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Long-Term Cardiovascular Risk in Women With Hypertension During Pregnancy

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ABSTRACT

BACKGROUND History of a hypertensive disorder of pregnancy (HDP) among women may be useful to refine atherosclerotic cardiovascular disease risk assessments. However, future risk of diverse cardiovascular conditions in asymptomatic middle-aged women with prior HDP remains unknown.

OBJECTIVES The purpose of this study was to examine the long-term incidence of diverse cardiovascular conditions among middle-aged women with and without prior HDP.

METHODS Women in the prospective, observational UK Biobank age 40 to 69 years who reported ≥1 live birth were included. Noninvasive arterial stiffness measurement was performed in a subset of women. Cox models were fitted to associate HDP with incident cardiovascular diseases. Causal mediation analyses estimated the contribution of conventional risk factors to observed associations.

RESULTS Of 220,024 women included, 2,808 (1.3%) had prior HDP. The mean age at baseline was 57.4 ± 7.8 years, and women were followed for median 7 years (interquartile range: 6.3 to 7.7 years). Women with HDP had elevated arterial stiffness indexes and greater prevalence of chronic hypertension compared with women without HDP. Overall, 7.0 versus 5.3 age-adjusted incident cardiovascular conditions occurred per 1,000 women-years for women with versus without prior HDP, respectively ($p = 0.001$). In analysis of time-to-first incident cardiovascular diagnosis, prior HDP was associated with a hazard ratio (HR) of 1.3 (95% CI: 1.04 to 1.60; $p = 0.02$). HDP was associated with greater incidence of CAD (HR: 1.8; 95% CI: 1.3 to 2.6; $p < 0.001$), heart failure (HR: 1.7; 95% CI: 1.04 to 2.60; $p = 0.03$), aortic stenosis (HR: 2.9; 95% CI: 1.5 to 5.4; $p < 0.001$), and mitral regurgitation (HR: 5.0; 95% CI: 1.5 to 17.1; $p = 0.01$). In causal mediation analyses, chronic hypertension explained 64% of HDP's association with CAD and 49% of HDP's association with heart failure.

CONCLUSIONS Hypertensive disorders of pregnancy are associated with accelerated cardiovascular aging and more diverse cardiovascular conditions than previously appreciated, including valvular heart disease. Cardiovascular risk after HDP is largely but incompletely mediated by development of chronic hypertension. (J Am Coll Cardiol 2019;■:■–■)
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ABBREVIATIONS AND ACRONYMS

ASCVD = atherosclerotic cardiovascular disease

ASI = arterial stiffness index

BMI = body mass index

CAD = coronary artery disease

HDP = hypertensive disorder(s) of pregnancy

HELLP = hemolysis, elevated liver enzymes, low platelet count

Complications arising in pregnancy, including hypertensive disorders of pregnancy (HDP) (i.e., gestational hypertension; preeclampsia; eclampsia; and hemolysis, elevated liver enzymes, low platelet count [HELLP] syndrome) (1–3), preterm delivery (4), and gestational diabetes (5), predict elevated future risk of cardiovascular disease among affected women. Incidence of gestational hypertension and preeclampsia is rising in the United States, and >10% of women will experience at least 1 hypertensive pregnancy (6,7). Prior studies suggest that HDP portends a 2-fold risk of future atherosclerotic cardiovascular disease (ASCVD), such as myocardial infarction and stroke (1,8). This understanding is reflected in the 2018 American College of Cardiology/American Heart Association cholesterol guidelines, which endorse using a history of preeclampsia to strengthen statin prescription recommendations among asymptomatic middle-aged women with intermediate 10-year ASCVD risk by conventional risk calculation (9).

However, unanswered questions about the links between HDP and cardiovascular risk remain. First, the degree to which HDP-associated cardiovascular disease risk persists into midlife and beyond is unclear, due in part to incomplete phenotyping and relatively short durations of follow-up in most studies performed to date (1,10–14), with very few studies following women into age 60 and 70 years (15,16), and with attenuated effects observed in studies with longer-term follow-up (15,17). Absolute risk for cardiovascular disease still remains low for a number of years after pregnancy due to young age. However, the long-term risks of diverse cardiovascular diseases among women in midlife who previously experienced HDP, the group now considered in prevention guidelines, remain largely unknown. Second, the risk of nonatherosclerotic cardiovascular diseases in women with HDP is currently unclear. Although prior studies reported increased risks of incident heart failure (1,18), atrial fibrillation (19), and venous thromboembolism (3), associations have been inconsistent after adjustments for comorbidities and over the longer term (15,17).

Here, we examined the incidence of diverse cardiovascular conditions among parous women with and without prior hypertensive disorders of pregnancy in the UK Biobank.

METHODS

STUDY COHORT. The UK Biobank is a prospective, observational, population-based cohort study that recruited >500,000 adult residents in the United Kingdom between 2006 and 2010 (20,21). The baseline study visit included health and sociodemographic questionnaires, physical assessment (e.g., blood pressure, anthropometrics), and phlebotomy, as well as additional noninvasive phenotyping in subsets of individuals. Methods for follow-up were previously described (20); briefly, incident disease diagnoses were gleaned from linkage of study records to national hospital inpatient and outpatient records, death registrations, and primary care diagnoses.

We included women who were age 40 to 69 years and reported ≥1 prior live birth at the baseline study

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visit. Given prior associations between some types of congenital heart disease and HDP (22) as well as multiple outcomes of interest, we excluded women with congenital heart disease (Online Appendix 1 for relevant diagnosis codes).

ARTERIAL STIFFNESS INDEX. Arterial stiffness index (ASI) is a noninvasive marker of vascular aging and an independent indicator of cardiovascular risk (23). Approximately 170,000 UK Biobank participants had finger photoplethysmography-derived ASI measured with the PulseTrace PCA2 (CareFusion, San Diego, California) at baseline (24). ASI is calculated by dividing standing height by the time between the initial systolic peak and reflected wave, and expressed as meters per second. Extreme ASI outliers were excluded as before to remove spurious values (25).

EXPOSURE, COMORBIDITIES, AND OUTCOMES. Women's reproductive history, including parity and menopausal status, was obtained at the baseline study visit. A diagnosis of HDP (i.e., gestational hypertension, preeclampsia, eclampsia, or HELLP syndrome) was ascertained by qualifying International Classification of Diseases (ICD) code or self-report at enrollment (Online Appendix 1). Prevalent comorbidities, including prevalent cardiovascular conditions, were captured from ICD codes and/or self-report at the first study visit. Because the cardiovascular conditions under study are not independent, the primary outcome was a composite of incident CAD, heart failure, aortic stenosis, mitral regurgitation, atrial fibrillation or flutter, ischemic stroke, peripheral artery disease, and venous thromboembolism. Individual diagnoses included in the composite primary outcome constituted secondary outcomes. Only new cardiovascular disease diagnoses from a qualifying ICD code (Online Appendix 2) were counted as incident diagnoses (e.g., recurrent myocardial infarction in a participant with prevalent CAD at enrollment did not count as an incident event).

STATISTICAL ANALYSIS. Baseline continuous variables were compared between women with and without HDP using the Student's *t*-test and categorical variables using either the Pearson chi-square test or Fisher exact test as appropriate. Odds ratios for prevalent comorbidities and cardiovascular conditions among women with HDP were calculated using multivariable logistic regression models, adjusted for age at enrollment and race. Multivariable linear regression models were used to compare ASI between groups. Age was incorporated as a quadratic term in ASI models to account for nonlinear effects.

To calculate overall age-adjusted incidence rates, the age-specific incidence of cardiovascular disease for each age group was calculated (in 5-year age bins) and then weighted for the proportion of the U.K. population belonging to each age group. Cox proportional hazard models estimated the association between HDP and first incident cardiovascular disease diagnosis, as well as between HDP and each of the 8 individual cardiovascular outcomes studied. Primary models were sparsely adjusted for age at enrollment and race. Secondary Cox models further adjusted for prevalent chronic hypertension to assess effects independent of hypertension, and additional models were stratified by age at enrollment. Women were excluded from each model for which they had a corresponding prevalent disease diagnosis (e.g., women with prevalent CAD were excluded from the models for incident CAD, and so on) (Online Appendix 3). For each participant, follow-up began at enrollment and was measured separately for each cardiovascular diagnosis. Time-to-censoring for each outcome was determined by the date a diagnosis newly appeared in the medical record or last encounter with the health care system. The proportional hazards assumption was tested with Schoenfeld residuals.

We performed causal mediation analysis to evaluate the proportional contribution of prevalent hypertension, hyperlipidemia, and diabetes mellitus to the association between HDP and cardiovascular disease risk using the "mediation" package in R (R Foundation for Statistical Computing, Vienna, Austria) (26). Briefly, causal mediation analysis attempts to estimate the proportional direct and indirect effects of an exposure-outcome relationship through mediators of the total exposure-outcome relationship (27). Each mediator model was adjusted for age, race, body mass index (BMI), ever-smoking, and the prevalent hypertension, hyperlipidemia, and diabetes mellitus statuses not under consideration. Each incident cardiovascular outcome model was adjusted for age, race, BMI, ever-smoking, and prevalent hypertension, hyperlipidemia, and diabetes mellitus. Each mediation analysis model was run using 100 simulations with a quasi-Bayesian approach to estimate variance. Mediation effects were bounded at 0 and 1.

Two-sided p values less than $\alpha = 0.05$ were considered statistically significant. All analyses were performed using R version 3.5 (R Foundation for Statistical Computing).

TABLE 1 Baseline Characteristics of the Study Cohort

	Overall Cohort (N = 220,024)	Women With Prior Hypertensive Disorder of Pregnancy (n = 2,808)	Women Without Prior Hypertensive Disorder of Pregnancy (n = 217,216)	p Value
Age, yrs	57.4 ± 7.8	52.3 ± 8.7	57.4 ± 7.8	<0.001
Caucasian, %	207,517 (94.3)	2,623 (93.4)	204,894 (94.3)	0.06
Number of live births at baseline	2.2 ± 0.9	2.16 ± 0.9	2.24 ± 0.9	<0.001
Age at first live birth, yrs	25.9 ± 5.1	28.7 ± 6.2	25.9 ± 5.1	<0.001
Time from first birth to baseline study visit, yrs	31.4 ± 10.2	23.7 ± 12.4	31.5 ± 10.1	<0.001
Mean age at menopause, yrs	49.8 ± 5.1	49.4 ± 5.3	49.8 ± 5.1	0.02
Menopause age <40 yrs, %	5,110 (2.3)	45 (1.6)	5,065 (2.3)	0.61
Body mass index, kg/m^2	27.2 ± 5.1	28.1 ± 5.6	27.1 ± 5.1	<0.001
Systolic blood pressure, mm Hg	137.7 ± 20.4	141.6 ± 20.4	137.7 ± 20.3	<0.001
Diastolic blood pressure, mm Hg	80.7 ± 10.5	84.7 ± 10.7	80.7 ± 10.5	<0.001
Hypertension, %	56,987 (25.9)	1,889 (67.3)	55,098 (25.4)	<0.001
Hyperlipidemia, %	24,828 (11.3)	305 (10.9)	24,523 (11.3)	0.49
Diabetes mellitus, %	9,005 (4.1)	177 (6.3)	8,828 (4.1)	<0.001
Ever smoking, %	89,327 (40.6)	928 (33.0)	88,399 (40.7)	<0.001
Chronic kidney disease, %	446 (0.2)	19 (0.7)	427 (0.2)	<0.001
Medication use at baseline				
Aspirin	21,863 (9.9)	246 (8.8)	21,617 (10.0)	0.04
Antihypertensive medication	40,084 (18.2)	628 (22.4)	39,456 (18.2)	<0.001
Cholesterol-lowering medication	29,042 (13.2)	336 (12.0)	28,706 (13.2)	0.06

Values are mean ± SD or n (%). The p values reflect comparison between women with and without prior hypertensive disorder of pregnancy.

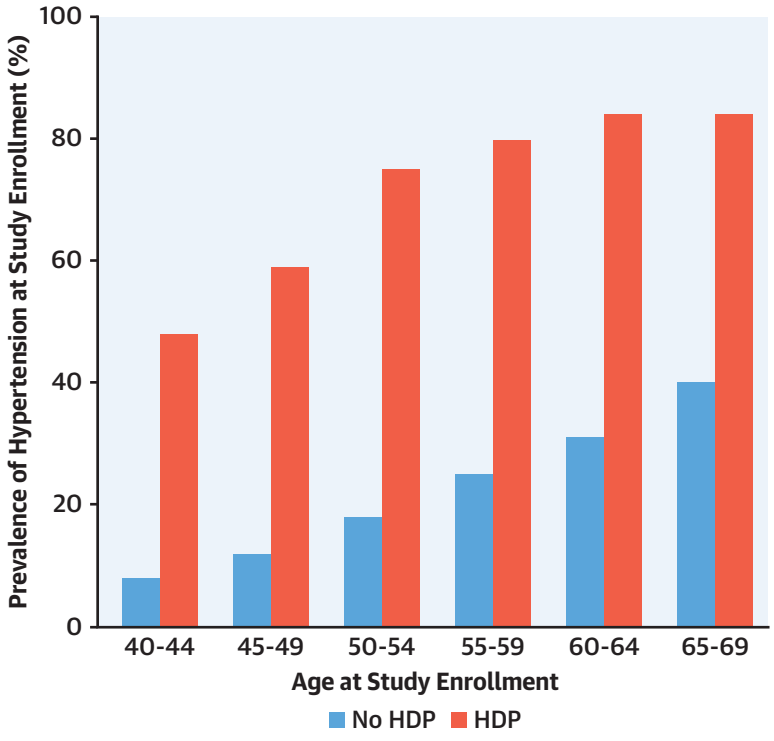
RESULTS

DESCRIPTION OF STUDY COHORT. After exclusions (Online Figure 1), the study cohort consisted of 220,024 women who were followed for a median 7 years (interquartile range: 6.3 to 7.7 years, overall range: 0 to 10 years). Distribution of follow-up time is shown in Online Figure 2. Mean (± SD) age at study enrollment was 57.4 ± 7.8 years, corresponding to mean duration since first birth of 31.4 ± 10.2 years, and 94.3% of the cohort was white (**Table 1**). Of the total cohort, 2,808 women (1.3%) had prior HDP. Women with prior HDP were younger at study enrollment (mean age 52.3 ± 8.7 years vs. 57.4 ± 7.8 years; $p < 0.001$) and older at first birth (28.7 ± 6.2 years vs. 25.9 ± 5.1 years; $p < 0.001$) (**Table 1**). Prevalence of ever-smoking was lower in women with prior HDP than in those without (33.0% vs. 40.7%; $p < 0.001$). Although women with prior HDP were more likely to be taking antihypertensive medications at enrollment (22.4% vs. 18.2%; $p < 0.001$), their blood pressures were higher at enrollment compared with women without prior HDP (systolic blood pressure 141.6 mm Hg vs. 137.7 mm Hg; $p < 0.001$, and diastolic blood pressure 84.7 mm Hg vs. 80.7 mm Hg; $p < 0.001$). Of women with prior HDP and chronic hypertension, 32.8% were taking antihypertensive medication at enrollment.

PREVALENT COMORBIDITIES AND CARDIOVASCULAR DIAGNOSES. Women with prior HDP had a higher unadjusted prevalence of chronic hypertension than women without HDP (67.3% vs. 25.4%; $p < 0.001$) (**Figure 1**). After adjustment for age and use of antihypertensive medication, women with prior HDP had higher systolic blood pressure by 9.0 mm Hg (95% CI: 8.3 to 9.8 mm Hg; $p < 0.001$) and higher diastolic blood pressure by 4.6 mm Hg (95% CI: 4.2 to 5.0 mm Hg; $p < 0.001$). After adjustment for age at enrollment and race, women with prior HDP were more likely to have prevalent hypertension (odds ratio [OR]: 11.6; 95% CI: 10.6 to 12.7; $p < 0.001$), as well as prevalent diagnoses of hyperlipidemia, diabetes mellitus, and chronic kidney disease (Online Table 1). Women with prior HDP had higher likelihood of prevalent CAD (OR: 1.6; 95% CI: 1.1 to 2.2; $p = 0.008$), heart failure (OR: 2.4; 95% CI: 1.3 to 4.2; $p = 0.002$), and venous thromboembolism (OR: 1.5; 95% CI: 1.2 to 1.9; $p < 0.001$) (Online Table 1).

ARTERIAL STIFFNESS INDEX. After exclusion of extreme outliers ($n = 30$), finger photoplethysmography-derived ASI data were available for 81,557 women in our cohort, including 1,191 with prior HDP (42.4% of women with HDP and 37.0% without HDP). Characteristics of the subgroup undergoing ASI measurement were similar to those of the rest of the cohort, including age at enrollment (57.5 years vs.

FIGURE 1 Prevalence of Chronic Hypertension By Age at Study Enrollment Among Women With and Without Prior HDP in the UK Biobank



Women with prior HDP had increased prevalence of chronic hypertension across age groups. HDP = hypertensive disorder of pregnancy.

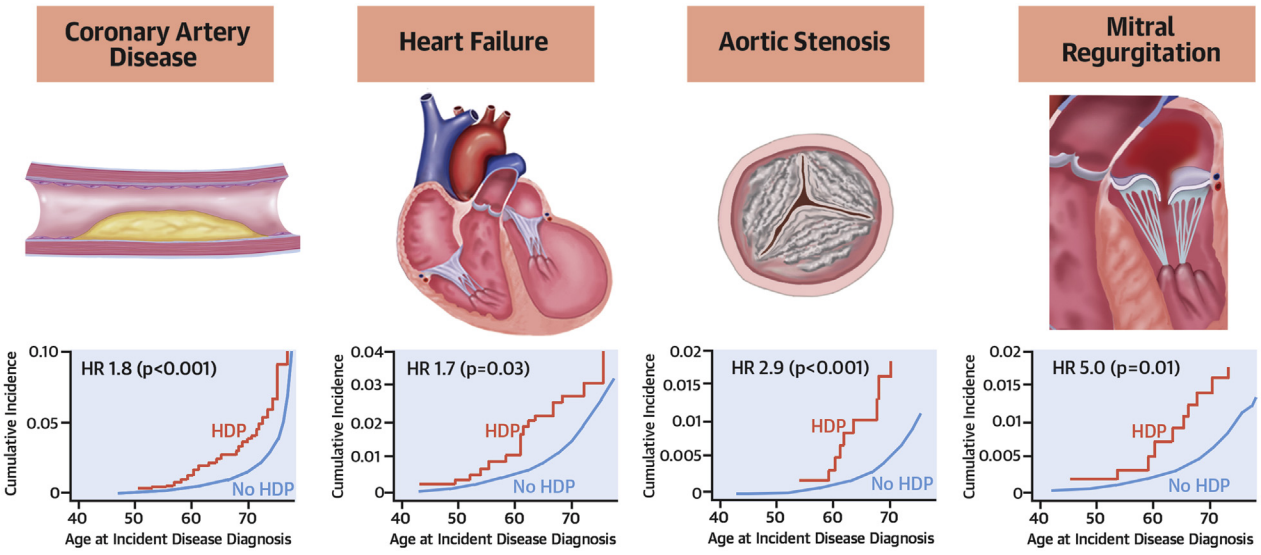
57.3 years), time since first birth (31.4 years vs. 31.6 years), and prevalence of chronic hypertension (25.6% vs. 26.1%).

Prior HDP was associated with higher ASI by 0.32 m/s (95% CI: 0.13 to 0.51 m/s; $p = 0.001$) after adjustment for age at enrollment and menopausal status. This association persisted after additionally adjusting for diabetes, ever-smoking, and BMI (+0.28 m/s; 95% CI: 0.09 to 0.47 m/s; $p = 0.004$). After further adjustment for prevalent hypertension, the association between HDP and ASI was no longer statistically significant (+0.18 m/s; 95% CI: −0.01 to 0.80 m/s; $p = 0.07$). In age-adjusted models stratified by menopausal status (28), prior HDP was associated with higher ASI among premenopausal women by 0.42 m/s (95% CI: 0.21 to 0.63 m/s; $p < 0.001$) and no significant association among postmenopausal women (+0.20 m/s; 95% CI: −0.09 to 0.49 m/s; $p = 0.18$) (**Central Illustration**). The estimated effect difference between premenopausal and postmenopausal women did not reach statistical significance in formal interaction testing (p for interaction = 0.26).

INCIDENT CARDIOVASCULAR DISEASE DIAGNOSES. Overall, 7.0 versus 5.3 total age-adjusted incident cardiovascular disease diagnoses occurred per 1,000 woman-years of follow-up in women with and without prior HDP, respectively ($p = 0.001$) (**Figure 2**), with persistent differences observed among women into their early 60s. In analysis of time-to-first incident cardiovascular diagnosis, prior HDP was associated with an HR of 1.3 (95% CI: 1.04 to 1.60; $p = 0.02$). Counts of unadjusted prevalent and incident disease diagnoses are summarized in Online Table 2. Notably, among women with prior HDP, 85% of incident cardiovascular diagnoses occurred in women also with prevalent chronic hypertension.

The proportional hazards assumption was met for all incident disease models except for mitral regurgitation; for mitral regurgitation, an interaction term between HDP and follow-up time was added to satisfy the proportional hazards assumption. **Figure 3** summarizes the hazards of individual incident cardiovascular diagnoses associated with prior HDP. After adjustment for age at enrollment and race, significant associations were observed between prior HDP and

CENTRAL ILLUSTRATION **Hypertensive Disorders of Pregnancy Are Associated With Long-Term Risk of Diverse Cardiovascular Diseases**



Honigberg, M.C. et al. J Am Coll Cardiol. 2019;■(■):■-■.

Hypertensive pregnancy was associated with long-term risk of incident coronary artery disease, heart failure, aortic stenosis, and mitral regurgitation. The cumulative incidence plots on the **bottom** reflect incident cardiovascular disease diagnoses among women without each prevalent condition plotted against participant age on the x-axis. The hazard ratios displayed reflect results of the primary survival (Cox proportional hazards) analysis, which were adjusted for age at study enrollment and race.

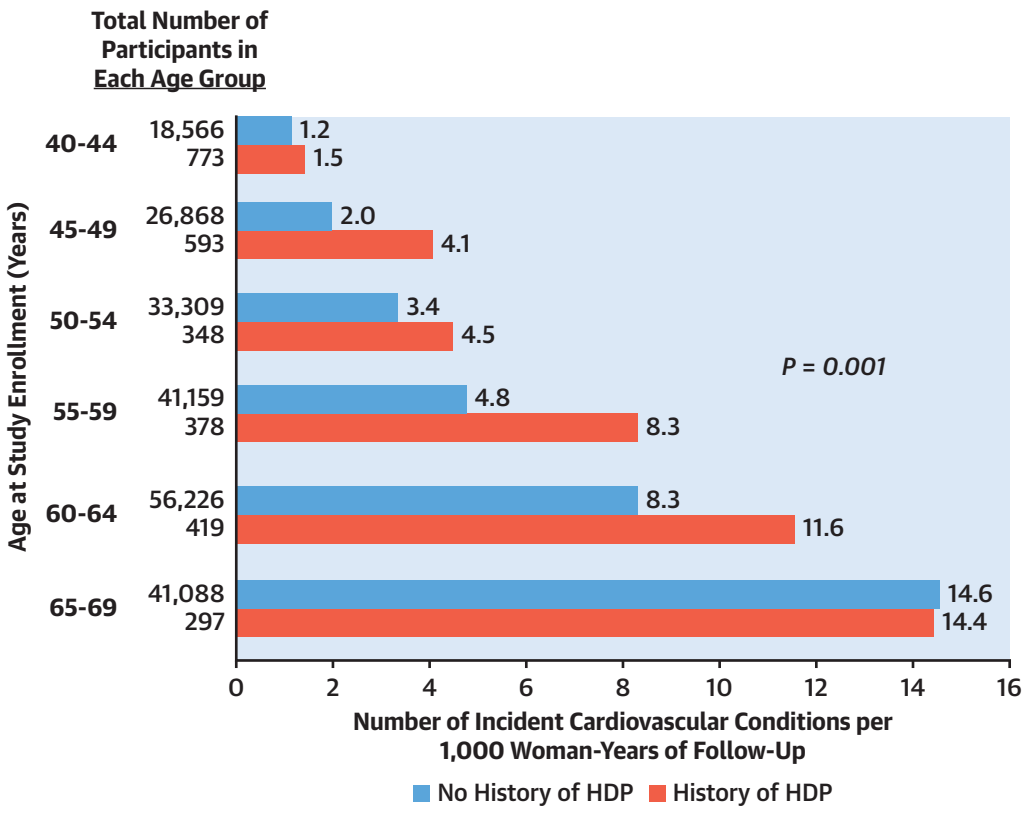
incident CAD (HR: 1.8; 95% CI: 1.3 to 2.6; $p < 0.001$), heart failure (HR: 1.7; 95% CI: 1.04 to 2.60; $p = 0.03$), aortic stenosis (HR: 2.9; 95% CI: 1.5 to 5.4; $p < 0.001$), and mitral regurgitation (HR: 5.0; 95% CI: 1.5 to 17.1; $p = 0.01$) (**Central Illustration**), but not with incident atrial fibrillation or flutter, ischemic stroke, peripheral artery disease, or venous thromboembolism. Online Figure 3 displays cumulative incidence of CAD, heart failure, aortic stenosis, and mitral regurgitation plotted against time from study enrollment, not adjusted for participant age at enrollment. In models stratified by age at study enrollment, risk of incident cardiovascular diseases persisted among women with prior HDP into their 60s, except for heart failure (Online Table 3). Associations between HDP and each incident cardiovascular diagnosis attenuated after incorporating prevalent hypertension into the models (Online Table 4).

In a secondary model for incident heart failure incorporating aortic stenosis and mitral regurgitation as covariates, the estimated effect of HDP was unchanged from the primary model (HR: 1.8; 95% CI: 1.1 to 2.9; $p = 0.02$). In exploratory analyses, HDP appeared to contribute additively with CAD for incident heart failure risk (Online Table 5).

In sensitivity analyses excluding 12,121 women in the cohort with any prevalent cardiovascular disease diagnosis, we still observed significant associations between HDP and incident CAD (HR: 1.7; 95% CI: 1.1 to 2.5; $p = 0.01$), aortic stenosis (HR: 2.2; 95% CI: 1.0 to 5.0; $p = 0.04$), and mitral regurgitation (HR: 2.2; 95% CI: 1.1 to 4.4; $p = 0.03$). In sensitivity analyses excluding 2,628 women with prevalent CAD, we observed similar results to the primary analysis with significant hazards of incident heart failure (HR: 1.7; 95% CI: 1.01 to 2.70; $p = 0.04$), aortic stenosis (HR: 2.9; 95% CI: 1.5 to 3.6; $p = 0.002$), and mitral regurgitation (HR: 2.0; 95% CI: 1.04 to 3.90; $p = 0.04$). Finally, in sensitivity analyses excluding 3,943 women with any prevalent ASCVD (CAD, ischemic stroke, or peripheral artery disease), results were again unchanged (for CAD, HR: 1.8; 95% CI: 1.3 to 2.6; $p = 0.001$; for heart failure, HR: 1.7; 95% CI: 1.1 to 2.6; $p = 0.03$; for aortic stenosis, HR: 2.6; 95% CI: 1.3 to 5.3; $p = 0.007$; for mitral regurgitation, HR: 2.1; 95% CI: 1.1 to 4.0; $p = 0.03$).

In sensitivity analyses excluding women with prevalent or incident heart failure to evaluate possible reverse causation bias, associations among HDP and CAD, aortic stenosis, and mitral

FIGURE 2 Age-Specific Unadjusted Rates of Incident Cardiovascular Diagnoses Per 1,000 Woman-Years of Follow-Up in Women With and Without Prior HDP in the UK Biobank



Women with prior HDP had increased incidence of cardiovascular diagnoses into their 60s. Incident cardiovascular disease diagnoses included coronary artery disease, heart failure, aortic stenosis, mitral regurgitation, atrial fibrillation or flutter, ischemic stroke, peripheral artery disease, and venous thromboembolism. HDP = hypertensive disorder of pregnancy.

regurgitation remained unchanged (Online Table 6). Results were additionally unchanged after excluding women with <1 year of follow-up (Online Table 7) and those with prevalent cancer (Online Table 8).

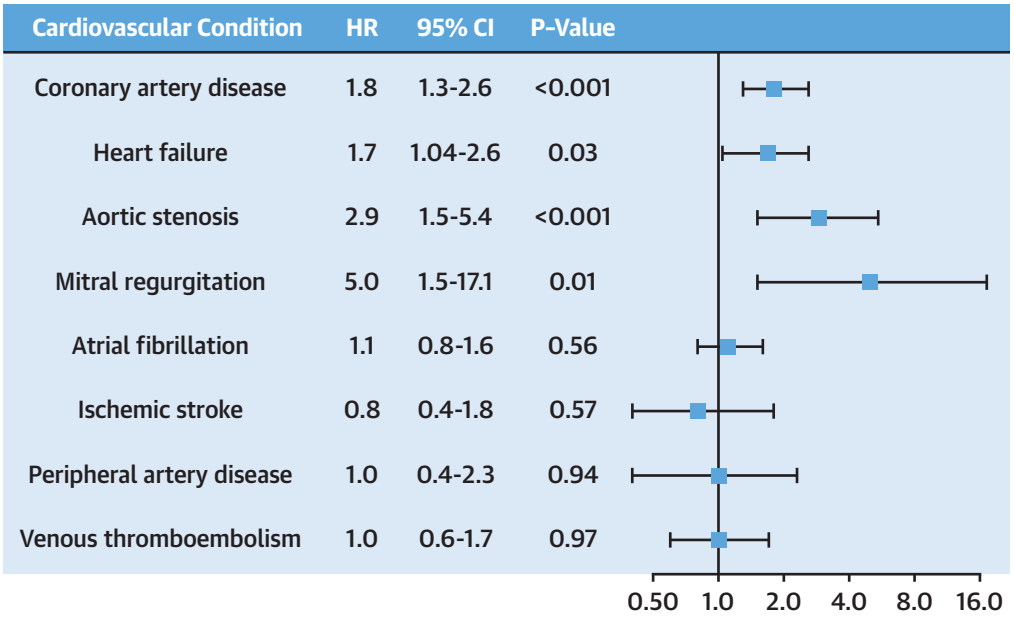
MEDIATION ANALYSIS. We performed causal mediation analysis to investigate the proportional contribution of chronic hypertension, hyperlipidemia, and diabetes mellitus to the risk of incident cardiovascular diagnoses associated with HDP, adjusting for other conventional ASCVD risk factors (age, race, BMI at study enrollment, and ever-smoking, in addition to hypertension, hyperlipidemia, and diabetes mellitus). Mediation analyses (**Table 2**) suggested that chronic hypertension accounted for 64% of the association between HDP and incident CAD (95% CI: 36% to 100%; $p < 0.001$) and 49% of HDP's association with incident heart failure (95% CI: 27% to 100%; $p = 0.02$). There were no significant mediation effects observed for prevalent hyperlipidemia or diabetes mellitus.

DISCUSSION

In a large, prospective, population-based cohort of middle-aged women, including 2,808 women with HDP, we found that prior HDP was associated with a range of cardiovascular conditions later in life. Specifically, HDP was associated with greater risk of incident CAD, heart failure, aortic stenosis, and mitral regurgitation. We also observed that HDP history was associated with persistently increased arterial stiffness. Furthermore, increased prevalence of hypertension among women with HDP largely, but incompletely, mediated the relationship between HDP and long-term cardiovascular risk.

Several findings are notable with respect to the development of cardiovascular disease in women

FIGURE 3 Hazard Ratios for Incident Cardiovascular Diagnoses in Women With Prior Hypertensive Disorders of Pregnancy in the UK Biobank



Women with prior hypertensive pregnancy had increased hazards of coronary artery disease, heart failure, aortic stenosis, and mitral regurgitation. Cox proportional hazards models begin follow-up at study enrollment and are adjusted for age at enrollment and race. The x-axis is presented in log scale. CI = confidence interval; HR = hazard ratio.

with a history of hypertensive pregnancy complications. First, the findings of increased arterial stiffness decades after pregnancy and increased risk of both vascular and nonvascular (e.g., valvular) pathology suggest that HDP are associated with a syndrome of accelerated cardiovascular aging. This hypothesis aligns with a prior study that found greater prevalence of subclinical atherosclerosis among women age 45 to 55 years with prior preeclampsia compared to a reference population (29). Women with HDP have greater endothelial dysfunction and arterial stiffness during pregnancy and the postpartum period (30), but prior work suggested that differences in affected women attenuate with time after pregnancy (23,31). Persistent differences in arterial stiffness beyond 10 years postpartum have not previously been

TABLE 2 Causal Mediation Analysis to Assess Mediation Effect of Prevalent Chronic Hypertension, Hyperlipidemia, and Diabetes Mellitus for Observed Associations Between HDP and Incident Cardiovascular Disease Risk

	Hypertension		Hyperlipidemia		Diabetes Mellitus	
	Proportion of Association With HDP Mediated by Hypertension (95% CI)	p Value	Proportion of Association With HDP Mediated by Hyperlipidemia (95% CI)	p Value	Proportion of Association With HDP Mediated by Diabetes Mellitus (95% CI)	p Value
Coronary artery disease	0.64 (0.36-1.00)	<0.001	0 (0.00-0.44)	0.60	0 (0.00-0.05)	0.50
Heart failure	0.49 (0.27-1.00)	0.02	0 (0.00-0.10)	0.26	0 (0.00-0.01)	0.32
Aortic stenosis	0.43 (0.00-1.00)	0.20	0 (0.00-0.18)	0.44	0 (0.00-0.01)	0.50
Mitral regurgitation	0.47 (0.00-1.00)	0.26	0 (0.00-0.06)	0.64	0 (0.00-0.01)	0.88

These analyses test the extent to which conventional cardiovascular risk factors mediate the associations of HDP with coronary artery disease, heart failure, aortic stenosis, and mitral regurgitation. For example, a mediation effect of 0 would indicate that a risk factor does not mediate the association with HDP, and a mediation effect of 1 would indicate that a risk factor mediates all of the association with HDP. The range of possible mediation effect is 0 to 1. The p value in this analysis reflects whether the proportion of the association with HDP mediated by each risk factor (hypertension, hyperlipidemia, and diabetes mellitus) is 0% (the null hypothesis) vs. not 0%. Each mediator model incorporated age, race, body mass index at study enrollment, ever-smoking, and the prevalent hypertension, hyperlipidemia, and diabetes mellitus statuses not under consideration. Each outcome model incorporated age, race, body mass index at study enrollment, ever-smoking, and prevalent hypertension, hyperlipidemia, and diabetes mellitus.

CI = confidence interval; HDP = hypertensive disorder of pregnancy.

demonstrated (32). Here, we observe a persistent association between HDP and elevated ASI >2 decades after first birth.

Second, our findings suggest that HDP may be associated with different cardiovascular conditions in the short term and long term following pregnancy. Most prior studies of cardiovascular risk after HDP began follow-up at the time of pregnancy and/or have had short durations of follow-up (1,10), and few studies have followed women into middle-age and beyond (15,16,33). Our study is unique in beginning prospective follow-up in women at midlife, which is the scenario specifically considered in the latest American College of Cardiology/American Heart Association cholesterol and prevention guidelines when using HDP history to support statin initiation. Prior work consistently showed a larger relative risk of cardiovascular disease closer to the time of pregnancy in women with HDP compared with unaffected women, but still with low absolute risk in these young women. Whether the increased risk of cardiovascular disease associated with HDP persists long-term, particularly as general cardiovascular disease risk increases in midlife, has been unclear (10). Our findings suggest that women with prior HDP face increased early risk of CAD and heart failure and retain increased risk for incident CAD and heart failure into midlife. Conversely, we observed an increased risk of prevalent, but not incident, venous thromboembolism in women with prior HDP, suggesting that the previously observed heightened risk (3) may not persist long-term. Meanwhile, we observed increased risk of premature valvular disease in the form of aortic stenosis and mitral regurgitation, associations that have not been previously described. Of note, sFlt-1, a circulating antiangiogenic protein implicated in the pathogenesis of preeclampsia (34), was recently found to have a strong association with calcific aortic stenosis in the general population (35). Additionally, a recent Mendelian randomization analysis found that genetically associated elevation in systolic blood pressure was associated with incident aortic stenosis, aortic regurgitation, and mitral regurgitation, further supporting the plausibility of our observed associations between HDP and valvular heart disease (36). Although hazards for aortic stenosis and mitral regurgitation among women with prior HDP were significant, absolute risks of both conditions remained low given lower incidence rates of valvular heart disease.

Importantly, cardiovascular disease risk after HDP is largely, but incompletely, mediated by the development of chronic hypertension. Elevated arterial stiffness may be a strong precursor to the development of hypertension (25), and accelerated arterial stiffening may underlie the greater prevalence of chronic hypertension that we observed among women with prior HDP; this elevated prevalence of hypertension is consistent with prior studies (15,33). Our findings additionally reinforce those of 2 recent studies (16,18) suggesting that chronic hypertension accounts for one-half to two-thirds of the excess cardiovascular disease risk in women with prior HDP. This suggests that blood pressure may represent an important therapeutic target for cardiovascular risk reduction in this population. Although 67% of women with prior HDP in our cohort had a diagnosis of hypertension at enrollment, only 33% of women with both HDP and chronic hypertension (and 22% of all women with prior HDP) were taking an antihypertensive medication, as similarly observed in another recent analysis from the UK Biobank (37). Current hypertension guidelines do not incorporate HDP into ASCVD risk assessment or discuss tailored blood pressure management in affected women (38,39). Strategies to optimize blood pressure management, including identification of suitable targets, and other interventions to slow vascular aging in women with HDP warrant dedicated study.

Notably, we did not observe an increased risk of prevalent or incident stroke in women with prior HDP, in contrast with some prior studies (1,15,17), although this association has not been consistent (5). We cannot rule out the possibility of low power hindering our ability to detect HDP-associated stroke risk.

STUDY LIMITATIONS. Although our study has several strengths, our findings should be interpreted in the context of some limitations. First, the exposure (any prior history of HDP) was ascertained largely by participant self-report. Prior work on maternal recall of HDP indicates limited sensitivity but high specificity for true HDP (40,41). Additionally, a "healthy volunteer" selection bias has been noted in the UK Biobank (42), which may explain a lower prevalence of HDP than expected in our cohort. "Sicker" women with a prior history of HDP may be less likely to enroll than healthier women with prior HDP as indicated by observed age differences; this would serve to minimize the effects we observed and bias our results to the null. HDP were combined as a lump exposure, as data were not available to allow stratification of gestational hypertension, mild preeclampsia, severe preeclampsia, preeclampsia superimposed on chronic hypertension, eclampsia, and HELLP syndrome. Further, data on other associated pregnancy complications (e.g., preterm delivery, growth restriction) were not available, nor were data on recurrent HDP; it

is possible that risks are higher among women with preeclampsia plus growth restriction and/or preterm delivery, as previous analyses have suggested for CAD (43). Further research is needed to show whether this effect modification extends to the diverse (non-ASCVD) conditions studied in the present analysis. Because women with HDP had higher baseline prevalence of CAD, heart failure, and venous thromboembolism, and because women with prevalent cardiovascular disease were excluded from incident disease models, our results may underestimate the magnitude of association between HDP and these conditions. However, the focus of our analysis was incident cardiovascular disease diagnoses among asymptomatic women in midlife, and we still found significant hazards of incident CAD and heart failure. Although ours is one of the first large, long-term cohort studies of HDP from outside of Scandinavia (15–17), as with these prior cohorts, the UK Biobank is predominantly (>90%) white, and further study is warranted to determine whether our findings generalize to other racial and ethnic groups.

CONCLUSIONS

HDP are associated with accelerated cardiovascular aging and greater incidence of diverse cardiovascular conditions than previously appreciated, including valvular heart disease, later in life. Further research is needed to further elucidate the mechanisms linking hypertensive pregnancy complications with long-term cardiovascular risk and to determine optimal strategies for screening, prevention, and management.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Women with hypertension during pregnancy are at increased risk of later cardiovascular diseases, including coronary artery disease, heart failure, aortic stenosis, and mitral regurgitation.

TRANSLATIONAL OUTLOOK: Strategies to mitigate long-term cardiovascular risk in women with prior hypertensive pregnancies, including specific blood pressure management strategies and other interventions to slow vascular aging, warrant dedicated study.

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APPENDIX For supplemental figures, tables, and appendixes, please see the online version of this paper.