Evidence of localized clustering of gastroschisis births in North Carolina, 1999-2004

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Abstract: Examining the geographic distribution of birth defects can be useful in exploratory etiologic research. Identification of clusters of certain defects may uncover possible environmental or socio-economic risk factors and assist with the generation of hypotheses about underlying causes of these conditions. In North Carolina, the prevalence of gastroschisis, a serious abdominal wall defect, has increased over the past decade and anecdotal evidence from clinicians suggests the possibility of clustering of this condition. This study uses a spatial scan statistic to identify the location and extent of clusters of gastroschisis births in North Carolina between 1999 and 2004. Data on cases of gastroschisis were obtained from the North Carolina Birth Defect Monitoring Program (NCBDMP) and control births were chosen from all resident live births without congenital birth defects contained in the NC composite linked birth files. The clusters were controlled for four major risk factors (age, race, parity and primary insurer) to ensure that the clusters were not an artifact of unequal population distribution. Results indicate a localized cluster of gastroschisis in the rural southern Piedmont of North Carolina which persists even after controlling for all major risk factors. Adjusting for age, race, parity and primary insurer shifted the location of the cluster substantially, demonstrating the importance of adjusting for underlying population distribution. Since clusters persisted after adjusting for risk factors, environmental factors may explain the excess of gastroschisis cases. This study is the first to identify spatial clusters of gastroschisis, demonstrates the importance of controlling for covariates in spatial analysis and illustrates the usefulness of the spatial scan statistic in exploratory etiologic research.

Keywords: birth defects, gastroschisis, spatial scan statistic, spatial cluster, covariates, SaTScan, geography

Introduction

Gastroschisis is a serious congenital abdominal wall defect in which the intestines and sometimes other internal organs develop outside the abdomen through an opening in the abdominal wall, resulting in the suspension of these structures in the amniotic sac. Gastroschisis is not usually associated with other birth defects and early diagnosis through ultrasound and modern surgical techniques have increased the survival rate to over 90% (Brantberg, Blaas, Salvesen, Haugen, & Eik-nes, 2004; Wilson & Johnson, 2004).

Estimates from state-based, active surveillance data compiled by the National Birth Defects Prevention Network suggest the prevalence of gastroschisis in the United States is approximately 3.82 per 10,000 live births, although there is considerable geographic variation (Canfield, Honein, Yuskiv, Xing, Mai, Collins et al., 2006a; NBDPN, 2007). In North Carolina, the birth prevalence of gastroschisis increased from 1.96 per 10,000 births in 1997 to 4.49 per 10,000 births in 2000 (Laughon, Meyer, Bose, Wall, Otero, Heerens et al., 2003) and has remained high with a rate of 4.26 per 10,000 live births in 2004. This apparent increase in gastroschisis is not unique to North Carolina; studies from around the world have reported an increase in prevalence over the past several decades (Calzolari, Bianchi, Dolk, Milan, Lechat, Leurquin et al., 1995; Forrester & Merz, 1999; Hougland, Hanna, Meyers, & Null, 2005; Martinez-Frias, Salvador, Prieto, & Zaplana, 1984; Penman, Fisher, Noblett, & Soothill, 1998; Penz, Menardi, & Brezinka, 1998; Rankin, Dillon, & Wright, 1999; Roeper, Harris, Lee, & Neutra, 1987; L. J. Williams, Kucik, Alverson, Olney, & Correa, 2005; Wilson & Johnson, 2004). These studies suggest a great deal of large-scale geographic variation in gastroschisis but very few have looked at small area variation of the defect. This is due, in part, to the relative rarity of gastroschisis births. The small number of cases born each year has traditionally made small-scale geographic analysis difficult.

While the prevalence of gastroschisis appears to be increasing, the etiology remains uncertain. Young maternal age is one of the few risk factors consistently associated with gastroschisis. In general, studies have shown that women younger than 20 years of age have significantly higher risk of a gastroschisis birth. Studies investigating the relationship between race/ethnicity and risk for gastroschisis show higher prevalence among Hispanic and white infants and lower prevalence among black infants (Canfield et al., 2006a; Lam & Torfs, 2006; Salihu, Aliyu, Pierre-Louis, Obuseh, Druschel, & Kirby, 2004). Since gastroschisis risk is significantly increased with young maternal age, a number of studies have investigated lifestyle and behavioral factors associated with younger women. Women who smoke or use alcohol during pregnancy may be more likely to have an infant with gastroschisis (Goldbaum, Daling, & Milham, 1990; Haddow, Palomaki, & Holman, 1993; Hougland et al., 2005; Torfs,

Katz, Bateson, Lam, & Curry, 1996; Torfs, Velie, Oechsli, Bateson, & Curry, 1994; Werler, Mitchell, & Shapiro, 1992). Thus, it is possible that the geographic variation in gastroschisis rates may be due to unequal distribution of mothers with certain risk factors.

Prior epidemiological research indicates that the causes of gastroschisis, like many birth defects, are most likely complex and multifactoral and include not only maternal characteristics and behaviors but also environmental teratogens and genetic factors (Curry, McKinney, Thornton, & Stringer, 2000). With so much uncertainty around the etiology of this condition, most epidemiological studies are exploratory in nature, testing possible associations between these birth defects and socioeconomic inequalities that are correlated with poor health outcomes or environmental contaminants that influence the development of other chronic conditions (e.g. cancer) or produce malformations in animal models (Brown, 1997). Understanding the geographic distribution of gastroschisis can be useful in exploratory etiologic research. Identification of disease clusters may uncover possible environmental or socio-economic risk factors and assist with the generation of hypotheses about the underlying socio-environmental causes of those clusters. But researchers must be careful in applying disease clustering techniques to ensure that identified clusters are not simply due to spatial variations in the density of the population being studied. If known covariates are not adjusted for, observed spatial patterns of birth defects may be due to the fact that individuals with similar risk factors live in the same geographic area, producing larger area-level patterns of disease. If, however, known individual-level risk factors are adjusted for and the cluster persists, environmental contaminants may be suspected as a possible cause of the birth defect. Given that such a wide variety of environmental, social and economic factors may influence the development of gastroschisis, it is important to understand how these factors interact and overlap in certain places to produce spatial patterns of disease.

While spatial cluster analysis is not new to epidemiology, its application to the study of birth defects has only recently become appreciated (Boyle, Johnson, Kelly, & McDonnell, 2004; Forand, Talbot, Druschel, & Cross, 2002) and there are no published studies specifically related to clusters of gastroschisis. Anecdotal evidence from clinicians in North Carolina suggests the possibility of clustering of gastroschisis in the state. In this study we use spatial cluster analysis to identify the location and extent of clusters of gastroschisis births in North Carolina. We sought to answer two main study questions: 1) Do significant clusters of gastroschisis occur in North Carolina and, if so, what are the approximate locations of these clusters? 2) If these clusters are adjusted for known risk factors (age, race, parity and Medicaid) do they persist or disappear?

Methods

Source of the data

Study data were obtained from the North Carolina Birth Defects Monitoring Program (NCBDMP). The NCBDMP is a population-based active surveillance system that collects data on congenital malformations diagnosed within the first year of life among all live births in North Carolina, as well as among fetal deaths and induced terminations. With the active surveillance system, trained field staff systematically review and abstract hospital medical records and discharge reports and report malformations to the Registry (NCSCHS, 2005). Records in the Registry are routinely linked to other data sources, such as birth records and Medicaid enrollment records, to obtain additional maternal and child characteristics.

We conducted a retrospective case-control study of North Carolina resident live births with gastroschisis between 1/1/1999 and 12/31/2004. To identify infants with gastroschisis, we searched the NCBDMP database using the Centers for Disease Control and Prevention modified British Pediatric Association code for gastroschisis (756.710). Infants with a chromosomal abnormality were excluded from this study. Controls were randomly chosen from all resident live births without congenital malformations contained in the North Carolina composite linked birth files. The composite birth file consists of all North Carolina resident birth certificates linked to maternal and infant Medicaid paid claims and health department service data, such as the Special Supplemental Nutrition Program for Women, Infants, and Children (WIC) and maternity care coordination (Buescher, Roth, Williams, & Goforth, 1991). Control births were matched to the NCBDMP registry database to exclude infants with congenital defects. Terminations of pregnancy and fetal deaths were not included in the study, as these comprise only a small fraction of gastroschisis cases in North Carolina.

A total of 264 cases and 12,488 controls were selected for analysis. The data included residential address at birth, which was used to geocode cases and controls. A majority of the geocoding was completed by the Health & Spatial Analysis Unit at the NC State Center for Health Statistics (SCHS), which provided the address-level latitude and longitude coordinates for all available records in the analysis file. Records not matched by the SCHS were geocoded using a multi-stage geocoding method (Lovasi, Weiss, Hoskins, Whitsel, Rice, Erickson et al., 2007). This method begins with preprocessing data to correct addresses with typos or unnecessary address elements (e.g. apartment number) and standardize them to United States Postal Service format (Krieger, Chen, Waterman, Rehkopf, & Subramanian, 2003; Krieger, Waterman, Lemieux, Zierler, & Hogan, 2001). Addresses were then matched in stages using different geocoding services including: Juice Analytics Geocoding Tool (Juice

Analytics, 2006), Google Earth and Microsoft Virtual Earth. While these may not be the gold standard for geocoding, they do utilize a combination of high-quality proprietary street files (e.g. Dynamap, NAVTEQ and TeleAtlas) and satellite imagery to locate addresses and are available at no cost. After each stage, the remaining unmatched addresses were geocoded using a different geocoding service. Since geocoding services use slightly different street files, this iterative process ensures that all possible addresses are geocoded.

Records with an invalid address were removed from the analysis. Using this process, we matched 242 of the 264 cases (91.7%) and 11,651 of the 12,488 controls (93.3%). Descriptive statistics were run on the unmatched versus matched records to see what, if any, differences existed between the two groups and we found some minor differences in race, parity and Medicaid status. We chose to exclude multiples in this analysis since multiple births are not independent events (e.g. they share the same fetal environment) and we did not want to count these locations twice in the spatial cluster analysis.

Once data were geocoded, we assigned individual-level records to several census areas: blocks, block groups and tracts. Initially, we used the individual-level point locations to scan for clusters but performed additional analyses with data aggregated to block, block group and tract in order to examine possible effects of geocoding errors. The results for all four analyses were nearly identical suggesting that any geocoding errors have a negligible effect on the size and location of identified clusters. We chose to use the census block groups for the remainder of the study because this geography yielded the highest p-values and is computationally less intensive and therefore faster to run on a desktop computer.

The data also contained potential covariates from the linked birth files including: mother's and father's age, race and ethnicity, marital status, number of prior births, singleton or multiple birth, month prenatal care began, mother's smoking status, and whether or not Medicaid paid for the delivery.

Statistical methodology

We used the spatial scan statistic available in the SaTScan computer software package (Kulldorff, 1997, 2005; Kulldorff & Nagarwalla, 1995) to test for the presence of purely spatial clusters of gastroschisis and to identify their approximate location. We assumed the number of births in each census block group to be Poisson distributed. The method tests the null hypothesis that within any covariate group (age, race, parity, etc.) the risk of a gastroschisis birth is the same in all census block groups. This means that the expected covariate-adjusted rate of gastroschisis is constant throughout

North Carolina. Despite the case-control design of our study, which would usually merit the use of a Bernoulli model, we chose to use the Poisson model for several reasons. First, prior research indicates several covariates that are related to gastroschisis including maternal age, race and parity. The Poisson model allows us to easily adjust for a large number of covariates, while the Bernoulli model does not. Second, in instances where there are few cases compared to controls (< 10%) the Poisson model is a very good approximation to the Bernoulli model and produces slightly conservative p-values (Kulldorff, 1997, 2006). We examined study data using both the Bernoulli and Poisson models and results were identical though, as predicted, p-values for the Poisson model were slightly higher. Finally, the computing power necessary to run the Poisson model is significantly less than for the Bernoulli model, allowing the analysis to be run on a desktop computer.

The scan statistic detects clusters by gradually scanning an elliptical window across the entire study area, noting the number of observed and expected cases of gastroschisis inside the ellipse at each location (Kulldorff, 1997; Kulldorff, Athas, Feurer, Miller, & Key, 1998; Kulldorff & Nagarwalla, 1995). In this study, the center point of all census block groups in North Carolina served as the center for the ellipses. The radii of the ellipses vary continuously in size from zero to a user-defined maximum, which is a percentage of the total North Carolina population. The ability to vary the size of the ellipse is important because we usually do not know the size of the area covered by a cluster (Emch & Ali, 2002; Kulldorff, 1997). Thus, the location and size of the ellipse changes creating an infinite number of distinct geographic areas. Each of these areas reflects a possible cluster. This method looks at varying spatial scales which is particularly appropriate for a birth defect with an unknown etiology because we do not know the scale at which the defect may exhibit spatial clustering.

The scan statistic uses a likelihood ratio test statistic, the methodology for which is described in detail elsewhere (Emch & Ali, 2002; Kulldorff, 1997; Kulldorff & Nagarwalla, 1995). For each ellipse, the likelihood of finding the observed number of gastroschisis births within the ellipse and outside the ellipse is calculated. The ellipse with the maximum likelihood is the most likely cluster, that is, the cluster least likely to be due to chance. In order to find the value of the test statistic, SaTScan uses a Monte Carlo simulation approach to find the maximum likelihood ratio over the entire range of ellipses. The same procedure (e.g. scanning the elliptical window of varying size across the study area) is repeated on a large number of random replications (we chose 9999). The maximum likelihoods of the study data and the Monte Carlo simulations are ranked in order to determine the distribution of the likelihood ratio and the corresponding p-value of the study data. SaTScan detects both primary and secondary clusters. The primary cluster is the window with the maximum likelihood ratio while

secondary clusters are additional clusters that have highly likelihood ratios but that do not overlap the primary cluster.

The maximum cluster size was initially set to include up to 50% of the population. However, repeated analyses showed that significant clusters included no more than 10% of the population, so we restricted the maximum cluster size to 25% of the population to minimize computing time. Both circular and elliptical windows of different shapes and angles were used to scan for clusters. We chose to use elliptical windows because prior research supports the possibility that an environmental contaminant induces gastroschisis (Dolk, Vrijheid, Armstrong, Abramsky, Bianchi, Garne et al., 1998; Drongowski, Smith, Coran, & Klein, 1991; Fielder, Poon-King, Palmer, Moss, & Coleman, 2000; Torfs et al., 1996). The elliptical shape more accurately follows certain geographic features, such as watersheds and rivers, which we hypothesize could transport contaminants from their source. SaTScan does impose a penalty for using less compact shapes so that the cluster is not unnecessarily elongated in order to "cherry pick" cases over a larger area. We chose to focus on clusters with statistically significant p-values (< 0.05), though we report one primary and one secondary cluster for each analysis.

After identifying statistically significant spatial clusters, the next step was to determine if these areas would change when the model was adjusted for known risk factors for gastroschisis. Since maternal age is the main risk factor consistently associated with gastroschisis, all analyses were age-adjusted using 3 categories: < 20 years of age, 20-24 years, and 25 years or more. We also classified births by race (white, black and other), parity (no prior births vs. one or more prior births) and Medicaid status (defined as the delivery paid for by Medicaid vs. other payer source) and conducted separate analyses for each covariate. All covariates and their classifications were determined using univariate and logistic regression analysis in SAS Version 9.1 (data not shown). We chose to include covariates in the cluster analysis that had significant odds ratios in the regression analysis. Covariates were introduced into the spatial scan in an iterative manner and we controlled for no more than two covariates at a time. From a computational standpoint, we did not have a large enough sample of cases to partition the data into more than 2 or 3 covariate categories because p-values generated by the scan statistic become less reliable when locations have categories with no data (Kulldorff, 1997, 2006). In addition, we were not only interested in the geographic location of the cluster, but also how specific covariates would change that location. By adding in one covariate at a time and observing the change, we can see how the underlying geographic distribution of that covariate affects the distribution of cases in the State.

Results

Figure 1 and table 1 show the results of the unadjusted scan statistic. Two statistically significant clusters were identified, both located in the southern Piedmont region of North Carolina. The primary cluster (p=0.016) encompassed a larger area and included 50 cases of gastroschisis, approximately 2.42 times more cases than expected. The secondary cluster (p=0.046) was geographically smaller in size and included 12 cases, approximately 6 times more cases than expected.

Table 1 and figure 2 indicate how the results of the spatial cluster analysis changed when covariates were included in the model. When the analysis is adjusted for age, only one statistically significant cluster remains (p=0.043). This cluster is different in size and shape and includes fewer census block groups than the primary cluster found in the unadjusted model. It contains 26 cases, 3.3 times more cases than expected. The age-adjusted cluster is in the same general geographic region (e.g. the southern Piedmont), however, and encompasses portions of both clusters found in the initial unadjusted model. The log likelihood ratio (LLR) dropped from 12.93 to 12.23, indicating that age explains some of the excess in gastroschisis cases.

In two subsequent models adjusting for age plus race and age plus parity the LLR dropped, indicating a decrease in the strength of most likely cluster which signifies that race and parity explain some of the excess in gastroschisis cases. The location of the most likely cluster in both the age/race- and age/parity-adjusted models included the same census block groups. This cluster encompassed a larger area than the age-adjusted model and included a greater number of cases, 59, nearly 2.2 times more than expected. Although the *p*-values for both the age-race (p=0.051) and age-parity (p=0.053) adjusted analyses were of borderline significance at the $p<0.05$ level, the fact that the cluster persists in the same general geographic location across all covariate-adjusted models is compelling and merits further investigation.

The final model adjusted for maternal age plus Medicaid status. Again, we found one significant cluster (p=0.014), which includes the same census block groups and has the same number of cases as the age-adjusted model. The LLR increased to 13.45 for the age/Medicaid-adjusted model, indicating that these covariates do not explain the excess in gastroschisis cases. The relative risk within the cluster was also the highest of any model at 3.5. The fact that the size and shape of the age/Medicaid cluster is the same as the age-adjusted model suggests that Medicaid does not explain any more of the excess of gastroschisis cases than age alone.

Discussion

The initial *unadjusted* model indicated two significant clusters of gastroschisis, the size and location of which changed dramatically when we adjusted the model for age, race and parity, the three covariates with the strongest relationship to gastroschisis prevalence in this study population. The large cluster to the east of Charlotte disappears when age is adjusted for, which suggests a disproportionately large number of young mothers in the area is responsible for the large number of gastroschisis cases. While the clusters we detected using the covariate-adjusted models did not overlap perfectly, they did consistently include an area in the rural southern Piedmont just north of the cities of Gastonia and Charlotte. There appears to be a localized cluster of gastroschisis in North Carolina that persists through all analyses and merits further investigation.

This finding fills an important gap in the literature. Prior research on gastroschisis in North Carolina has shown a gradual increase in the birth defect over the past 10 years (Laughon et al., 2003; Wall & Meyer, 2006) and anecdotal evidence from health professionals has suggested a higher prevalence in certain geographic areas of the State. However, this is the first statistical analysis done to formally evaluate the possibility of spatial clusters and test whether the prevalence of gastroschisis is significantly higher within those clusters when compared to the rest of North Carolina. We used a spatial scan statistic because it does not require a priori knowledge of the geographic location, spatial scale or size of a cluster before conducting the analysis, thereby ameliorating the problem of preselection bias. The scan statistic also allows us to adjust for underlying population density and demographic characteristics so we can be more confident that observed clusters are not simply an artifact of unequal population distribution.

We believe this cluster of gastroschisis cannot be readily dismissed as a chance occurrence, and our future analyses will examine potential underlying causal mechanisms. In this study, we adjusted for several risk factors: age, race, parity, and Medicaid status (usually a proxy for low income or poverty). There are additional risk factors hypothesized in the literature for which we, unfortunately, do not have individual-level or population-level data. For example, recreational drug use (cocaine, amphetamine, marijuana, or LSD) has been linked with increased risk for gastroschisis (Forrester & Merz, 2006; Torfs et al., 1994) as have some over-the-counter medications such as pseudoephedrine and aspirin (Kozer, Nikfar, Costei, Boskovic, Nulman, & Koren, 2002; Torfs et al., 1996; Werler et al., 1992). Maternal nutritional deficits have also been linked to increased risk for gastroschisis (Lam & Torfs, 2006; Torfs, Lam, Schaffer, & Brand, 1998). Unfortunately we have no information on the local or regional variation of these behaviors, so we cannot tell if they partly explain the observed cluster.

The cluster we observed in this study encompasses a region of North Carolina that is both geologically and economically unique. The soil composition (mainly metamorphic rocks such as slate and gneiss) is unique to the western Piedmont and the observed cluster is sandwiched between the slopes of the Blue Ridge Mountains and an area of sandy soils referred to as the Sandhills. This combination of soil types, among other factors, influences groundwater recharge and discharge and surface water flow in the region. The cluster also covers one of the main textile producing areas of the state. Textile mills use considerable quantities of water for wet-processing activities such as washing, bleaching and dyeing and mill water is often laden with chemicals when it is discharged into surface and groundwater sources. While we certainly do not have enough information to suggest that textile mill practices are the cause of high gastroschisis rates in the rural southern Piedmont, the geographic pattern of the cases coupled with the density of textile operations and soil composition suggests a possible direction for future research.

The increase in birth prevalence of gastroschisis in different populations and different geographic locations over time also suggests the possibility of exposure to environmental contaminants. Studies examining the relationship between gastroschisis births and proximity to point source pollutants are rare and far from conclusive. The EUROHAZCON multicenter case-control study found an increased risk of gastroschisis within 3km of a hazardous waste landfill but these results were only borderline significant (Dolk et al., 1998). Fielder, et al. (2000) also found significantly higher rates of gastroschisis than expected in electoral wards within 3km of a landfill site. However, a study by Morris, et al. (2003) found no association between gastroschisis and omphalocele (another type of abdominal wall defect) and residence within 2km of landfill. Data on some environmental risk factors, such as landfill and hazardous waste sites, are publicly available and will be incorporated into future analyses of the present data in order to determine whether such environmental hazards may explain the excess of gastroschisis cases in our observed cluster.

It is important to put into perspective the magnitude of the excess risk observed within the cluster in this study. The cluster observed in the age-adjusted model contains 26 of the 240 gastroschisis cases, approximately 10 percent of all cases in an area with only 5 percent of the total population. The larger cluster observed in the age/race- and age/parity-adjusted models contained 59 of the 240 gastroschisis cases, nearly one quarter of all the cases that occurred in the state, but only about 9 percent of the population lives in this area. This translates to a more than two-fold greater odds of gastroschisis within both the age-adjusted and age/race- or age/parity-adjusted clusters (odds ratio of 2.6 and 2.2, respectively) when compared to the rest of North Carolina.

This study demonstrates the usefulness of spatial cluster analysis in exploratory etiological research of birth defects. The methods adjust for known risk factors for gastroschisis and illustrate the importance of adjusting spatial clusters for underlying population. If the purpose of cluster analysis is not only to identify the approximate location of clusters but also to target future research activities or public health initiatives, finding the location of the "true" cluster after adjusting for the underlying population distribution can prevent researchers from focusing such efforts in the wrong area. Furthermore, the spatial patterns observed in the data can be used to elicit etiological clues about birth defects such as gastroschisis, and generate hypotheses about the causal mechanisms responsible for the cluster. Comparing the socio-environmental characteristics of clustered versus non-clustered cases may reveal similarities or differences, which may, in turn, give clues to disease etiology (Draper, 1997; J. R. Williams, Alexander, Cartwright, & McNally, 2001).

It is important to keep in mind that the geographic boundaries of the clusters detected in this study are approximations of the "true" clusters. This means that while we know the general location of the cluster, we are uncertain as to the exact boundaries. As with any ecological analysis, we cannot say that the whole population living within the cluster area is at the same risk for giving birth to an infant with gastroschisis. Women have varying levels of risk, which depend on their individual characteristics, behaviors, and family histories. However, the presence of the cluster suggests that an added risk factor, perhaps environmental, may exist in that area.

This geographic analysis uses residence at birth. Studies have shown that between 25 and 30 percent of women change residence between conception and birth (Fell, Dodds, & King, 2004; Khoury, Stewart, Weinstein, Panny, Lindsay, & Eisenberg, 1988; Shaw & Malcoe, 1992). However, a majority of these moves appear to be local (e.g. within the same city or county) (Fell et al., 2004; Khoury et al., 1988) and the characteristics of women who move are similar to those who do not (Canfield, Ramadhani, Langlois, & Waller, 2006b). Caution should be exercised when interpreting the results of geographic studies that use maternal residential address at delivery, especially if trying to ascribe the case of a cluster to some local environmental exposure.

In summary, we have identified a statistically significant excess of gastroschisis in the rural southern Piedmont of North Carolina which persists even after controlling for known covariates. While gastroschisis has increased in North Carolina over the past decade and anecdotal evidence from clinicians in the State suggested the presence of one or more clusters of this birth defect, no spatial statistical analysis had been conducted until now. The spatial scan statistic enabled us to evaluate more reliably the location and strength of the clustering effect without the bias that could be introduced

when researchers have some prior knowledge of the geographic location or size of a cluster. Future research will focus on possible environmental causes of the clustering.

Table 1: Spatial cluster analysis* of gastroschisis births in North Carolina, 1999-2004

Covariates	Type†	Cases	Expected	RR‡	LLR§	p-value
None	P	50	23.5	2.42	12.93	**0.016**
	S	12	2.1	6.17	11.50	**0.046**
Age	P	26	8.5	3.31	12.23	**0.043**
	S	4	0.17	24.20	8.87	0.336
Age, race	P	59	31.1	2.19	11.87	**0.051**
	S	4	0.18	22.93	8.66	0.469
Age, parity	P	59	31.1	2.19	11.83	**0.053**
	S	4	0.14	29.56	9.64	0.172
Age, Medicaid	P	26	7.96	3.54	13.45	**0.014**
	S	4	0.16	26.14	9.17	0.267

*SaTScan Poisson model using an elliptical scan window with a non-compactness penalty, maximum cluster of <25% of the NC population and overlapping clusters not reported

† P=primary cluster; S=secondary cluster

‡ RR= relative risk within the cluster compared to the rest of North Carolina

§ LLR=log likelihood ratio

Figure 1: Primary and secondary clusters of gastroschisis births detected using the *unadjusted* model, North Carolina, 1999-2004

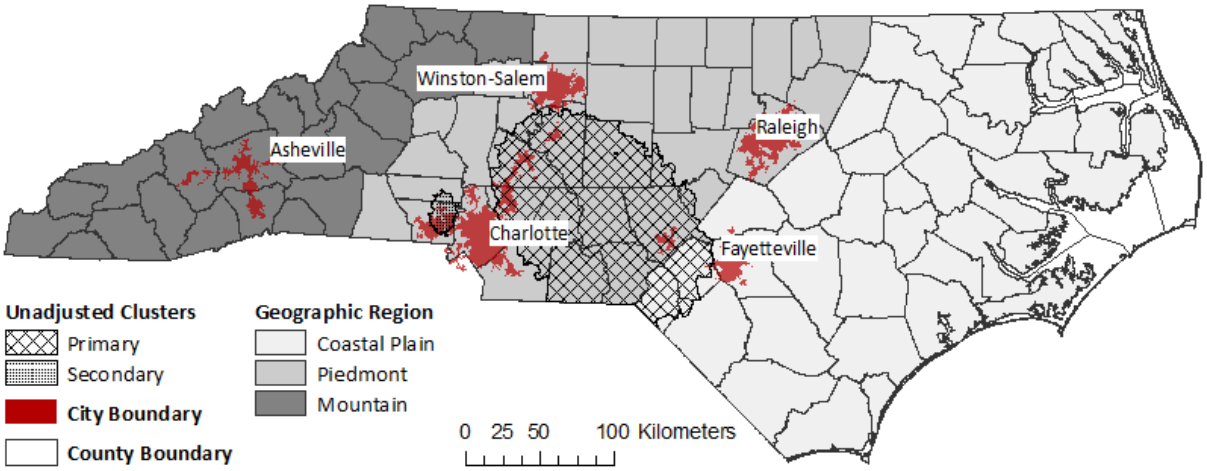
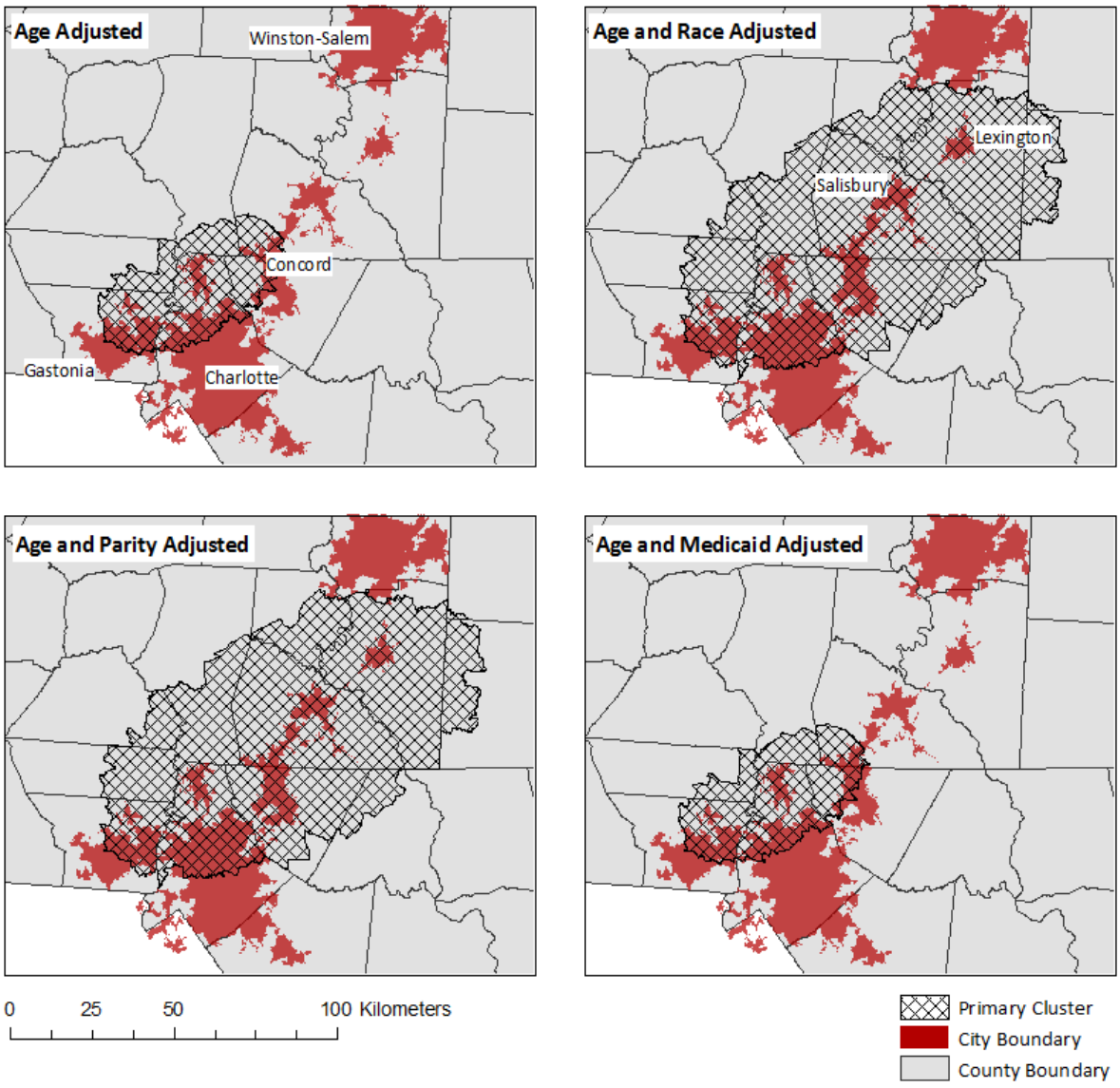


Figure 2: Close-up view of primary clusters of gastroschisis births detected using covariate-adjusted models, North Carolina, 1999-2004



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