two births	814 (1.0%)	>4-fold	5.12 (2.66, 9.86)	Serious risk

Note: Results are adjusted for the year of first birth, age at first birth, and education level.

women with a history of HDP. These mothers had term HDP in the first birth and one later birth without HDP.

4.2 | Strengths of the study

Strengths of the study include the large population-based dataset, the MBRN linked with the Cause of Death Registry. Additionally, the follow-up time of 50 years and sibling-linked successive births, with compulsory data registration at the time of birth allowed analysis of mothers' complete reproductive histories of HDP, a relatively rare condition.

4.3 | Limitations of the data

Despite the large number of observations in the study, we were limited to a small number of potential confounding variables, lacking important information such as BMI, smoking, and income. Previous studies including these variables have nonetheless shown that adjustment did not greatly alter results.[20] The variables we used for HDP have rather poor sensitivity but a high positive predictive value (preeclampsia diagnosis was confirmed in 88.3% of births and gestational hypertension was confirmed in 68% of births).[1] The time trends we observe in the incidence of preeclampsia in the study population are likely due to underreporting of milder forms of preeclampsia before 1999.[12] While this study has focused on highlighting the heterogeneity in our exposure variable, we acknowledge that CVD is also a disease with many subtypes, encompassing conditions with different pathophysiological aetiologies. Our definition of CVD death includes atherosclerotic CVD, and conclusions from this study may not be generalisable to other CVD outcomes.

While studying health disparities faced by Norwegians with immigrant backgrounds is an important topic, accounting for immigrant background was not feasible in this study design given the low proportion of immigrants in the population in the earlier years of the registry, when most of the mothers with our outcome gave birth. Future studies could compare the risk of mothers with HDP to people with no history of births to gain perspective on the full population. Future studies must also consider changes in obstetric practice, including the use of aspirin to prevent hypertensive disorders of pregnancy since 2014.

4.4 | Interpretation

It has been hypothesised that HDP is indicative of a chronic underlying CVD that manifests during the "stress-test" of pregnancy.[21,22] Our results add more nuance to the hypothesis, and propose that different manifestations of HDP across the reproductive history may indicate the severity or type of the underlying health condition. Aetiological differences between term and pre-term HDP are debated, including discussions about underlying chronic disease.[23–27] Pre-term HDP recurs more often in mothers' next births than term HDP,[10,12] and maybe a stronger indicator of future chronic disease. We found that the relationship between pregestational health, history of HDP, and long-term CVD is not uniform by lifetime reproductive history. A second birth without HDP, pre-term birth, or other complications associated with HDP[28] could indicate the first birth had transient health issues with less long-term impacts.

The over two-fold risk of CVD death found in mothers with two births and with non-HDP pre-term birth after term HDP is striking considering a second delivery at term was not associated with an increased risk of CVD death. Previous research on mothers with HDP at term and pre-term delivery in another non-HDP birth has suggested that the underlying aetiology between HDP and preterm is linked.[18] HDP, with pre-term delivery, even in another birth, may have a different aetiology with greater long-term impact than term HDP alone.

This study highlights the importance of including a mother's lifetime reproductive history in research examining associations between perinatal factors and future maternal health. Previous research on HDP has typically focused on the first birth, as HDP most often develops in the first birth,[10] and most studies do not have data on mothers' complete reproductive history. Our study finds that mothers with HDP in the first birth do not uniformly have a two-fold

risk of CVD death as previously seen,[29] but rather the risk ranges from 1- to 10-fold depending on if there were later births and HDP status in later births. Evaluating CVD mortality associated with HDP requires information on the full reproductive history of women and consideration of HDP as a heterogeneous disorder.

CVD mortality also differed by the number of non-HDP births after HDP in the first birth, with a higher risk for those with two or more births after an HDP birth compared to only one additional birth. The association with CVD mortality by lifetime number of births may be explained by some additional factors in the reproductive history such as pregnancy complications, fertility problems and interpregnancy interval. The relationship between HDP and long interpregnancy interval is a complicated one, yet to be fully understood.[16] The causal pathway between pregnancy complications and long-term health may include unmeasured factors such as underlying subfertility, pregestational health conditions, and socioeconomic status.[30,31] The low number of mothers with a third birth after two pre-term HDP births may also be an effect of selective fertility.[32]

The American College of Obstetrics and Gynecologists and the International Federation of Gynecology and Obstetrics now recommends that mothers who experience a birth complicated by any HDP should have annual cardiovascular risk assessments.[33,34] From a public health perspective, it is important to evaluate the inclusion of HDP as a risk factor alongside lifetime reproductive history or other cardiovascular risk factors.[21] Lifetime reproductive history of pregnancy complications is strongly associated with CVD mortality, in a dose-dependent manner based on the number of complicated pregnancies.[11] Mothers whose only reproductive risk factor is one birth with HDP, no other complications, pre-term births, or long interpregnancy interval, and who had other healthy births without HDP, are not necessarily at increased risk of CVD mortality. Individuals with this reproductive history are quite common in the population of women with HDP. Meanwhile, a very small number of mothers are at very high risk. Predictions of later CVD mortality cannot be based on HDP alone, but rather informed by lifetime reproductive history.

5 | CONCLUSIONS

Maternal health during pregnancy is associated with long-term health, and best utilised as a predictor when considering the influence of reproductive factors on CVD mortality. While most mothers with a history of HDP are at moderate risk of long-term CVD death, a third are not at increased risk, and only a very small number are at high risk. Previous analyses merging all cases of HDP into one condition may mask the true underlying risks of both low and high-risk mothers. This study adds to the evidence that CVD mortality cannot be predicted by a history of HDP alone but must be predicted in the context of multiple factors across a women's lifetime reproductive history.

AUTHOR CONTRIBUTIONS

RS, SW, and LGK conceived and designed the study. RS obtained access to the data. SW and AS conducted the data analysis. SW drafted the initial version of the manuscript. LGK, AS, TØ, and KK revised the manuscript and added insights to improve data analysis.

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CONFLICT OF INTEREST STATEMENT

The authors declare that there are no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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