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ORIGINAL RESEARCH

Cardiovascular Disease in Pregnancy

Clinical Outcomes and Cost-Associated Burdens From a National Cohort at Delivery

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ABSTRACT

BACKGROUND Cardiovascular disease (CVD) in pregnancy is a leading cause of maternal morbidity and mortality in the United States, with an increasing prevalence.

OBJECTIVES This study aimed to examine risk factors for adverse maternal cardiac, maternal obstetric, and neonatal outcomes as well as costs for pregnant people with CVD at delivery.

METHODS Using the National Inpatient Sample 2010-2019 and the Internal Classification of Diseases diagnosis codes, all pregnant people admitted for their delivery hospitalization were included. CVD diagnoses included congenital heart disease, cardiomyopathy, ischemic heart disease, arrhythmias, and valvular disease. Multivariable regressions were used to analyze major adverse cardiovascular events (MACE), maternal and fetal complications, length of stay, and resource utilization.

RESULTS Of the 33,639,831 birth hospitalizations included, 132,532 (0.39%) had CVD. These patients experienced more frequent MACE (8.5% vs 0.4%, $P < 0.001$), obstetric (24.1% vs 16.6%, $P < 0.001$), and neonatal complications (16.1% vs 9.5%, $P < 0.001$), and maternal mortality (0.16% vs 0.01%, $P < 0.001$). Factors associated with MACE included cardiomyopathy (adjusted OR [aOR]: 49.9, 95% CI: 45.2-55.1), congenital heart disease (aOR: 13.8, 95% CI: 12.0-15.9), Black race (aOR: 1.04, 95% CI: 1.00-1.08), low income (aOR: 1.06, 95% CI: 1.02-1.11), and governmental insurance (aOR: 1.03, 95% CI: 1.00-1.07). On adjusted analysis, CVD was associated with higher odds of maternal mortality (aOR: 9.28, 95% CI: 6.35-13.56), stillbirth (aOR: 1.66, 95% CI: 1.49-1.85), preterm birth (aOR: 1.33, 1.27-1.39), and congenital anomalies (aOR: 1.84, 95% CI: 1.69-1.99). CVD was also associated with an increase of $2,598 (95% CI: $2,419-2,777) per patient during admission for delivery.

CONCLUSIONS CVD in pregnancy is associated with higher rates of adverse outcomes. Our study highlights the association of key clinical and demographic factors with CVD during pregnancy to emphasize those at highest risk for complications. (JACC Adv 2024;3:101071) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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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.

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ABBREVIATIONS AND ACRONYMS

aOR = adjusted OR

CHD = congenital heart disease

CVD = cardiovascular disease

LOS = length of stay

MACE = major adverse cardiac events

NIS = National Inpatient Sample

Cardiovascular disease (CVD) is the leading cause of maternal morbidity and mortality in the United States.[1-3] During pregnancy, increased hemodynamic stress and alterations in cardiac function amplify the risk of heart failure, arrhythmias, and other major adverse cardiac events (MACE), as well as mortality[2,4] among those with CVD. Despite substantial advancements in its medical and surgical management, CVD remains responsible for >33% of pregnancy-related deaths in the United States, of which nearly half have been deemed preventable.[5-8] Pre-existing CVD frequently falls into five main groups: congenital heart disease (CHD), arrhythmias, ischemia, valvular disease, and cardiomyopathy. Grouped together, cardiomyopathy and other CVDs accounted for 10.8% of maternal deaths in the United States in 2011, which increased to 26.7% in 2019.[5,9] While morbidity from CVD increases individual mortality, it also requires substantial resource utilization among health care systems and patients alike.

Severe maternal morbidity, as defined by the Centers for Disease Control and Prevention criteria, has been associated with a 2.5-fold increase in hospitalization costs at the time of birth, rising to a 4-fold increase in costs with intensive care unit (ICU) admission.[10] It is estimated that in 2019 alone, nearly $32.3 billion was spent on the management of maternal morbidities.[11,12] The rising incidence, coupled with the considerable resources required to manage these morbidities, emphasizes the critical nature of improving outcomes for these vulnerable populations. We aim to characterize factors associated with maternal and neonatal morbidity for patients with CVD in efforts to identify at-risk individuals and improve cardio-obstetric outcomes. Similarly, we aim to highlight the health care expenditures required for this high-risk group in order to reduce hospital utilization costs and financial burdens on patients with CVD at the time of delivery.

METHODS

DATA SOURCE AND STUDY POPULATION. This analysis was a retrospective cohort study using the 2010-2019 National Inpatient Sample (NIS). Maintained by the Healthcare Cost and Utilization Project, the NIS is the largest all-payer, in-hospital database and uses specific hospital-based discharge weights to accurately estimate approximately 97% of hospitalizations in the United States. Pregnant people (≥18 years and <50 years) presenting for their birthing admission were identified using the International Classification of Diseases 9th-10th Revision diagnosis codes.[4] Patients were classified as having CVD if they had a diagnosis of CHD, cardiomyopathy, ischemic heart disease, arrhythmias, or valvular disease during their delivery hospitalization using coding definitions described in previous studies.[13-15] Patients missing key variables of interest including mortality, costs, and length of stay (LOS) were excluded (2.6%).

VARIABLE DEFINITIONS. Baseline patient and hospital characteristics, including age, race, income level, and insurance status, were defined according to the Healthcare Cost and Utilization Project Data Dictionary.[16] The Van Walraven modification of the Elixhauser Comorbidity Index, a validated composite of 30 comorbid conditions, was used to quantify the burden of chronic conditions.[17] Other clinical covariates and complications (**Table 1**) were tabulated using previously published International Classification of Diseases codes.[15,18] MACE was defined as cardiac death, cardiac arrest, heart failure, myocardial infarction, or vascular injury. Other maternal complications were defined as including strokes, thrombotic, respiratory, infectious, renal, hemorrhagic, or obstetric categories.[14] Fetal complications included poor fetal growth, preterm delivery (delivery before 37 weeks), stillbirth, and congenital anomalies. Hospitals were classified as low, medium, and high-volume centers based on the annual caseload of births and cut-off thresholds at the 33rd and 66th percentiles annually. Individual patient costs were normalized for comparison using hospital specific cost-to-charge ratios and inflation adjusted to the 2019 Personal Health Care Index.[19]

STATISTICAL ANALYSIS. Categorical variables were reported as proportions and compared using the Pearson's chi-square test. Continuous variables with approximately normal distributions (eg, age) were reported as means. Given the large sample size of the cohort, we used previously published methods to measure the effect sizes of outcome differences and estimate the clinical importance of significantly different comparisons.[20] Effect sizes of ≤0.2 are considered small, 0.5 medium, and >0.8 large. Multivariable logistic and linear regression models adjusting for demographic, clinical, and hospital factors were developed to assess key clinical outcomes including index hospitalization costs and length of stay (Supplemental Table 1). Model covariates were selected using elastic net regularization, a methodology that reduces bias and increases out-of-sample generalizability by combining least absolute shrinkable and selection operator and ridge regression.[21,22] This methodology allows for variable selection while

TABLE 1 Baseline Demographics of Birthing Patients by Cardiac Diagnosis

		Cardiovascular Disease						
	No Cardiovascular Disease (N = 33,507,299)	Congenital (n = 20,101)	Cardiomyopathy (n = 14,284)	Ischemic (n = 9,496)	Arrhythmia (n = 16,292)	Valvular Disease (n = 72,359)	Total (N = 132,532)	*P* Value
Demographics								
Age (y)	28.6	28.4	30.6	32.8	29.4	30.7	30.3	<0.001
Elixhauser	0.27	0.76	1.80	1.27	1.51	1.62	1.44	<0.001
Race								<0.001
Asian	5.9	3.9	4.1	3.8	4.0	4.1	4.0	
Black	14.6	13.1	31.2	25.2	17.9	12.1	15.9	
Hispanic	20.9	16.2	12.6	13.7	14.8	10.0	12.1	
White	53.3	61.7	46.9	52.8	58.4	69.5	63.3	
Income quartile								<0.001
Lowest (0-24th percentile)	28.2	26.9	36.5	35.0	28.0	23.3	26.7	
Second (25-49th percentile)	24.7	24.1	26.2	24.2	24.4	22.6	23.6	
Third (50-74th percentile)	24.9	26.6	20.9	23.2	24.7	25.2	24.7	
Highest (74-99th percentile)	22.3	22.4	16.4	17.6	22.8	28.9	25.0	
Insurance								<0.001
Private	50.7	51.4	40.3	39.8	51.1	56.4	55.9	
Public	43.2	40.8	50.6	50.7	42.6	31.0	37.4	
Comorbidities (%)								
Pre-eclampsia/eclampsia	5.2	8.5	28.1	18.2	10.8	8.2	11.4	<0.001
Gestational hypertension	4.5	5.7	5.3	5.3	6.4	5.2	5.6	<0.001
Gestational diabetes	7.2	7.2	9.4	9.5	7.9	7.6	7.9	<0.001
Hypertension	0.4	1.1	10.5	10.9	1.7	1.7	3.2	<0.001
Coagulopathy	1.9	5.1	7.1	6.0	4.0	3.8	4.5	<0.001
Renal failure	0.1	0.5	2.2	4.2	0.5	0.3	0.8	<0.001
Liver disease	0.3	0.6	1.6	2.7	0.7	0.6	0.8	<0.001
Obesity	7.2	9.9	20.6	20.3	12.7	7.8	11.0	<0.001
Anemia	1.4	2.1	4.9	3.5	2.9	2.3	2.7	<0.001
Delivery factors								
Induction of labor	49.8	48.6	42.4	44.0	48.5	50.9	48.8	<0.001
Multiple gestation	1.7	2.1	4.9	2.4	2.4	2.6	2.7	<0.001
Operative vaginal birth	24.4	17.4	14.9	14.1	17.5	27.2	22.3	<0.001
Spontaneous vaginal birth	42.5	42.8	24.9	33.6	38.9	31.0	33.3	<0.001
Cesarean birth	33.0	39.8	60.2	52.3	43.6	41.8	44.4	<0.001

reducing model overfitting by penalizing the addition of subsequent factors. Regression outputs were reported as adjusted ORs (aORs) and beta coefficients (β) with 95% CIs for dichotomous and continuous variables, respectively. Statistical significance was defined as $\alpha < 0.05$. All statistical analyses were performed using Stata software version 16.1 (StataCorp LP). Due to the de-identified nature of the NIS, this study was deemed exempt from full review by the Institutional Review Board at the University of California-Los Angeles (IRB:17-001112, approved July 26, 2017).

RESULTS

Of the estimated 33,639,831 hospitalizations included for analysis, 132,532 (0.39%) patients had a concomitant diagnosis of CVD. Compared to others, pregnant people with CVD were older (30.3 vs 28.6 years, $P < 0.001$) (Table 1) other than those with CHD. The CVD cohort was more frequently White, with the exception of those with cardiomyopathy (46.9% vs 53.3%, $P < 0.001$). Moreover, prevalence of comorbidities including gestational hypertension (5.6% vs 4.5%, $P < 0.001$), gestational diabetes (7.9% vs 7.2%, $P < 0.001$), pre-eclampsia/eclampsia (11.4% vs 5.2%, $P < 0.001$), and coagulopathy (4.5% vs 1.9%, $P < 0.001$) was significantly higher among pregnant people with CVD (Table 1). Additionally, the CVD group had more multifetal pregnancies (2.7% vs 1.7%, $P < 0.001$) and cesarean births (44.4% vs 33.0%, $P < 0.001$).

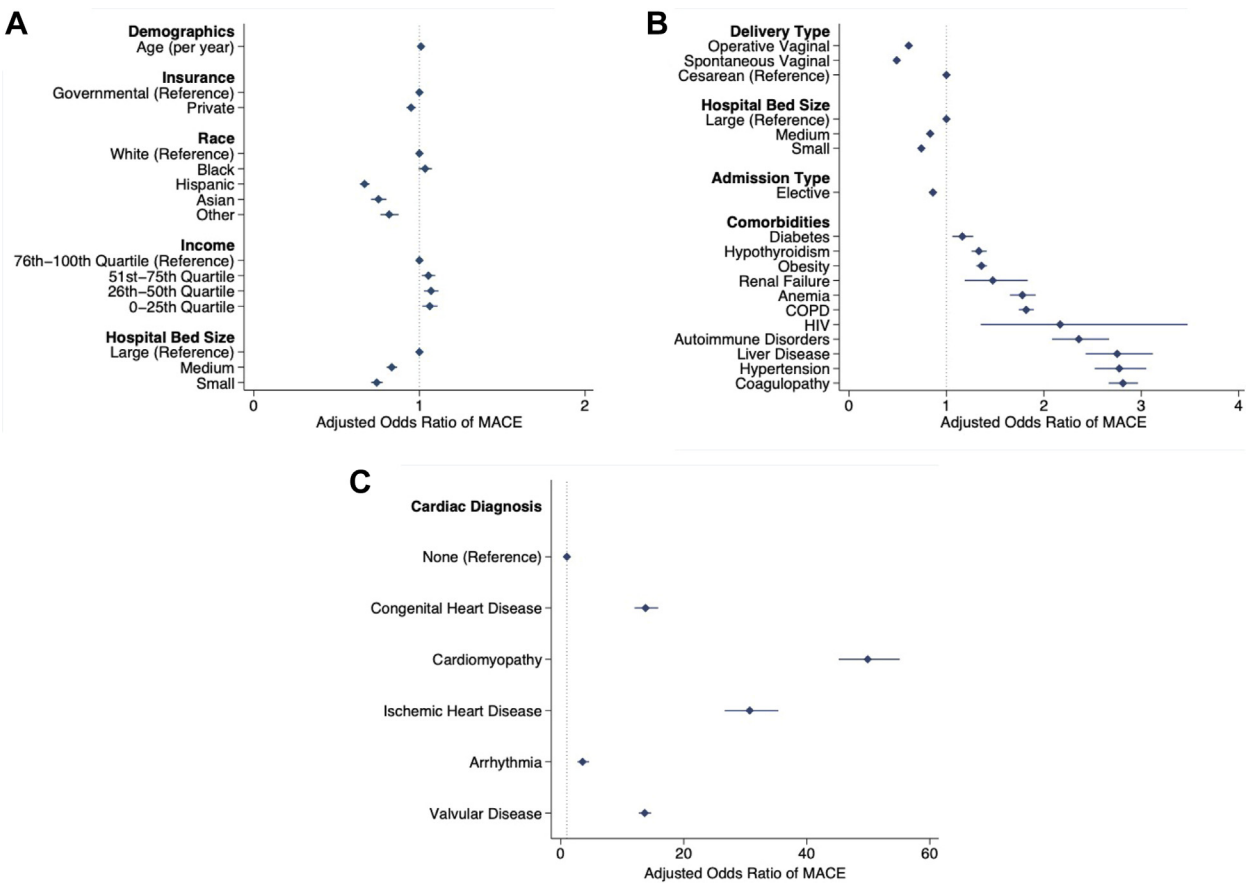
On univariate unadjusted analysis, MACE was significantly more prevalent among those with CVD (8.5% vs 0.4%, $P < 0.001$), as were obstetric complications (24.1% vs 16.6%, $P < 0.001$) and neonatal complications (16.1% vs 9.5%, $P < 0.001$). Notably,

TABLE 2 Univariate Outcomes of Birthing Patients by Cardiac Diagnosis

		Cardiovascular Disease (132,532)							
	No Cardiovascular Disease (33,507,299)	Congenital (20,101)	Cardiomyopathy (14,284)	Ischemic (9,496)	Arrythmia (16,292)	Valvular Disease (72,359)	Total (132,532)	*P* Value	Effect Size
MACE	0.4	6.1	25.6	17.8	1.8	6.1	8.5	<0.001	0.47
Acute heart failure	0.0	0.5	12.8	2.0	0.6	1.0	2.2	<0.001	0.30
Maternal nonpregnancy complications	27.3	43.0	61.0	49.3	39.5	33.9	31.9	<0.001	0.10
Pregnancy/obstetrical complication	16.6	23.8	38.8	29.6	24.8	20.5	24.1	<0.001	0.19
Any fetal/neonatal complication	9.5	19.7	24.9	19.0	15.0	13.2	16.1	<0.001	0.21
Maternal mortality	0.01	[a]	0.71	0.62	[a]	0.03	0.16	<0.001	0.06
Length of stay (d)	2.6	3.7	6.2	4.6	3.7	3.4	3.9	<0.001	
Hospitalization costs ($)	5,050	8,134	15,341	11,404	7,731	6,691	8,314	<0.001	

Values are % unless otherwise indicated. [a]Value not reported due to HCUP Privacy Guidelines.
MACE = major adverse cardiac events; HCUP = Healthcare Cost and Utilization Project.

FIGURE 1 Factors Associated With Major Adverse Cardiac Events



(A) Demographic, (B) clinical, and (C) cardiac factors associated with major adverse cardiac events (MACE) on multivariable adjusted analysis. COPD = chronic obstructive pulmonary disease.

pregnant persons with CVD had prolonged hospitalizations (3.9 vs 2.6 days, $P < 0.001$) and significant increases in rates of maternal mortality in their birth hospitalizations (0.16% vs 0.01%, $P < 0.001$, Table 2).

Following multivariable adjusted analysis, factors associated with MACE included all types of CVD: CHD (aOR: 13.8, 95% CI: 12.0-15.9), cardiomyopathy (aOR: 49.9, 95% CI: 45.2-55.1), ischemic disease (aOR: 30.7, 95% CI: 26.7-35.4), arrhythmias (aOR: 3.6, 95% CI: 2.7-4.6), and valvular disease (aOR: 13.7, 95% CI: 12.7-14.7, reference: no CVD). Other factors associated with MACE included hypertension (aOR: CI: 2.7, 95% 2.5-3.0), coagulopathy (aOR: 2.8, 95% CI: 2.7-3.0), liver disease (aOR: 2.7, 95% CI: 2.4-3.1), cesarean birth (aOR: 1.63, 1.6-1.7, reference: operative vaginal delivery), Black race (aOR: 1.04, 95% CI: 1.0-1.08), low income (aOR: 1.06, 1.02-1.11, reference: high income), and governmental insurance (aOR: 1.03, 95% CI: 1.00-1.07, reference: private) (Figure 1).

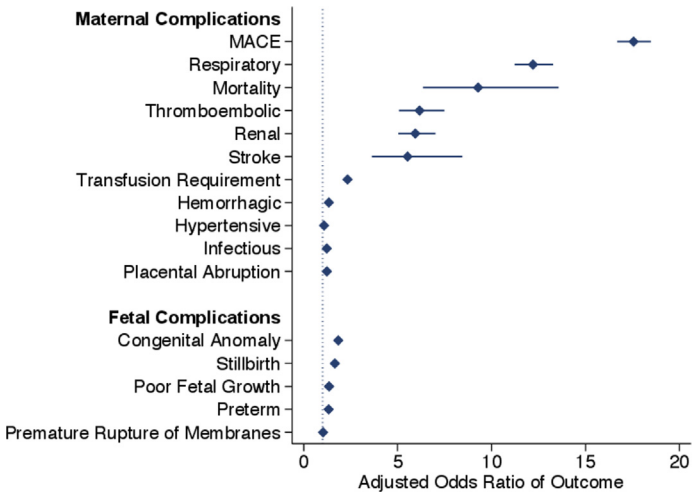
After adjustment for clinical and demographic factors, CVD remained associated with increased odds of obstetric and neonatal complications, including MACE (aOR: 17.6, 95% CI: 17.0-18.5), maternal mortality (aOR: 9.28, 95% CI: 6.35-13.56), stillbirth (aOR: 1.66, 95% CI: 1.49-1.85), preterm birth (aOR: 1.33, 95% CI: 1.27-1.39), and neonatal congenital anomalies (aOR: 1.84, 95% CI: 1.69-1.99) (Figure 2).

CVD was also similarly associated with an adjusted increase of $2,598 (95% CI: $2,419-2,777) per patient per hospitalization. As shown in Figure 3, complications following hospitalizations for those with CVD accounted for a total of $1,075,000,000 while comprising 0.39% of the cohort (Figure 3). Pregnant people with CVD also experienced a +0.87 day (95% CI: +0.80-0.93 days) increase in LOS, of which the longest LOS predicted was within the cardiomyopathy cohort of 5.37 days (95% CI: 5.00-5.73 days) compared to those without CVD (2.65 days, 95% CI: 2.64-2.65, Figure 4).

DISCUSSION

Utilizing more than 33,600,000 birthing hospitalizations, we identified significant clinical covariates and social factors associated with an increased risk of MACE and mortality in birthing patients with CVD. We then quantified the financial impact of CVD on birthing people at the time of delivery. Many of these findings warrant further discussion (Central Illustration).

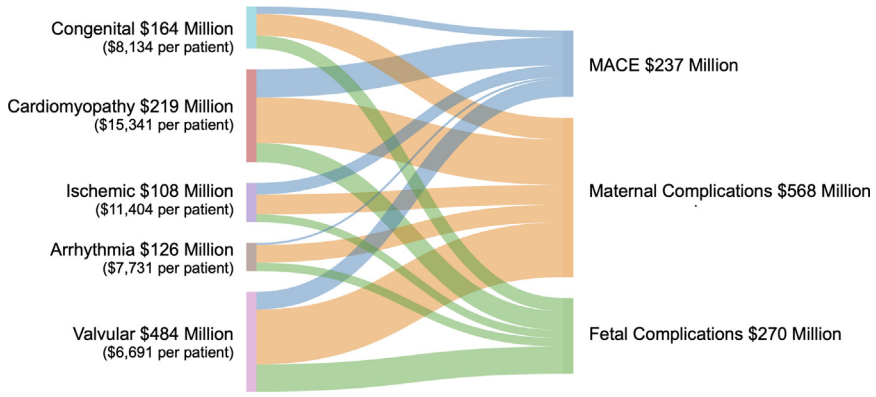
FIGURE 2 Complications Associated With Cardiac Disease in Pregnancy



Adjusted OR of complications due to cardiac disease during birthing hospitalization (reference: no cardiac disease). MACE = major adverse cardiac events.

ADVERSE CARDIOVASCULAR OUTCOME RISK FACTORS. Pregnant patients with CVD are at increased risk for adverse cardiovascular events in our cohort. Pregnant patients with cardiomyopathy and ischemic heart disease, in particular, were more likely to experience MACE. Strikingly, those with cardiomyopathy had nearly 50-fold greater odds of MACE, and those with ischemic heart disease had 30-fold greater odds of MACE compared to those without CVD. Our findings support numerous reports indicating that in pregnant patients with CVD, those with cardiomyopathy are at greatest risk for adverse cardiovascular outcomes at the time of delivery.[4,6,23] Although it is evident that cardiomyopathy increases the risk for adverse cardiac outcomes in pregnancy such as inducing heart failure, it is unclear why patients with cardiomyopathy remain at the greatest risk for cardiovascular events at delivery compared to other types of cardiac disease. Some have hypothesized that a pre-existing subclinical cardiomyopathy may not be identified until physiologic changes in pregnancy unmask symptoms, and such patients are thus not optimized prior to pregnancy.[4,6] It is additionally important to note that de novo development of left ventricular dysfunction due to peripartum cardiomyopathy may also occur during the third trimester of pregnancy.[24] While in our study, we grouped cardiomyopathy patients into a single cohort, this

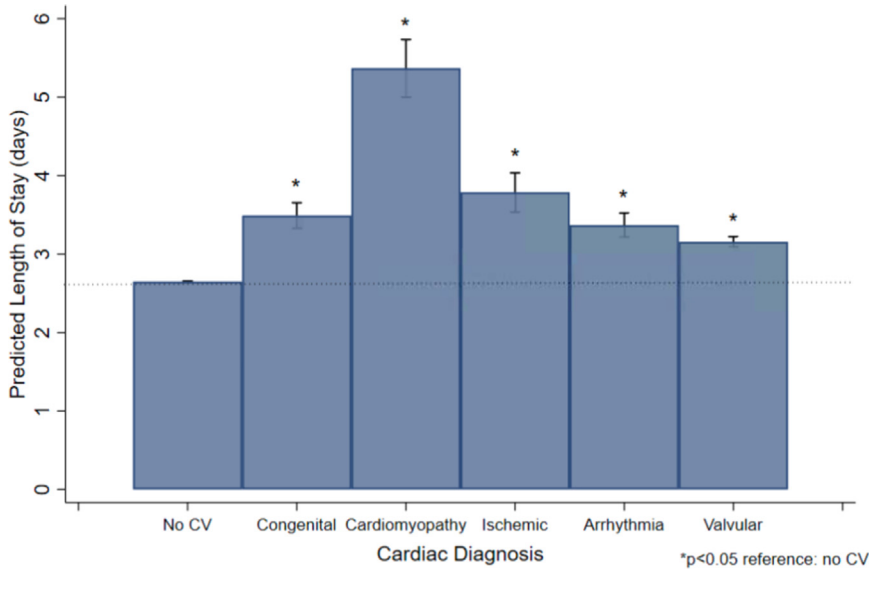
FIGURE 3 Sankey Diagram of Costs by Cardiac Diagnosis



MACE = major adverse cardiac events.

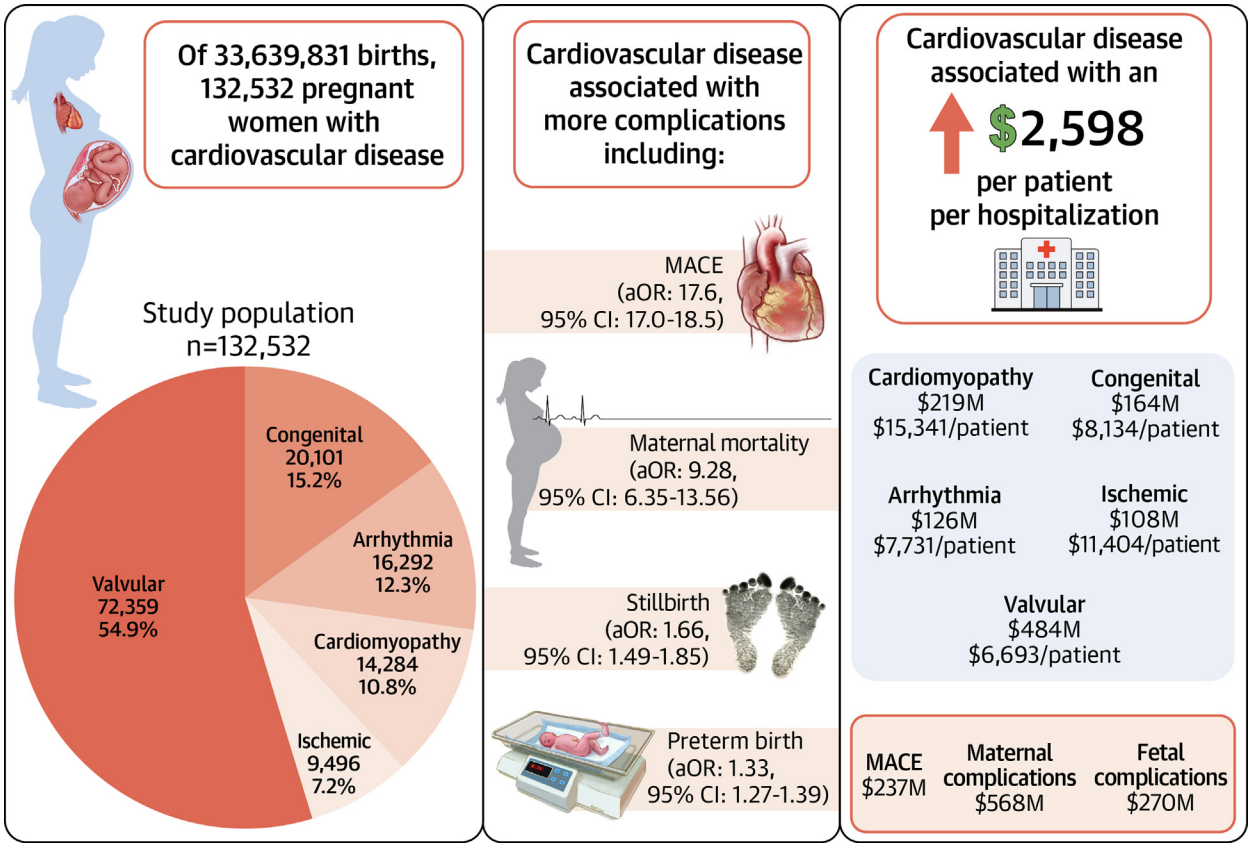
population does represent a spectrum of peripartum to hypertrophic cardiomyopathy. In a study by Lima et al,[25] MACE rates were significantly higher in women with peripartum cardiomyopathy compared with hypertrophic women, with peripartum cardiomyopathy having 2-fold odds of MACE in comparison to hypertrophic women. Further focused analysis may elucidate a better understanding of the severe effects of cardiomyopathy in pregnancy. One possible explanation may be that heart failure therapy is limited in pregnancy due to known teratogenicity or limited safety data. Comparatively, other pre-existing CVDs, such as CHD, are often known prior to conception, and thus cardiac risk stratification and optimization may be performed prior to conception. Regardless of CVD diagnosis, our results indicate that all patients with underlying CVD are at 18-fold greater odds of adverse cardiac outcomes and thus require appropriate management from a multidisciplinary team.

FIGURE 4 Cumulative Costs by Cardiac Diagnosis and Complication Category



Length of hospital stay by cardiac diagnosis. Adjusted length of stay by cardiac disease status. CV = cardiovascular.

CENTRAL ILLUSTRATION **Cardiovascular Disease in Pregnancy: Clinical Outcomes and Cost-Associated Burdens From a National Cohort at Delivery**



Williamson CG, et al. JACC Adv. 2024;3(8):101071.

aOR = adjusted odds ratio; MACE = major adverse cardiac events.

Notably, in our study, major adverse cardiac events were found to be associated with low income, public health insurance, and Black race, despite identifying greater proportions of all cardiac diagnoses other than cardiomyopathy in White patients. Our study confirms previously reported inequities in this population including the adverse impacts of social, racial, and structural inequities on pregnant patients with CVD. In a study by Creanga et al, cardiovascular conditions contributed to 46.8% of pregnancy-related deaths in non-Hispanic Black women, compared to 40.9% in non-Hispanic White women.[26] However, few studies recognize the initial burden of cardiac disease in the pregnant population by race. The higher percentage of CVD in White populations in our study may be due to an increased number of initial diagnoses for this group compared to underdiagnosis in the racially diverse subgroups. This underdiagnosis may further contribute to poor clinical outcomes due to delays in diagnosis and risk stratification. Further research is needed to identify strategies for improving maternal outcomes in patients with CVD in these populations.[6,27,28]

ASSOCIATED HEALTH CARE COSTS. Maternal and neonatal complications in patients with CVD, particularly cardiomyopathy, led to substantial health care cost burden. Between 2010 and 2019, complications in patients with CVD at the time of delivery resulted in a total of $1,075,000,000 in health care expenditures. Of this, $237 million went toward the management of MACE. In our study, pregnant people with cardiomyopathy had the worst pregnancy and cardiovascular outcomes, resulting in the longest hospital stays and the highest hospitalization costs of any CVD group. Over 25% of patients with cardiomyopathy experienced MACE, 39% experienced maternal complications (pregnancy-related), and 25% had neonatal

complications. The high rates of adverse complications resulted in multivariable adjusted LOS of 5.37 days and an average hospitalization cost of $15,341, nearly three times more costly than non-CVD patients. The second most costly group were those with ischemic disease, with a cost of $11,404, which is likely secondary to complications endured by this population. In our study, the occurrence of MACE was highly correlated with hospital expenditures, further supporting the hypothesis that reducing MACE may reduce resource utilization. To our knowledge, this is the first study to report on the financial burden of MACE in pregnant patients with CVD. Given the increasing prevalence of CVD in pregnancy and the financial impacts this may have on health care systems, early cardiac optimization and close management with a multidisciplinary team are needed to attenuate the adverse maternal and neonatal outcomes seen in this population. Further, targeted interventions to improve cardiac management in birthing persons with underlying cardiomyopathy may have the greatest cost reduction effect and should be prioritized.

STUDY LIMITATIONS. First, although cardiomyopathy was identified as a key risk factor for worse outcomes and increased health care costs, we were unable to identify the subtype of cardiomyopathy that patients had (ie, peripartum vs dilated vs hypertrophic cardiomyopathy). Classification of cardiomyopathy subtype may improve delivery management of pregnant patients with cardiomyopathy to reduce adverse outcomes. Additionally, in using the NIS as our data source, we were limited by the inability to utilize a validated cardiovascular risk score in our analyses. Furthermore, although we estimated health care costs at the time of delivery, we were unable to estimate the future financial and health impacts these adverse events may have on this population. There is growing evidence to suggest that those with cardiovascular insults in pregnancy, such as hypertensive disorder of pregnancy, have a twofold higher risk of developing future CVD.[29] Moreover, the NIS solely captures pregnant patients between the ages of 18 and 50 years, which may skew the results toward a slightly older population, not inclusive of teenage pregnancies, which carry a burden of pre-eclampsia, especially in Black, Indigenous, and people of color persons. Our results likely underestimate the financial burden faced by patients and health care systems following pregnancies complicated by CVD and do not take into consideration the implications of any cost associated with neonatal morbidity for preterm birth or anomalies.

CONCLUSIONS

In summary, this is one of the largest studies to date to identify key risk factors for adverse pregnancy and cardiovascular outcomes in pregnant persons with CVD and is the first to estimate the associated health care costs of morbidity and mortality in birthing persons with CVD. Our study emphasizes the need to improve risk stratification and delivery management in pregnancies complicated by CVD, specifically in those with cardiomyopathy, to address the growing morbidity rates within cardio-obstetrics. Pregnant people with CVD experience immense health care costs and poor clinical outcomes, requiring improved treatment paradigms and resource allocation.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: CVD in pregnancy is associated with high rates of adverse cardiac, obstetric, and fetal outcomes.

TRANSLATIONAL OUTLOOK: This study highlights the association of key clinical and demographic factors with CVD during pregnancy to emphasize those at highest risk for complications, allow for risk stratification, and provide individualized patient counseling. These findings translate directly to individual patient care practices, system-based practice, and inform resource allocation on a larger scale.

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