OBSTETRICS

Risks of cause-specific mortality in offspring of pregnancies complicated by hypertensive disease of pregnancy

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BACKGROUND: Fetal environment has a substantial influence on an individual's health throughout their life course. Animal models of hypertensive disease of pregnancy have demonstrated adverse health outcomes among offspring exposed to hypertensive disease of pregnancy in utero. Although there are numerous descriptions of the neonatal, infant, and pediatric outcomes of human offspring affected by hypertensive disease of pregnancy, there are few data in US populations on later life outcomes, including mortality.

OBJECTIVE: To assess risk for early mortality among offspring of pregnancies complicated by hypertensive disease of pregnancy.

STUDY DESIGN: This is a retrospective cohort study of offspring born to women with singleton or twin pregnancies between 1947 and 1967 with birth certificate information in the Utah Population Database. We identified offspring from delivery diagnoses of gestational hypertension, preeclampsia, or eclampsia. Offspring from these pregnancies (exposed) were matched to offspring of pregnancies without hypertensive disease of pregnancy (unexposed) by maternal age at delivery, birth year, sex, and multiple gestation. We also identified unexposed siblings of exposed offspring for a separate sibling analysis. Mortality follow-up of all offspring continued through 2016, at which time they would have been 49–69 years old. Adjusted hazard ratios for cause-specific mortality comparing exposed with unexposed offspring were estimated using Cox proportional hazard models.

RESULTS: We compared mortality risks for 4050 exposed offspring and 6989 matched unexposed offspring from the general population and 7496 unexposed siblings. Mortality risks due to metabolic, respiratory, digestive, nervous, and external causes of death did not differ between exposed and unexposed groups. Mortality risks from cardiovascular disease were greater in exposed offspring compared with unexposed offspring (adjusted hazard ratio, 1.57; 95% confidence interval, 1.16–2.12). In sex-specific models among the general population, cardiovascular disease mortality was significantly associated with exposure among male patients (adjusted hazard ratio, 1.92; 95% confidence interval, 1.27–2.88) but not among female patients (adjusted hazard ratio, 0.97; 95% confidence interval, 0.81–1.94). An interaction between hypertensive disease of pregnancy exposure and birth order on cardiovascular disease mortality was significant (P=.047), suggesting that the effect of hypertensive disease of pregnancy on cardiovascular disease mortality increased with higher birth order. Among siblings, the association between hypertensive disease of pregnancy exposure and cardiovascular disease mortality was not significant (adjusted hazard ratio, 1.39; 95% confidence interval, 0.99–1.95), and this was also true for sex-specific analyses of males (adjusted hazard ratio, 1.26; 95% confidence interval, 0.81–1.94) and females (adjusted hazard ratio, 1.71; 95% confidence interval, 0.96–3.04). As in the general population, there was a significant interaction between hypertensive disease of pregnancy exposure and birth order on cardiovascular disease mortality (P=.011).

CONCLUSION: In a US population, overall mortality risks are greater for offspring of pregnancies complicated by hypertensive disease of pregnancy compared with unexposed offspring. Among siblings, there was not a significant association between hypertensive disease of pregnancy exposure and cardiovascular disease mortality.

Key words: Barker hypothesis, cardiovascular disease, fetal programming, pregnancy as a window to future health

A growing body of evidence suggests that the fetal environment has a substantial influence on an individual's health throughout their life course. The theory of fetal programming indicates that alterations in the prenatal nutritional, hormonal, or environmental milieu can alter fetal gene expression, leading to permanent effects on a range of physiological functions. This hypothesis was proposed by Barker,[1,2] who demonstrated an association between low birthweight and cardiovascular disease later in life. Animal models of hypertensive disease of pregnancy (HDP) have demonstrated increases in fetal hypoxic–ischemic injury and subsequent abnormalities in postnatal growth, apoptosis rates, and neuronal migration in affected fetuses.[3,4] These findings suggest that HDP, either alone or in combination with growth restriction, may induce changes leading to the susceptibility of offspring to chronic diseases later in life.

HDP complicates 5%–10% of pregnancies in the United States.[5] Multiple studies have assessed the association between maternal HDP and adverse neonatal,[6–8] infant,[9] and adult[10–12] outcomes. However, these studies have limited numbers of participants, and there are few data on the US population on later life–course outcomes. In addition, the vast majority of these studies, including the ones that were able to follow offspring into adulthood, have focused on morbidity outcomes such as cardiovascular disease (CVD). Data regarding mortality outcomes among affected offspring are lacking. To address this knowledge gap, we examined the

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AJOG at a Glance

Why was this study conducted?

To assess mortality risk among offspring of pregnancies complicated by hypertensive disease of pregnancy.

Key findings

In a US population, male offspring of pregnancies complicated by hypertensive disease of pregnancy experience excess mortality risks, particularly from cardiovascular disease, when compared with offspring of pregnancies not complicated by hypertensive disease of pregnancy.

What does this add to what is known?

This study confirms that adults born from pregnancies complicated by hypertensive disease of pregnancy are not only at risk for cardiovascular disease, but also, their risk of mortality from it is significantly greater. These individuals could be targeted by earlier screening for cardiovascular disease and may benefit from interventions to improve long-term health outcomes.

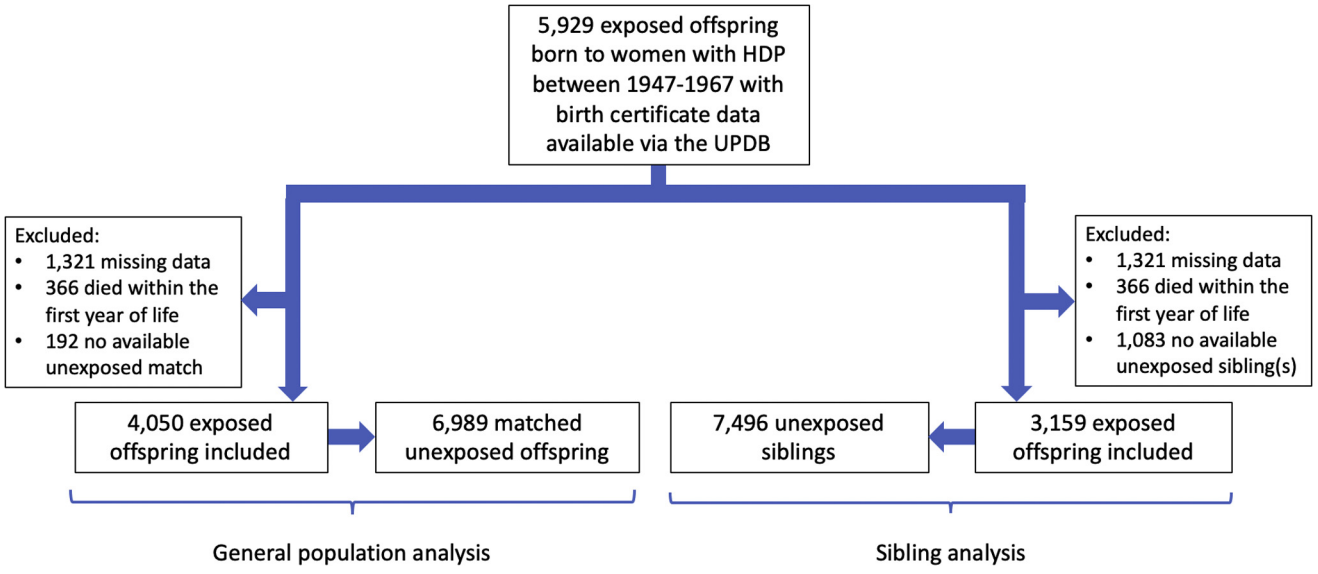
risk of all-cause and cause-specific mortality in offspring born from pregnancies complicated by HDP in relation both to population-based matched controls and to their unaffected siblings.

Materials and Methods

In this retrospective historical cohort study, we identified all offspring of women with singleton or twin pregnancies with birth certificate information in the Utah Population Database (UPDB). The overall design, methods, and development of the UPDB have been reported previously.[13,14] The UPDB is a comprehensive research database of linked records, which includes individual genealogical records from the Genealogical Society of Utah, official statewide birth and death certificates, and hospital discharge and ambulatory surgery records from the Utah Department of Health. It includes data on more than 11 million individuals. The study was approved by the Resource for Genetic and Epidemiologic Research, which oversees UPDB access, and the University of Utah Institutional Review Board.

The population represented in UPDB is predominantly of northern and western European Caucasian ancestry, reflecting the European-based pioneer population settling in Utah in the mid-1800s. The subjects under consideration were born as early as 1947, the first year that birthweight was recorded on Utah birth certificates. Using the text documented by the delivering provider on these birth certificate records, we identified pregnancies that were complicated by gestational hypertension, preeclampsia, eclampsia, and suspected HDP. We included the latter when the records indicated the presence of hypertension and edema or pregnancy-induced hypertension, but no definitive diagnosis noted on the birth certificate. Of note, HDP diagnoses and classifications were based solely on what was reported by the delivering provider on the birth certificate. These birth certificate data identified offspring of pregnancies with and

FIGURE 1
HDP offspring mortality STROBE diagram



HDP, hypertensive disease of pregnancy; *STROBE*, STrengthening the Reporting of OBservational studies in Epidemiology; *UPDB*, Utah Population Database.

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without HDP for inclusion in our analyses. For all analyses, the date of death was available in UPDB based on genealogies, Utah death certificates, and the Social Security Death Index. The Social Security Death Index is a national database and captures the death dates of persons in the Social Security Administration, including those who moved out of Utah. The causes of death were determined using Utah death certificates and the *International Classification of Diseases* (revisions spanning ICD-7 to ICD-10).

Exposed offspring were identified as children delivered from pregnancies affected by HDP. Unexposed offspring were identified as children delivered to mothers with no history of HDP in any pregnancy. Exposed offspring were matched to unexposed offspring from the general population in 1:2 ratio by birth year, sex, maternal age at birth, and multiple gestation. We did not match by parity to avoid conditioning on the future. Offspring were excluded if they had maternal age at birth younger than age 12 or after age 50 years, missing paternal age at birth or paternal age at birth younger than age 15 years, missing gestation age or gestation age less than 20 weeks or greater than 44 weeks, missing birthweight or birthweight less than 500 g or greater than 6000 g. We also excluded offspring if they died before their first birthday. We employed this restriction to focus our attention on postinfancy outcomes. This study only included offspring born between 1947 and 1967 to allow sufficient follow-up time to observe mortality events.

We performed 2 analyses. First, we compared mortality risks of exposed offspring with matching unexposed offspring from the general population (general population analysis). Exposed offspring with no matching unexposed offspring were excluded. Analyses were adjusted for birth order (the order of the child's birth within the mother's reproductive history), maternal parity, stratified by case ID to accommodate the matching design, and clustered by mother ID to account for natural clustering among siblings. We did not adjust for low birthweight and gestational age

TABLE 1
Descriptive statistics for exposed and matching unexposed from the general population born in 1947–1967 and survived the first year

	Exposed (N = 4050)	Unexposed (N = 6989)	*P* value
Sex			.944
Female	1973 (48.7%)	3411 (48.8%)	
Male	2077 (51.3%)	3578 (51.2%)	
Birthweight, g	3078.1 ± 640.0	3276.0 ± 534.9	<.001[a]
Small for gestational age			.774
No	3671 (90.6%)	6322 (90.5%)	
Yes	379 (9.4%)	667 (9.5%)	
Gestational age, wk	39.0 ± 2.0	39.5 ± 1.6	<.001[a]
Preterm			<.001[a]
No	3586 (88.5%)	6563 (93.9%)	
Yes	464 (11.5%)	426 (6.1%)	
Birth year	1957.6 ± 5.5	1957.6 ± 5.5	.868
Birth order (continuous)	2.8 ± 2.1	3.1 ± 2.1	<.001[a]
Birth order (categorical)			<.001[a]
1	1560 (38.7%)	1694 (24.4%)	
2	683 (17.0%)	1567 (22.6%)	
3	570 (14.2%)	1269 (18.3%)	
4	497 (12.3%)	978 (14.1%)	
5	317 (7.9%)	613 (8.8%)	
6	163 (4.0%)	367 (5.3%)	
7	108 (2.7%)	189 (2.7%)	
8	46 (1.1%)	124 (1.8%)	
9	34 (0.8%)	61 (0.9%)	
10	26 (0.6%)	30 (0.4%)	
11	9 (0.2%)	12 (0.2%)	
12	5 (0.1%)	17 (0.2%)	
13	5 (0.1%)	12 (0.2%)	
14	2 (0.0%)	5 (0.1%)	
15	2 (0.0%)	2 (0.0%)	
16	0 (0.0%)	2 (0.0%)	
Number of siblings	4.5 ± 2.2	4.9 ± 2.2	<.001[a]
Multiplicity			.600
No	3734 (92.9%)	6457 (93.2%)	
Yes	284 (7.1%)	470 (6.8%)	
Mothers' age at birth	26.7 ± 7.1	26.9 ± 7.1	.306
Mothers' HDP status			<.001[a]
None	0 (0.0%)	6989 (100.0%)	
Eclampsia	204 (5.0%)	0 (0.0%)	

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(continued)

TABLE 1
Descriptive statistics for exposed and matching unexposed from the general population born in 1947–1967 and survived the first year *(continued)*

	Exposed (N = 4050)	Unexposed (N = 6989)	*P* value
Gestational hypertension	281 (6.9%)	0 (0.0%)	
Pre-eclampsia	3544 (87.5%)	0 (0.0%)	
Questionable HDP	21 (0.5%)	0 (0.0%)	

HDP, hypertensive disease of pregnancy.

[a] Statically significant.

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because exposed offspring are at greater risk of lower birthweights and shorter gestation age. If included in the models, we would have variables that would correlate with each other in the model. Second, we compared mortality risks of exposed offspring with their unexposed siblings to control for unmeasured genetic and environmental factors (sibling analysis). Exposed offspring with no unexposed siblings were excluded. Because the oldest individuals in our cohort were 69 years old at the end of our study period, we did not anticipate being able to capture all differences in mortality; rather, we intended to determine whether in utero HDP exposure is associated with early mortality.

Demographic characteristics of exposed and unexposed offspring were compared using *t* tests for continuous variables and χ^2 tests for categorical variables. Conditional Cox proportional hazard models were used for all-cause mortality analysis, and standard competing risk models were used for specific causes of death, including circulatory system disease, respiratory system disease, cancer, nervous system/mental disorders, endocrine/nutritional/metabolic diseases, digestive system disease, and external causes.[15] Analyses were adjusted for sex, maternal age at birth, multiple gestation, and clustered by mother ID. Because HDP is associated with birth order (maternal parity), we tested for interaction between HDP, birth order, and mortality.[16,17] R version 3.5.0 (R Foundation for Statistical Computing, Vienna, Austria) was used to perform all analyses. *P* values <.05 from 2-sided tests were considered statistically significant.

TABLE 2
Most common causes of death after the first year of life with comparison with matching unexposed from general population as control

Cause of deaths	Exposed, N (%)	Unexposed, N (%)	aHR* (95% CI)	*P* value
Total deaths	430 (10.6)	609 (8.7)	1.19 (1.07–1.32)[a]	.002[a]
Neoplasms	70 (1.7)	94 (1.3)	1.37 (1.04–1.81)[a]	.026[a]
Metabolic/nutrition	18 (0.4)	28 (0.4)	1.14 (0.62–2.09)	.678
Nervous	11 (0.3)	27 (0.4)	0.62 (0.33–1.16)	.133
Cardiovascular	63 (1.6)	68 (1.0)	1.57 (1.16–2.12)[a]	.004[a]
Respiratory	21 (0.5)	29 (0.4)	1.37 (0.82–2.27)	.228
Digestive	18 (0.4)	25 (0.4)	1.32 (0.74–2.35)	.342
External causes	120 (3.0)	198 (2.8)	0.97 (0.80–1.18)	.755

Models controlled for: birth order, number of siblings, stratified by case identification code, and clustered by MaPersonID.

aHR, adjusted hazard ratio; *CI*, confidence interval.

[a] Statically significant.

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Results

General population analysis

We identified 5929 exposed offspring meeting our inclusion criteria within the UPDB. After we excluded those with missing data (1321), those who had died within the first year of life (366), and those who did not have at least one matching unexposed offspring (192), we were left with 4050 exposed offspring. We matched these to 6989 unexposed offspring (Figure 1). Exposed offspring were born from mothers with the following categories of hypertensive disease: 3544 preeclampsia, 281 gestational hypertension, 204 eclampsia, and 21 with suspected HDP. Descriptive statistics are shown in Table 1. Compared with matching unexposed offspring from the general population, exposed offspring had significantly lower birthweights, gestation age, preterm, birth order, and number of siblings.

Exposed offspring had significantly greater all-cause mortality risk than unexposed offspring (10.6% vs 8.7%; adjusted hazard ratio [aHR], 1.19; 95% confidence interval [CI], 1.07–1.32, *P*=.002). Table 2 describes the counts and mortality risks by most common causes of death among exposed and matched unexposed offspring in the general population. The most common causes of death in this population were external causes (trauma, suicide), followed by neoplasms and CVD.

The association between HDP and CVD mortality risk was the strongest (aHR, 1.57; 95% CI, 1.16–2.12, *P*=.04). Cancer mortality risk had the second strongest association with HDP (aHR, 1.37; 95% CI, 1.04–1.81, *P*=.026). When sex-specific analyses were performed (Figure 2), CVD mortality risk was significantly associated with HDP in male subjects (aHR, 1.92; 95% CI, 1.27–2.88, *P*=.002) but not in

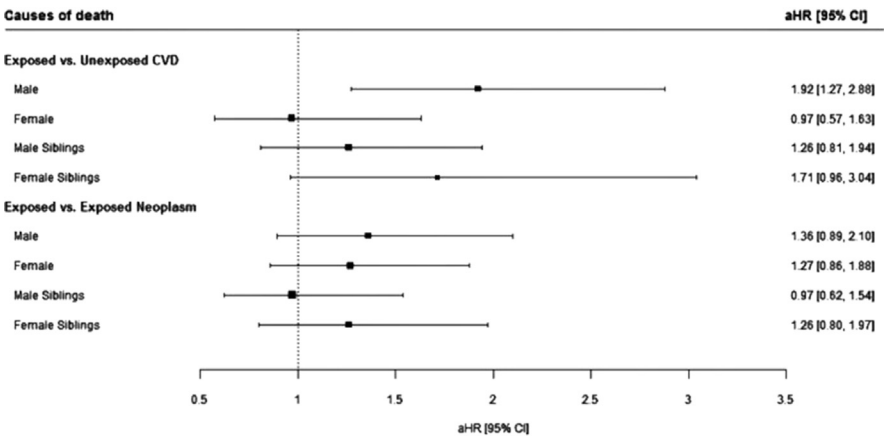
female subjects (aHR, 0.97; 95% CI, 0.57−1.63). The risk of cancer mortality was not significant in male subjects (aHR, 1.36; 95% CI, 0.89−2.10) or female subjects (aHR, 1.27; 95% CI, 0.86−1.88). An interaction between HDP and birth order on CVD mortality revealed a significant interaction (P=.047), suggesting that the effect of HDP on CVD mortality increased with higher birth order (Table 3).

Sibling analysis

For the sibling analysis, we also started with the 5929 exposed offspring who met our inclusion criteria within the UPDB. After we excluded those with missing data (1321), those who had died within the first year of life (366), and those who did not have at least one matching sibling (1083), we were left with 3159 exposed offspring. We matched these to their 7496 unexposed siblings (Figure 1). Exposed offspring were born from mothers with the following categories of hypertensive disease: 2763 preeclampsia, 227 gestational hypertension, 151 eclampsia, and 18 with suspected HDP. Descriptive statistics were compared between the exposed cohort and their unexposed siblings (Table 4). Compared with unexposed siblings, exposed offspring were significantly more likely to have lower birthweights, gestation age, preterm, birth order, and more likely to be part of a multifetal pregnancy.

Table 5 describes the counts and mortality risks by most common causes of death among exposed offspring and their unexposed siblings. A total of 330 (10.4%) exposed and 742 (9.9%) unexposed siblings had died by 2016. The most common causes of death in this population were external causes followed by neoplasms and CVD. Mortality from CVD risk had the strongest association with HDP; however, the association was not significant (1.39; 95% CI, 0.99−1.95). In the sex-specific analysis (Figure 2), the association with CVD mortality was not significant in either male (aHR, 1.26; 95% CI, 0.81−1.94) or female (aHR, 1.71; 95% CI, 0.96−3.04) subjects. Paired analysis comparing the exposed sibling to the closest sibling of the same sex within a 5-year age difference demonstrated no sex-specific differences in CVD mortality (male aHR, 2.58; 95% CI, 0.73−9.11; female aHR, 1.36; 95% CI, 0.47−3.94). Here as well, like in the general population, there was a significant interaction between HDP and birth order on CVD (P=.011) (Table 6).

FIGURE 2
Sex-specific analysis for CVD and neoplasm causes of death



The general population and siblings are shown.

aHR, adjusted hazard ratio; *CI*, confidence interval; *CVD*, cardiovascular disease.

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Discussion

Principal findings

We found that in utero exposure to HDP was significantly associated with excess mortality risk, particularly from cardiovascular causes. Although the trend was similar when comparing exposed offspring with their unexposed siblings, the association was not significant.

TABLE 3
CVD mortality risks of exposed vs unexposed with interaction between birth order and exposed/unexposed status; comparison with matching unexposed from general population

Model	Covariate	Est	SE	Z	*P* value	HR	LL	UL
1	Exposed vs unexposed	0.45	0.21	2.90	.004	1.57	1.16	2.12
	Birth order (centered)	0.03	0.18	0.20	.838	1.03	0.79	1.34
	Maternal parity	0.03	0.08	0.47	.638	1.03	0.91	1.16
2	Exposed vs unexposed	0.31	0.22	1.83	.067	1.36	0.98	1.88
	Birth order (centered)	−0.18	0.23	−0.94	.346	0.84	0.57	1.21
	Maternal parity	0.05	0.08	0.84	.400	1.05	0.94	1.18
	Exposed vs unexposed[a] birth order (centered)	0.32	0.20	1.99	.047	1.38	1.00	1.90

Likelihood ratio test: 2.69; P=.101.

CVD, cardiovascular disease; *HR*, hazard ratio; *LL*, xxx; *SE*, standard error; *UL*, xxx.

[a] Cox proportional hazard model was stratified by CaseID and clustered by MaPersonID.

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TABLE 4
Descriptive statistics for exposed offspring born in 1947–1967 and survived the first year and their unexposed siblings

	Exposed (N = 3159)	Unexposed (N = 7496)	*P* value
Sex			.062
Female	1512 (47.9%)	3738 (49.9%)	
Male	1647 (52.1%)	3758 (50.1%)	
Birthweight, g	3085.1 ± 640.5	3345.2 ± 530.5	<.001[a]
Small for gestational age			.780
No	2854 (90.3%)	6787 (90.5%)	
Yes	305 (9.7%)	709 (9.5%)	
Gestational age, wk	39.0 ± 2.0	39.6 ± 1.4	<.001[a]
Preterm			<.001[a]
No	2808 (88.9%)	7124 (95.0%)	
Yes	351 (11.1%)	372 (5.0%)	
Birth year	1957.3 ± 5.2	1957.7 ± 5.6	.001[a]
Birth order (continuous)	2.9 ± 2.1	3.3 ± 2.0	<.001[a]
Birth order (categorical)			<.001[a]
1	1087 (34.6%)	1058 (14.2%)	
2	545 (17.4%)	1825 (24.4%)	
3	457 (14.6%)	1648 (22.1%)	
4	425 (13.5%)	1218 (16.3%)	
5	277 (8.8%)	737 (9.9%)	
6	147 (4.7%)	442 (5.9%)	
7	92 (2.9%)	261 (3.5%)	
8	43 (1.4%)	128 (1.7%)	
9	27 (0.9%)	71 (1.0%)	
10	21 (0.7%)	33 (0.4%)	
11	6 (0.2%)	23 (0.3%)	
12	4 (0.1%)	9 (0.1%)	
13	4 (0.1%)	7 (0.1%)	
14	2 (0.1%)	5 (0.1%)	
15	2 (0.1%)	5 (0.1%)	

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Because the exposed and unexposed sample sizes were similar for both the general population and sibling analyses, the nonsignificant association between HDP exposure and offspring mortality risk among siblings suggests that genetic and lifestyle factors are powerful determinants of risk.

In the sex-specific subgroup analysis, the risk of CVD mortality remained significant in exposed vs unexposed male subjects in the general population but not among female subjects. Because the oldest individuals in our cohort were 69 years old and CVD presents later in women than men, it may be that we did not observe an increased risk of CVD mortality among women because our study period ended too soon to observe this increase in risk. In the sibling analysis, neither sex had significantly greater risk for CVD mortality when compared with their siblings of the same sex. There was a significant interaction between HDP and birth order in CVD mortality analysis, both in the general population as well as in the sibling analyses, suggesting that the association between HDP and CVD mortality was stronger with higher birth order.

In our initial analyses, cancer mortality was also more common in exposed offspring when compared with unexposed controls. However, this association became statistically insignificant in the sex-specific analysis and was not present in the sibling analyses.

Results of the study in the context of other observations

Our findings are consistent with those of previously published studies on the association between in utero exposure to HDP and cardiovascular morbidity.[9–26] These CVD risks can be identified early in life, as demonstrated by Fugelseth et al,[9] who showed an excess CVD incidence in exposed offspring at 5–8 years of age. Palmsten et al[11] were able to obtain 34–44 years of follow-up on children born during the US Collaborative Perinatal Project (1959–1966) and demonstrated those adult offspring of pregnancies complicated by pregnancy-related hypertension were more likely to have been prescribed antihypertensive medication. Kajantie et al[27] analyzed the Helsinki birth cohort (1934–1944) and demonstrated that preeclampsia (and severe preeclampsia in particular) was associated with increased risks for stroke and hypertension in the adult offspring 60–70 years after their birth. Barclay and Kolk[28] demonstrated, using the Swedish population register with a cohort of individuals born between 1938 and 1960, a positive and statistically significant relationship between birth order and mortality. These findings are consistent with ours. Although there is a body of published literature on the association between HDP exposure and offspring cardiovascular morbidity, our study addresses a knowledge gap regarding the association between HDP exposure and offspring mortality.

With regards to the association of HDP and cancer, one study analyzed the effect of preeclampsia and susceptibility to breast cancer in the offspring[29] and found it to be protective specifically due to lower levels of hematopoietic, endothelial, and putative breast stem cells in umbilical cord samples from preeclamptic mothers. Aagaard-Tillery et al,[30] also using the UPDB, showed preeclampsia significantly decreased the relative risk of cancer incidence in the mothers but not in the offspring. Few studies, to our knowledge, have looked at the association of HDP and cancer in offspring.

Pathophysiology

The pathophysiology underlying the association between fetal exposure to HDP and CVD is poorly understood, but recent studies have implicated DNA methylation as well as renin–angiotensin–aldosterone mRNA upregulation.[31,32] Julian et al[31] identified 6 differentially methylated regions, including 3 genes (SMOC2, *ARID1B*, and *CTRHC1*) predisposing offspring of HDP to vascular disease later in life. Xue et al[32] showed that maternal HDP causes an increase in blood pressure in adult male offspring that is associated with upregulation of microRNA expression of several renin–angiotensin–aldosterone systems in the brain. The study showed that male offspring of hypertensive mothers had an enhanced hypertensive response to systemic angiotensin II when compared with male offspring of normotensive mothers and female offspring of either normotensive or hypertensive mothers. These data suggest that maternal HDP induces a sex-specific sensitization of angiotensin II–induced hypertension and microRNA expression of the brain, increasing the risk for CVD. They also noted a protective effect of estrogen in female offspring.[32] These conclusions are consistent with our findings in the sex-specific analyses.

Strengths and limitations

Strengths of our study include the ability to follow a large population of offspring across their life course using the UPDB.

TABLE 4
Descriptive statistics for exposed offspring born in 1947–1967 and survived the first year and their unexposed siblings *(continued)*

	Exposed (N = 3159)	Unexposed (N = 7496)	*P* value
Multiplicity			<.001[a]
No	2875 (91.7%)	8667 (98.5%)	
Yes	260 (8.3%)	135 (1.5%)	
Mothers' age at birth	26.4 ± 6.8	26.5 ± 5.6	.411
Mothers' HDP status			<.001[a]
None	0 (0.0%)	7496 (100.0%)	
Eclampsia	151 (4.8%)	0 (0.0%)	
Gestational hypertension	227 (7.2%)	0 (0.0%)	
Preeclampsia	2763 (87.5%)	0 (0.0%)	
Questionable HDP	18 (0.6%)	0 (0.0%)	

HDP, hypertensive disease of pregnancy.

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An additional strength was the ability to perform a sibling analysis. This is the first such study to involve offspring who were born and lived in the United States, specifically Utah, and can thus control, at least in part, for society-specific cultural and dietary influences.

Limitations of our study include the retrospective design covering almost 70 years, with variation in definitions of exposures and outcomes over time, as well as secular trends within a given era, such as variation in causes of death related to socioeconomic conditions. We attempted to mitigate these issues by matching exposed and unexposed subjects on birth year. We included the entire population of eligible subjects to avoid sampling error. Another possible limitation is selection bias of fetal origins; the number of surviving exposed fetuses/infants could be significantly different from their unexposed counterparts. For this reason, there could be a

TABLE 5
Most common causes of death after the first year of life with comparison with unexposed siblings

Cause of deaths	Exposed N (%)	Unexposed N (%)	aHR[a] (95% CI)	*P* value
Total deaths	330 (10.4)	742 (9.9)	1.12 (0.97–1.28)	.117
Neoplasms	59 (1.9)	126 (1.7)	1.20 (0.87–1.65)	.257
Metabolic/nutrition	13 (0.4)	51 (0.7)	0.71 (0.38–1.32)	.274
Nervous	12 (0.4)	14 (0.2)	2.08 (0.88–4.92)	.096
Cardiovascular	53 (1.7)	98 (1.3)	1.39 (0.99–1.95)	.054
Respiratory	14 (0.4)	26 (0.3)	1.24 (0.60–2.57)	.553
Digestive	15 (0.5)	35 (0.5)	1.14 (0.59–2.19)	.700
External causes	81 (2.6)	205 (2.7)	0.97 (0.74–1.27)	.827

aHR, adjusted hazard ratio; *CI*, confidence interval.

[a] Models controlled for sex, maternal age at birth, and multiplicity and were clustered by MaPersonID.

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TABLE 6
CVD mortality risks of exposed vs unexposed with interaction between birth order and exposed/unexposed status; comparison with unexposed siblings

Model	Covariate	Est	SE	Z	*P* value	HR	LL	UL
1	Exposed vs unexposed	0.34	0.17	1.92	.055	1.41	0.99	1.99
	Male vs female	0.62	0.17	3.50	.000	1.86	1.31	2.64
	Birth order (centered)	0.05	0.07	0.61	.539	1.05	0.89	1.25
	Multiplicity	−0.39	0.51	−0.78	.437	0.68	0.25	1.81
2	Exposed vs unexposed	0.19	0.19	0.99	.323	1.20	0.83	1.74
	Male vs female	0.62	0.17	3.48	.001	1.86	1.31	2.63
	Birth order (centered)	−0.10	0.09	−0.90	.366	0.90	0.72	1.13
	Multiplicity	−0.41	0.51	−0.81	.420	0.67	0.25	1.79
	Exposed vs unexposed[a] birth order (centered)	0.35	0.13	2.54	.011	1.42	1.08	1.85

Likelihood ratio test: 7.138; *P*=.008.

CVD, cardiovascular disease; *HR*, hazard ratio; *LL*, xxx; *SE*, standard error; *UL*, xxx.

[a] Cox proportional hazard model was clustered by MaPersonID.

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selection/survival bias, and it should be acknowledged.

We acknowledge that the distribution of the different types of HDP seems unbalanced, especially the disproportion of cases of preeclampsia relative to gestational hypertension. This disproportion can be explained by the historical timing in which the terminology of gestational hypertension became more prevalent. A review of older obstetric and gynecology manuscripts[33] shows that gestational hypertension became a common diagnosis only in the late 1970s. Before that period, preeclampsia was the more common diagnosis. Because we grouped all types of HDP into a single exposure group, misclassification of individual HDP diagnoses would not affect our findings. Exposure to HDP cannot be confirmed by chart review in this population, so it is possible that misclassification between exposed and unexposed groups may have biased our results toward the null. Similarly, the accuracy of cause-specific mortality estimates depends on the accuracy of the cause of death reported on the death certificate.

Although we tried to adjust for potential confounders via matching and using a multivariate Cox proportional hazard regression model, residual confounding may be present in the form of genetic predisposition to certain chronic diseases and lifestyle influences, including exercise, diet, and exposure to medications, chemicals, or drugs. We attempted to address this issue with our sibling-based analysis. That being said, the sibling-based analysis addresses the confounding due to genetic predisposition and early childhood condition, not the lifestyle in adulthood.

Finally, while being representative of Utah residents, the UPDB consists of a predominantly Caucasian population with limited representation of minority populations. The prevalence of HDP in African-American and Hispanic populations is greater, and its impact on offspring morbidity and mortality could be more severe.

Conclusions and Clinical Implications

Our findings are relevant from a public health perspective. Male adults born from pregnancies complicated by HDP may be targeted by earlier screening for CVD and may benefit from interventions to improve long-term health outcomes. ■

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