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Risk Factors for Isolated Total Anomalous Pulmonary Venous Return, National Birth Defects Prevention Study, 1997-2011

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Bachelor of Science
Michigan State University
2014

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An abstract of
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Abstract

Risk Factors for Isolated Total Anomalous Pulmonary Venous Return, National Birth Defects Prevention Study, 1997-2011

By Stephanie Eick

BACKGROUND: Total anomalous pulmonary venous return (TAPVR) is a critical congenital heart defect. The causes of TAPVR are unknown and there is limited information on risk factors for the condition. This analysis aimed to update previous findings and examine a spectrum of risk factors for TAPVR in a large, diverse population.

METHODS: Data from the National Birth Defects Prevention Study (NBDPS) (1997-2011) were used to examine characteristics of infants with isolated TAPVR and potential associated risk factors. Multiple logistic regression was used to estimate adjusted odds ratios (OR).

RESULTS: Using data from 258 cases and 11,829 controls, we found that paternal occupation as a landscaper/groundskeeper was significantly associated with increased odds for TAPVR (aOR=2.06, 95% Confidence Interval (CI)=(1.12, 2.79)). Maternal and paternal non-Hispanic black race/ethnicity compared to non-Hispanic white were associated with decreased odds of TAPVR (aOR=0.52, 95% CI=(0.30, 0.91), aOR=0.60, 95% CI=(0.34, 0.99), respectively). One or more pregnancies was associated with increased odds of TAPVR (aOR=1.55, 95% CI=(1.14, 2.12). Borderline significant associations between prepregnancy obesity and maternal education and TAPVR were also observed.

CONCLUSION: These analyses provide support for previous reports of association between isolated TAPVR and paternal occupation as landscaper/groundskeeper. Race/ethnicity of non-Hispanic black was associated with a decreased risk of TAPVR. Mothers who had more than one previous pregnancy were at increased risk for TAPVR. Despite exhaustive efforts, the cause of isolated TAPVR remains largely unknown. A larger sample size is needed to further evaluate these relationships.

KEY WORDS: TAPVR, risk factors, NBDPS

Word Count: 246

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Acknowledgements

Risk Factors for Isolated Total Anomalous Pulmonary Venous Return, National Birth Defects Prevention Study, 1997-2011

By Stephanie Eick

MPH

I would like to thank my parents, Susan and Steve. Dad, I could not have done this without you, I have never been more grateful for your PhD in statistics than these last two years. I would like to thank my advisors at Emory University, Matt and Jena, and my advisors at the Centers for Disease Control and Prevention, you have all taught me so much. To my Atlanta friends who have become family, I couldn't have done this without you all either, you all have truly made this the best two years.

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BACKGROUND

Total anomalous pulmonary venous return (TAPVR), a critical congenital heart defect (CCHD) in which all four pulmonary veins return abnormally to the heart, typically requires surgery in the first year of life. There are few identified risk factors for TAPVR and the cause of TAPVR remains largely unknown. TAPVR has a reported incidence of 0.8 per 10,000 live births and accounts for 2.2% of CCHDs (Cooley et al., 2008). TAPVR cases range in severity, depending on the clinical characteristics and pathology. Most cases are diagnosed during the neonatal period and infancy, typically by echocardiography. If diagnosed and corrected with surgery quickly, survival to adulthood is expected. Without surgery within the first year of life, survival to adulthood is rare (Cooley et al., 2008).

Previous studies of risk factors for TAPVR have been limited due to sample size. The Baltimore-Washington Infant Study (BWIS, 1981-1989) was a population-based case control study that investigated risk factors for a wide variety of CHDs. Based on 60 cases, BWIS investigators reported that TAPVR was significantly associated with maternal exposure during pregnancy to paint, lead, and pesticides, as well as maternal use of medications such as corticosteroids and phenothiazine during pregnancy (Correa-Villasenor et al., 1991). Studies from the National Birth Defects Prevention Study, a multi-site case-control study (NBDPS, 1997-2011) have examined TAPVR as one of many birth defect outcomes in analyses of particular risk factors (e.g. body mass index [BMI] or smoking). In these previous NBDPS analyses, TAPVR was associated with young maternal age, high maternal pre-pregnancy BMI, and paternal occupations of landscapers and groundskeepers (Gill et al., 2012; Gilboa et al., 2010; Desrosiers et al,

2012., respectively. However, there have been no NBPDS studies that examined multiple potential risk factors together for the specific outcome of TAPVR for all available years of data.

The purpose of this study was to further evaluate previously identified and potentially new significant, non-genetic risk factors for TAPVR using fourteen years of data from the NBDPS.

MATERIALS AND METHODS

STUDY POPULATION

The data for our analysis included TAPVR cases which were simple (TAPVR with no other CHDs except atrial sept defect) and isolated (no extracardiac defects), and control infants (infants with no known birth defects) from the NBDPS. Sponsored by the Centers for Disease Control and Prevention, the NBDPS was a population-based case-control study of environmental risk factors for over thirty major birth defects. Cases born from October 1997 to December 2011 were ascertained from birth defects surveillance programs at ten sites. Participation in NBDPS varied by site over time: Arkansas (1998 – 2011), California (1997 – 2011), Georgia (1997 – 2011), Iowa (1997 – 2011), Massachusetts (1997 – 2011), New Jersey (1998 – 2002), New York (1997 – 2002; 2004 – 2011), North Carolina (2003 – 2011), Texas (1997 – 2011), and Utah (2003 – 2011). Cases are livebirths (all sites), stillbirths (all sites except New York prior to 2000 and New Jersey), and elective terminations of pregnancies (Arkansas, California, Georgia (starting in 1999), Iowa, Massachusetts (starting in 2011), New York (starting in 2000), North Carolina, Texas, and Utah). Controls are singleton livebirths without major birth defects who were randomly selected from the same base populations as the cases from birth certificates or hospital birth records. Potential cases are reviewed at each NBDPS site by a clinical geneticist for study eligibility. Computer-assisted telephone interviews (CATI) were administered to case and control mothers to obtain information on maternal health, pregnancy, family demographics, occupation, diet and substance use (Reefhuis et al., 2015).

CASE CLASSIFICATION

All potential cases with TAPVR were reviewed and classified by experts trained in pediatric cardiology according to primary CHD phenotype and complexity based on previously published standard case definition (Botto et al., 2007). If TAPVR was one of the primary defects, the cardiac complexity was either simple (TAPVR alone or with an atrial septal defect), association (TAPVR plus another distinct CHD, e.g., ventricular septal defect), or complex (TAPVR plus several distinct CHDs). The cases were also reviewed for the presence of extra-cardiac defects and determined to be either isolated (only cardiac defects), multiple (TAPVR and at least one other unrelated non-cardiac defect), or complex (TAPVR and another situs anomaly) (Rasmussen et al., 2003). There were 753 reported cases of TAPVR, of these only 466 participated in the maternal interview. Of the interviewed cases, 307 were classified as primarily having TAPVR while 159 also had TAPVR but were classified as other primary CHDs (e.g laterality defects, single ventricle, or hypoplastic left heart syndrome). Only the 258 cases which were classified as simple, isolated TAPVR were included in this analysis due to possible differences in risk factors between cases with one and more than one defect (Sokol et al., 2003).

This analysis includes case and control infants born on or after October 1, 1997 and infants with an estimated date of delivery on or before December 31, 2011 and whose mother participated in the maternal interview.

EXPOSURE CLASSIFICATION

We examined the association between TAPVR and the covariates that have been previously associated with TAPVR in the literature. In addition, we included possible associations of risk factors for TAPVR that were not statistically significant, and factors that had significant associations with other CHDs in prior NBDPS analyses. All exposures were self-reported by mothers in the CATI. Maternal and paternal occupations were coded using the Standard Occupational Classification (SOC) system. We examined maternal age at delivery (<20, 20-34, 35-39, ≥40), maternal and paternal race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, Asian/Pacific Islander, Native American/Alaskan Native, Other), prepregnancy BMI (<18.5, 18.5 to <25, 25 to <30, ≥30), gravidity (0, 1 or more), maternal hypertension (yes or no), maternal occupation (teacher, nurse, janitor/cleaner/maid, landscaper/groundskeeper, artist, food server/processor, other, unemployed), paternal occupation (motor vehicle operator, landscaper/groundskeeper, chemical worker, food server/processor, artist, other, unemployed), and maternal education (≤high school, >high school).We assessed periconceptional (from one month before pregnancy [B1] through the third month of pregnancy [P3]) maternal cigarette smoking, maternal report of febrile illness (any vs. none), use of corticosteroids, and use of phenothiazine. We also assessed use of folic acid during the exposure period from one month before pregnancy [B1] to one month after conception [P1]. Tubal pregnancies, miscarriages, and stillbirths were combined to create a dichotomous previous history of fetal loss variable.

In addition, our study included the following covariates: study site (Arkansas, California, Georgia/CDC, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas, and Utah); family history of any NBDPS heart defect in a first degree relative or

pregnancy history (yes or no); birth plurality (yes or no); and maternal history of seizures (yes or no).

STATISTICAL METHODS

Exposure variables and covariates, as indicated previously, were determined *a priori* after reviewing the epidemiologic literature. For each variable we conducted chi-squared tests to determine if differences in distributions between case and control groups were statistically significant. When cell counts were 5 or less, we used Fisher's and Monte Carlo exact tests.

We used logistic regression to estimate crude odds ratios and 95% confidence intervals for all potential exposure variables examined in the univariate analysis (Table II). Multiple logistic regression was used to estimate adjusted odds ratios and 95% confidence intervals (Table II) for the associations between TAPVR and maternal hypertension, prepregnancy BMI, paternal occupation, maternal age at delivery, and maternal smoking. These exposures were chosen because they were previously associated with TAPVR in the literature, as described in the background. Paternal race, maternal race, and maternal education also warranted further investigation because there were strong differences between groups after conducting chi-squared tests. We created directed acyclic graphs (DAGs) to determine which covariates to adjust for for each main exposure of interest. Maternal characteristics, including age, education, race, and smoking, were used in the adjusted models for paternal occupation. Although paternal characteristics were available, they were missing a substantial percentage of the time so maternal characteristics were used (weighted kappa for race/ethnicity=0.77). SAS 9.3

was used to conduct all analyses. Confidence intervals that did not include one were considered statistically significant.

RESULTS

Our analysis included 258 isolated, simple TAPVR cases and 11,829 controls from the period of 1997 to 2011 (Table 1). Control mothers and fathers were more likely to be non-Hispanic white, while case mothers and fathers were more likely to be Hispanic (p-value 0.001 and 0.02, respectively). A larger percentage of case mothers had a high school education or less compared to controls (p-value 0.02). Case fathers were more likely to be landscapers or groundskeepers (4.7% vs 2.1%).

In our crude analyses (Table 1), maternal race/ethnicity of Hispanic and Asian/Pacific Islander, Hispanic paternal race/ethnicity, gravidity, maternal education, and landscaper/groundskeeper as a paternal occupation were associated with TAPVR. Phenothiazine use was inversely associated with TAPVR. Maternal age at delivery, prepregnancy BMI, hypertension, birth plurality, maternal occupation, maternal smoking, folic acid use, receipt of prenatal care, maternal history of febrile illness, history of fetal loss, maternal history of seizures, family history of heart defects, and corticosteroid use were not associated with TAPVR in our crude analyses.

As previously described, exposures were included in the adjusted analyses if they warranted further investigation after reviewing the literature and/ or conducting the univariate analysis. Compared to non-Hispanic white mothers or fathers, there was a decreased risk of TAPVR among mothers or fathers who were non-Hispanic black (aOR=0.52, 95% CI=(0.30, 0.91), aOR=0.60, 95% CI=(0.37, 0.99), respectively). After adjusting for maternal age, race/ethnicity and study center, compared to first pregnancies, mothers who had previous pregnancies were 50% more likely to have a child with TAPVR (aOR=1.55, 1(.14, 2.12)). While no maternal occupation that we examined was

associated with risk for TAPVR, paternal occupation as a landscaper or groundskeeper was associated with increased risk for TAPVR compared to those who were employed but were not motor vehicle operators, chemical workers, servers and processors or artists (aOR=2.06, 95% CI=(1.12, 3.79)). Maternal obesity and lower education were weakly associated with occurrence of TAPVR but did not reach statistical significance in this analysis (aOR=1.30, 95%CI=(0.92,1.67), aOR= 1.28, 95% CI=(0.95, 1.72), respectively). Maternal age at delivery, maternal hypertension, maternal smoking, corticosteroid use, and phenothiazine use were not associated with TAPVR after adjusting for confounders (Table 2).

DISCUSSION

We looked at a wide range of potential risk factors for the occurrence of TAPVR without other CHDs or birth defects in a recent, large population-based cohort from multiple centers across the United States. Our findings suggest that fathers who are landscapers or groundskeepers may be more likely to have a child with TAPVR, while parents who are non-Hispanic black may be less likely to have a child with TAPVR. Mothers who had more than one previous pregnancy were also at increased odds for having a child with TAPVR. Other factors, such as maternal prepregnancy obesity (BMI greater than or equal to 30) and lower education (high school education or less), suggest possible associations with TAPVR.

According to our findings, non-Hispanic black parents are less likely to have an infant with TAPVR when compared to non-Hispanic white parents. This association was significant after controlling for maternal age, maternal education, birth plurality, and study center. This relationship is similar to previous NBDPS findings examining a variety of birth defects and maternal race/ethnicity. Cardiovascular birth defects including transposition of the great arteries, aortic valve stenosis and coarctation of the aorta showed significantly lower prevalence ratios compared to non-Hispanic white (Mark et al., 2014). TAPVR was not examined in this study.

Our analysis also showed differences were also seen across study centers, California reported a larger number of TAPVR cases than other study sites. Mothers who had previous pregnancies were more likely to have a child with TAPVR in our adjusted analyses. Our findings are consistent with previous NBDPS studies in the respect that landscaper and groundskeeper as a paternal occupation is associated with TAPVR

(Desrosiers et al., 2012). Our analyses also found that high prepregnancy BMI was weakly associated with TAPVR; this association is similar to previous NBDPS findings that used a smaller sample size (Gilboa et al., 2010). In addition, previous NBDPS and BWIS studies reported null associations between smoking status and TAPVR (Malik et al., 2008; Alverson et al., 2011, respectively), this was confirmed in our study. Caton et al. (2009) showed a null association between hypertension and TAPVR, our findings were also not statistically significant, confirming these findings. A previous NBDPS study (Gill et al., 2012) reported that TAPVR was significantly associated with young maternal age, which our results did not support. However, our study had 258 cases compared to the 190 cases in the Gill et al. (2012) analysis. It is important to note that our findings are consistent with findings of prior NBDPS studies because our study samples came from the same data source. Overall our findings are similar, some possible reasons for differences in point estimates include model adjustment and sample size. In addition, our sample include only isolated, simple cases. There were many cases of TAPVR with other defects, such as single ventricle or laterality defects, that were not included in this study. Some of these previously mentioned studies included these such cases, leading to a more heterogeneous case group which can potentially explain the differences in results.

Previously, BWIS showed a significant association between exposure to lead or pesticides and TAPVR (Correa-Villasenor et al., 1991). Information regarding lead and occupational exposure to pesticides was unavailable for half of our study population, and for this reason we decided not to look at lead and pesticides as potential exposures in this analysis, which is a limitation of our study. Desrosiers et al. (2012) examined a variety of paternal occupation categories and birth defects, in these findings TAPVR was the only

birth defect significantly associated with landscapers and groundskeepers. However, borderline significance was seen for Anencephaly, Biliary atresia, and ASD, highlighting the importance of further research. Looking at maternal occupational exposure to pesticides and CHDs, Rocheleau et al. (2015) found that high pesticide exposure use was significantly associated with higher odds of secundum ASD, hypoplastic left heart syndrome, pulmonary valve stenosis, and tetralogy of Fallot. TAPVR was not examined in this analysis. Although pesticide exposure was broadly not associated with CHDs (Rocheleau et al., 2015), it may still be important to evaluate TAPVR separately.

Another limitation of this analysis is that we considered many exposure variables, which increases the likelihood of false-positive findings. Although we did have a larger sample size than previous studies, we categorized variables (maternal age, prepregnancy BMI, maternal education) in order to have larger numbers when conducting analyses, which potentially leads to a loss of information. Recall bias may also be a potential issue in our study; we were not able to confirm exposures reported during the periconceptional period. Because our data are reported through a retrospective maternal interview, mothers of cases may report different periconceptional exposures, resulting in differential misclassification. However, we do not believe that differential recall is a problem with our study because exposures such as number of pregnancies, occupation and race/ethnicity are likely not to be subject to recall bias.

Despite these limitations, our study has many strengths. One strength of this study is its large, geographically diverse sample size. A second strength is the detailed information is available on a wide range of potential risk factors. Further, we were able to use only isolated, simple cases, leading to a more homogenous case group. Cases with

more than one defect may have differing risk factors, which is why they were excluded from these analyses. In addition, this case group is larger than that of previous studies. Finally, the NBDPS case definition for TAPVR is well-defined and the clinician review and classification helps ensure consistency.

CONCLUSION

Our study is, to the best of our knowledge, the largest study to date examining a spectrum of risk factors for isolated simple TAPVR. We found that maternal and paternal non-Hispanic black race/ethnicity compared to non-Hispanic white were associated with decreased odds of TAPVR, and that number of previous pregnancies and paternal occupation as groundskeeper/landscaper were associated with increased odds of TAPVR. Borderline significant associations between prepregnancy obesity and maternal education and TAPVR were also observed. Future research should aim to explore potential mechanisms of these associations. Despite this exhaustive analysis and large sample size, there are not many known risk factors for isolated TAPVR. There are still a large percentage of CHDs of unknown origin, these cases may be sporadic or yet undefined risk factors. An additional potential risk factor for TAPVR is abnormal cell signaling, which may occur in the formation of laterality defects, however these types of cases were excluded from these analyses.

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Table 1. Description of total anomalous pulmonary venous return case and control study population, National Birth Defects Prevention Study, 1997-2011

Characteristic	Cases (N)	%	Controls (N)	%	P-Value
Total Cases	258	100	11,829	100.0	
Maternal age at delivery					0.11
<20	34	13.18	1,177	10.0	
20-34	188	72.87	8,988	76.0	
35-39	26	10.08	1,388	11.7	
>40	10	3.88	276	2.3	
Missing	0	0	0	0.0	
Maternal Race/Ethnicity					**0.002**
Non-Hispanic White	136	52.71	6836	57.8	
Non-Hispanic Black	16	6.20	1308	11.1	
Hispanic	79	30.62	2908	24.6	
Asian/Pacific Islander	14	5.43	353	3.0	
Native American/Alaskan Native	3	1.16	51	0.4	
Other	10	3.88	366	3.1	
Missing	0	0	7	0.1	
Paternal Race/Ethnicity					**0.03**
Non-Hispanic White	133	51.55	6517	55.1	
Non-Hispanic Black	20	7.75	1404	11.9	
Hispanic	78	30.23	2738	23.2	
Asian/Pacific Islander	10	3.88	310	2.6	
Native American/ Alaskan Native	2	0.78	52	0.4	
Other	4	1.55	322	2.7	
Missing	11	4.26	486	4.1	
Maternal Prepregnancy BMI					0.1
<18.5	15	5.81	599	5.1	
18.5 to <25	126	48.84	6,045	51.1	
25 to <30	48	18.60	2,557	21.6	
>30	53	20.54	2,074	17.5	
Missing	16	6.20	554	4.7	
Maternal Hypertension					0.73
Yes	37	14.34	1,609	13.6	
No	219	84.88	10,145	85.8	
Missing	2	0.78	75	0.6	
Gravidity					**0.04**
0	60	23.26	3,471	29.3	
1 or more	195	75.58	8,307	70.2	
Missing	3	1.16	51	0.4	
Birth Plurality					0.12
Singleton	246	95.35	11,452	96.8	
Multiple	12	4.65	351	3.0	
Missing	0	0	26	0.2	

Maternal Education					**0.02**
≤ High School	120	46.51	4,630	39.1	
>High School	131	50.78	6,854	57.9	
Missing	7	2.71	345	2.9	
Maternal Occupation					0.25
Teacher	1	0.39	124	1.1	
Nurse	2	0.78	313	2.7	
Janitor, Maid, Cleaner	8	3.10	310	2.6	
Landscaper, Groundskeeper	0	0	4	0.0	
Artist	0	0	0	0.0	
Server/Processor	0	0	1	0.0	
Other-Employed	159	61.63	7,477	63.2	
Unemployed	82	31.78	3,282	27.8	
Missing	6	2.33	318	2.7	
Paternal Occupation					**0.009**
Motor Vehicle Operator	1	0.39	1	0.0	
Landscaper, Groundskeeper	12	4.65	247	2.1	
Chemical Worker	0	0	1	0.0	
Server/Processor	0	0	5	0.0	
Artist	0	0	0	0.0	
Other-Employed	215	83.33	10,269	86.8	
Unemployed	17	6.59	743	6.3	
Missing	13	5.04	568	4.8	
Maternal Smoking [a]					0.59
Yes	42	16.28	2,075	17.5	
No	210	81.40	9,454	79.9	
Missing	6	2.33	300	2.5	
Folic Acid Use [b]					0.17
Yes	127	49.2	6,358	52.4	
No	123	47.7	5172	46.2	
Missing	8	3.1	299	1.3	
Receipt of Prenatal Care					0.18
Yes	256	99.22	11,644	98.4	
No	0	0	114	1.0	
Missing	2	0.78	71	0.6	
Maternal history of febrile illness [a]					0.59
Yes	53	20.54	2,596	22.0	
No	203	78.68	9,137	77.2	
Missing	2	0.78	96	0.8	
Previous history of fetal loss					0.61
Yes	66	25.58	2,887	24.4	
No	189	73.26	8,891	75.2	
Missing	3	1.16	51	0.4	
Maternal history of seizures					0.43
Yes	9	3.49	319	2.7	

No	246	95.35	11,429	96.6	
Missing	3	1.16	81	0.7	
Family history of heart defect					0.55
Yes	4	1.55	139	1.2	
No	254	98.45	11,690	98.8	
Missing	0	0	0	0.0	
Corticosteroid Use [a]					1.00
Yes	5	1.94	253	2.1	
No	253	96.90	11,576	96.0	
Missing	0	1.16	0	2.1	
Phenothiazine Use [a]					**0.03**
Yes	3	1.16	432	3.7	
No	255	97.67	11,178	94.5	
Missing	0	1.16	219	1.9	
Study Center					**0.001**
Arkansas	24	9.30	1,471	12.4	
California	46	17.83	1,263	10.7	
Georgia	27	10.47	1,267	10.7	
Iowa	15	5.81	1,300	11.0	
Massachusetts	36	13.95	1,402	11.9	
North Carolina	16	6.20	1,016	8.6	
New Jersey	19	7.36	578	4.9	
New York	26	10.08	989	8.4	
Texas	25	9.69	1,416	12.0	
Utah	24	9.30	1,127	9.5	

[a] Exposure during periconceptional period (B1-P3)
[b] Exposure during periconceptional period (B1-P1)

Table 2. Crude and adjusted analyses of total anomalous pulmonary venous return, National Birth Defects Prevention Study 1997-2011.

Characteristic	Crude Odds Ratio	95% Confidence Interval	Adjusted Odds Ratio	95% Confidence Interval
Maternal Age at Delivery [a]				
<20	1.38	(0.95, 2.00)	1.32	(0.86, 2.03)
20-34	Ref.			
35-39	0.90	(0.59, 1.36)	0.94	(0.61, 1.44)
>40	1.73	(0.91, 3.31)	1.81	(0.94, 3.49)
Maternal Race/ Ethnicity [b]				
Non-Hispanic White	Ref.		Ref.	
Non-Hispanic Black	0.62	(0.37, 1.04)	**0.52**	(0.30, 0.91)
Hispanic	**1.37**	(1.03, 1.81)	1.17	(0.82, 1.68)
Asian/Pacific Islander	**1.99**	(1.14, 3.49)	1.76	(1.00, 3.11)
Native American/ Alaskan Native	2.96	(0.91, 9.59)	2.62	(0.80, 8.60)
Other	1.37	(0.72, 2.63)	1.30	(0.67, 2.52)
Paternal Race/Ethnicity [b]				
Non-Hispanic White	Ref.		Ref.	
Non-Hispanic Black	0.70	(0.44, 1.12)	**0.60**	(0.37, 0.99)
Hispanic	**1.40**	(1.05, 1.85)	1.22	(0.85, 1.75)
Asian/Pacific Islander	1.58	(0.82, 3.04)	1.34	(0.69, 2.59)
Native American/ Alaskan Native	1.89	(0.45, 7.82)	1.78	(0.43, 7.48)
Other	0.61	(0.22, 1.66)	0.57	(0.21, 1.56)
Materanl Prepregnancy BMI [c]				
<18.5	1.20	(0.70, 2.07)	1.09	(0.62, 1.91)
18.5 to <25	Ref.		Ref.	
25 to <30	0.90	(0.64, 1.26)	0.90	(0.63, 1.28)
≥30	1.23	(0.89, 1.70)	1.30	(0.92, 1.84)
Maternal Hypertension [d]				
Yes	1.07	(0.75, 1.52)	1.15	(0.80, 1.67)
No	Ref.		Ref.	
Gravidity [e]				
0	Ref.		Ref.	
1 or more	**1.36**	(1.01, 1.82)	**1.55**	(1.14, 2.12)
Maternal Education [e]				
≤ High School	**1.36**	(1.06, 1.74)	1.28	(0.95, 1.72)
>High School	Ref.		Ref.	
Maternal Occupation [f]				

Teacher	0.38	(0.05, 2.73)	0.40	(0.06, 2.93)
Nurse	0.30	(0.07, 1.22)	0.35	(0.09, 1.43)
Janitor, Maid, Cleaner	1.21	(0.59, 2.49)	1.16	(0.56, 2.42)
Landscaper, Groundskeeper	N/A		N/A	
Artist	N/A		N/A	
Server/Processor	N/A		N/A	
Other-Employed	Ref.		Ref.	
Unemployed	1.18	(0.90, 1.54)	1.05	(0.79, 1.40)
Paternal Occupation [f]				
Motor Vehicle Operator	N/A		N/A	
Landscaper, Groundskeeper	**2.32**	(1.28, 4.21)	**2.06**	(1.12, 3.79)
Chemical Worker	N/A		N/A	
Server/Processor	N/A		N/A	
Artist	N/A		N/A	
Other-Employed	Ref.		Ref.	
Unemployed	1.09	(0.66, 1.80)	1.05	(0.62, 1.75)
Maternal Smoking [gi]				
Yes	0.91	(0.65, 1.27)	0.97	(0.68, 1.38)
No	Ref.		Ref.	
Corticosteroid Use [ie]				
Yes	0.90	(0.37, 2.21)	0.93	(0.38, 2.29)
No	Ref.		Ref.	
Phenothiazine Use [ie]				
Yes	**0.31**	(0.10, 0.97)	0.38	(0.12, 1.20)
No	Ref.		Ref.	

[a] Model adjusted for maternal race, maternal education, prepregnancy BMI, folic acid use during periconceptional period, maternal smoking, and study center

[b] Model adjusted for maternal age, maternal education, birth plurality, and study center

[c] Model adjusted for maternal age, maternal race, maternal education, maternal hypertension, birth plurality, maternal smoking, folic acid use during periconcpetional period, and study center

[d] Model adjusted for maternal age, maternal race, maternal education, pregnancy BMI, folic acid use during periconceptinal period, maternal smoking, and study center

[e] Model adjusted for maternal age, maternal race, study center

[f] Model adjusted for study center, maternal age, maternal race, maternal education, folic acid use during periconceptional period, and maternal smoking

[g] Model adjusted for maternal age, maternal race, prepregnancy BMI, folic acid use during periconceptional period, family history of CHD, and study center

[i] Exposure during periconceptional period (B1-P3)

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