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Spatial analysis of gastroschisis in Massachusetts and Texas

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Abstract

Purpose—Previous research has suggested gastroschisis, a congenital malformation, may be linked to environmental or infectious factors and cases can occur in clusters. The objective of this study was to identify geographic areas of elevated gastroschisis risk.

Methods—Cases of gastroschisis were identified from birth defect registries in Massachusetts and Texas. Random samples of live births were selected as controls. Generalized additive models were used to create a continuous map surface of odds ratios (OR) by smoothing over latitude and longitude. Maternal age, race/ethnicity, education, cigarette smoking, and insurance status (MA only) were assessed for confounding. We used permutation tests to identify statistically significant areas of increased risk.

Results—An area of increased risk was identified in north-central Massachusetts, but was not significant after adjustment (p-value=0.07; OR=2.0). In Texas, two statistically significant areas of increased risk were identified after adjustment (p-value=0.02; OR=1.3 and 1.2). Texas had sufficient data to assess the combination of space and time, which identified an increased risk in 2003 and 2004.

Conclusion—This study suggests there were areas of elevated gastroschisis risk in Massachusetts and Texas that cannot be explained by the risk factors we assessed. Additional exploration of underlying artifactual, environmental, infectious, or behavioral factors may further our understanding of gastroschisis.

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Keywords

Gastroschisis; Congenital Abnormalities; Spatial Analysis; Spatio-Temporal Analysis

Introduction

Gastroschisis is a rare congenital malformation where loops of bowel are protruding from the abdominal wall of an infant [1]. The recurrence risk of gastroschisis in siblings is small and concordance is low in monozygotic twins suggesting that genetics does not play a large role in the etiology of gastroschisis [2-4]. In addition, gastroschisis often occurs in the absence of other congenital anomalies and is rarely associated with chromosomal anomalies or syndromes further suggesting that environmental or infectious factors are involved [3, 5].

From 1964 to 2004 the prevalence of gastroschisis has increased 10 to 20-fold worldwide, leading some to call it a pandemic [6]. The prevalence of gastroschisis in the US is estimated to be 1 per 2,700 [7]; however, when stratified by maternal age the prevalence changes to 1 per 800 in mothers <20 years old, 1 per 1900 in 20-24 year olds, 1 per 4900 in 25-29 year olds, and 1 per 17,600 in ≥30 year olds [8, 9]. No other risk factor has consistently been associated with gastroschisis.

One possible clue in understanding the etiology of gastroschisis is that it has been observed to occur in clusters [10-15]. Only a few studies to date have used systematic methods for assessing clustering of gastroschisis. One case-control study of gastroschisis used interview data [16]. They employed an arbitrary definition of a spatio-temporal cluster (defined as at least 3 cases within a 30-day period within one study site) and found that 35% of cases occurred in a ‘cluster’. Comparing cases that occurred in a cluster to those that did not, the authors found that clustered cases had higher odds of having a fever versus non-clustered cases. Because this study was not population based, systematic identification of clusters was not possible. Another study using data from the Metropolitan Atlanta Congenital Defects Program found a temporal cluster in 1988, with 3 times more cases than expected [14]. In response, a case-control study was conducted to further assess if cocaine use could account for the cluster. However, the study was limited by small numbers (15 cases) and did not report other risk factors besides cocaine use. The third study to examine clustering of gastroschisis used the North Carolina Birth Defect Registry and a sample of controls from birth certificate data [15]. This study used the most rigorous method of any study to date utilizing cases from the entire state and individual level data to control for confounding. They identified one spatial cluster in the rural southern Piedmont area. No study to date has formally assessed the interaction of space and time for clustering of gastroschisis using population-based data.

The objective of the present study was to use rigorous systematic methods to identify areas of elevated gastroschisis risk in space and time using population-based data from Massachusetts and Texas. The different population characteristics of the two states allow us to account for social and ethnic variables that may explain underlying patterns of risk. Any remaining spatial variation may suggest hypotheses for further investigation.

Materials and Methods

Data were obtained from the Texas Birth Defects Registry and the Massachusetts Birth Defects Monitoring Program. Both data sources are population-based registries that actively ascertain cases with congenital malformations diagnosed within the first year of life. Cases included live births, stillbirths, and elective terminations (TX only). The study has been approved by the Institutional Review Board approval at Boston University, the Massachusetts Department of Public Health, and the Texas Department of State Health Services.

We conducted a case-control study, where cases with gastroschisis were identified in the birth defect registries using the modified British Pediatric Association code (756.710). In each state, a random sample of live births was selected from the state Birth Registry to serve as controls and represent the underlying population. The maternal residence at birth, as reported on the birth certificate, was used in the spatial analysis and served as a proxy for the address during early pregnancy when gastroschisis develops. Addresses in Massachusetts and Texas were geocoded by the Massachusetts Department of Public Health and the Texas Department of State Health Services, respectively. An attempt was made to geocode mothers with missing geocodes using ArcGIS[17] and Google maps. Mothers with missing geocodes or addresses that could not be geocoded (e.g. post office boxes) were excluded from the main analysis.

Spatial analysis

Generalized additive models (GAMs) were used to examine spatial and spatio-temporal clustering [18, 19]. The model used was: Logit $[p(x)] = \alpha + \gamma'z + S(x1, x2)$. The left hand side of the equation is the log of the disease odds, α is the intercept, and z is a vector of the covariates. The last term is the non-parametric smoothing function, without which the model simplifies to an ordinary logistic regression model. A bivariate smooth function (S(x1, x2)) was used to model location for the spatial analysis where x1 and x2 were the longitude and latitude. A loess smoother was used for the smoothing term because it adapts to changes in neighborhood size and weights points nearby more heavily than those further away. The span size determined the amount of data the smoother would use in the smoothing process. For example, a span size of 0.20 indicated 20% of the data closest to the point of interest would be used in the smoothing process. In a large metropolitan area, 20% of the data may correspond to a smaller geographic area; while in a rural area, where there is less data, 20% of the data may encompass a larger spatial area. The use of a larger span size results in a smoother surface with less variability but increased bias; the use of a small span size leads to increased variability and the detection of random patterns. Consequently, there is a trade-off between bias and variability in choosing a span size. To determine the optimal span size for the model, a series of span sizes were tested and the value that minimized the Akaike's Information Criterion was chosen as the final span size [19].

For the spatial analysis, a rectangular grid was overlaid on the study area. Using the spatial model, the log odds were predicted at each grid point. Adjusted log odds were predicted at each grid point by holding the covariate values constant which resulted in predicting for specific values of the covariate (e.g., predicting for non-Hispanic White women). To convert

the log odds to odds ratios (ORs), the log odds at each point in the grid was divided by the log odds of the GAM without the smoothing term (the aspatial model). Omitting the smoothing term from the model results in calculating the odds of disease over the entire study area; therefore when converting the grid points from log odds to ORs, the reference group becomes the entire study area. All modeling was performed with the MapGAM package in R [20] and the results of the analysis were exported into ArcGIS, [17] where the grids were visualized over the study area.

In Texas, there was a sufficient number of cases within each year to assess the combination of space and time. To examine space and time, the data were partitioned into one year time spans, with a 6 month overlap between each time span, and a series of maps were created for each time span. The maps were assembled into movie format, resulting in the smoothing of both space and calendar time [21].

A global test was conducted to assess if location was significant in the study area. The null hypothesis that case status was not dependent on location was tested by comparing the deviance from the model with the smoothing term to the model without the smoothing term. The smoothing term is a measure of location and therefore the comparison with and without serves to test the significance of location. Once the deviance statistic was calculated, it was compared to a distribution of deviance statistics generated under the null hypothesis. To obtain this distribution, the data were permutated by randomly re-assigning a new residential location to each participant, under the null hypothesis that case status was not associated with location. The models were re-run with the permuted data and the deviance statistic was calculated. These steps were repeated 999 times in order to create a distribution of the statistic under the null hypothesis [19]. The deviance statistic from the main analysis was compared to this distribution and a p-value less than 0.05 was determined to be a statistically significant association.

If the global test indicated that location was important, the next step was to determine where areas of significantly increased or decreased odds were located. The local test examined the pointwise departure from the null hypothesis that the map had no areas of considerably high or low log odds. We used the models fitted to the permuted datasets to generate a distribution of predicted log odds at every grid point. The results from the main analysis were compared to the distribution to assess how likely it was that the log odds from our results were due to chance. All log odds that fell into the upper or lower 2.5% of the distribution were considered statistically significant. Areas that were identified as statistically significant by the local test were denoted with black contour bands on the maps.

The following covariates obtained from the birth certificates were assessed for confounding: maternal age (modeled as a continuous and categorical variable), race/ethnicity, years of education, and cigarette smoking, and insurance status (MA only). Spatial confounding is present if the covariate is a risk factor and varies spatially. To identify the final list of risk factors to adjust for in the models, risk factors were added one at a time to the model and adjusted maps were generated. If there were changes in the span size or spatial predictions, or if there was spatial variability of the risk factor, the variable was considered for inclusion in the final model.

Due to the strong association between gastroschisis and young maternal age, we stratified the data by maternal age to examine effect measure modification; the results are presented in the supplemental materials (Figures S1 and S2). In addition, we conducted a sensitivity analysis to assess if the results changed when mothers with missing geocodes were included in the analysis. The missing geocodes were imputed by creating a grid of points within the boundaries of the city and/or zip code provided by the mother on the birth certificates. One grid point within the city and/or zip code was randomly chosen and served as the imputed address. The analysis was repeated three times and each time a random location was selected for each mother. Maps were generated for all 3 iterations of the sensitivity analysis and compared to the main analysis.

Results

Massachusetts

After restricting to only in-state resident births, 156 cases of gastroschisis were identified and 9,000 controls were randomly selected from birth certificates, representing births from 2000 through 2007. One case and 81 controls were missing geocoded addresses and excluded from the main analysis, resulting in a total of 155 cases and 8,919 controls. Compared to control mothers, case mothers were more likely to be younger, smoke, not have private insurance, of other race ethnicities, and have less years of education (Table 1).

The spatial distribution of case and control mothers reflects a denser population in eastern Massachusetts and areas of sparse population in western Massachusetts (Figure 1). The crude map of Massachusetts showed elevated risks in the northern area of the state, with the highest ORs at 2.4 (global p-value <0.01; span size=0.65; Table 2). The local test identified areas of statistically significant increased and decreased risks that are denoted by the black bands in Figure 2A. Only maternal age appeared to alter the appearance of the maps and change the span sizes, but maternal race/ethnicity was also included as it was found to vary spatially. For race/ethnicity we chose only to predict for non-Hispanic white women; predicting for other race/ethnicities would not change the risk pattern observed on the map because changing the value of one variable in the prediction model would change all the values in the prediction grid by the same amount. Given the strong association between gastroschisis and maternal age we opted to present predicted maps for both younger and older mothers. Once the map was adjusted for maternal age and race/ethnicity, the ORs in the north-central area were attenuated and predicted ORs were 2.0 for non-Hispanic white women ≥25 years of age (Figure 2B) and 1.9 for non-Hispanic white women <25 years of age (Figure 2C). After adjustment for age and race/ethnicity the risks for the eastern portion of Cape Cod were elevated for women ≥25 years of age (OR=2.4) (Figure 2B) and for women <25 years of age (OR=2.3) (Figure 2C); though after adjustment location overall was no longer statistically significant (predicting for older women: global p-value=0.07, span size=0.85; predicting for younger women: global p-value=0.07, span size=0.85; Table 2).Results were similar when maternal age was modeled continuously with a loess smoother (Supplemental Material, Figure S3).

The majority of mothers (70%) with missing geocodes lived in rural towns (population <50,000) and were evenly distributed throughout the state (see Supplemental Material,

Figure S5). The addresses of all 82 mothers with missing geocodes were imputed and included in the sensitivity analysis. When the imputed geocodes were included, the ORs adjusted for non-Hispanic White women ≥25 years of age were slightly higher for all three iterations of the sensitivity analysis; the maximum ORs ranged from 2.7 – 2.8, depending on the iteration, and were located on the eastern portion of Cape Cod. ORs were also elevated in the north-central area and were around 1.9 in all three iterations (see Supplemental Material, Figure S6). In addition, the global test was borderline significant with p-values of 0.04 for all three iterations and the local test identified Cape Cod and the north-central area as having elevated ORs that were significant.

Texas

In Texas a total of 1,756 cases were identified and 10,000 controls were randomly sampled from the birth certificates. Of those, 1,687 cases and 9,706 controls had valid geocoded addresses and were included in the main analysis. Compared to control mothers, case mothers were more likely to be younger, of Hispanic ethnicity, and have less years of education (Table 3).

Figure 3 shows the spatial distribution of case and control mothers in Texas. The crude map revealed elevated ORs (maximum OR: 1.7) in the center of the state and along the coast near Corpus Christi (global p-value <0.01; span-size=0.30) (Figure 4A). These regions were found to be statistically significant as depicted by the significance bands. After adjustment, the maximum predicted OR was 1.3 for both non-Hispanic white women ≥25 years of age (Figure 4B) and non-Hispanic white women <25 years of age (Figure 4C). Even with the attenuation in risk, the p-value remained statistically significant and the significance bands identified the north-central and Corpus Christi regions as areas of statistically significant increased risk (predicting for older women: global p-value=0.02, span size=0.45; predicting for younger women: global p-value=0.02, span size=0.45; Table 2). Results were similar when maternal age was modeled continuously with a loess smoother (Supplemental Material, Figure S4).

Only 41% of mothers with missing geocodes lived in a county that had a population less than 50,000, with many of the mothers being located in the eastern half of the state (see Supplemental Material, Figure S7). Of the 363 mothers with missing geocodes, we were able to impute addresses for 359 mothers to include in the sensitivity analysis. The results were similar to the main analysis, with all three iterations identifying a location with adjusted OR of 1.3. The global tests indicated location was significant with p-values at 0.01 or less for all three iterations (see Supplemental Material, Figure S8). Additionally, the same regions as in the main analysis were identified as statistically significant.

Given the large number of cases in Texas we were able to assess the combination of space and time. First, the data were partitioned into calendar years (January 1st – December 31st) and maps were generated for each year (see Supplemental Material, Table S1 for summary of model specifications). The data were also partitioned into overlapping years (July 1st – June 30th) and maps were created for each year of data. To create a movie representing the combination of space and time, the maps for calendar year were placed in succession and the July through June maps were placed between the calendar year maps to smooth over time.

The addition of maternal race/ethnicity did not change the appearance of the maps (see Supplemental Material, Figures S9 and S10 for maps with race/ethnicity included) and therefore we elected to omit race/ethnicity from the models to preserve degrees of freedom. A loess smoother was used for maternal age with a span size 0.45 for all years. Figure 5 shows the calendar year maps for the early years of the study when areas with elevated ORs were identified; the entire movie can be seen in the supplemental materials. In 2001 (p-value=0.09), 2003 (p-value=0.03), and 2004 (p-value <0.01) there appeared to be elevated risks in the western, central, and northern parts of Texas, though only 2003 and 2004 had a statistically significant p-value with a maximum OR of 2.1 and 2.6, respectively.

Discussion

These analyses suggested geographic areas of elevated risks for gastroschisis in both Massachusetts and Texas. In Massachusetts ORs were elevated when we predicted for older mothers (maximum OR: 2.4), as well as when we stratified (maximum OR: 2.5), with the latter analysis being statistically significant. In Texas, ORs were elevated and significant when we stratified and examined patterns of risk among older mothers (maximum OR: 2.3). Adjusting for covariates other than maternal age made little difference in the appearance of the maps which is consistent with other studies of gastroschisis where maternal age is often the strongest confounder. In the maps maternal race/ethnicity was also included as a covariate as it has been previously associated with gastroschisis and the spatial distributions of maternal race varied across our study areas [5, 7, 9].

Our finding in Texas confirms a previous study by Benjamin et al. that found the highest prevalence of gastroschisis to be in the county where Corpus Christi is located for earlier years (1999-2003) [22]. In the same study, the lowest prevalence of gastroschisis was found in the Houston/Galveston area, which is where we also identified a decreased risk of gastroschisis. The study by Benjamin et al. did not stratify by maternal age when investigating the prevalence of gastroschisis by counties.

The areas of increased risk we identified may be due to risk factors that tend to aggregate spatially, such as environmental or infectious exposures. For example, the Corpus Christi region has extensive petrochemical plants in the area and air pollution or environmental contamination from these plants could potentially be one such exposure. In Massachusetts a possible environmental exposure could be from the Massachusetts Military Reservation (MMR) located on Cape Cod. The MMR is located over the Cape Cod aquifer, which is the sole source of public drinking water on Cape Cod. The aquifer is an unconfined sand and gravel aquifer and because of its composition has been contaminated by past activities at the MMR [23-25].

Massachusetts and Texas are both populous states and have annual birth populations >75,000, but are distinctly different from each other. The racial and ethnic make-up of pregnant women varies in both states, with Texas having three times as many births to women of Hispanic ethnicity than Massachusetts [26]. Texas has a younger birth population and, in particular, a higher rate of teenage pregnancies (63.4 births per 1,000 15-19 year olds) than Massachusetts (20.1 per 1,000) [27]. In addition, there are socioeconomic

differences between the two populations. These differences in age, race/ethnicity, and socioeconomic status suggest that the distinct potential exposures that are associated with them will also differ greatly between the two states and therefore it is unlikely that one exposure alone may explain the elevated risk of gastroschisis observed in both states.

There were many advantages of using GAMs to examine spatial variability and identify areas of increased or decreased risk. The first was that it allowed us to use individual level data so that we did not have to aggregate cases to artificial boundaries (e.g., county or census tract). In addition, we were also able to simultaneously adjust for many individual-level covariates. Given that both states included rural and urban areas, another advantage was the use of the smoothing term which adapted to changes in population density.

There are several limitations to our study. First, we cannot rule out the possibility that some of the spatial variation detected was due to residual spatial confounding. Spatial confounding occurs when there is an uneven spatial distribution of an uncontrolled risk factor. For example, if one neighborhood has a high density of cigarette smokers, then a cluster of lung cancer may be observed in that neighborhood; however, no cluster would have been detected if smoking had been controlled for. To reduce the possibility of confounding, we assessed a variety of individual level sociodemographic and behavioral factors as possible covariates in the models but were limited to the variables available from the birth certificate. In both Massachusetts and Texas we identified elevated ORs near the edge of our study area and cannot rule out the possibility of edge effects. Edge effects result in biased estimates near the edges of the study area due to a lack of data across the border of the study area; though a previous study using simulated data and GAMs found no edge effects when an edge was self-imposed on the study area [19].

There have been numerous critiques of using statistical tests to interpret data due to misinterpretation of significance tests, the arbitrariness of cut-offs, as well as the fact that many readers will equate statistical significance with a real or valid association [28-31]. While in this study we chose to use p-values, we did so to assist in determining when to interpret spatial variability and to prevent over interpretation of the data. In our study some areas had sparse data which could have led to spurious results. We therefore were using the non-significant p-value to suggest a more cautious interpretation of these results. It is also possible that some of the elevated areas may be evidence of a true increased risk and that the numbers were too small to reach statistical significance. Another approach we could have used was to calculate confidence intervals around the estimates, however they would have been difficult to display visually.

In our main analysis we excluded mothers with an address that could not be geocoded, which could have introduced a bias, especially if addresses were not missing at random. When we conducted a sensitivity analysis with imputed geocodes, the results did not change for the Texas data. In Massachusetts, the ORs were slightly larger when the missing geocodes were added, though the pattern of disease odds remained the same.

Lastly, our use of the birth address as a proxy for the address during pregnancy could have led to some misclassification. Previous studies have suggested that mobility during

pregnancy can range from 12-31% and young maternal age was associated with increased mobility [32-35]. However, when mothers moved during pregnancy, the majority of moves occurred intracounty (51%) rather than intercounty (23%).[33] A study in Texas found that while mobility during pregnancy was high (33%), particularly among younger mothers, the rates of moving were similar between cases and controls in each trimester of pregnancy; [35] these findings were confirmed in another study that compared mobility during pregnancy among mothers of infants with birth defects and those without [33]. These results suggest that while the use of delivery address as a proxy may be subject to some misclassification, especially for the younger mothers, it is likely to be non-differential. Given that residential address is considered our exposure in this analysis, we would expect that the result of this misclassification would lead to an underestimate of the true effect.

Conclusion

From a public health perspective, the rising prevalence of gastroschisis is of concern, as is the fact that it disproportionately affects infants of younger mothers. Given that little is known about the etiology of gastroschisis, more research is needed to explore novel exposures and help direct future research. The goal of the present study was to explore the possibility that gastroschisis occurs in clusters and add to the knowledgebase in order to generate possible hypotheses on the etiology of gastroschisis. Our results suggested that gastroschisis may in fact occur in clusters and that additional exploration of possible artifactual, environmental, infectious, or behavioral factors in these areas may further our understanding of the etiology of gastroschisis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

GAMs	Generalized additive models
OR	Odds ratios

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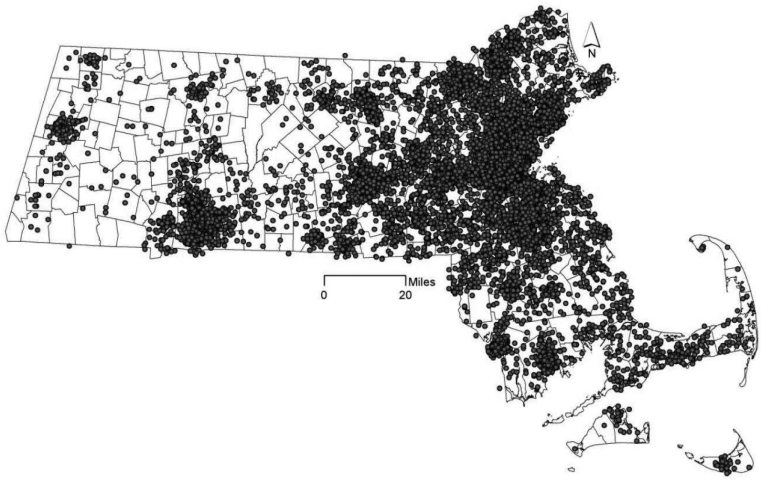

Figure 1.
Distribution of cases, Massachusetts Birth Defects Registry, and controls, Massachusetts Birth Registry, 2000—2007. Locations have been altered to preserve confidentiality.

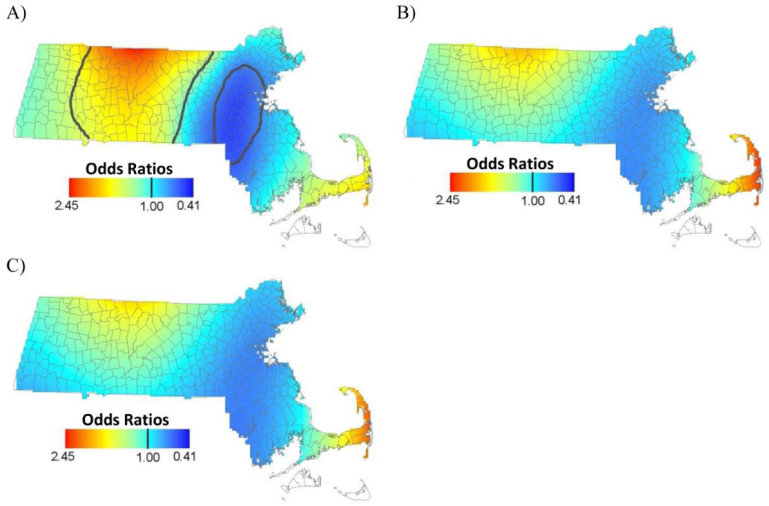

Figure 2.

Map of crude odds ratios (A), predicted odds ratios for non-Hispanic White women ≥25 years of age (B), predicted odds ratios for non-Hispanic White women <25 years of age (C), Massachusetts Birth Defects Registry, 2000—2007.

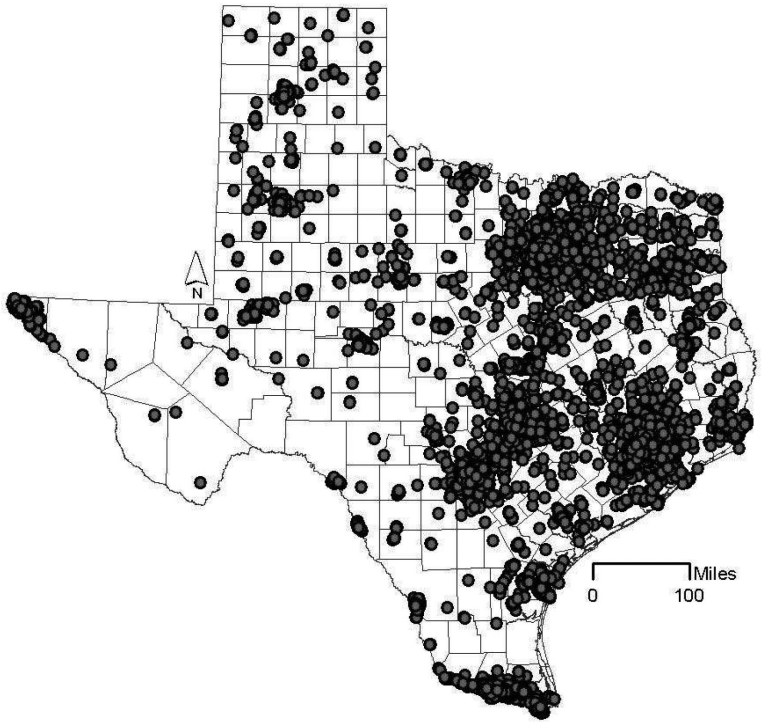

Figure 3.

Distribution of cases, Texas Birth Defects Registry, and controls, Texas Birth Registry, 1999—2008. Locations have been altered to preserve confidentiality.

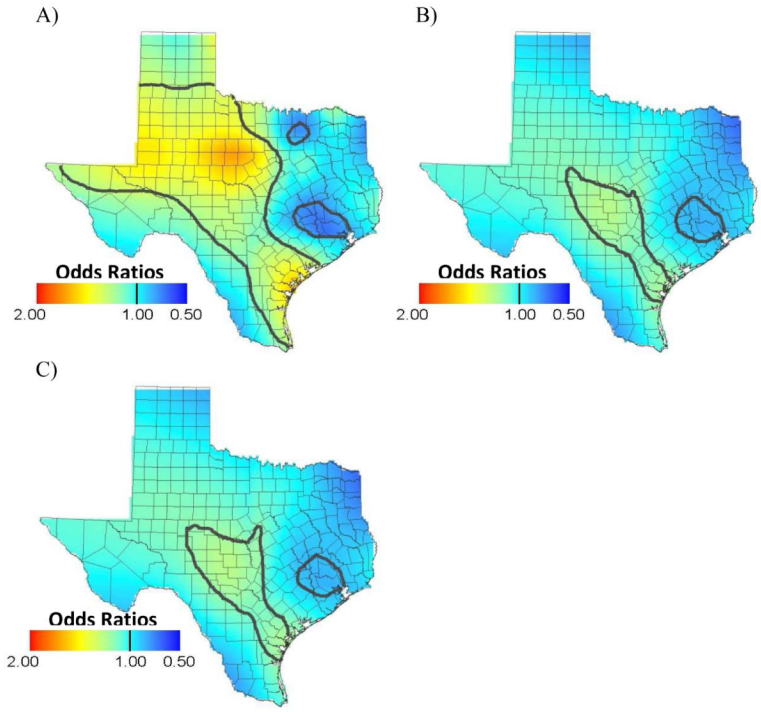

Figure 4.

Map of crude odds ratios (A), odds ratios adjusted for maternal age and race/ethnicity predicted for non-Hispanic White women ≥25 years of age (B), predicted odds ratios for non-Hispanic White women <25 years of age (C), Texas Birth Defects Registry, 1999—2008.

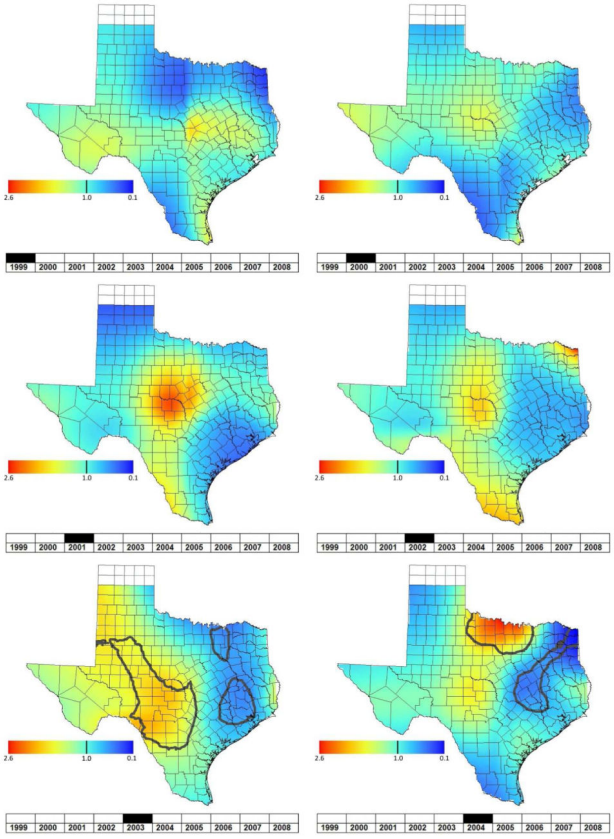

Figure 5.
Map of age adjusted odds ratios for Texas by birth year, Texas Birth Defects Registry, 1999—2004.

Table 1

Sociodemographic and behavioral factors for cases and controls, Massachusetts Birth Defects Registry, 2000—2007.

	Cases	Control
	n (%)	n (%)
Total	155 (100.0)	8919 (100.0)
Age		
< 20	53 (34.2)	566 (6.3)
20-24	58 (37.4)	1364 (15.3)
25-29	30 (19.4)	2069 (23.2)
30-34	12 (7.7)	2858 (32.0)
≥35	2 (1.3)	2062 (23.1)
Race / ethnicity		
Non-Hispanic White	87 (56.1)	5957 (66.8)
Other Races	68 (43.9)	2946 (33.0)
Missing	0 (0.0)	16 (0.2)
Education		
<12 years	35 (22.6)	963 (10.8)
12 years	91 (58.7)	3445 (38.6)
> 12 years	27 (17.4)	4511 (50.6)
Missing	2 (1.3)	0 (0.0)
Smoked during pregnancy		
Yes	20 (12.9)	737 (8.3)
No	134 (86.5)	8166 (91.6)
Missing	1 (0.6)	16 (0.2)
Insurance status		
Private insurance	47 (30.3)	6002 (67.3)
Government insurance, self-pay, none	101 (65.2)	2662 (29.8)
Missing	7 (4.5)	255 (2.9)

Table 2

Summary of GAM specifications and results for Massachusetts and Texas.

Model	OR Range	Span Size	Referent odds	Global p-value	Figure
Massachusetts					
Crude model	0.6-2.4	0.65	0.02	<0.01	2A
Predicting for non-Hispanic White women ≥25 years of age	0.8-2.4	0.85	0.01	0.07	2B
Predicting for non-Hispanic White women <25 years of age	0.7-2.3	0.85	0.06	0.07	2C
Texas					
Crude model	0.7-1.7	0.30	0.17	<0.01	4A
Predicting for non-Hispanic White women ≥25 years of age	0.7-1.3	0.45	0.05	0.02	4B
Predicting for non-Hispanic White women <25 years of age	0.7-1.3	0.45	0.40	0.02	4C

Table 3

Sociodemographic and behavioral factors for cases and controls, Texas Birth Defects Registry, 1999—2008.

	Cases	Control
	N	N
Total	1687 (100.0)	9706 (100.0)
Age		
<20	727 (43.1)	1368 (14.1)
20-24	689 (40.8)	2695 (27.8)
25-29	185 (11.0)	2560 (26.4)
30-34	50 (3.0)	1981 (20.4)
≥35	29 (1.7)	1097 (11.3)
Missing	7 (0.4)	5 (0.1)
Race / ethnicity		
Non-Hispanic White	606 (35.9)	3592 (37.0)
Hispanic	940 (55.7)	4565 (47.0)
Other Races	139 (8.2)	1534 (15.8)
Missing	2 (0.1)	15 (0.2)
Education		
<12 years	731 (43.3)	2945 (30.3)
12 years	581 (34.4)	2826 (29.1)
≥ 12 years	361 (21.4)	3839 (39.6)
Missing	14 (0.8)	96 (1.0)
Smoked during pregnancy		
Yes	130 (7.7)	577 (5.9)
No	1553 (92.1)	9076 (93.5)
Missing	4 (0.2)	53 (0.5)