Supplemental Appendix

Cardiovascular Risk Factors Mediate the Long-Term Maternal Risk Associated with Hypertensive Disorders of Pregnancy

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Hypertensive Disorders of Pregnancy

The secondary analysis, which examined HDP exposure across all lifetime pregnancies, included ever HDP and recurrent HDP using 3 categories (number of HDP pregnancies: 0 [ref], 1, 2+) and 6 categories (jointly based on HDP exposure in the first pregnancy and then in second or later pregnancies). The ever HDP and 3-category recurrent HDP exposure variables provide easily interpretable results that can be easily compared with the existing literature. The 6-category recurrent HDP exposure variable was based on a previous analysis that demonstrated variations in the risk of CVD-related mortality when jointly considering HDP status and parity (one lifetime pregnancy vs. two or more lifetime pregnancies) within the Medical Birth Registry of Norway (1). They also demonstrated a "one child mother" phenomenon in which women with one lifetime pregnancy exhibit elevated rates of CVD-related mortality when compared to women with two or more lifetime pregnancies whose first pregnancy was normotensive term. This increased rate of CVD-related death in Norway was observed across HDP and preterm delivery exposure groups; women whose one lifetime pregnancy was normotensive term had a 2-fold increased rate of CVD-related death (CI: 1.8-2.2) while this rate was 3.4- and 9.4-fold among women whose one lifetime pregnancy was preeclamptic term (CI: 2.6-4.6) and preeclamptic preterm (CI: 6.5-13.7), respectively. Given this, we additionally modeled lifetime HDP exposure using a 6-category exposure variable that classified participants based on HDP status in first pregnancy and HDP status in second or later pregnancies: 1) normotension in all pregnancies (reference), 2) normotension in first pregnancy, no additional pregnancies, 3) normotension in first pregnancy, HDP (preeclampsia or gestational hypertension) in at least one

later pregnancy, 4) HDP in first pregnancy, normotension in all subsequent pregnancies, 5) HDP in first pregnancy, no additional pregnancies, and 6) HDP in first pregnancy with recurrence in at least one later pregnancy.

Covariates: Validation of Nurse Participant Self-Report

Recalled weight at age 18 and self-reported current height correlated well with measured weight and height from physical examination records in a NHSII validation study (r=0.87 for weight; r=0.94 for height) (2). Self-reported diet and physical activity have also been shown to be reliable within this cohort and/or the original Nurses' Health Study cohort (NHS; 1976 enrollment) (3,4). Dietary assessment using a semiquantitative food frequency questionnaire provided valid estimates of intake when compared to either 7-day dietary records (7DDRs; r=0.63) or automated self-administered 24-hour recalls (ASA24s; r=0.62) among a subset of participants in the NHS and NHSII (4). Physical activity levels self-reported on the biennial questionnaire had correlations of 0.79 with recall and 0.62 with diary recordings in a validation among a representative sample of NHSII participants (3).

Supplemental Results: Sensitivity Analyses

When we considered only the definite CVD cases that were confirmed through medical record review (52% of cases; n=560) and excluded probable CVD cases, we found a slightly stronger hazard ratio for the overall relationship between HDP and CVD in our fully adjusted model (HR=1.7, CI: 1.4-2.2). As only incident CVD events during active NHSII follow-up (1989-2017) were confirmed, participants could not develop CVD before 1989 in order to be eligible for inclusion in this analysis. Therefore, for the 83% of NHSII participants whose first birth occurred

before NHSII enrollment in 1989, the time between age at first birth and 1989 was inherently "immortal" (5). Therefore, we conducted a sensitivity analysis excluding person-time contributed between first birth and 1989; hazard ratios for gestational hypertension, preeclampsia, and HDP with CVD were essentially unchanged and remained statistically significant. Inclusion in this analysis was also dependent on survival to 2009 (and return of the 2009 biennial questionnaire ascertaining lifetime pregnancy history), so we also conducted a sensitivity analysis with follow-up time from 2009 to 2017, among those free of CVD in 2009—an analysis that excluded 49% of CVD cases. With 551 CVD cases between 2009 and 2017, fully adjusted hazard ratios remained significant for HDP and CVD (HR=1.6, CI: 1.3-2.1) and became stronger among women with gestational hypertension in first pregnancy (HR=1.7, CI: 1.1-2.5). Although we were unable to include fatal CVD events prior to 2009 in this analysis, overall mortality remains low in the cohort and 98.2% of participants were alive in 2009. To examine the robustness of our findings when using an alternative method to handle missing covariate data, we conducted a sensitivity analysis using multiple imputation by chained equations. For this analysis, we generated five imputed datasets, separately analyzed each imputed dataset, and then combined the parameter estimates and corresponding standard errors across the five imputed datasets. Analyses using multiple imputation to handle missing data produced estimates comparable to those from the primary analysis. To test whether the observed associations could be explained by potential unmeasured confounding, we calculated E-values using the publicly available online E-value calculator (https://www.evalue-calculator.com/) (6,7). E-values for the observed point estimates ranged from 2.0 for HDP and stroke to 3.9 for preeclampsia and CHD (Supplemental Table 3).

References

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Supplemental Tables

Supplemental Table 1. Hypertensive disorders in first pregnancy and cardiovascular disease by years since first birth and age

CVD (CAD or Stroke)	Cases/Person-Years (PY)	Normotensive Pregnancy n=54,756 (90.7%)	Hypertensive Disorder in First Pregnancy n=5,623 (9.3%)		
			Model 1	Model 2	Excess Cases per 100,000 PY
Age					
20-29 years	0/227,300	1.00 (ref)	---	---	--
30-39 years	31/554,760	1.00 (ref)	2.12 (0.87, 5.16)	1.98 (0.80, 4.90)	7
40-49 years	228/601,361	1.00 (ref)	1.86 (1.30, 2.66)	1.71 (1.19, 2.46)	29
50-59 years	468/518,898	1.00 (ref)	1.55 (1.19, 2.03)	1.41 (1.07, 1.85)	44
60-69 years	342/166,787	1.00 (ref)	2.01 (1.49, 2.72)	1.81 (1.34, 2.46)	191
Years Since First Birth					
1-10 years	18/603,711	1.00 (ref)	---	---	-3
11-20 years	146/599,488	1.00 (ref)	1.73 (1.11, 2.71)	1.52 (0.96, 2.39)	19
21-30 years	357/531,356	1.00 (ref)	1.88 (1.41, 2.49)	1.68 (1.26, 2.24)	56
31-40 years	397/284,158	1.00 (ref)	1.87 (1.41, 2.49)	1.76 (1.32, 2.34)	111
41-50 years	153/53,376	1.00 (ref)	1.75 (1.08, 2.83)	1.62 (0.99, 2.63)	208

CAD: coronary artery disease; CVD: cardiovascular disease; PY: person-years. Hypertensive disorder in first pregnancy includes both gestational hypertension and preeclampsia. Hazard ratios and corresponding 95% confidence intervals are provided for Models 1 and 2. Excess cases (rate differences) were calculated by subtracting the incidence (cases/person-years) in the unexposed from the incidence in the exposed.

Model 1 is adjusted for age at first birth (years), age in 1989 (years), race/ethnicity (Black, Hispanic/Latina, Asian, White [ref], other/multi-race), and parental education (<9, 9-11, 12, 13-15, ≥16 years [ref]).

Model 2 is additionally adjusted for physical activity at ages 18-22 (never, 1-3 [ref], 4-6, 7-9, 10-12 mo/yr), pre-pregnancy smoking (never [ref], past, current), pre-pregnancy BMI (<18.5, 18.5-24.9 [ref], 25-29.9, ≥30 kg/m^2), pre-pregnancy alcohol consumption (none [ref], ≤1 drink/week, 2-6 drinks/week, ≥1 drink/day), pre-pregnancy Alternative Healthy Eating Index (AHEI) score (quintiles with the fifth quintile [ref] representing the healthiest diet category), pre-pregnancy oral contraceptive use (never [ref], <2, 2-<4, ≥4 years), pre-pregnancy hypercholesterolemia (no [ref], yes), and parental history of CHD and/or stroke before age 60 (CHD only for CHD model, stroke only for stroke model, CHD or stroke for CVD models; no [ref], yes)

--- Models between 20-29 years of age and 1-10 years after first birth do not converge due to few or no cases. All 18 events at 1-10 years since first birth were among women with normotensive first pregnancies (there were no CVD events among women with a hypertensive disorder in first pregnancy).

Supplemental Table 2. Sensitivity analyses of the relationship between hypertensive disorders in first pregnancy and cardiovascular disease

CVD (CAD or Stroke)	Hypertensive Disorder in First Pregnancy Status			
	Normotensive Pregnancy	**Gestational Hypertension**	**Preeclampsia**	**Hypertensive Disorders of Pregnancy**
Original Analysis (n=60,379)				
Cases/Person-Years	920/1,885,474	41/57,900	113/128,840	154/186,740
HR (95% CI)	1.00 (ref)	1.41 (1.03, 1.93)	1.72 (1.42, 2.10)	1.63 (1.37, 1.94)
Sensitivity Analyses				
Excluding probable CVD cases (restricted to definite CVD cases, n=59,813)				
Cases/Person-Years	473/1,869,479	24/57,279	58/127,134	82/184,413
HR (95% CI)	1.00 (ref)	1.62 (1.07, 2.45)	1.75 (1.33, 2.30)	1.71 (1.35, 2.17)
Excluding person-time contributed from first birth through NHSII enrollment in 1989 (restricted to observed follow-up 1989-2017, n=60,379)				
Cases/Person-Years	920/1,437,266	41/46,361	113/99,979	154/146,340
HR (95% CI)	1.00 (ref)	1.41 (1.03, 1.93)	1.71 (1.40, 2.08)	1.62 (1.36, 1.92)
Excluding person-time contributed before self-report of lifetime pregnancy history (restricted to 2009-2017 follow-up, n=59,606)				
Cases/Person-Years	472/376,806	24/12,182	55/26,082	79/38,264
HR (95% CI)	1.00 (ref)	1.66 (1.10, 2.51)	1.64 (1.24, 2.17)	1.64 (1.29, 2.09)
Using multiple imputation by chained equations to handle missing covariate data (n=60,379)				
Cases/Person-Years	920/1,885,474	41/57,900	113/128,840	154/186,740
HR (95% CI)	1.00 (ref)	1.40 (1.02, 1.92)	1.72 (1.41, 2.10)	1.62 (1.37, 1.93)

CAD: coronary artery disease; CI: confidence interval; CVD: cardiovascular disease; HR: hazard ratio. Models are adjusted for age at first birth (years), age in 1989 (years), race/ethnicity (Black, Hispanic/Latina, Asian, White [ref], other/multi-race), parental education (<9, 9-11, 12, 13-15, ≥16 years [ref]), physical activity at ages 18-22 (never, 1-3 [ref], 4-6, 7-9, 10-12 mo/yr), pre-pregnancy smoking (never [ref], past, current), pre-pregnancy BMI (<18.5, 18.5-24.9 [ref], 25-29.9, ≥30 kg/m^2), pre-pregnancy alcohol consumption (none [ref], ≤1 drink/week, 2-6 drinks/week, ≥1 drink/day), pre-pregnancy Alternative Healthy Eating Index (AHEI) score (quintiles with the fifth quintile [ref] representing the healthiest diet category), pre-pregnancy oral contraceptive use (never [ref], <2, 2-<4, ≥4 years), pre-pregnancy hypercholesterolemia (no [ref], yes), and parental history of CHD and/or stroke before age 60 (CHD only for CHD model, stroke only for stroke model, CHD or stroke for CVD models; no [ref], yes). For this analysis using multiple imputation, we generated five imputed datasets, separately analyzed each imputed dataset, and then combined the parameter estimates and corresponding standard errors across the five imputed datasets.

Supplemental Table 3. E-Values for the observed associations between hypertensive disorders in first pregnancy and cardiovascular disease*

	Hypertensive Disorder in First Pregnancy Status		
	Gestational Hypertension n=1,789 (3.0%)	**Preeclampsia** n=3,834 (6.4%)	**Hypertensive Disorders of Pregnancy** n=5,623 (9.3%)
CVD (CAD or Stroke)			
Observed association	1.41 (1.03, 1.93)	1.72 (1.42, 2.10)	1.63 (1.37, 1.94)
E-value (point estimate)	2.17	2.83	2.64
E-value (CI)	1.21	2.19	2.08
CAD			
Observed association	1.27 (0.80, 2.02)	2.21 (1.73, 2.84)	1.93 (1.54, 2.41)
E-value (point estimate)	--	3.85	3.27
E-value (CI)	--	2.85	2.45
Stroke			
Observed association	1.56 (1.01, 2.40)	1.21 (0.87, 1.68)	1.32 (1.00, 1.73)
E-value (point estimate)	2.49	--	1.97
E-value (CI)	1.11	--	1.00

CAD: coronary artery disease; CI: confidence interval; CVD: cardiovascular disease. Hazard ratios and corresponding 95% confidence intervals are provided for the observed association (also reported in Table 2, Model 2).

-- E-values were not calculated for hazard ratios that were not statistically significant; the hazard ratio for the association between stroke and hypertensive disorders of pregnancy was statistically significant (p=0.0467; 95% CI: 1.004, 1.726)

* The observed associations are the fully adjusted hazard ratios presented in Table 2 and are shown here for reference. E-values were calculated using the publicly available online calculator (www.evalue-calculator.com) based on a "hazard ratio (outcome prevalence <15%)." E-values for the point estimate and for the limit of the 95% CI closest to the null (i.e., the lower limit for the above CIs) represent the magnitude of the association that an unmeasured confounder would have to have with both the exposure (hypertensive disorders in first pregnancy) and the outcome (cardiovascular disease) above and beyond measured confounding to explain away the observed association and to render the observed association no longer statistically significant, respectively. Models are adjusted for age at first birth (years), age in 1989 (years), race/ethnicity (Black, Hispanic/Latina, Asian, White [ref], other/multi-race), parental education (<9, 9-11, 12, 13-15, ≥16 years [ref]), physical activity at ages 18-22 (never, 1-3 [ref], 4-6, 7-9, 10-12 mo/yr), pre-pregnancy smoking (never [ref], past, current), pre-pregnancy BMI (<18.5, 18.5-24.9 [ref], 25-29.9, ≥30 kg/m^2), pre-pregnancy alcohol consumption (none [ref], ≤1 drink/week, 2-6 drinks/week, ≥1 drink/day), pre-pregnancy Alternative Healthy Eating Index (AHEI) score (quintiles with the fifth quintile [ref] representing the healthiest diet category), pre-pregnancy oral contraceptive use (never [ref], <2, 2-<4, ≥4 years), pre-pregnancy hypercholesterolemia (no [ref], yes), and parental history of CHD and/or stroke before age 60 (CHD only for CHD model, stroke only for stroke model, CHD or stroke for CVD models; no [ref], yes).