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Adverse Maternal Fetal Environment Partially Mediates Disparate Outcomes in Non-White Neonates with Major Congenital Heart Disease

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Abstract

Objective—To determine whether differential exposure to an adverse maternal fetal environment partially explains disparate outcomes in infants with major congenital heart disease (CHD).

Study design—Retrospective cohort study utilizing a population-based administrative California database (2011-2017). Primary exposure: Race/ethnicity. Primary mediator: Adverse maternal fetal environment (evidence of maternal metabolic syndrome and/or maternal placental syndrome). Outcomes: Composite of 1-year mortality or severe morbidity and days alive out of hospital in the first year of life (DAOOH). Mediation analyses determined the percent contributions of mediators on pathways between race/ethnicity and outcomes after adjusting for CHD severity.

Results—Included were 2747 non-Hispanic White infants (reference group), 5244 Hispanic, and 625 non-Hispanic Black infants. Hispanic and non-Hispanic Black infants had a higher risk for composite outcome (crude OR: 1.18; crude OR: 1.25, respectively) and fewer DAOOH (−6 & −12 days, respectively). Compared with the reference group, Hispanic infants had higher maternal metabolic syndrome exposure (43% vs 28%, OR: 1.89), and non-Hispanic Black infants had higher maternal metabolic syndrome (44% vs 28%; OR: 1.97) and maternal placental syndrome exposure (18% vs 12%; OR, 1.66). Both maternal metabolic syndrome exposure (OR: 1.21) and

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maternal placental syndrome exposure (OR: 1.56) were related to composite outcome and fewer DAOOH (−25 & −16 days, respectively). Adverse maternal fetal environment explained 25% of the disparate relationship between non-Hispanic Black race and composite outcome and 18% of the disparate relationship between Hispanic ethnicity and composite outcome. Adverse maternal fetal environment explained 16% (non-Hispanic Black race) and 21% (Hispanic ethnicity) of the association with DAOOH.

Conclusions—Increased exposure to adverse maternal fetal environment contributes to racial and ethnic disparities in major CHD outcomes.

In children who have undergone cardiac surgery, several large, multicenter observational studies have identified consistent relationships between race/ethnicity and adverse outcomes including operative mortality, postoperative length of hospital stay, and complications such as unplanned transcatheter interventions and cardiac reoperations.[1-7] A population-based analysis found that although overall mortality attributable to congenital heart disease (CHD) has decreased over the last 2 decades, disparities persist based on race and ethnicity.[8] Recent studies have found that socioeconomic factors and other social determinants of health may explain a portion of the observed disparate outcomes.[9-11] However, the etiology for these disparate outcomes is not fully understood and in need of urgent evaluation.

Infant CHD outcomes are known to be influenced by a number of noncardiac factors, such as premature birth, low birth weight (BW), and noncardiac abnormalities, among others.[12-15] Certain maternal conditions, such as diabetes and hypertensive disorders of pregnancy (ie, preeclampsia, eclampsia, and gestational hypertension), can complicate pregnancies and have been associated with adverse intermediate-term maternal outcomes, while also contributing to neonatal morbidity even in neonates without CHD.[15-17] These conditions may lead to an adverse maternal fetal environment. Recent studies by our group and others have found important associations between the presence of an adverse maternal fetal environment and adverse outcomes in infants with major CHD.[18-20]

In this study, we sought to determine whether the previously reported disparate outcomes experienced by non-Hispanic Black and Hispanic infants with major CHD may be explained in part by greater rates of prior exposure to an adverse maternal fetal environment. Given that in utero growth restriction and premature delivery may be downstream effects of an adverse maternal fetal environment, we hypothesized that some of the disparate outcomes observed in infants with CHD may be related to differential exposure to an unfavorable environment in utero.

Methods

We utilized the California Department of Health Care Access and Information database. This population-based database includes detailed information on infant characteristics derived from all California licensed hospital discharge records (birth hospitalization and readmissions) from birth to 1 year of age, as well as infant birth and death certificates. This information was linked to maternal clinical and demographic characteristics derived from hospital discharge records from 1 year before birth of the infant. The linkage algorithm is described elsewhere.[21] The database contains a total of 3 161 875 linked live births

from years 2011 to 2017. The file provides diagnosis and procedure codes based on the *International Classification of Diseases, 9th and 10th Revision, Clinical Modification* (ICD-9-CM and ICD-10-CM, respectively). The same database has previously been used in multiple studies examining birth and outcomes in infants with CHD.[10,15,19,20] Institutional review board approval was obtained from the Committee for the Protection of Human Subjects within the Health and Human Services Agency of the State of California, and the need for informed consent was waived.

We included all live-born infants with a gestational age of 22-42 completed weeks with major CHD. To classify CHD in infants with multiple ICD codes, we used the framework proposed by the National Quality Forum (PCS-021-09, http://www.qualityforum.org/Home.aspx) and cross-referenced with ICD-9 and ICD-10. A pediatric cardiologist and a pediatric cardiac intensivist reviewed cases to ensure the correct classification of infants with multiple diagnostic or procedure codes. The final diagnosis was reached by consensus. We defined major CHD according to the criteria suggested by Ewer et al as a congenital heart lesion that either required surgery or would be expected (in case of early death) to require surgery within the first year of life.[22] We excluded infants with only minor CHD (mainly consisting of diagnoses of ventricular septal defects without procedure codes and codes for atrial septal defects). We excluded newborns with known chromosomal abnormalities or major structural birth defects other than the cardiac lesions of interest. Structural birth defects were considered “major” if determined by clinical review to result in mortality or major morbidity and likely to be identified at birth or lead to hospitalization during the first year of life.[23]

The primary predictor was maternal race/ethnicity classified as non-Hispanic White, non-Hispanic Black, and any Hispanic ethnicity. For the purposes of this study, cases that self-classified as a race other than those stated earlier in the study were excluded given relatively small sample sizes. Additionally, infants of Asian race were excluded as their outcomes did not differ from those of non-Hispanic White. Race and ethnicity of the mother were self-reported, obtained from the infant’s birth certificate record, and we assumed that the infants were the same race/ethnicity as their mothers.

For the purposes of this study, we defined adverse maternal fetal environment as the presence of either maternal placental syndrome and/or maternal metabolic syndrome. Maternal placental syndrome was defined as the presence of one or more of the following: maternal preeclampsia or eclampsia, gestational hypertension, or placental abruption.[24] Based on available ICD-9 and ICD-10 codes, maternal metabolic syndrome was defined as the presence of one or more of the following: pre-existing diabetes or gestational diabetes, body mass index > 30, or hyperlipidemia. Other exposure variables included prematurity (gestational age [GA] at birth < 37 weeks) and small for gestational age (SGA), a surrogate for in utero growth restriction. We used the method by Fenton et al to generate BW z-scores based on GA and sex.[25] SGA was defined as a BW below the 10th percentile for GA and sex (ie, BW z-score below −1.3).

The primary outcome was a composite measure of 1-year mortality or severe morbidity. Severe morbidity was defined as the occurrence of any of the following procedures

or complications based on ICD-9 and ICD-10 codes: mechanical circulatory support, renal dialysis, diaphragm paralysis, tracheostomy, cardiac arrest, pacemaker, cerebral vascular event, interventricular hemorrhage greater than grade II, necrotizing enterocolitis, periventricular leukomalacia, chronic lung disease, or retinopathy of prematurity (ROP; surgical procedure codes were used to capture the most severe forms of ROP because ICD-9-CM did not capture ROP staging).[15,26] Our secondary outcome was days alive and out of hospital (DAOOH) in the first year of life.

Descriptive statistics are presented using counts (percentages) for binary/categorical variables. We used univariable logistic regression to show the association between race/ethnicity and our predictors and mediators of interest. Similarly, we used univariable logistic regression to show the association between race/ethnicity and the dichotomous outcomes and linear regression to show the association between race/ethnicity and our continuous outcome of DAOOH.

To understand the complex interplay between race/ethnicity, adverse maternal fetal environment (ie, maternal metabolic syndrome and/or maternal placental syndrome), GA at birth, BW z-scores, and outcomes, we considered the conceptual framework shown as a directed acyclic graph in Figure, A. We were interested in 4 potential mediators: maternal metabolic syndrome, maternal placental syndrome, prematurity, and SGA. A mediator is defined as a variable that is on the causal pathway between the predictor and outcome of interest. Our directed acyclic graph proposes that the effects of race/ethnicity on the outcome are partially mediated through maternal metabolic syndrome, maternal placental syndrome, prematurity, and SGA. Furthermore, based on the pathophysiologic concept, maternal placental syndrome and maternal metabolic syndrome are upstream from prematurity and SGA on the causal pathway between race/ethnicity and outcomes.

To perform a mediation analysis, the following conditions need to be met: (1) The primary predictor needs to be associated with the outcome, (2) the primary predictor needs to be associated with the mediators of interest, and (3) the mediators of interest need to be associated with the outcome. To assess these associations, we used univariable logistic or linear regression as appropriate. Results are reported in ORs for logistic regressions and linear coefficients for linear regression with 95% CIs.

Given the complicated framework with several mediators on a single pathway, we used structural equation modeling (SEM) to perform the mediation analysis. SEM is a multivariate statistical framework that is used to model complex relationships between multiple variables. It is a general framework that involves simultaneously solving systems of linear equations and has been used to perform mediation analyses.[27] Using SEM, we calculated the contribution of each pathway in the directed acyclic graph and expressed it as a percentage of the total effect. The total effect is the sum of all the possible pathways between race/ethnicity and outcomes including the direct effect of race/ethnicity and the outcome. We used bootstrapping to obtain bias-corrected estimates and CIs. The bootstrap method is a resampling technique used to estimate statistics on a population by sampling a data set with replacement. By sampling with replacement, each sample observation has 1/n probability of being selected each time. Drawing resamples with replacement from the

observed data, the point estimate found in a large number of resamples is recorded. Looking over this set of point estimates, the values that bound 95% of the entries can be recorded as 95% CI.

We adjusted for severity of CHD using modified Risk Adjustment in Congenital Heart Surgery-1 mortality categories. It was not possible to use the Risk Adjustment in Congenital Heart Surgery-1 risk adjustment tool in its original form because specific surgical details needed for classification are not available in California's Health Care Access and Information database, and the original tool is not applicable to infants who die before undergoing a cardiac surgical procedure.[15]

Missing data were rare in this cohort; however, if a patient was missing data for any variable of interest, he/she was excluded from the analysis. A P value of <0.05 was considered significant for all analyses. All analyses were performed by using Stata version 16.1 (StataCorp LP).

Results

We identified 8616 infants with major CHD, of whom 2747 were of non-Hispanic White race, 5244 were of Hispanic ethnicity, and 625 were of non-Hispanic Black race (Table I; available at www.jpeds.com). SGA was present in 18.5% of non-Hispanic Black patients, compared with 10.9% of Hispanic patients and 10.5% of non-Hispanic White patients. Premature birth occurred in 26% of non-Hispanic Black patients and 18% in each of the Hispanic and non-Hispanic White patient groups. Maternal placental syndrome exposure was highest in mothers of non-Hispanic Black infants at 18.1%, followed by Hispanic (12.1%) and non-Hispanic White (11.7%). Relative to non-Hispanic White infants, non-Hispanic Black and Hispanic infants had greater maternal metabolic syndrome exposure (44.2% and 43.1%, respectively) than non-Hispanic White infants (28.4%) (Table I).

To establish the first condition necessary to perform mediation analyses, we show that our predictor of interest, race/ethnicity, is associated with outcomes. The 1-year mortality was 7.6% (210/2747) in non-Hispanic White infants, 8.2% (51/625) in non-Hispanic Black infants, and 8.3% (437/5244) in Hispanic infants. The composite morbidity/mortality outcome was highest in non-Hispanic Black infants (20.2%), followed by Hispanic infants (19.2%) and non-Hispanic White infants (16.8%). Compared with non-Hispanic White infants, both Hispanic infants and non-Hispanic Black infants had a higher risk for the composite morbidity/mortality outcome (crude OR: 1.18, 95% CI: 1.04-1.33; crude OR: 1.25, 95% CI: 1.01-1.56, respectively). Median DAOOH was highest in non-Hispanic White infants (348, IQR: 323-357), followed by non-Hispanic Black infants (344, IQR: 301-356) and Hispanic infants (345, IQR: 313-357). Thus, Hispanic and non-Hispanic Black infants had fewer DAOOH (−6 days, 95% CI: −11.4 to −2.2 days; −12 days, 95% CI: −21.1 to −3.7 days, respectively) than their non-Hispanic White counterparts (Table II).

To establish the second condition necessary for the mediation analyses, we show the associations between race/ethnicity and our mediators of interest. Compared with non-Hispanic White, non-Hispanic Black race is significantly associated with all 4 mediators

of interest with higher ORs: OR for maternal placental syndrome 1.66 (95% CI: 1.31-2.10), maternal metabolic syndrome 1.97 (95% CI: 1.65-2.36), prematurity 1.65 (95% CI: 1.35-2.02), SGA 1.94 (95% CI: 1.53-2.54) (Table III). In contrast, compared with non-Hispanic White, Hispanic ethnicity was only significantly associated with maternal metabolic syndrome (OR: 1.89, 95% CI: 1.71-2.08) but not with the other 3 potential mediators (Table III). Thus, in these analyses, we did not find that maternal placental syndrome, prematurity, and SGA are potential mediators in the relationship between Hispanic ethnicity and outcomes.

Finally, to establish the third condition necessary for the mediation analyses, we assessed whether the mediators of interest are associated with poor outcomes. Both maternal metabolic syndrome exposure (crude OR: 1.21; 95% CI: 1.09-1.33) and maternal placental syndrome exposure (crude OR: 1.56; 95% CI: 1.36-1.79) were individually associated with the composite morbidity/mortality outcome. Additionally, both maternal placental syndrome and maternal metabolic syndrome exposure were associated with fewer number of DAOOH in the first year of life (−16 days, 95% CI: −20.3 to −12.4 days; and −25.4 days, 95% CI: −33.9 to −16.9 days, respectively) (Table II). Similarly, prematurity and SGA were both associated with an increased composite morbidity/mortality outcome (crude OR: 2.57; 95% CI: 2.30-2.87; and crude OR: 1.65; 95% CI: 1.44-1.9, respectively) and fewer DAOOH (−47.7 days, 95% CI: −52.5 to −42.9 days; and −29.1 days, 95% CI: −34.9 to −23.2 days, respectively) (Table II).

Given the aforementioned conditions, we performed the mediation analyses for non-Hispanic Black vs non-Hispanic White infants according to the directed acyclic graph depicted in Figure B. Its results suggest that adverse maternal fetal environment explained 25% (95% CI: 7.4-40.3%) of the disparate composite outcome between non-Hispanic Black vs non-Hispanic White race and 16.5% (95% CI: 8.0-37.2%) of the difference in DAOOH between those two race groups (Table IV).

For Hispanic infants, the mediation analysis only considered maternal metabolic syndrome as a potential mediator as maternal placental syndrome, prematurity, and SGA were not significantly associated with Hispanic ethnicity and as such did not qualify as mediators (Figure C). The mediation analysis indicated that the maternal metabolic syndrome component of adverse maternal fetal environment explained 18% (95% CI: 8.4-27.2%) of the disparate effect of Hispanic ethnicity vs non-Hispanic White on the composite morbidity/mortality outcome and 20.8% (95% CI: 16.4-26.5%) of the disparate outcome of number of DAOOH (Table IV).

Discussion

Consistent with prior studies, our population-based investigation shows that Hispanic and non-Hispanic Black infants with major CHD have worse outcomes than their non-Hispanic White counterparts. In addition, we found that exposure to an adverse maternal fetal environment (ie, maternal placental syndrome and/or maternal metabolic syndrome) was associated with worse outcomes in the first year of life. The novel finding of our study is that a significant component of the disparate outcomes experienced by non-Hispanic Black

and Hispanic infants compared with non-Hispanic White infantsis explained by differential exposure to an adverse maternal fetal environment.

Although racial and ethnic disparities and inequities in outcomes of children with CHD have been well documented, only recently have investigators turned their focus on potential underlying reasons.[1-7] Race/ethnicity itself is unlikely the reason why these disparities exist, but just a surrogate marker for other factors (ie, mediators) on the pathway between race/ethnicity and outcomes. Several studies have found relationships between maternal socioeconomic status and disparate CHD outcomes.[7,10,28] However, these factors are not able to explain the whole extent of racial or ethnic disparate outcomes.

Outcomes research in CHD has traditionally focused on specific anatomical details, surgical techniques, and postnatal complications.[29] Only recently have investigators focused on the role that maternal conditions present during the pregnancy may have on outcomes of infants with CHD. Gaynor et al reported in a single-center study that an impaired maternal-fetal environment, defined as the presence of gestational hypertension/preeclampsia, SGA, or preterm birth, was common in neonates with critical CHD and associated with worse survival by 3 years of age.[18] Using a population-based administrative database from California, our group found that infants with CHD who had been exposed to an impaired fetal environment had a significantly increased hazard of death in the first year of life compared with controls without such exposure.[20]

The goal of this current study was to examine this newly recognized risk factor of impaired fetal environment as a potential mediator that might explain some of the disparities in outcomes for infants with CHD. We found that relative to their non-Hispanic White counterparts, non-Hispanic Black and Hispanic infants with CHD had greater prevalence of exposure to an adverse maternal fetal environment and that this differential exposure was associated with worse outcomes. The mediation analysis in this study assessed the relationships between race/ethnicity and CHD outcomes through different mediators. We found that up to one-quarter of the effect of race/ethnicity on poor outcomes is mediated through an adverse maternal fetal environment. These are novel findings and potentially of great interest to clinicians caring for expecting mothers with a fetus afflicted with CHD. Further studies should focus on early recognition, treatment, or prevention of these maternal factors which could lead not only to decreased mortality in infants with CHD overall but also to a reduction in related health care inequities.

Although our study examined important factors for risk stratification in CHD patients, there are likely other mediators that have not been accounted for that may explain some of the residual direct effects we reported between non-Hispanic Black race, Hispanic ethnicity, and outcomes.[16] We speculate that upstream social determinants of health contribute to an additional portion of the association between race/ethnicity and poor outcomes in patients with CHD. An expanding literature highlights the contribution of structural racism to an adverse birth outcome.[30,31] Given that non-Hispanic Black and Hispanic (compared with non-Hispanic White) infants are more likely to reside in impoverished urban neighborhoods, differential exposure to health-promoting environments including access to preventative pediatric health services is a plausible explanation.[9] We encourage researchers to take

upstream contextual causes of health inequities into account when examining the relation adverse maternal fetal environment to racial and ethnic group disparities in the outcome of infants with CHD.

Larger studies using multistate or national data sets would be useful to expand upon these findings and identify associations for racial groups that were not included in these analyses. Analyses of other potential upstream mediators such as maternal smoking, substance abuse, or maternal mental health are important to understand why adverse maternal fetal environment, SGA, or prematurity is more common in certain racial and ethnical groups. Additionally, interventional trials designed to optimize the management of maternal conditions such as hypertensive disorders of pregnancy, gestational diabetes, and obesity, with targeted recruitment of underrepresented minorities, are needed in order to identify treatment pathways that we will optimize the maternal-fetal environment.

This study had several limitations. The use of administrative data is known to be inferior to clinical registry data.[32] The use of ICD codes in these administrative datasets is prone to misclassification; however, this misclassification is most likely nondifferential and would bias our findings toward the null. The data set used for this analysis provided us with a unique opportunity to obtain linked, granular maternal, and infant data, while current CHD clinical registries are just starting to incorporate data on maternal conditions and the fetal environment. An additional benefit of a population-based data set is the ability to include all live-born infants with CHD, including those who died prior to undergoing any cardiac surgery, thus reducing the potential for selection bias. We were not able to include those pregnancies that resulted in fetal demise or stillbirth, and thus, it is possible that we underestimated the full effect of adverse maternal fetal environment on disparate CHD outcomes. Finally, the sample size was inadequate to assess mortality as an independent outcome.

Cases with a race other than non-Hispanic White or non-Hispanic Black, or Hispanic ethnicity, as well as those classified as mixed races or mixed ethnicities, were excluded due to relatively small sample sizes, which would prohibit meaningful statistical analyses. We also excluded cases for whom race or ethnicity was self-reported as “other” or “no response,” in part because of relatively small sample sizes, and in part because we felt imputation was not appropriate as the values were likely not missing at random (eg, in minorities who elected not to self-report for fear of discrimination). Thus, our findings may be impacted by sampling bias and are not generalizable to infants of races that were excluded. Future studies utilizing larger data sets would be helpful to overcome the sample size limitations.

Our findings suggest that increased exposure to an adverse maternal fetal environment is a significant contributor to disparate outcomes in non-Hispanic Black and Hispanic infants with CHD. Clinical CHD registries should start to track factors related to adverse maternal fetal environment. Further studies should investigate targeted maternal interventions that may improve these disparate CHD infant outcomes.

Data Statement

Data sharing statement available at www.jpeds.com.

Glossary

BMI
Body mass index

CHD
Congenital heart disease

DAOOH
Days alive and out of hospital in the first year of life

GA
Gestational age

ICD-9-CM and ICD-10-CM
International Classification of Diseases, 9th and 10th Revision, Clinical Modification

ROP
Retinopathy of prematurity

SGA
Small for gestational age

SEM
Structural equation modeling

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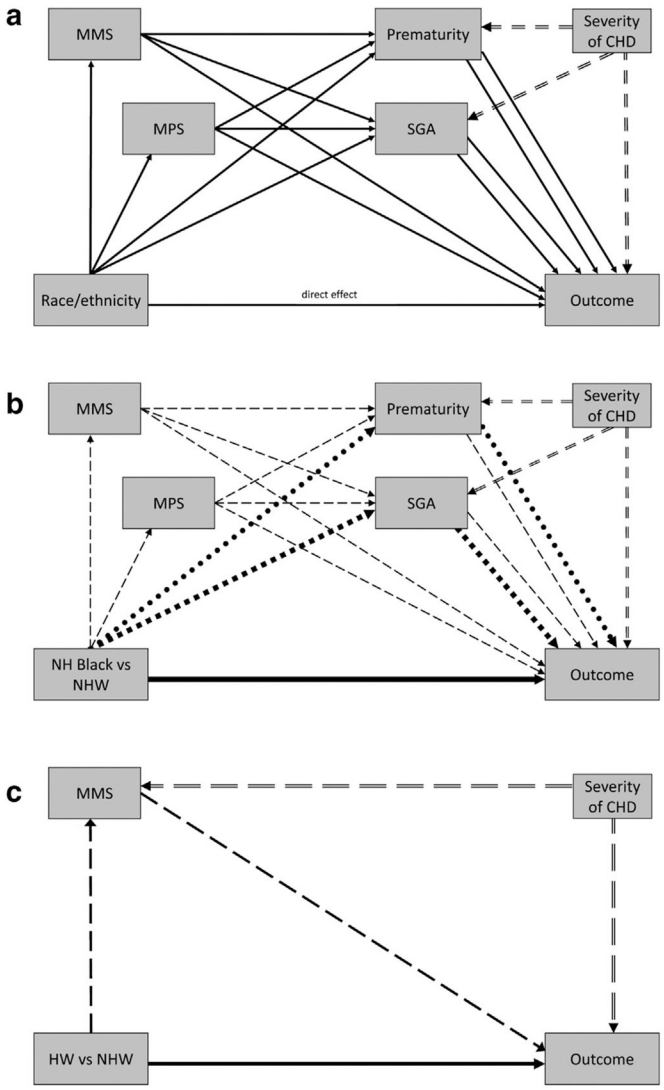

Figure.

Direct acyclic graphs for the conceptual framework of the relationship between race/ethnicity and outcomes in major CHD. **A,** General conceptual framework. **B,** non-Hispanic White vs non-Hispanic Black infants. **C,** non-Hispanic White vs Hispanic infants. Each arrow represents a different pathway by which the predictor (race/ethnicity) affects the outcome through the mediator, ie, in (**B**), the *square dash arrow* shows race/ethnicity effect on outcome as mediated by SGA. *NH*, Non-Hispanic; *NHW*, Non-Hispanic White; *MPS*, maternal placental syndrome; *MMS*, maternal metabolic syndrome.

Table I.

Baseline characteristics for all infants (n = 8616)

Variables	Non-Hispanic White (n = 2747)	Hispanic (n = 5244)	Non-Hispanic Black (n = 625)
Maternal factors			
Adverse maternal fetal environment	979 (35.6)	2529 (48.2)	325 (52.0)
Maternal placental syndrome	322 (11.7)	635 (12.1)	113 (18.1)
Preeclampsia or eclampsia	167 (6.1)	365 (7.0)	69 (11.0)
Gestational hypertension	115 (4.2)	179 (3.4)	29 (4.6)
Placental abruption	47 (1.7)	112 (2.1)	17 (2.7)
Maternal metabolic syndrome	779 (28.4)	2259 (43.1)	276 (44.2)
Pre-existing DM	41 (1.5)	195 (3.7)	15 (2.4)
Gestational DM	254 (9.3)	783 (14.9)	67 (10.7)
BMI >30	582 (21.2)	1768 (33.7)	244 (39.0)
Pre-existing hypertension	44 (1.6)	95 (1.8)	29 (4.6)
Hyperlipidemia	24 (0.9)	40 (0.8)	6 (1.0)
Advanced maternal age (≥35 years)	733 (26.7)	1062 (20.3)	129 (20.6)
Maternal smoking	194 (7.1)	103 (2.0)	55 (9.4)
Infant factors			
Female sex	1188 (43.3)	2369 (45.2)	298 (47.7)
Multiple gestation	210 (7.6)	187 (3.6)	48 (7.7)
Prematurity	498 (18.1)	961 (18.3)	167 (26.7)
SGA	289 (10.5)	573 (10.9)	116 (18.6)
Modified RACHS-1			
1	142 (5.2)	246 (4.7)	22 (3.5)
2	1130 (41.1)	2085 (39.8)	264 (42.2)
3	720 (26.2)	1301 (24.8)	161 (25.8)
4	275 (10.0)	543 (10.4)	39 (6.2)
5	261 (9.5)	625 (11.9)	75 (12.0)
6	219 (8.0)	444 (8.5)	64 (10.2)

DM, diabetes mellitus; *RACHS-1*, Risk Adjustment in Congenital Heart Surgery.

Data are reported as count (%).

Table II.

Univariate analysis for infant outcomes

Variables	Mortality OR (95% CI)	Composite morbidity/mortality outcome OR (95% CI)	DAOOH, coefficient (95% CI)
Race/ethnicity			
Non-Hispanic White	Reference	Reference	Reference
Hispanic	1.02 (0.93-1.30)	**1.18 (1.04-1.33)**	**−6.8 (−11.4 to −2.2)**
Non-Hispanic Black	1.07 (0.78-1.48)	**1.25 (1.01-1.56)**	**−12.4 (−21.1 to −3.7)**
Maternal placental syndrome	1.18 (0.97-1.44)	**1.56 (1.36-1.79)**	**−16.3 (−20.3 to −12.4)**
Maternal metabolic syndrome	**1.18 (1.03-1.36)**	**1.21 (1.09-1.33)**	**−25.4 (−33.9 to −16.9)**
Prematurity	**1.98 (1.70-2.31)**	**2.57 (2.30-2.87)**	**−47.7 (−52.5 to −42.9)**
SGA	**2.00 (1.67-2.38)**	**1.65 (1.44-1.90)**	**−29.1 (−34.9 to −23.2)**
Modified RACHS-1			
1	Reference	Reference	Reference
2	**1.18 (0.73-1.91)**	0.99 (0.50-1.29)	**−0.8 (−10.0 to 8.5)**
3	**1.83 (1.13-2.97)**	**1.20 (0.91-1.58)**	**−10.3 (−19.8 to −0.8)**
4	**3.23 (1.96-5.30)**	**1.81 (1.35-2.42)**	**−33.6 (−44.2 to −22.9)**
5	**3.44 (2.11-5.62)**	**1.75 (1.31-2.33)**	**−27.2 (−37.6 to −16.9)**
6	**6.94 (4.27-11.28)**	**3.28 (2.45-4.38)**	**−70.4 (−81.3 to −59.4)**

DAOOH, days alive and out of hospital; *RACHS-1*, Risk Adjustment in Congenital Heart Surgery; *SGA*, small for gestational age.

Statistically significant findings are depicted in bold font.

Table III.

Associations between predictors and race/ethnicity

Variables	Non-Hispanic White	Hispanic	Non-Hispanic Black
Maternal placental syndrome	Reference	1.04 (0.90-1.20)	**1.66 (1.31-2.10)**
Maternal metabolic syndrome	Reference	**1.89 (1.71-2.08)**	**1.97 (1.65-2.36)**
Prematurity	Reference	1.01 (0.90-1.14)	**1.65 (1.35-2.02)**
SGA	Reference	1.04 (0.90-1.21)	**1.94 (1.53-2.54)**
Modified RACHS-1			
2 vs 1	Reference	1.07 (0.86-1.33)	1.51 (0.94-2.41)
3 vs 1	Reference	1.04 (0.83-1.3)	1.44 (0.89-2.33)
4 vs 1	Reference	1.14 (0.89-1.47)	0.92 (0.52-1.60)
5 vs 1	Reference	**1.38 (1.07-1.78)**	**1.85 (1.11-3.11)**
6 vs 1	Reference	**1.17 (0.90-1.52)**	**1.89 (1.11-3.20)**

Statistically significant findings are depicted in bold font.

Table IV.

Mediation analysis for non-Hispanic Black and Hispanic infants with CHD

Variables	Composite mortality/morbidity outcome, % of total effect explained (95% CI)	DAOOH, % of total effect explained (95% CI)
Non-Hispanic Black infants		
Effect through adverse maternal fetal environment *	**25.0 (7.4, 40.3)**	**16.5 (8.0, 37.2)**
Effect through SGA †	**15.7 (7.8, 22.4)**	**15.1 (8.3, 24.0)**
Effect through prematurity ‡	**36.9 (20.2, 57.5)**	**28.3 (14.0, 36.6)**
Direct effect of non-Hispanic Black race	22.4 (−19.1, 48.0)	40.2 (−20.8, 61.8)
Hispanic infants		
Effect through adverse maternal fetal environment (maternal metabolic syndrome)	**18.1 (8.4 to 27.2)**	**20.8 (16.4 to 26.5)**
Direct effect of Hispanic ethnicity	**81.9 (7.3 to 91.6)**	**79.2 (73.5 to 83.6)**

Statistically significant findings are depicted in bold font.

* This includes the effect through maternal metabolic syndrome and maternal placental syndrome (single dash arrows in Figure B).

† This represents the square dash arrows depicted in Figure B.

‡ This represents the circle dash arrows depicted in Figure B.