Trends and Associated Maternal Risk Factors for Cyanotic Congenital Heart Defects From 2016 To 2022 In the United States

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Cyanotic Congenital Heart Defects (CCHD) are major birth defects and a leading cause of infant deaths in the United States, with a 25% mortality rate. From 2016 to 2022, the CCHD rate increased by 18%, yet few studies have identified causes for this increasing trend. This study assessed the influence of maternal risk factors on CCHD and identified risk factors associated with this increasing trend. Odds ratios (ORs) from multivariate logistic regression analysis show significant associations between CCHD and maternal age 35 (OR: 1.13, 95% CI: 1.02-1.25), smoking (OR: 1.26, 95% CI: 1.03-1.55), pre-pregnancy diabetes (OR:4.31, 95% CI: 3.53-5.27), gestational diabetes (OR: 1.32, 95% CI 1.14-1.52), and prenatal care initiation in the 2nd trimester (OR: 1.33, 95% CI: 1.19-1.49) and 3rd trimester (OR: 2.63, 95% CI: 2.28-3.04). The odds ratios were consistently higher for prenatal care initiated in the 3rd trimester compared to the 2nd trimester, indicating that the later prenatal care begins, the greater the risk for CCHD. In addition, pre-pregnancy diabetes had the highest odds ratios, ranging from 4.31 to 5.62 for these seven study years, suggesting pre-pregnancy diabetes is one of the major risk factors for CCHD. Thus, reducing these identified maternal risk factors may decrease the risk of CCHD.

Keywords: Cyanotic Congenital Heart Defects, Birth Defects, Maternal Age, BMI, Smoking, Prenatal Care, Pre-pregnancy Diabetes, and Gestational Diabetes

Introduction

The leading cause of infant deaths in the United States is birth defects, which account for 20% of all infant deaths[1]. Among 12 major birth defects, Cyanotic Congenital Heart Defects (CCHD) has the highest rate of 60.7 cases per 100 000 live births and makes up 20% of all birth defects in the U.S.[2]. In addition, CCHD has a mortality rate of 25%[3]. Thus, CCHD is one of severe birth defect issues in the United States.

Birth defects are caused by a complex mix of genetic, behavioral, and environmental factors[1]. Previous studies have reported many risk factors. For example, mothers age, lifestyle such as smoking, and health issues such as diabetes, are identified as maternal risk factors. Although many risk factors have been identified as a potential cause of birth defects, the etiology remains unknown for about 70% of cases[4]. Moreover, the influence and magnitude of maternal risk factors varies across studies and over time, likely due to changes in human behavior, health issues, and environmental exposures[4–7].

Recent data from the Centers for Disease Control and Prevention (CDC) show that the national rate of CCHD has increased 18% from 55.6 in 2016 to 66.0 in 20222. During this period, national screening policies for CCHD remained the same[8,9], and the national abortion rate decreased by 0.3, from 11.5 in 2016 to 11.2 in 2022[10]. Therefore, the increase in CCHD cases is less likely due to changes in screening or termination practices. However, few studies have investigated causes for this CCHD increasing trend and the risk factors for this increasing trend are still unknown[7]. Hence, this study conducts a systematic investigation on the influence of maternal risk factors, specifically maternal age, body mass index (BMI), pre-pregnancy and gestational diabetes, smoking, prenatal care, and trimester of prenatal care initiation, on CCHD from 2016 to 2022, based on the annual birth data provided by CDC.

Methods

Previous research has reported maternal age $\geq$35, pre-pregnancy diabetes, obesity, smoking, gestational diabetes, alcohol use, preeclampsia, and paternal smoking as important risk factors for CCHD for various US states during various time frames[3,5–7]. To the best of our knowledge, no other study has conducted a systematic analysis of maternal risk factors associated with the CCHD increasing trend from 2016 to 2022. This study hypothesizes that maternal risk factors, specifically maternal age, BMI, pre-pregnancy and gestational diabetes, smoking, prenatal care access, and trimester of prenatal care initiation, may be associated with the CCHD increasing trend, and conducts a

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systematic investigation on the influence of these maternal risk factors on CCHD.

Data Source

Birth data were collected from the CDC National Center for Health Statistics (NCHS) live birth database[2]. The CDC NCHS collects birth data from the standard certificate of birth, which is mandatory to be completed and published for every birth occurring in the United States. The birth data only includes births from US residents and non-residents inside the US. Births occurring to US citizens or residents outside of the US are not included. Data not reported by parents on birth certificates were labeled as unknown in the CDC NCHS dataset.

The CDC NCHS dataset provides the health status of pregnant women and infants, with the focus on the demographic, health, and risk factors of maternal and infant health. However, CDC restricts access to birth data with less than 10 live birth cases and individual case location due personal confidentiality[2]. Thus, these data and unknown data were not used in this research. This study used the anonymized, singleton births with individual birth data from January 2016 to December 2022. A total of 25,417,949 births with 15,134 CCHD cases were analyzed. Details of the yearly number of total births and CCHD cases is listed in Appendix A.

Maternal Risk Factors

This study analyzed major identified risk factors available in the CDC dataset, including maternal age, prenatal care, trimester of prenatal care initiation, pre-pregnancy diabetes, BMI, smoking, and gestational diabetes on CCHD[6].

The following variables were extracted and cleaned from the CDC dataset: maternal age, BMI, smoking, prenatal care, trimester of prenatal care initiation, pre-pregnancy diabetes, and gestational diabetes, and infant congenital anomalies and year of birth. BMI was categorized as underweight ($<$ 18.5), normal (18.5-24.9), overweight (25-29.9), and obese ($\geq$30). Age was categorized as under 20 years old, 20 to 34 years old, and 35 years or older. Although the average maternal age increased from 28.7 years in 2016 to 29.4 years in 2023[11], this shift had minimal impact on the distribution of mothers within the age categories and negligible effect on the analysis. The trimester of prenatal care initiation was categorized as 1st trimester, 2nd trimester, and 3rd trimester.

Statistical Analysis

Birth defect rates were calculated annually from 2016 to 2022 as the number of cases per 100,000 live births to evaluate trends over this study period. Logistic regression was used to analyze the relationship between CCHD and maternal risk factors. Initially, the independent variables were added into a univariate logistic model to provide the crude odds ratios, confidence intervals, and p-values. Next, those variables were analyzed in the adjusted multivariable logistic model, with maternal age, BMI, smoking, prenatal care, pre-pregnancy diabetes, and gestational diabetes as covariates. P-values were adjusted using the Benjamini-Hochberg procedure to control the false discovery rate[12]. The model fit was assessed using the p-value of the Hosmer-Lemeshow (HL) test and sensitivity analyses were performed to assess the robustness of the results[13]. All statistical analyses were performed using IBM SPSS, p-value $<$0.05 was considered statistically significant.

Results

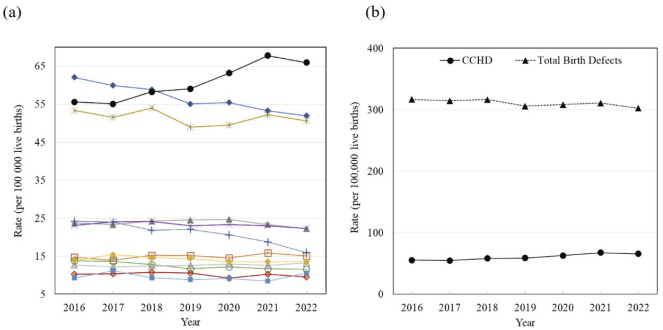

Fig. 1 Trends and rates (per 100,000 live births) of birth defects from 2016 to 2022. **(a)** shows the trends and rates of twelve major birth defects. Black Circle: CCHD, Blue diamond: Hypospadias, Gold Snowflake: Cleft lip, Empty Grey Triangle: Congenital diaphragmatic hernia, Orange Square: Suspected Chromosomal Disorder, Green Circle: Limb Reduction Defect, Yellow Diamond: Spina Bifida, Filled Grey Triangle: Down Syndrome, Blue Plus Sign: Gastroschisis, Blue Square: Anencephaly, Purple Cross: Cleft Palate, Red Diamond: Omphalocele. **(b)** shows the rates of CCHD and total birth defects.

Figure 1(a) shows the trends and rates (per 100,000 live births) of twelve major birth defects from 2016 to 2022. CCHD has the highest birth defect rate among 12 major birth defects, followed by Hypospadias and Cleft lip with or without palate. In addition, CCHD shows a continuous increasing trend. The rest of the birth defect types show relatively low rates and stable trends compared to CCHD. Figure 1 (b) shows the rates of CCHD and total birth defects from 2016 to 2022. In those seven years, the CCHD rate increased from 55.6 to 66.0, accounting for 18% to 22% of total birth defects. The high and continuous increasing rate of CCHD trend indicates that CCHD is the dominant birth defect in the United States.

Table 1 shows the associations between CCHD and maternal risk factors. In 2022, CCHD showed significant associations with maternal age $\geq$35 (OR: 1.13, 95% CI: 1.02-1.25), smoking (OR: 1.26, 95% CI: 1.03-1.55), pre-pregnancy diabetes (OR:

Year		Maternal Age			Prenatal Care		Smoking		BMI				Pre-Pregnancy Diabetes		Gestational Diabetes	
		<20	20-34	≥35	Yes	No	Yes	No	<18.5	18.5-24.9	25-29.9	≥30	Yes	No	Yes	No
2016	Odds Ratio	0.99	Ref	1.32	Ref	1.40	1.33	Ref	0.86	Ref	0.94	1.01	5.55	Ref	1.58	Ref
	95% CI	0.80-1.23	-	1.18-1.48	-	1.01-1.95	1.14-1.56	-	0.65-1.13	-	0.84-1.05	0.90-1.12	4.45-6.92	-	1.34-1.86	-
	P-value[a]	0.971	-	<0.001	-	0.088	<0.001	-	0.381	-	0.371	0.964	<0.001	-	<0.001	-
2017	Odds Ratio	0.95	Ref	1.19	Ref	1.32	1.33	Ref	0.82	Ref	0.91	0.96	5.55	Ref	1.36	Ref
	95% CI	0.76-1.19	-	1.06-1.33	-	0.95-1.82	1.13-1.56	-	0.61-1.08	-	0.81-1.02	0.86-1.08	4.47-6.90	-	1.15-1.61	-
	P-value[a]	0.752	-	0.008	-	0.187	<0.001	-	0.254	-	0.197	0.644	<0.001	-	<0.001	-
2018	Odds Ratio	1.00	Ref	1.19	Ref	1.28	1.46	Ref	1.06	Ref	1.07	1.08	5.62	Ref	1.52	Ref
	95% CI	0.81-1.24	-	1.07-1.33	-	0.93-1.76	1.25-1.71	-	0.82-1.38	-	0.95-1.19	0.97-1.20	4.57-6.91	-	1.31-1.78	-
	P-value[a]	0.990	-	0.005	-	0.215	<0.001	-	0.759	-	0.377	0.287	<0.001	-	<0.001	-
2019	Odds Ratio	1.08	Ref	1.25	Ref	1.52	1.24	Ref	1.23	Ref	0.95	1.10	4.66	Ref	1.34	Ref
	95% CI	0.87-1.34	-	1.12-1.40	-	1.14-2.04	1.04-1.47	-	0.95-1.58	-	0.84-1.07	0.98-1.22	3.72-5.82	-	1.14-1.57	-
	P-value[a]	0.741	-	<0.001	-	0.312	0.602	-	0.191	-	0.479	0.888	<0.001	-	<0.001	-
2020	Odds Ratio	0.95	Ref	1.31	Ref	1.22	1.07	Ref	1.24	Ref	0.95	0.99	5.04	Ref	1.65	Ref
	95% CI	0.75-1.19	-	1.18-1.45	-	0.89-1.68	0.89-1.29	-	0.96-1.59	-	0.85-1.06	0.89-1.10	4.10-6.20	-	1.43-1.89	-
	P-value[a]	0.741	-	<0.001	-	0.312	0.602	-	0.191	-	0.479	0.888	<0.001	-	<0.001	-
2021	Odds Ratio	0.95	Ref	1.18	Ref	1.06	1.38	Ref	1.21	Ref	0.95	0.97	5.24	Ref	1.52	Ref
	95% CI	0.76-1.20	-	1.07-1.30	-	0.78-1.44	1.16-1.64	-	0.95-1.55	-	0.85-1.06	0.88-1.08	4.33-6.35	-	1.33-1.74	-
	P-value[a]	0.763	-	0.003	-	0.794	<0.001	-	0.212	-	0.471	0.725	<0.001	-	<0.001	-
2022	Odds Ratio	1.01	Ref	1.13	Ref	0.65	1.26	Ref	1.04	Ref	1.08	1.10	4.31	Ref	1.32	Ref
	95% CI	0.80-1.27	-	1.02-1.25	-	0.44-0.95	1.03-1.55	-	0.79-1.37	-	0.970-1.20	0.99-1.22	3.53-5.27	-	1.14-1.52	-
	P-value[a]	0.972	-	0.040	-	0.059	0.056	-	0.861	-	0.265	0.144	<0.001	-	<0.001	-

[a]P-values adjusted using the Benjamini-Hochberg procedure

Table 1. Adjusted odds ratios, 95% confidence intervals, and adjusted p-values for associations between CCHD and maternal risk factors in the United States from 2016 to 2022

4.31, 95% CI: 3.53-5.27), and gestational diabetes (OR: 1.32, 95% CI 1.14-1.52). These associations remained significant across all seven study years, except for smoking, which was significant in four of the seven years. The confidence intervals for these odds ratios are all greater than 1 with relatively narrow ranges, indicating that these odds ratios are relatively precise. In addition, the odds ratios of maternal age ≥35, smoking, pre-pregnancy diabetes, and gestational diabetes all show decreasing trends from 2016 to 2022, suggesting their influence on CCHD is decreasing. CCHD showed no significant associations with prenatal care, BMI, or maternal age <20.

Although prenatal care access shows no significant associations with CCHD, recent studies suggest that the timing of prenatal care initiation may influence CCHD risk [14,15]. For example, periconceptional multivitamin use was associated with a reduced risk for CCHD, however, beginning multivitamin use after the first month of pregnancy showed no reduction in CCHD risk [14]. Thus, to further investigate the influence of prenatal care, this study examined prenatal care access and the trimester of prenatal care initiation.

Figure 2 (a) shows the percentage of mothers in relation to prenatal care. The percentage of mothers with and without prenatal care remained stable from 2016 to 2022, averaging 98% and 2%, respectively. Since CCHD develops in the first 10 weeks

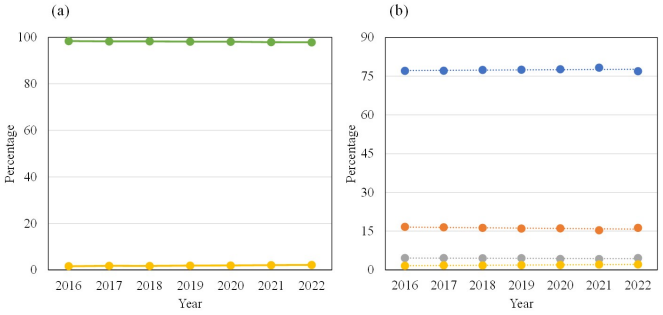

Fig. 2 Trends in the percentage of mothers in relation to prenatal care from 2016 to 2022. **(a)** shows the percentage of mothers with and without prenatal care. Green: Received prenatal care, Yellow: No prenatal care. **(b)** shows the percentage of mothers by trimester of prenatal care initiation. Blue: Began prenatal care in the 1st trimester, Orange: Began prenatal care in the 2nd trimester, Gray: Began prenatal care in the 3rd trimester, Yellow: No prenatal care

of pregnancy [16], the timing of prenatal care initiation might be associated with CCHD. Figure 2(b) displays the percentage of mothers across four groups: mothers who began prenatal care in the first, second, or third trimester, and mothers who received no care. The percentages in these groups remained stable over

time, with the majority of mothers (77%) initiating care in the first trimester, followed by 16% in the second trimester, 5% in the third trimester, and 2% receiving no prenatal care. Among mothers who received prenatal care, 79% of mothers-initiated care during the first trimester.

Year		Trimester of Prenatal Care Initiation		
		1st	2nd	3rd
2016	Odds Ratio	Ref	1.57	2.49
	95% CI	-	1.41-1.76	2.13-2.91
	P-value[a]	-	<0.001	<0.001
	HL p-value		0.169	
2017	Odds Ratio	Ref	1.49	2.46
	95% CI	-	1.33-1.67	2.10-2.89
	P-value[a]	-	<0.001	<0.001
	HL p-value		0.409	
2018	Odds Ratio	Ref	1.36	2.93
	95% CI	-	1.21-1.52	2.54-3.38
	P-value[a]	-	<0.001	<0.001
	HL p-value		0.262	
2019	Odds Ratio	Ref	1.53	3.20
	95% CI	-	1.36-1.72	2.77-3.70
	P-value[a]	-	<0.001	<0.001
	HL p-value		0.450	
2020	Odds Ratio	Ref	1.77	3.89
	95% CI	-	1.59-1.97	3.39-4.45
	P-value[a]	-	<0.001	<0.001
	HL p-value		0.034	
2021	Odds Ratio	Ref	1.57	3.63
	95% CI	-	1.41-1.75	3.19-4.14
	P-value[a]	-	<0.001	<0.001
	HL p-value		0.698	
2022	Odds Ratio	Ref	1.33	2.63
	95% CI	-	1.19-1.49	2.28-3.04
	P-value[a]	-	<0.001	<0.001
	HL p-value		0.206	

[a]P-values adjusted using the Benjamini-Hochberg procedure

Table 2. Association between CCHD and the trimester of prenatal care initiation from 2016 to 2022

Table 2 shows the association between the trimester of prenatal care initiation and CCHD. CCHD shows significant associations with prenatal care initiated in the 2nd and 3rd trimesters, with odds ratios ranging from 1.33 to 1.57 for the 2nd trimester and from 2.65 to 3.63 for the 3rd trimester. The HL p-values calculated from 2016 to 2022 (excluding 2020) ranges from 0.169 to 0.698 indicating a good model fit. However, the HL p-value in 2020 shows a poor model fit with a value of 0.034, suggesting there might be major risk factors missing in the 2020 analysis.

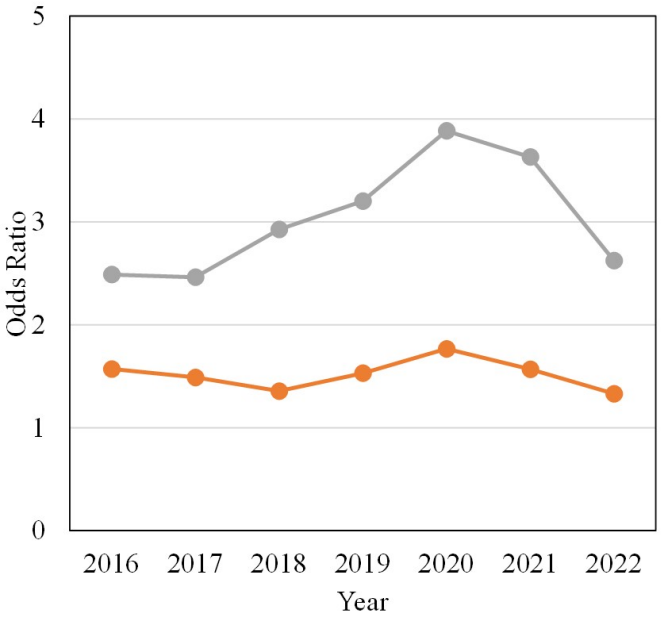

Fig. 3 Trends and odds ratios for the trimester of prenatal care initiation in relation to CCHD from 2016 to 2022. Orange: Prenatal care initiated in the 2nd trimester, Gray: Prenatal care initiated in the 3rd trimester

Figure 3 shows the odds ratios for associations between the trimester of prenatal care initiation and CCHD. The odds ratios for initiating care in the 2nd and 3rd trimesters showed similar trends, increasing from 2016 to 2019, peaking in 2020 at 1.77 and 3.89, respectively, and then decreasing to 1.77 and 2.63, respectively, by 2022. In those years, all of the odds ratios are greater than 1, suggesting that delayed prenatal care is a risk factor for CCHD. In addition, odds ratios were consistently higher for prenatal care initiated in the 3rd trimester compared to the 2nd trimester, indicating that the later prenatal care begins, the greater the risk for CCHD.

Discussion

This study examined the association between maternal risk factors and CCHD in the United States from 2016 to 2022. In 2022, maternal age ≥35 (OR: 1.13, 95% CI: 1.02-1.25), smoking (OR: 1.26, 95% CI: 1.03-1.55), pre-pregnancy diabetes (OR:4.31, 95% CI: 3.53-5.27), gestational diabetes (OR: 1.32, 95% CI 1.14-1.52), and prenatal care initiation in the 2nd trimester (OR:

1.33, 95% CI: 1.19-1.49) and 3rd trimester (OR: 2.63, 95% CI: 2.28-3.04) all show statistically significant associations with CCHD. These associations remained significant across all seven study years, except for smoking, which was significant in four of the seven years. BMI and Maternal age <20 show no statistical correlation with CCHD, which is consistent with previous studies [17,18].

Of the maternal risk factors studied, pre-pregnancy diabetes showed the strongest association with CCHD, with a large effect size of 5.55, suggesting pre-pregnancy diabetes is the major risk factor. Indeed, research has shown pre-pregnancy diabetes can interfere with fetal organ development, including the heart during the first 10 weeks of pregnancy, which may increase the risk of CCHD [12]. Consequently, mothers with pre-pregnancy diabetes may be at a higher risk for having a child with CCHD. Research shows that pre-pregnancy and early pregnancy education for diabetes can decrease the risk of CCHD [19]. However, studies show 53% of pregnant women with preexisting diabetes received no pre-pregnancy education about how diabetes could affect pregnancy [20]. Thus, providing pre-pregnancy education for all women with diabetes may improve diabetes management during early pregnancy and reduce the risk of CCHD.

The trimester of prenatal care initiation is significantly associated with CCHD, with good model fit in six of the seven years of analysis. The poor model fit in the 2020 analysis suggests there might be other risk factors impacting CCHD births in 2020. One major health related event in 2020 was the COVID-19 pandemic. Recent studies have reported maternal COVID-19 infection during pregnancy may impact fetal heart development [21]. In addition, studies have reported that COVID-19 is associated with the increasing trend in the heart defects rate [21]. Thus, COVID-19 might be one of the maternal risk factors influencing CCHD during the pandemic years. However, COVID-19 data is currently not complete and thus, the influence of COVID-19 on CCHD remains unclear and requires further research. Future studies may include parity, socioeconomic status, race, ethnicity, and COVID-19 as covariates to better understand the risk factors contributing to the CCHD increasing trend from 2016 to 2022.

Conclusion

This study conducted a systematic analysis of the association between six major maternal risk factors and the CCHD increasing trend from 2016 to 2022, and identified significant associations between CCHD and maternal age ≥ 35, smoking, pre-pregnancy diabetes, gestational diabetes, and prenatal care initiation in the 2nd trimester and 3rd trimester. Pre-pregnancy diabetes, with the highest odds ratios ranging from 4.31 to 5.62 for these seven study years, is one of the major risk factors for CCHD.

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Appendix A. Crude and adjusted odds ratios, 95% confidence intervals, p-values, adjusted p-values, and HL p-values for the association between maternal risk factors and CCHD.

Year			Maternal Age			Prenatal Care		Smoking		BMI				Pre-Pregnancy Diabetes		Gestational Diabetes	
			<20	20-34	≥35	Yes	No	Yes	No	<18.5	18.5-24.9	25-29.9	≥30	Yes	No	Yes	No
2016	**Adjusted**	Odds Ratio	0.99	Ref	1.32	Ref	1.40	1.33	Ref	0.86	Ref	0.94	1.01	5.55	Ref	1.58	Ref
Cases = 2200		95% CI	0.80-1.23	-	1.18-1.48	-	1.01-1.95	1.14-1.56	-	0.65-1.13	-	0.84-1.05	0.90-1.12	4.45-6.92	-	1.34-1.86	-
Total Births = 3810149		P-value[a]	0.971	-	<0.001	-	0.088	<0.001	-	0.381	-	0.371	0.964	<0.001	-	<0.001	-
		P-value	0.940	-	<0.001	-	0.042	<0.001	-	0.272	-	0.253	0.918	<0.001	-	<0.001	-
		HL p-value	0.991	-	0.991	-	0.991	0.991	-	0.991	-	0.991	0.991	0.991	-	0.991	-
	Crude	Odds Ratio	0.92	Ref	1.41	Ref	1.35	1.35	Ref	0.86	Ref	0.96	1.14	6.07	Ref	1.55	Ref
		95% CI	0.75-1.12	-	1.27-1.57	-	1.00-1.84	1.17-1.57	-	0.66-1.11	-	0.86-1.07	1.03-1.27	4.97-7.40	-	1.34-1.81	-
		P-value[a]	0.447	-	<0.001	-	0.081	<0.001	-	0.305	-	0.491	0.023	<0.001	-	<0.001	-
		P-value	0.394	-	<0.001	-	0.053	<0.001	-	0.243	-	0.438	0.013	<0.001	-	<0.001	-
		HL p-value	1.000	-	1.000	-	1.000	1.000	-	1.000	-	1.000	1.000	1.000	-	1.000	-
2017	**Adjusted**	Odds Ratio	0.95	Ref	1.19	Ref	1.32	1.33	Ref	0.82	Ref	0.91	0.96	5.55	Ref	1.36	Ref
Cases = 2130		95% CI	0.76-1.19	-	1.06-1.33	-	0.95-1.82	1.13-1.56	-	0.61-1.08	-	0.81-1.02	0.86-1.08	4.47-6.90	-	1.15-1.61	-
Total Births = 3723273		P-value[a]	0.752	-	0.008	-	0.187	<0.001	-	0.254	-	0.197	0.644	<0.001	-	<0.001	-
		P-value	0.633	-	0.003	-	0.095	<0.001	-	0.157	-	0.103	0.511	<0.001	-	<0.001	-
		HL p-value	0.577	-	0.577	-	0.577	0.577	-	0.577	-	0.577	0.577	0.577	-	0.577	-
	Crude	Odds Ratio	0.88	Ref	1.24	Ref	1.25	1.38	Ref	0.86	Ref	0.95	1.08	5.39	Ref	1.33	Ref
		95% CI	0.71-1.09	-	1.11-1.38	-	0.92-1.69	1.19-1.60	-	0.66-1.12	-	0.85-1.06	0.970-1.20	4.38-6.62	-	1.13-1.55	-
		P-value[a]	0.304	-	<0.001	-	0.219	<0.001	-	0.326	-	0.415	0.225	<0.001	-	<0.001	-
		P-value	0.246	-	<0.001	-	0.159	<0.001	-	0.268	-	0.356	0.169	<0.001	-	<0.001	-
		HL p-value	1.000	-	1.000	-	1.000	1.000	-	1.000	-	1.000	1.000	1.000	-	1.000	-
2018	**Adjusted**	Odds Ratio	1.001	Ref	1.194	Ref	1.282	1.464	Ref	1.060	Ref	1.066	1.076	5.620	Ref	1.524	Ref
Cases = 2216		95% CI	0.81-1.24	-	1.07-1.33	-	0.93-1.76	1.25-1.71	-	0.82-1.38	-	0.95-1.19	0.97-1.20	4.57-6.91	-	1.31-1.78	-
Total Births = 3664651		P-value[a]	0.990	-	0.005	-	0.215	<0.001	-	0.759	-	0.377	0.287	<0.001	-	<0.001	-
		P-value	0.990	-	0.002	-	0.126	<0.001	-	0.663	-	0.263	0.187	<0.001	-	<0.001	-
		HL p-value	0.908	-	0.908	-	0.908	0.908	-	0.908	-	0.908	0.908	0.908	-	0.908	-
	Crude	Odds Ratio	1.02	Ref	1.24	Ref	1.24	1.50	Ref	1.13	Ref	1.12	1.21	5.65	Ref	1.49	Ref
		95% CI	0.83-1.25	-	1.12-1.38	-	0.92-1.68	1.29-1.73	-	0.88-1.44	-	1.00-1.25	1.09-1.34	4.66-6.86	-	1.29-1.73	-
		P-value[a]	0.885	-	<0.001	-	0.225	<0.001	-	0.415	-	0.068	<0.001	<0.001	-	<0.001	-
		P-value	0.853	-	<0.001	-	0.166	<0.001	-	0.351	-	0.043	<0.001	<0.001	-	<0.001	-
		HL p-value	1.000	-	1.000	-	1.000	1.000	-	1.000	-	1.000	1.000	1.000	-	1.000	-

[a]P-values adjusting using the Benjamini-Hochberg procedure

Year			Maternal Age			Prenatal Care		Smoking		BMI				Pre-Pregnancy Diabetes		Gestational Diabetes	
			<20	20-34	≥35	Yes	No	Yes	No	<18.5	18.5-24.9	25-29.9	≥30	Yes	No	Yes	No
2019	**Adjusted**	Odds Ratio	1.08	Ref	1.25	Ref	1.52	1.24	Ref	1.23	Ref	0.95	1.10	4.66	Ref	1.34	Ref
Cases = 2221		95% CI	0.87-1.34	-	1.12-1.40	-	1.14-2.04	1.04-1.47	-	0.95-1.58	-	0.84-1.07	0.98-1.22	3.72-5.82	-	1.14-1.57	-
Total Births = 3623963		P-value[a]	0.637	-	<0.001	-	0.013	0.041	-	0.200	-	0.488	0.185	<0.001	-	<0.001	-
		P-value	0.516	-	<0.001	-	0.005	0.017	-	0.114	-	0.364	0.103	<0.001	-	<0.001	-
		HL p-value	0.587	-	0.587	-	0.587	0.587	-	0.587	-	0.587	0.587	0.587	-	0.587	-
	Crude	Odds Ratio	1.02	Ref	1.32	Ref	1.60	1.23	Ref	1.22	Ref	0.98	1.19	4.71	Ref	1.33	Ref
		95% CI	0.83-1.26	-	1.19-1.46	-	1.23-2.08	1.04-1.46	-	0.96-1.55	-	0.87-1.09	1.07-1.32	3.83-5.80	-	1.14-1.54	-
		P-value[a]	0.876	-	<0.001	-	<0.001	0.023	-	0.164	-	0.704	<0.001	<0.001	-	<0.001	-
		P-value	0.824	-	<0.001	-	<0.001	0.013	-	0.113	-	0.654	<0.001	<0.001	-	<0.001	-
		HL p-value	1.000	-	1.000	-	1.000	1.000	-	1.000	-	1.000	1.000	1.000	-	1.000	-
2020	**Adjusted**	Odds Ratio	0.95	Ref	1.31	Ref	1.22	1.07	Ref	1.24	Ref	0.95	0.99	5.04	Ref	1.65	Ref
Cases = 2288		95% CI	0.75-1.19	-	1.18-1.45	-	0.89-1.68	0.89-1.29	-	0.96-1.59	-	0.85-1.06	0.89-1.10	4.10-6.20	-	1.43-1.89	-
Total Births = 3498335		P-value[a]	0.741	-	<0.001	-	0.312	0.602	-	0.191	-	0.479	0.888	<0.001	-	<0.001	-
		P-value	0.635	-	<0.001	-	0.208	0.468	-	0.103	-	0.365	0.832	<0.001	-	<0.001	-
		HL p-value	0.993	-	0.993	-	0.993	0.993	-	0.993	-	0.993	0.993	0.993	-	0.993	-
	Crude	Odds Ratio	0.94	Ref	1.37	Ref	1.19	1.13	Ref	1.15	Ref	1.00	1.11	4.81	Ref	1.56	Ref
		95% CI	0.76-1.17	-	1.24-1.51	-	0.89-1.59	0.95-1.34	-	0.89-1.47	-	0.90-1.12	1.00-1.23	3.96-5.86	-	1.36-1.78	-
		P-value[a]	0.645	-	<0.001	-	0.297	0.235	-	0.346	-	0.970	0.083	<0.001	-	<0.001	-
		P-value	0.591	-	<0.001	-	0.233	0.179	-	0.288	-	0.958	0.055	<0.001	-	<0.001	-
		HL p-value	1.000	-	1.000	-	1.000	1.000	-	1.000	-	1.000	1.000	1.000	-	1.000	-
2021	**Adjusted**	Odds Ratio	0.95	Ref	1.18	Ref	1.06	1.38	Ref	1.21	Ref	0.95	0.97	5.24	Ref	1.52	Ref
Cases = 2490		95% CI	0.76-1.20	-	1.07-1.30	-	0.78-1.44	1.16-1.64	-	0.95-1.55	-	0.85-1.06	0.88-1.08	4.33-6.35	-	1.33-1.74	-
Total Births = 3547198		P-value[a]	0.763	-	0.003	-	0.794	<0.001	-	0.212	-	0.471	0.725	<0.001	-	<0.001	-
		P-value	0.678	-	0.001	-	0.718	<0.001	-	0.128	-	0.344	0.598	<0.001	-	<0.001	-
		HL p-value	0.417	-	0.417	-	0.417	0.417	-	0.417	-	0.417	0.417	0.417	-	0.417	-
	Crude	Odds Ratio	1.00	Ref	1.24	Ref	1.13	1.40	Ref	1.20	Ref	0.99	1.10	5.06	Ref	1.54	Ref
		95% CI	0.81-1.23	-	1.12-1.36	-	0.86-1.49	1.18-1.65	-	0.94-1.52	-	0.89-1.10	1.00-1.21	4.21-6.07	-	1.36-1.74	-
		P-value[a]	0.963	-	<0.001	-	0.426	<0.001	-	0.209	-	0.883	0.088	<0.001	-	<0.001	-
		P-value	0.963	-	<0.001	-	0.370	<0.001	-	0.149	-	0.841	0.060	<0.001	-	<0.001	-
		HL p-value	1.000	-	1.000	-	1.000	1.000	-	1.000	-	1.000	1.000	1.000	-	1.000	-

[a]P-values adjusting using the Benjamini-Hochberg procedure

Year			Maternal Age			Prenatal Care		Smoking		BMI				Pre-Pregnancy Diabetes		Gestational Diabetes	
			<20	20-34	≥35	Yes	No	Yes	No	<18.5	18.5-24.9	25-29.9	≥30	Yes	No	Yes	No
2022	**Adjusted**	Odds Ratio	1.01	Ref	1.13	Ref	0.65	1.26	Ref	1.04	Ref	1.08	1.10	4.31	Ref	1.32	Ref
Cases = 2426		95% CI	0.80-1.27	-	1.02-1.25	-	0.44-0.95	1.03-1.55	-	0.79-1.37	-	0.970-1.20	0.99-1.22	3.53-5.27	-	1.14-1.52	-
Total Births = 3550380		P-value[a]	0.972	-	0.040	-	0.059	0.056	-	0.861	-	0.265	0.144	<0.001	-	<0.001	-
		P-value	0.957	-	0.017	-	0.027	0.025	-	0.793	-	0.168	0.071	<0.001	-	<0.001	-
		HL p-value	0.376	-	0.376	-	0.376	0.376	-	0.376	-	0.376	0.376	0.376	-	0.376	-
	Crude	Odds Ratio	0.99	Ref	1.20	Ref	0.71	1.27	Ref	1.08	Ref	1.09	1.17	4.26	Ref	1.30	Ref
		95% CI	0.80-1.22	-	1.09-1.32	-	0.50-0.99	1.05-1.55	-	0.83-1.40	-	0.98-1.21	1.06-1.29	3.52-5.177	-	1.14-1.49	-
		P-value[a]	0.931	-	<0.001	-	0.067	0.026	-	0.621	-	0.169	0.004	<0.001	-	<0.001	-
		P-value	0.909	-	<0.001	-	0.043	0.015	-	0.562	-	0.119	0.002	<0.001	-	<0.001	-
		HL p-value	1.000	-	1.000	-	1.000	1.000	-	1.000	-	1.000	1.000	1.000	-	1.000	-

[a]P-values adjusting using the Benjamini-Hochberg procedure

Appendix B. The number of CCHD cases and state population-normalized rate of CCHD cases in all 50 states from 2016 to 2022. The rate listed in the table is multiplied by 100,000. Due to CDC confidentiality restrictions, exact birth counts could not be reported for states with fewer than 10 CCHD cases.

State	2016		2017		2018		2019		2020		2021		2022	
	Cases	Rate	Cases	Rate	Cases	Rate	Cases	Rate	Cases	Rate	Cases	Rate	Cases	Rate
Alabama	<10	-	<10	-	<10	-	<10	-	<10	-	17	29	24	41
Alaska	12	107	13	124	<10	-	11	112	10	106	16	171	15	160
Arizona	45	53	34	42	47	58	50	63	45	58	72	92	62	79
Arkansas	12	31	13	35	14	38	16	44	<10	-	<10	-	<10	-
California	49	10	44	9	32	7	67	15	31	7	63	15	60	14
Colorado	36	54	38	59	33	52	30	48	35	57	27	43	71	114
Connecticut	36	100	19	54	19	55	20	58	18	54	27	76	30	85
Delware	13	118	27	249	17	17	<10	-	15	144	10	95	<10	-
Florida	18	8	15	7	14	6	22	10	23	11	20	9	22	10
Georgia	37	28	39	30	20	16	28	22	27	22	19	15	18	14
Hawaii	0	0	<10	-	<10	-	<10	-	<10	-	<10	-	<10	-
Idaho	35	156	43	194	47	220	50	227	44	204	38	169	40	179
Illinois	95	62	90	60	123	85	105	75	82	62	94	71	95	74
Indiana	46	55	57	69	82	100	90	111	95	121	81	101	44	55
Iowa	33	84	62	161	63	167	48	128	37	102	41	111	69	189
Kansas	10	26	17	47	25	69	24	68	17	49	13	37	20	58
Kentucky	63	114	63	115	73	135	44	83	58	112	88	169	42	80
Louisiana	42	66	32	52	39	65	44	75	35	61	72	125	72	127
Maine	<10	-	11	89	<10	-	<10	-	<10	-	<10	-	<10	-
Maryland	93	127	93	130	116	163	99	141	84	123	104	152	121	176
Massachusetts	17	24	27	38	20	29	11	16	16	24	88	127	89	130
Michigan	<10	-	<10	-	<10	-	0	0	<10	-	10	10	<10	-
Minnesota	36	52	28	41	33	49	22	33	39	61	48	75	67	105
Mississippi	<10	-	<10	-	<10	-	15	41	<10	-	27	77	13	37
Missouri	43	58	37	51	33	45	38	53	18	26	28	40	32	46
Montana	<10	-	<10	-	14	122	<10	-	<10	-	<10	-	17	152
Nebraska	27	102	22	85	22	86	25	101	29	119	21	85	36	148
Nevada	25	69	28	78	25	70	13	37	15	45	25	74	11	33
New Hampshire	<10		<10	-	<10	-	<10	-	0	0	<10	-	11	91
New Jersey	104	101	59	58	51	50	60	60	67	68	66	65	54	52
New Mexico	15	61	24	101	16	69	13	57	12	55	19	89	27	125
New York	168	72	178	77	157	69	179	81	163	78	187	89	146	70
North Carolina	40	33	24	20	42	35	33	28	27	23	29	24	30	25
North Dakota	10	88	<10	-	14	132	<10	-	12	119	<10	-	<10	-
Ohio	198	143	179	131	193	143	176	131	142	110	180	139	147	115
Oklahoma	<10	-	<10	-	<10	-	15	31	20	42	24	50	15	31
Oregon	65	143	68	156	79	187	67	160	67	168	37	90	25	63
Pennsylvania	82	59	79	57	81	60	64	48	56	43	69	52	57	44
Rhode Island	<10	-	<10	-	11	105	<10	-	<10	-	<10	-	<10	-
South Carolina	34	59	46	81	52	92	58	102	68	122	113	198	91	157
South Dakota	15	122	13	107	<10	-	15	131	12	109	10	88	16	143
Tennessee	38	47	40	49	31	38	33	41	26	33	39	48	26	32
Texas	92	23	101	26	85	22	125	33	288	78	148	40	150	38
Utah	196	388	179	368	183	388	221	472	242	530	263	564	307	671
Vermont	<10	-	0	0	<10	-	<10	-	<10	-	<10	-	12	226
Virginia	<10	-	<10	-	22	22	11	11	20	21	23	24	23	24
Washington	134	148	99	113	110	128	115	135	104	125	90	107	59	71
West Virginia	26	136	30	161	28	153	14	77	16	92	18	105	30	177
Wisconsin	93	140	93	143	86	164	104	164	115	190	72	117	68	113
Wyoming	<10	-	<10	-	<10	-	<10	-	<10	-	<10	-	<10	-