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Authors
Yazdy, Mahsa M
Werler, Martha M
Feldkamp, Marcia L
et al.

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Spatial analysis of gastroschisis in the National Birth Defects Prevention Study

Mahsa M. Yazdy[a], **Martha M. Werler**[a], **Marcia L. Feldkamp**[b], **Gary M Shaw**[c], **Bridget S. Mosley**[d], **Veronica M. Vieira**[e], and **The National Birth Defects Prevention Study**

[a]Slone Epidemiology Center at Boston University, Boston, Massachusetts

[b]Department of Pediatrics, University of Utah School of Medicine, Salt Lake City, UT

[c]Stanford University, Stanford, California

[d]Department of Pediatrics, College of Medicine, University of Arkansas for Medical Sciences, Arkansas Children's Hospital Research Institute, Little Rock, Arkansas

[e]Program in Public Health, University of California, Irvine, California

Abstract

Background—Gastroschisis is a birth defect where loops of bowel are protruding from the abdominal wall at birth. Previous research has suggested that gastroschisis cases can occur in clusters. The objective of this study was to identify if there were areas of elevated gastroschisis risk using data from the National Birth Defects Prevention Study (NBDPS), 1997 through 2007.

Methods—We obtained data on cases (n=371) through population-based birth defects surveillance systems in Arkansas, California, and Utah; controls (n=2,359) were selected from the same geographic areas as cases. Mothers were interviewed on demographic information and exposures during pregnancy, including residential history. We used first trimester maternal addresses and generalized additive models to create a continuous map surface of odds ratios (OR) by smoothing over latitude and longitude. Permutation tests were used to assess whether location of maternal residence was important and identify locations with statistically significant ORs.

Results—In Arkansas, adjusted ORs in the southwest corner were 2.0 and the global deviance was not statistically significant (p-value: 0.57). Adjusted ORs for California indicated areas of increased risk with ORs 1.3 (p-value: 0.34). In Utah, the adjusted ORs were elevated (OR: 2.4) in the south-eastern corner of the study area (p-value: 0.34).

Conclusion—The results of this study, while not statistically significant, suggest there were spatial variations in gastroschisis births. We cannot rule out that these variations were due to edge effects or residual confounding.

Keywords

Gastroschisis; Congenital Abnormalities; Spatial Analysis

Corresponding author (present address): Mahsa M Yazdy, Channing Division of Network Medicine, Brigham and Women's Hospital, Harvard Medical School, 181 Longwood Ave, Boston, MA 02115, Telephone: 617-525-0399, Fax: 617-525-2578, mahsa.yazdy@channing.harvard.edu.

Introduction

Gastroschisis is a rare malformation where intestinal loops herniate through the abdominal wall of the fetus in the first trimester of pregnancy.(Sadler, 2011) Gastroschisis often occurs in the absence of other structural defects and is rarely associated with chromosomal anomalies or syndromes.(Salihu and others, 2003; Williams and others, 2005) In addition, the recurrence risk is small and the concordance risk in monozygotic twins is low,(Bugge and others, 1994; Torfs and Curry, 1993) suggesting genetics does not play a large role in the etiology of gastroschisis.

The prevalence of gastroschisis is approximately 1 per 2,700 in the US,(Canfield and others, 2006) with the highest prevalence among teenage mothers (1 per 800).(Feldkamp and others, 2008; Salemi and others, 2009) The prevalence has been found to be increasing over time both in the US and internationally.(Alvarez and Burd, 2007; Collins and others, 2007; Hougland and others, 2005; Laughon and others, 2003; Srivastava and others, 2009) Studies have indicated that the increasing prevalence is occurring more so among younger mothers. (Chabra and others, 2011; Kilby, 2006; Kirby and others, 2013; Vu and others, 2008) Additionally, studies have reported clustering of gastroschisis by geography and time, (Chabra and Hall, 2008; Elliott and others, 2009; Friedman and others, 2006; Lynberg and others, 1992; Root and others, 2009; Werler and others, 2002) suggesting that environmental factors such as infectious or toxic factors may underlie the etiologies of gastroschisis.

The objective of this study was to use rigorous systematic methods to identify if there were spatial areas of elevated gastroschisis risk using data from a large population based case-control study.

Methods

Study data

The National Birth Defects Prevention Study (NBDPS) is an ongoing multi-site population based case-control study. The goal of the study is to identify environmental and genetic risk factors for birth defects. Over 35 structural birth defects were ascertained, including gastroschisis. The study included 10 study centers; however, for the present analysis only data from Arkansas, California, and Utah were used owing to the unavailability of geocoded data from the other centers. Cases were ascertained from the birth defect surveillance systems; prenatally diagnosed and electively terminated cases were included. Live-born infants with no major structural malformations were chosen as controls to represent the underlying population that gave rise to the cases. Controls were selected from birth certificates (Arkansas [2000–2007] and Utah) and birth hospitals (Arkansas [1997–1999], California).(Canfield and others, 2009; Robitaille and others, 2009; Yoon and others, 2001) In Arkansas and California, the present analysis was comprised of cases and controls born from 1997 through 2007. Utah joined the NBDPS in 2003; therefore, cases and controls were selected among births from 2003 through 2007. The NBDPS catchment area for Arkansas and Utah include the entire state. In California the catchment area is located in the San Joaquin Valley and is comprised of Fresno, Kern, Kings, Madera, Merced, San Joaquin,

Stanislaus, and Tulare counties; these counties represent 13% of the birth population in California.

Mothers of case and control infants were contacted and interviewed in English or Spanish within 6 weeks to two years after the estimated due date (EDD) to ascertain demographic data and exposures during pregnancy, including illness history, medication use, occupational history, and residential history. Participation for the interview was 67% for gastroschisis case mothers and 66% for control mothers. Medical records for cases were reviewed by clinical geneticists and cases with known or strongly suspected single gene conditions or chromosome abnormalities were excluded.

In the interview mothers reported their residential addresses from 3 months before pregnancy until delivery. Since multiple residences could be reported, the residence at the midpoint of the first trimester was chosen for this analysis. When reporting addresses, mothers were asked what month and year they started and stopped residing at an address. Since only the month and year were specified, we assigned the first of the month as the start and stop day. If the start or stop month was missing, but the year was available, two assumptions were made in an attempt to fill in the missing month. If the month the mother started residing at an address was missing and the year of residence occurred prior to the pregnancy, then the month of December was assigned to the missing start month. By assigning December to the missing month we were conservatively assuming a mother only lived at that address for one month out of the year. If the date the mother stopped living at an address was missing and the year of residence occurred after the year of her first trimester of pregnancy, then the month of January was assigned to the missing stop month, consequently only assuming 1 month of residence at that address. The addresses were assigned a latitude and longitude (i.e., geocoded) by the Agency for Toxic Substances and Disease Registry. If a mother did not report an address at the mid-point of the first trimester or resided out of state during this time period, she was excluded from the main analysis.

Spatial analysis

We used the following generalized additive model (GAM) to assess spatial clustering: logit $[p(x)] = \alpha + \gamma'z + S(x1, x2)$. The left side of the equation is the log of the disease odds, α is the intercept, z is a vector of the covariates, and $(S(x1, x2))$ is a non-parametric smoothing function, where x1 and x2 are the latitude and longitude of the maternal residence. Without the smoothing function the model reduces to an ordinary logistic regression model. A loess smoother was used, as it adjusts to changes in data density and gives more weight to nearby points and less to those further away. The percentage of data used in the smoothing process was determined by the span size. For instance, when a span size of 0.20 was used, the smoothing process would use 20% of the data around the location. In general, the use of a small span size results in increased variability (e.g., the detection of random patterns) but reduced bias, while the use of a large span size produces a smoother surfaces resulting in less variability but increased bias. To determine the optimal span size and balance the tradeoff between bias and variance, various span sizes were tested and the value that minimized the Akaike's Information Criterion was chosen as the optimal amount of smoothing.

To create the final maps, a grid was placed over the study area and grid points that fell outside the area were removed. Additionally, areas where people cannot live (e.g., large lakes) or with sparse populations were clipped from the grid. The log odds were predicted at each grid point using the GAM. In the adjusted models, the covariates were held constant and the adjusted log odds were predicted at each point. Using the entire study population as the reference, the log odds were converted to odds ratios (ORs) by dividing the log odds at each grid point by the log odds from the model without the smoothing term. The smoothing term serves as a measure of location; therefore, omitting the smoothing term results in computing the log odds for the entire study population. All modeling was performed with the MapGAM package in R and the maps were visualized using ArcGIS.(ESRI, 2011; R Development Core Team, 2009)

We conducted a global test with a null hypothesis that case status was not dependent on location. The global test compared the deviance from the model with the smoothing term to the model without the smoothing term; since the smoothing term serves as a measure of location, the comparison with and without the smoothing term serves to test the significance of location. We compared the deviance statistic to a distribution of the statistics generated under the null hypothesis. The distribution was obtained by randomly assigning a new location to each mother, under the null hypothesis that case status was not associated with location. The dataset was permutated in this manner 999 times and each time the models were re-run and the deviance statistic was calculated to obtain a distribution of deviance. A p-value cut-off of 0.05 was used to identify significant associations.

If the global test indicated that location was significant, a local test was conducted to identify areas of significantly increased or decreased odds on the map. A distribution of log odds at each grid point was calculated using the permutated data from the global test. To determine if our results were due to chance, we compared the log odds at each grid point to the distribution of log odds. All points from the main analysis that fell in the upper or lower 2.5% of the distribution were considered statistically significant.

The following covariates from the interview were assessed for confounding: maternal age, maternal race/ethnicity, maternal education, income, body mass index, first trimester alcohol use, first trimester smoking, illicit drug use anytime during pregnancy, gestational diabetes, nativity, season of conception, and total number of residences during pregnancy. The covariates were added to the model and the maps were visually inspected. If the variable changed the appearance of the map surface, it was included in the final model. In addition, if the optimal span size changed with the addition of a covariate, the variable was also considered for inclusion in the final model.

We conducted a sensitivity analysis to assess if the results of the main analysis changed when excluded mothers were added to the analysis. To identify a residence for mothers missing an address at the mid-point of the first trimester, all reported addresses were examined and the address closest in time to the mid-point of the first trimester was chosen for the sensitivity analysis.

Results

A total of 371 case and 2,361 control mothers had geocoded in-state addresses and were included in the main analysis. Compared to case mothers, control mothers were more likely to be older, more educated, obese, multiparous, and less likely to smoke or use illicit drugs during pregnancy (Table 1). In addition, control mothers reported a longer average residence at the address used in the analysis than case mothers (44.9 and 33.2 months, respectively); the same pattern of longer residence for controls was observed for mothers < 25 years of age (33.0% and 40.6%, respectively) and mothers ≥25 years of age (33.8% and 48.2%, respectively).

Arkansas

A total of 198 (16.4%) mothers were excluded from the analysis due to not reporting an address at the mid-point of the first trimester (27 cases and 141 controls) or residing out of state (7 cases and 23 controls), resulting in a total of 100 cases and 907 controls used in the spatial analysis. The cases and controls represented births from January 1998 through December 2007. In Arkansas the NBDPS catchment area encompasses the entire state and the spatial distribution of mothers' residences can be seen in Figure 1A. To preserve confidentiality the location of the maternal residences were altered in the point data maps but in all analyses the exact locations were used.

The spatial analysis revealed elevated crude ORs in the southwest corner of the state, with the highest ORs equaling 2.2 (p-value: 0.48; span size: 0.95) (Figure 1B). After adjustment for maternal age and race/ethnicity, predicted ORs for a non-Hispanic white woman ≥25 years of age in the southwest corner were attenuated to 2.0 and the global deviance remained non-statistically significant (p-value: 0.57; span size: 0.95) (Figure 1C). For the sensitivity analysis, alternate addresses were identified for 45 mothers that were missing addresses at the midpoint of the first trimester. These mothers were added to the sensitivity analysis, along with the 30 mothers that resided out of state. The addition of the 75 mothers resulted in an attenuation of the predicted ORs in the southwest corner of the state (maximum OR: 1.2; p-value: 0.07; span size: 0.95) (Figure 1D).

California

In California, 158 (12.7%) mothers were excluded from the analysis due to not reporting an address at the mid-point of the first trimester (20 cases and 112 controls) or residing out of state (2 cases and 24 controls), resulting in a total of 193 cases and 892 controls. Due to the geography of this area and sparse population, the prediction grid was clipped to exclude the mountains in the east and western region of the catchment area. The distribution of mothers' residences can be seen in Figure 2A and the counties included in the catchment area are outlined. To determine the optimal span size for the models, only data from the 8 counties were used. Once the optimal span size was determined, all the data were used in the final models (i.e. California mothers that resided outside the catchment area in the first trimester were included in the modeling).

The results of the crude spatial analysis indicated a slight elevation in risk along the eastern and western borders of the study area (Figure 2B), with the maximum predicted ORs at 1.3 (p-value: 0.27; span-size: 0.95). After adjustment for maternal age and race/ethnicity the maximum predicted ORs did not change (maximum OR: 1.3) and the pattern of risk did not change substantially (p-value: 0.34; span-size: 0.85) (Figure 2C). A total of 83 mothers were included in the sensitivity analysis (57 with alternate addresses and 26 out of state mothers). Seven of the out of state mothers resided on the east coast at the mid-point of the first trimester, due to the large distance between the modeling area and these addresses, the model would not converge; therefore, for these seven mothers in-state addresses were chosen from their residential history. The predicted ORs were attenuated on the western portion of the study area in the sensitivity analysis, however the maximum predicted OR did not change and remained at 1.3 (p-value: 0.36; span-size: 0.85) (Figure 2D).

Utah

In this center, 64 (9.0%) mothers were excluded from the analysis due to not reporting an address at the mid-point of the first trimester (6 cases and 35 controls) or residing out of state (2 cases and 21 controls). A total of 78 cases and 562 controls were used in the spatial analysis.

The NBDPS catchment area in Utah included the entire state; however, the spatial analysis was restricted to the geographic area around Salt Lake Valley where the majority of the population resided (Figure 3A). The grid was clipped to exclude the lakes around Salt Lake Valley as well as the southern part of the state and the mountains in the east due to sparse population. Removing these points ensured the model was not predicting ORs for locations where no one resided. Data from the 5 counties around Salt Lake City that contained the clipped grid were utilized to determine the optimal span size for the final models. When running the final models, all the data in the state were used to predict the ORs at each grid point. Prior to adjustment the maximum predicted OR was 2.5 (p-value: 0.61; span-size: 0.30) and after adjustment for maternal age and race/ethnicity there was a slight decrease in the maximum predicted OR for a non-Hispanic white woman ≥25 years of age (maximum OR: 2.4; p-value: 0.34; span-size: 0.45) (Figures 3B and 3C). For the sensitivity analysis, 38 mothers were added to the analysis. Due to issues with the model converging, out-of-state addresses were not used and instead an in-state address was chosen when available. The appearance of the map did not change substantially with the addition of the excluded mothers (maximum OR: 2.7; p-value: 0.20; span size: 0.45) (Figure 3D).

Discussion

Elevated risks were identified in all study centers, though none were statistically significant. In Arkansas, elevated risks of 2.0 were identified around Miller and Lafayette counties. The risk of gastroschisis was elevated on the north-western side of Utah Lake and on the eastern edge of Salt Lake City, with adjusted ORs of 2.4. In California, a slight elevated risk of gastroschisis (OR=1.3) was observed along the eastern and western edges of the study area.

One explanation for the observed spatial variation in gastroschisis risk is the possibility of residual confounding. While we examined a number of potential confounding factors, it is

possible that confounding from unmeasured variables exists. We also cannot rule out the possibility that the elevated ORs along the edges of the prediction grid were the result of edge effects. Edge effects often occur with cluster detection methods, including GAMs, and arise from a lack of data outside the study area. When smoothing near the boundaries of a study area, the absence of data at the edge may lead to inaccurate estimations. There may be less concern of edge effects for states where the grids were clipped (CA and UT only), since data outside the modeling area were used in the predictions. While the possibility of this effect cannot be ruled out, a previous study using simulated data found that no edge effects were apparent when using GAMs, even when an edge was self-imposed on the data by cutting the spatial area in half.(Webster and others, 2006)

The present analysis focused solely on spatial clustering over the entire time period of the study. Due to small numbers we were not able to assess changes in spatial risk over time; therefore, our results considered changes in risk that would come from semi-static exposures over the study period. In addition, spatial patterns of gastroschisis risk have been found to vary by maternal age;(Yazdy and others, 2015) however, we were unable to stratify by maternal age due to insufficient numbers. This is a limitation of our study, as gastroschisis has been associated with environmental exposures among older mothers. Two previous studies have linked gastroschisis to atrazine, a commonly used herbicide; (Agopian and others, 2013; Waller and others, 2010) one of the studies assessed the association by maternal age and identified an OR of 2.0 (95% confidence interval (CI): 1.2, 3.3) among mothers ≥25 years and no association among younger mothers. (Agopian and others, 2013) Polycyclic aromatic hydrocarbons, which result from the incomplete combustion of organic matter, have been associated with gastroschisis only among mothers who are >20 years (OR: 2.0; 95% CI: 1.3, 5.0).(Lupo and others, 2012)

One limitation of our study was the possibility that the spatial distribution of cases and controls could have been affected by ascertainment methods and how mothers' sought obstetric care within each study area. For example, in Arkansas controls were selected from all liveborn infants delivered in an in-state hospital, while cases came from all in-state births as well as births at 2 hospitals in neighboring Texas where agreements were in place to share information on Arkansas residents. A previous paper examined the possibility of incomplete ascertainment of cases and controls in Arkansas.(Mosley and others, 2002) The authors identified the potential for underascertainment of cases along the northeastern border of the state and suggested this may be due to mothers with high risk pregnancies (such as those with a birth defect) seeking care across the border in Tennessee. Since no agreements were in place with Tennessee, these deliveries to Arkansas mothers would have been missed. If there was also underascertainment of cases along the northeastern border in the NBDPS, this may explain the decreased risks we observed around that area.

Another limitation was that we excluded mothers from the analysis who did not participate in the interviews or have geocoded addresses or mothers that resided out-of-state; we cannot rule out the possibility that the exclusion of these women may have introduced a bias. Unfortunately we did not have information on the > 30% of women who did not participate in the study to assess if they differed from study participant. The proportions of women that were excluded (due to not having a geocoded address or resided out-of-state) were similar

between cases and controls (14.7% and 13.1%, respectively, in AR, CA and UT combined), suggesting that the exclusion was non-differential. When looking at the demographics of the excluded mothers, cases were slightly more likely to be younger and both cases and controls were more likely to report a non-white race/ethnicity than those mothers included in the main analysis. For the sensitivity analyses, we were able to include some of the excluded mothers to the analyses and the interpretation of the results did not change for California and Utah. In Arkansas, however, the elevated risk area in the southwest corner of the state was attenuated with the inclusion of the excluded mothers, suggesting the elevated ORs may have been an artifact of the missing data. To assess if timing of maternal address changed the results, we also used the reported address at birth and the results did not change substantially for any of the centers (data not shown).

The NBDPS is the largest population based study with gastroschisis cases in the US. One of the strengths of using the NBDPS was the detailed maternal questionnaire, which included numerous individual level demographic and behavioral characteristics that we were able to assess as potential confounders. In addition, the information on residential history allowed us to use the residential address during the first trimester, which is the etiologically relevant time period for gastroschisis. All the cases in the NBDPS have undergone a rigorous review by a clinical geneticist to ensure they met the eligibility criteria for inclusion in the study.

The small sample size may have affected the statistical significance of our analyses. The results of this exploratory analysis found spatial variations in gastroschisis risk across all three centers. These elevated risks could be due to environmental exposures and further evaluation would be needed to assess this possibility. Additionally, the variation observed could be due to underlying artifactual or behavioral factors.

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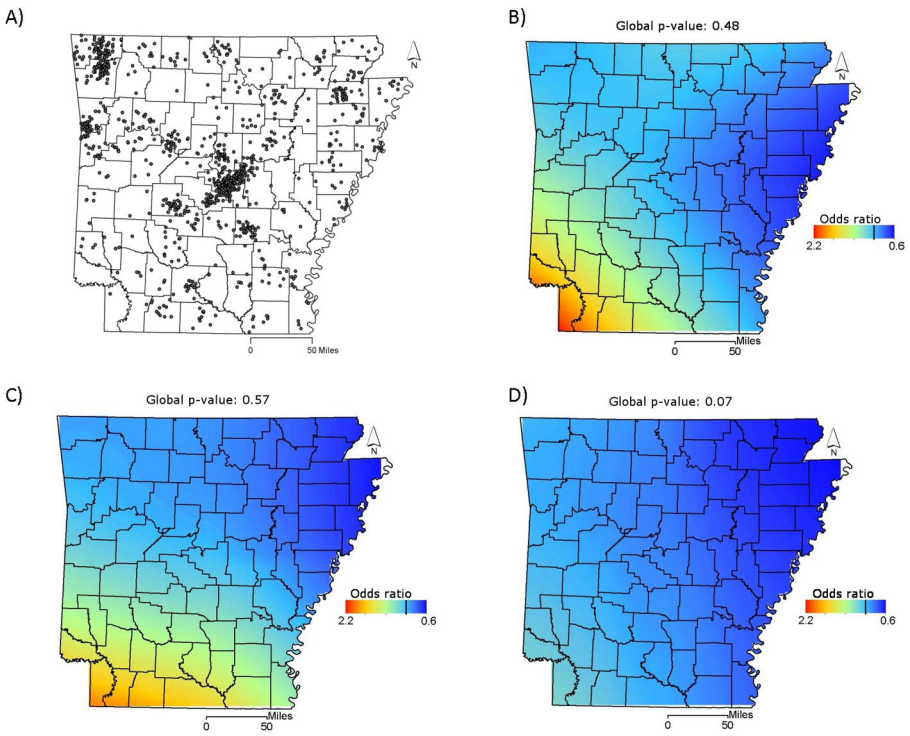

Figure 1.

Distribution of cases and controls (A); map of crude (B) and adjusted odds ratio (C); and map of sensitivity analysis including mothers with missing geocodes (D) in Arkansas, National Birth Defects Prevention Study, 1997—2007.

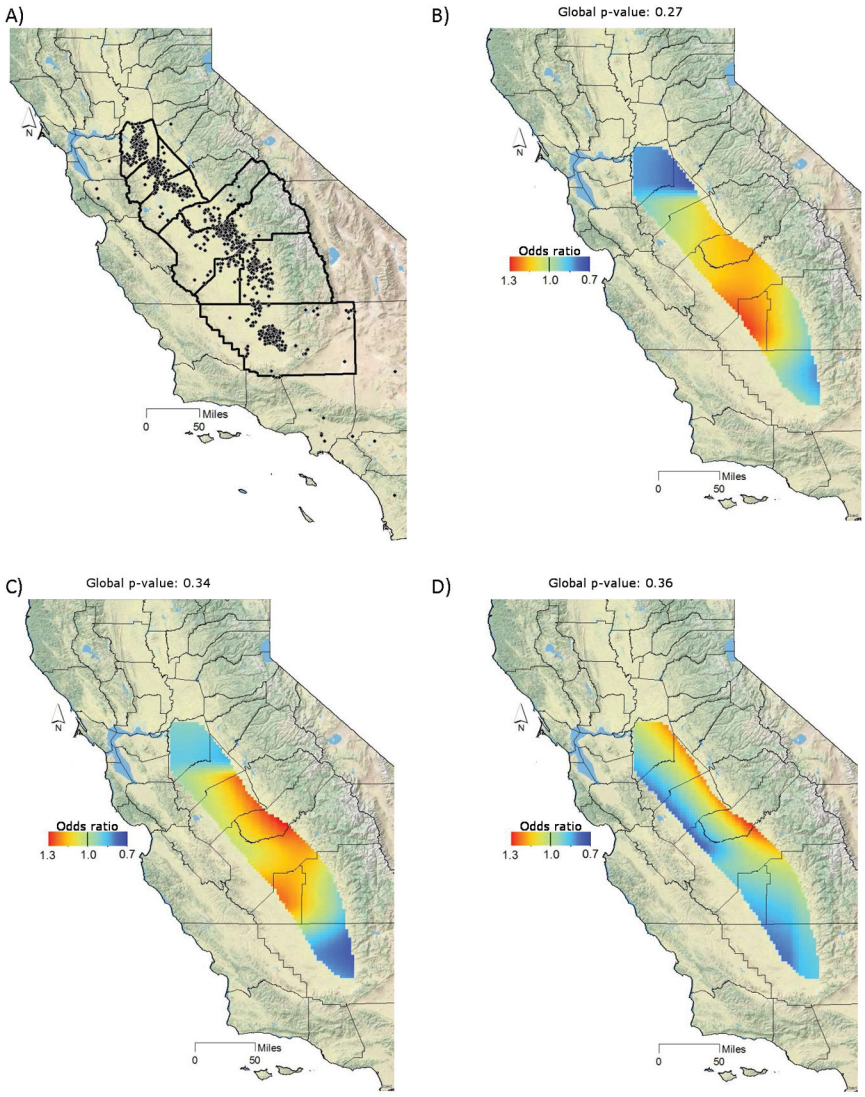

Figure 2.

Distribution of cases and controls (A); map of crude (B) and adjusted odds ratio (C); and map of sensitivity analysis including mothers with missing geocodes (D) in California, National Birth Defects Prevention Study, 1997—2007.

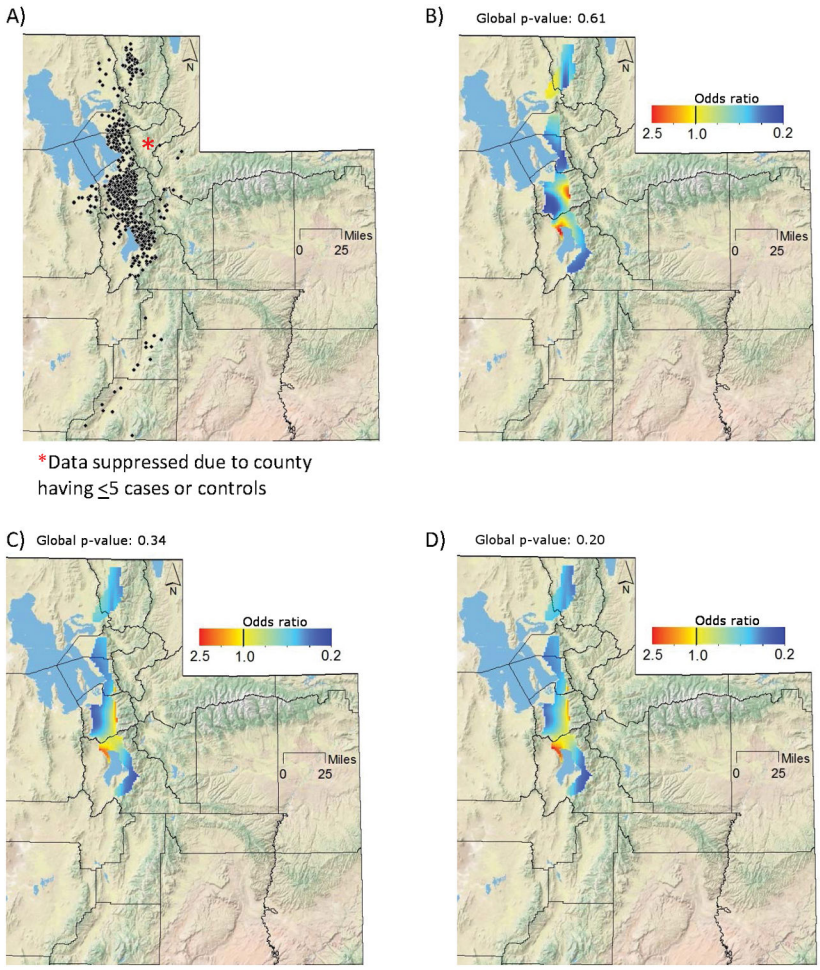

Figure 3.

Distribution of cases and controls (A); map of crude (B) and adjusted odds ratio (C); and map of sensitivity analysis including mothers with missing geocodes (D) in Utah, National Birth Defects Prevention Study, 2003—2007.

Table 1

Sociodemographic and behavioral factors for cases and controls, Arkansas, California, and Utah, 1997–2007.

	Cases	Controls
	n (%)	n (%)
Total	371 (100.0)	2361 (100.0)
Maternal age (years)		
<20	137 (36.9)	311 (13.2)
20–24	161 (43.4)	690 (29.2)
25–29	54 (14.6)	702 (29.7)
30–34	17 (4.6)	445 (18.9)
35+	2 (0.5)	213 (9.0)
Maternal education (years)		
<12 years	108 (29.1)	472 (20.0)
12 years	152 (41.0)	659 (27.9)
>12 years	109 (29.4)	1222 (51.8)
Missing	2 (0.5)	8 (0.3)
Maternal race / ethnicity		
Non-Hispanic white	188 (50.7)	1387 (58.8)
Non-Hispanic Black	14 (3.8)	223 (9.5)
Hispanic	122 (32.9)	594 (25.1)
Other	46 (12.4)	155 (6.6)
Missing	1 (0.3)	2 (0.1)
Nativity		
Born in the US	312 (84.1)	1927 (81.6)
Foreign Born	56 (15.1)	427 (18.1)
Missing	3 (0.8)	7 (0.3)
Annual household income (US dollars)		
<$10,000	110 (29.6)	487 (20.6)
$10,000–$50,000	194 (52.3)	1200 (50.8)
>$50,000	31 (8.4)	497 (21.1)
Missing	36 (9.7)	177 (7.5)
Pregnancy intention		
No / didn't care / wanted to wait	174 (46.9)	794 (33.6)
Yes	125 (33.7)	1097 (46.5)
Missing	72 (19.4)	470 (19.9)
Season of conception		
Spring	89 (24.0)	574 (24.3)
Summer	89 (24.0)	584 (24.7)
Fall	97 (26.1)	617 (26.1)
Winter	96 (25.9)	586 (24.8)
Parity		

	Cases	Controls
	n (%)	n (%)
0	249 (67.1)	892 (37.8)
1	76 (20.5)	771 (32.6)
2	33 (8.9)	415 (17.5)
3+	13 (3.5)	283 (12.0)
Body mass index (kg/m^2)		
<18.5	24 (6.5)	124 (5.3)
18.5–24.9	261 (70.4)	1195 (50.6)
25–29.9	59 (15.9)	512 (21.7)
30+	21 (5.7)	425 (18.0)
Missing	6 (1.6)	105 (4.4)
Gestational diabetes in index pregnancy		
No	368 (99.2)	2259 (95.7)
Yes	3 (0.8)	99 (4.2)
Missing	0 (0.0)	3 (0.1)
Alcohol from 1 month before pregnancy through the 3rd month of pregnancy		
No	252 (67.9)	1730 (73.3)
Yes B1–M3	119 (32.1)	618 (26.2)
Missing	0 (0.0)	13 (0.6)
Smoking from 1 month before pregnancy through the 3rd month of pregnancy		
No	259 (69.8)	1941 (82.2)
Yes B1–P3	112 (30.2)	415 (17.6)
Missing	0 (0.0)	5 (0.2)
Drug use from 3 months before pregnancy through the end of pregnancy		
No	312 (84.1)	2222 (94.1)
Yes	59 (15.9)	139 (5.9)
Gestational diabetes in index pregnancy		
No	368 (99.2)	2259 (95.7)
Yes	3 (0.8)	99 (4.2)
Missing	0 (0.0)	3 (0.1)
Number of residential addresses reported from 3 months before pregnancy through the end of pregnancy		
1	167 (45.0)	1636 (69.4)
2	144 (38.8)	574 (24.3)
3+	60 (16.2)	150 (6.3)
Missing	0 (0.0)	1 (0.0)
Study center		
Arkansas	100 (27.0)	907 (38.4)
California	193 (52.0)	892 (37.8)
Utah	78 (21.0)	562 (23.8)