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Associations between maternal periconceptional alcohol consumption and risk of craniosynostosis among offspring, National Birth Defects Prevention Study, 1997–2011

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Abstract

Background: Previous studies of maternal alcohol consumption and craniosynostosis have reported null or inverse associations. We updated a previous analysis of National Birth Defects Prevention Study (NBDPS) data to further examine associations between maternal alcohol consumption and craniosynostosis.

Methods: NBDPS was a multi-site, population-based case-control study. Mothers of craniosynostosis cases and randomly selected liveborn controls delivered during 1997–2011 completed a telephone interview about pregnancy exposures. We examined associations for self-reported periconceptional maternal alcohol consumption (during the month before conception through the third gestational month) and odds of craniosynostosis in offspring. We used logistic regression to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for associations between any alcohol consumption and binge consumption and craniosynostosis, overall and by affected suture. Finally, we performed a probabilistic bias analysis using a range of assumptions about sensitivity and specificity of self-reported consumption by case/control status.

Results: We analyzed interview data from 1,435 mothers of craniosynostosis cases and 11,216 mothers of controls. Periconceptional alcohol consumption prevalence was similar among case (36.9%) and control (38.2%) mothers. We observed point estimates near or below 1.0 for alcohol

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Ethics approval statement: All interviewed study participants provided informed consent. The Centers for Disease Control and Prevention Institutional Review Board (IRB), along with the IRBs for each participating site, have approved the NBDPS. (See 45 C.F.R. part 46; 21 C.F.R. part 56)

consumption (any and binge) and all suture subtypes of craniosynostosis, with all CIs including the null. Our bias-adjusted estimates for periconceptional alcohol consumption were higher than our conventional estimates but supported the null findings.

Conclusions: We observed primarily null associations between maternal periconceptional alcohol consumption and craniosynostosis. However, our findings do not diminish the prevailing clinical guidance in the US that pregnant people should abstain from alcohol consumption.

Keywords

craniosynostosis; birth defects; alcohol; pregnancy; NBDPS; bias

Introduction

Craniosynostosis affects approximately 4/10,000 live births in the United States¹ and is characterized by premature fusion of one or more skull sutures. In normal development, the skull sutures begin to fuse around age 2 years and reach maturity in adulthood², allowing for the skull to expand to accommodate brain growth during childhood. With craniosynostosis, this fusion occurs earlier, which can result in dysmorphic skull and facial features, as well as restricted brain development.³ Craniosynostosis subtypes can be defined by the affected suture (sagittal, metopic, coronal, lambdoidal, and multiple sutures), with some variation in risk factors for each subtype. Risk factors consistently associated with craniosynostosis include infant sex (excess among males for all subtypes except coronal),^{1,4–7} non-Hispanic White maternal race/ ethnicity,^{1,5,8} plural gestation,^{1,7,9,10} and older maternal or paternal age.^{1,7,8,11} Valproic acid has been reported to be associated with increased risk of craniosynostosis,^{12–14} but evidence for other modifiable risk factors, such as smoking^{15–17} and fertility treatment,^{14,18,19} is mixed.

Alcohol is a common exposure among women of reproductive age²⁰ and is known to be associated with other adverse pregnancy outcomes.²¹ Analysis of 1997–2005 data from the National Birth Defects Prevention Study (NBDPS) showed a null association between maternal periconceptional (one month before conception through the third gestational month) alcohol consumption and craniosynostosis among offspring, but an inverse association with later pregnancy alcohol consumption.²² Another small study also observed an inverse association between maternal alcohol consumption and sagittal craniosynostosis.²³ Both studies were based on maternal self-reported alcohol consumption and authors noted the possibility of exposure misclassification.

Given the relative paucity of literature on alcohol consumption and craniosynostosis, further exploration of this relationship is needed. Towards this end, we used the complete NBDPS dataset, incorporating an additional six years of participant data, to update and expand upon previous NBDPS analyses of maternal alcohol consumption during pregnancy and craniosynostosis. NBDPS is one of the largest population-based studies of birth defects. We capitalized on this robust sample to examine associations by craniosynostosis subtype and incorporate a formal analysis of bias due to potential alcohol exposure misclassification.

Methods

NBDPS was a multi-site, population-based case-control study designed to investigate risk factors for major structural birth defects. Methods have been described in detail elsewhere.²⁴ Briefly, NBDPS was implemented in 10 US states (Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas, and Utah) and enrolled people with pregnancies ending on or after October 1, 1997 with estimated dates of delivery (EDDs) through December 31, 2011. Mothers of infants with birth defects (cases) were identified via birth defects surveillance programs in each state; cases could be liveborn, stillborn at 20 weeks gestation or later, or prenatally diagnosed and terminated at any gestational age. Mothers of liveborn infants without birth defects (controls) were randomly selected from hospital records or birth certificates in the same geographic regions as cases. Overall, 65% of controls and 66% of craniosynostosis cases participated in the interview. Participants self-reported demographic and pregnancy exposure data via telephone interview at least six weeks and up to two years after their EDD. Mothers were eligible to participate in the interview if they could speak English or Spanish, were not incarcerated, had legal custodial rights to their child, and had not already participated in the NBDPS with a previous child. Mothers provided informed consent and institutional review boards at each site and the Centers for Disease Control and Prevention approved the study protocol.

Outcome Assessment

Craniosynostosis cases were identified using International Classification of Disease (ICD)-9 code 756.0 and required diagnostic confirmation either by postnatal imaging, corrective surgery, or autopsy. Clinical geneticists reviewed abstracted medical records for each case to determine eligibility and to further classify cases based on the affected suture(s) (sagittal, metopic, coronal, lambdoidal, and/or unspecified), presence or absence of other birth defects, and overall complexity. Cases were classified as isolated (craniosynostosis was the only major defect, or only occurred with another developmentally-related defect) or multiple (craniosynostosis occurred with one or more unrelated major structural defects in another organ system).²⁵ Craniosynostosis that occurred post-shunt due to hydrocephalus was considered secondary to the hydrocephalus and excluded. Otherwise, hydrocephalus and craniosynostosis were generally considered separate defects and classified as “multiple”. Cases with known or strongly suspected genetic causes were excluded. For our analysis, we excluded cases with more than one affected suture (n=120), so craniosynostosis subtypes are mutually exclusive. Cases in which the affected suture was not specified (n=3) were included in the overall craniosynostosis analyses but excluded from subtype analyses.

Exposure Assessment

Because the developing embryo is most susceptible to teratogens early in gestation, our main analysis focused on maternal periconceptional alcohol consumption. We classified participants who did not report any alcohol consumption during pregnancy as unexposed and excluded those with missing periconceptional alcohol exposure status (n=339 controls, n=43 cases). Finally, we excluded participants who reported alcohol consumption only outside of the periconceptional period from our main analysis (n=271 controls, n=24 cases), but included them in a sub-analysis of later pregnancy exposure (described below).

Consistent with previously published NBDPS studies,^{22,26–33} we assessed self-reported maternal alcohol consumption in response to six interview questions about the timing, frequency, amount, and type of alcohol consumption during each pregnancy month. We created dichotomous variables for any alcohol consumption and any binge consumption (defined as ≥ 4 drinks per occasion) and categorical variables indicating the average number of drinks consumed per month and the number of days per month in which alcohol was consumed (i.e., frequency). Because we analyzed exposure for the entire periconceptional period, we used the values assigned to the month with the highest number of drinks consumed (henceforth, maximum average number of alcoholic drinks per month) and highest number of days in which alcohol was consumed (henceforth, maximum frequency of alcohol consumption per month). We calculated duration of alcohol exposure as the number of gestational months during which alcohol consumption was reported.

Statistical Analysis

We used unconditional logistic regression to estimate adjusted odds ratios (AORs) and 95% confidence intervals (CIs) for maternal periconceptional alcohol consumption and binge alcohol consumption and craniosynostosis in offspring, by suture subtype, compared to no pregnancy alcohol consumption. We constructed a directed acyclic graph (DAG) to identify potential confounders, based on a thorough literature review and subject area expertise. Our final model adjusted for maternal age at delivery (<20 , 20–24, 30–34, ≥ 35 years vs. 24–29 years), race/ethnicity (non-Hispanic Black, Hispanic, Other vs. non-Hispanic White), fertility treatment status (any vs. none), pregnancy intention (intended vs. unintended), and study site. Because the dataset included some data that were previously analyzed,²² we assessed differences in the distribution of covariates between the prior and newly added study participants. We assessed each potential covariate included in the DAG and Table 1, including those that were not included in the minimum set selected for the final model (Supplemental Table 1). We estimated one-sided 95% CIs for the absolute difference in proportions between the two samples, among controls. We determined *a priori* that a lower confidence bound of $>5\%$ would be considered meaningful and that any variable meeting that threshold would be included in the adjusted model. Ultimately, the only variable that met this criterion was study site, which was already included in the minimum set of covariates identified from our DAG.

We performed several sub-analyses. To facilitate comparisons with previously published NBDPS results,^{22,34} we stratified our main results by EDDs that were (1997–2005) and were not (2006–2011) included in the previous NBDPS analysis. Due to sample size limitations, and to maintain comparability to previous findings, we focused this sub-analysis on craniosynostosis overall, rather than individual suture types. To isolate the effect of early versus late alcohol exposure, we conducted a sub-analysis restricting the periconceptional exposure group to participants who reported alcohol consumption only during the periconceptional period and excluding those who reported alcohol consumption later in pregnancy. Because premature suture closure may be influenced by exposures after the periconceptional period, we also explored associations between later pregnancy alcohol consumption and craniosynostosis. For this sub-analysis, we classified exposure as reported

alcohol use only during the second or third trimester (T2/T3) and excluded participants who reported periconceptional alcohol consumption.

Finally, we performed a probabilistic bias sub-analysis to evaluate the role of alcohol exposure misclassification in our main results, following the methods described by Fox, et al.³⁵ We assumed specificity to be high for both case and control mothers and sensitivity to be lower than specificity. Data on sensitivity and specificity of self-reported alcohol exposure during pregnancy are not readily available to inform bias analysis parameters, although evidence suggests lower prevalence when measured by self-report compared to meconium testing.³⁶ As an alternative, we assumed that estimates from studies of the validity of self-reported smoking status provided a reasonable framework.^{37–41} Due to uncertainty about whether exposure misclassification differs by case/control status, we estimated bias-adjusted ORs based on five scenarios: lower sensitivity among cases and lower specificity among controls, lower sensitivity among cases and non-differential specificity, lower sensitivity among cases and higher specificity among controls, higher sensitivity among cases and non-differential specificity, and non-differential sensitivity and specificity. For each scenario, we assumed a trapezoidal distribution and generated 10,000 simulation datasets with cases and controls reclassified according to the bias parameters. We used results from these simulations to estimate median bias-adjusted ORs and 95% simulation intervals (SI), reflecting the 2.5th and 97.5th percentiles of the adjusted OR distribution. We stipulated high correlation (0.85) between misclassification parameters, given that case and control data were collected using the same survey instrument, and used a standard normal deviate to incorporate sampling error into the simulation interval to account for both random and systematic bias.³⁵ We used SAS 9.4 (SAS Institute, Cary, NC) for all analyses.

Results

We included mothers of 1,435 craniosynostosis cases and 11,216 controls in our main analysis. Case characteristics varied by affected suture, but in general, compared to controls, cases more frequently reported older age at delivery, non-Hispanic White race/ethnicity, family history of craniosynostosis, and fertility treatment (Table 1). We observed an excess of male infants among all craniosynostosis subtypes except coronal craniosynostosis, among which we observed an excess of female infants. Mothers of metopic and coronal cases more frequently reported obese BMIs, whereas mothers of lambdoidal cases reported disproportionately high rates of cigarette smoking during pregnancy.

Similar proportions of case and control mothers reported periconceptional alcohol consumption during pregnancy (Table 2). Overall, 36.9% (n=529) of case and 38.2% (n=4,280) of control mothers reported consumption, of whom about one-third of each reported at least one binge episode. In general, among those who reported alcohol consumption, patterns of frequency and quantity were similar between case and control mothers and most mothers reported consumption in only one (cases: 59.6%; controls: 56.0%) or two (cases: 29.5%; controls: 29.9%) gestational months. Further, most alcohol consumption was restricted to the periconceptional period, with 83.2% of case and 79.6% of control mothers reporting consumption only during the periconceptional period

(Supplemental Table 2). Among those who reported consumption in the second or third trimester (n=92 cases, 924 controls), 75.0% of cases (n=69) and 70.7% of controls (n=653) reported consumption in the periconceptional period as well.

Estimated AORs for any periconceptional alcohol consumption and craniosynostosis in offspring, overall and by affected suture, ranged from 0.78–0.93, with all 95% CIs including the null (Table 3). Most AORs were slightly higher for associations between periconceptional binge drinking and craniosynostosis and its subtypes, but CIs were wider and included the null. Restricting to mothers who only reported alcohol consumption during the periconceptional period, estimates were slightly closer to the null but very similar to our main results (Supplemental Table 3). Our sub-analysis of later pregnancy consumption was based on 23 exposed cases, of whom only 1 mother reported binge drinking, prohibiting meaningful analysis by affected suture or quantity of consumption. Our estimate for the association between later pregnancy alcohol consumption and craniosynostosis was further from the null than our periconceptional estimate (AOR 0.67, 95% CI 0.43, 1.04) (data not shown). When stratified by time period, AORs for any periconceptional alcohol consumption and for periconceptional binge drinking were similar among mothers with 1997–2005 EDDs and 2006–2011 EDDs (Supplemental Table 4).

Our bias-adjusted estimates for periconceptional alcohol consumption and craniosynostosis tended to be slightly higher than our conventional estimates (Table 4) but remained close to null. When we assumed higher sensitivity among case mothers and non-differential specificity, the bias-adjusted estimates moved lower. Under the most plausible scenario—lower sensitivity among case mothers and non-differential specificity—our bias-adjusted estimates shifted upwards to 1.03 (0.80, 1.33) for any periconceptional alcohol consumption and to 1.13 (0.87, 1.46) for any periconceptional binge consumption.

Discussion

In our study, estimates for associations between maternal periconceptional alcohol consumption and craniosynostosis in offspring were either near or below the null, with many estimates imprecise and all 95% CIs including the null. These results are consistent with those previously published using NBDPS data^{22,42} and with one non-NBDPS study of alcohol and craniosynostosis that we identified.²³

We encourage caution in interpreting the inverse associations we observed, as most participants who reported alcohol use in our study did not report any binge episodes. If craniosynostosis is associated with heavy alcohol consumption, but not lower levels of consumption, our study may have been underpowered to detect this effect. Our study had 80% power to detect a minimum effect size of 1.25 for binge consumption; it would require a study almost seven times larger to detect a statistically significant effect size of 1.09, the OR that we observed for binge consumption. Our ORs for participants who reported at least one binge drinking episode were generally higher than those for any alcohol consumption, but some estimates remained inverse, and all CIs included the null. NBDPS did not collect data on frequency of binge episodes, so we have limited ability to explore a dose-response effect with higher intensity consumption.

Unlike most other structural birth defects, which occur early in gestation, premature suture closure can occur any time, extending the etiologically relevant exposure window for craniosynostosis through the end of pregnancy. However, we were limited in our ability to analyze the association between later pregnancy alcohol exposure and craniosynostosis due to the small number of participants who reported alcohol consumption only in the second or third trimester. Most mothers who reported alcohol consumption during the second or third trimester also reported periconceptional consumption; to isolate the effect of timing, we excluded these participants from our sub-analysis. Our inverse AOR for second or third trimester alcohol consumption was similar to that reported earlier²² but should be interpreted with caution given the limited scope of this sub-analysis. We cannot rule out the possibility that later pregnancy alcohol consumption is associated with craniosynostosis.

Our study is limited by several potential sources of bias. We relied on self-reported exposure data. Alcohol is a known teratogen and participants were asked about consumption patterns after their pregnancy outcome was known. If case mothers were more likely to underreport alcohol consumption than control mothers, due to social stigma, this could bias estimates downward. Our bias-adjusted estimates based on this assumption (scenarios 1–3) were indeed higher than our conventional estimates for periconceptional alcohol consumption, but not high enough to suggest a meaningfully positive association.

Although the NBDPS interview was wide ranging in scope, allowing us to adjust for known confounders, it remains possible that our results are biased by unmeasured confounding. Misclassification of the covariates included in our model could also lead to incomplete control for confounding. We based our modeling strategy on a DAG, which we developed based on a review of the existing literature and expert opinion. However, we made certain assumptions which may or may not be correct, potentially affecting the validity of our statistical model. Nevertheless, our results presented in Table 1 generally confirmed associations in our sample that had been demonstrated in others informing our DAG and did not yield any additional variables strongly associated with craniosynostosis.

Finally, selection bias could play a role in our results. Almost one-third of mothers of eligible cases and controls did not participate in the NBDPS interview.²⁴ Non-participants are likely systematically different than participants, and to the extent that those differences are associated with craniosynostosis risk and/or alcohol use, our results could be biased in either direction. Furthermore, 2.6% of case and 2.9% of control participants did not respond to questions about periconceptional alcohol use and were excluded from our analysis. Among those non-respondents for whom data are available, we know they were younger at the time of delivery, more frequently reported non-Hispanic Black or Hispanic race/ethnicity, and more frequently reported unintended pregnancy than those included in the analysis (data not shown). These are characteristics generally associated with higher rates of alcohol use,⁴³ however given that exclusion due to missing data did not differ by case status, any bias is likely towards the null. In a previous NBDPS analysis of alcohol consumption and gastroschisis, results in which alcohol consumption status was imputed did not meaningfully differ from those in which participants with missing data were excluded.²⁸

Despite these limitations, our study has several notable strengths. The NBDPS is among the largest population-based studies of birth defects, enabling us to analyze associations with specific craniosynostosis subtypes. Our robust case classification process is another major strength, minimizing outcome misclassification, ruling out syndromic cases, and further supporting our ability to analyze subtypes. Our population-based, multi-center design also promotes geographic and demographic diversity in our sample, increasing external validity. Finally, our quantitative bias analysis is a distinct strength, offering an estimate of the magnitude and direction of bias due to the self-reported data on maternal alcohol exposure in our study.

Conclusions

Our results are consistent with the sparse existing literature suggesting that maternal alcohol consumption is not associated with increased risk of craniosynostosis. The inverse associations that we observed should be interpreted cautiously. The results of our bias sub-analysis suggest that conventional estimates that do not take alcohol exposure underreporting into account may be biased downward, away from the null. Our observed lack of association between alcohol and craniosynostosis may inform future hypotheses about the biologic mechanisms involved in the development of craniosynostosis, through process of elimination. Given that alcohol is associated with other adverse pregnancy outcomes, including other types of major birth defects, our findings do not diminish the prevailing clinical guidance in the US that pregnant people should abstain from alcohol consumption.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability statement:

The study questionnaires and process for accessing the data used in this study is described at <https://www.cdc.gov/birth-defects/php/bd-steps-nbdps-data/index.html>. The code book and analytic code may be made available upon request.

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Table 1.
Characteristics of participants, by study group, NBDPS 1997–2011. Values are n (%).

Characteristic	Controls	Craniosynostosis Cases, by Affected Suture*			
		Sagittal	Metopic	Coronal	Lambdoidal
Overall	11,216	829	278	273	52
Maternal age at delivery					1,435
<20 years	1,097 (9.8)	36 (4.3)	16 (5.8)	10 (3.7)	2 (3.9)
20–24 years	2,523 (22.5)	125 (15.1)	66 (23.7)	49 (18.0)	9 (17.3)
25–29 years	3,111 (27.7)	253 (30.5)	68 (24.5)	68 (24.9)	16 (30.8)
30–34 years	2,910 (26.0)	240 (29.0)	86 (24.5)	104 (38.1)	15 (28.9)
≥35 years	1,575 (14.0)	175 (21.1)	42 (15.1)	42 (15.4)	10 (19.2)
Missing	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Maternal race/ethnicity					
Non-Hispanic White	6,541 (58.3)	652 (78.7)	196 (70.5)	172 (63.0)	35 (67.3)
Non-Hispanic Black	1,226 (10.9)	27 (3.3)	20 (7.2)	11 (4.0)	0 (0)
Hispanic	2,702 (24.1)	116 (14.0)	52 (18.7)	65 (23.8)	16 (30.8)
Other	745 (6.6)	34 (4.1)	10 (3.6)	25 (9.2)	1 (1.9)
Missing	2 (0.02)	0 (0)	0 (0)	0 (0)	0 (0)
Maternal education level					
< High school diploma	1,840 (16.4)	80 (9.7)	34 (12.2)	38 (13.9)	4 (7.8)
High school diploma	2,663 (23.7)	172 (20.8)	62 (22.3)	69 (25.3)	8 (15.4)
Some college	2,986 (26.6)	236 (28.5)	74 (26.6)	75 (27.5)	25 (48.1)
Bachelor's degree or more	3,685 (32.9)	340 (41.0)	108 (38.9)	90 (33.0)	15 (28.9)
Missing	42 (0.4)	1 (0.1)	0 (0)	1 (0.4)	0 (0)
Annual household income					
<\$30,000	4,698 (41.9)	267 (32.2)	106 (38.1)	110 (40.3)	20 (38.5)
\$30,000–\$49,999	1,813 (16.2)	144 (17.4)	47 (16.9)	48 (17.6)	17 (32.7)
≥\$50,000	3,786 (33.8)	389 (46.9)	116 (41.7)	102 (37.4)	14 (26.9)
Missing	919 (8.2)	29 (3.5)	9 (3.2)	13 (4.8)	1 (1.9)
Plurality >1	330 (2.9)	43 (5.2)	26 (9.4)	12 (4.4)	1 (1.9)
Missing	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Male infant sex	5,698 (50.8)	619 (74.7)	207 (74.5)	102 (37.4)	35 (67.3)
					966 (67.3)

Characteristic	Craniosynostosis Cases, by Affected Suture*					
	Controls	Sagittal	Metopic	Coronal	Lambdoidal	Any Suture
<i>Missing</i>	10 (0.1)	1 (0.1)	0 (0)	0 (0)	0 (0)	1 (0.1)
Thyroid disease	242 (2.2)	29 (3.5)	14 (5.0)	8 (2.9)	0 (0)	51 (3.6)
<i>Missing</i>	71 (0.6)	3 (0.4)	2 (0.7)	2 (0.7)	0 (0)	7 (0.5)
Prepregnancy body mass index (BMI)						
Underweight (BMI<18.5)	571 (5.1)	40 (4.8)	14 (5.0)	15 (5.5)	2 (3.9)	71 (5.0)
Normal (BMI 18.5–24.9)	5,752 (51.3)	408 (49.2)	127 (45.7)	129 (47.3)	28 (53.9)	695 (48.4)
Overweight (BMI 25–29.9)	2,449 (21.8)	207 (25.0)	72 (25.9)	57 (20.9)	11 (21.2)	347 (24.2)
Obese (BMI ≥30)	1,984 (17.7)	158 (19.1)	57 (20.5)	66 (24.2)	10 (19.2)	291 (20.3)
<i>Missing</i>	460 (4.1)	16 (1.9)	8 (2.9)	6 (2.2)	1 (1.9)	31 (2.2)
Preexisting diabetes	80 (0.7)	4 (0.5)	4 (1.4)	5 (1.8)	0 (0)	13 (0.9)
<i>Missing</i>	817 (7.3)	71 (8.6)	24 (8.6)	33 (12.1)	6 (11.5)	134 (9.3)
Family history of craniosynostosis	5 (0.04)	37 (4.5)	14 (5.0)	4 (1.5)	2 (3.9)	57 (4.0)
<i>Missing</i>	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Intended pregnancy	6,790 (60.5)	549 (66.2)	189 (68.0)	168 (61.5)	36 (69.2)	943 (65.7)
<i>Missing</i>	720 (6.4)	52 (6.3)	17 (6.1)	17 (6.2)	1 (1.9)	87 (6.1)
Any periconceptual recreational drug use	127 (1.1)	8 (1.0)	2 (0.7)	0 (0)	1 (1.9)	11 (0.8)
<i>Missing</i>	397 (3.5)	22 (2.6)	8 (2.8)	10 (3.7)	0 (0)	40 (2.7)
Any periconceptual cigarette smoking	2,002 (17.9)	148 (17.9)	39 (14.0)	44 (16.1)	14 (26.9)	246 (17.1)
<i>Missing</i>	2 (0.02)	1 (0.1)	0 (0)	0 (0)	0 (0)	1 (0.1)
Any fertility treatment	521 (4.7)	61 (7.4)	36 (13.0)	26 (9.5)	5 (9.6)	129 (9.0)
<i>Missing</i>	268 (2.4)	4 (0.5)	2 (0.7)	0 (0)	0 (0)	6 (0.4)
Any periconceptual ** folic acid supplement use	5,950 (53.1)	521 (62.9)	171 (61.5)	160 (58.6)	32 (61.5)	885 (61.7)
<i>Missing</i>	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Study site						
AR	1,401 (12.5)	119 (14.4)	24 (8.6)	34 (12.5)	6 (11.5)	183 (12.8)
CA	1,205 (10.7)	72 (8.7)	22 (7.9)	36 (13.2)	6 (11.5)	136 (9.5)
IA	1,250 (11.1)	82 (9.9)	28 (10.1)	28 (10.3)	3 (5.8)	141 (9.8)
MA	1,365 (12.2)	127 (15.3)	33 (11.9)	42 (15.4)	7 (13.5)	209 (14.6)
NJ	541 (4.8)	22 (2.7)	2 (0.7)	7 (2.6)	5 (9.6)	37 (2.6)
NY	930 (8.3)	55 (6.6)	13 (4.7)	18 (6.6)	0 (0)	86 (6.0)

Characteristic	Craniosynostosis Cases, by Affected Suture*				
	Controls	Sagittal	Metopic	Coronal	Lambdoidal / Any Suture
TX	1,286 (11.5)	44 (5.3)	18 (6.5)	18 (6.6)	7 (13.5) 89 (6.2)
GA	1,197 (10.7)	61 (7.4)	18 (6.5)	25 (9.2)	6 (11.5) 110 (7.7)
NC	951 (8.5)	62 (7.5)	50 (18.0)	28 (10.3)	1 (1.9) 141 (9.8)
UT	1,090 (9.7)	185 (22.3)	70 (25.2)	37 (13.6)	11 (21.2) 303 (21.1)

* n=3 cases did not specify the affected suture so are included in the “Any Suture” group, but not elsewhere

** One month before and after conception

Table 2. Maternal periconceptional alcohol exposure, by study group, NBDPS 1997–2011. Values are n(%).

Exposure	Controls (n=11,216)	Cases (n=1,435)
Any consumption	4,280 (38.2)	529 (36.9)
<i>Among those who report alcohol consumption:</i>		
Any binge consumption	1,431 (33.4)	183 (34.6)
Missing	61 (1.4)	7 (1.3)
Maximum average number of alcoholic drinks/month		
1–4 drinks/month	1,986 (46.4)	233 (44.1)
5–15 drinks/month	1,301 (30.4)	173 (32.7)
16–30 drinks/month	607 (14.2)	74 (14.0)
>30 drinks/month	344 (8.0)	43 (8.1)
Missing	42 (1.0)	6 (1.1)
Maximum frequency of periconceptional alcohol consumption/month		
1–4 days/month	3,035 (70.9)	361 (68.2)
5–15 days/month	967 (22.6)	139 (26.3)
16–30 days/month	255 (6.0)	25 (4.7)
Missing	23 (0.5)	4 (0.8)
Maximum average number of drinks per occasion		
1–2	2,813 (65.7)	345 (65.2)
3+	1,433 (33.5)	179 (33.8)
Missing	34 (0.8)	5 (1.0)
Binge drinking frequency		
Drinking but no binge drinking	2,788 (65.1)	339 (64.1)
Some binge but less than monthly	1,352 (31.6)	176 (33.3)
At least monthly	54 (1.3)	3 (0.6)
Missing	86 (2.0)	11 (2.1)
Any high intensity drinking (8+ drinks on any one occasion)		
	325 (7.6)	40 (7.6)
Missing	68 (1.6)	8 (1.5)
Periconceptional drinking duration (months) *		
1	2,397 (56.0)	315 (59.6)
2	1,278 (29.9)	156 (29.5)

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Exposure	Controls (n=11,216)	Cases (n=1,435)
3	270 (6.3)	29 (5.5)
4	323 (7.6)	28 (5.3)
Missing	12 (0.3)	1 (0.2)
Type of alcohol consumed (not mutually exclusive)		
Beer	1,921 (44.9)	239 (45.2)
Wine	2,341 (54.7)	308 (58.2)
Mixed drink/liquor	1,732 (40.5)	206 (38.9)
Other	16 (0.4)	2 (0.4)

* Number of periconceptional months in which alcohol consumption was reported; months are not necessarily consecutive.

Table 3. Association between maternal periconceptual alcohol consumption and craniosynostosis in offspring, by affected suture, NBDPS 1997–2011.

Outcome	Any Periconceptual Alcohol Consumption			Any Periconceptual Binge Consumption		
	n exposed	Crude OR (95% CI)	Adjusted OR (95% CI)*	n exposed	Crude OR (95% CI)	Adjusted OR (95% CI)*
Controls	4,280	ref	ref	1,431	ref	ref
Craniosynostosis, any suture	529	0.95 (0.84, 1.06)	0.89 (0.78, 1.01)	183	0.98 (0.83, 1.16)	1.09 (0.90, 1.30)
Affected suture						
Sagittal	316	1.00 (0.86, 1.15)	0.93 (0.79, 1.09)	102	0.96 (0.77, 1.20)	1.05 (0.83, 1.34)
Metopic	97	0.87 (0.68, 1.12)	0.91 (0.69, 1.21)	41	1.10 (0.78, 1.55)	1.30 (0.89, 1.90)
Coronal	92	0.82 (0.64, 1.06)	0.78 (0.59, 1.03)	29	0.78 (0.53, 1.16)	0.86 (0.56, 1.31)
Lambdoidal	22	1.19 (0.69, 2.06)	**	9	1.45 (0.69, 3.07)	**

Abbreviations: NBDPS, National Birth Defects Prevention Study; OR, odds ratio; CI, confidence interval

* Adjusted for maternal age, fertility treatment status, race/ethnicity, pregnancy intention, and study site

** Model did not converge

Table 4.

Association between maternal periconceptional alcohol consumption and craniosynostosis in offspring, adjusted for various levels of estimated exposure misclassification, NBDPS 1997–2011.

Bias Assumption Scenario	Parameter	Cases			Controls			AOR (95% SI)*		
		Se	Sp	Se	Sp	Se	Sp	Any Alcohol	Binge Alcohol	
Conventional analysis	N/A	1.00	1.00	1.00	1.00	1.00	1.00	0.91 (0.80, 1.03)	1.09 (0.90, 1.30)	
Scenario 1: Lower sensitivity among cases, lower specificity among controls	Minimum	0.60	0.97	0.65	0.97	0.65	0.97	1.05 (0.82, 1.35)	1.10 (0.85, 1.42)	
	Mode 1	0.70	0.98	0.75	0.98					
	Mode 2	0.80	0.99	0.85	0.985					
Scenario 2: Lower sensitivity among cases, higher specificity among controls	Maximum	0.85	1.00	0.90	0.99					
	Minimum	0.60	0.97	0.65	0.97	0.65	0.97	1.02 (0.80, 1.31)	1.10 (0.85, 1.42)	
	Mode 1	0.70	0.98	0.75	0.98					
	Mode 2	0.80	0.985	0.85	0.99					
	Maximum	0.85	0.99	0.90	1.00					
Scenario 3: Lower sensitivity among cases, non-differential specificity	Minimum	0.60	0.97	0.65	0.97	0.65	0.97	1.03 (0.80, 1.33)	1.13 (0.87, 1.46)	
	Mode 1	0.70	0.98	0.75	0.98					
	Mode 2	0.80	0.99	0.85	0.99					
	Maximum	0.85	1.00	0.90	1.00					
Scenario 4: Higher sensitivity among cases, non-differential specificity	Minimum	0.65	0.97	0.60	0.97	0.60	0.97	0.78 (0.61, 1.00)	0.94 (0.73, 1.21)	
	Mode 1	0.75	0.98	0.70	0.98					
	Mode 2	0.85	0.99	0.80	0.99					
	Maximum	0.90	1.00	0.85	1.00					
Scenario 5: Non-differential sensitivity, non-differential specificity	Minimum	0.65	0.97	0.65	0.97	0.65	0.97	0.90 (0.71, 1.14)	1.03 (0.81, 1.32)	
	Mode 1	0.75	0.98	0.75	0.98					
	Mode 2	0.85	0.99	0.85	0.99					
	Maximum	0.90	1.00	0.90	1.00					

Abbreviations: NBDPS, National Birth Defects Prevention Study; Se, sensitivity; Sp, specificity; AOR, adjusted odds ratio; SI, simulation interval.

* Adjusted for maternal age, race/ethnicity, fertility treatment status, pregnancy intention, and study site.