

Preeclampsia Predicts Risk of Hospitalization for Heart Failure With Preserved Ejection Fraction



Dominique Williams, MD,^a Molly J. Stout, MD, MSCI,^b Joshua I. Rosenbloom, MD, MPH,^c Margaret A. Olsen, PhD, MPH,^d Karen E. Joynt Maddox, MD, MPH,^a Elena Deych, MS,^a Victor G. Davila-Roman, MD,^a Kathryn J. Lindley, MD^{a,c}

ABSTRACT

BACKGROUND Preeclampsia is associated with increased risk of future heart failure (HF), but the relationship between preeclampsia and HF subtypes are not well-established.

OBJECTIVES The objective of this analysis was to identify the risk of HF with preserved ejection fraction (HFpEF) following a delivery complicated by preeclampsia/eclampsia.

METHODS A retrospective cohort study using the New York and Florida state Healthcare Cost and Utilization Project State Inpatient Databases identified delivery hospitalizations between 2006 and 2014 for women with and without preeclampsia/eclampsia. The authors identified women admitted for HF after discharge from index delivery hospitalization until September 30, 2015, using International Classification of Diseases-9th Revision-Clinical Modification diagnosis codes. Patients were followed from discharge to the first instance of primary outcome (HFpEF hospitalization), death, or end of study period. Secondary outcomes included hospitalization for any HF and HF with reduced ejection fraction, separately. The association between preeclampsia/eclampsia and HFpEF was analyzed using Cox proportional hazards models.

RESULTS There were 2,532,515 women included in the study: 2,404,486 without and 128,029 with preeclampsia/eclampsia. HFpEF hospitalization was significantly more likely among women with preeclampsia/eclampsia, after adjusting for baseline hypertension and other covariates (aHR: 2.09; 95% CI: 1.80-2.44). Median time to onset of HFpEF was 32.2 months (interquartile range: 0.3-65.0 months), and median age at HFpEF onset was 34.0 years (interquartile range: 29.0-39.0 years). Both traditional (hypertension, diabetes mellitus) and sociodemographic (Black race, rurality, low income) risk factors were also associated with HFpEF and secondary outcomes.

CONCLUSIONS Preeclampsia/eclampsia is an independent risk factor for future hospitalizations for HFpEF. (J Am Coll Cardiol 2021;78:2281-2290) © 2021 by the American College of Cardiology Foundation.

Hypertensive disorders of pregnancy affect 5%-10% of pregnancies and are a leading cause of maternal morbidity and mortality (1). Preeclampsia, defined as new-onset hypertension associated with end-organ damage after the 20th

week of gestation, is a risk factor for future cardiovascular disease, and is associated with a 3- to 4-fold risk of developing heart failure (HF) (2-5).

However, the reason for the increased risk of HF among women with a history of preeclampsia is not



Listen to this manuscript's audio summary by Editor-in-Chief Dr Valentin Fuster on JACC.org.

From the ^aCardiovascular Imaging and Clinical Research Core Laboratory, Cardiovascular Division, Washington University in St Louis, St Louis, Missouri, USA; ^bDepartment of Obstetrics and Gynecology, Division of Maternal Fetal Medicine, University of Michigan, Ann Arbor, Michigan, USA; ^cDepartment of Obstetrics and Gynecology, Division of Maternal Fetal Medicine, Washington University in St Louis, St Louis, Missouri, USA; and the ^dDivision of Infectious Diseases, Department of Medicine, Division of Public Health Sciences, Department of Surgery, Washington University in St Louis, St Louis, Missouri, USA.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the [Author Center](#).

Manuscript received June 14, 2021; revised manuscript received September 7, 2021, accepted September 13, 2021.

**ABBREVIATIONS
AND ACRONYMS****HF** = heart failure**HFpEF** = heart failure with preserved ejection fraction**HFrEF** = heart failure with reduced ejection fraction**SID** = Statewide Inpatient Databases

known, and prior studies that have examined the long-term risk of HF in women with a history of preeclampsia do not distinguish between heart failure with reduced ejection fraction (HFrEF) or heart failure with preserved ejection fraction (HFpEF) (2,3,5). HFpEF, characterized by a left ventricular ejection >50%, is a disease that predominantly affects middle-aged and older women and is associated with chronic inflammation; traditional risk factors such as hypertension, diabetes mellitus, and obesity; and nontraditional risk factors such as autoimmune disease (6,7). The prevalence of HFpEF is increasing, now accounting for one-half of HF hospital admissions, and carries a high 5-year mortality (8). Diastolic dysfunction and asymptomatic left ventricular concentric remodeling are increased in preeclamptic women years after pregnancy (9). Patients with abnormal cardiac remodeling, particularly concentric hypertrophy with diastolic dysfunction, are at increased risk for adverse cardiovascular events including the development of clinical HF (10,11); this raises the possibility that preeclampsia could be associated with HFpEF through these pathways.

The goal of this retrospective cohort study of state inpatient billing databases from the Healthcare Cost and Utilization Project was to characterize the relationship between preeclampsia and long-term risk for HFpEF hospital admission. We hypothesized that preeclampsia is associated with a high incidence of HFpEF hospitalizations.

SEE PAGE 2291

METHODS

DATA AND PATIENT SAMPLE. Through the Center for Administrative Data Research at Washington University School of Medicine in St Louis, we obtained access to the Statewide Inpatient Databases (SID) for New York and Florida between 2005 and 2015 from the Healthcare Cost and Utilization Project, Agency for Healthcare Research and Quality. The SID include approximately 97% of all acute care community hospital discharges (including teaching and nonteaching hospitals). Data elements available in the SID include International Classification of Diseases-9th Revision-Clinical Modification (ICD-9-CM) diagnosis and procedure codes, demographics, length of stay, and payment source, among others.

Women aged 16-50 years discharged from a delivery hospitalization between January 2006 and September 2014 were identified based on evidence for a vaginal delivery or cesarean delivery using the

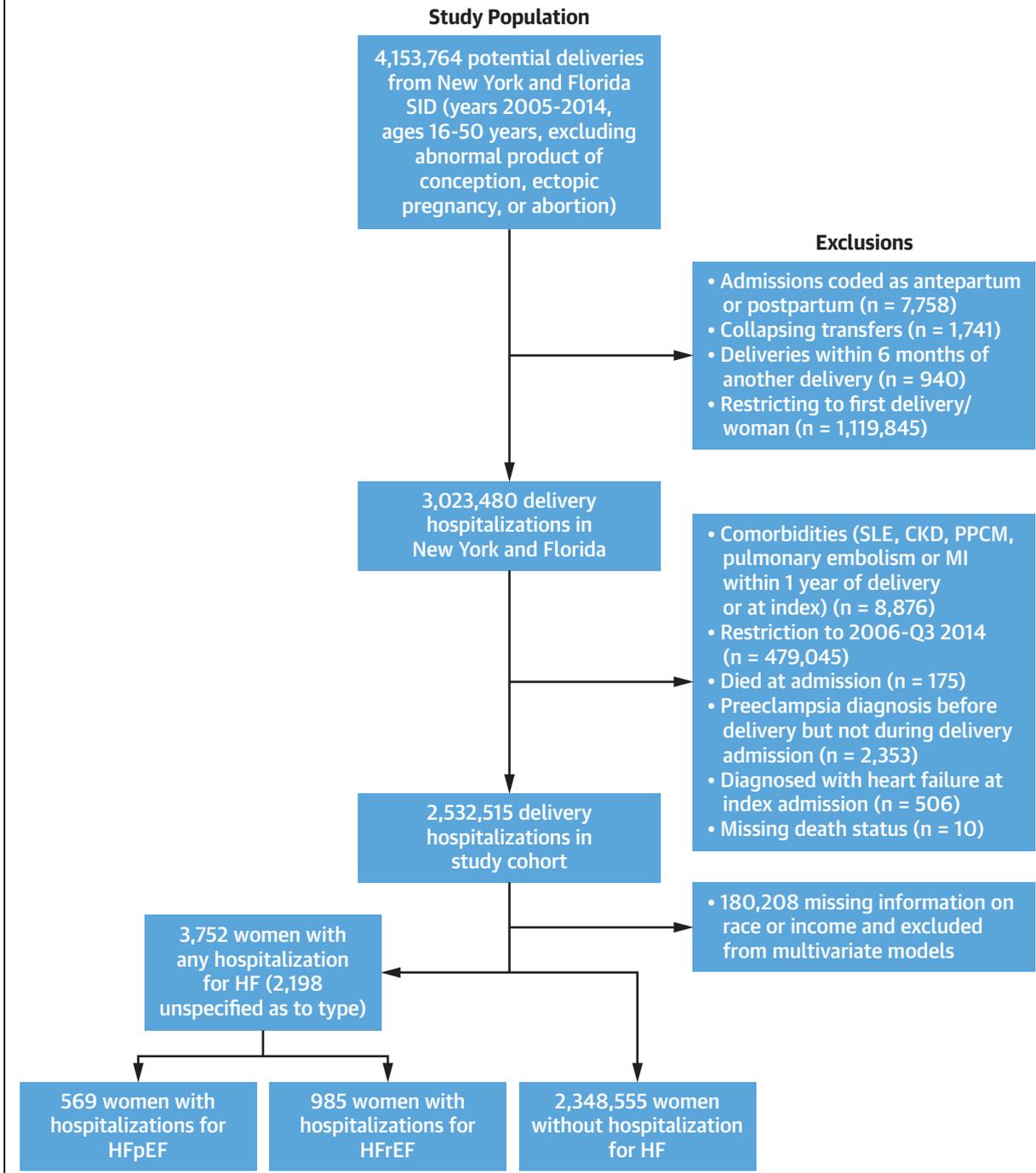
algorithm of Kuklina et al (12) based on ICD-9-CM diagnosis and procedure codes (13). Hospitalizations were excluded from the analysis if the admission was coded only for an antepartum or postpartum condition but no delivery was identified. The first eligible delivery during the study period for each woman was considered the index hospitalization. Women with preeclampsia, preeclampsia with severe features, and eclampsia were identified by ICD-9-CM codes (Supplemental Appendix) and compared with women who delivered without preeclampsia, preeclampsia with severe features, or eclampsia during the index hospitalization. Women with gestational hypertension were included in the control group unless they also carried a diagnosis of preeclampsia or eclampsia, because the association with subsequent HF was not expected to be as strong as in the preeclampsia/eclampsia group (14-16).

Among women who had an index delivery hospitalization, we identified the first subsequent event of the following: the first hospitalization coded for HF, death, subsequent delivery hospitalization coded for preeclampsia or eclampsia, or the end of the data (September 30, 2015). The primary outcome, maternal hospitalization for HFpEF after the index delivery, was identified based on ICD-9-CM diagnosis codes for HFpEF (Supplemental Table 1). Subsequent hospitalizations for women after delivery were tracked through September 30, 2015, using the encrypted identifier in the SID.

To reduce the risk of confounding caused by patients who may be at increased risk of developing HF unrelated to their preeclampsia diagnosis, patients were excluded if they had any of the following diagnoses in the 6 months before or during the index delivery hospitalization: chronic kidney disease, systemic lupus erythematosus, ischemic heart disease, hypertensive heart disease, pulmonary embolism, myocardial infarction, and heart failure, including cardiomyopathies and peripartum cardiomyopathy (Supplemental Appendix). Patients who died during the index delivery hospitalization were also excluded.

Clinical and sociodemographic variables included in our analysis included age (<35, 35-39, and ≥40 years), race (White, Black, or other), tobacco use, diabetes mellitus, gestational diabetes, chronic hypertension, gestational hypertension, preeclampsia (mild, superimposed on chronic hypertension, severe, eclampsia), preterm delivery, cesarean delivery, median household income quartile based on zip code, Medicaid insurance, urban/rural locality (large metropolitan, small metropolitan, micropolitan, and nonmetropolitan/nonmicropolitan), and selected

FIGURE 1 Attrition Diagram



This algorithm was used to arrive at the final population included in this analysis. CKD = chronic kidney disease; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrfEF = heart failure with reduced ejection fraction; PPCM = peripartum cardiomyopathy; Q3 = third quarter; SID = State Inpatient Database; SLE = systemic lupus erythematosus

TABLE 1 Baseline Demographics

	No Preeclampsia (n = 2,404,486)	Preeclampsia or Eclampsia (n = 128,029)
Number from Florida/New York	1,069,512/1,334,974 (44.5/55.5)	59,471/68,558 (46.5/53.5)
Age, y		
<35	1,992,541 (82.9)	102,364 (80.0)
35-39	322,078 (13.4)	18,448 (14.4)
≥40	89,867 (3.7)	7,217 (5.6)
Race		
White	1,139,319 (47.4)	52,342 (40.9)
Black	435,219 (18.4)	35,698 (27.9)
Other	791,896 (32.9)	38,298 (29.9)
Missing	38,052 (1.6)	1,691 (1.3)
Elixhauser score		
0	2,060,473 (85.7)	85,480 (66.8)
1	292,110 (12.1)	30,964 (24.2)
≥2	51,903 (2.2)	11,585 (9.0)
Diabetes mellitus	19,657 (0.8)	4,386 (3.4)
Gestational diabetes	139,988 (5.8)	13,170 (10.3)
Chronic hypertension	50,658 (2.1)	17,842 (13.9)
Gestational hypertension	85,362 (3.6)	3,066 (2.4)
Tobacco use	98,896 (4.1)	4,787 (3.7)
Income quartile		
Quartile 1, lowest-income	647,372 (26.9)	39,022 (30.5)
Quartile 2	560,180 (23.3)	28,342 (22.1)
Quartile 3	567,633 (23.6)	28,589 (22.3)
Quartile 4, highest-income	497,816 (20.7)	22,271 (17.4)
Missing	131,485 (5.5)	9,805 (7.7)
Medicaid insurance	1,089,637 (45.3)	61,262 (47.9)
Urban/rural		
Large metro	1,776,519 (73.9)	96,864 (75.7)
Small metro	483,034 (20.1)	24,269 (19.0)
Micropolitan	102,852 (4.3)	4,790 (3.7)
Nonmetro or micro	41,407 (1.7)	2,070 (1.6)
Missing	674 (0.0)	36 (0.0)
Postindex mortality	0.06	0.15

Values are n (%) unless otherwise indicated.

Elixhauser comorbidities (17,18). Elixhauser comorbidities are a well-established method for identifying common medical conditions using claims data (17), and have been used in many prior studies in this and other datasets.

OUTCOMES. The primary outcome was hospitalization for HFpEF after index delivery hospitalization for women with vs without preeclampsia/eclampsia. Prespecified secondary analyses were performed for time to hospitalization for any HF (HFpEF, HFrEF, or unspecified) and HFrEF for women with vs without preeclampsia/eclampsia.

ANALYSES. The effect of preeclampsia/eclampsia on the primary outcome of HFpEF hospitalization was evaluated in time to event analysis. Analysis was performed for HFpEF admissions and for the secondary outcomes of any HF and HFrEF

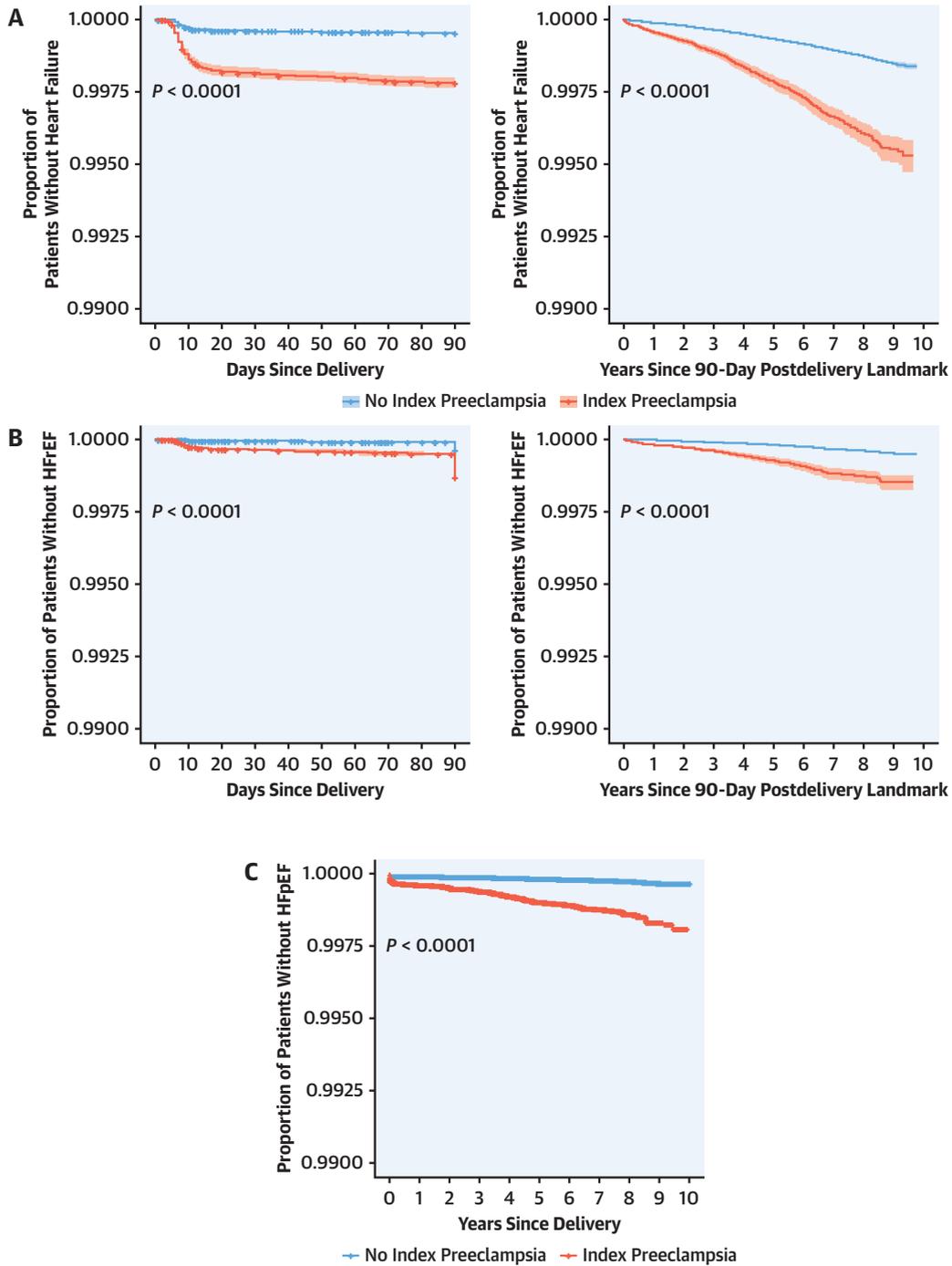
hospitalizations. Observations were censored at the earliest of death, end of follow-up, or preeclampsia/eclampsia in a subsequent pregnancy. In addition, for HFpEF, observations were censored at the time of HFrEF. For HFrEF, observations were censored at the time of HFpEF. The outcome was first compared between subjects with and without preeclampsia using the log-rank test with Kaplan-Meier curves. Proportionality assumptions were tested by Schoenfeld residuals for both individual covariates and the global Schoenfeld test. This revealed time-dependency in the association of preeclampsia/eclampsia with overall HF and HFrEF outcomes. Therefore, 2 separate Cox proportional hazards models were fit for these outcomes: 1 for the early (0-90 days post-index delivery) and 1 for the late outcomes (91 or more days post-index delivery). The 90-day time point was chosen because of a natural break identified on visual examination of the curves, and because this was a clinically logical timepoint, given that 97% of peripartum cardiomyopathy (HFrEF) hospitalizations occur within 3 months of delivery (19). No violation of proportionality assumption was found for HFpEF. The models were adjusted for relevant demographic and clinical comorbidities. Observations with missing covariate information were excluded from the models. To account for within-state correlation, observations were clustered by state in the models. As a sensitivity analysis, we evaluated the primary outcome after excluding control subjects with gestational hypertension. Sensitivity analyses were also performed for the primary outcome of HFpEF considering both potential extreme scenarios for unspecified HF admissions. One sensitivity analysis was performed censoring each unspecified HF event (ie, assuming all were non-events), and 1 analysis was performed considering each unspecified HF event as an event (ie, assuming all were HFpEF events).

This study was considered exempt by the Washington University Human Research Protection Office, and the requirement for informed consent was waived because of the deidentified nature of the data (IRB #201810063). Statistical analyses were done with SAS version 9.4 (SAS Institute) and R version 4.0 (R Foundation).

RESULTS

PATIENT POPULATION. Of the 2,532,515 women with a delivery hospitalization between 2006 and 2014 who met the inclusion criteria (Figure 1), 128,029 (5.1%) had preeclampsia/eclampsia during the index delivery hospitalization. Median follow-up time was 72 months (range: 0-120 months; interquartile range

CENTRAL ILLUSTRATION Heart Failure Hospitalizations Following Delivery Complicated by Preeclampsia/Eclampsia



Williams, D. et al. *J Am Coll Cardiol.* 2021;78(23):2281-2290.

(A) Kaplan-Meier curves for any heart failure rehospitalization within the first 90 days and between 90 days and 10 years postpartum. (B) Kaplan-Meier curves for rehospitalizations for heart failure with reduced ejection fraction (HFrEF) following delivery within the first 90 days and between 90 days and 10 years postpartum. (C) Kaplan-Meier curve for rehospitalizations for heart failure with preserved ejection fraction (HFpEF) following delivery.

TABLE 2 Risk of Subsequent Hospitalization for Heart Failure With Preserved Ejection Fraction Following Delivery

	Hazard Ratio	Confidence Interval
Preeclampsia or eclampsia	2.09	1.80-2.44
Age 35-39 y vs <35 y	1.78	1.55-2.06
Age ≥40 y vs <35 y	1.59	1.51-1.67
Black	2.89	2.51-3.32
Diabetes mellitus	5.35	5.08-5.64
Gestational diabetes	1.67	1.61-1.74
Cesarean delivery	1.79	1.69-1.89
Chronic hypertension	4.36	3.18-5.98
Preterm delivery	1.51	1.48-1.53
Medicaid insurance	1.41	1.31-1.51
Income Q1 vs Q4 (highest)	1.22	1.07-1.38
Income Q2 vs Q4 (highest)	0.93	0.72-1.19
Income Q3 vs Q4 (highest)	0.97	0.90-1.05
Small metro vs large metro	1.30	1.07-1.58
Micropolitan vs large metro	1.42	1.27-1.59
Nonmetro or micropolitan vs large metro	1.59	1.38-1.84

Model includes all variables listed in table.
Q1 = lowest income quartile; Q4 = highest income quartile.

[IQR]: 45-99 months). A total of 2,320 (0.1%) records did not have information on HF type. Of the remaining records, 180,086 (7.1%) were missing information on race or income and were excluded from the multivariate models. There were 569 women with hospitalizations for HFpEF and 985 women with hospitalizations for HFrfEF. The baseline characteristics of the cohort are summarized in [Table 1](#) and [Supplemental Table 2](#). Women with preeclampsia/eclampsia during the index delivery hospitalization were more likely to have underlying chronic hypertension (13.9% vs 2.1%), diabetes mellitus (3.4% vs 0.8%), and gestational diabetes (10.3% vs 5.8%). Women with preeclampsia/eclampsia were more likely to be ≥40 years of age (5.6% vs 3.7%) and Black (27.9% vs 18.1%) compared with those without preeclampsia/eclampsia. Women with preeclampsia/eclampsia during the index delivery hospitalization were also more likely to have Medicaid insurance and to live in a zip code with median household income <25th percentile compared with women without preeclampsia/eclampsia.

PREECLAMPSIA/ECLAMPSIA AND HFpEF. There were 603 women with subsequent hospitalization(s) for HFpEF ([Central Illustration](#)). Preeclampsia/eclampsia during the index hospitalization was independently associated with increased risk of HFpEF compared with women without preeclampsia/eclampsia, with an adjusted HR (aHR) of 2.09 (95% CI: 1.80-2.44), median time to onset of 32.2 months (IQR:

0.3-65.0 months), and median age at diagnosis of HFpEF of 34 years (IQR: 29-39 years). Chronic hypertension, diabetes mellitus, and Black race were the most significant additional risk factors for hospitalization for HFpEF (aHR: 4.36 [95% CI: 3.18-5.98], 5.35 [95% CI: 5.08-5.63], and 2.89 [95% CI: 2.51-3.32], respectively) ([Table 2](#)). Rural locality (aHR: 1.59 [95% CI: 1.38-1.84]) and markers of poverty, including the lowest income quartile (aHR: 1.22 [95% CI: 1.07-1.38]) and Medicaid insurance (aHR: 1.41 [95% CI: 1.31-1.51]), were also associated with increased risk of HFpEF.

A sensitivity analysis was performed excluding control subjects with gestational hypertension. In this subsample of 2,269,814 women, preeclampsia/eclampsia during the index hospitalization was independently associated with increased risk of HFpEF compared with women without preeclampsia/eclampsia, with an aHR of 2.20 (95% CI: 1.97-2.46; $P < 0.001$) ([Supplemental Table 3](#)). Sensitivity analyses were performed to account for the unspecified HF hospitalizations and did not change the results in a clinically meaningful way ([Supplemental Table 4](#)). Preeclampsia/eclampsia during the index hospitalization remained independently associated with increased risk of HFpEF compared with women without preeclampsia/eclampsia, both considering unspecified HF hospitalizations as HFpEF events (aHR: 1.91; 95% CI: 1.89-1.93) and considering unspecified HF hospitalizations as HFrfEF events (aHR: 2.09; 95% CI: 1.79-2.44).

PREECLAMPSIA/ECLAMPSIA AND HFrfEF. There were 1,072 women with subsequent hospitalization(s) caused by HFrfEF, with median time to onset of 31.5 months ([Central Illustration](#), [Supplemental Table 5](#)) and median age at diagnosis of 33.4 years. Preeclampsia/eclampsia during the index hospitalization was independently associated with increased risk of 90-day HFrfEF, with an aHR of 2.13 (95% CI: 2.08-2.18) and of late HFrfEF, with an aHR of 1.92 (95% CI: 1.76-2.10) compared with women without preeclampsia/eclampsia. Other major risk factors for 90-day HFrfEF included older age, Black race, chronic hypertension, diabetes, and cesarean delivery. Other major risk factors for late HFrfEF included Black race, diabetes mellitus, and chronic hypertension. Markers of poverty including Medicaid insurance and median income in the lowest 3 quartiles were also associated with increased risk of late HFrfEF.

RELATIONSHIP BETWEEN HOSPITALIZATION FOR PREECLAMPSIA/ECLAMPSIA AND ANY HF. There were 3,995 women who developed HF of any type.

Women with a history of preeclampsia/eclampsia were at increased risk of developing both 90-day (short-term) and late HF, with median time to onset of HF hospitalization of 20.8 months and median age at diagnosis of 33.0 years. In the first 90 days post-index delivery, the risk of HF was >2-fold higher for women with eclampsia/preeclampsia (aHR: 2.65; 95% CI: 2.61-2.70) (**Central Illustration, Supplemental Table 4**) compared with women without preeclampsia/eclampsia. Age, Black race, chronic hypertension, diabetes mellitus, cesarean delivery, Medicaid enrollment, and rural locality were also associated with increased risk of short-term HF. Preeclampsia/eclampsia, age ≥ 40 years, and Black race were the strongest predictors of 90-day HF. Preeclampsia/eclampsia remained a significant predictor for late HF after adjusting for other clinical and demographic factors (aHR: 1.66; 95% CI: 1.65-1.66). The strongest predictors of late HF were diabetes mellitus, chronic hypertension, and Black race.

COMPARISON BETWEEN HFpEF AND HFrEF. There were a total of 1,072 reported HFrEF hospitalizations and 603 HFpEF hospitalizations. There were no significant differences in age, race, insurance type, or urbanicity/rurality between the HFpEF and HFrEF groups. Importantly, women diagnosed with HFpEF were more likely than those with HFrEF to carry a diagnosis of chronic hypertension (24.9% vs 20.0%; $P = 0.02$) or diabetes mellitus (14.4% vs 8.5%; $P < 0.001$).

DISCUSSION

This large retrospective study identified a strong, independent association of preeclampsia/eclampsia with HFpEF in the decade following pregnancy after adjusting for other major HF risk factors including diabetes mellitus and chronic hypertension. These findings support current published data linking hypertensive disorders of pregnancy with future cardiovascular disease, and specifically HF (2). Importantly, preeclampsia/eclampsia was independently associated with both HFrEF and HFpEF, an important distinction given the female sex predominance of HFpEF. The reasons for the sex disparities in HFpEF remain elusive, although risk factors including obesity, hypertension, and diabetes mellitus, which are more common in women than in men and are also risk factors for preeclampsia/eclampsia, have been proposed to contribute to the development of HFpEF (20). Thus, this sex-specific risk factor may in part explain the predominance of HFpEF in women.

Although prior studies investigating the relationship between preeclampsia/eclampsia and future HF have not specified HF type, based on the current study it can be speculated that at least one-third of the reported cases are caused by HFpEF (**Figure 1**). Many hospitalizations for HF in this study did not specify HF type; thus, all HF hospitalizations were also analyzed together as “any heart failure.” Preeclampsia/eclampsia remained a significant independent predictor of any HF in this analysis, consistent with prior studies investigating hypertensive disorders of pregnancy (HDP) and future HF risk (2,3,5). Based upon the breakdown of HFpEF and HFrEF in the specified HF analyses and the number of unspecified HF hospitalizations, it is likely that the incidence of HFpEF is under-reported in this study.

HDP are an emerging, sex-specific risk factor for future cardiovascular disease in women. HDP cover a broad range of hypertensive disorders including gestational hypertension, chronic hypertension, chronic hypertension with superimposed preeclampsia, preeclampsia (with or without severe features), eclampsia, and the HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome (21,22). Although it has previously remained unclear whether HDP were a marker or contributor to future cardiovascular risk, an increasing number of studies suggest an independent association of HDP with future cardiovascular events (15,16,23-25).

The presentation of HFpEF in this study occurred with a median time to event of 32.2 months and median age of 34.0 years, consistent with onset of HF during the reproductive years for the majority of the patients included in the study. Preeclampsia/eclampsia have previously been associated with increased risk of short-term HF in the form of peripartum cardiomyopathy, a distinct subtype of HFrEF that occurs within the first 5 months after delivery (26,27). More recently, several studies have also identified HDP as a risk factor for acute peripartum HFpEF, suggesting that peripartum HF may present along the spectrum of ejection fractions (28,29). Although Briller et al (29) recently identified that preeclampsia/eclampsia is associated with increased risk of HFpEF during pregnancy and the early postpartum period, the present study importantly indicates that women with preeclampsia/eclampsia also remain at risk for longer-term HFpEF even after the physiological changes of pregnancy have resolved. When compared with age- and sex-matched control subjects, patients <55 years of age with HFpEF have a 3-fold increase in death at 1 year compared with

control subjects (30). Thus, our study likely identifies a particularly high-risk cohort of women with HF who could potentially benefit from early identification and risk factor modification.

Chronic hypertension and diabetes mellitus were also identified as independent risk factors for HFpEF hospitalization in this study, and were found to be more common among women developing HFpEF than HFrEF. These traditional cardiovascular risk factors are known risk factors for the development of HFpEF (20). Women with preexisting hypertension or diabetes mellitus are at increased risk of developing preeclampsia/eclampsia, and conversely women with preeclampsia/eclampsia are also at 4-fold risk of developing future hypertension and 2-fold risk of developing future diabetes mellitus (4,22,31,32). Thus, the findings that both traditional and nontraditional cardiovascular risk factors were independently associated with the development of early HFpEF in this cohort is consistent with what is already known about both HFpEF and preeclampsia, and supports a multi-risk model of phenotype development.

In the present study, hospital admissions for HFpEF after a diagnosis of preeclampsia/eclampsia disproportionately affected Black women, women with low income, women living in rural locations, and women receiving Medicaid insurance. It is also known that Black patients have a 50% higher incidence of HF than white patients, and it occurs at an earlier age (33). These findings highlight previously recognized sociodemographic disparities in maternal morbidity and mortality (34-38). Potential contributors to these disparities include lack of postpartum access to health care services, structural racism, and increased burden of underlying cardiovascular risk factors. These findings, in light of the knowledge that cardiovascular disease is the leading cause of maternal mortality as well as the leading cause of overall mortality in women in the United States, support the need for postpartum cardiovascular risk stratification and counseling, bias reduction efforts, and continued access to health care for women with adverse pregnancy outcomes.

STUDY LIMITATIONS. We used ICD-9-CM diagnosis codes to identify hospitalizations for heart failure which are subject to coding error. Importantly, “HFpEF” was added as a new definition to the multi-disciplinary American College of Cardiology Foundation/American Heart Association heart failure

guidelines in October 2013 (6). It is therefore likely that many women with a diagnosis of HFpEF were not coded as such, consistent with the large number of “unspecified” HF admissions. However, our results remained robust after multiple sensitivity analyses. We did not have access to outpatient data, and thus were not able to identify those who developed HF in the outpatient setting. Given these 2 factors, it is likely that the present study underestimates the true risk of HFpEF in women following a pregnancy complicated by preeclampsia/eclampsia. Although our follow-up was long compared with many prior studies, longer-term follow-up (ie, 30-50 years) is needed to develop a complete picture of the relationship between preeclampsia and women’s lifetime cardiovascular risk for HFpEF. Despite these limitations, our study provides an important contribution to the published data through further delineation of HF phenotypes, suggesting development of both HFrEF and HFpEF are increased in women with a history of preeclampsia.

CONCLUSIONS

Preeclampsia/eclampsia is an independent risk factor for future HF hospitalizations for HFpEF in the decade following a pregnancy complicated by preeclampsia/eclampsia. Additional risk factors include traditional cardiovascular risk factors such as hypertension and diabetes mellitus, as well as sociodemographic risk factors including Black race, markers of poverty, and living in a rural setting. These findings suggest that preeclampsia/eclampsia may share common pathophysiologic mechanisms in women with HFpEF and HFrEF.

ACKNOWLEDGMENT The writing group thanks Joanna Buss for data programming.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

This study was supported in part by the Washington University Institute of Clinical and Translational Sciences grant UL1 TR002345 from the National Center for Advancing Translational Sciences of the National Institutes of Health, by grant number R24 HS19455 through the Agency for Healthcare Research and Quality (AHRQ), and by The Longer Life Foundation Grant # 2020-005. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Kathryn J. Lindley, Washington University in St Louis, 660 South Euclid Avenue, Box 8086, St Louis, Missouri 63110, USA. E-mail: Kathryn.lindley@wustl.edu.

PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS:

Hypertensive disorders, including preeclampsia and eclampsia, occur in up to 10% of all pregnancies and are associated with adverse pregnancy outcomes and long-term cardiovascular effects, including hypertension, dyslipidemia, insulin resistance,

and (HFpEF, beginning within the first few years after delivery.

TRANSLATIONAL OUTLOOK: Future research should address the mechanisms, prevention, and treatment of preeclampsia to reduce the subsequent development of cardiovascular complications, including HFpEF.

REFERENCES

1. Abalos E, Cuesta C, Grosso AL, Chou D, Say L. Global and regional estimates of preeclampsia and eclampsia: a systematic review. *Eur J Obstet Gynecol Reprod Biol.* 2013;170:1-7.
2. Wu P, Haththotuwa R, Kwok CS, et al. Preeclampsia and future cardiovascular health: a systematic review and meta-analysis. *Circ Cardiovasc Qual Outcomes.* 2017;10(2):e003497. <https://doi.org/10.1161/CIRCOUTCOMES.116.003497>
3. McDonald SD, Malinowski A, Zhou Q, Yusuf S, Devereaux PJ. Cardiovascular sequelae of preeclampsia/eclampsia: a systematic review and meta-analyses. *Am Heart J.* 2008;156:918-930.
4. Stuart JJ, Tanz LJ, Missmer SA, et al. Hypertensive disorders of pregnancy and maternal cardiovascular disease risk factor development: an observational cohort study. *Ann Intern Med.* 2018;169:224-232.
5. Brouwers L, van der Meiden-van Roest AJ, Savelkoul C, et al. Recurrence of pre-eclampsia and the risk of future hypertension and cardiovascular disease: a systematic review and meta-analysis. *BJOG.* 2018;125:1642-1654.
6. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2013;62:e147-e239.
7. Nieminen MS, Harjola VP, Hochadel M, et al. Gender related differences in patients presenting with acute heart failure. Results from EuroHeart Failure Survey II. *Eur J Heart Fail.* 2008;10:140-148.
8. Benjamin EJ, Virani SS, Callaway CW, et al. Heart disease and stroke statistics-2018 update: a report from the American Heart Association. *Circulation.* 2018;137:e67-e492.
9. Ghossein-Doha C, van Neer J, Wissink B, et al. Pre-eclampsia: an important risk factor for asymptomatic heart failure. *Ultrasound Obstet Gynecol.* 2017;49:143-149.
10. Krumholz HM, Larson M, Levy D. Prognosis of left ventricular geometric patterns in the Framingham Heart Study. *J Am Coll Cardiol.* 1995;25:879-884.
11. Konstam MA, Kramer DG, Patel AR, Maron MS, Udelson JE. Left ventricular remodeling in heart failure: current concepts in clinical significance and assessment. *J Am Coll Cardiol Img.* 2011;4:98-108.
12. Kuklina EV, Whiteman MK, Hillis SD, et al. An enhanced method for identifying obstetric deliveries: implications for estimating maternal morbidity. *Matern Child Health J.* 2008;12:469-477.
13. HCUP State Inpatient Databases (SID) Healthcare Cost and Utilization Project (HCUP) 2005-2015. Agency for Healthcare Research and Quality. Accessed April 5, 2021. <http://www.hcup-us.ahrq.gov/sidoverview.jsp>
14. Ackerman CM, Platner MH, Spatz ES, et al. Severe cardiovascular morbidity in women with hypertensive diseases during delivery hospitalization. *Am J Obstet Gynecol.* 2019;220:582.e1-582.e11.
15. Honigberg MC, Riise HKR, Daltveit AK, et al. Heart failure in women with hypertensive disorders of pregnancy: insights from the Cardiovascular Disease in Norway Project. *Hypertension.* 2020;76:1506-1513.
16. Chen SN, Cheng CC, Tsui KH, et al. Hypertensive disorders of pregnancy and future heart failure risk: A nationwide population-based retrospective cohort study. *Pregnancy Hypertens.* 2018;13:110-115.
17. Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity measures for use with administrative data. *Med Care.* 1998;36:8-27.
18. Moore BJ, White S, Washington R, Coenen N, Elixhauser A. Identifying increased risk of readmission and in-hospital mortality using hospital administrative data: the AHRQ Elixhauser Comorbidity Index. *Med Care.* 2017;55:698-705.
19. Elkayam U, Akhter MW, Singh H, et al. Pregnancy-associated cardiomyopathy: clinical characteristics and a comparison between early and late presentation. *Circulation.* 2005;111:2050-2055.
20. Pepine CJ, Merz CNB, El Hajj S, et al. Heart failure with preserved ejection fraction: Similarities and differences between women and men. *Int J Cardiol.* 2020;304:101-108.
21. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics. ACOG practice bulletin no. 203: chronic hypertension in pregnancy. *Obstet Gynecol.* 2019;133:e26-e50.
22. Gestational hypertension and preeclampsia: ACOG practice bulletin, number 222. *Obstet Gynecol.* 2020;135:e237-e260.
23. Leon LJ, McCarthy FP, Direk K, et al. Preeclampsia and cardiovascular disease in a large uk pregnancy cohort of linked electronic health records: a CALIBER Study. *Circulation.* 2019;140:1050-1060.
24. Rosenbloom JI, Lewkowicz AK, Lindley KJ, et al. Expectant management of hypertensive disorders of pregnancy and future cardiovascular morbidity. *Obstet Gynecol.* 2020;135:27-35.
25. Rosenbloom JI, Stwalley D, Lindley KJ, Michael Nelson D, Olsen MA, Stout MJ. Latency of preterm hypertensive disorders of pregnancy and subsequent cardiovascular complications. *Pregnancy Hypertens.* 2020;21:139-144.
26. Bello N, Rendon IS, Arany Z. The relationship between pre-eclampsia and peripartum cardiomyopathy: a systematic review and meta-analysis. *J Am Coll Cardiol.* 2013;62:1715-1723.
27. Lindley KJ, Conner SN, Cahill AG, Novak E, Mann DL. Impact of preeclampsia on clinical and functional outcomes in women with peripartum cardiomyopathy. *Circ Heart Fail.* 2017;10(6):e003797. <https://doi.org/10.1161/CIRCHEARTFAILURE.116.003797>
28. Lindley KJ, Williams D, Conner SN, Verma A, Cahill AG, Davila-Roman VG. The spectrum of pregnancy-associated heart failure phenotypes: an echocardiographic study. *Int J Cardiovasc Imaging.* 2020;36:1637-1645.
29. Briller JE, Mogos MF, Muchira JM, Piano MR. Pregnancy associated heart failure with preserved ejection fraction: risk factors and maternal morbidity. *J Cardiac Fail.* 2021;27:143-152.
30. Tromp J, MacDonald MR, Tay WT, et al. Heart failure with preserved ejection fraction in the young. *Circulation.* 2018;138:2763-2773.
31. Bellamy L, Casas JP, Hingorani AD, Williams DJ. Pre-eclampsia and risk of

- cardiovascular disease and cancer in later life: systematic review and meta-analysis. *BMJ*. 2007;335:974.
32. Timpka S, Markovitz A, Schyman T, et al. Midlife development of type 2 diabetes and hypertension in women by history of hypertensive disorders of pregnancy. *Cardiovasc Diabetol*. 2018;17:124.
33. Lewis EF, Claggett B, Shah AM, et al. Racial differences in characteristics and outcomes of patients with heart failure and preserved ejection fraction in the Treatment of Preserved Cardiac Function Heart Failure Trial. *Circ Heart Fail*. 2018;11:e004457.
34. Luke AA, Huang K, Lindley KJ, Carter EB, Joynt Maddox KE. Severe maternal morbidity, race, and rurality: trends using the National Inpatient Sample, 2012-2017. *J Womens Health (Larchmt)*. 2021;30(6):837-847. <https://doi.org/10.1089/jwh.2020.8606>
35. Admon LK, Winkelman TNA, Zivin K, Terplan M, Mhyre JM, Dalton VK. Racial and ethnic disparities in the incidence of severe maternal morbidity in the United States, 2012-2015. *Obstet Gynecol*. 2018;132:1158-1166.
36. U.S. Centers for Disease Control and Prevention. Trends in pregnancy-related mortality in the United States: 1987-2016. Accessed September 5, 2020. <https://www.cdc.gov/reproductivehealth/maternal-mortality/pregnancy-mortality-surveillance-system.htm#trends>
37. Leonard SA, Main EK, Scott KA, Profit J, Carmichael SL. Racial and ethnic disparities in severe maternal morbidity prevalence and trends. *Ann Epidemiol*. 2019;33:30-36.
38. Petersen EE, Davis NL, Goodman D, et al. Vital signs: pregnancy-related deaths, United States, 2011-2015, and strategies for prevention, 13 states, 2013-2017. *MMWR Morb Mortal Wkly Rep*. 2019;68:423-429.

KEY WORDS heart failure, HFpEF, preeclampsia, pregnancy, women

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