# Comparison of severe maternal morbidity in pregnancy by modified World Health Organization Classification of maternal cardiovascular risk



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## Abstract

**Background** To compare rates of severe maternal morbidity (SMM) for pregnant patients with a cardiac diagnosis classified by the modified World Health Organization (mWHO) classification to those without a cardiac diagnosis.

**Methods** This retrospective study using the 2015-2019 Nationwide Readmissions Database identified hospitalizations, comorbidities, and outcomes using diagnosis and procedure codes. The primary exposure was cardiac diagnosis, classified into low-risk (mWHO class I and II) and moderate-to-high-risk (mWHO class II/III, III, or IV). The primary outcome was SMM or death during the delivery hospitalization; secondary outcomes included cardiac-specific SMM during delivery hospitalizations and readmissions after the delivery hospitalization.

**Results** A weighted national estimate of 14,995,122 delivery admissions was identified, including 46,541 (0.31%) with mWHO III diagnoses and 37,330 (0.25%) with mWHO II/III-IV diagnoses. Patients with mWHO II/III-IV diagnoses experienced SMM at the highest rates (22.8% vs 1.6% for no diagnosis; with adjusted relative risk (aRR) of 5.67 [95% CI: 5.36-6.00]). The risk of death was also highest for patients with mWHO II/III-IV diagnoses (0.3% vs <0.1% for no diagnosis; aRR 18.07 [95% CI: 12.25-26.66]). Elevated risk of SMM and death persisted to 11 months postpartum for those patients with mWHO II/III-IV diagnoses.

**Conclusions** In this nationwide database, SMM is highest among individuals with moderate-to-severe cardiac disease based on mWHO classification. This risk persists in the year postpartum. These results can be used to enhance pregnancy counseling. (Am Heart J 2022;250:11–22.)

Cardiovascular disease is the leading cause of maternal mortality in the United States. Data extracted from the Centers for Disease Control and Prevention's Pregnancy Mortality Surveillance System from 2011 to 2013 suggest that cardiovascular conditions and cardiomyopathy together account for 26% of pregnancy-related deaths.<sup>1</sup>

E-mail address: anna.denoble@yale.edu. 0002-8703 © 2022 Elsevier Inc. All rights reserved. https://doi.org/10.1016/j.ahj.2022.04.009 The rising impact of cardiovascular disease in pregnancy is attributed to rising maternal age and obesity, increasing prevalence of acquired cardiovascular co-morbidities among women of childbearing age, improved pediatric congenital heart disease outcomes permitting survival into adulthood, and persistent racial/socioeconomic disparities.<sup>2-7</sup> Pregnant people with cardiac disease are at higher risk for adverse cardiovascular, neonatal, and obstetric complications, although the degree and breadth of risk can vary widely depending on the underlying diagnosis and is often not well-quantified in the literature.<sup>8,9</sup>

There are currently 3 primary risk or classification models used to predict adverse cardiovascular events in pregnancy for women with pre-existing cardiac disease. These are the CARPREG II risk score, the ZA-HARA risk score, and the modified World Health Organization classification of maternal cardiovascular risk (mWHO).<sup>10-12</sup> The ZAHARA risk score is specifically designed for women with congenital heart disease, while

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CARPREG II and the mWHO classification provide estimates of the risk of adverse cardiac events for women with both congenital and acquired heart disease. None of these models are comprehensive in their inclusion of cardiac diagnoses. The mWHO classification outperforms CARPREG I (the first iteration of CARPREG) and ZAHARA in terms of predicting adverse cardiac events in pregnancy among women with congenital heart disease<sup>13,14</sup> and acquired heart disease.<sup>15,16</sup> The performance of the mWHO classification has not been directly compared to CARPREG II. The outcome predicted for all the models is adverse cardiac events, typically including arrhythmia, heart failure or pulmonary edema, transient ischemic attack, stroke, dissection, myocardial infarction, cardiac arrest, or maternal death. The models do not capture the risk of other adverse maternal outcomes, such as mechanical ventilation, sepsis, preeclampsia, or transfusion. However, the mWHO classification does divide the risk of maternal morbidity and mortality into no, small, intermediate, significantly and extremely high risk, providing a general guide to the overall risks of pregnancy for individuals with cardiac disease.

The mWHO classification divides cardiac diagnoses into 5 classes based on risk of pregnancy and provides predicted maternal adverse cardiac event rates.<sup>12,17,18</sup> Women in mWHO class I are considered at no detectable increased risk of maternal morbidity and mortality, mWHO II are at small increased risk, mWHO II/III are at intermediate increased risk, mWHO III are at significantly increased risk, and mWHO IV are at such high risk of maternal morbidity and mortality that pregnancy is considered contraindicated. Validation of the predicted maternal adverse cardiac event rates and risk of morbidity and mortality associated with the mWHO classes in a large United States population has yet to be completed.

The primary aim of this study was to quantify and compare rates of severe maternal morbidity (SMM) and mortality during delivery hospitalization in a large, nationwide database among pregnant women with no, low-, and high-risk cardiac disease using the mWHO classification. Secondly, we aimed to examine SMM and mortality up to 11 months postpartum and to compare outcomes between those who did and did not experience cardiac morbidity during their delivery hospitalization.

### Methods

This was a retrospective cohort study utilizing the Nationwide Readmissions Database (NRD), Healthcare Cost and Utilization Project, Agency for Healthcare Research and Quality.<sup>19</sup> The NRD dataset is a large administrative dataset that, in 2019, contained hospitalizations for 30 states, representing 61.8% of the US population and 60.4% of all hospitalizations. Data available in each record include demographic information (eg, age, gender, primary payer), diagnosis and procedure

codes, hospital characteristics, including location and academic affiliation, hospital length of stay, inpatient charges, and discharge disposition. Methods used for the purposes of this analysis are further described in detail elsewhere.<sup>20</sup> Delivery hospitalizations from October 1, 2015 to December 31, 2019 were included. The final quarter of 2015 was selected as the start date for the study as this was the date of adoption of International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10) for billing in the United States, which provided a significant increase in the granularity of disease coding. At the time of this analysis, December 2019 was the most recent NRD data available for review.

The exposure of interest was a diagnosis code during the delivery hospitalization consistent with cardiac disease in pregnancy. ICD-10 codes were used to identify women with a cardiac disease diagnosis (Supplementary Table 1). Women were divided into 3 comparator groups. The first included all women with a delivery hospitalization within the given timeframe who did not have one of the cardiac diagnosis codes of interest. The remaining 2 groups included women with a diagnosis of cardiac disease, which were subsequently classified by mWHO classification and divided into groups by mild or moderate-to-severe cardiac disease.<sup>12</sup> The use of billing codes limited the degree of precision of the cardiac diagnoses and ability to divide into the 5 separate mWHO classes. For example, repaired congenital heart disease (CHD) lesions could not be differentiated from unrepaired CHD lesions, as they are in the mWHO classification, and moderate left ventricular impairment cannot be differentiated from severe. However, when mWHO class I and mWHO class II diagnoses were combined, they were mutually exclusive of the diagnoses included in mWHO classes II-III, III, and IV (Supplementary Table 1). This allowed a comparison of the outcomes between diagnoses included in mWHO classes I and II, which are associated with a lower risk of adverse cardiac events, and those diagnoses included in mWHO classes II/III, III, and IV, which are associated with a moderate-to-high risk of adverse cardiac events. Repaired aortic coarctation was only included in the mWHO I-II group. To summarize, the cohorts included women without cardiac disease, women with mWHO I-II cardiac disease (mWHO I-II), and women with mWHO II-III, III, or IV cardiac disease (mWHO II/III-IV). For individuals who might have more than 1 cardiac diagnosis in different mWHO categories, the individual was assigned a cohort according to the most severe diagnosis. Aortic root dilation was excluded from the exposures of interest for 2 reasons. First, the degree of aortic root dilation was unable to be specified by ICD-10 codes. Second, the ICD-10 code for aortic aneurysm was included in the SMM primary outcome, as noted below. Underlying aortopathies, such as Marfan syndrome and bicuspid aortic valve, were included.

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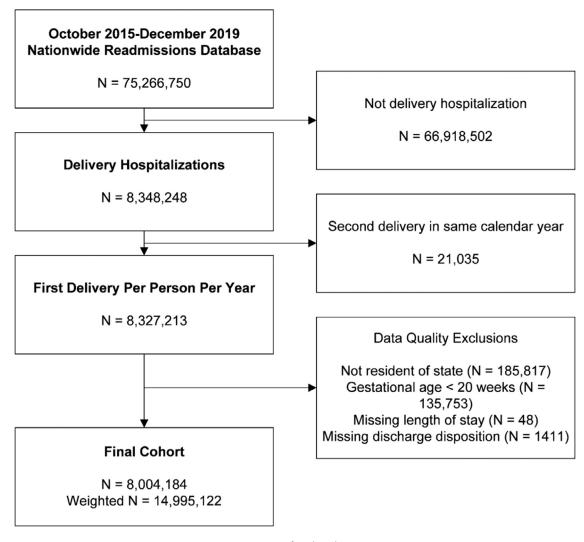
#### Table 1. Primary and secondary outcomes

Primary outcome		Secondary outcomes
Severe maternal morbidity (SMM) o	r mortality	Nontransfusion SMM or mortality
Acute myocardial infarction	Puerperal cerebrovascular	SMM minus blood product
Aortic aneurysm	disorders	transfusion
Acute renal failure	Pulmonary edema/acute	Cardiac SMM or
Adult respiratory distress	heart failure	mortality
syndrome	Severe anesthesia	Acute myocardial infarction
Ámniotic fluid embolism	complications	Aortic aneurysm
Cardiac arrest/ventricular	Sepsis	Cardiac arrest/ventricular
fibrillation	Shock	fibrillation
Conversion of cardiac rhythm	Sickle cell disease with crisis	Conversion of cardiac rhythm
Disseminated intravascular	Air and thrombotic embolism	Heart failure/arrest during
coagulation	Blood products transfusion	surgery or procedure
Eclampsia	Hysterectomy	Pulmonary edema/acute
Heart failure/arrest during	Temporary tracheostomy	heart failure
surgery or procedure	Mechanical ventilation	Preterm birth
577 F		Cesarean delivery

The primary outcome was a composite of severe maternal morbidity, as defined by the Centers for Disease Control and Prevention (CDC), and maternal mortality occurring during the delivery hospitalization. Table 1 includes the specific CDC Severe Maternal Morbidity Indicators included in the primary outcome, as well as secondary outcomes.<sup>21</sup> Secondary outcomes during the delivery hospitalization included cardiac-specific severe maternal morbidity (as outlined in Table 1) and mortality, nontransfusion severe maternal morbidity or mortality, preterm birth (defined by presence of ICD-10 code Z3A.xx, with xx the digits coding gestational age < 37weeks), and cesarean delivery rather than vaginal delivery.

In addition to analyzing events during the delivery hospitalization, we also evaluated readmissions for SMM and cardiac-specific SMM, as well as readmissions ending in death following delivery. The NRD is a calendar year dataset (ie, there is no crossover between years of the dataset) and reports discharge date at the level of month; making the conservative assumption that discharges occur at the end of the month, the longest follow-up period available is thus 11 months (for patients discharged in January), and we accordingly treated patients as being censored (lost to follow-up) based on their month of discharge (eg, 1 month for November, 2 months of October, etc.). In evaluating readmissions, patients were stratified based on whether they had experienced a cardiacspecific SMM event during their delivery hospitalization in order to examine rates of SMM occurring after the delivery admission both for those who had an initial adverse cardiac event during their delivery hospitalization and those that did not.

Covariates of interest that were available in the NRD dataset included age in years at admission, calendar year and quarter, primary expected payer, hospital characteristics, delivery type, and medical comorbidities, using a previously validated obstetric-specific comorbidity index.<sup>22</sup> The comorbidity index includes preexisting heart disease and pulmonary hypertension as comorbid conditions, and since these were incorporated into the mWHO categories, we removed these variables from our comorbidity adjustment. Univariate statistical methods, incorporating the weighted, stratified, and clustered nature of the NRD, were used to assess the univariate associations between demographics, cardiac disease, and outcomes. Relative risk regression (incorporating the NRD's weighting, stratification, and clustering) using a Poisson model was used to assess for associations between cardiac disease and delivery hospitalization outcomes, adjusting for patient age, comorbidities, delivery mode (except for the cesarean outcome), and calendar year and quarter. Similarly, a weighted Cox proportional hazards model was used to analyze readmissions data, controlling for the same covariates and again accounting for the complex survey methods of the NRD. Kaplan-Meier failure estimates were calculated for readmissions for SMM or mortality, cardiac-specific SMM or mortality, death, or readmission for any reason or death occurring after discharge from the delivery hospitalization for each mWHO classification group and by whether any cardiac-specific SMM had occurred during the delivery stay. Stratification by whether subjects had experienced cardiac SMM during their delivery hospitalization was performed to further examine the risks of cardiac disease in the postpartum period based on the outcome of their delivery hospitalization. Statistical analysis was completed in Stata Statistical Software, Version 16.1 (Statacorp, College Station, TX). A 2-sided alpha value of 0.05 was considered statistically significant. Given the retrospective nature of



Derivation of study cohort.

this analysis using an existing, limited dataset, the Duke University School of Medicine Institutional Review Board deemed it exempt from review.

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#### Results

A total of 8,004,184 patients experienced a delivery hospitalization between October 2015 and December 2019 (Figure 1). When weighted to produce estimates of the national population, rather than only the sample included in the NRD dataset, this sample

equated to 14,995,122 patients. For the remainder of this manuscript, numbers are reported as a weighted statistic. Of the total weighted delivery hospitalizations, 14,911,251 (99.5%) women did not have cardiac disease, 46,541 (0.3%) had mWHO I-II cardiac disease. The sample sizes for individual cardiac diagnoses, when available, are provided in Supplementary Table 1. Women with cardiac disease differed in age (28.8 vs 30.2 vs 29.8 years for no cardiac disease, mWHO I-II, and mWHO II/III-IV, respectively; *P* < .001), delivery at a metropolitan teaching hospital (69.5%, 76.6% and 81.2% for no cardiac disease, mWHO I-II, II/III-IV, and unclassified, respectively; *P* < .001), and comorbid conditions compared to women without cardiac disease (Table 2).

Detailed SMM event rates are provided in Supplementary Table 2. All delivery hospitalization outcomes demonstrated increased probability in unadjusted analyses with increasing severity of mWHO class (Figure 2). Specifically, mWHO I-II was associated with higher rates of SMM, including nontransfusion SMM and cardiacspecific SMM, death, preterm birth, and cesarean delivery when compared to patients without cardiac disease; mWHO II-III/IV was associated with even higher rates of all outcomes. These findings were confirmed in adjusted analyses (Figure 3). Patients with mWHO II/III-IV disease had a 5.67-times higher adjusted probability of any SMM or mortality during their delivery hospitalization (95% confidence interval: 5.36, 6.00) compared with no cardiac disease, with similar notably higher rates of nontransfusion and cardiacspecific SMM. Death, preterm birth, and cesarean delivery rates were similarly elevated with one-quarter of those with mWHO II/III-IV disease delivering preterm and one-half delivering by cesarean. Results from unweighted regression models (not incorporating the complex design of the NRD) were similar (Supplementary Figure 1).

Among patients surviving their delivery hospitalization, we examined outcomes for those with cardiac disease compared to no cardiac disease up to 11 months postpartum following the delivery hospitalization (Figure 4). Occurrence of a cardiac SMM event during the delivery hospitalization was observed to be a powerful predictor of subsequent adverse outcomes, and for this reason, analyses were performed stratified on this variable. In unadjusted analyses, with the exception of death for those with mWHO I-II cardiac disease, rates of adverse outcomes were higher for patients with cardiac disease than those without cardiac disease regardless of whether they had experienced cardiac SMM during their delivery stay. These differences in postpartum outcomes were less pronounced for those with mWHO class I-II disease.

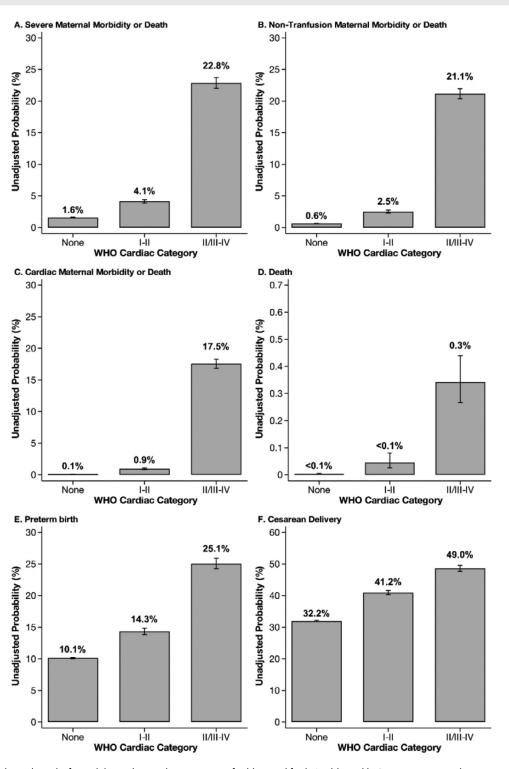
Finally, comparisons were adjusted for potential confounding factors in Cox proportional hazard models (Table 3). For patients with cardiac SMM during their delivery stay, associations between mWHO I-II disease versus no cardiac disease and rates of adverse outcome were not statistically significant. In contrast, except for death, there were significant positive associations noted between mWHO II/III-IV disease and adverse outcomes. Among patients without cardiac SMM during the delivery stay, both mWHO I-II and mWHO II/III-IV cardiac disease compared to no cardiac disease was associated with increased risk of SMM-related rehospitalizations. However, death was only positively associated with mWHO II/III-IV cardiac disease, but not mWHO I-II cardiac disease, compared to no cardiac disease in this group that did not experience cardiac SMM during the delivery stay. Results from unweighted regression models (not incorporating the complex design of the NRD were similar (Supplementary Table 3)).

## Discussion

In this nationwide cohort, pregnant people with mWHO II/III, III, or IV cardiac lesions in pregnancy, as defined by the modified World Health Organization classification of maternal cardiovascular risk, were more likely to experience severe maternal morbidity or mortality both during their delivery hospitalization and during readmissions up to 11 months postpartum compared to pregnant people without cardiac disease. In fact, nearly one-quarter of pregnant people with mWHO II/III-IV cardiac lesions experienced severe maternal morbidity or mortality or death, 18% experienced cardiac-specific morbidity or mortality, and the risk of death alone was 0.3% during the delivery hospitalization.

Our results also provide important insight into the temporal relationship between cardiac disease and SMM and mortality. Notably, regardless of whether they had experienced cardiac SMM during their delivery hospitalization, those with mWHO II/III-IV cardiac disease experienced a significantly increased risk of SMM, nontransfusion SMM, and cardiac SMM throughout the 11 months postpartum compared to those without a cardiac diagnosis. In contrast, only those with a mWHO I-II cardiac diagnosis who did not experience cardiac SMM during their delivery hospitalization remained at increased risk for SMM and death in the 11 months postpartum. It is possible that this group with lower risk cardiac disease who do not experience cardiac SMM during the delivery hospitalization are followed less closely in the postpartum period. These findings suggest that vigilance must be maintained throughout the postpartum period in people with mWHO II/III-IV and mWHO I-II cardiac disease, even if they do not experience significant adverse cardiac events during their delivery hospitalization. Such vigilance could be accomplished by continued close followup by the pregnancy heart team during the year postpartum.<sup>12,18</sup>

Our findings corroborate the mWHO classification of maternal cardiovascular risk. The mWHO classification was initially devised based on expert opinion and theoretical risk, with the risk of adverse cardiac events ranging from 2% to 5% in mWHO class I, to 11% to 19% in mWHO class II/III, to >27% in mWHO class IV.<sup>18</sup> The unadjusted probability of cardiac SMM or mortality in our study for the higher-risk mWHO classes was 18%, which is consistent with the predicted adverse cardiac event rates. Albeit based on expert opinion, this classification system often performs superiorly in the prediction of adverse cardiac events in pregnancy to other risk prediction models, such as CARPREG and ZAHARA.<sup>13-16</sup> The data from our large, nationwide study provides one of the most comprehensive assessments, based on standardized



Unadjusted results from delivery hospitalizations, stratified by modified World Health Organization cardiac category.

	Modified World Health Organization classification				
	Overall (N = 8,004,184) (Weighted N = 14,995,122)	No heart disease (N = 7,959,609) (Weighted N = 14,911,251)	WHO I-II (N = 24,947) (Weighted N = 46,541)	WHO II/III-IV (N = 19,628) (Weighted N = 37,330)	P*
	Mean (Standard Dev	iation) or %			
Patient demographics Age in years at admission	28.8 (5.8)	28.8 (5.8)	30.2 (5.9)	29.8 (6.0)	<0.001
Primary expected payer <sup>†</sup>	20.0 (0.0)	20.0 (0.0)	30.2 (3.7)	27.0 (0.0)	<0.001
Medicare	119,392 (0.8)	117,712 (0.8)	635 (1.4)	1,045 (2.8)	
Medicaid	6,300,543 (42.1)	6,268,908 (42.1)	15,512 (33.4)	16,124 (43.2)	
Private	7,902,339 (52.8)	7,855,343 (52.7)	28,396 (61.1)	18,600 (49.9)	
Self-pay	220,180 (1.5)	219,297 (1.5)	446 (1.0)	437 (1.2)	
No charge	7,558 (0.1)	7,528 (0.1)	11 (0.0)	19 (0.1)	
Other Zie Golde Madiene Unwerkald Incoment	427,594 (2.9)	425,058 (2.9)	1,478 (3.2)	1,057 (2.8)	0.001
Zip Code Median Household Income† Quartile 1 (Lowest)	4,107,300 (27.6)	4,085,289 (27.6)	11,134 (24.1)	10,877 (29.3)	<0.001
Quartile 2	3,894,478 (26.1)	3,873,575 (26.1)	11,221 (24.3)	9,681 (26.1)	
Quartile 3	3,780,479 (25.4)	3,758,884 (25.4)	12,423 (26.9)	9,172 (24.7)	
Quartile 4 (Highest)	3,116,885 (20.9)	3,098,057 (20.9)	11,467 (24.8)	7,361 (19.8)	
Hospital characteristics		.,,			
Hospital Bed Size					< 0.001
Small	2,514,262 (16.8)	2,503,663 (16.8)	6,294 (13.5)	4,305 (11.5)	
Medium	4,295,153 (28.6)	4,275,238 (28.7)	11,865 (25.5)	8,050 (21.6)	
Large	8,185,708 (54.6)	8,132,350 (54.5)	28,382 (61.0)	24,976 (66.9)	
Hospital location / teaching status			=		<0.001
Metropolitan nonteaching	3,178,062 (21.2)	3,165,133 (21.2)	7,804 (16.8)	5,125 (13.7)	
Metropolitan teaching	10424392 (69.5)	10358423 (69.5)	35,668 (76.6)	30,302 (81.2)	
Nonmetropolitan hospital Comorbid conditions	1,392,668 (9.3)	1,387,695 (9.3)	3,070 (6.6)	1,904 (5.1)	
Advanced maternal age	2,624,113 (17.5)	2,604,334 (17.5)	11,210 (24.1)	8,570 (23.0)	<0.001
Asthma	785,843 (5.2)	774,202 (5.2)	5,189 (11.1)	6,453 (17.3)	< 0.001
Bariatric surgery	41,532 (0.3)	41,056 (0.3)	245 (0.5)	231 (0.6)	< 0.001
Bleeding disorder	327,773 (2.2)	323,751 (2.2)	2,009 (4.3)	2,013 (5.4)	< 0.001
BMI greater or equal to 40	501,552 (3.3)	497,045 (3.3)	2,088 (4.5)	2,419 (6.5)	< 0.001
Chronic hypertension	499,773 (3.3)	491,341 (3.3)	3,324 (7.1)	5,109 (13.7)	< 0.001
Chronic renal disease	38,633 (0.3)	37,375 (0.3)	270 (0.6)	988 (2.6)	<0.001
Connective tissue or autoimmune disease	30,824 (0.2)	29,970 (0.2)	352 (0.8)	502 (1.3)	< 0.001
Gastrointestinal disease	847,655 (5.7)	837,319 (5.6)	5,587 (12.0)	4,749 (12.7)	< 0.001
Gestational Diabetes Mellitus	1,143,423 (7.6)	1,136,040 (7.6)	3,997 (8.6)	3,386 (9.1)	< 0.001
Gestational hypertension / preeclampsia without severe features	1,240,779 (8.3)	1,232,357 (8.3)	4,541 (9.8)	3,881 (10.4)	<0.001
HIV/AIDS	13,531 (0.1)	13,406 (0.1)	50 (0.1)	75 (0.2)	<0.001
Mental health disorder	1,149,200 (7.7)	1,135,363 (7.6)	7,801 (16.8)	6,036 (16.2)	< 0.001
Multiples gestation	269,703 (1.8)	267,374 (1.8)	1,187 (2.6)	1,142 (3.1)	< 0.001
Neuromuscular disease	74,543 (0.5)	73,461 (0.5)	547 (1.2)	535 (1.4)	< 0.001
Placenta accreta spectrum	16,928 (0.1)	16,729 (0.1)	102 (0.2)	98 (0.3)	< 0.001
Placenta previa	69,523 (0.5)	68,954 (0.5)	338 (0.7)	232 (0.6)	< 0.001
Placental abruption	161,879 (1.1)	160,470 (1.1)	642 (1.4)	767 (2.1)	< 0.001
Preeclampsia with severe features	496,658 (3.3)	489,464 (3.3)	2,437 (5.2)	4,756 (12.7)	<0.001
Preexisting anemia	1,971,304 (13.1)	1,955,613 (13.1)	8,131 (17.5)	7,560 (20.3)	<0.001
Preexisting diabetes mellitus	203,955 (1.4)	201,432 (1.4)	969 (2.1)	1,555 (4.2)	< 0.001
Preterm birth	1,497,610 (10.0)	1,481,719 (9.9)	6,586 (14.2)	9,304 (24.9)	< 0.001
Prior cesarean birth Substance use disorder	2,630,037 (17.5)	2,611,406 (17.5)	9,855 (21.2)	8,775 (23.5)	<0.001
Thyrotoxicosis	978,538 (6.5) 39,656 (0.3)	970,828 (6.5) 38,979 (0.3)	3,311 (7.1) 392 (0.8)	4,399 (11.8) 284 (0.8)	<0.001 <0.001
Delivery type	37,000 (0.3)	50,777 (0.5)	572 (0.0)	204 (0.0)	<0.001 <0.001
Spontaneous vaginal	9,494,266 (63.7)	9,451,868 (63.8)	25,389 (54.9)	17,009 (46.0)	~0.001
Operative vaginal	608,019 (4.1)	604,398 (4.1)	1,778 (3.8)	1,844 (5.0)	
Cesarean	4,802,249 (32.2)	4,765,067 (32.2)	19,046 (41.2)	18,136 (49.0)	

Table 2. Baseline characteristics, stratified by Modified World Health Organization Classification.

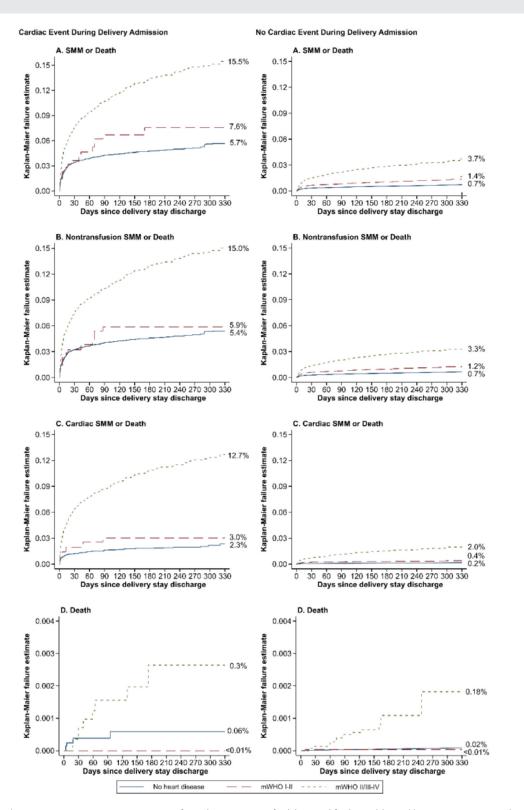
\*P-values by weighted linear regression for continuous variables and weighted chi2 test for binary/categorical variables.

†Missing values in Payer (8,744 observations) and ZIP Code Income Quartile (54,174 observations).

Adjusted Relative	<b>Risk (9</b> 1 2	5% Co	8	ence 16	Inter 32	<b>val)*</b> 64
Severe Maternal Morbi mWHO I-II mWHO II/III-IV	1	.87 (1.	75, 2		6, 6.0	0)
Non-Transfusion Mater mWHO I-II 2.47 (2.24, 2 mWHO II/III-IV 8.		-		lorta	lity	
Cardiac Maternal Morb mWHO I-II 4.80 (4 mWHO II/III-IV	14, 5.56			, 47.7	74) ⊫	4
<b>Death</b> mWHO I-II 5.83 (3.15, mWHO II/III-IV 18	 , 10.79) 9.07 (12.2				-1	
Preterm Birth mWHO I-II mWHO II/III-IV	■ 1.15 ■ 1.32	(1.12, 2 (1.28,		)		
Cesarean section mWHO I-II mWHO II/III-IV * All comparisons relative age, delivery type (excep comorbid conditions, ca	e to no h ot for ces	(1.13, eart di arean	1.17) sease outco	ome),	usted	for

Adjusted in-hospital outcomes, stratified by modified World Health Organization cardiac category, compared to no heart disease.

definitions, of severe maternal morbidity and mortality in individuals with cardiac disease to date. While representing an average of 3 of the mWHO classes (mWHO classes II/III, III, and IV), this study confirms the significantly elevated risk of severe complications among pregnant people with mWHO class II/III-IV heart disease compared to no heart disease and compared to mWHO class I-II disease. Not to be trivialized, however, our results also highlight the increased risk of severe complications in those with cardiac diagnoses considered to be mild (mWHO class I and II). "Low risk" is not the equivalent of "no risk," with this group experiencing a nearly 2-fold increase in the risk of severe maternal morbidity and mortality compared to those with no cardiac diagnosis. These findings can be used to strengthen the mWHO classification. Furthermore, the results may also aid clin-



Unadjusted Kaplan-Maier curves comparing rates of readmission, stratified by modified World Health Organization cardiac category, compared to no heart disease.

	Cardiac SMM during delivery hospitalization Adjusted hazard ratio (95% confidence interval) <sup>=</sup>	No Cardiac SMM during delivery hospitalizatio
Any SMM or death		
mWHO I-II	1.72 (0.996, 2.98)	1.53 (1.34, 1.76)
mWHO II/III-IV	1.70 (1.42, 2.03)	3.17 (2.84, 3.54)
Nontransfusion SMM or death		
mWHO I-II	1.46 (0.79, 2.69)	1.57 (1.36, 1.81)
mWHO II/III-IV	1.69 (1.42, 2.02)	3.20 (2.85, 3.59)
Cardiac SMM or death		
mWHO I-II	1.75 (0.73, 4.17)	1.89 (1.48, 2.40)
mWHO II/III-IV	3.03 (2.41, 3.81)	6.97 (5.99, 8.01)
death		
mWHO I-II	t	0.48 (0.07, 3.29)
mWHO II/III-IV	2.16 (0.59, 7.95)	9.61 (5.13, 18.02)

Table 3. Covariate-adjusted outcomes for events following delivery hospitalization

\* All comparisons versus patients without cardiac disease. Adjusted for age, delivery type, comorbid conditions, calendar year/quarter, and patient age.

<sup>†</sup> Unable to estimate due to low event rate.

icians in counseling patients with cardiac disease about the risks of pregnancy, delivery, and the postpartum period.

Finally, our results shed light on some of the increased obstetric risks for patients with cardiac disease in pregnancy. Both those with mWHO I-II and those with mWHO II/III-IV cardiac disease were at higher risk for preterm birth and cesarean delivery. While we were unable to determine what proportions of these differences were due to iatrogenic causes, these differences are notable. Preterm birth carries long-term risks to the neonate,<sup>23</sup> while cesarean delivery carries increased risks of maternal complications.<sup>24,25</sup> Most guidelines regarding management of cardiovascular disease in pregnancy recommend vaginal delivery over cesarean in the absence of obstetric indications for cesarean delivery.<sup>12,26</sup> In fact, data from the ROPAC registry suggests that planned cesarean delivery in patients with cardiac disease results in earlier delivery and lower neonatal birth weight.<sup>27</sup> There are only a select few cardiac diagnoses, mostly in mWHO class IV, that warrant a planned cesarean birth. The discrepancy in cesarean birth rates seen in our data between those without cardiac disease and those with mWHO class I-II and class II/III-IV cardiac disease highlights the need for continued education of obstetric and cardiology providers regarding the safe and appropriate intrapartum management of cardiac disease in pregnancy.

The strengths of this study include the use of a large, nationwide database providing one of the largest samples available to analyze outcomes of cardiac disease in pregnancy. Additional strengths include the use of the CDC's standardized definition of severe maternal morbidity, as well as the use of validated ICD-10 comorbidity indices.<sup>21,22</sup> While assessment of outcomes was limited to a maximum of 11-months postpartum given lack of linkage between years in the NRD database, the analysis of

outcomes for such a long postpartum period provides insight into the potential delayed risks of pregnancy for individuals with cardiac disease and is consistent with the definition of pregnancy-related death.

We recognize several limitations. The NRD dataset only provides data on hospitalizations and readmissions. Rather than only including pregnant patients with antepartum admissions, which could have overestimated rates of adverse events, we included delivery hospitalizations (which would capture most pregnancies ending in delivery) and subsequent readmissions. However, this limitation may have resulted in an underestimation of the true event rate in this population. For example, events (eg, ICU admission) occurring prior to a delivery hospitalization that did not culminate in delivery were not included in the estimation. These limitations further highlight that the true risk of any severe maternal morbidity or death related to cardiac disease in pregnancy is likely higher than what is presented here. As is true for all retrospective analyses utilizing administrative datasets, this study was further limited by reliance on ICD-10 diagnosis codes, which may not have captured all exposures and outcomes. Under-coding may have led to an underestimation cardiac diagnoses, comorbidities, and outcomes. For example, the 3.3% of subjects identified as having a BMI  $\geq$  40 is lower than the expected rate of 9% in the US population reported by the CDC in 2017-2018.<sup>28</sup> The reliance on ICD-10 diagnosis codes prevented more granular division of the mWHO classes into classes I, II, II/III, III, and IV.

In conclusion, the results of this study provide valuable supporting data that can be used when counseling people with cardiac disease in pregnancy. Beyond insights into the absolute risk of severe maternal morbidity and mortality from a large, nationwide database, this study highlights that the risks of pregnancy complicated by cardiac disease extend beyond delivery into the year postpartum. While pregnant people with mWHO II/III-IV disease are at highest risk for SMM and mortality, those with lower risk lesions classified as mWHO I-II also have a significantly elevated risk compared to those without cardiac disease that should not be minimized.

## **Credit Author Statement**

Anna E. Denoble: conceptualization, methodology, validation, writing – original draft; Lauren A. Wein: methodology, validation, resources, project administration; Sarah A. Goldstein: conceptualization, methodology, writing – review and editing; Chad A. Grotegut: conceptualization, methodology, writing – review and editing; Jerome J. Federspiel: conceptualization, methodology, validation, formal analysis, resources, supervision.

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## **Conflict of interest**

The authors of this manuscript have no conflicts of interest to disclose.

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## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ahj. 2022.04.009.

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