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Factors associated with infant sex and preterm birth status for selected birth defects from the National Birth Defects Prevention Study, 1997–2011

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Abstract

Background: Birth defects and preterm birth co-occur, with some overlapping risk factors. Many birth defects and preterm births tend to have a male preponderance. We explored potential

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CONFLICT OF INTEREST STATEMENT
The authors report no conflicts of interest.

SUPPORTING INFORMATION
Additional supporting information can be found online in the Supporting Information section at the end of this article.

risk factors impacting sex and preterm (<37 weeks of gestation) birth differences among infants with selected birth defects delivered from 1997 to 2011 using data from the National Birth Defects Prevention Study (NBDPS).

Methods: The NBDPS was a large multisite, population-based case–control study. Using random forests, we identified important predictors of male preterm, female preterm, and male term, each compared with female term births for each birth defect. Using logistic regression, we estimated odds ratios for associations between important predictors and sex-preterm birth status by birth defect.

Results: We examined 11,379 infants with nine specific birth defects. The top 10 most important predictors of sex-preterm birth status from the random forests varied greatly across the birth defects and sex-preterm comparisons within a given defect group, with several being novel factors. However, one consistency was that short interpregnancy interval was associated with sex-preterm birth status for many of the studied birth defects. Although obesity has been identified as a risk factor for preterm birth and birth defects in other research, it was not associated with sex-preterm birth status for any of the examined defects.

Conclusions: We confirmed expected associations for sex-preterm birth status differences and found new potential risk factors for further exploration among the studied birth defects.

Keywords

birth defects; preterm birth; random forests; sex

1 | INTRODUCTION

In the United States, birth defects occur in approximately 3% of live births (Prevention, 2008). Preterm birth affects 10% of all births but 21% of infants with birth defects (Purisch & Gyamfi-Bannerman, 2017; Rasmussen et al., 2001; Reefhuis et al., 2015). Understanding birth defects and preterm births can be complex, as risk factors for many birth defects overlap with risk factors for preterm birth, including short interpregnancy interval (time from end of one pregnancy to the start of the next), pre-pregnancy obesity, no folic acid-containing supplement intake, pre-gestational diabetes, and maternal smoking (Dolan et al., 2009; Shaw, 2015).

Additionally, a preponderance of male sex has been observed for both preterm birth and some birth defects (Michalski et al., 2015; Shaw et al., 2003, 2021). This male excess is particularly striking among deliveries before 32 weeks of gestation (Shaw et al., 2021). Historically, a female preponderance has been observed among infants with neural tube defects; however, in recent years this difference has narrowed (Poletta et al., 2018; Shaw et al., 2020). To our knowledge, a comprehensive inquiry has not been made of potential maternal perinatal risk factors for the joint outcome of infant sex (male vs. female) and preterm birth status for a given birth defect. Identifying factors associated with sex and preterm birth differences for a given birth defect phenotype may stimulate new hypotheses regarding the etiologies of birth defects as well as preterm birth. More broadly, such consideration may enhance the understanding of sexual dimorphism and human development. In this study, we conducted exploratory analyses for potential risk

factors impacting jointly defined sex and preterm birth groupings among selected birth defects by investigating data from the National Birth Defects Prevention Study (NBDPS).

2 | METHODS

The NBDPS was a large multisite, population-based case–control study that included data from pregnancies with estimated delivery dates (EDD) from October 1997 through December 2011 ascertained through birth defects surveillance programs from selected geographic regions in 10 states (Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas, and Utah) (Reefhuis et al., 2015). Institutional review board approval was obtained for each study site, and participants provided informed consent. Clinical geneticists reviewed medical record information on each case to determine eligibility and to classify cases as having isolated (one major birth defect), multiple (two or more major defects in more than one organ system), or complex birth defects (Reefhuis et al., 2015). In addition, birth defects attributed to a known chromosomal abnormality or single-gene condition were excluded. Infants with congenital heart defects (CHDs) were classified based on cardiac phenotype, complexity, and presence of non-cardiac birth defects (Botto et al., 2007).

Our analysis included infants with at least one of the following birth defects: spina bifida, D-transposition of the great arteries, tetralogy of Fallot, cleft palate without cleft lip, cleft lip with or without cleft palate, longitudinal/intercalary limb deficiency, transverse limb deficiency, craniosynostosis, or gastroschisis. We chose these nine birth defects (n = 12,276) for their well-defined phenotypic classification and larger sample sizes. Cases included live births, stillbirths (spontaneous loss at 20 weeks of gestation or later), and induced terminations. We included cases classified as having isolated, multiple, or complex defects in our analyses. We excluded cases with ambiguous or missing sex, or unknown gestational age at delivery. Our analysis excludes data from controls. For each specific birth defect, we categorized the infants into four distinct groups by sex (male or female) and gestational age at delivery dichotomized as term or preterm (≥37 or <37 weeks of gestation). We obtained gestational age from the infant's birth or medical record. The outcome variable for this study was a composite of infant sex and gestational age at delivery with four levels: male preterm, female preterm, male term, and female term. We compared each sex-preterm birth combination to a common sex-preterm birth referent category (female term births).

As pre-gestational diabetes (i.e., type I or II) has been reported to be associated with these selected birth defects, infants whose mothers had these conditions were excluded from the analyses (n = 254, 2.1%) (Correa et al., 2008). We further excluded multiple births from the analyses (n = 560, 4.7% cases) since the etiologies of preterm birth may differ between singleton and multiple births (Tingleff et al., 2023).

Trained interviewers conducted computer-assisted telephone interviews in English or Spanish with participating women between 6 weeks and 24 months after their EDD. Women answered questions about their demographics, pregnancy history, health conditions, and other exposures before or during pregnancy. We considered four potential risk factors selected a priori for differences in sex and gestational age at delivery: (1) folic acid-

containing supplement intake (yes or no) in early pregnancy, (2) maternal smoking (yes or no) in early pregnancy, (3) pre-pregnancy obesity (body mass index (BMI) ≥30 kg/m^2 or <30 kg/m^2), and (4) interpregnancy interval (no previous pregnancies, ≤12 months, or >12 months) (Dolan et al., 2009; Shaw et al., 2021). We defined interpregnancy interval as the difference in months between the date of conception of the index pregnancy and the end date of the last previous pregnancy before the index pregnancy. Early pregnancy is the critical period in embryonic development associated with most structural defects and was defined as the month before conception through the second month of pregnancy. The month before conception was included, as it is difficult to determine the exact date of conception.

For each birth defect, we used a multinomial, multivariable logistic regression model to analyze the association between the four-level outcome and the four potential risk factors selected a priori described above. We calculated adjusted odds ratios (aORs) and associated 95% confidence intervals (CIs) for each model using female term as the referent outcome and adjusting for three other a priori potential risk factors. We used likelihood ratio tests to investigate all possible two-way statistical interactions between the four potential risk factors.

To further understand predictors of joint sex and preterm birth status among infants with birth defects, we conducted an exploratory (hypothesis-generating) analysis with random forests. We used this data-mining procedure to identify potential risk factors by birth defect. Random forests are a supervised machine-learning method that models a number of decision trees to classify observations as, for example male preterm versus female term, based on a set of predictors (Strobl et al., 2009). We ran three separate models (male preterm vs. female term, female preterm vs. female term, and male term vs. female term) for each defect. For our analysis, we modeled 5000 conditional inference trees (sufficiently large number of trees to achieve stable results) with 15 variables (square-root of the number of variables) randomly sampled to determine each split in a given tree with a minimum sum of weights in a node of five (results were stable across different random seeds) (Strobl et al., 2009). Since the variables differed in scale of measurement and to remove bias towards correlated variables, we utilized conditional inference trees, as they produce unbiased trees and use an adequate resampling method (Hothorn et al., 2006; Strobl et al., 2009). The variables were ranked based on the metric mean decrease accuracy (MDA) that was calculated for each variable as a measure of variable importance (Strobl et al., 2009).

We included a total of 241 variables in the random forests including dietary, demographic, and behavioral characteristics (Appendix A). For interview questions that asked about specific timing before and during pregnancy, separate variables for each month during early pregnancy were included (the month before conception, the first month of pregnancy, and the second month of pregnancy). Overall, missingness was low, ranging from 0% to 10% across the 241 variables, with only five variables having missing values for more than 5% of the women. We excluded women with missing responses for more than 10% of the variables considered (n = 752, 6.6%). For variables with ≤10% missing values, missingness was imputed with the most frequent response for categorical variables and the median for continuous variables (Schafer, 1999; Weber et al., 2018).

To quantify the associations between the top 10 most important predictors from the random forests and sex-preterm birth status, conventional aORs and 95% CIs were estimated from logistic regression models with Firth penalization (Firth, 1993).

Random forest analyses were performed using the Party Package in R software (V4.1.3). All other analyses were performed in SAS version 9.4 (SAS Institute, Cary, NC).

3 | RESULTS

We analyzed nine birth defects among 11,379 infants in total; the number of infants with each birth defect ranged from 465 to 2930 (Table 1). Infants with D-transposition of the great arteries had the lowest proportion of preterm birth (9.2%), whereas infants with gastroschisis had the highest (62.0%). Among control infants, 4.1% (n = 468) were male preterm, 3.8% (n = 428) were female preterm, 46.9% (n = 5311) were male term, and 45.1% (n = 5108) were female term births.

3.1 | A priori selected potential risk factor results

The a priori selected potential risk factors were tabulated by sex and preterm birth status for each birth defect (Table 2). Among infants with spina bifida with mothers not taking a folic acid-containing supplement during early pregnancy, there was a higher proportion of males compared with females for both preterm (17.2% vs. 10.0%) and term (40.5% vs. 32.3%) births. Among infants with spina bifida, there was a higher proportion of male preterm births among mothers who had an interpregnancy intervals of ≤12 months (17.1%) compared with mothers in the other interpregnancy interval categories (12.4% for no previous pregnancies and 10.8% for >12 months). A similar pattern was observed among gastroschisis (36.7% male preterm births among mothers with interpregnancy intervals of ≤12 months, compared with 30% among those with no previous pregnancies and 30% among those with interpregnancy intervals >12 months). Among infants with longitudinal/intercalary limb deficiency, regardless of sex, there was a higher proportion of preterm births among obese mothers (14.8% for males and 16.1% for females) compared with non-obese mothers (11.6% for males and 9.7% for females).

Multinomial, multivariable logistic regression results are presented in Table 3. For infants with spina bifida, compared with female term births, mothers of male preterm births were more likely to have not used folic acid-containing supplements (aOR [95% CI]: 1.95 [1.25–3.04]) and less likely to have pre-pregnancy obesity (aOR [95% CI]: 0.59 [0.36–0.97]). Additionally, mothers of male term births were less likely to have interpregnancy intervals of ≤12 months compared with mothers of female term births (aOR [95% CI]: 0.67 [0.46–0.97]). For infants with D-transposition of the great arteries, compared with female term births, mothers of female preterm births were more likely to be smokers (aOR [95% CI]: 4.22 [1.50–11.92]) or have an interpregnancy interval of ≤12 months (aOR [95% CI]: 5.14 [1.54–17.21]). For infants with cleft palate without cleft lip, compared with female term births, mothers of male preterm and male term births were more likely to have an interpregnancy interval ≤12 months (aOR [95% CI]: 2.01 [1.16–3.48] and 1.66 [1.22–2.27], respectively). For infants with craniosynostosis, compared with female term births, mothers of male preterm births were more likely to have an interpregnancy interval of ≤12 months

(aOR [95% CI]: 1.76 [1.05–2.94]) and mothers of male term births were more likely to take folic acid-containing supplements (aOR [95% CI]: 0.70 [0.51–0.95]).

3.2 | Random forests results

Our analyses employing random forests sought to identify variables associated with the outcome in each of the three models (male preterm vs. female term, female preterm vs. female term, and male term vs. female term) by birth defect. Table 4 provides the top 10 most important predictors from the random forests, with female term as the referent outcome for each model by birth defect. Tables S1–S9 present the aORs and corresponding 95% CIs for each logistic regression model with the top 10 most important predictors from the random forests for the studied defects.

Household smoke exposure was among the top 10 most important predictors from the random forests for two of the models (in the male preterm vs. female term model and the male term vs. female term model) for infants with spina bifida (Table 4). Household smoke exposure in early pregnancy was identified as a risk factor for male preterm births (aOR [95% CI]: 1.34 [0.80–2.21]) but had a reduced aOR for male term births compared with female term births (aOR [95% CI]: 0.69 [0.45–1.06]) (Table S1). Consistent with the multinomial, multivariable logistic regression model with the a priori potential risk factors (Table 3), mothers of male preterm births were more likely to not take folic acid-containing supplements during the second month of pregnancy (aOR [95% CI]: 1.81 [1.14–2.85]) compared with mothers of female term births (Table S1).

There were no commonalities in the top 10 most important predictors from the random forests across the three models for infants with D-transposition of the great arteries or tetralogy of Fallot (Table 4). Mothers of female preterm births were more likely to smoke during the first 2 months of pregnancy compared with mothers of female term births (aOR [95% CI]: 3.17 [1.04–9.31]) (Table S2), consistent with the multinomial, multivariable logistic regression model for that association among infants with D-transposition of the great arteries (Table 3). Among infants with tetralogy of Fallot, mothers of male preterm births were more likely to have no previous pregnancies versus a >12 month interpregnancy interval (aOR [95% CI]: 1.73 [1.04–2.87]) compared with mothers of female term births (Table S3).

There were no commonalities in the top 10 most important predictors from the random forests across the three models for infants with cleft palate without cleft lip (Table 4). Mothers of male term births were more likely to have an interpregnancy interval of ≤12 months (aOR [95% CI]: 1.55 [1.13–2.12]) compared with mothers of female term births (Table S4), consistent with the multinomial, multivariable logistic regression model with the a priori potential risk factors (Table 3). Two commonalities, though not statistically significant, were observed in the top 10 most important predictors from the random forests among infants with cleft lip with or without cleft palate (Table 4): eating cantaloupe (in the male preterm vs. female term model and the female preterm vs. female term model) and paternal race/ethnicity (in the male preterm vs. female term model and the male term vs. female term model).

Among infants with longitudinal/intercalary limb deficiency, vitamin E as alpha-tocopherol intake was identified among the top 10 most important predictors from the random forests in more than one model (in the male preterm vs. female term model and the female preterm vs. female term model) (Table 4). Mothers of male preterm births were more likely to have had fertility treatment compared with mothers of female term births (aOR [95% CI]: 3.97 [1.15–15.53]) among infants with longitudinal/intercalary limb deficiency (Table S6). For infants with transverse limb deficiency, total carbohydrate, caffeine from soda, vitamin C intake, maternal race/ethnicity, paternal race/ethnicity, and vitamin E intake were identified in the top 10 most important predictors from the random forests in more than one model (Table 3). Mothers of male preterm births were more likely to consume caffeine (mg per day) from soda (aOR [95% CI] for a 10-unit change: 1.05 [1.02–1.10]) compared with mothers of female term births (Table S7). The association of caffeine from soda with female preterm versus female term was not statistically significant.

For infants with craniosynostosis, frequency of baths at home and study site were identified in more than one model (in the male preterm vs. female term model and the female preterm vs. female term model) among the top 10 most important predictors from the random forests (Table 4). Among infants with craniosynostosis, compared with female term births, mothers of male preterm birth were less likely to not use folic acid-containing supplements during the first month of pregnancy (aOR [95% CI]: 0.62 [0.38–0.98]) (Table S8). Folic acid-containing supplement use in early pregnancy was found to be statistically significant for male term, but not for male preterm births compared with female term births in the a priori selected potential risk factors analysis (Table 3). Among infants with gastroschisis, caffeine consumption from coffee (mg per day) was identified as a top 10 most important predictor from the random forests by all three models.

4 | DISCUSSION

The objective of this study was to perform exploratory and hypothesis generating analyses of sex and preterm birth differences to identify areas for future research. We investigated known and agnostically identified factors that might contribute to the differences in sex and gestational age at delivery for specific birth defects. Short interpregnancy interval (≤12 months) was associated with some sex-preterm birth status differences among many of the birth defects studied. While obesity has been associated with select birth defects and preterm birth in prior research (Challis et al., 2013; Liu et al., 2019; Stothard et al., 2009), it was not associated with any sex-preterm birth status differences.

The top 10 most important predictors identified agnostically from the random forests varied greatly across sex-preterm comparisons within each birth defect and across birth defects within a given sex-preterm birth comparison. Overall, the results from the logistic regression models suggested non-null associations with the top 10 most important predictors identified from the random forests. Findings were most consistent between the random forests and the multinomial, multivariable logistic regression models with a priori potential risk factors for sex-preterm birth status among infants with spina bifida, D-transposition of the great arteries, or tetralogy of Fallot. However, it is important to note that these modeling strategies

have important differences (e.g., logistic regression is parametric whereas random forests are nonparametric), so we would not necessarily expect them to always agree.

In this exploratory analysis, we utilized random forests, a non-hypothesis-driven data-mining algorithm. This approach allowed us to investigate a large number of potential risk factors simultaneously and rank the variables for each model based on the MDA. Random forests confirmed some of the four a priori identified associations and allowed us to observe new potential risk factors for further exploration of sex-preterm birth status differences in future birth defects studies.

Caffeine consumption was identified as an important predictor for sex-preterm birth status multiple models among infants with transverse limb deficiency (caffeine from soda) or gastroschisis (caffeine from coffee). Previous NBDPS analyses have observed some small, elevated effect estimates between pre-pregnancy total caffeine consumption and birth defects, including transverse limb deficiency (Williford et al., 2023). We observed that the association of caffeine consumption from soda differed between male preterm and female preterm compared with female term births among infants with transverse limb deficiency. Among infants with gastroschisis the associations between caffeine consumption from coffee and sex-preterm birth status were not statistically significant. Inconsistent results have been observed in the literature for the association of caffeine consumption during pregnancy and risk of preterm delivery (Maslova et al., 2010).

Study site was identified among the top 10 most important predictors in two out of the three models among infants with craniosynostosis (male preterm vs. female term and female preterm vs. female term). Arkansas was more likely to have male preterm and female preterm births compared with many of the other study sites adjusted for all other predictors in the models. Among infants with craniosynostosis, 18.7% were preterm births in Arkansas (43% with gestational age at delivery of 36 weeks among preterm births). This is a larger percentage of craniosynostosis cases that were preterm births than other sites, which ranged from 4.1% (New York) to 14.0% (Georgia). The percentage of infants with craniosynostosis classified as isolated was consistent across study sites, ranging from 88% (California) to 93% (Arkansas). Case ascertainment for some pregnancy outcomes and prenatal diagnosis procedures differed over time for some sites (Reefhuis et al., 2015). This hypothesis generating analysis has identified study site as an area of future work in sex and preterm differences among infants with craniosynostosis.

Our findings are consistent with some of the prior research of infant sex and identified risk factors, although existing work has not examined the combined outcome of sex-preterm birth status among infants with birth defects. Others have observed that maternal cigarette smoking may negatively impact growth in male fetuses more than female fetuses (Shaw et al., 2003). In our analysis, we found maternal cigarette smoking in early pregnancy to be associated with female preterm births compared with female term births among infants with D-transposition of the great arteries. We did not find maternal cigarette smoking to be associated with male preterm or term births for any of the studied birth defects. A previous analysis explored folic acid use and infant sex among neural tube defects and reported more females in the two studies with pregnancies before mandatory folate fortification in the

United States (Shaw et al., 2020). However, for infants with spina bifida, we observed that mothers of male preterm births were more likely to not be taking folic-acid supplementation during early pregnancy compared with mothers of female term births. Another study found older paternal age to be associated with female births among infants with cleft lip with or without cleft palate, and gravidity to be associated with female births among infants with spina bifida (Rittler et al., 2004). We did not identify either of those variables among the top 10 most important predictors from the random forests for the models with either cleft lip or spina bifida. Discrepancies between our findings and those of previous research may be explained by a wide range of factors, including differences in data sources, methods, outcome definitions, and exposure assessments.

This study has many strengths including the large multi-site population-based design, the clinical classification of birth defects, and a detailed standardized questionnaire. The use of random forests allowed for the exploration of a large number of variables, capitalizing on the breadth of potential risk factors captured in these data, without concerns regarding correlations between the variables. Limitations of this study include that exposure data were collected after delivery, which could impact recall, and the potential for selection bias due to participation refusals and non-response. Our observations may be biased if a particular birth defect and sex combination was more likely to result in a pregnancy loss that was not ascertained (spontaneous pregnancy loss before 20 weeks gestation). Such bias could be further amplified if studied factors also increased the likelihood of the particular birth defect and sex combination to result in a pregnancy loss. In addition, our observations could be biased for some of the birth defects (e.g., craniosynostosis, D-transposition of the great arteries, or tetralogy of Fallot) that may not have been diagnosed in pregnancy terminations or losses which would bias the gestational age to term births (Heinke et al., 2020; Liberman et al., 2023; McPherson et al., 2017). For infants with gastroschisis, preterm delivery may be initiated by the provider due to the presence of the defect (Friedman et al., 2016); however, in our data we are unable to distinguish if the preterm delivery was spontaneous or provider-initiated. The literature suggests that spontaneous preterm birth occurs frequently and the optimal timing of delivery is not conclusive for infants with gastroschisis (Baer et al., 2019; Friedman et al., 2016; Goldstein et al., 2022). Thus, results may be biased and should interpreted with caution for defects such as gastroschisis, where there may be a preference for an early delivery at some facilities. We defined preterm birth using the standard definition of less than 37 weeks gestation at delivery. In our analysis of 11,379 infants with selected birth defects, 4.6% (n = 525) were delivered at 35 weeks gestation and 6.7% (n = 759) were delivered at 36 weeks gestation. There are two potential limitations of our definition of preterm birth, which could be explored in future work. We may have observed different results using other definitions of preterm birth (e.g., less than 32 weeks gestation) or by focusing on spontaneous preterm births (the reason for preterm birth was not collected in NBDPS). In addition, some of the outcome categories within each birth defect were small, resulting in imprecise estimates. The impact of predictor classification errors on the performance of random forests is unclear without formal bias analysis (Jiang et al., 2021). Lastly, there are alternative approaches for calculating variable importance for random forests (e.g., Gini impurity importance) (Strobl et al., 2007). We did not evaluate whether modifying the variable importance measure or tuning parameters might affect our

results from random forests. A limitation of evaluating so many risk factors at once is the concern of multiple testing (365 estimates across the three models for the nine birth defects); some observed associations may be due to chance. We did not perform multiple comparison adjustment methods and presented all estimates and confidence intervals calculated as recommended by Rothman (1990) and Greenland (2008). Results should therefore be interpreted cautiously.

5 | CONCLUSION

Our findings suggest that there are differences in infant sex and preterm birth status and their predictors among the studied birth defects. Our analysis confirmed some known risk factors for preterm birth and birth defects (short interpregnancy interval and no folic acid-containing supplement use). Further exploration of the newly identified factors may help advance understanding of sex differences among birth defects and preterm birth.

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/ncbddd/birthdefects/nbdps-public-access-procedures.html.

APPENDIX A: Variables from the National Birth Defects Prevention Study included in random forests.

Variable	
Study site	Arkansas, California, Iowa, Massachusetts, New Jersey, New York, Texas, Georgia, North Carolina, Utah
Maternal residency ever moved B1-P2	Yes, no
Season of date of conception	Winter, spring, summer, fall

Variable	
Maternal race/ethnicity	Non-Hispanic white, Hispanic foreign born, Hispanic US born, non-Hispanic black, other
Paternal race/ethnicity	Non-Hispanic white, Hispanic foreign born, Hispanic US born, non-Hispanic black, other
Maternal education	Less than high school, high school, greater than high school
Paternal education	Less than high school, high school, greater than high school
Maternal feelings about pregnancy	Wanted to be pregnant, wanted to wait until later, did not want to become pregnant, did not care, pregnant despite consistent contraceptive use
Timing of pregnancy discovery	Trimester 1, Trimester 2, or Trimester 3
Timing of first prenatal visit	Trimester 1, Trimester 2, Trimester 3, none
Household income	<$10,000, $10,000–50,000, >$50,000
Interpregnancy interval	No previous pregnancies, ≤12 months, >12 months
Obesity	Yes, no
Antihypertensive medication use during B1-P3	Yes, no
Anti-depressant medication use during B1	Yes, no
Anti-depressant medication use during P1	Yes, no
Anti-depressant medication use during P2	Yes, no
Anti-fever medication use during B1	Yes, no
Anti-fever medication use during P1	Yes, no
Anti-fever medication use during P2	Yes, no
Anti-folate medication use during B1	Yes, no
Anti-folate medication use during P1	Yes, no
Anti-folate medication use during P2	Yes, no
Anti-infective medication use during B1	Yes, no
Anti-infective medication use during P1	Yes, no
Anti-infective medication use during P2	Yes, no
Anti-psychotic medication use during B1	Yes, no
Anti-psychotic medication use during P1	Yes, no
Anti-psychotic medication use during P2	Yes, no
Anti-anxiety medication use during B1	Yes, no
Anti-anxiety medication use during P1	Yes, no
Anti-anxiety medication use during P2	Yes, no
Thyroid medication use during B1	Yes, no
Thyroid medication use during P1	Yes, no
Thyroid medication use during P2	Yes, no
Aspirin use during B1	Yes, no
Aspirin use during P1	Yes, no
Aspirin use during P2	Yes, no
NSAIDs use during B1	Yes, no
NSAIDs use during P1	Yes, no
NSAIDs use during P2	Yes, no
Opioid use during B1	Yes, no
Opioid use during P1	Yes, no

Variable	
Opioid use during P2	Yes, no
Steroid use during B1	Yes, no
Steroid use during P1	Yes, no
Steroid use during P2	Yes, no
Vasoactive medication use during B1-P3	Yes, no
Antitussive use during B1	Yes, no
Antitussive use during P1	Yes, no
Antitussive use during P2	Yes, no
Epilepsy	Yes, no
Seizures	Yes, no
Respiratory disease during B1	Yes, no
Respiratory disease during P1	Yes, no
Respiratory disease during P2	Yes, no
Urinary tract infection during B1	Yes, no
Urinary tract infection during P1	Yes, no
Urinary tract infection during P2	Yes, no
Pelvic inflammatory disease during B1	Yes, no
Pelvic inflammatory disease during P1	Yes, no
Pelvic inflammatory disease during P2	Yes, no
Any type of fever during B1	Yes, no
Any type of fever during P1	Yes, no
Any type of fever during P2	Yes, no
Sexually transmitted infections during B1	Yes, no
Sexually transmitted infections during P1	Yes, no
Sexually transmitted infections during P2	Yes, no
Autoimmune disease	Yes, no
Any thyroid disease	Yes, no
Injury during B1	Yes, no
Injury during P1	Yes, no
Injury during P2	Yes, no
CT/CAT scan during B1	Yes, no
CT/CAT scan during P1	Yes, no
CT/CAT scan during P2	Yes, no
MRI during B1	Yes, no
MRI during P1	Yes, no
MRI during P2	Yes, no
Other X-ray or scan during B1	Yes, no
Other X-ray or scan during P1	Yes, no
Other X-ray or scan during P2	Yes, no
X-ray during B1	Yes, no
X-ray during P1	Yes, no
X-ray during P2	Yes, no

Variable	
Surgery during B1	Yes, no
Surgery during P1	Yes, no
Surgery during P2	Yes, no
Birth control pill use during B1	Yes, no
Birth control pill use during P1	Yes, no
Birth control pill use during P2	Yes, no
Other birth control use during B1	Yes, no
Other birth control use during P1	Yes, no
Other birth control use during P2	Yes, no
Fertility treatment	Yes, no
Nausea during P1	Yes, no
Nausea during P2	Yes, no
Medication for pregnancy nausea	Yes, no
Chorionic villus sampling	Yes, no
Folic acid-containing supplement use during B1	Yes, no
Folic acid-containing supplement use during P1	Yes, no
Folic acid-containing supplement use during P2	Yes, no
Cereal intake during B1	Yes, no
Cereal intake during P1	Yes, no
Cereal intake during P2	Yes, no
Food supplement intake during B1	Yes, no
Food supplement intake during P1	Yes, no
Food supplement intake during P2	Yes, no
Cigarette smoking during B1	Yes, no
Cigarette smoking during P1	Yes, no
Cigarette smoking during P2	Yes, no
Household smoke exposure during B1	Yes, no
Household smoke exposure during P1	Yes, no
Household smoke exposure during P2	Yes, no
Work/school smoke exposure during B1	Yes, no
Work/school smoke exposure during P1	Yes, no
Work/school smoke exposure during P2	Yes, no
Alcohol consumption during B1	Yes, no
Alcohol consumption during P1	Yes, no
Alcohol consumption during P2	Yes, no
Beer intake	Yes, no
Wine intake	Yes, no
Mixed drink intake	Yes, no
Shots of liquor intake	Yes, no
Other drink intake	Yes, no

Variable	
Paternal substance abuse during B1	Yes, no
Paternal substance abuse during P1	Yes, no
Paternal substance abuse during P2	Yes, no
Maternal substance abuse during B1	Yes, no
Maternal substance abuse during P1	Yes, no
Maternal substance abuse during P2	Yes, no
Frequency of showers at home	<1 per day, 1 per day, <1 per day
Frequency of baths at home	Never or <1 per month, ≥1 per month
Hot tub/jacuzzi/sauna use during B1	Yes, no
Hot tub/jacuzzi/sauna use during P1	Yes, no
Hot tub/jacuzzi/sauna use during P2	Yes, no
Maternal active military duty	Yes, no
Paternal active military duty	Yes, no
Any household participation in occupational pesticide application	Yes, no
Father employed	Yes, no
Private well drinking water source	Yes, no
Skim/low fat milk (8 oz. glass)	Never or <1 per month, ≥1 per month
Whole milk (8 oz. glass)	Never or <1 per month, ≥1 per month
Yogurt (1 cup)	Never or <1 per month, ≥1 per month
Ice cream (1/2 cup)	Never or <1 per month, ≥1 per month
Cottage or ricotta cheese (1/2 cup)	Never or <1 per month, ≥1 per month
Other cheese (1 slice or 1 oz. serving)	Never or <1 per month, ≥1 per month
Margarine (pat)	Never or <1 per month, ≥1 per month
Butter (pat)	Never or <1 per month, ≥1 per month
Apples or pears (1)	Never or <1 per month, ≥1 per month
Oranges (1)	Never or <1 per month, ≥1 per month
Orange juice (1 glass)	Never or <1 per month, ≥1 per month
Peaches, apricots, plums, or nectarines (1 fresh or 1/2 cup canned)	Never or <1 per month, ≥1 per month
Bananas (1)	Never or <1 per month, ≥1 per month
Other fruits, fresh, frozen, or canned (1/2 cup)	Never or <1 per month, ≥1 per month
Tomatoes (1) or tomato juice (small glass)	Never or <1 per month, ≥1 per month
String beans (1/2 cup)	Never or <1 per month, ≥1 per month
Broccoli (1/2 cup)	Never or <1 per month, ≥1 per month
Cabbage, cauliflower, or brussel sprouts (1/2 cup)	Never or <1 per month, ≥1 per month
Carrots, raw (1/2 carrot or 2–4 sticks)	Never or <1 per month, ≥1 per month
Carrots, cooked (1/2 cup)	Never or <1 per month, ≥1 per month
Corn (1 ear or 1/2 cup frozen, canned)	Never or <1 per month, ≥1 per month
Peas or lima beans (1/2 cup frozen, canned)	Never or <1 per month, ≥1 per month
Yams or sweet potatoes (1/2 cup)	Never or <1 per month, ≥1 per month
Spinach or collard greens, cooked (1/2 cup)	Never or <1 per month, ≥1 per month

Variable	
Beans or lentils, baked or dried (1/2 cup)	Never or <1 per month, ≥1 per month
Yellow squash (1/2 cup)	Never or <1 per month, ≥1 per month
Eggs (1)	Never or <1 per month, ≥1 per month
Chicken or turkey (4–6 oz.)	Never or <1 per month, ≥1 per month
Bacon (2 slices)	Never or <1 per month, ≥1 per month
Hot dogs (1)	Never or <1 per month, ≥1 per month
Processed meats, e.g., sausage, salami, bologna, chorizo, etc. (piece or slice)	Never or <1 per month, ≥1 per month
Liver (3–4 oz.)	Never or <1 per month, ≥1 per month
Hamburger (1 patty)	Never or <1 per month, ≥1 per month
Beef, pork, lamb or cabrito as a sandwich or mixed dish, e.g., stew, casserole, lasagna, etc.	Never or <1 per month, ≥1 per month
Beef, pork, lamb or cabrito as a main dish, e.g., steak, roast, ham, etc. (4–6 oz.)	Never or <1 per month, ≥1 per month
Fish (3–5 oz.)	Never or <1 per month, ≥1 per month
Chocolate (1 oz.)	Never or <1 per month, ≥1 per month
Candy without chocolate (1 oz.)	Never or <1 per month, ≥1 per month
Pie (slice)	Never or <1 per month, ≥1 per month
Cake (slice)	Never or <1 per month, ≥1 per month
Cookies (1)	Never or <1 per month, ≥1 per month
White bread (slice), including pita bread	Never or <1 per month, ≥1 per month
Dark bread (slice), including wheat pita bread	Never or <1 per month, ≥1 per month
French fried potatoes (4 oz.)	Never or <1 per month, ≥1 per month
Potatoes, baked, boiled (1) or mashed (1 cup)	Never or <1 per month, ≥1 per month
Rice or pasta, e.g., Spanish rice, spaghetti, noodles, etc. (1 cup)	Never or <1 per month, ≥1 per month
Potato chips or corn chips (small bag or 1 oz.)	Never or <1 per month, ≥1 per month
Nuts (small packet or 1 oz.)	Never or <1 per month, ≥1 per month
Peanut butter (1 Tbs)	Never or <1 per month, ≥1 per month
Oil and vinegar dressing, e.g., Italian (1 Tbs)	Never or <1 per month, ≥1 per month
Cantaloupe (1/4 melon)	Never or <1 per month, ≥1 per month
Avocado (1) or guacamole (1 cup)	Never or <1 per month, ≥1 per month
Raw chile peppers, jalapeno (1)	Never or <1 per month, ≥1 per month
Salsa (1 cup)	Never or <1 per month, ≥1 per month
Chicken livers (1 oz.)	Never or <1 per month, ≥1 per month
Organ meats, Barbacoa, Menudo, sweetbreads, tongue, intestines (3–4 oz.)	Never or <1 per month, ≥1 per month
Tortilla (1)	Never or <1 per month, ≥1 per month
Refried Beans (1 cup)	Never or <1 per month, ≥1 per month
Maternal age at delivery	Continuous (years)
Father age at delivery	Continuous (years)
Number of previous live births	Continuous
Gravidity	Continuous
Number of people supported with household income	Continuous

Variable	
Time spent per shower	Continuous (min)
Time spent per bath	Continuous (min)
Number of jobs from B1-P1	Continuous
Diet quality index	Continuous
Alanine	Continuous (g)
Betaine	Continuous (mg)
Calcium	Continuous (mg)
Alpha-carotene	Continuous (μg)
Beta-carotene	Continuous (μg)
Total carbohydrate	Continuous (g)
Total choline	Continuous (mg)
Copper	Continuous (mg)
Cystine	Continuous (g)
Total lipid	Continuous (g)
Iron	Continuous (mg)
Folate	Continuous (μg, dietary folate equivalents)
Glycemic index	Continuous
Lutein and zeaxanthin	Continuous (μg)
Methionine	Continuous (g)
Magnesium	Continuous (mg)
Niacin	Continuous (mg)
Total protein	Continuous (g)
Retinol	Continuous (μg)
Riboflavin	Continuous (mg)
Selenium	Continuous (μg)
Thiamin	Continuous (mg)
Vitamin E	Continuous (mg, alpha-tocopherol)
Vitamin A	Continuous (international units)
Vitamin A	Continuous (μg, retinoic acid equivalents)
Vitamin B12	Continuous (μg)
Vitamin B6	Continuous (mg)
Vitamin C	Continuous (mg)
Zinc	Continuous (mg)
Caffeine from coffee	Continuous (mg)
Caffeine from tea	Continuous (mg)
Caffeine from soda	Continuous (mg)
Total caffeine	Continuous (mg)

Abbreviations: B1, month before conception; P1, first month of pregnancy; P2, second month of pregnancy; P3, third month of pregnancy.

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TABLE 1

Distribution of preterm birth for selected defects.

Defect	Total, *N*	Preterm (<37 weeks gestation), *n* (%)	Preterm (<35 weeks gestation), *n* (%)
Spina bifida	1204	295 (24.5)	189 (15.7)
D-transposition of the great arteries	732	67 (9.2)	20 (2.7)
Tetralogy of Fallot	1102	200 (18.2)	96 (8.7)
Cleft palate without cleft lip	1517	248 (16.4)	120 (7.9)
Cleft lip ± cleft palate	2930	390 (13.3)	172 (5.9)
Longitudinal/intercalary limb deficiency	465	106 (22.8)	66 (14.2)
Transverse limb deficiency	667	133 (19.9)	78 (11.7)
Craniosynostosis	1516	172 (11.4)	77 (5.1)
Gastroschisis	1404	871 (62.0)	357 (25.4)

Birth Defects Res. Author manuscript; available in PMC 2024 November 14.

TABLE 2

A priori potential risk factors by sex and preterm birth status.[a]

		Male preterm	Female preterm	Male term	Female term
Defect	**Characteristic**	***n*[b] (%*)**	***n*[b] (%)**	***n*[b] (%)**	***n*[b] (%)**
Spina bifida	Folic acid-containing supplement use[c]				
	Yes	95 (10.8)	111 (12.7)	337 (38.5)	333 (38.0)
	No	50 (17.2)	29 (10.0)	118 (40.5)	94 (32.3)
	Maternal smoking[c]				
	Yes	26 (12.6)	32 (15.5)	74 (35.7)	75 (36.2)
	No	121 (12.5)	111 (11.4)	386 (39.8)	353 (36.4)
	Pre-pregnancy body mass index				
	<30 kg/m^2	114 (13.8)	99 (11.9)	321 (38.7)	295 (35.6)
	≥30 kg/m^2	27 (9.3)	37 (12.8)	114 (39.5)	111 (38.4)
	Interpregnancy interval				
	No previous pregnancies	38 (12.4)	32 (10.5)	131 (42.8)	105 (34.3)
	≤12 months	43 (17.1)	33 (13.1)	79 (31.4)	97 (38.5)
	>12 months	66 (10.8)	72 (11.8)	246 (40.3)	227 (37.2)
	Total	150 (12.5)	145 (12.0)	470 (39.0)	439 (36.5)
D-transposition of the great arteries	Folic acid-containing supplement use[c]				
	Yes	34 (6.2)	15 (2.7)	348 (63.4)	152 (27.7)
	No	9 (5.4)	6 (3.6)	108 (64.3)	45 (26.8)
	Maternal smoking[c]				
	Yes	5 (3.7)	8 (5.8)	90 (65.7)	34 (24.8)
	No	39 (6.7)	13 (2.2)	371 (63.8)	159 (27.3)
	Pre-pregnancy body mass index				
	<30 kg/m^2	34 (5.8)	21 (3.6)	372 (63.6)	158 (27.0)
	≥30 kg/m^2	6 (5.0)	1 (0.8)	81 (67.5)	32 (26.7)
	Interpregnancy interval				
	No previous pregnancies	12 (5.7)	6 (2.9)	126 (60.3)	65 (31.1)
	≤12 months	8 (6.2)	9 (6.9)	83 (63.9)	30 (23.1)

Defect	Characteristic	Male preterm n^b (%*)	Female preterm n^b (%)	Male term n^b (%)	Female term n^b (%)
	>12 months	22 (6.0)	6 (2.9)	245 (66.2)	97 (26.2)
	Total	44 (6.0)	23 (3.1)	466 (63.7)	199 (27.2)
Tetralogy of Fallot	Folic acid-containing supplement use[c]				
	Yes	86 (10.0)	70 (8.1)	408 (47.3)	298 (34.6)
	No	20 (9.2)	18 (8.3)	121 (55.5)	59 (27.1)
	Maternal smoking[c]				
	Yes	17 (9.6)	17 (9.6)	83 (46.9)	60 (33.9)
	No	89 (9.9)	69 (7.7)	446 (49.5)	297 (33.0)
	Pre-pregnancy body mass index				
	<30 kg/m^2	82 (9.8)	66 (7.9)	407 (48.8)	279 (33.5)
	≥30 kg/m^2	21 (9.5)	19 (8.6)	108 (48.9)	73 (33.0)
	Interpregnancy interval				
	No previous pregnancies	49 (13.7)	30 (8.4)	166 (46.5)	112 (31.4)
	≤12 months	16 (8.2)	17 (8.7)	91 (46.7)	71 (36.4)
	>12 months	40 (7.9)	39 (7.7)	266 (52.3)	164 (32.2)
	Total	110 (10.0)	90 (8.2)	540 (49.0)	362 (32.8)
Cleft palate without cleft lip	Folic acid-containing supplement use[c]				
	Yes	90 (7.8)	96 (8.4)	408 (35.5)	555 (48.3)
	No	20 (6.1)	28 (8.5)	116 (35.3)	165 (50.2)
	Maternal smoking[c]				
	Yes	29 (9.0)	28 (8.7)	115 (35.8)	149 (46.4)
	No	86 (7.4)	99 (8.5)	412 (35.4)	567 (48.7)
	Pre-pregnancy body mass index				
	<30 kg/m^2	99 (8.4)	105 (8.9)	418 (35.3)	563 (47.5)
	≥30 kg/m^2	13 (4.8)	23 (8.5)	101 (37.1)	135 (49.6)
	Interpregnancy interval				
	No previous pregnancies	41 (10.0)	38 (9.3)	142 (34.7)	188 (46.0)
	≤12 months	27 (9.3)	27 (9.3)	121 (41.7)	115 (39.7)
	>12 months	47 (6.2)	59 (7.7)	255 (33.4)	402 (52.7)

Defect	Characteristic	Male preterm n^b (%*)	Female preterm n^b (%)	Male term n^b (%)	Female term n^b (%)
	Total	117 (7.7)	131 (8.6)	536 (35.3)	733 (48.3)
Cleft lip ± cleft palate	Folic acid-containing supplement use[c]				
	Yes	201 (9.1)	96 (4.4)	1257 (57.0)	651 (29.5)
	No	64 (9.4)	24 (3.5)	375 (55.3)	215 (31.7)
	Maternal smoking[c]				
	Yes	57 (8.4)	28 (4.1)	385 (56.9)	207 (30.6)
	No	204 (9.3)	93 (4.2)	1241 (56.5)	659 (30.0)
	Pre-pregnancy body mass index				
	<30 kg/m^2	205 (9.1)	94 (4.2)	1280 (57.0)	665 (29.6)
	≥30 kg/m^2	51 (9.7)	23 (4.4)	294 (55.8)	159 (30.2)
	Interpregnancy interval				
	No previous pregnancies	89 (10.4)	42 (4.9)	491 (57.2)	236 (27.5)
	≤12 months	43 (7.8)	24 (4.3)	299 (53.9)	189 (34.1)
	>12 months	125 (8.8)	51 (3.6)	822 (57.9)	423 (29.8)
	Total	267 (9.1)	123 (4.2)	1664 (56.8)	876 (29.9)
Longitudinal/intercalary limb deficiency	Folic acid-containing supplement use[c]				
	Yes	41 (11.7)	35 (10.0)	161 (45.9)	114 (32.5)
	No	12 (11.4)	16 (15.2)	43 (41.0)	34 (32.4)
	Maternal smoking[c]				
	Yes	9 (9.2)	14 (14.3)	39 (39.8)	36 (36.7)
	No	43 (12.2)	36 (10.2)	163 (46.1)	112 (31.6)
	Pre-pregnancy body mass index				
	<30 kg/m^2	42 (11.6)	35 (9.7)	164 (45.3)	121 (33.4)
	≥30 kg/m^2	12 (14.8)	13 (16.1)	30 (37.0)	26 (32.1)
	Interpregnancy interval				
	No previous pregnancies	24 (15.1)	20 (12.6)	67 (42.1)	48 (30.2)
	≤12 months	6 (6.7)	8 (9.0)	49 (55.1)	26 (29.2)
	>12 months	22 (11.0)	22 (11.0)	83 (41.3)	74 (36.8)
	Total	54 (11.6)	52 (11.2)	208 (44.7)	151 (32.5)

Defect	Characteristic	Male preterm n^b (%*)	Female preterm n^b (%)	Male term n^b (%)	Female term n^b (%)
Transverse limb deficiency	Folic acid-containing supplement use[c]				
	Yes	56 (11.2)	47 (9.4)	213 (42.4)	186 (37.1)
	No	18 (12.1)	10 (6.7)	73 (49.0)	48 (32.2)
	Maternal smoking[c]				
	Yes	17 (13.0)	13 (9.9)	49 (37.4)	52 (39.7)
	No	55 (10.6)	42 (8.1)	238 (45.7)	186 (35.7)
	Pre-pregnancy body mass index				
	<30 kg/m^2	60 (11.7)	47 (9.2)	219 (42.8)	186 (36.3)
	≥30 kg/m^2	11 (9.4)	8 (6.8)	55 (47.0)	43 (36.8)
	Interpregnancy interval				
	No previous pregnancies	32 (14.7)	19 (8.7)	89 (40.8)	78 (35.8)
	≤12 months	14 (13.0)	10 (9.3)	52 (48.2)	32 (29.6)
	>12 months	28 (8.6)	26 (8.0)	147 (45.0)	126 (38.5)
	Total	76 (11.4)	57 (8.5)	293 (43.9)	241 (36.1)
Craniosynostosis	Folic acid-containing supplement use[c]				
	Yes	95 (7.8)	39 (3.2)	745 (61.1)	341 (28.0)
	No	21 (8.4)	11 (4.4)	131 (52.6)	86 (34.5)
	Maternal smoking[c]				
	Yes	20 (7.9)	13 (5.2)	150 (59.5)	69 (27.4)
	No	97 (7.9)	38 (3.1)	733 (59.6)	362 (29.4)
	Pre-pregnancy body mass index				
	<30 kg/m^2	95 (8.0)	41 (3.5)	710 (60.1)	335 (28.4)
	≥30 kg/m^2	25 (8.4)	9 (3.0)	171 (57.2)	94 (31.4)
	Interpregnancy interval				
	No previous pregnancies	33 (8.5)	14 (3.6)	237 (61.1)	104 (26.8)
	≤12 months	34 (11.1)	14 (4.6)	170 (55.6)	88 (28.8)
	>12 months	50 (6.4)	22 (2.8)	475 (61.1)	230 (29.6)
	Total	121 (8.0)	51 (3.4)	904 (59.6)	440 (29.0)
Gastroschisis	Folic acid-containing supplement use[c]				

Defect	Characteristic	Male preterm n^b (%*)	Female preterm n^b (%)	Male term n^b (%)	Female term n^b (%)
	Yes	295 (31.5)	288 (30.7)	170 (18.1)	185 (19.7)
	No	129 (30.8)	131 (31.3)	87 (20.8)	72 (17.2)
	Maternal smoking[c]				
	Yes	145 (30.2)	140 (29.2)	95 (19.8)	100 (20.8)
	No	272 (31.3)	280 (32.3)	163 (18.8)	153 (17.6)
	Pre-pregnancy body mass index				
	<30 kg/m^2	408 (31.9)	386 (30.1)	247 (19.3)	240 (18.7)
	≥30 kg/m^2	19 (25.7)	28 (37.8)	14 (18.9)	13 (17.6)
	Interpregnancy interval				
	No previous pregnancies	206 (30.0)	215 (31.3)	126 (18.3)	140 (20.4)
	≤12 months	87 (36.7)	68 (28.7)	41 (17.3)	41 (17.3)
	>12 months	127 (30.3)	127 (30.3)	92 (22.0)	73 (17.4)
	Total	441 (31.4)	430 (30.6)	269 (19.2)	264 (18.8)

[a] Row percentages.

[b] Numbers vary because of missing values.

[c] Month before conception through the second month of pregnancy.

TABLE 3

Adjusted odds ratios and 95% confidence intervals from multinomial regression models for associations between folic acid-containing supplement use,[a,b] maternal smoking,[a,c] pre-pregnancy obesity,[d] interpregnancy interval,[e] and sex and preterm birth status.

		Male preterm	Female preterm	Male term
Defect	**Effect**	**aOR (95% CI)**	**aOR (95% CI)**	**aOR (95% CI)**
Spina bifida	No vs. yes folic acid-containing supplement use	**1.95 (1.25–3.04)**	0.91 (0.54–1.52)	1.36 (0.96–1.91)
	Yes vs. no smoking	1.00 (0.60–1.66)	1.42 (0.87–2.32)	0.84 (0.58–1.22)
	Yes vs. no pre-pregnancy obesity	**0.59 (0.36–0.97)**	0.92 (0.58–1.46)	0.96 (0.70–1.32)
	≤12 months IPI vs. >12 months IPI	1.50 (0.93–2.42)	1.14 (0.69–1.87)	**0.67 (0.46–0.97)**
	No prev. pregnancies vs. >12 months IPI	1.20 (0.74–1.97)	1.03 (0.63–1.70)	1.21 (0.87–1.69)
D-transposition of the great arteries	No vs. yes folic acid-containing supplement use	0.72 (0.28–1.87)	0.60 (0.16–2.27)	1.08 (0.71–1.65)
	Yes vs. no smoking	0.75 (0.27–2.10)	**4.22 (1.50–11.92)**	1.07 (0.68–1.70)
	Yes vs. no pre-pregnancy obesity	0.66 (0.22–2.01)	0.30 (0.04–2.35)	1.16 (0.72–1.86)
	≤12 months IPI vs. >12 months IPI	1.19 (0.45–3.13)	**5.14 (1.54–17.21)**	1.07 (0.66–1.76)
	No prev. pregnancies vs. >12 months IPI	0.94 (0.42–2.11)	1.23 (0.34–4.48)	0.79 (0.53–1.17)
Tetralogy of Fallot	No vs. yes folic acid-containing supplement use	0.90 (0.48–1.71)	1.13 (0.59–2.15)	1.42 (0.99–2.04)
	Yes vs. no smoking	1.05 (0.57–1.94)	1.33 (0.71–2.48)	0.96 (0.66–1.40)
	Yes vs. no pre-pregnancy obesity	1.10 (0.63–1.95)	1.05 (0.56–1.94)	1.07 (0.75–1.51)
	≤12 months IPI vs. >12 months IPI	0.88 (0.44–1.74)	0.89 (0.46–1.74)	0.74 (0.51–1.09)
	No prev. pregnancies vs. >12 months IPI	**1.89 (1.14–3.12)**	0.98 (0.56–1.72)	0.94 (0.68–1.29)
Cleft palate without cleft lip	No vs. yes folic acid-containing supplement use	0.73 (0.42–1.28)	1.04 (0.64–1.68)	1.03 (0.77–1.37)
	Yes vs. no smoking	1.41 (0.88–2.27)	1.09 (0.68–1.75)	1.06 (0.80–1.42)
	Yes vs. no pre-pregnancy obesity	0.61 (0.33–1.13)	0.99 (0.59–1.63)	0.99 (0.74–1.34)
	≤12 months IPI vs. >12 months IPI	**2.01 (1.16–3.48)**	1.64 (0.97–2.76)	**1.66 (1.22–2.27)**
	No prev. pregnancies vs. >12 months IPI	**1.77 (1.10–2.85)**	1.41 (0.89–2.22)	1.17 (0.89–1.55)
Cleft lip ± cleft palate	No vs. yes folic acid-containing supplement use	1.00 (0.71–1.42)	0.75 (0.45–1.26)	0.94 (0.76–1.15)
	Yes vs. no smoking	0.85 (0.60–1.20)	0.91 (0.57–1.46)	0.98 (0.80–1.19)
	Yes vs. no pre-pregnancy obesity	1.08 (0.75–1.55)	1.04 (0.63–1.71)	0.95 (0.76–1.19)
	≤12 months IPI vs. >12 months IPI	0.76 (0.51–1.14)	1.06 (0.62–1.80)	**0.79 (0.63–0.99)**
	No prev. pregnancies vs. >12 months IPI	1.25 (0.90–1.74)	1.53 (0.98–2.39)	1.06 (0.87–1.30)
Longitudinal/intercalary limb deficiency	No vs. yes folic acid-containing supplement use	0.83 (0.37–1.86)	1.24 (0.57–2.72)	0.88 (0.51–1.52)

		Male preterm	Female preterm	Male term
Defect	**Effect**	**aOR (95% CI)**	**aOR (95% CI)**	**aOR (95% CI)**
	Yes vs. no smoking	0.51 (0.21–1.23)	1.31 (0.61–2.80)	0.78 (0.46–1.32)
	Yes vs. no pre-pregnancy obesity	1.55 (0.71–3.42)	1.45 (0.63–3.34)	0.80 (0.44–1.46)
	≤12 months IPI vs. >12 months IPI	0.63 (0.21–1.85)	0.90 (0.32–2.52)	1.68 (0.94–2.99)
	No prev. pregnancies vs. >12 months IPI	1.68 (0.83–3.38)	1.59 (0.75–3.38)	1.06 (0.63–1.76)
Transverse limb deficiency	No vs. yes folic acid-containing supplement use	1.30 (0.67–2.51)	0.95 (0.44–2.04)	1.13 (0.73–1.75)
	Yes vs. no smoking	1.24 (0.65–2.37)	1.08 (0.53–2.24)	0.79 (0.51–1.25)
	Yes vs. no pre-pregnancy obesity	0.87 (0.41–1.87)	0.83 (0.36–1.91)	1.07 (0.68–1.70)
	≤ 12 months IPI vs. >12 months IPI	1.91 (0.85–4.31)	1.40 (0.58–3.33)	1.34 (0.80–2.26)
	No prev. pregnancies vs. >12 months IPI	**2.00 (1.07–3.74)**	1.20 (0.61–2.36)	0.92 (0.62–1.38)
Craniosynostosis	No vs. yes folic acid-containing supplement use	0.89 (0.52–1.54)	1.16 (0.56–2.40)	**0.70 (0.51–0.95)**
	Yes vs. no smoking	1.17 (0.67–2.04)	1.94 (0.97–3.90)	1.15 (0.83–1.59)
	Yes vs. no pre-pregnancy obesity	0.94 (0.56–1.58)	0.83 (0.38–1.78)	0.89 (0.66–1.19)
	≤12 months IPI vs. >12 months IPI	**1.76 (1.05–2.94)**	1.66 (0.80–3.48)	1.00 (0.74–1.37)
	No prev. pregnancies vs. >12 months IPI	1.54 (0.93–2.56)	1.55 (0.76–3.19)	1.20 (0.90–1.60)
Gastroschisis	No vs. yes folic acid-containing supplement use	1.23 (0.86–1.77)	1.12 (0.78–1.62)	1.34 (0.90–2.00)
	Yes vs. no smoking	0.81 (0.58–1.14)	0.75 (0.53–1.05)	0.92 (0.63–1.34)
	Yes vs. no pre-pregnancy obesity	0.70 (0.33–1.49)	1.22 (0.61–2.44)	0.93 (0.42–2.06)
	≤12 months IPI vs. >12 months IPI	1.20 (0.73–1.96)	0.98 (0.59–1.62)	0.72 (0.41–1.24)
	No prev. pregnancies vs. >12 months IPI	0.81 (0.55–1.18)	0.85 (0.59–1.24)	0.69 (0.46–1.03)

Note: The referent group is “female term”. The estimates in bold have statistically significant adjusted odds ratios.

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; IPI, interpregnancy interval.

[a]Month before conception through the second month of pregnancy.

[b]Adjusted for maternal smoking, pre-pregnancy obesity, and interpregnancy interval.

[c]Adjusted for folic acid-containing supplement use, pre-pregnancy obesity, and interpregnancy interval.

[d]Adjusted for folic acid-containing supplement use, maternal smoking, and interpregnancy interval.

[e]Adjusted for folic acid-containing supplement use, maternal smoking, and pre-pregnancy obesity.

TABLE 4

Top 10 most important predictors from the random forests for each model by birth defect.

Spina bifida		
Male preterm	**Female preterm**	**Male term**
Lutein and zeaxanthin (μg/day)	Wine intake	**Any type of fever during P2**
Folic acid-containing supplement use during P2	***Household income***	**Work/school smoke exposure during B1-P2**
Maternal race/ethnicity	Diet quality index	**Nausea during P1**
Showers at home	Alcohol consumption during B1	**Cantaloupe (1/4 melon)**
Carrots, cooked (1/2 cup)	Beer intake	**Interpregnancy interval**
Household smoke exposure during B1-P2[a]	Folate, DFE (μg/day)	Refried beans (1 cup)
Paternal substance abuse during P2	Total carbohydrate (g/day)	Household smoke exposure during B1
Baths at home	Study site	Tomatoes or tomato juice
Ice cream (1/2 cup)	Thiamin (mg/day)	Maternal residency ever moved B1-P2
Paternal race/ethnicity	**Parity**	Candy without chocolate (1 oz.)
D-transposition of the great arteries		
Male preterm	**Female preterm**	**Male term**
Bacon (2 slices)	**Showers at home**	**Fertility treatment**
Paternal education	**Orange juice**	**Nausea during P1-P2**
Betaine (mg/day)	Bananas (1)	**Household income**
Spinach/collard greens (1/2 cup)	Magnesium (mg/day)	Alanine (g/day)
Time spent per shower (min)	Vitamin A, RAE (μg/day)	Vasoactive medication use during B1-P3
Carrots, cooked (1/2 cup)	Folate, DFE (μg/day)	**Magnesium (mg/day)**
Nuts (1 oz)	Anti-fever medication use during B1	Calcium (mg/day)
French fries (4 oz)	***Cigarette smoking during P1-P2***	**Urinary tract infection during P2**
Baths at home	Vitamin C (mg/day)	Hot dogs
Paternal race/ ethnicity	Copper (mg/day)	Whole milk (8 oz. glass)
Tetralogy of Fallot		
Male preterm	**Female preterm**	**Male term**
Showers at home	***Liver (3–4 oz.)***	***Mixed drink intake***
String beans (1/2 cup)	**Number of people supported with household income**	Pie (slice)
Interpregnancy interval	Parity	***Dark bread (slice)***
Cottage/ricotta cheese (1/2 cup)	Maternal age at delivery	Total carbohydrate (g/day)
Carrots, cooked (1/2 cup)	Carrots, raw (1/2 carrot or 2–4 sticks)	Thiamin (mg/day)
Spinach/collard greens (1/2 cup)	Alpha-carotene (μg/day)	Gravidity
Eggs (1)	Paternal education	Folic acid-containing supplement use during B1
Organ meats/barbacoa/menudo/sweetbreads/ tongue/intestines (3–4 oz.)	Oranges (1)	**Cottage/ricotta cheese (1/2 cup)**
Baths at home	Maternal education	Antihypertensive medication use during B1-P3
NSAIDs use during P1	Private well drinking water source	Processed meats

Cleft palate without cleft lip

Male preterm	Female preterm	Male term
Niacin (mg/day)	**Household income**	***String beans (1/2 cup)***
Glycemic index	Broccoli (1/2 cup)	**Bananas (1)**
Showers at home	Baths at home	***Interpregnancy interval***
Retinol (μg/day)	***Seizures***	***Anti-anxiety medication use during B1-P1***
Paternal race/ethnicity	Timing of first prenatal visit	Alcohol consumption during B1
Vitamin E (mg/day)	Cantaloupe (1/4 melon)	***Butter (pat)***
Anti-fever medication use during P2	Vitamin E (mg/day)	Wine intake
Vitamin B12 (μg/day)	Vitamin A, RAE (μg/day)	Caffeine from tea (mg/day)
Total lipid (g/day)	Beans/lentils (1/2 cup)	**Cake (slice)**
Folate, DFE (μg/day)	***Any type of fever during B1***	***Birth control pill during P2***

Cleft lip ± cleft palate

Male preterm	Female preterm	Male term
Total choline (mg/day)	Maternal education	***Father employed***
Cantaloupe (1/4 melon)	***Lutein and zeaxanthin (μg/day)***	Number of people supported with household income
Timing of pregnancy discovery	Folic acid-containing supplement use during P1	Parity
Salsa (1 cup)	Paternal age at delivery	Paternal race/ethnicity
Maternal residency ever moved B1-P2	Maternal age at delivery	Maternal race/ethnicity
Caffeine from soda (mg/day)	Cantaloupe (1/4 melon)	Showers at home
Paternal race/ethnicity	Broccoli (1/2 cup)	Total carbohydrate (g/day)
Beans/lentils (1/2 cup)	**Chicken/turkey (4–6 oz.)**	Other cheese (slice or 1 oz.)
Carrots, cooked (1/2 cup)	Cigarette smoking during P2	Copper (mg/day)
Peanut butter (1 Tbs)	Magnesium (mg/day)	Gravidity

Longitudinal/intercalary limb deficiency

Male preterm	Female preterm	Male term
Fertility treatment	***Raw jalapeno peppers (1)***	String beans (1/2 cup)
Carrots, cooked (1/2 cup)	Baths at home	Pie (slice)
Vitamin E (mg/day)	Anti-fever medication use during P1	***White bread (slice)***
NSAIDs use during B1	**Tomatoes/tomato juice**	Maternal education
Folic acid-containing supplement use during B1	Potatoes, baked, boiled (1) or mashed (1 cup)	**Tomatoes/tomato juice**
Household income	Number of people supported with household income	Peanut butter (1 Tbs)
Maternal education	Vitamin E (mg/day)	Paternal education
Wine intake	Father employed	Alpha- carotene (μg/day)
Cottage/ricotta cheese (1/2 cup)	Peas/lima beans (1/2 cup)	Hamburger (1 patty)
Yams/sweet potatoes (1/2 cup)	Timing of first prenatal visit	Diet quality index

Transverse limb deficiency

Male preterm	Female preterm	Male term
Total choline (mg/day)	***Maternal race/ethnicity***	***Oranges (1)***

Total carbohydrate (g/day)	Paternal race/ethnicity	**Paternal race/ethnicity**
Caffeine from soda (mg/day)	Vitamin E (mg/day)	Glycemic index
Maternal age at delivery	Nausea during P2	Vitamin C (mg/day)
Maternal residency ever moved B1-P2	Bananas (1)	**Chocolate (1 oz.)**
Vitamin C (mg/day)	Caffeine from soda (mg/day)	***Showers at home***
Total lipid (g/day)	***Birth control pill during P1***	Maternal race/ethnicity
Parity	Total carbohydrate (g/day)	***Respiratory disease during P2***
Alanine	Baths at home	Vasoactive medication use during B1-P3
Beer intake	Bacon (2 slices)	Vitamin E (mg/day)
Craniosynostosis		

Male preterm	**Female preterm**	**Male term**
Folic acid-containing supplement use during P1	**Selenium (μg/day)**	***Skim/low fat milk (8 oz. glass)***
Baths at home	**Study site**	Potatoes, baked, boiled (1) or mashed (1 cup)
Study site	Betaine (mg/day)	Hamburger (1 patty)
Paternal race/ethnicity	Baths at home	Corn (1 ear or 1/2 cup)
White bread (slice)	Other fruits (1/2 cup)	Bacon (2 slices)
Thiamin (mg/day)	Vitamin E (mg/day)	Beef/pork/lamb, main dish (4–6 oz.)
Tortilla (1)	Niacin (mg/day)	Lutein and zeaxanthin (μg/day)
Riboflavin (mg/day)	Medication for pregnancy nausea	**Fertility treatment**
Vitamin E (mg/day)	Maternal feelings about pregnancy	Beef/pork/lamb, mixed dish
Copper (mg/day)	Total choline (mg/day)	**Broccoli (1/2 cup)**
Gastroschisis		

Male preterm	**Female preterm**	**Male term**
Total caffeine (mg/day)	***Vitamin E (mg/day)***	Caffeine from coffee (mg/day)
String beans (1/2 cup)	**Cabbage/cauliflower/brussel sprouts (1/2 cup)**	**Anti-fever medication use during P1-P2**
Gravidity	**String beans (1/2 cup)**	Gravidity
Caffeine from coffee (mg/day)	***Cantaloupe (1/4 melon)***	Corn (1 ear or 1/2 cup)
Potato chips or corn chips (1 oz.)	Caffeine from coffee (mg/day)	***Work/school smoke exposure during P2***
NSAIDs use during P1	NSAIDs use during P1-P2	**Skim/low fat milk (8 oz. glass)**
Vitamin B6 (mg/day)	***Study site***	Interpregnancy interval
Broccoli (1/2 cup)	Yellow squash (1/2 cup)	Organ meats/barbacoa/ menudo/sweetbreads/ tongue/intestines (3–4 oz.)
Parity	Broccoli (1/2 cup)	Avocado (1)
Wine intake	Mixed drink intake	Dark bread (slice)

Note: Predictors in bold have a statistically significant odds ratio less than one, and predictors in bold and italics have a statistically significant odds ratio greater than one (see Tables S1–S9 for all model estimates from the logistic regressions). The referent group is “female term”.

Abbreviations: B1, month before conception; DFE, dietary folate equivalents; NSAIDs, nonsteroidal anti-inflammatory drugs; P1, first month of pregnancy; P2, second month of pregnancy; P3, third month of pregnancy; RAE, retinoic acid equivalents.

[a]Household smoke exposure is defined by the presence of anyone in the household smoking cigarettes.