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Descriptive and risk factor analysis of nonsyndromic sacral agenesis: National Birth Defects Prevention Study, 1997–2011

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Abstract

Sacral agenesis is a rare birth defect characterized by partial or complete absence of the sacrum. We sought to (a) describe case characteristics, (b) estimate birth prevalence, and (c) identify risk factors for nonsyndromic sacral agenesis using data from the National Birth Defects Prevention Study (NBDPS). The NBDPS was a population-based, case–control study involving pregnancies with estimated dates of delivery from October 1997 through December 2011. We estimated birth prevalence using all NBDPS eligible cases. Using self-reported maternal exposure information, we conducted multivariable logistic regression analysis to identify potential risk factors overall and among women without diabetes. The birth prevalence of sacral agenesis was 2.6/100,000 live births. In the multivariable analysis, multifetal pregnancy, pre-existing Type 1 diabetes, and pre-existing Type 2 diabetes were positively and significantly associated with sacral agenesis, albeit estimates were imprecise. Pre-existing Type 1 diabetes was the strongest risk factor (adjusted odds ratio = 96.6, 95% confidence interval = 43.5–214.7). Among women without diabetes, periconceptional smoking was positively and significantly associated with sacral agenesis. Our findings underscore the importance of smoking cessation programs among women planning pregnancy and the importance of better understanding the role of glycemic control before and during pregnancy when designing interventions for primary prevention of sacral agenesis.

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CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

DATA ACCESSIBILITY

All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Data from the NBDPS are not released to the public. Qualified researchers can be granted access to NBDPS data for analysis through collaboration with one of the Centers for Birth Defects Research and Prevention.

Keywords

birth defect; birth prevalence; diabetes; sacral agenesis

1 | INTRODUCTION

Sacral agenesis is a rare birth defect characterized by partial or complete absence of the sacrum (Andrish, Kalamchi, & MacEwen, 1979). The defect occurs due to insufficient formation of caudal mesoderm during the gastrulation and axial elongation stage of the embryological development, resulting from a teratogenic insult before the fourth week of gestation (Ferrer-Vaquer & Hadjantonakis, 2013; Sadler & Langman, 2011). Sacral agenesis can present as an isolated birth defect, but is more often associated with other major birth defects of the genitourinary, musculoskeletal, cardiovascular, nervous, and respiratory systems (Andrish et al., 1979; Balioglu et al., 2016; Caird, Hall, Bloom, Park, & Farley, 2007; Emami-Naeini, Rahbar, Nejat, Kajbafzadeh, & El Khashab, 2010; Nievelstein, Valk, Smit, & Vermeij-Keers, 1994; Pang, 1993; Wilmshurst, Kelly, & Borzyskowski, 1999). Complex cases of sacral agenesis with the involvement of the vertebral column and other organ systems are distinguished as caudal regression syndrome, although in the literature the terms “sacral agenesis” and “caudal regression syndrome” are often used interchangeably (Balioglu et al., 2016; Ferrer-Vaquer & Hadjantonakis, 2013; Pang, 1993). Sacral agenesis can present as a part of a Currarino triad, an autosomal dominant syndrome, including sacral bone defects, anorectal malformations, and presacral mass (Cretolle et al., 2008; Currarino, Coln, & Votteler, 1981; Lynch et al., 1995; Markljung et al., 2012). Also, sacral agenesis is often associated with the omphalocele– exstrophy of the cloaca–imperforate anus–spinal defects complex (OEIS) and VATER/VACTERL association defects (vertebral anomalies [V], anorectal defects [A], cardiac defects [C], tracheoesophageal fistula [T], esophageal atresia [E], renal defects [R], limb defects [L]) (Balioglu et al., 2016; Pang, 1993). In addition to motor dysfunction, children with sacral agenesis often suffer from urinary incontinence, constant dribbling, and recurrent urinary tract infections (Emami-Naeini, Nejat, Rahbar, Kajbafzadeh, & El Khashab, 2012; Pang, 1993; White & Klauber, 1976; Wilmshurst et al., 1999).

The estimates of birth prevalence of sacral agenesis reported in the literature range from 1 to 5 per 100,000 live births (Andrish et al., 1979). Given that sacral agenesis is rare, the literature on nongenetic risk factors is sparse, although several studies have reported positive associations between maternal diabetes and sacral agenesis (Banta & Nichols, 1969; Correa et al., 2008; Emami-Naeini et al., 2010; Guzman et al., 1983; Kucera, 1971; Martinez-Frias, 1994; Pang, 1993; Passarge & Lenz, 1966; Renshaw, 1978; Wilmshurst et al., 1999). A previous analysis of maternal pre-existing diabetes (Type 1 or Type 2) and birth defects using data on pregnancies from October 1997 through December 2003 within the National Birth Defects Prevention Study (NBDPS) reported an odds ratio of over 100 for sacral agenesis (Correa et al., 2008). Other studies reported that 12–40% of sacral agenesis cases were attributed to maternal diabetes (Emami-Naeini et al., 2010; Guzman et al., 1983; Pang, 1993; Passarge & Lenz, 1966). Because sacral agenesis was more commonly observed among women with Type 1 (insulin dependent) diabetes (Banhidy, Acs, Puho, &

Czeizel, 2010; O'Neill, Piatt Jr., Mitchell, & Roman-Goldstein, 1995; Pang, 1993; Rusnak & Driscoll, 1965), several human (Boskovic et al., 2003; Chung & Myrianthopoulos, 1975; Fuhrmann et al., 1983; Pollex, Feig, Lubetsky, Yip, & Koren, 2010) and animal (Eriksson & Styrud, 1985; Kuwata et al., 2017; Sadler & Horton Jr., 1983; Tanigawa, Kawaguchi, Tanaka, & Kato, 1991) studies explored the teratogenic effects of insulin. The studies involving pregnant women with Type 1 diabetes did not observe evidence of the teratogenic effect of insulin (Chung & Myrianthopoulos, 1975; Fuhrmann et al., 1983). Moreover, studies reported that appropriate glycemic control by insulin that started before conception was preventive for the development of a birth defect in the fetus (Fuhrmann et al., 1983; Wong, Suwandarathne, & Russell, 2013). Additionally, in vitro studies showed that therapeutic doses of insulin do not cross the human placenta (Boskovic et al., 2003; Pollex et al., 2010). Animal studies also did not report positive associations between insulin and major birth defects in the fetus (Eriksson & Styrud, 1985; Sadler & Horton Jr., 1983). Although insulin by itself was not teratogenic, a long-lasting (>9 hr) insulin-induced hypoglycemia caused delayed ossifications and skeletal abnormalities in fetuses of pregnant rats (Kuwata et al., 2017; Tanigawa et al., 1991).

In addition to diabetes, a limited number of sacral agenesis case reports have mentioned maternal use of hormones (progesterone, estrogens, thyroid hormones) (Rusnak & Driscoll, 1965), medications (diuretics [Renshaw, 1978; Rusnak & Driscoll, 1965], antibiotics [Rusnak & Driscoll, 1965], anti-seizure medications [Renshaw, 1978]), and exposure to fat solvents (Kucera, 1968; Renshaw, 1978) during pregnancy. Agents that have induced sacral agenesis in laboratory animals include adriamycin (Naito et al., 2009), retinoic acid (Padmanabhan, 1998; Pitera, Smith, Woolf, & Milla, 2001), and trypan blue (Lendon, 1975). In addition, extreme temperatures such as hypothermia (32°C) or hyperthermia (40°C) caused sacral agenesis in chick embryos (Peterka, Peterkova, & Likovsky, 1996). We used the final version of the NBDPS with estimated dates of delivery (EDDs) from October 1997 through December 2011 to (a) describe clinical characteristics and associated defects, (b) estimate birth prevalence, and (c) examine associations between a broad range of potential nongenetic risk factors and sacral agenesis.

2 | METHODS AND MATERIALS

The NBDPS was a large, population-based, case–control study of over 30 major structural birth defects, involving 10 states (Arkansas, California, Georgia, Iowa, Massachusetts, North Carolina, New Jersey, New York, Texas, and Utah) (Reefhuis et al., 2015). Details of the NBDPS are presented in previous publications (Rasmussen et al., 2003; Reefhuis et al., 2015). Briefly, the study involved pregnancies with EDDs from October 1, 1997 through December 31, 2011 (Reefhuis et al., 2015). Cases were ascertained from population-based birth defects surveillance systems and included live births, still births (≥20 weeks), and pregnancy terminations. Cases with known chromosomal or single-gene abnormalities were excluded from the NBDPS. Clinical geneticists reviewed clinical information on all cases to ensure study eligibility and to classify them as isolated (only one major birth defect or organ system involved), multiple (major birth defects in multiple organ systems), or complex (a pattern of embryologically related major birth defects). Controls were live born infants without a major birth defect, born at the same time, and in the same geographic

area as cases. They were randomly selected from birth certificates or hospital records and were representative of the source population (Cogswell et al., 2009). Each study site received Institutional Review Board approval, and verbal informed consent was obtained from mothers of both cases and controls.

2.1 | Data collection

Clinical data on all NBDPS eligible cases were abstracted from medical records and included birth information (infant sex, birth weight, and gestational age at delivery) and medical diagnoses. Mothers of all cases and controls eligible for the NBDPS were invited to participate in a structured, computer-assisted telephone interview, conducted 6 weeks to 24 months after their EDDs (Reefhuis et al., 2015). Trained interviewers conducted interviews in English or Spanish. The interview collected information on demographics, maternal health conditions, pregnancy history, maternal medication use, and other exposures 3 months before pregnancy through delivery. The Slone Epidemiology Center Drug Dictionary was used to code all reported medications. The interview participation rate in the NBDPS was 64% for control mothers and 63% for mothers of sacral agenesis cases.

2.2 | Case classification

Cases described as sacral agenesis, partial sacral agenesis, or hemisacrum were eligible for the NBDPS. Cases described as missing elements of the sacrum, sacral hypoplasia, sacral dysgenesis, sacral regression, or caudal regression were excluded, unless there was a more detailed description of the defect or X-ray evidence to confirm the diagnosis. Different sources of information (prenatal ultrasound, postnatal examinations—ultrasound, X-ray, computed tomography, magnetic resonance imaging, clinicians' notes, autopsy) were used to confirm the diagnosis. The NBDPS definition of sacral agenesis excluded cases with sirenomelia and OEIS complex.

For the current analysis, a clinical geneticist (C.M.C.) rereviewed all nonisolated (multiple and complex) sacral agenesis cases and grouped the co-occurring major birth defects by organ systems. If a birth defect was secondary to sacral agenesis (including hip dislocation, abnormal limb position, clubfoot, ectopic or horseshoe kidney), then the case was classified as isolated. Also, a clinical geneticist reviewed all nonisolated sacral agenesis cases and identified the presence of VATER/VACTERL association defects. The case was classified as having VATER/VACTERL association defects if at least three of the component features were present. The cases of VACTERL association defects accompanied by hydrocephalus were considered as a separate entity and were not counted as VATER/VACTERL association defects.

2.3 | Exposure classification

We explored a broad range of exposure variables, including (a) infant characteristics—sex (male, female), gestational age at delivery among live births (<32, 32–36, ≥37 weeks), plurality (singleton, multiple), season of conception (spring, summer, autumn, winter), and the history of sacral agenesis in a first-degree relative (yes, no); (b) maternal demographics —age at delivery (continuous; <20, 20–34, ≥35 years), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, other), education at delivery (<12, 12 [high school diploma],

13–15 [some college], ≥16 years [≥college degree]), birth place (U.S. born, foreign born), and study site; (c) maternal health conditions— prepregnancy body mass index (<25 [under/normal weight], ≥25 [overweight/obese] kilograms/m^2), pre-existing epilepsy (yes, no), pre-existing Type 1 diabetes (yes, no), pre-existing Type 2 diabetes (yes, no), gestational diabetes during current pregnancy (yes, no), hypertension during current pregnancy (yes, no), periconceptional (the month prior through the third month of pregnancy) respiratory illness (yes, no), fever (yes, no), kidney, bladder, or urinary tract infection (yes, no), sexually transmitted infection (yes, no), and pelvic inflammatory disease (yes, no); (d) maternal supplement/medication use—periconceptional antifolate medication use (yes, no), vasoactive medication use (yes, no), antihypertensive medication use (yes, no), and folic acid containing supplement use for the month prior through the first month of pregnancy (yes, no); (e) maternal behaviors—periconceptional binge drinking (yes, no), smoking (yes, no), and recreational drug use (yes, no); and (f) pregnancy-related characteristics—pregnancy intention (wanted to be pregnant, wanted to wait until later, did not want to be pregnant, and did not care), parity (0, 1, ≥2), previous miscarriages (yes, no), and maternal infertility treatment (yes, no).

We calculated the date of conception by subtracting 280 from the EDDs and adding 14 days (2 weeks after the last menstrual period). Using the month of conception, we created the following seasonal categories: spring (March–May), summer (June–August), autumn (September–November), and winter (December–February). Binge drinking was defined as having four or more drinks per occasion (National Institute on Alcohol Abuse and Alcoholism, n.d.). Maternal infertility treatment was assessed by combining responses to questions on surgical procedures for current pregnancy and use of fertility medications or other procedures in the 2 months prior to the current pregnancy. In addition to responses to specific questions on “cold and flu,” we manually searched open text fields to identify any other respiratory illnesses that women reported. Based on the search results, we created a combined variable for all respiratory illnesses during the periconceptional period. Similarly, we reviewed all open-ended questions on maternal infections and identified reports of periconceptional sexually transmitted infections.

2.4 | Statistical analyses

We used the total number of NBDPS eligible sacral agenesis cases identified from the participating population-based surveillance systems (those whose mothers completed the interview and those whose mothers did not) to estimate the birth prevalence per 100,000 live births. We calculated the overall birth prevalence by dividing the total number of cases (n = 174) by the total number of live births (N = 6,572,497) in the source population from which the cases were ascertained. In addition, we estimated the birth prevalence for each complete study year (1998–2011) separately and conducted the Cochran-Armitage trend test to determine if there was a difference in birth prevalence between study years at 0.05 level of statistical significance. As diabetes is a known strong risk factor for sacral agenesis, we estimated the birth prevalence among women without any type of diabetes (pre-existing Type 1, pre-existing Type 2, or gestational during the current pregnancy). To do this, we estimated the number of women without diabetes by applying the proportion of case and control mothers who did not report any type of diabetes during the interview (62.5% of cases

and 94.7% of controls) to the total number of sacral agenesis cases in the study area and to the total number of live births in the study area during the study period.

Using the limited information available on all NBDPS eligible sacral agenesis cases (infant sex, gestational age at delivery, birth weight, plurality, birth year, and birth outcome; maternal age at delivery and race/ethnicity; study site), we conducted Pearson's chi-square tests to detect statistically significant differences based on maternal interview participation. For cases and controls of interviewed mothers, we conducted bivariate logistic regression analyses to estimate crude odds ratios (cORs) and 95% confidence intervals (CIs) for various exposures. For exposures with three or four exposed cases, we calculated exact 95% CIs. We did not calculate estimates for exposures with less than three exposed cases.

We included exposures in the multivariable logistic regression analysis, if the crude Wald p value was <.15 and there were five or more exposed cases. As our analysis lacked a specific exposure of interest, each exposure was adjusted for other exposures included in the multivariable regression analysis, and adjusted odds ratios (aORs) and 95% CIs were estimated for all included exposures. As diabetes is a known strong risk factor for sacral agenesis, we repeated the regression analysis for cases and controls whose mothers did not report any type of diabetes (pre-existing Type 1, pre-existing Type 2, or gestational during the current pregnancy). All statistical analyses were conducted using SAS v9.4 (SAS Institute Inc., Cary, NC).

3 | RESULTS

From October 1, 1997 through December 31, 2011, 174 cases of nonsyndromic sacral agenesis identified in the study areas were eligible for the NBDPS. Of those 174 cases, 23 (13.2%) were classified as isolated, 142 (81.6%) as multiple, and 9 (5.2%) as complex (Table 1). Of the 151 nonisolated cases, 44.4% had one, 33.1% had two, and 22.5% had three or more additional major birth defects. The other major birth defects included 88 (58.3%) cases with gastrointestinal, 58 (38.4%) cases with congenital heart, 43 (28.5%) cases with genitourinary, 40 (26.5%) cases with musculoskeletal, 26 (17.2%) cases with central nervous system, 11 (7.3%) cases with ear/eye, 8 (5.3%) cases with orofacial, and 2 (1.3%) cases with respiratory defects. Among the 88 cases with major gastrointestinal defects, 75 (85.2%) had imperforate anus and 20 (22.7%) had esophageal atresia. Lastly, of the 151 nonisolated sacral agenesis cases, 31 (20.5%) had VATER/VACTERL association defects, and 17 (11.3%) had myelomeningocele.

The birth prevalence of sacral agenesis was 2.6 per 100,000 live births. We observed statistically significant variations in birth prevalence by year (Cochran–Armitage trend test, asymptotic test p value = .02), ranging from 0.8 per 100,000 live births in 2000 to 4.3 per 100,000 live births in 2007 (data not shown). Of the 174 NBDPS eligible sacral agenesis cases, mothers of 110 cases participated in the telephone interview. There were no statistically significant differences on available infant and maternal characteristics of sacral agenesis cases based on maternal interview participation (Table 1).

Mothers of the 110 sacral agenesis cases and 11,829 controls completed the NBDPS interview with the median time between EDD and maternal interview of 10.6 months for case and 7.5 months for control mothers. Cases and controls with available exposure information were included in the risk factor analysis. In unadjusted analyses, cases were more likely to be born from multifetal pregnancies compared to control infants (Table 2). We also found that compared to controls, live-born cases were more likely be delivered either very preterm (<32 weeks) or preterm (32–36 weeks). Compared to control mothers, those of cases were less likely to have at least 16 years of education. Also, case mothers were more likely to report pre-existing Type 1 diabetes, pre-existing Type 2 diabetes, hypertension during pregnancy, or a periconceptional kidney, bladder, or urinary tract infection than control mothers. Other exposures with significant, positive crude associations between case and control mothers were overweight/obesity, Hispanic race/ethnicity, history of a previous miscarriage, periconceptional antihypertensive medication use, and periconceptional smoking. We also observed some differences between cases and controls by maternal residence at delivery. No statistically significant associations were observed for the other exposures analyzed.

In multivariable model, multifetal pregnancy, pre-existing Type 1 diabetes, and pre-existing Type 2 diabetes, remained positively and statistically significantly associated with sacral agenesis (Table 3). While both pre-existing Type 1 and Type 2 diabetes were strong risk factors for sacral agenesis, the risk was higher for mothers with Type 1 diabetes (aOR = 96.6, 95% CI = 43.5–214.7), albeit the estimate was imprecise.

Among mothers who completed the NBDPS interview, 62.5% (n = 65) of case and 94.7% (n = 10,840) of control mothers did not report having any type of diabetes (pre-existing Type 1, pre-existing Type 2, or gestational in the current pregnancy) (Table 2). Applying these proportions, the estimated birth prevalence of sacral agenesis among mothers without diabetes was 1.7 per 100,000 live births. For the 65 cases and 10,840 controls whose mothers did not report having diabetes in the interview, we conducted a separate risk factor analysis and observed positive and statistically significant crude associations between sacral agenesis and maternal education <16 years, periconceptional kidney, bladder, or urinary tract infection, and periconceptional smoking (Table 4). In the multivariable analysis, only periconceptional smoking remained positively and significantly associated with sacral agenesis (aOR = 1.85, 95% CI = 1.05–3.24) (Table 5).

4 | DISCUSSION

Of the 174 NBDPS eligible sacral agenesis cases, 151 (86.8%) had at least one major birth defect of another organ system, and more than one-half of the nonisolated cases had two or more additional major birth defects. Defects of the gastrointestinal system, specifically imperforate anus, were the most commonly observed birth defects among sacral agenesis cases, which has been reported previously (Emami-Naeini et al., 2010; Pang, 1993). Other major birth defects frequently associated with sacral agenesis in the NBDPS were genitourinary and congenital heart defects. Of the 151 nonisolated cases, 31 (20.5%) had VATER/VACTERL association defects, which is lower than the estimate reported in the previous analysis of 38 sacral agenesis cases, where VACTERL association defects were

present in 11 (29%) cases (Balioglu et al., 2016). However, the authors did not specify criteria used to diagnose VACTERL association defects, which might have differed from our approach of having at least three component features.

The birth prevalence of nonsyndromic sacral agenesis in the NBDPS was 2.6 per 100,000 live births, which is within the range of previously reported prevalence estimates (Andrish et al., 1979). Mothers of 62.5% of cases and 94.7% of controls did not report having any type of diabetes. The prevalence of sacral agenesis among mothers without diabetes, calculated by applying the proportion of interviewed case and control mothers without diabetes to the total number of cases and livebirths, was 1.7 per 100,000 live births. Because we did not find statistically significant differences between interviewed and noninterviewed case mothers across clinical characteristics compared (Table 1) and NBDPS controls were found to be representative of the source population for several maternal characteristics (Cogswell et al., 2009), we expect the prevalence estimate calculated by extrapolating the available diabetes information to be a reasonable estimate.

Compared to control infants, sacral agenesis cases were more likely to be born from multifetal pregnancies, or have mothers with pre-existing Type 1 or pre-existing Type 2 diabetes. Also, although statistically nonsignificant, the aORs were >2.0 for the maternal education <13 years and a periconceptional kidney, bladder, or urinary tract infection. The associations that we observed between maternal pre-existing diabetes and sacral agenesis were previously reported using an earlier release of the NBDPS data (EDDs 1997–2003) (Correa et al., 2008). In the analyses of 28 sacral agenesis cases classified as multiple, Correa et al. (2008) reported an elevated risk (cOR = 130.2) for the combined exposure of pre-existing maternal diabetes (Type 1 or Type 2). In our analyses, we examined the associations between sacral agenesis and pre-existing Type 1 or pre-existing Type 2 diabetes separately. Although both types of diabetes were strong risk factors for sacral agenesis, we observed that the risk estimate was higher for Type 1 diabetes. Several studies reported that the level of glycemic control was a strong predictor for the development of a birth defect (Hanson, Persson, & Thunell, 1990; Murphy et al., 2011; Suhonen, Hiilesmaa, & Teramo, 2000; Wender-Ozegowska et al., 2005). A study on maternal Type 1 diabetes reported that even slightly elevated levels of glycated hemoglobin A_{1c} (HbA_{1c}) were associated with an increased risk for major birth defects (Suhonen et al., 2000). Another study (Murphy et al., 2011) reported that women with Type 2 diabetes had better glycemic control during pregnancy compared to those with Type 1 diabetes. The observed difference in glycemic control between two types of maternal diabetes (Type 1 or Type 2) may partially explain our observation of a higher risk for sacral agenesis among mothers with Type 1 diabetes. Murphy et al. (2011) also explored the longer duration of Type 1 diabetes at the time of conception compared to that in Type 2 diabetes, and the association between the duration of diabetes and the risk of birth defects was statistically nonsignificant. Another study, however, reported that within a group of women with Type 1 diabetes, having diabetes for five and more years was associated with a higher risk of major birth defects compared to diabetes duration of less than 5 years (Chung & Myrianthopoulos, 1975). Animal studies found that hyperglycemia during pregnancy caused delayed caudal ossification and skeletal hypoplasia among offspring of diabetic rats (Al Ghafli, Padmanabhan, Kataya, & Berg, 2004; Wilson, Howe, & Stover, 1985). The alterations in the differentiation of embryonic

stem cells into osteoblasts and osteoclasts, reduced bone calcification, and over production of reactive oxygen species were suggested as possible causal pathways leading to abnormal skeletal development in the fetus (Al Ghafli et al., 2004; Dienelt & zur Nieden, 2011).

We observed that cases from multifetal pregnancies were more than three times as likely to have sacral agenesis as singleton births, although the aOR was based on eight cases and resulted in a wide CI. Of those eight cases, mothers of four did not report any type of diabetes, and in the crude analysis of women without diabetes, the association was no longer statistically significant. Although previous studies on multifetal pregnancies have not explored the association with sacral agenesis, an elevated risk for other birth defects, such as intestinal (Forrester & Merz, 2004) and anal (Forrester & Merz, 2002) atresia, has been reported among multiple births. In addition, a previous NBDPS analysis by Dawson et al. reported that, overall, birth defects were more common among twin pregnancies.

Although statistically nonsignificant, we observed aOR >2.0 for the association between periconceptional kidney, bladder, or urinary tract infection and sacral agenesis in our main analysis, which was closer to the null in the sub-analysis of women without diabetes. Our results are consistent with a recent NBDPS analysis of urinary tract infections among nondiabetic mothers (Howley et al., 2018). Overall, compared to nondiabetic women, those with Type 1 or Type 2 diabetes are at higher risk for urinary tract infections (Geerlings et al., 2000; Hirji, Guo, Andersson, Hammar, & Gomez-Caminero, 2012), which might explain why the association between periconceptional kidney, bladder, or urinary tract infection and sacral agenesis was closer to the null after excluding women with diabetes. We observed an elevated (aOR > 2.0), nonsignificant association between lower levels of maternal education (<13 years) and sacral agenesis, regardless of the presence of maternal diabetes. While not a direct risk factor, maternal education may be correlated with other risk factors that contribute to the development of birth defects. Studies have reported an association between lower maternal education and lower utilization of prenatal care (Stativa et al., 2014; Tsegay et al., 2013). Without prenatal care, any diseases/health conditions present during pregnancy might remain uncontrolled and/or untreated and could lead to the development of a birth defect such as sacral agenesis.

In the analysis of cases and controls whose mothers did not report diabetes, we observed positive and statistically significant crude associations between lower levels of maternal education (<16 years), periconceptional kidney, bladder, or urinary tract infection, and periconceptional smoking. In the adjusted analysis, only periconceptional smoking remained statistically significantly associated with sacral agenesis. Previous human studies have not explored the association between maternal smoking and sacral agenesis specifically. In vitro studies revealed that nicotine crosses the human placenta (Mohammadi et al., 2017) and causes restriction of blood flow (Stone, Bailey, & Khraisha, 2014) and inhibition of trophoblast differentiation (Genbacev, Bass, Joslin, & Fisher, 1995). Animal studies found that prenatal nicotine exposure had some adverse effects on bone development in mice, such as delayed ossification and reduction in the number of ossification centers (Hu et al., 2018; Paulson, Shanfeld, Prause, Iranpour, & Paulson, 1991; Seller & Bnait, 1995). Nicotine-induced oxidative stress has been suggested as a possible causal pathway for the

adverse effects of smoking during pregnancy, nevertheless, the exact pathophysiological mechanisms are yet not established (Stone et al., 2014).

Our study had some limitations. The NBDPS case definition of sacral agenesis included cases of caudal regression syndrome, without separating those anatomically and clinically different entities, which limited our capacity to study them separately. While interviewed and noninterviewed sacral agenesis cases were similar in terms of available characteristics, noninterviewed cases may have differed in terms of potential risk factors. All exposure information in NBDPS was self-reported and might be less accurate for interviews conducted well after delivery (e.g., up to 2 years after the EDD) (Reefhuis et al., 2015). Like other case–control studies, some extent of recall bias might be present in the NBDPS (Dolk, 2015). For some exposures analyzed, the small number of exposed cases created imprecise estimates with wide CIs. Also, due to the many statistical tests conducted, we would expect 5% of the associations to appear by chance alone. Nevertheless, while we identified some new associations, we confirmed well-known risk factors for sacral agenesis, such as maternal Type 1 or Type 2 diabetes. However, due to lack of clinical data we were unable to examine the variations in the risk of sacral agenesis by the levels of HbA_{1c} during pregnancy.

Our study had several strengths. The NBDPS was a population-based study well suited to examine risk factors for sacral agenesis. It had a large sample size and included participants from various geographic areas and different ethnic backgrounds (Reefhuis et al., 2015). All cases were reviewed and classified by clinical geneticists using a standard case definition (Rasmussen et al., 2003). The study by Cogswell et al. (2009) observed that the NBDPS controls were representative of the source population from which they were selected. The exposure information was collected by trained interviewers using a standardized approach for mothers of both cases and controls (Reefhuis et al., 2015).

5 | CONCLUSIONS

Consistent with previous literature, we observed that pre-existing maternal diabetes (Type 1 or Type 2) were strong risk factors for sacral agenesis, with higher risk among Type 1 diabetics. We also observed that periconceptional smoking was positively and significantly associated with sacral agenesis among women without diabetes. Our findings underscore the importance of smoking cessation programs among women planning pregnancy. Additionally, further understanding the role of glycemic control before and during pregnancy will be useful in designing interventions for primary prevention of sacral agenesis.

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TABLE 1

Clinical characteristics of sacral agenesis cases by maternal interview participation, National Birth Defects Prevention Study, 1997–2011

Characteristics	Non-Interviewed (*n* = 64) *n* (%)[a]	Interviewed (*n* = 110) *n* (%)[a]	Total (*N* = 174) *n* (%)[a]
Case classification			
Isolated	9 (14.1)	14 (12.7)	23 (13.2)
Multiple	52 (81.3)	90 (81.8)	142 (81.6)
Complex	3 (4.7)	6 (5.5)	9 (5.2)
Infant sex			
Male	31 (50.8)	58 (53.2)	89 (52.4)
Female	30 (49.2)	51 (46.8)	81 (47.6)
Birth outcome			
Live birth	58 (90.6)	104 (94.5)	162 (93.1)
Stillbirth/pregnancy termination	6 (9.4)	6 (5.5)	12 (6.9)
Gestational age at delivery among live births			
<32 weeks	4 (6.9)	7 (6.7)	11 (6.8)
32–36 weeks	19 (32.8)	27 (26.0)	46 (28.4)
≥37 weeks	35 (60.3)	70 (67.3)	105 (64.8)
Birth weight among live births			
<1,500 g	6 (10.3)	7 (6.7)	13 (8.0)
1,500–2,499 g	21 (36.2)	38 (36.6)	59 (36.4)
2,500–3,999 g	29 (50.0)	57 (54.8)	86 (53.1)
≥4,000 g	2 (3.5)	2 (1.9)	4 (2.5)
Plurality			
Singleton	58 (92.1)	102 (92.7)	160 (92.5)
Multiple	5 (7.9)	8 (7.3)	13 (7.5)
Birth year[b]			
1997	2 (3.1)	1 (0.9)	3 (1.7)
1998	6 (9.4)	5 (4.5)	11 (6.3)
1999	4 (6.3)	6 (5.4)	10 (5.7)
2000	0 (0)	4 (3.6)	4 (2.3)

Characteristics	Non-Interviewed (n = 64) n (%)[a]	Interviewed (n = 110) n (%)[a]	Total (N = 174) n (%)[a]
2001	2 (3.1)	7 (6.4)	9 (5.2)
2002	3 (4.7)	8 (7.3)	11 (6.3)
2003	9 (14.1)	5 (4.5)	14 (8.1)
2004	5 (7.8)	9 (8.2)	14 (8.1)
2005	1 (1.5)	16 (14.6)	17 (9.8)
2006	4 (6.3)	7 (6.4)	11 (6.3)
2007	8 (12.5)	12 (10.9)	20 (11.5)
2008	3 (4.7)	9 (8.2)	12 (6.9)
2009	7 (10.9)	8 (7.3)	15 (8.6)
2010	8 (12.5)	7 (6.4)	15 (8.6)
2011	2 (3.1)	6 (5.4)	8 (4.6)
Maternal age at delivery			
<20 years	6 (9.4)	11 (10.0)	17 (9.8)
20–34 years	52 (81.2)	88 (80.0)	140 (80.4)
≥35 years	6 (9.4)	11 (10.0)	17 (9.8)
Maternal race/ethnicity			
Non-Hispanic white	30 (46.9)	57 (51.8)	87 (50.0)
Non-Hispanic black	5 (7.8)	8 (7.3)	13 (7.5)
Hispanic	23 (35.9)	37 (33.6)	60 (34.5)
Other	6 (9.4)	8 (7.3)	14 (8.0)
Study site			
Arkansas	2 (3.1)	15 (13.6)	17 (9.8)
Califomia	9 (14.0)	21 (19.1)	30 (17.2)
Iowa	8 (12.5)	6 (5.5)	14 (8.0)
Massachusetts	4 (6.3)	10 (9.1)	14 (8.0)
New Jersey	2 (3.1)	4 (3.6)	6 (3.5)
New York	11 (17.2)	12 (10.9)	23 (13.2)
Texas	11 (17.2)	10 (9.1)	21 (12.1)
CDC/Atlanta	4 (6.3)	9 (8.2)	13 (7.5)
North Carolina	6 (9.4)	7 (6.4)	13 (7.5)
Utah	7 (10.9)	16 (14.5)	23 (13.2)

Abbreviation: CDC, Centers for Disease Control and Prevention.

[a] Numbers vary because of missing information.

[b] Data for 1997 was collected from October 1 through December 31.

TABLE 2

Distribution of selected characteristics of sacral agenesis cases and controls, National Birth Defects Prevention Study, 1997–2011[a]

Characteristics	Controls (*n* = 11,829), *n* (%)[b]	Cases (*n* = 110), *n* (%)[b]	cOR (95% CI)
Infant			
Sex			
Male	6,024 (51.0)	58 (53.2)	Ref.
Female	5,793 (49.0)	51 (46.8)	0.91 (0.63–1.33)
Gestational age at delivery among live births			
<32 weeks	159 (1.3)	7 (6.7)	6.72 (3.04–14.9)
32–36 weeks	940 (8.0)	27 (26.0)	4.39 (2.80–6.87)
≥37 weeks	10,691 (90.7)	70 (67.3)	Ref.
Plurality			
Singleton	11,452 (97.0)	102 (92.7)	Ref.
Multiple	351 (3.0)	8 (7.3)	2.56 (1.24–5.30)
Season of conception			
Spring (March–May)	2,897 (24.5)	29 (26.3)	0.99 (0.59–1.64)
Summer (June–August)	2,944 (24.9)	30 (27.3)	1.01 (0.61–1.66)
Autumn (September–November)	3,057 (25.8)	31 (28.2)	Ref.
Winter (December–February)	2,931 (24.8)	20 (18.2)	0.67 (0.38–1.18)
Positive family history			
No	11,829 (100.0)	109 (99.1)	–
Yes	0	1 (0.9)	–
Maternal			
Age at delivery			
<20 years	1,177 (9.9)	11 (10.0)	0.96 (0.51–1.79)
20–34 years	8,988 (76.0)	88 (80.0)	Ref.
≥35 years	1,664 (14.1)	11 (10.0)	0.68 (0.36–1.27)
Race/ethnicity			
Non-Hispanic white	6,836 (57.8)	57 (51.8)	Ref.
Non-Hispanic black	1,308 (11.1)	8 (7.3)	0.73 (0.35–1.54)
Hispanic	2,908 (24.6)	37 (33.6)	1.53 (1.01–2.31)

Characteristics	Controls (n = 11,829), n (%)[b]	Cases (n = 110), n (%)[b]	cOR (95% CI)
Other	770 (6.5)	8 (7.3)	1.25 (0.59–2.62)
Education			
<12 years	1905 (16.6)	28 (25.9)	4.27 (2.21–8.26)
12 years	2,725 (23.7)	35 (32.4)	3.73 (1.97–7.06)
13–15 years	3,079 (26.8)	32 (29.6)	3.02 (1.58–5.76)
≥16 years	3,775 (32.9)	13 (12.1)	Ref.
Birth place			
Foreign born	2,392 (20.8)	27 (25.0)	1.27 (0.82–1.97)
U.S. born	9,102 (79.2)	81 (75.0)	Ref.
Body mass index			
<25 kg/m^2	6,644 (58.9)	48 (48.0)	Ref.
≥25 kg/m^2	4,631 (41.1)	52 (52.0)	1.55 (1.05–2.31)
Pregnancy intention			
Wanted to be pregnant	7,101 (64.4)	55 (55.6)	Ref.
Wanted to wait until later	1963 (17.8)	23 (23.2)	1.51 (0.93–2.47)
Did not want to be pregnant	1,114 (10.1)	11 (11.1)	1.28 (0.67–2.44)
Did not care	844 (7.7)	10 (10.1)	1.53 (0.78–3.01)
Previous miscarriage			
No	9,105 (77.3)	73 (66.4)	Ref.
Yes	2,673 (22.7)	37 (33.6)	1.73 (1.16–2.57)
Infertility treatment[c,d]			
No	10,966 (95.5)	103 (96.3)	Ref.
Yes	515 (4.5)	4 (3.7)	0.83 (0.22–2.20)
Parity			
0	4,614 (39.2)	41 (37.3)	Ref.
1	3,836 (32.6)	32 (29.1)	0.94 (0.59–1.49)
≥2	3,328 (28.2)	37 (33.6)	1.25 (0.80–1.96)
Diabetes[e]			
Pre-existing Type 1 diabetes	31 (0.3)	20 (19.2)	107.6 (58.3–198.6)
Pre-existing Type 2 diabetes	40 (0.4)	13 (12.5)	54.2 (27.7–106.1)

Characteristics	Controls (*n* = 11,829), *n* (%)[b]	Cases (*n* = 110), *n* (%)[b]	cOR (95% CI)
Gestational diabetes	536 (4.7)	6 (5.8)	1.87 (0.81–4.33)
No diabetes	10,840 (94.7)	65 (62.5)	Ref.
Hypertension during pregnancy			
No	10,503 (90.5)	89 (80.9)	Ref.
Yes	1,109 (9.5)	21 (19.1)	2.24 (1.38–3.61)
Periconceptional respiratory illness[f]			
No	8,475 (75.1)	89 (80.9)	Ref.
Yes	2,803 (24.9)	21 (19.1)	0.71 (0.44–1.15)
Periconceptional fever[f]			
No	8,902 (82.8)	77 (76.2)	Ref.
Yes	1853 (17.2)	24 (23.8)	1.50 (0.94–2.37)
Periconceptional kidney, bladder, or urinary tract infection[f]			
No	10,758 (92.5)	91 (84.3)	Ref.
Yes	872 (7.5)	17 (15.7)	2.31 (1.37–3.89)
Periconceptional sexually transmitted infection[c,f]			
No	11,553 (98.5)	107 (97.3)	Ref.
Yes	178 (1.5)	3 (2.7)	1.82 (0.37–5.55)
Folic acid containing supplement use[g]			
No	5,507 (47.2)	58 (52.7)	1.25 (0.86–1.82)
Yes	6,165 (52.8)	52 (47.3)	Ref.
Periconceptional antifolate medication use[c,f]			
No	11,482 (98.9)	107 (97.3)	Ref.
Yes	122 (1.1)	3 (2.7)	2.64 (0.53–8.10)
Periconceptional vasoactive medication use[f]			
No	7,680 (67.0)	64 (59.8)	Ref.
Yes	3,778 (33.0)	43 (40.2)	1.37 (0.93–2.01)
Periconceptional antihypertensive medication use[f]			
No	10,447 (98.8)	88 (94.6)	Ref.
Yes	124 (1.2)	5 (5.4)	4.79 (1.91–12.0)

Characteristics	Controls (*n* = 11,829), *n* (%)[b]	Cases (*n* = 110), *n* (%)[b]	cOR (95% CI)
Periconceptional binge drinking[f,h]			
No	9,998 (87.5)	97 (90.6)	Ref.
Yes	1,431 (12.5)	10 (9.4)	0.72 (0.38–1.39)
Periconceptional smoking[f]			
No	9,454 (82.0)	78 (72.9)	Ref.
Yes	2075 (18.0)	29 (27.1)	1.69 (1.10–2.60)
Periconceptional recreational drug use[f]			
No	11,009 (95.6)	101 (93.5)	Ref.
Yes	501 (4.4)	7 (6.5)	1.52 (0.70–3.29)
Study site			
Arkansas	1,471 (12.4)	15 (13.6)	0.61 (0.32–1.20)
California	1,263 (10.7)	21 (19.1)	Ref.
Iowa	1,300 (11.0)	6 (5.5)	0.28 (0.11–0.69)
Massachusetts	1,402 (11.8)	10 (9.1)	0.43 (0.20–0.91)
New Jersey	578 (4.9)	4 (3.6)	0.42 (0.14–1.22)
New York	989 (8.4)	12 (10.9)	0.73 (0.36–1.49)
Texas	1,416 (12.0)	10 (9.1)	0.43 (0.20–0.91)
CDC/Atlanta	1,267 (10.7)	9 (8.2)	0.43 (0.20–0.94)
North Carolina	1,016 (8.6)	7 (6.4)	0.41 (0.18–0.98)
Utah	1,127 (9.5)	16 (14.5)	0.85 (0.44–1.64)
	Mean (*SD*)	Mean (*SD*)	
Maternal age (years)	27.7 (6.1)	26.7 (5.7)	0.97 (0.94–1.00)

Abbreviations: CDC, Centers for Disease Control and Prevention; CI, confidence interval; cOR, crude odds ratio; SD, standard deviation.

[a] Cases and controls of interviewed mothers.

[b] Numbers vary because of missing information.

[c] Exact confidence intervals computed.

[d] Surgical procedures for current pregnancy, use of fertility medications or other fertility procedures in the two months before current pregnancy.

[e] Gestational diabetes includes women diagnosed during the current pregnancy only. The reference group includes women without pre-existing (Type 1 or Type 2) or gestational diabetes.

[f] One month prior through the third month of pregnancy.

[g] One month prior through the first month of pregnancy.

[h] Four or more drinks per occasion.

TABLE 3

Multivariable analysis for potential risk factors and sacral agenesis, National Birth Defects Prevention Study, 1997–2011

Characteristics[a]	Controls (*n* = 11,829), *n* (%)	Cases (*n* = 110), *n* (%)	aOR (95% CI)
Plurality			
Singleton	11,452 (97.0)	102 (92.7)	Ref.
Multiple	351 (3.0)	8 (7.3)	**3.22 (1.10–9.43)**
Race/ethnicity			
Non-Hispanic white	6,836 (57.8)	57 (51.8)	Ref.
Non-Hispanic black	1,308 (11.1)	8 (7.3)	0.53 (0.19–1.45)
Hispanic	2,908 (24.6)	37 (33.6)	1.15 (0.61–2.18)
Other	770 (6.5)	8 (7.3)	1.05 (0.40–2.75)
Education			
<12 years	1905 (16.6)	28 (25.9)	2.01 (0.74–5.50)
12 years	2,725 (23.7)	35 (32.4)	2.27 (0.97–5.33)
13–15 years	3,079 (26.8)	32 (29.6)	1.77 (0.78–4.05)
≥16 years	3,775 (32.9)	13 (12.1)	Ref.
Body mass index			
<25 kg/m^2	6,644 (58.9)	48 (48.0)	Ref.
≥25 kg/m^2	4,631 (41.1)	52 (52.0)	0.84 (0.49–1.45)
Previous miscarriage			
No	9,105 (77.3)	73 (66.4)	Ref.
Yes	2,673 (22.7)	37 (33.6)	1.68 (0.97–2.89)
Diabetes[b]			
Pre-existing Type 1 diabetes	31 (0.3)	20 (19.2)	**96.6 (43.5–214.7)**
Pre-existing Type 2 diabetes	40 (0.4)	13 (12.5)	**45.0 (16.9–119.8)**
Gestational diabetes	536 (4.7)	6 (5.8)	0.46 (0.06–3.37)
No diabetes	10,840 (94.7)	65 (62.5)	Ref.
Hypertension during pregnancy			
No	10,503 (90.5)	89 (80.9)	Ref.
Yes	1,109 (9.5)	21 (19.1)	1.41 (0.39–5.07)
Periconceptional fever[c]			

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Characteristics[a]	Controls (*n* = 11,829), *n* (%)	Cases (*n* = 110), *n* (%)	aOR (95% CI)
No	8,902 (82.8)	77 (76.2)	Ref.
Yes	1853 (17.2)	24 (23.8)	0.99 (0.39–2.52)
Periconceptional kidney, bladder, or urinary tract infection[c]			
No	10,758 (92.5)	91 (84.3)	Ref.
Yes	872 (7.5)	17 (15.7)	2.27 (0.80–6.47)
Periconceptional vasoactive medication use[c]			
No	7,680 (67.0)	64 (59.8)	Ref.
Yes	3,778 (33.0)	43 (40.2)	1.46 (0.87–2.46)
Periconceptional smoking[c]			
No	9,454 (82.0)	78 (72.9)	Ref.
Yes	2075 (18.0)	29 (27.1)	1.48 (0.82–2.67)
	Mean (*SD*)	Mean (*SD*)	
Maternal age (years)	27.7 (6.1)	26.7 (5.7)	0.97 (0.92–1.02)

Note: Bold font indicates a statistically significant finding.

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; SD, standard deviation.

[a]Exposures with crude Wald *p* value <.15 and at least five exposed cases were included in the multivariable logistic regression analysis.

[b]Gestational diabetes includes women diagnosed during the current pregnancy only. The reference group includes women without pre-existing (Type 1 or Type 2) or gestational diabetes.

[c]One month prior through the third month of pregnancy.

TABLE 4

Distribution of selected characteristics of sacral agenesis cases and control infants of women without diabetes, National Birth Defects Prevention Study, 1997–2011

Characteristics	Controls (*n* = 10,840), *n* (%)[a]	Cases (*n* = 65), *n* (%)[a]	cOR (95% CI)
Infant			
Sex			
Male	5,528 (51.0)	37 (56.9)	Ref.
Female	5,304 (49.0)	28 (43.1)	0.79 (0.48–1.29)
Gestational age at delivery among live births			
<32 weeks	142 (1.3)	2 (3.2)	–
32–36 weeks	833 (7.7)	12 (19.1)	–
≥37 weeks	9,831 (91.0)	49 (77.8)	–
Plurality[b]			
Singleton	10,513 (97.1)	61 (93.9)	Ref.
Multiple	312 (2.9)	4 (6.2)	2.21 (0.58–6.01)
Season of conception			
Spring (March–May)	2,656 (24.5)	15 (23.1)	0.80 (0.41–1.56)
Summer (June–August)	2,713 (25.0)	20 (30.8)	1.04 (0.56–1.93)
Autumn (September–November)	2,815 (26.0)	20 (30.8)	Ref.
Winter (December–February)	2,656 (24.5)	10 (15.4)	0.53 (0.25–1.13)
Maternal			
Age at delivery			
<20 years	1,127 (10.4)	9 (13.9)	1.29 (0.63–2.63)
20–34 years	8,251 (76.1)	51 (78.5)	Ref.
≥35 years	1,462 (13.5)	5 (7.7)	0.55 (0.22–1.39)
Race/ethnicity[b]			
Non-Hispanic white	6,376 (58.9)	41 (63.1)	Ref.
Non-Hispanic black	1,207 (11.1)	5 (7.7)	0.64 (0.20–1.63)
Hispanic	2,573 (23.8)	15 (23.1)	0.91 (0.47–1.68)
Other	678 (6.3)	4 (6.2)	0.92 (0.24–2.55)
Education			

Characteristics	Controls (n = 10,840), n (%)[a]	Cases (n = 65), n (%)[a]	cOR (95% CI)
<12 years	1,723 (16.3)	15 (23.4)	3.08 (1.38–6.88)
12 years	2,489 (23.5)	18 (28.1)	2.56 (1.18–5.56)
13–15 years	2,820 (26.7)	21 (32.8)	2.64 (1.24–5.61)
≥16 years	3,542 (33.5)	10 (15.6)	Ref.
Birth place			
Foreign born	2,114 (20.0)	15 (23.4)	1.23 (0.69–2.19)
U.S. Born	8,470 (80.0)	49 (76.6)	Ref.
Body mass index			
<25 kg/m^2	6,305 (60.6)	38 (62.3)	Ref.
≥25 kg/m^2	4,098 (39.4)	23 (37.7)	0.93 (0.55–1.57)
Pregnancy intention			
Wanted to be pregnant	6,533 (64.4)	34 (55.7)	Ref.
Wanted to wait until later	1833 (18.1)	14 (23.0)	1.47 (0.79–2.74)
Did not want to be pregnant	1,012 (10.0)	5 (8.2)	0.95 (0.37–2.43)
Did not care	761 (7.5)	8 (13.1)	2.02 (0.93–4.38)
Parity			
0	4,375 (40.4)	26 (40.0)	Ref.
1	3,524 (32.6)	18 (27.7)	0.86 (0.47–1.57)
≥2	2,925 (27.0)	21 (32.3)	1.21 (0.68–2.15)
Previous miscarriage			
No	8,434 (77.9)	47 (72.3)	Ref.
Yes	2,390 (22.1)	18 (27.7)	1.35 (0.78–2.33)
Infertility treatment[b,c]			
No	10,094 (95.6)	58 (93.6)	Ref.
Yes	461 (4.4)	4 (6.5)	1.51 (0.40–4.11)
Hypertension during pregnancy			
No	9,753 (91.1)	58 (89.2)	Ref.
Yes	951 (8.9)	7 (10.8)	1.24 (0.56–2.72)
Periconceptional respiratory illness[d]			
No	7,810 (75.2)	50 (76.9)	Ref.

Characteristics	Controls (n = 10,840), n (%)[a]	Cases (n = 65), n (%)[a]	cOR (95% CI)
Yes	2,577 (24.8)	15 (23.1)	0.91 (0.51–1.62)
Periconceptional fever[d]			
No	8,215 (83.0)	46 (75.4)	Ref.
Yes	1,681 (17.0)	15 (24.6)	1.59 (0.89–2.86)
Periconceptional kidney, bladder, or urinary tract infection[d]			
No	9,931 (92.6)	55 (85.9)	Ref.
Yes	791 (7.4)	9 (14.1)	2.06 (1.01–4.17)
Periconceptional sexually transmitted infection[d]			
No	10,645 (98.5)	63 (96.9)	–
Yes	161 (1.5)	2 (3.1)	–
Folic acid containing supplement use[e]			
No	5,064 (47.1)	29 (44.6)	0.91 (0.55–1.48)
Yes	5,688 (52.9)	36 (55.4)	Ref.
Periconceptional antifolate medication use[d]			
No	10,580 (99.0)	64 (98.5)	–
Yes	107 (1.0)	1 (1.5)	–
Periconceptional vasoactive medication use[d]			
No	7,067 (67.0)	36 (57.1)	Ref.
Yes	3,484 (33.0)	27 (42.9)	1.52 (0.92–2.51)
Periconceptional antihypertensive medication use[d]			
No	9,705 (99.1)	58 (100.0)	–
Yes	92 (0.9)	0	–
Periconceptional binge drinking[d,f]			
No	9,188 (87.3)	57 (89.1)	Ref.
Yes	1,334 (12.7)	7 (10.9)	0.85 (0.39–1.86)
Periconceptional smoking[d]			
No	8,698 (81.9)	40 (63.5)	Ref.
Yes	1918 (18.1)	23 (36.5)	2.61 (1.56–4.37)

Characteristics	Controls (*n* = 10,840), *n* (%)[a]	Cases (*n* = 65), *n* (%)[a]	cOR (95% CI)
Periconceptional recreational drug use[b,d]			
No	10,126 (95.6)	60 (93.8)	Ref.
Yes	472 (4.5)	4 (6.3)	1.43 (0.38–3.88)
Study site			
Arkansas	1,358 (12.5)	10 (15.4)	1.05 (0.42–2.68)
California	1,145 (10.6)	8 (12.3)	Ref.
Iowa	1,183 (10.9)	3 (4.6)	0.36 (0.10–1.37)
Massachusetts	1,318 (12.2)	7 (10.8)	0.76 (0.28–2.10)
New Jersey	558 (5.2)	4 (6.2)	1.03 (0.31–3.42)
New York	902 (8.3)	10 (15.4)	1.59 (0.62–4.04)
Texas	1,258 (11.6)	3 (4.6)	0.34 (0.09–1.29)
CDC/Atlanta	1,150 (10.6)	5 (7.7)	0.62 (0.20–1.91)
North Carolina	913 (8.4)	6 (9.2)	0.94 (0.33–2.72)
Utah	1,055 (9.7)	9 (13.9)	1.22 (0.47–3.18)
	Mean (*SD*)	Mean (*SD*)	
Maternal age (years)	27.5 (6.1)	26.0 (5.6)	0.96 (0.92–1.00)

Abbreviations: CDC, Centers for Disease Control and Prevention; CI, confidence interval; cOR, crude odds ratio; SD, standard deviation.

[a] Numbers vary because of missing information. Percentages do not sum to 100, because of rounding.

[b] Exact confidence intervals computed.

[c] Surgical procedures for current pregnancy, use of fertility medications or other fertility procedures in the 2 months before current pregnancy.

[d] One month prior through the third month of pregnancy.

[e] One month prior through the first month of pregnancy.

[f] Four or more drinks per occasion.

TABLE 5

Multivariable analysis for potential risk factors and sacral agenesis among women without diabetes, National Birth Defects Prevention Study, 1997–2011

Characteristics[a]	**Controls (*n* = 10,840), *n* (%)**	**Cases (*n* = 65), *n* (%)**	**aOR (95% CI)**
Education			
<12 years	1,723 (16.3)	15 (23.4)	2.43 (0.94–6.28)
12 years	2,489 (23.5)	18 (28.1)	1.90 (0.77–4.65)
13–15 years	2,820 (26.7)	21 (32.8)	2.12 (0.93–4.87)
≥16 years	3,542 (33.5)	10 (15.6)	Ref.
Periconceptional fever[b]			
No	8,215 (83.0)	46 (75.4)	Ref.
Yes	1,681 (17.0)	15 (24.6)	1.21 (0.52–2.85)
Periconceptional kidney, bladder, or urinary tract infection[b]			
No	9,931 (92.6)	55 (85.9)	Ref.
Yes	791 (7.4)	9 (14.1)	1.52 (0.54–4.29)
Periconceptional vasoactive medication use[b]			
No	7,067 (67.0)	36 (57.1)	Ref.
Yes	3,484 (33.0)	27 (42.9)	1.57 (0.92–2.67)
Periconceptional smoking[b]			
No	8,698 (81.9)	40 (63.5)	Ref.
Yes	1918 (18.1)	23 (36.5)	**1.85 (1.05–3.24)**
	Mean (*SD*)	Mean (*SD*)	
Maternal age (years)	27.5 (6.1)	26.0 (5.6)	0.98 (0.93–1.03)

Note: Bold font indicates a statistically significant finding.

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; SD, standard deviation.

[a]Exposures with crude Wald *p* value <.15 and at least five exposed cases were included in the multivariable logistic regression analysis.

[b]One month prior through the third month of pregnancy.