EFFECT OF RACE ON THE PREVALENCE OF CONGENITAL MALFORMATIONS AMONG NEWBORNS IN THE UNITED STATES

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Background: Racial variability in certain prenatal risk factors, such as prenatal vitamin supplementation and termination of pregnancy for fetal anomaly, has altered the racial prevalence of congenital malformation (CM). Analysis of a single large representative population is required to analyze current racial differences in prevalence of CM in the United States.

Method: This is a population-based cross-sectional study to analyze racial differences in prevalence of CM diagnoses. We reviewed all live births in the 2008 Nationwide Inpatient Sample (NIS) database and determined birth prevalence of 55 selected CM diagnoses in Caucasians. We then calculated the relative risk of these CM diagnoses in African American, Hispanics and Asians relative to Caucasians.

Result: Overall CM prevalence was 29.2 per 1,000 in a cohort of 1,048,252 live births of which 51% were Caucasians. Compared to Caucasian, risk of overall CM was lower in African Americans (RR=.9, CI .8–.9) and Hispanics (RR=.9, CI .8–.9). Risk of overall CM was similar in Caucasians and Asians. Relative to the Caucasians, African Americans had lower risk of cardiac, genitourinary, and craniofacial malformations but higher risk of musculoskeletal malformations. Hispanics had lower risk of genitourinary and gastrointestinal malformation. Asians had higher risk of craniofacial and musculoskeletal malformation.

Conclusions: This is a comprehensive description of racial difference in risk of CM in the United States. Observed racial differences in risk of CM may be related to genetic susceptibilities, to cultural or social differences that could modify exposures, or to the many potential combinations between susceptibilities and exposures. (*Ethn Dis*. 2015;25[2]:226–231)

Key Words: Race, Congenital Malformation, Epidemiology, Newborn

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INTRODUCTION

Congenital malformation or birth defect is the leading cause of infant mortality and morbidity.

The proportion of infant mortality due to congenital malformations (CM) has increased significantly from 15.1% in the 1970s to 22.1% in the late 1990s, making it the leading cause of infant mortality.[1,2] Congenital malformation accounts for about 12% of all pediatric hospitalizations and a significant portion of health care cost in the United States.[3] The burden of CM goes beyond childhood because it is responsible for about 2.3% of the cases of premature death and disability, as measured by disability-adjusted life years, among the United States population.[4] Based on the above evidence, it is apparent that CM is a major public health problem because of its significant contribution to mortality and morbidity.

Variability in reproductive outcomes exists among difference racial groups. For instance, the risk of preterm delivery, low birth weight, and infant mortality is higher among African Americans and lowest among Caucasians.[5–7] Prior studies have described racial differences in prevalence of selected birth defects[8–10] but there is a paucity of data showing comprehensive analysis of racial differences in prevalence of all major CM diagnosis. Modification of certain prenatal risk factors, such as prenatal vitamin supplementation and termination of pregnancy for fetal anomaly (TOPFA), have been shown to alter CM prevalence in the general population.[11–14] However there is significant variability in the rate of TOPFA and general prenatal care based on race, socioeconomic status and geographic location.[15–17] We hypothesized that racial variability in prenatal risk factors has altered the racial prevalence of CM in the United States. Our study objective was to provide population-based estimates of racial differences on CM prevalence among newborns in the United States.

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MATERIAL AND METHODS

Data Collection

All data were derived from the Nationwide Inpatient Sample (NIS), Healthcare Cost and Utilization Project (HCUP), Agency for Healthcare Research and Quality.[18] The 2008 NIS is an all-payer administrative database reporting clinical and resource use information representative of hospitalizations in 42 states. We chose the NIS database instead of other databases such the Kids' Inpatient Database (KID) because NIS is the largest available inpatient care database in the United States; it contains approximately eight

Table 1. Racial distribution of congenital anomalies

	Caucasian	African American		Hispanic		Asian	
	n	*n*	RR (CI) / *P*	*n*	RR (CI) / *P*	*n*	RR (CI) / *P*
Total CA	15932	4967	.9 (.8–.9) / <.001[a]	6245	.9 (.8–.9) / <.001[a]	1426	1.0 (1.0–1.1) / .3
Multiple CA	683	191	1.0 (.8–1.2) / .1	321	.9 (.7–1.3) / .09	46	1.1 (.8–1.4) / .3
Genetic syndrome	795	201	.9 (.8–1.1) /. 09	360	1.1 (1.0–1.3) / .08	57	.8 (.6–1.1) / .1
CA prevalence[b]	29.8	27.8		28.3		30.1	
Live births	534608	178292		220182		47427	

CA, congenital anomalies; multiple CA: congenital anomalies affecting ≥ 2 organ-systems; RR, relative risk.
[a] $P<.05$.
[b] Prevalence per 1,000 live births.

million hospital stays each year from about 1,000 hospitals sampled to approximate a 20% stratified sample of the United States community hospitals. The NIS large sample size makes it ideal for analysis of rare conditions such as specific congenital malformations. In addition, most newborns are delivered in adult hospitals and NIS captures these hospitalizations, which provide an invaluable resource in achieving our primary objective, which is to estimate birth prevalence of congenital malformations. Approval for this study was obtained from both HCUP (Healthcare Cost and Utilization) and the institutional review board.

We reviewed the NIS database from January to December 2008 and identified 1,204,887 live births (birth hospitalizations); we included 1,048,252 live births (87%) with available race data in our final cohort. All cases of CM diagnoses during birth hospitalization were identified based on ICD9 code 740.0–759.9. These diagnoses were made either clinically or by autopsy for live births that died during birth hospitalization. In order to avoid double counting, we restricted our inclusion criteria to CM diagnoses made during birth hospitalization. We ensured this by including only hospitalizations with ICD-9 code for normal and complicated delivery (650.0–669.0); hence, we excluded diagnoses made during inter-hospital transfer or readmission hospitalization.

Disease and Racial Classification

In patients with multiple CM, each malformation was counted separately. We grouped all CM into different organ-systems. Based on the classification system used by Christensen et al,[19] we defined multi organ-system involvement as live births with CM involving two or more organ-systems. For racial classification, we adopted the classification system used in the NIS database, which coded all birth entries into five ethnic/racial categories: Caucasians (non-Hispanic Whites), African Americans (Blacks), Hispanics, Asians and Pacific Islander, and Native Americans based on the ethnicity of the mother.[18] In cases where a mother's racial data were not available, NIS coded such birth entries as unknown. As per HCUP data use agreement prohibiting reporting of cell size ≤10, CM diagnoses with one cell size ≤10 were excluded from sub-analysis. For the purpose of our study, we excluded Native Americans from our analysis because almost all CM diagnoses in the racial group had insufficient cell size.

Statistical Analysis

Data weighting was performed with SAS in accordance with HCUP recommendations.[20] We estimated birth prevalence of CM diagnoses among Caucasians. We then used MedCalc for Windows, version 12.5 (MedCalc Software, Ostend, Belgium) to estimate the relative risk (RR) and 95% confidence interval (CI) for 55 selected CM diagnoses in African Americans, Hispanics and Asians and Pacific Islander relative to Caucasians.

RESULTS

There were 1,204,887 live birth hospitalizations in the 2008 NIS dataset and, from this population, we included 1,048,252 live births (87%) with available race data. Our cohort comprised 534,608 (51%) Caucasians; 178,292 (17%) African Americans; 220,182 (21%) Hispanics; and 47,427 (4.5%) Asians and Pacific Islanders. The racial distribution in our cohort was consistent with national racial distribution as reported in 2008 US report census.[21,22] Birth prevalence of CM was 29.2 per 1,000 live births in our cohort. However, CM prevalence was 29.8 per 1,000 among Caucasians (n=15,932); 27.8 per 1,000 among African Americans (n=4,967), 28.3 per 1,000 among Hispanics (n=6,245), and 30.1 per 1,000 among Asians (n=1,426). Compared to Caucasians, risk of CM was lower in African Americans (RR=.9, C.I .8–.9) and Hispanics (RR=.9, C.I .8–.9). Risk of CM was similar in Caucasians and Asians (Table 1).

Relative to the Caucasians, African Americans had lower risk of CM (RR .9; CI .8–.9); genitourinary malformations (RR .7; CI .7–.8); craniofacial malformations (RR .4; CI .3–.6); and higher risk of musculoskeletal malformations (RR 1.2; CI 1.1–1.4). Hispanics had lower risk of genitourinary malformation (RR .8; CI .7–.8) and

Table 2. Racial differences of congenital anomalies prevalence

	Caucasian	African-American		Hispanic		Asian	
	n	*n*	RR (CI)	*n*	RR (CI)	*n*	RR (CI)
Cardiac	6038	1452	.9 (.8–.9)[a]	2319	.9 (.9–1.0)	482	.9 (.8–1.0)
TOF/DORV	181	50	1.0 (.7–1.4)	72	1.0 (.8–1.3)	16	1.0 (.6–1.7)
Atrial septal defect	905	244	.9 (.8–1.1)	433	1.2 (1.1–1.3)[a]	84	1.1 (.9–1.3)
Ventricular septal defect	2266	465	.7 (.7–.8)*	844	.9 (.8–1.0)	156	.8 (.7–.9)[a]
Tricuspid atresia	45	12	1.0 (.5–1.8)	19	1.1 (.6–1.8)	[b]	
Aortic stenosis	159	44	1.0 (.7–1.4)	65	1.0 (.7–1.3)	14	1.0 (.6–1.7)
COA/IAA	176	48	1.0 (.7–1.4)	71	1.0 (.7–1.3)	15	.9 (.6–1.7)
Truncus arteriosus	43	12	1.0 (.5–1.9)	18	1.0 (.6–1.8)	[b]	
HLHS	72	20	1.0 (.6–1.6)	29	1.0 (.7–1.5)	[b]	
D-TGA	169	46	1.0 (.7–1.4)	68	1.0 (.8–1.3)	15	1.0 (.6–1.7)
Endocardial cushion defect	131	37	1.0 (.7–1.5)	54	1.0 (.8–1.4)	12	1.0 (.6–1.9)
Pulmonary valve disease	399	112	1.0 (.8–1.2)	165	1.0 (.9–1.2)	36	1.0 (.7–1.5)
APVR	39	13	1.2 (.6–2.3)	16	1.0 (.6–1.8)	[b]	
Genitourinary	6113	1223	.7 (.7–.8)[a]	1948	.8 (.7–.8)[a]	544	1.1 (.9–1.6)
Polycystic kidney disease	59	11	.7 (.4–1.3)	18	.8 (.4–1.3)	[b]	
Cystic kidney disease NOS	60	15	.7 (.4–1.3)	18	.8 (.4–1.3)	[b]	
UPJ Obstruction	24	[b]		11	1.1 (.6–2.3)	[b]	
Lower urinary tract obst	1323	162	.4 (.4–.5)[a]	526	1.0 (.9–1.1)	167	1.5 (1.2–1.7)[a]
Renal agenesis	176	32	.7 (.5–1.0)	60	.9 (.6–1.1)	16	1.0 (.6–1.7)
Renal displasia	126	44	1.3 (.9–1.8)	86	1.7 (1.3–2.2)[a]	12	1.1 (.6–2.0)
Kidney anomaly NOS	195	43	.8 (.6–1.1)	82	1.1 (.8–1.4)	18	1.1 (.7–1.8)
Hypospadias	1721	329	.7 (.6–.8)[a]	297	.4 (.4–.5)[a]	100	.7 (.5–.8)[a]
Epispadias	467	73	.6 (.4–.7)	74	.4 (.3–.5)	52	1.3 (1.0–1.7)
Genital anomaly NOS	240	52	.8 (.6–1.1)	86	.9 (.701.1)	19	.9 (.6–1.4)
Gastrointestinal	781	249	1.2 (1.0–1.3)	246	.8 (.7–.9)[a]	99	1.5 (1.2–1.9)[a]
TEF/esophageal anomaly	110	20	.6 (.4–1.0)	41	.9 (.6–1.3)	13	1.3 (.7–2.4)
Intestinal atresia	147	42	1.1 (.7–1.5)	62	1.1 (.8–1.4)	18	1.4 (.9–2.3)
Hirschsprung disease	49	15	1.1 (.6–2.0)	14	.8 (.5–1.4)	12	2.8 (1.5–5.3)[a]
Upper GI anomaly NOS	289	91	1.2 (.9–1.5)	48	.4 (.3–.6)[a]	23	.9 (.6–1.4)
Lower GI anomaly NOS	142	49	1.2 (.9–1.8)	43	.8 (.5–1.1)	21	1.7 (1.1–2.7)
Hepatobiliary disease	41	18	1.6 (.9–2.8)	35	1.5 (.9–2.5)	[b]	

TOF/DORV, tetralogy of fallot/double outlet right ventricle; COA/IAA, coarctation of aorta/interrupted aortic arch; HLHS, hypoplastic left heart syndrome; D-TGA, complete transposition of great arteries; APVR, anomalous pulmonary venous return; NOS, not otherwise specified; UPJ, Uteropelvic junction; obst, obstruction; TEF, tracheoesophageal fistula; GI, gastrointestinal.

[a] $P<.05$.

[b] Cell size <11.

gastrointestinal malformation (RR .8; CI .7–.9). Asians and Pacific Islanders had higher risk of craniofacial malformation (RR 1.7; CI 1.3–2.2), and musculoskeletal malformation (RR 1.2; CI 1.1–1.4) (Tables 2 and 3).

In regard to lesion-specific risk, six CM diagnoses (ventricular septal defect, lower urinary tract obstruction, hypospadias, neural tube defect, cleft lip, and cleft lip-palate) were less prevalent in African Americans while two CM diagnoses (congenital hip dislocation and congenital foot anomaly) were more prevalent in African Americans compared to Caucasians. Two CM diagnoses (hypospadias and upper gastrointestinal anomaly) were less prevalent in Hispanics while two CM diagnoses (atrial septal defect, renal dysplasia and omphalocele/gastroschisis) were more prevalent in Hispanics. Asians and Pacific Islanders had higher risk of lower urinary tract anomaly, Hirschsprung disease, and congenital hip dislocation but lower risk of ventricular septal defect and hypospadias compared to Caucasians. (Tables 2 and 3). Apart from risk of Down syndrome that was significantly higher in Hispanics, our cohort did not show any racial difference in overall and lesion-specific risk of genetic syndromes (Table 4).

DISCUSSION

Our study presents up-to-date population-based estimates and comprehensive analysis of racial differences in birth prevalence of CM in the Unites States. Birth prevalence of CM in our cohort was 29.2 per 1,000 live births with lower risk of CM among African Americans and Hispanics compared to Caucasians and Asians / Pacific Islanders. Difference between our data and

Table 3. Racial differences of congenital anomalies prevalence

	Caucasians	African-American		Hispanic		Asian	
	n	*n*	RR (CI)	*n*	RR (CI)	*n*	RR (CI)
Neurologic	858	259	1.1 (.9–1.3)	239	1.1 (.9–1.3)	121	.8 (.5–1.1)
Anencephaly	97	30	1.1 (.8–1.7)	41	1.0 (.7–1.5)	18	.8 (.4–1.5)
Encephalocele	143	39	.8 (.6–1.2)	44	1.2 (.9–1.6)	22	1.0 (.5–1.9)
Microcephaly	169	43	.9 (.7–1.3)	36	1.0 (.8–1.3)	13	.9 (.5–1.6)
Hydrocephalus	91	39	.8 (.6–1.2)	31	1.2 (.9–1.6)	17	1.0 (.5–1.9)
Brain anomaly NOS	103	43	.9 (.7–1.3)	38	1.0 (.8–1.3)	13	.9 (.5–1.6)
Spinal bifida/NTD	109	32	.6 (.4–.9)[a]	26	1.2 (.9–1.5)	13	.8 (.4–1.3)
Craniofacial	451	84	.4 (.3–.6)[a]	142	1.1 (.9–1.3)	68	1.7 (1.3–2.2)[a]
Cleft lip and palate	282	46	.4 (.3–.5)[a]	80	1.2 (.8–1.3)	52	1.7 (1.3–2.0)
Ear anomaly NOS	29	13	1.6 (.9–3.1)	20	1.7 (.9–3.0)	[b]	
Microphthalmos	44	14	1.0 (.8–1.3)	11	.8 (.4–1.5)	13	1.5 (.7–1.9)
Eye anomaly NOS	55	11	1.2 (.6–2.3)	14	1.0 (.5–1.9)	11	1.8 (.6–2.2)
Respiratory	620	149	1.0 (.8–1.2)	246	1.1 (.9–1.3)	45	.9 (.7–1.3)
Choanal atresia	41	11	1.0 (.5–1.9)	15	.9 (.5–1.6)	[b]	
Laryngotracheal anomaly	269	67	.9 (.7–1.2)	96	.9 (.7–1.1)	34	1.6 (.9–3.1)
Cystic lung malformations	79	31	1.6 (.9–3.1)	11	.9 (.4–1.9)	[b]	
Agenesis of lung	46	21	1.7 (1.0–2.8)	28	1.5 (.9–2.4)	14	1.2 (.6–2.3)
Lung malformation NOS	160	45	1.0 (.7–1.4)	78	1.2 (.9–1.5)	19	1.3 (.8–2.2)
Musculoskeletal	974	323	1.2 (1.1–1.4)[a]	446	.7 (1.0–1.3)	117	1.2 (1.1–1.4)[a]
Congenital hip dislocation	480	167	1.2 (1.1–1.5)[a]	223	1.2 (1.0–1.4)	67	1.6 (1.2–2.0)[a]
Congenital foot abnormal	355	151	1.2 (1.0–1.5)	210	1.2 (.9–1.4	47	1.2 (.9–1.6)
Pectus	89	24	1.7 (1.0–2.8)	23	.8 (.4–1.6)	14	1.5 (.9–2.4)
Others	407	100	.9 (.7–1.1)	205	1.3 (1.1–1.5)	28	.8 (.5–1.2)
Omph/gastroschisis	305	82	1.0 (.8–1.3)	157	1.3 (1.1–15)[a]	15	.6 (.3–1.0)
Diaphragmatic hernia	102	18	.6 (.4–1.1)	48	1.2 (.8–1.7)	13	1.5 (.8–2.6)

NTD, neural tube defect; NOS, not otherwise specified; Omph, Omphalocele.
[a] $P<.05$.
[b] Cell size <11.

estimates from prior studies serves as an indirect measure of the effect of modification of prenatal risk factors such as prenatal vitamin supplementation and termination of pregnancy for fetal anomalies. Our data will also help in determining the resources needed for basic and public health research of major birth defects.

Apart from Carmichael et al,[5] we were unable to identify any large population-based study that performed a comprehensive analysis of racial difference in prevalence of major CM diagnoses in the United States. Although such comprehensive data are lacking, data on a racial differences in prevalence of a few specific congenital malformations do exist. For example, in agreement with our findings, several studies have shown that Hispanics have

Table 4. Racial difference of genetic syndromes prevalence

	Caucasians	African American		Hispanic		Asian	
Genetic Syndromes	*n*	*n*	RR (CI)	*n*	RR (CI)	*n*	RR (CI)
Down	533	155	1.1 (.9–1.3)	288	1.3 (1.2–1.5)[a]	57	1.2 (.9–1.0)
Patau	25	11	1.6 (.8–3.3)	13	1.3 (.7–2.5)	[b]	
Edward	24	12	1.8 (.9–3.7)	17	1.7 (.9–3.2)	[b]	
Turner	23	11	1.6 (.8–3.5)	15	1.6 (.8–3.1)	[b]	
Klinefelter	15	[b]		11	1.8 (.8–4.0)	[b]	
Noonan	25	12	1.6 (.8–3.3)	16	1.6 (.9–3.0)	[b]	
All genetic syndromes	795	201	.9 (.8–1.1)	360	1.1 (1.0–1.3)	57	.8 (.6–1.1)

[a] $P<.05$.
[b] Cell size <11.

Birth prevalence of CM in our cohort was 29.2 per 1,000 live births with lower risk of CM among African Americans and Hispanics compared to Caucasians and Asians / Pacific Islanders.

low risk of hypospadias but higher risk of atrial septal defect and renal dysplasia compared to Caucasians.[9,23–27] However, unlike prior studies, our data did not show any difference in risk of neural tube defect (NTD) or hypoplastic left heart syndrome in Hispanics. In the African American cohort, our data were consistent with some prior studies that showed lower risk of NTD, hypospadias, cleft lip-palate, and ventricular septal defect in this population relative to Caucasians.[8,9,24,27–29] However, unlike the above-cited studies, our data showed increased risk of congenital hip dislocation in African Americans. There is a paucity of comparative data on the risk of CM among Asians and Pacific Islanders in the United States. Our study showed that, although the risk of overall CM was similar in Caucasians and Asians, Asian newborns had higher risk of Hirschsprung disease and congenital hip dislocation but lower risk of ventricular septal defect and hypospadias relative to Caucasians. Thus, our data confirm some previous findings, but in general contribute to a relatively sparse literature base about the racial differences of CM prevalence in the United States.

A national estimate of prevalence of CM is an important foundation in our understanding of the public health burden posed by these conditions. Although some previous studies have looked at racial differences in the occurrence of selected CM diagnoses,[8–10,24–29] there are certain strengths and novelty in our study that makes it different from any other prior study. First, our data were derived from the largest national database of hospitalization information with a sample size of 1.2 million live births marking the largest study of CM birth prevalence in the United States. Because of our large sample size, our study was powered enough for comprehensive analysis of racial differences in prevalence of 55 different CM diagnoses. Second, our estimates were based on weighted data collected from about 1,000 hospitals in 42 states and sampled to approximate a 20% of the United States community hospitals. As a result, our study population is representative of the general newborn population in the country. In support of this, the racial distribution of our cohort was strikingly similar to the racial distribution of the national newborn population as reported in the 2008 US Census Bureau database.[21,22] Finally, most prior studies that looked at the effect of race on birth defect prevalence only focused on a few selected diagnoses. Our data, on the other hand, provide opportunity for a comprehensive analysis of all major birth defects in the newborn population. Carmichael et al[30] performed a comprehensive analysis of major birth defects among Caucasians, African Americans and Hispanics; our study went a step further by including Asians and Pacific Islanders in our analysis because there is paucity of epidemiologic data for this racial group.

Our study has some limitations. It is a retrospective review of entries from a de-identified administrative database. We studied CM prevalence among live births, excluding all CM diagnoses in stillbirths and electively terminated fetuses. It has been reported that prenatal diagnosis of malformations is less likely among Hispanic and African American women than Caucasian women.[15,16] This situation could have led to underestimation of CM prevalence in Caucasians. We only included CM diagnosis made during birth hospitalization and, as a result, we could not have missed cases that presented after birth hospitalization. Newborn data in the NIS database were not linked to maternal data and, hence, we were unable to control for confounding factors such as maternal age and exposure to other prenatal risk factors. Finally, the NIS database had some missing race/ethnicity data and this factor has to be taken into consideration when interpreting our results.

CONCLUSION

Despite the above limitations, our data represent a comprehensive description of the risks of congenital malformations among newborns in the different racial groups and represent an important descriptive resource for comparison with other studies. Race-ethnicity may serve as surrogates for a variety of potential exposures (eg, socioeconomic level, nutrition, stress, access to medical care, migration decisions). It remains to be clarified whether the observed racial differences in risk of CM are related to potential underlying genetic susceptibilities, to cultural or social differences that could modify exposures, or to the many potential combinations between susceptibilities and exposures.

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