THE ECOLOGY OF BIRTH DEFECTS: SOCIO-ECONOMIC AND ENVIRONMENTAL DETERMINANTS OF GASTROSCHISIS IN NORTH CAROLINA

Elisabeth Dowling Root

A dissertation submitted to the faculty of the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Department of Geography.

Chapel Hill
2009

Approved by:

Michael Emch

Larry Band

John Florin

Melinda Meade

Robert Meyer

ABSTRACT

Elisabeth Root: The ecology of birth defects: Socio-economic and environmental determinants of gastroschisis in North Carolina
(Under the direction of Michael Emch, Larry Band, John Florin, Melinda Meade and Robert Meyer)

Gastroschisis is a serious birth defect that has increased in prevalence in North Carolina over the past decade. The causes of the defect, and the reasons for this increase, are largely unknown. This study uses the disease ecology framework and spatial methodologies – spatial statistics, Geographic Information Systems, and hydrological modeling – to explore the geographic distribution of gastroschisis in North Carolina and suggest possible socioeconomic and environmental factors that may contribute to the disease. Specific questions addressed in this study include: 1) Do significant geographic clusters of gastroschisis exist in North Carolina? 2) Do clusters suggest the presence of point-source environmental pollutants? 3) What area-level socioeconomic characteristics are related to gastroschisis outcomes? 4) What can this tell us about possible causes of the disease?

Using data from a population-based birth defects registry, this study uses Kulldorff's spatial scan statistic to identify the location and extent of clusters of gastroschisis births in North Carolina between 1999 and 2004. Spatial clusters are controlled for four major risk factors (maternal age, race, prior births and Medicaid status) to ensure that the clusters are not an artifact of the population composition of the State. The relationship between neighborhood socioeconomic characteristics (e.g., race, poverty, education and unemployment) and gastroschisis outcomes are examined using logistic regression models, which combine individual-level and neighborhood-level variables. Finally, simple hydrological models are used to determine if exposure to upstream textile mill effluent increases the risk for a gastroschisis affected pregnancy.

Results indicate the presence of a localized cluster of gastroschisis in the rural southern Piedmont of North Carolina. In addition, both individual-level (Medicaid status) and neighborhood-level (poverty and unemployment) socioeconomic factors appear to contribute to the risk of a gastroschisis affected pregnancy, suggesting that neighborhood-level socioeconomic factors exert an independent causal effect on gastroschisis. Despite the localized nature of the cluster, which often suggests the presence of an environmental contaminant, there is no evidence to support this hypothesis. These results may help understanding the myriad social, economic and environmental factors that combine and interact to influence gastroschisis outcomes.

AKNOWLEDGEMENTS

Though this dissertation is considered an individual work, good research is never conducted in a vacuum. This research represents the culmination of years of study, but also a network of educators, colleagues and friends who have supported, guided and inspired me during my graduate program. To each and every one of you I offer my gratitude.

To my advisor – Mike Emch – who has been an extraordinary mentor. Thank you for supporting me and guiding me and teaching me what it means to be a strong researcher and productive academic. Your flexibility, acceptance and determination to see me through this process has been invaluable.

To my committee – Larry Band, Melinda Meade, John Florin and Bob Meyer – thank you for your encouraging words, thoughtful criticism, and time and attention during busy semesters.

To my lab-mates – Maggie, Caryl, Veronica, Sophia and Janie – thank you for your friendship and for sharing your enthusiasm and feedback. I certainly wouldn’t have made it through this process without each of you.

To my parents – Bill and Sandi – for their love, support and understanding during the long years of my education.

And finally, to my husband – Morgan – what would I do without you? Thank you for listening, loving, counseling, and supporting me. You have been my voice of reason, my emotional crutch and my staunchest supporter.

TABLE OF CONTENTS

LIST OF TABLES

Table

LIST OF FIGURES

Figure

ABBREVIATIONS

AIC	Akaike Information Criterion
BASINS	Better Assessment Science Integrating Point and Nonpoint Sources
CI	Confidence Interval
DEM	Digital Elevation Model
DF	Degrees of Freedom
EPA	Environmental Protection Agency
GDT	Geographic Data Technology
GIS	Geographic Information Systems
LLR	Log Likelihood Ratio
NBDPN	National Birth Defects Prevention Network
NCBDMP	North Carolina Birth Defects Monitoring Program
NCGIS	North Carolina Center for Geographic Information and Analysis
NED	National Elevation Dataset
NHD	National Hydrography Dataset
NIOSH	National Institute for Occupational Safety and Health
NPDES	National Pollution Discharge Elimination System
OR	Odds Ratio
RR	Relative Risk
SCHS	North Carolina State Center for Health Statistics
SES	Socioeconomic Status
SIC`	Standard Industry Classification Code

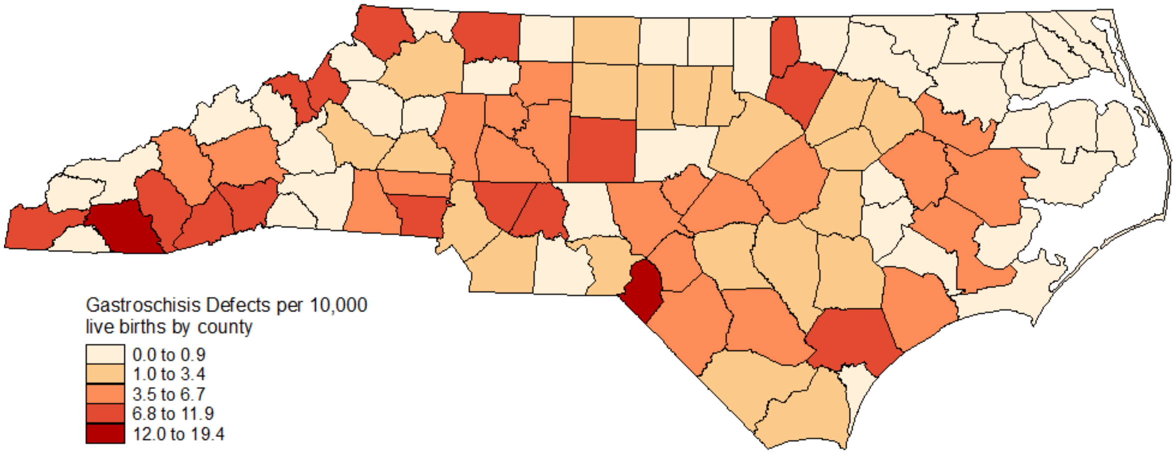
SWI	Surface Water Intake
TRI	Toxic Release Inventory
WIC	Women, Infant and Children Program

CHAPTER 1

INTRODUCTION

During the summer of 2006, the Raleigh *News and Observer* published a small article describing three babies born to agricultural workers in North Carolina with major birth defects. The NC Department of Health and Human Services investigated the matter and reported that a link between pesticide exposure and the malformed children was possible but they did not “have the data to prove it definitively”(Collins 2006). Each year in North Carolina more than 3,500 infants are born with a serious birth defect (Wall and Meyer 2006). Occurrences of birth defects are not randomly distributed across the state as shown by county-level gastroschisis rates in Figure 1.1. Numerous factors are believed to be behind the distribution of birth defects. Contextual factors which also cluster in space, such as environmental exposures, have been associated with the development of birth defects (Shaw et al. 1999; Garry et al. 2002; Dolk et al. 1998; Marshall et al. 1997). Birth defects also appear to occur more frequently among children born to women of lower socioeconomic status (SES) (Olshan, Baird, and Lo 1991; Womersley and Stone 1987; Torfs et al. 1994; Werler, Mitchell, and Shapiro 1992a). Clustering may therefore be due to compositional effects, or the fact that individual or family-level risk factors that contribute to birth defects may cluster in an area to produce larger area-level effects. Area-level characteristics that have been associated with birth defects include indices of deprivation, low education, high poverty, high unemployment, poor housing quality and neighborhood crowding (Vrijheid et al. 2000; Wasserman et al. 1998; Carmichael et al. 2003; Bound et al. 1997). Increasingly, public health researchers have shown that area characteristics may be related to health and are important for understanding population distributions of disease (Kawachi and Berkman 2003b). This view of public health suggests that disease is not determined entirely by an individual's biologic composition, or 'who you are', but also by a person's context, or 'where you are'. While this "ecological" approach to population health may be relatively new to public health, it has existed in the field of geography as "disease ecology" for over a century.

Figure 1.1. Rate of Gastroschisis per 10,000 live births by county: 1999-2003



Source: North Carolina State Center for Health Statistics: 1999-2003.

The purpose of this study is to examine the environmental and socio-economic factors that contribute to the geographic variation gastroschisis in North Carolina. In order to understand the effects of potential environmental contaminants (i.e. pollution, solid or hazardous waste or pesticide use) it is imperative that the social and economic compositional effects are adequately accounted for or model estimates of the effects of environmental factors will be biased. The specific study questions addressed in this study include:

1) Do significant spatial clusters of gastroschisis exist in North Carolina?

2) Is the clustering in birth defects a consequence of compositional factors (i.e. people with similar risk factors living near each other)?
3) If compositional factors are controlled for, what environmental factors explain variability in birth defects (i.e. proximity to hazardous waste, superfund, etc.)?
4) Do models using hydrogeography to define areas of high contamination risk estimate the risk of gastroschisis better than models using Euclidean distance?

These study questions have been chosen to address three major deficits in the literature. First, few studies use methods appropriate for determining whether differences in birth defect rates across areas are due to characteristics of the areas themselves ("contextual" factors) or to differences between the types of people living in areas ("compositional" factors). While environmental exposures in an area can lead to birth defects, this relationship may be confounded by characteristics of the population that live in that area which are also risk factors for birth defects. The few studies that have incorporated area-level socioeconomic indicators have not used methods that adjust for hierarchical data structures. Second, the concept of "neighborhood" is complex and critics suggest that the spatial scale at which neighborhood factors influence health may vary based on the socioeconomic measure and health outcome used. Very few studies use empirical methods to define neighborhoods or compare model results across different geographic scales in order to examine how spatial scale affects model results. Finally, geographic features, such as hydrology, and hydrological modeling techniques have not yet been applied to exposure assessments in the birth defects literature. Studies using secondary data to assess exposure have used "as the crow flies" distance measures from a potential contaminant site to an individual's place of residence.

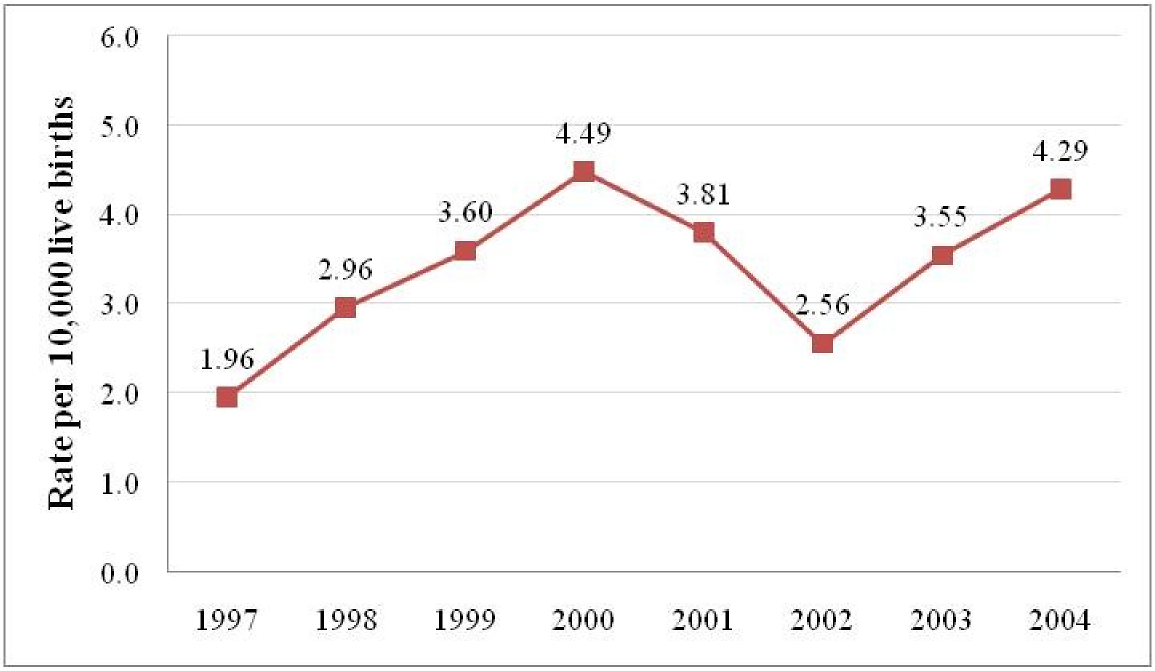
This may result in misclassification bias if contaminants are not equally distributed within a specified Euclidean distance from the contaminant origin.

As the etiology of the majority of cases of birth defects remains unknown, the presence or absence of environmental contaminants and socioeconomic characteristics, and the geographic extent of such factors, can be an important etiological clue. The extent of socioeconomic factors also determines the potential for confounding in investigations of environmental risk factors, such as residence near industrial sites. In addition, understanding the link between contaminants, the hydrology of the region and birth defects may provide insight into how contaminants are affecting surface and groundwater. The design of this study will address the complex relationship between social, economic and environmental factors and gastroschisis. *Ultimately, this study exemplifies how spatial analytical tools – spatial statistics, Geographic Information Systems, and hydrological modeling – can be used in exploratory etiological research*.

Literature Review on Gastroschisis

Gastroschisis is an abdominal wall defect typically located on the right side of the umbilicus. No membranes cover the internal organs and the organs develop outside the body and float in the amniotic fluid. Estimates from the National Birth Defects Prevention Network suggest a great deal of geographic variation; the prevalence of gastroschisis in the United States ranges from 1.22 to 5.11 per 10,000 live births (NBDPN 2005). In North Carolina, the birth prevalence of gastroschisis increased from 1.96 per 10,000 births in 1997 to 4.29 per 10,000 births in 2004 (Laughon et al. 2003) (see Figure 1.2).

Figure 1.2. Rate of Gastroschisis per 10,000 live births in North Carolina: 1997-2004



Source: (Laughon et al. 2003; Wall and Meyer 2006; Mattix, Winchester, and Scherer 2007).

Gastroschisis is thought to have complex or unknown origins. From a research perspective, its causes and developmental origin are largely speculative or unknown (Curry et al. 2000; Feldkamp and Botto 2008). From a public health perspective, it is worrisome because it has increased in prevalence dramatically over the past several decades in most countries around the world (for a review, see (Castilla, Mastroiacovo, and Orioli 2008). With so much uncertainty around the etiology of gastroschisis, most epidemiological studies are exploratory in nature, testing possible associations between this defect 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 have produce malformations in animal models (Brown 1997).

Environmental Teratogens

Typically, when the etiology of a birth defect is unclear, researchers rely on animal models to provide information on specific environmental teratogens that may induce gastroschisis *in utero*. The development of the human abdominal wall, however, is unique and there are few animal models that mimic human development close enough to support research on specific environmental teratogens that may induce gastroschisis (Feldkamp, Carey, and Sadler 2007; Williams 2008). Drongowski, et al (1991) provide a comprehensive review of the few animal studies that have been done. Studies reviewed by the authors suggest that heavy metals such as cadmium and platinum have induced gastroschisis in rat models. **Methylmercury**, which is found in hazardous waste and certain insecticides and is released from burning fossil fuels, may also induce gastroschisis. Case-control studies of gastroschisis affected infants suggest that a variety of illegal and over the counter drugs may increase gastroschisis risk. The link between maternal **cocaine** use and increased gastroschisis risk is of particular interest because cocaine is a vasoconstrictor (Drongowski et al. 1991; Torfs et al. 1996; Draper et al. 2008). One hypothesis offered for the etiology of gastroschisis is that it is a vascular disruption defect (Hoyme, Jones, and Jones 1983). Support for this hypothesis is provided by studies that found increased rates of gastroschisis among infants born to mothers who had used vasoactive medications such as **aspirin**, **acetaminophen, and pseudoephedrine combined with acetaminophen** (Martinez-Frias et al. 1984; Torfs et al. 1996; Werler, Mitchell, and Shapiro 1992b, 1992a). These ingredients are commonly used in over-the-counter cough, cold, and allergy medications. In addition, Lin, et al (2008) found an elevated statistically significant risk of gastroschisis among infants of women who used **bronchodilators** to control asthma during pregnancy.

There are very few studies that examine the relationship between gastroschisis and proximity to hazardous waste and land fill or occupational exposures (refer to Table 1.1). Many studies group gastroschisis with other birth defects and examine gastrointestinal or digestive system defects together and, therefore, were not specific enough to be evaluated for this study. A study by Fielder, et al (2000) found significantly higher rates of gastroschisis than expected in electoral wards within 3km of a landfill site while another study found no association between gastroschisis and exomphlos and residence within 2km of landfill (Morris et al. 2003). Dolk, et al (1998) found an increased risk of gastroschisis within 3km of a hazardous waste landfill but these results were only borderline significant. Finally, one study found an association between gastroschisis and maternal exposure to industrial **solvents** (Torfs et al. 1996**).** To date, there are no studies examining the impact of pesticide exposure (secondary or occupational) on gastroschisis incidence. Given how little research has been done there is a clear need for more research on the possible relationship between environmental exposures and gastroschisis.

Table 1.1. Summary of studies examining the relationship between gastroschisis and environmental exposures

Study	Proximity Measure	Type of NTD	Exposure	Odds Ratio
Hazardous Waste and Landfill				
Morris, et al 2004	Residence in a postal code located within 2 km of a landfill site	Gastroschisis and exomphalos	Special waste landfill sites	NS
Dolk, et al, 1998	Residence within 3 km buffer around hazardous waste site	Gastroschisis	Hazardous waste landfill	3.19 (0.99, 10.77)
Fielder, et al 2000	Residence in an electoral ward within 3km of a landfill site	Gastroschisis	Landfill site	Rate ratio: 8.89 (2.42, 22.8)
Industrial Solvents				
Torfs, et al 1996	Maternal occupational exposure to industrial solvents	Gastroschisis	High-levels of solvents	3.8 (1.69, 8.7)

NS=Not Significant

Maternal Behavior

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** may be more likely to have an infant with gastroschisis. Many studies have shown an increased risk of gastroschisis when the mother or the father report smoking during pregnancy (Feldkamp, Alder, and Carey 2008; Hougland et al. 2005; Torfs et al. 1996; Torfs et al. 1994; Haddow, Palomaki, and Holman 1993; Goldbaum, Daling, and Milham 1990). Maternal **alcohol** use has been linked to higher rates of gastroschisis (Torfs et al. 1994; Werler, Mitchell, and Shapiro 1992b), as has **recreational drug** use (cocaine, amphetamine, marijuana, or LSD) (Torfs et al. 1996; Torfs et al. 1994; Drongowski et al. 1991; Draper et al. 2008). One study found that marijuana use was highest among young mothers and declined with increasing maternal age, exhibiting the same pattern as gastroschisis rates (Forrester and Merz 2006).

Socioeconomic and Maternal Characteristics

Young maternal age has consistently been identified as a risk factor for gastroschisis (Hougland et al. 2005; Salihu et al. 2003; Forrester and Merz 1999; Rankin, Dillon, and Wright 1999; Byron-Scott et al. 1998; Calzolari et al. 1995; Haddow, Palomaki, and Holman 1993; Werler, Mitchell, and Shapiro 1992a; Goldbaum, Daling, and Milham 1990; Torfs, Curry, and Roeper 1990; Laughon et al. 2003). Studies show that the rate of gastroschisis among infants of mothers less than 20 years of age is between three and six times higher than the rate among mothers 25 years and older (Williams et al. 2005; Salihu et al. 2003; Forrester and Merz 1999; Torfs et al. 1994; Forrester and Merz 2006). However, some of this difference may be due to the fact that older mothers are more likely to receive proper prenatal screening and elect to terminate a pregnancy if gastroschisis is found.

Studies investigating the relationship between **race/ethnicity** and risk for gastroschisis show the highest prevalence among Hispanic infants followed by white infants and the lowest prevalence among black infants (Canfield, Honein et al. 2006; Salihu et al. 2004; Lam and Torfs 2006). In addition, one study found the gastroschisis prevalence to be lower in Far East Asians than whites, Pacific Islanders, and Filipinos; however, this difference disappeared when the rates were adjusted for maternal age (Forrester and Merz 1999). There have also been differences reported in the survival rate for infants with gastroschisis. White/Caucasian infants with this defect are more likely to survive than Black infants with this defect (Salihu et al. 2004). This may be due to differentials in access to health care among different racial/ethnic and socioeconomic groups.

Factors related to maternal health and/or medical conditions also appear to be related to gastroschisis. A recent meta-analysis reported women with a lower **body mass index** (BMI) are at the greatest risk for a gastroschisis affected pregnancy (Stothard et al. 2009). Feldkamp, et al (2008b) reported an association between increased gastroschisis risk and maternal **genitourinary infections**.

Very few studies have examined the relationship between socioeconomic status and risk of gastroschisis. One study reported that lower levels of **maternal education** and lower **family income** were associated with increased rates of gastroschisis (Torfs et al. 1994). However, another investigation failed to find an association between less than twelve years of education and gastroschisis risk (Werler, Mitchell, and Shapiro 1992a). Only one study incorporated area-level measures of socioeconomic status while simultaneously controlling for individual-level confounders and this study grouped all digestive system defects together (Vrijheid et al. 2000). Using the Carstairs deprivation index linked to residence at birth, Vrijheid et al. found a significantly increased risk of digestive system defects in the most deprived communities compared to the most affluent communities. One study investigated the difference in gastroschisis between mothers in rural and urban settings. This study indicated that gastroschisis was more likely to occur in **rural areas** than urban ones (Salihu et al. 2003).

Limitations of Studies Examining Environmental Exposures

There is a great deal of variation in the proximity measures used to classify women as exposed or unexposed. The distance from a contaminant site within which a woman may be exposed will undoubtedly differ by type of site, the topography of the land and the mechanism through which contamination is hypothesized to occur. Studies are difficult to compare, however, because they define "proximity" or exposure to hazardous waste and landfill sites differently. Some studies use predefined geopolitical boundaries and compare risk of congenital anomalies within areas where contamination occurred to areas where no contamination occurred while other studies use a specified distance around a hazardous waste or landfill site and compared risk among residents living within that distance to those living outside. There are no studies that empirically choose the distance around contaminant sites using environmental or geologic data. In addition, I have not found any studies that classify exposure using several areas of differing size and then compare model results to examine the sensitivity of the analysis to size of exposure area.

Few studies acknowledge the importance of geographic features of the land in the transport of contaminants through soil, ground and surface water. For example, women living downhill or downstream from a hazardous waste or landfill site have a higher chance of exposure to chemicals due to water runoff than women who live uphill from the site. The geographic features of the landscape may act to modify the size and shape of exposure areas.

GIS technology allows estimation of impact to drinking water wells through analysis of land use within geographic areas delineated as recharge areas for groundwater wells. These modeling techniques are well known in hydrology and environmental geography (Swartz et al. 2003) but, for the most part, have not been applied to public health research. One exception is the Cape Cod Breast Cancer and Environment Study which used pre-defined "zones of concentration" (e.g. the area through which precipitation infiltrates) to determine the nitrate concentrations women may be exposed from well water. I am not aware of any studies of birth defects that use hydrological flow data to look at contaminant transport through soil, surface runoff and groundwater. Incorrect specification of exposure areas may result in misclassification bias whereby unexposed pregnant women are classified as exposed because they are in a designated exposure area. This can bias estimates from risk models and lead to incorrect interpretation of the results.

Theoretical Framework

This research is guided by two bodies of theoretical work, both of which are situated within the human-environment tradition of geography. The *theory of disease ecology* considers the numerous social, economic, behavioral, cultural, environmental and biological factors which create disease in specific places at specific time. Disease ecology provides a framework with which to theorize the socioeconomic, environmental and biological links and interactions between specific features of a place and specific health outcomes (e.g. birth defects). The newer body of research in *neighborhoods and health* complements disease ecology in that it provides a theoretical basis for defining which places or "neighborhoods" to use as units of analysis as well as a variety of statistical models and GIS techniques that can be used to develop and analyze the study data.

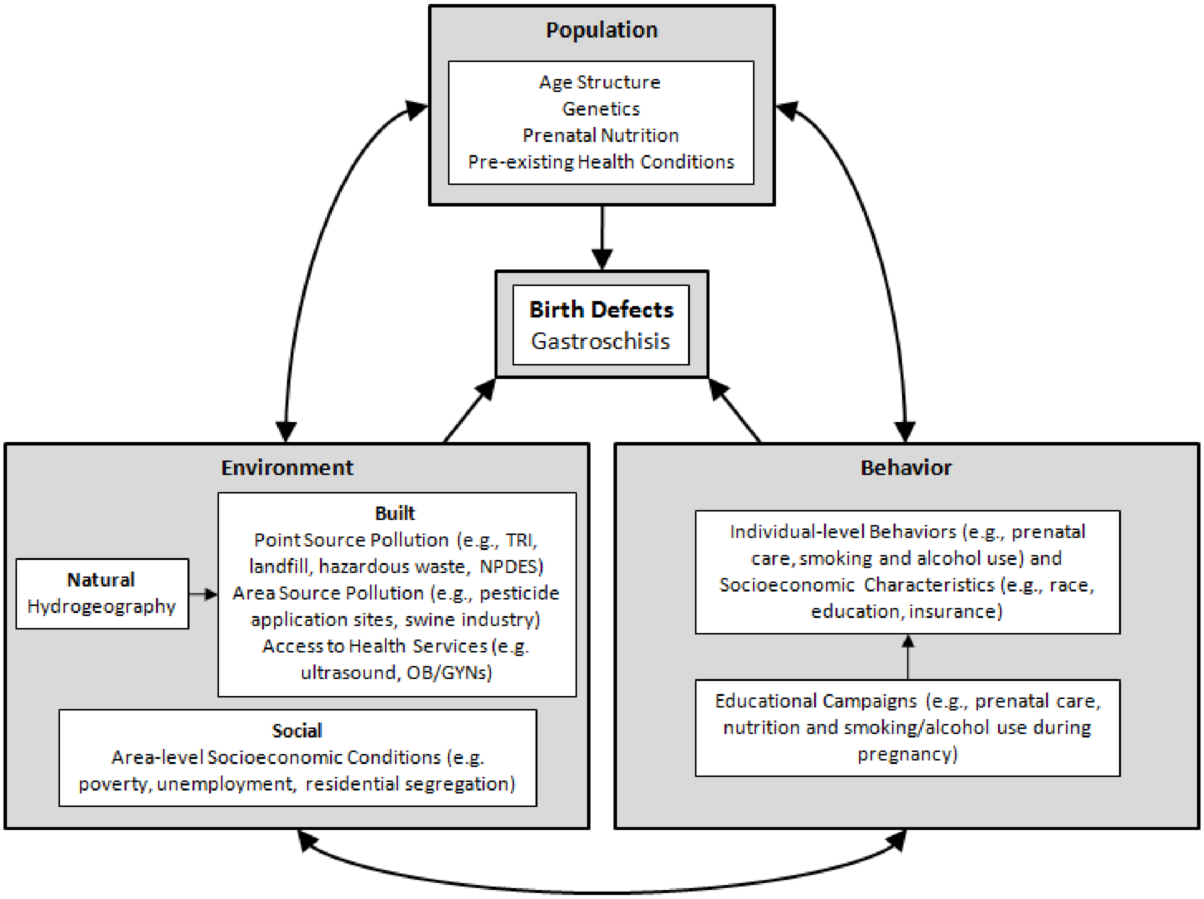
Disease Ecology

The central idea of disease ecology, originally articulated by May (1958) and Dubos (1965), is that disease is an interaction between agent, host and environment: "Agent and host mutually interact, and both concurrently interact with the matrix of the total environment" (Hunter 1974, 4). May suggests that disease is a product of the coincidence of a wide array of environmental and "sociocultural" factors. By sociocultural, May implied certain disease associations were related to various aspects of behavior in human culture (May 1958). Thus, the need for an understanding of the basic dynamics of man-environment interaction is apparent. Disease ecology is concerned with "the ways human behavior, in its cultural and socioeconomic context, interacts with environmental conditions to produce or prevent disease" (Meade and Earickson 2000, 21). Population, society and the physical and biological environments exist in a dynamic equilibrium. The human-environment relationship, if disturbed enough by major changes in land use, pollution, migration, population pressure, or other stressors can lead to a state of instability, which manifests as an increase in disease rates or the appearance of new diseases (Mayer 2000). At the same time, inherent in disease ecology is idea that people do not respond passively to disease, but rather act purposely to mitigate the impact of disease. In this way, social and cultural circumstances can actually create (or prevent) disease. Disease ecology is inherently concerned with integrating the social and physical aspects of human existence (Mayer and Meade 1994).

This framework suggests that disease results from complex interactions between population, environment and behavior or culture (Meade 1977). The *population* dimension involves variables such as genetics, immunological and nutritional status, and demographic composition and structure. *Environment* is the context in which people live and includes aspects of the natural and built environments as well as the social environment. *Behavior* as a dimension includes social organization, social structures that convey power and control of resources, belief systems, values, norms and the creation of technology. None of these factors exist independent of each other; they are constantly interacting and influencing one another in an ongoing recursive relationship. Thus, health outcomes are situational; they are specific to the environmental, behavioral and population conditions experienced by individuals in their daily lives. A graphical representation of the "ecological triangle" as it relates to this research is shown in Figure 1.3. In this model, birth defects (gastroschisis) are influenced by the interactions between the population characteristics of a place as well as aspects of the built, natural and social environment and individual-level behaviors that occur in a certain place (the "neighborhood") at a certain point in time. The specific measures shown in this framework were included because prior epidemiological evidence suggests they may cause gastroschisis.

Aspects of population that may cause high rates of gastroschisis include age structure as younger women have higher rates of this particular defect. Pre-existing health conditions, such as high blood pressure or genitourinary infections, can also contribute to gastroschisis. The nutritional status of the population may impact birth defect outcomes. Adequate prenatal care, which typically includes dietary counseling, can decrease the probability of nutritional deficiencies in a population. Finally, genetic predisposition is also important, though gastroschisis does not appear to have a strong genetic component.

Figure 1.3. Theoretical framework for the disease ecology of birth defects



Several aspects of the built environment are hypothesized to affect gastroschisis. Access to health services such as OB/GYNs, midwives, ultrasound facilities and hospitals may improve diagnosis of birth defects, leading to higher rates in certain areas or, possibly lower rates if pregnant women find out early and choose to terminate the pregnancy. There are also many aspects of the built environment that lead to contaminant deposition into the natural environment. Point source pollution sources, such as TRI sites, landfills and superfund sites, hazardous waste facilities and national pollution discharge sites can all release substances that may cause birth defects. Certain types of land use lead to the application of other contaminants, such as pesticides, municipal waste and swine effluent, onto large areas of land. The hydrogeography is an aspect of the natural environment that impacts the ways in which contaminants from the built environment are transported through the ground or surface water and ultimately come in contact with the human population.

The social environment, the social and cultural structures that influence individual behaviors related to childbearing, are particularly difficult to measure without large scale surveys. To represent this aspect of the disease ecology triangle, area-level measures of social and economic conditions can be used as proxies. High rates of poverty or unemployment signify certain social and economic circumstances that may influence individual level behaviors, such as those related to prenatal care or diet. Similarly, segregated communities and areas of high poverty may create situations where economic constraints create barriers to quality health care and good nutrition as well as poor environmental conditions.

Behavior, as manifest by cultural and social norms, economic constraints and individual choices, also influences birth defect rates. Currently, there is no way to measure health behaviors, aside from smoking and alcohol use and prenatal care, which impact the development of birth defects using the birth defects registry data. However, race, education and employment tend to correspond to poorer health, health care options, and health seeing behaviors. Education, employment and health insurance all represent economic constraints. Education, such as health campaigns encouraging women to quit smoking or seek prenatal care early in pregnancy, may decrease the occurrence of birth defects.

Neighborhoods and Health

Researchers have long recognized that people residing in different areas have differing health outcomes. There has been extensive documentation of small-area variations in morbidity, mortality and health related behaviors over the past 150 years (Macintyre and Ellaway 2003; Gordon 2003; Kawachi and Berkman 2003a). Researchers suggest that these observable differences in health between places could be due to neighborhood effects, or "the independent causal effect of a neighborhood (i.e. residential community) on a number of health and/or social outcomes" (Oakes 2004, 1938). These neighborhood effects can further be broken down into contextual and compositional effects (Diez Roux 2001, 2004; Oakes 2004; Kawachi and Berkman 2003b; Macintyre and Ellaway 2003). Observable differences in health outcomes between places may be due to differences in the kinds of people who live in these places (composition) or differences in the physical or social environment (contextual). For example, high rates of orofacial clefts in a county may reflect a large poor population or the presence of an environmental hazard, such as a municipal landfill or hazardous waste site. Referring back to the triangle of disease ecology presented in Figure 3, it is easy to see how these concepts fit into this framework. Contextual effects are included in the environment and behavior vertices, which include aspects of the physical and built environments as well as larger social context. Compositional effects are represented in the population and behavior vertices, which include individual demographic and economic characteristics. All of these factors exist in a certain place (the "neighborhood") at a certain point in time.

Prior research into neighborhood health effects also provide useful methodological tools for defining relevant geographic areas (neighborhoods) and modeling neighborhood effects after individual-level confounders have been controlled. The size and definition of the geographic area relevant to studying birth defects outcomes may vary according to the processes through which the area effect is hypothesized to operate and the outcome being studied. This requires the development and testing of hypotheses regarding the precise geographic area that is relevant for specific birth defects. Most research on birth defects has used geopolitical boundaries such as counties, census tracts or electoral wards to examine the relationship between area-level socioeconomic and environmental variables and birth defects. Although use of these proxies was probably a practical alternative, they are limited in that they do not necessarily correspond to the theoretically relevant geographic neighborhood. Geographic areas should be validated by geocoding study respondents to several different areas and evaluating the model separately for each area. Such an analysis would help determine how sensitive results are to changes in neighborhood definition. Relevant geographic areas can be defined using information collected through qualitative studies or using quantitative methods that detect areas where groups of people with similar characteristics cluster. For example, the spatial scan statistic can be used to define geographic areas with high concentrations of several population characteristics and census SES data can be aggregated to the areas and linked to the study sample in this neighborhood.

The recognition of the need to distinguish the effects of “context” and “composition” when examining area effects on health has lead to the use of multilevel analysis. Multilevel, or hierarchical, models are used with hierarchical datasets where individuals are nested within areas or neighborhoods. They utilize individuals as the unit of analysis, but include both individual-level and area-level predictors in regression equations to examine area-level socioeconomic effects after individual-level confounders have been controlled. They allow for the “simultaneous examination of within- and between-area variability in outcomes and of the extent to which between-area variability is “explained” by individual and area-level factors” (Diez Roux 2001, 1784). Multilevel models allow researchers to answer four broad research questions:

1) Are there any differences in health outcomes between areas (neighborhoods)?
2) Are there differences in health outcomes between areas (neighborhoods) after taking into account the individual compositional characteristics of the neighborhood?
3) Which demographic, economic or environmental factors explain neighborhood differences in health outcomes, after taking into account the individual composition of the neighborhood?
4) Is the strength of association between these factors and health outcomes similar across areas or are some factors more important predictors of health outcomes in some areas than others?

One of the primary assumptions of traditional regression models is that observations are independent (spatially and temporally). However, people who live in the same neighborhood tend to be more similar that people randomly sampled from the entire population so observations based on these individuals are not fully independent. Thus, modeling birth defect outcomes at the individual level without consideration for similarities between individuals residing within the same neighborhood would lead to violations of the assumption of independence of observations made in standard statistical analyses (including regression models). Ignoring such within-location correlations (or clustering) generally results in estimated variances of contextual effects that are biased downward, making confidence intervals too narrow. To account for such within-location correlations in hierarchical models, the variability in birth defect outcomes is explicitly decomposed into individual-level and location-level components. This allows for proper inferences to be made regarding the impact of contextual factors on birth defect outcomes as well as compositional factors, while accounting for any within-location correlations.

CHAPTER 2

EVIDENCE OF LOCALIZED CLUSTERING OF GASTROSCHISIS BIRTHS IN NORTH CAROLINA, 1999-2004

Elisabeth D. Root

Dr. Robert E. Meyer

Dr. Michael E. Emch

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 et al. 2004; Wilson and 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 et al. 2006; 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 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 et al. 1995; Forrester and Merz 1999; Hougland et al. 2005; Martinez-Frias et al. 1984; Penman et al. 1998; Penz, Menardi, and Brezinka 1998; Rankin, Dillon, and Wright 1999; Roeper et al. 1987; Williams et al. 2005; Wilson and 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 compared to older women. 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, Honein et al. 2006; Torfs et al. 2006; Salihu et al. 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 (Feldkamp, Alder, and Carey 2008; Goldbaum, Daling, and Milham 1990; Haddow, Palomaki, and Holman 1993; Hougland et al. 2005; Torfs et al. 1996; Torfs et al. 1994; Werler, Mitchell, and Shapiro 1992a). Recently, Feldkamp and colleagues (2008a) reported an association between gastroschisis risk and genitourinary infections. 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 et al. 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. Birth defects are particularly well suited to this type of geographic analyses because the lag time between exposure to environmental and socioeconomic conditions and the development of the birth defect outcome is relatively short, at least for conditions that lack a substantial genetic component. This minimizes the potential bias introduced when study subjects move during the exposure period and allows for stronger hypotheses about the area-level factors that may cause the disease. Understanding the geographic distribution of diseases with a long latency period (e.g. cancer) may be less informative because study subjects are much more likely to move several times between exposure and diagnosis of the disease.

Researchers must also 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. Furthermore, 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 et al. 2004; Forand et al. 2002) and there is a dearth of 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, Medicaid status, and maternal smoking) 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 (NC SCHS2005). 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 et al. 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 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 et al. 2003; Krieger et al. 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.

Using this process, we matched 242 of the 264 cases (91.7%) and 11,651 of the 12,488 controls (93.3%). The 22 cases and 837 controls that could not be geocoded were excluded from the cluster analysis. 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 excluded 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 our analysis.

Once data were geocoded, we assigned individual-level records to several census areas: blocks, block groups and tracts. The U.S. Census Bureau has developed a number of geopolitical areas to assist in the collection and reporting of census data. Census areas have a hierarchical structure. A census block is the smallest unit of geography bounded on all sides by visible features, such as streets, rivers or railroad tracks. Census block groups are clusters of contiguous blocks, typically containing from 600 to 3,000 people and census tracts comprise groups of contiguous block groups and have a population ranging from 2,500 to 8,000. 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, 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 and 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 et al. 1998; Kulldorff and 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 and 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 and Ali 2002; Kulldorff 1997). 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 et al. 1998; Drongowski et al. 1991; Fielder et al. 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), Medicaid status (defined as the delivery paid for by Medicaid vs. other payer source) and maternal smoking (mother reported smoking during pregnancy vs. mother did not report smoking) 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). 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.

Results

Figure 2.1 and table 2.1 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.

Figure 2.1. Primary and secondary clusters of gastroschisis births detected using the *unadjusted* model, North Carolina

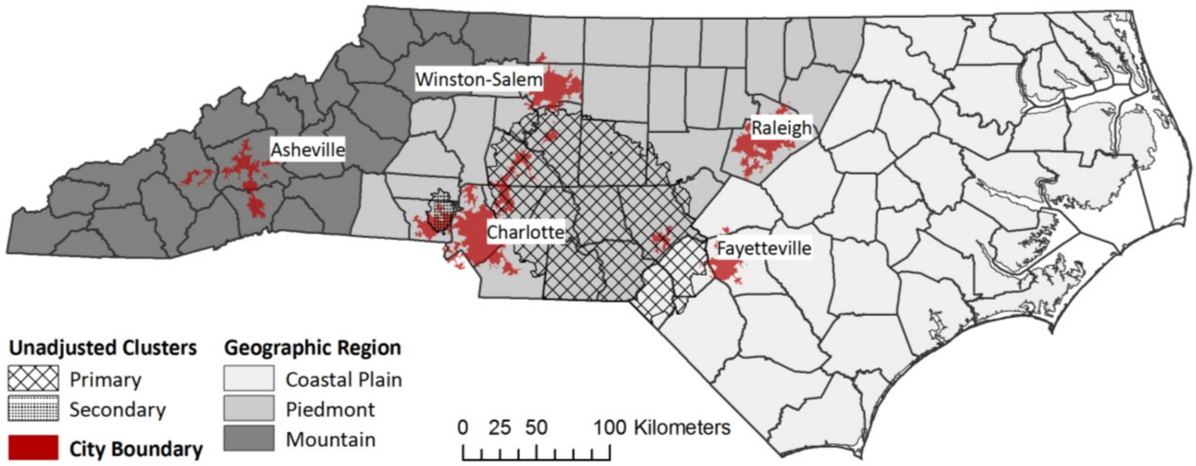


Table 2.1 and figure 2.2 indicate how the results of the spatial cluster analysis changed when covariates were included in the model. When the analysis is adjusted for age,

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.

Table 2.1. Spatial cluster analysis* of gastroschisis births in North Carolina

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
Age, smoking	P	26	8.33	3.38	12.62	**0.028**
	S	4	0.19	21.30	8.39	0.462

*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

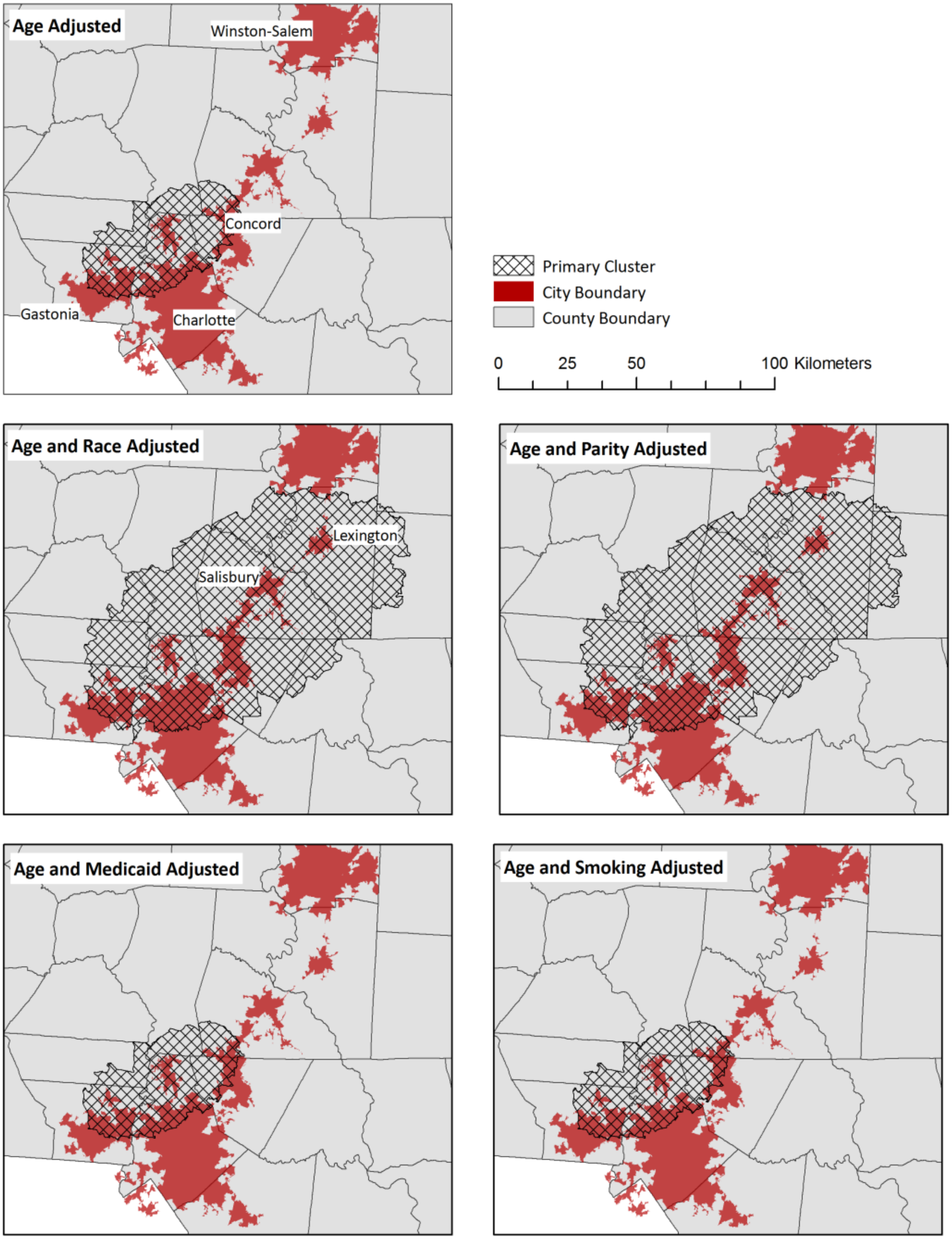
In two subsequent models adjusting for age plus race and age plus parity the LLR dropped, indicating a decrease in the strength of most likely cluster which signifies that race and parity explain some of the excess in gastroschisis cases. The location of the most likely cluster in both the age/race- 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 two models adjusted for maternal age plus Medicaid status and age plus smoking status. For both analyses we found one significant cluster (p=0.014 for age/Medicaid and p=0.028 for age/smoking), both of which include the same census block groups and the same number of cases as the age-adjusted model. The LLR increased to 12.61 for the age/smoking-adjusted model and 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 3.4 for the age/smoking model and 3.5 for the age/Medicaid model, the highest of any model. The fact that the size and shape of the age/Medicaid and age/smoking cluster is the same as the age-adjusted model suggests that Medicaid and smoking status do 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, parity and smoking status, the four 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

Figure 2.2. Close-up view of primary clusters of gastroschisis births detected using covariate-adjusted models, North Carolina



Age Adjusted

Age and Race Adjusted

Age and Parity Adjusted

Age and Medicaid Adjusted

Age and Smoking Adjusted

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 and 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 environmental exposures in this population. In this study, we adjusted for several risk factors: age, race, parity, smoking 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 and Merz 2006; Torfs et al. 1996) as have some over-the-counter medications such as pseudoephedrine and aspirin (Kozer et al. 2002; Torfs et al. 1996; Werler, Mitchell, and Shapiro 1992a). Maternal nutritional deficits have also been linked to increased risk for gastroschisis (Torfs et al. 2006; Torfs et al. 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 parent material (mainly metamorphic rocks such as slate and gneiss) is unique to the 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. Since no data on occupation or industry association is available from the birth record, contextual data from the census on labor force participation could be used to examine this relationship.

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; Williams et al. 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, and King 2004; Khoury et al. 1988; Shaw and Malcoe 1992). However, a majority of these moves appear to be local (e.g. within the same city or county) (Fell, Dodds, and King 2004; Khoury et al. 1988) and the characteristics of women who move are similar to those who do not (Canfield, Ramadhani et al. 2006). 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 risk factors. 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.

CHAPTER 3

EXAMINING THE ENVIRONMENTAL HYPOTHESIS

The previous chapter provides evidence for a localized cluster of gastroschisis in the rural southern piedmont, sandwiched between the cities of Charlotte and Gastonia and the Triad region of Winston-Salem, Greensboro and High Point. The cluster persists, though changes slightly in size and shape, when individual-level maternal factors are controlled for (e.g., age, race, parity, smoking and Medicaid status), suggesting that the cluster is not a result of compositional factors. It does not appear that the geographic distribution of individual-level risk factors for gastroschisis is responsible for the geographic location of the cluster. These results suggest that contextual factors, either social or environmental, may ultimately be responsible for the clustering of the disease.

Localized clusters are often used as evidence for the presence of an environmental contaminant. Individuals living near a point source pollutant are assumed to have higher rates of exposure to chemicals agents and, therefore, higher rates of disease. The area encompassed by the gastroschisis cluster has for centuries been the heart of the textile industry in North Carolina. The conclusion of Chapter 2 hypothesizes a relationship between gastroschisis and proximity to textile mills which release effluent into nearby surface waters. Textile mills use large quantities of water in processing activities and the dyes and solvents used have carcinogenic, mutagenic, or teratogenic effects. Mills treat wastewater using a variety of methods, but are permitted to release this wastewater into open waterways. The following chapter explores the hypothesized relationship between textile mills and gastroschisis using GIS and simple hydrological models to assess exposure to mill effluent. This approach and these methodologies for assessing individual-level exposure have not yet been applied in the birth defects literature.

CHAPTER 4

AN ECOLOGICAL STUDY OF THE RELATIONSHIP BETWEEN TEXTILE MILLS AND GASTROSCHISIS IN NORTH CAROLINA, 1998-2004

Elisabeth D. Root

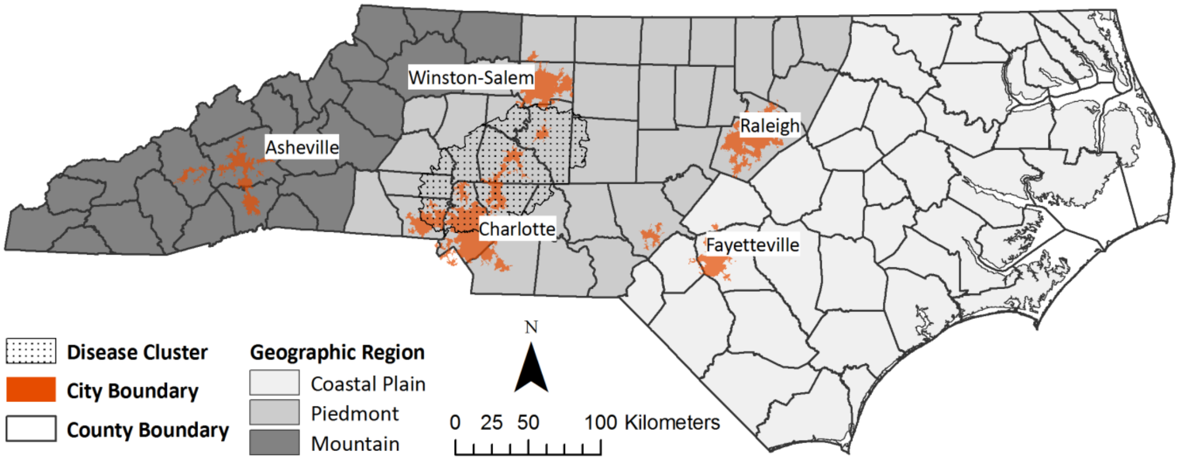
Michael E. Emch

Introduction

Gastroschisis is a rare abdominal wall defect, affecting approximately 3.82 per 10,000 live births each year in the United States (Canfield, Honein et al. 2006; NBDPN 2007). Despite the relative rarity of this birth defect, gastroschisis is worrisome from a public health perspective because it has increased in prevalence dramatically over the past several decades in most countries around the world (for a review, see (Castilla, Mastroiacovo, and Orioli 2008). From a research perspective, its causes and developmental origin are largely speculative or unknown (Curry et al. 2000; Feldkamp and Botto 2008). Animal models currently support no specific mechanism, hindering our ability to attribute gastroschisis to specific environmental teratogens (Drongowski et al. 1991; Feldkamp and Botto 2008). Given that the etiology of gastroschisis is largely unknown, exploratory studies like this one are important because they can provide important etiological clues and help to generate hypotheses about potential environmental teratogens associated with the defect.

In a previous study, we reported the presence of a local cluster of gastroschisis in North Carolina identified using spatial cluster analysis, as shown in Figure 4.1 (Root, Meyer, and Emch 2009). The localized nature of the cluster suggested the possibility of an environmental contaminant in the area. Since the cluster covered one of the main textile producing areas of the state, we hypothesized a relationship between the exposure to the chemicals in textile mill effluent and gastroschisis. Textile mills use considerable quantities of water for wet-processing activities and mill water is often laden with chemicals when it is discharged into surface water sources. Ecological studies of other birth outcomes have found evidence for increased risk of central nervous system defects (Castilla, Campana, and Camelo 2000), orofacial clefts (Bianchi et al. 1997), and low birth weight (Farrow, Shea, and Little 1998; Meyer et al. 2008) associated with the textile industry.

Figure 4.1. Location of a cluster of gastroschisis in North Carolina.



The textile industry consists of a diverse group of establishments engaged in producing fabric products from raw natural and manmade fibers. This process usually involves three steps: fiber preparation and yarn or thread spinning, manufacture of knit and woven fabrics and dyeing and finishing fibers (EPA 1997). Some processes, such as yarn production, spinning and weaving, hardly generate any chemical waste while other processes, such as scouring, bleaching and dyeing generate large amounts of wastewater which are laden with a variety of chemicals (Bisschops and Spanjers 2003). The composition of this wastewater fluctuates depending on where a mill is in the production process, which varies over time. Toxicology studies suggest that many dyes and solvents used in the textile industry have carcinogenic, mutagenic, or teratogenic effects (NIOSH 1985; Birhanli and Ozmen 2005; Schneider, Hafner, and Jäger 2004). However, toxicity data for chronic low-level exposures for most of the commercial textile dyes and their derivatives are lacking. To propose potentially teratogenic effects of textile mill effluent, our research was guided by two assumptions:

1) Textile mills have few air emissions but use large quantities of water for processing activities which are discharged into open waters. Therefore, the most likely exposure pathway is through surface water.
2) The nearly complete absence of data on specific environmental teratogens that induce gastroschisis makes it difficult to select specific textile chemicals and examine these relative to gastroschisis risk. Therefore, we cannot model the movement of specific chemicals through the water system and must rely on proxy measures of exposure.

In the present study, we report the relationship between the concentration of textile mills upstream from public surface water intakes and risk of gastroschisis in North Carolina. Traditionally, exposure risk assessments of birth defects using secondary data to determine exposure have used Euclidean distance from a contaminant source to classify exposure among study cases and controls (Brender et al. 2006; Croen et al. 1997; Dolk et al. 1998; Fielder et al. 2000; Morris et al. 2003; Shaw et al. 1999; White et al. 1988). However, there are many hydrological processes that dictate how contaminants move with surface water. This study is the first birth defect studies to employ modeling techniques that use digital elevation models (DEMs) or known river/stream flow to determine water and contaminant movement and distribution along organized hydrologic flow paths (Tarboton 1997, 2005; Tarboton and Ames 2001). Using these techniques, we sought to answer two study questions: 1) Is drinking water source related to the risk of a gastroschisis birth? 2) Is the risk of a gastroschisis birth increased among women exposed to a textile mill upstream from their surface water intake?

Materials and Methods

Selection of study population

Data on infants with gastroschisis 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 (NC SCHS 2005). This process ensures that nearly all infants born with a congenital malformation are reported to the state. 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). 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 et al. 1991). Control births were matched to the NCBDMP registry database to exclude infants with congenital defects.

Infants with a chromosomal abnormality in addition to gastroschisis were excluded from this study. Terminations of pregnancy and fetal deaths were also not included, as these comprise only a small fraction of gastroschisis cases in North Carolina. We also excluded 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 geographic analysis. Given these exclusions, a total of 264 cases with gastroschisis and 12,488 control births were initially selected for analysis.

Geocoding of residential addresses

Residential address at birth, obtained from the birth record, 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), using Geographic Data Technology (GDT) and parcel data from the NC Department of Transportation. Records not matched by the SCHS were geocoded using a multi-stage geocoding method and different web-based geocoding services (Lovasi 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 et al. 2001; Krieger, Chen, Waterman, Rehkopf et al. 2003). Addresses were then matched in stages using different geocoding services including: Juice Analytics Geocoding Tool (Juice Analytics 2006), Google Earth and Microsoft Virtual Earth. These geocoding methods 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. During the geocoding process we excluded 22 cases and 837 controls due to incorrect, missing or unmatchable address information. This left a total sample size of 242 cases and 11,651 controls for analysis.

Exposure source data

We obtained the geographic location of textile mills in North Carolina, Virginia and Tennessee from the U.S. Environmental Protection Agency's BASINS 4.0 software system (EPA 2008). BASINS is a multipurpose environmental analysis system designed for use by regional, state, and local agencies in performing watershed and water quality-based studies. The BASINS system contains data on textile mills permitted through the National Pollution Discharge Elimination System (NPDES). The NPDES permit program regulates direct discharges from industrial wastewater treatment facilities into open waters of the United States (EPA 2005). Textile mills were identified using the three digit Standard Industrial Classification (SIC) code for the principal activity causing the discharge. We included broadwoven and narrow fabric mills (SIC 221-224), knitting mills (SIC 225), textile finishing mills (SIC 226), carpet and rug mills (SIC 227), yarn and thread mills (SIC 228), and cordage and twine mills (SIC 2298). Only textiles with an active permit (e.g. actively discharging effluent) during the study period were included in the analysis. Using these criteria, we identified 52 textile mills currently permitted to discharge effluent into North Carolina open waterways.[1]

Public drinking water data

Geographic service area boundaries for current public water systems were obtained from North Carolina Center for Geographic Information and Analysis (NCGIA). Due to security concerns, we were unable to obtain information on the location of pipes that distribute water to residential customers. We created a residential address to public water system link using point-in-polygon methods within ArcGIS 9.2 software to allocate study subjects to their water supply system. To account for changes in public water system boundaries over time we compared two geographic files from surveys done in 1997 and 2003 to examine what expansions had occurred over the course of our study period. We found few changes to public water systems served by surface water sources during the study period.

It is possible for study subjects to live within a public water system service area and not draw water from that system, but rather utilize water from personal wells. To account for this, we developed a probability of being connected to public water for each public water system using data on the total number of residential customers as reported by each water system owner linked to census block-level population data from the U.S. Census Bureau. This process is illustrated in Figure 4.2. Census blocks were linked to public water system using point-in-polygon methods within the GIS. The total number of residential customers was then divided by the total population of all census blocks that fell within the water system. Study subjects were assigned a probability for the water system to which they were

---

[1] We included several textile mills that were physically located in Tennessee and Virginia but discharge effluent into waterways that cross into North Carolina.

allocated. Subjects not living within a public water system were assumed to use personal well water and were assigned a probability of 0. Public water systems were linked to their corresponding surface or groundwater intake location within the GIS. The geographic locations of intakes were obtained from NCGIA for both the 1997 and 2003 surveys. Study subjects could therefore be assigned a probability of using: *a)* public surface water, *b)* public groundwater and, *c)* personal well (ground) water.

Figure 4.2. Geographic Information Systems process used to develop individual-level probability of being served by a public water system.

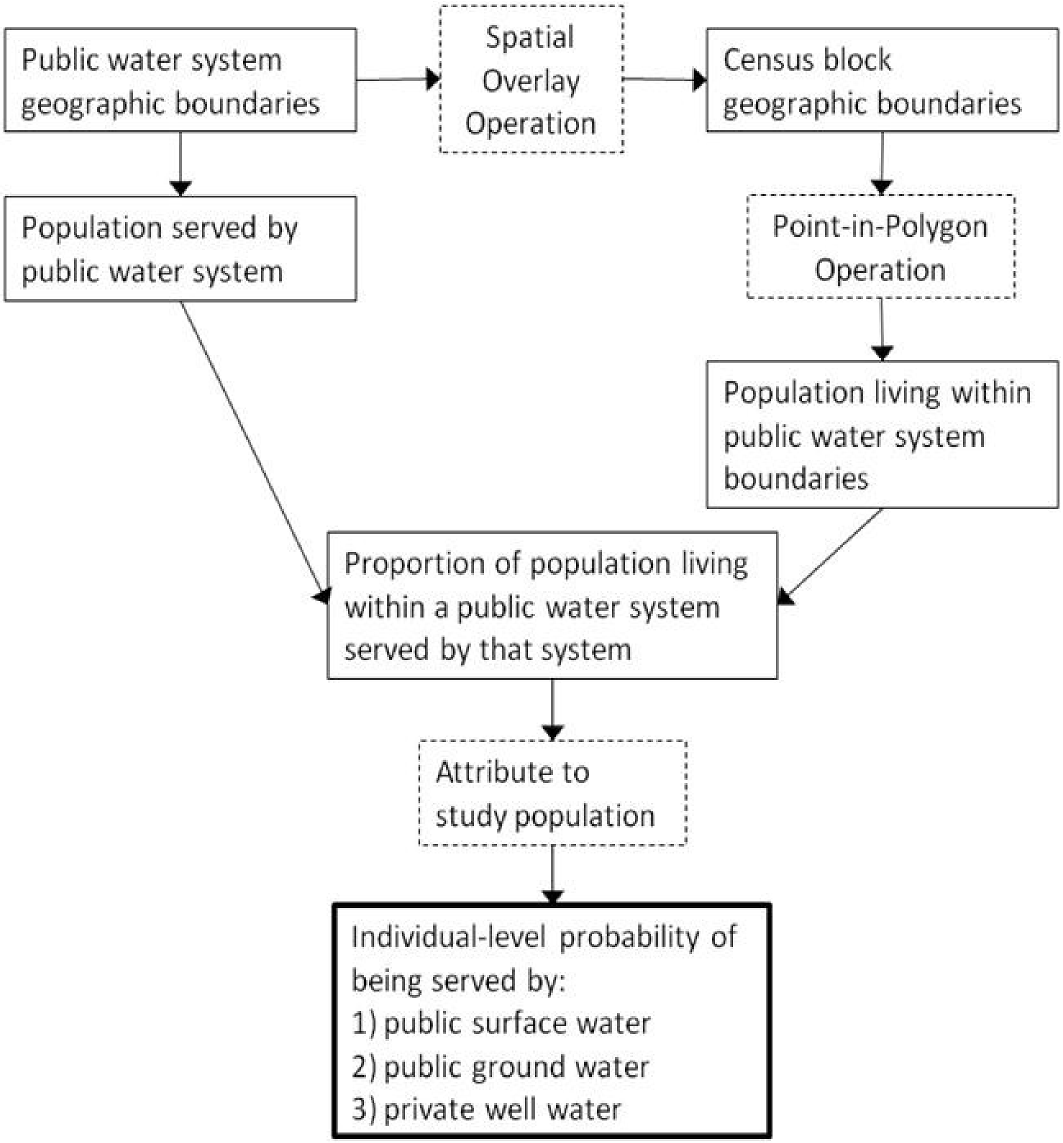
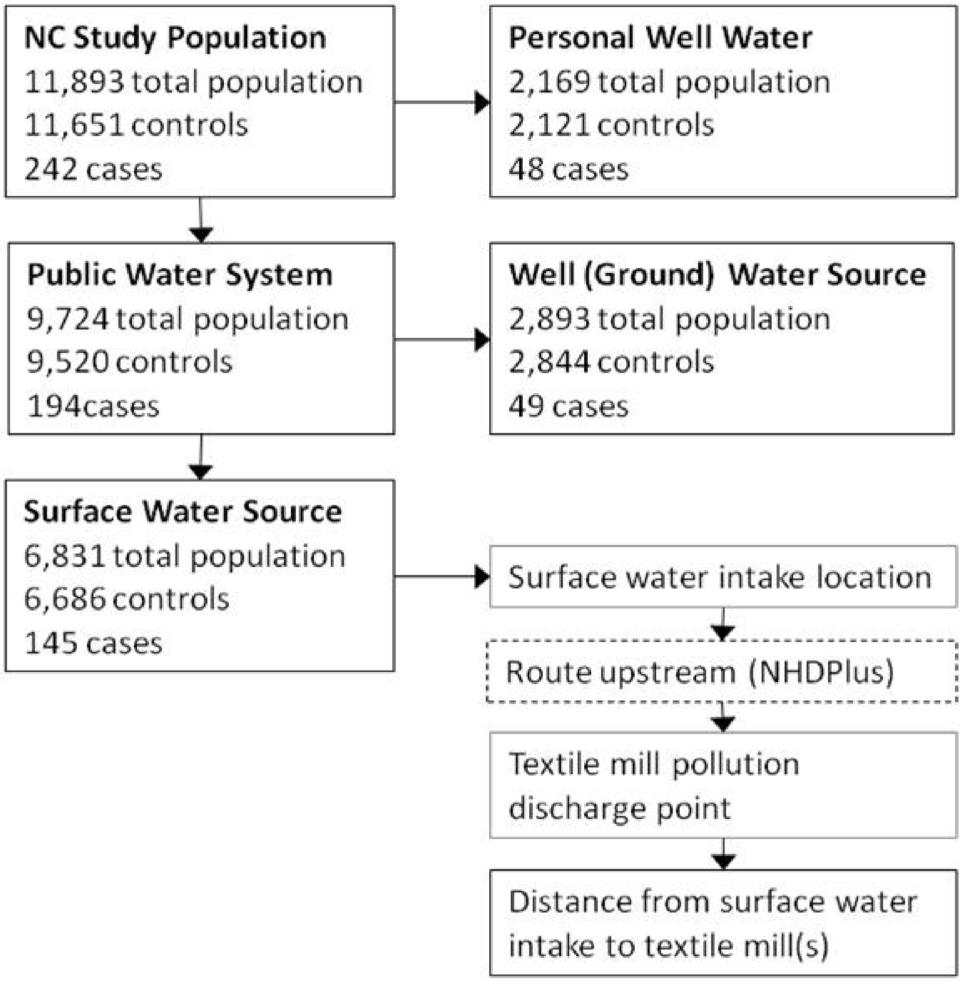


Figure 4.3. Schematic of study subject selection and process by which surface water intakes were classified as exposed to upstream textile mill effluent.



Exposure assessment

We used public water system intake locations to examine potential exposure to upstream textile mill effluent (see Figure 4.3). There were a total of 1,475 public water system intakes in North Carolina serving residential customers. To enhance the specificity of the association between textile effluent and gastroschisis, we made several assumptions when developing our hypotheses: *a)* public water systems drawing from surface water sources have a higher risk of contamination from textile mills because of the large quantity of water used in wet processing discharged into open waters and *b)* there is little evidence as to specific teratogens that may induce gastroschisis making it difficult to model the flow (e.g., velocity and range) of specific chemicals downstream. Given these assumptions, we limited our exposure assessment to the 190 public *surface water* intakes and categorized the number of textiles upstream from each surface water intake at specific distances.

We used NHDPlus to trace upstream influence of textile effluent on surface water intakes. NHDPlus is an integrated set of geospatial data products, including the National Hydrography Dataset (NHD) and the National Elevation Dataset (NED) developed by the United States Environmental Protection Agency to support water quality modeling and assessment (EPA and Horizon Systems 2008). NHDPlus includes a stream network, based on the medium resolution NHD (1:100,000 scale), and tools to model flow direction and navigate up or down stream networks. Using the NHDPlus upstream flow navigation tool within ArcGIS, we traced upstream from surface water intakes to identify relevant textile mill discharge locations (see Figure 4.4). For each surface water intake, we recorded the total number of textile mills (of any type) within 10 km, 20 km, 30 km, 40 km, 50 km, 75 km and 100 km upstream and created a series of categorical variables which indicated the number of upstream textile mills (categorized as 0, 1 or 2 or more) within each distance.

This analysis was repeated classifying textile mills according to the types of products made at each mill using the SIC codes, since the quality and amount of effluent depends heavily on the products being produced, and repeated the analysis. We created categories for: manufacture of knit and woven fabrics and carpets from yarn (SIC 221-225 and 227), fiber preparation and manufacture of yarn, thread or cord (SIC 228 and 2298), and dyeing and finishing of fibers, yarns, fabrics and knitted goods (SIC 226) (see Table 4.1). Several thread/yarn mills were also included in the dyeing and finishing category because those mills produce and finish their threads and yarns in the same location.

Figure 4.4. NHDPlus upstream trace tool used to determine which textile mills were upstream from each surface water intake

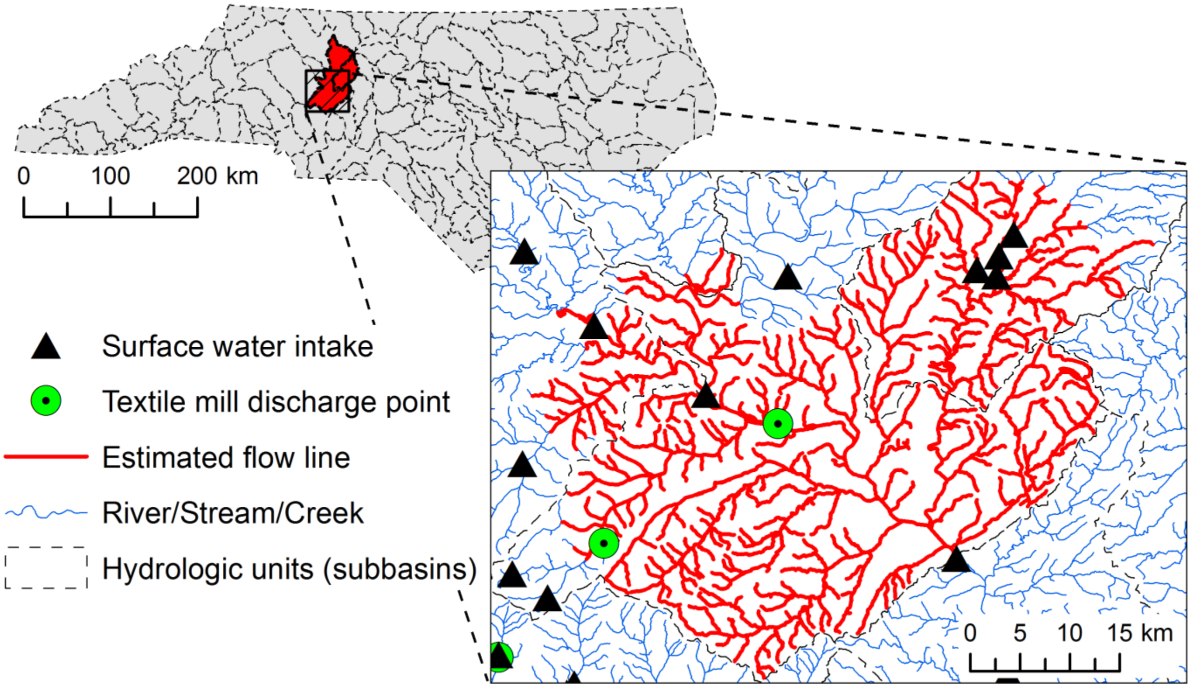


Table 4.1. Number of textile mills affecting open waters by principal activity

Mill classification	SIC code	Number[†]
Manufacture of knit and woven fabrics and carpets from yarn	221-225 and 227	29
Fiber preparation and manufacture of yarn, thread or cord	228 and 2298	12
Dyeing and finishing of fibers, yarns, fabrics and knitted goods	226 and 228 (some)	26
Total number of textile mills	221-228 and 2298	52

SIC, Standard Industry Classification code

[†] The number of mills in each category does not add up to the total number of textile mills since some yarn/thread mills were also included in the dyeing/finishing category.

Statistical Analysis

Descriptive analysis and univariate and multilevel logistic regression modeling were conducted using R v2.7.2 statistical software. To estimate the risk of gastroschisis-affected pregnancy associated with drinking water source and exposure to textile mill effluent, risk ratios (RR) and 95% confidence intervals (CI) were estimated using a log-binomial model. Considered as potential confounders were: *a)* age (categorized as < 20 years of age, 20-24 years, and 25 years or more); *b)* race/ethnicity (categorized as non-Hispanic white, non-Hispanic black, Hispanic and other); *c)* parity (no prior births vs. one or more prior births); *d)* smoking during pregnancy (categorized as yes or no) and; *e)* Medicaid status (categorized as delivery paid for by Medicaid vs. other payer source). Only those covariates that showed a significant risk associated with gastroschisis during univariate and multivariate analyses were included in the exposure analysis.

Since study subjects were nested within public water systems and assigned group-level variables associated with their water system, we estimated multilevel logistic regression models with a fixed slope value for each predictor variable and random intercepts for each public water system. Using the entire sample (n=11,893) we estimated multilevel logistic regression models to examine the effect of drinking water source type (categorized as the probability of using public surface water, public groundwater or personal well water) on risk of a gastroschisis birth. We then used a subset of the sample to examine only those study subjects associated with a public surface water source (n=6,831). Estimates from these multilevel models were used to obtain an overall summary estimate of the effect of exposure to textile mill effluent, allowing for heterogeneity in the water system-specific estimates. The probability of using public surface water was considered a moderating variable in the relationship between gastroschisis outcomes and exposure to upstream textile mills. We included an interaction term between the probability of using public surface water and the number of textile mills upstream to account for this moderating effect. To interpret this interaction effect, relative risk of gastroschisis for different levels of textile mill exposure (1 vs. 0 mills, 2 vs. 0 mills and 2 vs. 1 mills) were estimated, conditioned on the probability of using surface water at 3 different levels: low (60%), medium (80%) and high (100%).

Table 4.2. Prevalence (%) of potential confounding variables among cases and controls for all study subjects and those using public surface water only

	All water source type		Public surface water only	
	Cases (n=242)	Controls (n=11,651)	Cases (n=145)	Controls (n=6,686)
Maternal Age				
< 20	101 (41.7)	1385 (11.9)	58(40.0)	783 (11.7)
20 – 24	92 (38.0)	3134 (26.9)	63 (43.5)	1726 (25.8)
25 to 29	37 (15.3)	3177 (27.3)	21 (14.5)	1774 (26.5)
>= 30	12 (5.0)	3955 (33.9)	3 (2.0)	2403 (35.9)
Maternal Race				
White	162 (66.9)	7167 (61.5)	81 (55.9)	3597 (53.8)
Black	36 (14.9)	2695 (23.1)	29 (20.0)	1879 (28.1)
Hispanic	37 (15.3)	1356 (11.6)	31 (21.4)	951 (14.2)
Other	7 (2.9)	433 (3.7)	4 (2.8)	259 (3.9)
Birth Parity				
No prior births	164 (67.8)	4846 (41.6)	96 (66.2)	2747 (41.1)
1 or more prior births	78 (32.2)	6805 (58.4)	49 (33.8)	3939 (58.9)
Smoker vs. Nonsmoker				
Non-smoking	180 (74.7)	10125 (87.0)	108 (75.0)	5941 (88.9)
Mother reported smoking	61 (25.3)	1515 (13.0)	36 (25.0)	738 (11.1)
Medicaid				
Birth paid for by other payer	78 (32.2)	7013 (60.2)	46 (31.7)	4050 (60.6)
Birth paid for by Medicaid	164 (67.8)	4638 (39.8)	99 (68.3)	2636 (39.4)

Results

Of the 11,893 births available for analysis, 6,831 were to mothers who lived within a public water system supplied by surface water. Table 4.2 shows the prevalence of covariates among cases and controls. Characteristics were similar for the total study population and the subset the population on public surface water, though there were some minor differences in race and age. Relative to control mothers, mothers of infants with birth defects were more likely to be young (<20 years of age), white, have no prior births (nulliparous), reported smoking during pregnancy and had their birth paid for by Medicaid. Table 4.3 provides descriptive statistics on the number of people exposed to each type of textile mills and the characteristics of exposure. A total of 1,509 mothers were exposed to textile mill effluent from one or more upstream textile mills, 36 of which were cases and 1,473 of which were controls.

Table 4.3. Characteristics of the exposed population and exposure levels

	Characteristics of exposure[†]				**No. of individuals exposed to textile mill effluent**					
					Cases			*Controls*		
	Mean	*SD*	*Min*	*Max*	*Total*	*1 mill*	*2+ mills*	*Total*	*1 mill*	*2+ mills*
All textile mills	0.60	1.35	0	5	36	12	24	1473	318	1155
Finishing mills	0.11	0.32	0	1	17	17	-	797	797	-
Weaving/knitting mills	0.14	0.36	0	2	24	23	1	916	888	28
Yarn/thread mills	0.04	0.24	0	2	6	6	-	255	209	46

[†] Descriptive statistics for the number of mills each person being served by a public surface water system is exposed to.

When we examined the entire study population, we found a statistically significant relationship between the probability of being on public surface water or public ground water and risk for gastroschisis. Table 4.4 shows the relative increase or decrease in risk for a gastroschisis birth with a 10% increase in the probability of being on a specific water source. Only the relative risks for public surface water and public ground water sources were significantly related to gastroschisis outcomes. For women living in a public water system drawing from a surface water source, there was a 4.1% increase in risk associated with a 10% *increase* in probability of being serviced by the public water system. For women living in a public water system drawing from a ground water sources, there was a nearly 5% *decrease* in risk associated with a 10% increase in the probability of being on public ground water. These results suggest that exposure to public surface water sources increases risk of gastroschisis while exposure to public ground water sources reduces risk.

Table 4.4. Relative risk and 95% confidence interval (CI) of gastroschisis for the probability of exposure to each water source type

Drinking water source	Relative risk (95% CI) †	p-value
Probability of public surface water	1.041 (1.008 – 1.075)	0.0143
Probability of public ground water	0.952 (0.910 – 0.995)	0.0305
Probability of private well water	0.986 (0.951 – 1.022)	0.4501

Relative risks represent the percent change in risk given a 10% increase in the probability of exposure to each water source type.

† Relative risks adjusted for maternal age, race, birth parity, smoking status and Medicaid

When we examined only births to women being served by public surface water, we found no evidence of greater risk associated with exposure to upstream textile mill effluent. While we did estimate exposure models using a variety of distances to classify exposure to textile effluent (ranging from 10km to 100km, results not shown), the models estimated using the 50km distance upstream to classify exposure yielded the best fit so we chose to present those results here in Table 4.5. Since the probability of being on surfaces water was considered to be a moderating variable in the relationship between birth outcomes and exposure to textile mill effluent, we examined the relative risk of a gastroschisis birth at several different probabilities. Women exposed to one or more upstream textile mills had no greater risk than women exposed to no textile mills of having a gastroschisis affected pregnancy (RR=0.95, 95% CI=0.48-1.85 with a high probability of surface water). While we found an elevated relative risk when we examined weaving mills only, this relationship was not statistically significant (RR=1.5, 95% CI=0.49-4.59 with a high probability of surface water). Exposure to finishing mills, the most likely source of polluted effluent, showed an unexpected relationship with an elevated, though not statistically significant, relative risk at the lowest probability of surface water (RR=1.23, 95% CI=0.53-9.41) and a decreased risk at the highest probability of surface water (RR=0.47, 95% CI=0.17-1.28). There was not a sufficient size population exposed to yarn and thread mills to examine this type separately.

Table 4.5. Adjusted relative risks and 95% confidence interval (CI) for exposure to textile mills, by principle activity, conditioned by the probability of being on public surface water

Probability of being on surface water	**RR (95% CI) of exposure to 1 or more mills vs. 0 mills**[†]
All textile mills	
Low	0.94 (0.46 – 1.95)
Med	0.94 (0.60 – 1.49)
High	0.95 (0.48 – 1.85)
Finishing	
Low	2.23 (0.53 – 9.41)
Med	1.34 (0.59 – 3.04)
High	0.47 (0.17 – 1.28)
Weaving	
Low	0.84 (0.39 – 1.83)
Med	1.02 (0.63 – 1.64)
High	1.50 (0.49 – 4.59)

[†] Relative risks (RR) adjusted for maternal age, race, birth parity, smoking status and Medicaid
Probability of being on surface water category (low, 60%; medium, 80%; high, 100%)

In order to examine a dose-dependent risk, we grouped all textile mills together and classified exposure into 3 categories (no mill exposure, exposure to 1 mill or exposure to 2 or more mills) and found no evidence of elevated risk for a gastroschisis birth with higher levels of exposure (see Table 4.6). We found an elevated relative risk for exposure to 2 or more mills (vs. no mills) when the probability of surface water was low (RR=1.12, 95% CI=0.49-2.59), though this relationship was not significant. We also found an elevated risk for gastroschisis for exposure to 1 mill (vs. no mills) when the probability of surface water was high (RR=1.67, 95% CI=0.66-4.25). However, there was a decreased risk for exposure to 2 or more mills (vs. no mills) (RR=0.67, 95% CI=0.28-1.6). These results do not indicate a clear relationship between textile mill exposure and risk for a gastroschisis birth.

Table 4.6. Adjusted relative risks and 95% confidence interval (CI) for exposure to textile mills at different doses, conditioned by the probability of being on public surface water

	RR (95% CI) of exposure to: [†]		
	1 mill vs. 0 mills	*2 or more mills vs. 0 mills*	*2 or more mills vs. 1 mill*
Probability of being on surface water			
Low (60%)	0.70 (0.19 – 2.58)	1.12 (0.49 – 2.59)	1.61 (0.37 – 7.01)
Med (75%)	0.93 (0.40 – 2.13)	0.95 (0.57 – 1.58)	1.02 (0.41 – 2.58)
High (100%)	1.67 (0.66 – 4.25)	0.67 (0.28 – 1.60)	0.40 (0.12 – 1.32)

[†] Relative risks (RR) adjusted for maternal age, race, birth parity, smoking status and Medicaid
Probability of being on surface water category (low, 60%; medium, 80%; high, 100%)

Discussion

The results of this study suggest that prenatal exposure to textile mill effluent does not have an impact on the risk for a gastroschisis-affected pregnancy. Compared with unexposed mothers, the relative risk for mothers exposed to 1 or more mills (of any type) upstream was approximately 0.95, regardless of the probability of being on surface water. While we did find elevated risk ratios for exposure to one or more mills engaged in textile finishing (1.34) and weaving (1.5), these were not statistically significant and were difficult to interpret when the probability of being served by a public surface water system was considered. In addition, when we attempted to examine a dose-dependent risk for gastroschisis by categorizing exposure by the number of upstream mills we did not find evidence for increased risk with increasing exposure to upstream textile mills.

The directly relevant literature to which these results can be compared is extremely limited. A few studies have reported an association between solvents, which are used extensively in the textile industry, and gastroschisis. Most notably, a case-control study by Torfs, et al. (1996) found increased odds for women with an occupational exposure to solvents (both aliphatic and aromatic hydrocarbons) which are also used in the textile industry. They also found increased odds for gastroschisis with a hobby-related exposure to colorants. A 1979 study by Earickson, et al (1979) reported an association between gastroschisis and occupation in the printing industry, which uses similar chemical processes as textile dyeing.

We did find a statistically significant increase in risk associated with the probability of being served by a public water system drawing from a surface water source. The greater the probability of being on surface water, the greater the risk of a gastroschisis affected pregnancy. Conversely, women served by public water systems using ground water and those on private well water had a decreased risk for a gastroschisis birth. While these results certainly cannot suggest a specific mechanism, they suggest the possibility that surface water sources may contain something, possibly a teratogen that can induce gastroschisis. A recent study by Mattix, et al (2007) reported a positive correlation between an increase in surface water atrazine levels, a chemical common in fertilizers, and gastroschisis. The lack of animal studies that suggest possible teratogens makes pursuing this etiological clue through ecological studies difficult. An alternative hypothesis for this finding relates to the condition of the various water systems' infrastructure. Many towns in North Carolina grew around a local textile mill and public utilities were built and maintained for the mill and residents in the mill town. As textile mills have closed down over the past 30 years, many of these small towns experienced a decrease in tax revenue and some public water systems have fallen into disrepair. This hypothesis merits further investigation, and our future analyses will focus on measuring the effect of age of public health infrastructure on gastroschisis outcomes.

These results are undoubtedly affected by exposure misclassification. Because individual exposure measurements were unavailable, we used a proxy for textile mill effluent exposure based on proximity of textile mills to surface water intakes serving a residential population. In addition, we were only able to obtain geographical boundaries for public water systems and could not positively attribute each individual in the study population to a public water source and had to develop a probability of being on a public water system. While we did account for these limitations in our statistical analysis, they may contribute to the absence of adverse effects of textile mill exposure in our study. Another potential limitation of our study is that we use residence at birth to assess exposure. Studies have shown that between 25 and 30 percent of women change residence between conception and birth (Fell, Dodds, and King 2004; Khoury et al. 1988; Shaw and Malcoe 1992). However, a majority of these moves appear to be local (e.g. within the same city or county), to areas that we assume would be served by the same local public water system (Fell, Dodds, and King 2004; Khoury et al. 1988) and the characteristics of women who move are similar to those who do not (Canfield, Ramadhani et al. 2006). Caution should be exercised when interpreting the results of geographic studies that use maternal residential address at delivery, especially when using residence to assign exposure to potential environmental contaminants.

Gastroschisis is a rare birth defect and the small sample size could also have contributed to our failure to find an effect of textile mill exposure. Out of 6831 women living with in a public water system drawing on surface water sources, only 1509 women were expose to textile mill effluent, 36 of which were cases. The rarity of the outcome being studied necessitated the use of a retrospective study design which limits the options available for exposure assessment. While the approach presented in the paper is a reasonable and novel way to assess exposure, it is only a proxy for true exposure to the chemicals contained in textile mill effluent, contributing to the problem of exposure misclassification.

The present study was motivated by the location of a cluster of gastroschisis in North Carolina which suggested a possible increased risk of this pregnancy outcome associated with the textile industry. Although we moved beyond the use of occupational titles and buffers to assess exposure, our inability to definitively assess the source of study subject's residential drinking water means we cannot confidently exonerate exposures for which no associations were found. Future efforts at exposure assessment will need to improve upon the approach taken in the present study. A study capable of addressing specific exposures would require household-level evaluation and measurement of the quality of drinking water, which might be feasible if gastroschisis were identified *in utero* via ultrasound. This birth outcome is rare, however, and it is uncertain whether a large enough sample size could be obtained to have sufficient statistical power to study the relationship between textile mill exposure and gastroschisis. In addition, the evidence presented here to does suggest a strong enough association for such a study to be warranted.

One innovation of this study is the use of hydrological modeling to assess exposure of downstream surface water intakes to upstream textile mill effluent. The geography of the land is very important in the transport of contaminants through surface water. For example, women served by a public water system with a surface water intake downstream from a textile mill have greater exposure to chemicals than women upstream from the site. Thus, the geographic features of the landscape may act to modify the size and shape of exposure areas. We are not aware of any studies of birth defects that used geographic features, such as hydrology, to designate contamination risk. Studies using secondary data to assess exposure have used "as the crow flies" distance measures from a potential contaminant site to an individual's place of residence. This may result in misclassification bias if contaminants are not equally distributed within a specified Euclidean distance from the contaminant origin. Hydrologists have developed models that utilize characteristics of the terrain and surface water flow to estimate contaminant transport and deposition from a point source (Tarboton 2005; Tarboton and Ames 2001; Wilson and Gallant 2000). These modeling techniques are well known in hydrology and environmental geography (Swartz et al. 2003) but, for the most part, have not been applied to public health research. Ultimately understanding the link between contaminants, the hydrology of the region and birth defects may provide insight into how contaminants are affecting surface water sources. We believe that this novel approach to exposure assessment is a valid and valuable contribution to the environmental epidemiology literature.

CHAPTER 5

THE ROLE OF SOCIOECONOMIC ENVIRONMENT IN DISEASE CLUSTERS

The previous two chapters demonstrate ways in which spatial methodologies can be used to hypothesize factors that may contribute to uneven distributions of disease. The spatial cluster analysis in Chapter 2 revealed the geographic location of a cluster of gastroschisis in the rural southern piedmont of North Carolina. Since localized clusters often suggest the presence of a point source environmental contaminant, the analysis in Chapter 4 examined the relationship between the textile mill industry, which is highly concentrated in the rural southern piedmont, and gastroschisis outcomes. Using GIS and simple hydrological modeling techniques, the study population was associated with a public water system and mothers using public *surface* water were assigned an exposure status based on the presence of upstream textile mills. The results were largely inconclusive, showing no increase in risk for gastroschisis associated with exposure to textile mills, but do suggest the possibility increased risk among mothers using pubic surface water sources vs. public ground water or private wells.

The neighborhoods and health literature (reviewed in Chapter 1) provides an alternative theory that can be used to explain the spatial clustering of gastroschisis. The cluster analysis in Chapter 2 controlled for individual-level risk factors, which ensures the cluster is not a consequence of compositional factors. But, area-level socioeconomic measures of unemployment and poverty, which capture the larger social environment, may exert an independent causal effect on health outcomes and contribute to the uneven distribution of disease. Thus, clusters may encompass areas with specific socioeconomic conditions that increase risk for gastroschisis in that location. The following chapter uses the neighborhoods and health framework, as well as the methodologies developed in that literature, to examine the possible influence of area-level socioeconomic conditions on risk for a gastroschisis-affected pregnancy. Many demographic variables were examined for this study, including median age of housing stock and household income and the proportion of the population that is white, black and employed in mill work (including textile, furnishing and wood). The variables discussed in the following chapter were included because prior research suggests that they influence health (specifically birth outcomes) and they showed a statistical relationship to gastroschisis.

Similar to cluster analysis, neighborhood studies may assist in the generation of hypotheses about proximal social, economic or cultural factors that influence disease distribution. To date, no studies have examined the relationship between gastroschisis and area-level socioeconomic factors. Since the etiology of gastroschisis is largely unknown, neighborhood studies have the potential to advance our understanding of this birth outcome.

CHAPTER 6

THE ASSOCIATION BETWEEN NEIGHBORHOOD POVERTY AND UNEMPLOYMENT AND GASTROSCHISIS IN NORTH CAROLINA, 1998-2004

Elisabeth D. Root

Dr. Robert Meyer

Dr. Michael E. Emch

Introduction

Public health research has long recognized that people residing in different geographic areas have differing health outcomes and that many health outcomes cluster in space. Geographic variation in health and disease may be due to differences in the kinds of people who live in these places (composition) or differences in the physical or social environment (context). Individuals with similar risk factors may live in the same geographic area, producing larger area-level patterns of disease. At the same time, an individual's proximal environment exerts a variety of social, psychological and biological pressures which can directly influence health. But how do we examine the different, and often complimentary, roles composition and context play in the geographic distribution of disease? The recent resurgence of research on social determinants of health and the growing acceptance of the utility of an ecological perspective of health have lead to a large body of literature examining the role of "neighborhood effects" on health (Diez Roux 2001; Kawachi and Berkman 2003b; Macintyre, Ellaway, and Cummins 2002). These studies use a variety of methods to examine the influence of an individual’s contextual environment (e.g., their neighborhood) on health outcomes after controlling for individual-level risk factors.

While neighborhoods and health studies can be used to confirm hypothesized mechanisms by which area-level characteristics affect health, they can also be useful in exploratory etiological research. When the cause of a disease is unknown or speculative, area-level characteristics can provide important clues about plausible social, psychological and biological mechanisms that may influence the disease. For example, many birth defects are thought to have complex or unknown origins and most epidemiological studies are exploratory in nature, testing possible associations between these birth defects and socioeconomic inequalities that are correlated with poor health outcomes (Brown 1997). Studies in the United States and other countries have revealed that area-level measures of socioeconomic status (SES) are associated with several birth defects including: orofacial clefts (Carmichael et al. 2003; Clark et al. 2003; Vrijheid et al. 2000), neural tube defects (Vrijheid et al. 2000; Wasserman et al. 1998) and heart defects (Carmichael et al. 2003). However no studies to date examine the effect of area-level SES measures on gastroschisis, a serious abdominal wall defect that has increased in prevalence over the past several decades (Rankin, Dillon, and Wright 1999; Wilson and Johnson 2004; Martinez-Frias et al. 1984; Roeper et al. 1987; Calzolari et al. 1995; Penman et al. 1998; Penz, Menardi, and Brezinka 1998; Hougland et al. 2005; Williams et al. 2005).

Gastroschisis is a rare birth defect, affecting approximately 3.82 per 10,000 live births each year in the United States (Canfield, Honein et al. 2006; NBDPN 2007). Its causes and developmental origin are largely speculative or unknown (Curry et al. 2000; Feldkamp and Botto 2008). Animal models currently support no specific mechanism, hindering our ability to attribute gastroschisis to specific environmental teratogens (Drongowski et al. 1991; Feldkamp and Botto 2008). Furthermore, the role of specific genetic factors is unclear. Familial occurrence of gastroschisis has been reported, as has concordance in monozygotic twins, though the reoccurrence risk appears to be low, suggesting that genetic factors are only responsible for a small fraction of all cases or the possibility of gene-environment interactions (Torfs et al. 2006; Torfs and Curry 1993; Opitz and Pysher 2008; Schmidt et al. 2005).

Young maternal age has consistently been identified as a risk factor for gastroschisis (Hougland et al. 2005; Salihu et al. 2003; Forrester and Merz 1999; Rankin, Dillon, and Wright 1999; Byron-Scott et al. 1998; Calzolari et al. 1995; Haddow, Palomaki, and Holman 1993; Werler, Mitchell, and Shapiro 1992a; Goldbaum, Daling, and Milham 1990; Torfs, Curry, and Roeper 1990; Laughon et al. 2003). Studies show that the rate of gastroschisis among infants of mothers less than 20 years of age is between three and six times higher than the rate among mothers 25 years and older (Williams et al. 2005; Salihu et al. 2003; Forrester and Merz 1999; Torfs et al. 1994; Forrester and Merz 2006). This consistent pattern has lead many investigators to search for social or environmental factors to which younger women might more likely be exposed. Age is the most conspicuous factor correlated with some underlying causal factors and young maternal age could be a proxy for environmental exposures, individual behaviors, socioeconomic factors or some combination of the three. Results are inconsistent, but recent studies suggest that young maternal age may be an indicator of obstetrical high risk group, possibly correlated to social deprivation (Vrijheid et al. 2000; Torfs et al. 1994), environmental risks including malnutrition (Lam, Torfs, and Brand 1999; Waller et al. 2007; Torfs et al. 1998), poor health care, increased consumption of medical or social drugs (Draper et al. 2008; Forrester and Merz 2006; Werler, Mitchell, and Shapiro 1992b, 1992a), and chemical exposures (Dolk et al. 1998; Torfs et al. 1996).

Given that the etiology of gastroschisis is largely unknown, examining the influence of neighborhood-level SES measures may assist in the generation of hypotheses about the underlying causal factors associated with socioeconomic factors. In this study we examine the relationship between gastroschisis and five area-based measures of SES after controlling for known individual-level risk factors. Two study questions guided this study: 1) To what extent are neighborhood-level SES variables related to the risk of a gastroschisis birth? 2) Does this relationship differ when different spatial scales are used to define neighborhoods? Throughout this study, we also sought to address a major criticism that has arisen in the neighborhoods and health literature. The concept of "neighborhood" is complex and critics suggest that relevant neighborhoods need to be carefully defined and operationalized based on the underlying processes and causal mechanisms presumed to affect the health outcome being studied (Diez Roux 2001). This means that the spatial scale at which neighborhood factors influence health may vary based on *both* the socioeconomic measure and health outcome used. In this study, we attempt to address these critiques by empirically defining neighborhoods and comparing model results across different geographic scales.

Methods

Birth Defects Data

Birth defect and maternal characteristics 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. 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 (Buescher et al. 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. We also excluded 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.

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), using Geographic Data Technology (GDT) and parcel data from the NC Department of Transportation. Records not matched by the SCHS were geocoded using a multi-stage geocoding method and different web-based geocoding services (Lovasi et al. 2007). Using this process, we matched 242 of the 264 cases (91.7%) and 11,651 of the

12,488 controls (93.3%). Records with an invalid or unmatched address were removed from the analysis.

The data also contained potential covariates from the linked birth files including: mother's age, race and ethnicity, marital status, number of prior births, month prenatal care began, mother's smoking status, and whether or not Medicaid paid for the delivery. These individual-level attributes are possible confounders to the neighborhood environment-gastroschisis relationship, and are reliably measured on the birth record. 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.

SES Data

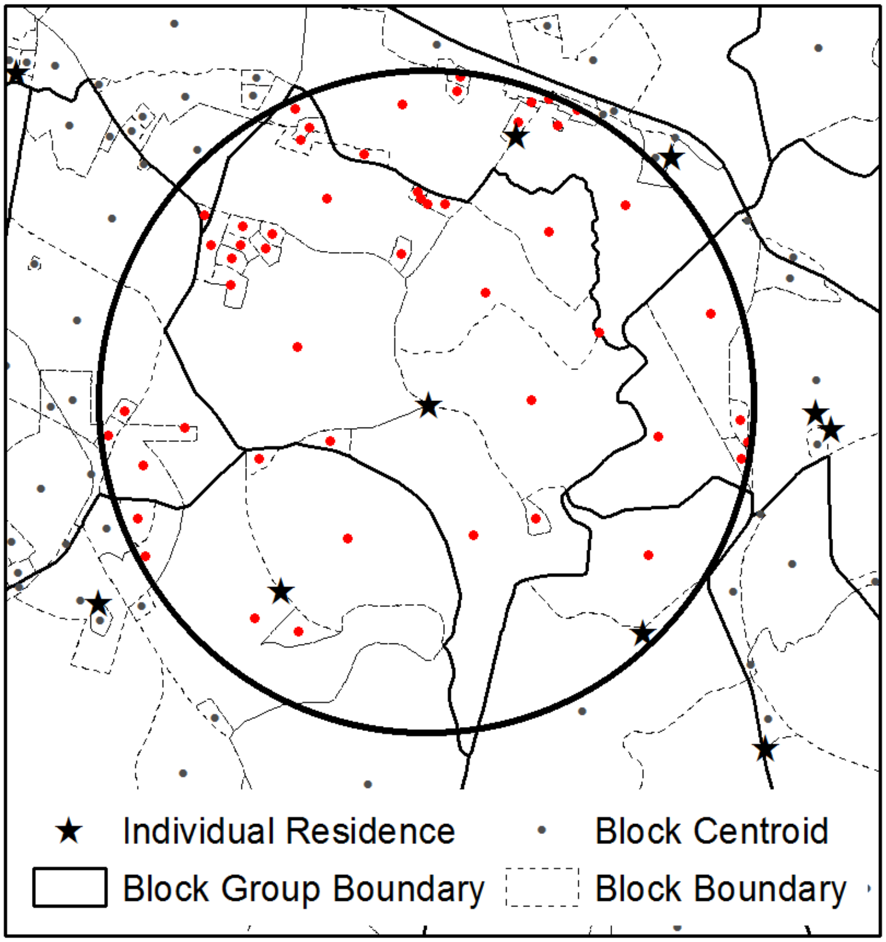
Socioeconomic variables for census tracts, block groups and blocks were obtained from the 2000 Census of Population and Housing Data from the U.S. Census Bureau. Following the approach of several previous studies that examine area-level effects on various birth outcomes (Krieger, Chen, Waterman, Soobader et al. 2003; Wasserman et al. 1998; Carmichael et al. 2003; Messer et al. 2008) six census variables were used to estimate neighborhood-level socioeconomic characteristics: percent of the population living below 100% and 200% of federal poverty level, percent of the population with less than a high school education, percent of the population unemployed, and percent of the population reporting African American race. These measures quantify several socioeconomic domains that effect health: "education", "employment", "poverty", and "racial composition". While some researchers have advocated the use of indices to measure the cumulative effects of several different measures of SES (Carmichael et al. 2003; Messer et al. 2008) others have found that estimates of effects detected using a single variable measure of poverty were similar to those based on indices or composite measures (Krieger, Chen, Waterman, Soobader et al. 2003). For this study, we chose to examine single variable measures because we were interested in the separate effects of each SES domain on gastroschisis outcomes. Each census measure was divided into quartiles based on the distribution among controls.

Construction of Neighborhood Variables

Prior research linking neighborhood SES indicators to health outcomes have relied heavily on geopolitical areas, such as counties or census tracts, to approximate "neighborhoods" or "communities". While they may be a practical alternative given the availability of SES data for these geographic areas, they may not truly capture a person's proximal environment or properly measure how that environment affects health (Diez Roux 2001). Therefore, it is important to develop and test hypotheses regarding the precise geographic area that is relevant for a specific health outcome in order to strengthen inferences regarding area effects. At the very least, several definitions of neighborhood should be specified, and model results from each evaluated to determine sensitivity of results to changes in neighborhood definition. To address this issue, cases and controls were geocoded to several different neighborhoods.

We first assigned cases and controls to year 2000 census block groups and tracts. Next, we developed a set of "neighborhoods" by creating circular windows of various sizes around each study subject. Based on the size of the study area and the distribution of the population, we set the minimum size to a 500-meter radius neighborhood and increased the size stepwise by 500 meters until at 5500 meter size was reached. This resulted in 11 different neighborhood sized from which to select an optimal neighborhood size. The neighborhood level social variables were estimated by aggregating census block group data by each of the circular windows. In cases where the circular window contained only a portion of a census block group, social variables were weighted by the proportion of the population from that census block group that was encompassed by the window. The circle in figure 6.1 illustrates a 2500 meter circular neighborhood while the dark black lines represent census block groups. We summed the population of the census blocks contained in the circular neighborhood (represented by light dashed lines and red dots) and divided this number by the total census block group population. This proportion was then applied to the census block group variables.

Figure 6.1. Example of aggregating census block group data, weighting by census block populations, for a 2500 meter radius neighborhood



Statistical Analysis

Choosing neighborhood scale

In order to choose the optimal neighborhood size, we employed a method developed by Ali et al. (2005) which examines the variation of the variable of interest (e.g., disease incidence or known risk factors) at several different geographic scales. The underlying assumption of this method is that smaller neighborhoods will have a high variance value while larger neighborhoods will have a low variance. A high variance value means that the data are local or individualistic while a low variance means that they are global. The optimal neighborhood ensures that the aggregate socioeconomic data is neither local nor global, but somewhere in between.

Following Ali et al. (2005), we applied Hartley's test of homogeneity of variance (F_{max}) to socioeconomic (e.g. education and race) and birth defect data (e.g. gastroschisis birth prevalence) across several different neighborhood sizes. The test statistic, F_{max}, was calculated as:

$$F_{max} = \frac{s_{max}^2}{s_{min}^2}$$

where:

s_{max}^2 = maximum value of the variances among neighborhoods

s_{min}^2 = minimum value of the variances among neighborhoods

The test assumes that the variances are equal under the null hypothesis. The critical value was calculated using an F-distribution with (k, n_{MAX} - 1) degrees of freedom where k is the number of groups and n_{MAX} is the maximum sample size among groups. A threshold value of $\alpha = 0.05$ was used to test for significance.

Using an iterative process, we compared the variance of each neighborhood to the highest neighborhood variance (upper, F_{max1}) and with the lowest neighborhood variance (lower, F_{max2}). A significant value of F_{max1} indicates that the neighborhood does not reveal the global structure of data, and in contrast, a significant value in F_{max2} implies that the neighborhood data are not individualistic. The neighborhoods between the lower and the upper limits are the optimal neighborhood sizes.

Logistic regression

To estimate the risk of gastroschisis-affected pregnancy associated with lower neighborhood SES, maximum likelihood estimates of odds ratios (OR) and 95% confidence intervals (CI) were calculated from logistic regression models. The combined influence of individual- and neighborhood-level indicators was examined to determine whether risk for women living in a lower SES neighborhood varied even after controlling for individual characteristics. Considered as potential confounders were age (< 20 years of age, 20-24 years, and 25 years or more), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic and other), parity (no prior births vs. one or more prior births), smoking during pregnancy (yes, no) and Medicaid status (delivery paid for by Medicaid vs. other payer source). Only those covariates that showed a significant risk associated with gastroschisis during univariate and multivariate analyses were included in the neighborhood-level analysis.

We estimated logistic regression models for neighborhoods of 2000, 2500, 3000, and 3500 meter radius and neighborhoods defined using census tracts and block groups in order to test our assumption of the optimal neighborhood size obtained from the F_{max} test statistic. For the models using census tracts and block groups as neighborhoods, we estimated multilevel logistic regression models with a fixed slope value for each predictor variable and random tract or block group intercepts. This was not necessary for models with neighborhoods defined using circular windows since these neighborhoods were created for each individual case and control. Univariate analysis, logistic regression and multilevel modeling were conducted in R v2.7.2 and WinBUGS v1.4.3 software.

Results

The data variances for gastroschisis birth prevalence rates show a declining trend with an increase in neighborhood size. The test results for homogeneity of variance for gastroschisis rates under various neighborhood sizes are listed in Table 6.1. The F_{max1} test statistic at the level $\alpha = 0.05$ shows a neighborhood size of approximately 2500 meters is optimal. Below 2500 meters, data are individualistic while above this size the neighborhoods capture the global structure of the data. When looking at education, the F_{max1} test statistic shows similar results. A neighborhood above 2500 meters would reveal the global pattern of the data, and the F_{max2} test statistic demonstrates any neighborhoods below 2000 meters would make the data individualistic (Table 6.2). Given these results, we believe that a neighborhood size of approximately 2500 meters is the optimal size for modeling the local variation of gastroschisis prevalence.

Table 6.1. Descriptive statistics and results for variance ratio (F_{max}) test for the gastroschisis incidence rates for various neighborhood sizes, North Carolina

r[†]	Population size			Incidence Rate/100000 Births				Upper F_{max} test			Lower F_{max} test		
	Min	*Max*	*Mean*	*Min*	*Max*	*Mean*	*Variance*	F_{max1}	*DF**	*CV***	F_{max2}	*DF**	*CV***
500	1	17	2.25	0	100000	2049.88	139889226.2	7.386	11	2.456	1.000	1	4.494
1000	1	32	4.42	0	100000	2034.96	99534818.3	5.255	10	2.142	1.405	2	3.304
1500	1	53	7.48	0	100000	2057.19	80283272.7	4.239	9	2.065	1.742	3	2.782
2000	1	61	11.36	0	100000	2035.21	63523993.1	3.354	8	2.097	2.202	4	2.525
2500	1	75	15.92	0	100000	2021.08	50666378.1	**2.675**	7	2.136	**2.761**	5	2.338
3000	1	97	21.23	0	100000	2017.85	39239794.9	2.072	6	2.194	3.565	6	2.194
3500	1	125	27.14	0	100000	2041.76	32846589.8	1.734	5	2.287	4.259	7	2.084
4000	1	155	33.67	0	100000	2057.33	28788457.4	1.520	4	2.430	4.859	8	1.999
4500	1	177	40.71	0	100000	2066.82	25255870.3	1.333	3	2.656	5.539	9	1.933
5000	1	213	48.27	0	100000	2054.85	22609821.1	1.194	2	3.038	6.187	10	1.875
5500	1	243	56.24	0	100000	2046.60	18940054.1	1.000	1	3.880	7.386	11	1.828

[†] r = size of the neighborhood radius in meters

[*] DF = degrees of freedom

[**] CV_1 and CV_2 = critical values at 95% confidence level for Upper F_{max} and Lower F_{max}

Bold figures in the F_{max1} and F_{max2} are the upper and lower limit of optimal neighborhoods, and the bold figure in “r” column is the choice of optimal neighborhood size

Table 6.2. Descriptive statistics and results for variance ratio (F_{max}) test for the education rates for various neighborhood sizes, North Carolina

r[†]	Population size			Incidence Rate/100000 Population				Upper F_{max} test			Lower F_{max} test		
	Min	*Max*	*Mean*	*Min*	*Max*	*Mean*	*Variance*	F_{max1}	*DF**	*CV***	F_{max2}	*DF**	*CV***
500	1	9832	262.54	0	100000	51038.04	1669446751.2	6.372	11	1.789	1.000	1	3.842
1000	1	10338	937.43	0	100000	49366.13	1131443497.7	4.319	10	1.831	1.476	2	2.996
1500	1	12821	1994.96	0	100000	49092.17	842974731.7	3.218	9	1.880	1.980	3	2.605
2000	1	17789	3349.32	0	100000	48920.54	657043741.2	2.508	8	1.938	**2.541**	4	2.372
2500	1	24914	5021.95	0	100000	48883.84	527081663.5	**2.012**	7	2.009	3.167	5	2.214
3000	1	32196	6963.42	0	100000	48859.69	426123809.0	1.627	6	2.098	3.918	6	2.098
3500	1	42269	9167.15	0	100000	48781.21	365489778.9	1.395	5	2.214	4.568	7	2.009
4000	1	52213	11596.14	0	100000	48617.52	325265650.6	1.242	4	2.372	5.133	8	1.938
4500	1	62323	14222.35	0	100000	48567.32	294887502.7	1.126	3	2.605	5.661	9	1.880
5000	1	76393	17031.06	0	100000	48530.11	274798546.4	1.049	2	2.996	6.075	10	1.831
5500	1	89190	20042.92	0	100000	48478.29	261983711.1	1.000	1	3.842	6.372	11	1.789

r = size of the neighborhood radius in meters

DF = degrees of freedom

** CV_1 and CV_2 = critical values at 95% confidence level for Upper F_{max} and Lower F_{max}

Bold figures in the F_{max1} and F_{max2} are the upper and lower limit of optimal neighborhoods, and the bold figure in "r" column is the choice of optimal neighborhood size

Table 6.3. Prevalence (%) and odds ratios and 95% confidence intervals (CI) for gastroschisis adjusting for individual-level covariates, North Carolina

	Prevalence		Multivariate	
	Cases (%)	Controls (%)	OR*	95% CI*
Maternal Age				
< 20	101 (41.7)	1,385 (11.9)	2.10	1.55 - 2.86
20 – 24	92 (38.0)	3,134 (26.9)	Reference	-
25 to 29	37 (15.3)	3,177 (27.3)	0.46	0.31 - 0.68
>= 30	12 (5.0)	3,955 (33.9)	0.14	0.07 - 0.24
Maternal Race				
White	162 (66.9)	7,167 (61.5)	Reference	-
Black	36 (14.9)	2,695 (23.1)	0.39	0.26 - 0.56
Hispanic	37 (15.3)	1,356 (11.6)	0.90	0.60 - 1.31
Other	7 (2.9)	433 (3.7)	0.73	0.31 - 1.47
Birth Parity				
No prior births	78 (32.2)	6,805 (58.4)	Reference	-
1 or more prior births	164 (67.8)	4,846 (41.6)	0.58	0.43 - 0.78
Smoker vs. Nonsmoker				
Non-smoking	180 (74.4)	10,125 (86.9)	Reference	-
Mother reported smoking	61 (25.2)	1,515 (13.1)	1.50	1.08 - 2.07
Medicaid				
Birth not paid for by Medicaid	164 (67.8)	4,638 (39.8)	Reference	-
Birth paid for by Medicaid	78 (32.2)	7,013 (60.2)	1.66	1.23 - 2.27

* OR = Odds ratio, adjusted for other maternal characteristics; CI = confidence interval

Table 6.3 shows the prevalence of covariates among cases and controls and risk estimates for gastroschisis as measured by odds ratios. Relative to control mothers, mothers of infants with birth defects were more likely to be young (<20 years of age), white, have no prior births (nulliparous), have smoked during pregnancy and have had their birth paid for by Medicaid. The logistic regression of individual-level covariates only, young maternal age (age <20 years) showed the strongest association with increased risk for a gastroschisis birth (OR=2.1; 95% CI = 1.55-3.86) while maternal age over 25 years, black race and parity showed significant protective effects. In addition, mothers whose birth was paid for by Medicaid (a proxy for low income), showed an increased risk for a gastroschisis birth (OR=1.66; 95% CI=1.23-2.27).

While we did estimate neighborhood SES models for 2000 and 3500 meter radius neighborhoods and neighborhoods defined using census block groups and tracts (results not shown), only the models estimated using the 2500 and 3000 meter radius neighborhoods showed significant associations with gastroschisis so we only present results for these two neighborhood sizes. Table 6.4 presents the crude and adjusted odds ratios of SES measures in relation to gastroschisis. Crude ORs for gastroschisis associated with single indicators of neighborhood-level SES were uniformly elevated. For both the 2500 and 3000 meter radius neighborhood models, crude odds ratios were significantly elevated for residence in a poverty neighborhood (where at least 20% of the residents were living below 200% of the federal poverty level or 10% were living below 100% of federal poverty level), a high unemployment neighborhood (where at least 4% of the residents were unemployed) and residence in a less educated neighborhood (where at least 12% of residents have less than a high school education).

Adjustment for maternal age, race/ethnicity, parity smoking and Medicaid status, resulted in odds ratios that were uniformly lower than their crude counterparts. For both the 2500 and 3000 meter neighborhood, residence in a neighborhood in the 3rd quartile of poverty (where at 30% to 40% of the residence were living below 200% of the federal poverty level) was associated with increased odds of a gastroschisis birth, compare with residence in the 1st quartile. The 2500 meter neighborhood showed the strongest association (OR=1.85; 95% CI=1.19-2.83), indicating that this may be the optimal neighborhood size to measure area-level poverty effects on gastroschisis. Residence in a neighborhood in the 2nd or 3rd quartile of unemployment (where 4% to 7% of residents were unemployed) was associated with increased odds of a gastroschisis birth, compared with residence in the 1st quartile. For this SES measure, the 3000 meter neighborhood showed the strongest association (OR=1.89; 95% CI=1.25-2.94), indicating that this slightly larger neighborhood size may be optimal for measuring area-level unemployment effects on gastroschisis. Odds ratios for neighborhood-level measures of percent of black residents, percent of residents

Table 6.4. Crude odds ratios, adjusted odds ratios, and their 95% confidence intervals (CI) for SES measures in relation to gastroschisis for 2500 meter radius and 3000 meter radius neighborhoods, North Carolina

	2500 meter radius neighborhood		**3000 meter radius neighborhood**	
	Crude OR (95% CI)	*Adjusted OR[a] (95% CI)*	*Crude OR (95% CI)*	*Adjusted OR[a] (95% CI)*
100% of federal poverty level				
Q2	1.34 (0.88 - 2.06)	0.85 (0.56 - 1.33)	1.53 (1.01 - 2.32)	0.98 (0.64 - 1.50)
Q3	2.26 (1.55 - 3.36)	1.33 (0.90 - 2.00)	2.03 (1.38 - 3.03)	1.18 (0.79 - 1.78)
Q4	1.76 (1.19 - 2.65)	1.14 (0.74 - 1.76)	1.81 (1.22 - 2.72)	1.17 (0.77 - 1.81)
AIC*		*2092.6*		*2097.3*
200% of federal poverty level				
Q2	2.00(1.29 - 3.18)	1.21 (0.77 - 1.93)	2.00 (1.29 - 3.17)	1.20 (0.76 - 1.93)
Q3	3.34 (2.23 - 5.17)	1.85 (1.19 - 2.83)	3.31 (2.21 - 5.11)	1.79 (1.18 - 2.80)
Q4	2.00 (1.29 - 3.17)	1.15 (0.73 - 1.88)	2.03 (1.31 - 3.22)	1.20 (0.76 - 1.95)
AIC*		***2087.3***		*2088.3*
Unemployment				
Q2	1.73 (1.15 - 2.63)	1.40 (0.92 - 2.15)	2.20 (1.45 - 3.42)	1.81 (1.18 - 2.83)
Q3	2.25 (1.53 - 3.38)	1.61 (1.08 - 2.44)	2.58 (1.72 - 3.97)	1.89 (1.25 - 2.94)
Q4	1.74 (1.16 - 2.67)	1.27 (0.82 - 1.98)	2.03 (1.33 - 3.17)	1.50 (0.96 - 2.39)
AIC*		*2098.6*		***2088.2***
Less than a high school education				
Q2	1.69 (1.11 - 2.59)	1.09 (0.71 - 1.69)	1.47 (0.98 - 2.25)	0.94 (0.62 - 1.45)
Q3	1.97 (1.32 - 3.00)	1.01 (0.66 - 1.57)	1.84 (1.25 - 2.77)	0.94 (0.62 - 1.44)
Q4	2.25 (1.52 - 3.40)	1.09 (0.72 - 1.69)	2.05 (1.40 - 3.06)	0.98 (0.65 - 1.50)
AIC*		*2097.6*		*2098.8*
Percent black				
Q2	0.90 (0.63 - 1.30)	1.06 (0.73 - 1.55)	1.10 (0.77 - 1.59)	1.31 (0.90 - 1.90)
Q3	0.95 (0.66 - 1.36)	1.03 (0.71 - 1.50)	1.07 (0.74 - 1.54)	1.15 (0.79 - 1.69)
Q4	1.05 (0.74 - 1.49)	1.24 (0.83 - 1.84)	1.07 (0.74 - 1.54)	1.27 (0.84 - 1.91)
AIC*		*2093.1*		*2096.7*

Each socioeconomic measure was estimated separately
Reference category = 1st quartile
[a] Odds ratios adjusted for maternal age, race/ethnicity, parity, smoking and Medicaid status
*AIC = Akaike information criterion; a lower AIC score implies a better model fit

with less than a high school education, and percent of residents living below 100% of federal poverty level were no longer significant after controlling for individual-level covariates. The Akaike Information Criterion (AIC), used to compare the fit of different models, confirms that the 2500 meter neighborhood model is the best fit for the poverty measure and the 3000 meter neighborhood model is the best fit for the unemployment measure.

To investigate the possibility that the risk of having a gastroschisis-affected pregnancy among women of lower SES differed depending on the neighborhood social condition in which they lived, we evaluated a cross-level interaction which combined individual Medicaid status with neighborhood poverty (Table 6.5). Crude odds ratios revealed that women whose birth was paid for by Medicaid were at highest risk for a gastroschisis-affected pregnancy, regardless of neighborhood SES. When odds ratios were adjusted for individual maternal characteristics, women on Medicaid who lived in a high poverty area were at greatest risk for a gastroschisis-affected pregnancy. These results indicate that neighborhood social conditions do contribute to the elevated risk of gastroschisis, though individual Medicaid status may be more important.

Table 6.5 Crude odds ratios, adjusted odds ratios, and their 95% confidence intervals (CI) for combined individual and neighborhood indicators of socioeconomic status, North Carolina

Neighborhood Poverty[a]	Individual Medicaid status	Cases	Controls	OR	Adjusted OR[b]
Low	non-Medicaid	30	4228	Reference	Reference
Low	Medicaid	57	1594	5.03 (3.25 - 7.96)	2.09 (1.30 - 3.43)
High	non-Medicaid	48	2785	2.43 (1.54 - 3.88)	1.72 (1.09 - 2.78)
High	Medicaid	107	3044	4.95 (3.34 - 7.57)	2.45 (1.57 - 3.91)

[a] High poverty neighborhood was defined as areas where 30% or more of the residents lived below 200% of the federal poverty level

[b] Odds ratios adjusted for maternal age, race, parity and smoking status

Discussion

This study indicates that residence in a lower SES neighborhood, as measured by poverty and unemployment, increases the risk of having a gastroschisis-affected pregnancy, even after controlling for individual-level risk factors. In addition, if Medicaid status is considered a proxy for individual-level SES, then *both* individual and neighborhood measures of SES combined increase the risk for a gastroschisis birth. Adjusted odds ratios were significantly elevated for the 3rd quartile of poverty and 2nd and 3rd quartiles of unemployment measures, though not the 4th. This finding is difficult to interpret, though it indicates that gastroschisis births disproportionately affect women of lower-middle socioeconomic class. In addition, cross-level interactions indicate that women whose birth was paid for by Medicaid and who lived in a high poverty neighborhood had the greatest risk of a gastroschisis-affected birth.

This study is the first to examine neighborhood-level SES effects on the risk of gastroschisis births. Only one previous study incorporated area-level measures of socioeconomic status while simultaneously controlling for individual-level confounders and this study grouped several digestive system birth defects (Vrijheid et al. 2000). Using the Carstairs deprivation index, Vrijheid et al. found a significant increase in risk of digestive system defects in the most deprived communities compared to the most affluent communities. Very few studies have even examined the relationship between *individual-level* socioeconomic status and risk of gastroschisis. Only one other study has reported a significant positive association between lower individual SES (family income) and gastroschisis (Torfs et al. 1994). Our study supports prior research as we found an elevated risk of gastroschisis among women whose birth was paid for by Medicaid (a proxy for low SES) and who lived in a high poverty community.

Given our findings and the results of prior research, can we begin to develop theories about plausible links between specific socioeconomic features of the neighborhood and gastroschisis? While no studies have examined gastroschisis specifically, prior research on birth outcomes suggests that women who experience high levels of psychosocial stress are at greater risk for preterm and low birth weight births (for a review of this literature see Hobel et al. (2008). While the causal mechanisms behind this are not entirely clear, some researchers suggest that chronic psychosocial stress stimulates the production of cortisol in the mother's system which may cause the developing fetus to mount a stress response which can adversely affect fetal development (Diego et al. 2006; Field et al. 2006; Hobel, Goldstein, and Barrett 2008). In our sample, Medicaid recipients living in a high poverty area had the greatest risk for a gastroschisis birth. Women may find unfavorable neighborhood characteristic stressful (e.g., high crime rates, racial or economic discrimination or poor access to necessary health or municipal services). Perhaps women exposed to both individual-level economic stress and poor proximal environments have higher overall or chronic levels of stress. To further understand this hypothesized relationship, future research could explicitly examine psychosocial and physiological reactions to exposure to poor environments and the effect on gastroschisis and other birth outcomes.

This study also demonstrates the usefulness of using Hartley's test of homogeneity of variance (F_{max}) to empirically determine the optimal neighborhood size at which to study a disease outcome (in this case gastroschisis). The causes of gastroschisis, like many birth defects, are complex and multifactoral and may include not only maternal characteristics and behaviors but also environmental teratogens and genetic factors (Curry et al. 2000). The geographic scale at which neighborhood-level poverty and unemployment measures affect gastroschisis outcomes may offer new etiological clues about gastroschisis, help to generate hypotheses about causal mechanisms and, eventually, lead to an understanding of *how* psychosocial stressors such as poverty and unemployment may affect gastroschisis risk. The F_{max} test statistic can assist researchers in finding the geographic scale at which neighborhood-level measures are most strongly associated with disease outcomes.

Results from the logistic regression analysis using different sized neighborhoods appear to confirm that the optimal neighborhood size for studying gastroschisis is approximately 2500 meters, thereby validating the F_{max} analysis. Also of note is that census block group and census tract based socioeconomic measures did not detect significant area-level SES effects, even when 2500 and 3000 meter radius areas did. This suggests that geopolitical boundaries, though convenient and easy to use, are not the optimal way to measure a person’s proximal environment or properly measure how that environment affects health. Many studies of area or neighborhood effects on health use census boundaries and may find spurious results if an individual’s neighborhood is incorrectly defined. In addition, socioeconomic processes may influence health outcomes at different scales. In our study, the poverty and unemployment measures showed the strongest association with gastroschisis risk at different neighborhood sizes, suggesting that researchers may not be able to use the same size neighborhoods to examine the effect of all area-level SES measures.

One potential limitation of our study is that we use residence at birth to define neighborhood-level SES measures. Studies have shown that between 25 and 30 percent of women change residence between conception and birth (Fell, Dodds, and King 2004; Khoury et al. 1988; Shaw and Malcoe 1992). However, a majority of these moves appear to be local (e.g. within the same city or county), to areas with a similar socioeconomic make-up (Fell, Dodds, and King 2004; Khoury et al. 1988) and the characteristics of women who move are similar to those who do not (Canfield, Ramadhani et al. 2006). Caution should be exercised when interpreting the results of geographic studies that use maternal residential address at delivery, especially when using residence to develop and assign area-level variables to study subjects.

Related to the limitation above, this study uses cross-sectional data which cannot account for changes in residence or changes in the SES environment over time. We used 2000 Census data to measure SES, which was collected within the 1999 – 2004 timeframe from which our sample was drawn. It is our belief that the SES environment changes gradually over time and that SES data from 2000 will accurately capture the neighborhood SES environment between 1999 and 2004. In addition, cross-sectional studies are problematic in that they focus on current exposures rather than neighborhood exposures that happen earlier in time. Since many conditions have a long time lag between effect of neighborhood and health outcome, neighborhood effects may be incorrectly attributed to current social conditions. However, for most birth defects the lag time between the critical period of exposure and diagnosis is relatively short so we believe a cross-sectional design is adequate for examining the relationship between neighborhood exposure and health outcome.

In summary, we have identified both individual-level and neighborhood-level socioeconomic factors that contribute to the risk of a gastroschisis affected pregnancy. Our findings indicate that neighborhood-level socioeconomic factors exert an independent causal effect on gastroschisis.   While gastroschisis has increased in North Carolina over the past decade and exhibits an uneven geographic distribution across the State, this the first study to explore neighborhood effects on gastroschisis outcomes. We believe these findings allow us to hypothesize plausible causal mechanisms by which proximal environment may affect birth outcomes, which may in turn inform the complex etiology of this birth defect.

CHAPTER 7

CONCLUSION
THE DISEASE ECOLOGY OF GASTROSCHISIS

Does a non-communicable disease like gastroschisis have an ecology? Most researchers would agree that chronic or non-communicable conditions are not caused by a single factor. Rather, individual-level risk factors and behaviors – such as genetics, diet or age – combine with, or are moderated by, aspects of the natural, social and built environment to increase or decrease risk. If disease ecology is the study of the wide array of environmental, population, social, economic and behavioral factors that interact and contribute to the occurrence of a disease in a certain place at a certain time, then non-communicable diseases do indeed have an ecology. For centuries, disease ecology has been a mainstay of medical geography; one of the dominant conceptual frameworks for studying the geographic distribution of disease. So why has this framework largely been neglected in the public health literature, especially as it applies to the study of chronic conditions?

In the new edition of *Medical Geography*, Meade and Emch suggest that the term "ecology" is problematic for many researchers because different disciplines use it to mean a diverse array of frameworks, processes, systems, and methodologies. For a long time, researchers in the field of public health believed that "ecological" studies had a very limited application, since they seemed to be full of confounding variables and examined populations and population-level health outcomes rather than individual level risk factors and outcomes.

In epidemiology, as Meade and Emch (2009) suggest: "'Ecological' came to mean multivariate, multiple-scaled, complex, uncontrollable, fuzzy, interesting perhaps but of limited scientific use. The real environment and its ecology largely disappeared from perspective" (in press). The very word medical geographers use to describe the multifactoral nature of disease – ecology – has hindered the application of disease ecology because of the disparate and conflicting interpretations of the word.

If we critically examine the literature on gastroschisis, each published study tells a story. Torfs and colleagues (Torfs et al. 1996; Torfs et al. 1994) and Werler and colleagues (Werler, Sheehan, and Mitchell 2002; Werler, Mitchell, and Shapiro 1992b) have shown how common over-the-counter medications and illicit drugs increase the risk for gastroschisis. Other researchers suggest that proximity to point source pollutants may increase risk (Fielder et al. 2000; Dolk et al. 1998) and nearly every study of gastroschisis has found evidence for age or race related risk factors (Castilla, Mastroiacovo, and Orioli 2008; Feldkamp and Botto 2008). Taken together, these studies contribute to a greater understanding of the disease. But do they tell the whole story? Are they holistic? Do they examine the myriad behavioral, social, environmental and population factors that interact to influence the risk of a gastroschisis affected pregnancy? I think it is clear that no single mechanism is responsible for gastroschisis and that multiple factors, and perhaps the combination or interaction of multiple factors, have contributed to the increase in incidence and scope of this particular birth defect. I also think it is clear that no study published in the literature to date has attempted to account for the multifactoral nature of gastroschisis. This does not diminish the importance of single factor studies; it is imperative we understand how each individual risk factor is related to the outcome before trying to integrate multiple factors which may act at multiple scales, complicate methodologies and require information not available. At the same time, it is important to try to integrate many factors which appear to affect gastroschisis to examine the relative importance of each.

As a case in point, table 7.1 integrates the data used in Chapters 4 and 6 to examine the effect of both area-level poverty (social or economic environment) and the probability of surface water (built and natural environment) on the risk for a gastroschisis-affected pregnancy. When the probability of surface water is 0, women living in areas with higher poverty rates (Q2, Q3, Q4) appear to have a higher risk of a gastroschisis birth than women who live in the lowest poverty areas (Q1), though this is not a linear relationship and not all categories are statistically significant. When the probability of surface water is 100, the risk of gastroschisis increases across all poverty categories, suggesting a multiplicative effect. Women who receive water from a surface water source have an increased risk for gastroschisis (as shown in Chapter 4) and women living in a higher-poverty area have a greater risk for gastroschisis (as shown in Chapter 6). Women living in a high poverty area *and* drinking from surface water source have an even greater risk of a gastroschisis birth. It appears that both the natural/built environment and social environment act to increase the risk for a gastroschisis affected pregnancy in North Carolina.

Table 7.1. Integration of area-level social and natural/built environment variables in the study of gastroschisis

	Relative risk (95% CI) of gastroschisis[†]	
	Probability of Surface Water = 0	*Probability of Surface Water = 100*
Poverty Q2 vs. Q1	1.24 (0.79 – 1.98)	1.73 (0.97 – 3.08)
Poverty Q3 vs. Q1	**1.80 (1.16 – 2.79)**	**2.50 (1.44 – 4.32)**
Poverty Q4 vs. Q1	1.07 (0.64 – 1.81)	1.49 (0.80 – 2.78)
Poverty Q3 vs. Q2	**1.44 (1.02 – 2.03)**	**2.01 (1.27 – 3.17)**
Poverty Q4 vs. Q2	0.86 (0.57 – 1.31)	1.20 (0.70 – 2.04)
Poverty Q4 vs. Q3	**0.60 (0.41 – 0.86)**	0.83 (0.50 – 1.37)

[†] Relative risk adjusted for maternal age, race/ethnicity, parity, smoking status and Medicaid status.

Part of the challenge of integrating all possible factors that appear to contribute to a disease is that much of the time, the data, study design and statistical methodology cannot support integration and still provide valid results. As the neighborhoods and health literature points out: “the size and definition of the relevant geographic area may vary according to the processes through which the area effect is hypothesized to operate and the outcome being studied” (Diez Roux 2001, 1785). Most geographers would recognize this as a statement about scale; a description of the multitude of factors in our lives (social, economic, political and environmental) that act at different levels of geography to influence or limit our behaviors, decisions and actions. The factors that affect a disease outcome do not operate at a single scale (as shown in Chapter 6) and this can complicate analysis and interpretation of study results, especially in statistical or epidemiological studies. Scale becomes one of the main issues researchers need address when implementing “ecological” studies.

Study design, data and statistical methodology are all affected by scale. Data collection can be particularly problematic. The scale at which it is possible to measure risk factors of disease may not be the scale at which that factor acts to impact disease outcomes. We could choose to collect the same data at multiple scales. But this requires that we have a general sense of how the process actually produces disease and method for discerning which scales is the “best” or “correct” one. The best possible study design would collect data for each individual on all possible factors influencing the disease outcome and characterize an individual’s social, economic and built environments as well as behaviors in which they engage. Leaving the question of exactly what to quantify behind (since the etiology may be uncertain), this problem may be intractable because we may not know *a priori* at what scale each of these factors operate and fail to collect data at the “correct” scale. In such cases, the “gold standard” for epidemiology, the randomized control trial, may not be the best option for studies examining the ecology of a disease and/or applying the disease ecology framework. This limitation helps make a strong case for developing statistical methodologies that will provide valid and insightful results in spite of imperfect study design. Though multilevel modeling has provided researchers with a valuable tool for exploring the relationship between data and 2 or 3 different scales, more work is needed to develop statistical techniques that can integrate and interpret data at multiple scales.

So can we use the tools that are available to us to study the ecology of non-communicable disease? Can we learn something about gastroschisis using the imperfect data and methodologies we have available to us? I think it depends on the research or study question. If the research is intended to discern *concrete* causal mechanisms and the *specific* pathways by which agents cause a health outcome, then ecological studies are insufficient. If the research is intended to gather clues, propose hypotheses and provide an *indication* of an agent that *may* cause a health outcome, then ecological studies can accomplish this goal. Indication of harm, rather than proof of harm, is an important scientific undertaking and disease ecology is an important scientific tool toward that end. As the precautionary principle states:

> *Indication of harm, rather than proof of harm, should be the trigger for action…precautionary measures should be taken even if some cause and effect relationships are not fully established scientifically (Steingraber 1997, 284).*

REFERENCES

Ali, M., J. K. Park, V. D. Thiem, D. G. Canh, M. Emch, and J. D. Clemens. 2005. Neighborhood size and local geographic variation of health and social determinants. *Int J Health Geogr* 4 (1):12.

Bianchi, F., D. Cianciulli, A. Pierini, and A. Seniori Costantini. 1997. Congenital malformations and maternal occupation: a registry based case-control study. *Occup Environ Med* 54 (4):223-8.

Birhanli, A., and M. Ozmen. 2005. Evaluation of the toxicity and teratogenity of six commercial textile dyes using the frog embryo teratogenesis assay-Xenopus. *Drug Chem Toxicol* 28 (1):51-65.

Bisschops, I., and H. Spanjers. 2003. Literature review on textile wastewater characterisation. *Environ Technol* 24 (11):1399-411.

Bound, J. P., P. W. Harvey, B. J. Francis, F. Awwad, and A. C. Gatrell. 1997. Involvement of deprivation and environmental lead in neural tube defects: a matched case-control study. *Arch Dis Child* 76 (2):107-12.

Boyle, E., H. Johnson, A. Kelly, and R. McDonnell. 2004. Congenital anomalies and proximity to landfill sites. *Ir Med J* 97 (1):16-8.

Brantberg, A., H. G. Blaas, K. A. Salvesen, S. E. Haugen, and S. H. Eik-Nes. 2004. Surveillance and outcome of fetuses with gastroschisis. *Ultrasound Obstet Gynecol* 23 (1):4-13.

Brender, J. D., F. B. Zhan, L. Suarez, P. H. Langlois, and K. Moody. 2006. Maternal residential proximity to waste sites and industrial facilities and oral clefts in offspring. *J Occup Environ Med* 48 (6):565-72.

Brown, N. 1997. Chemical Teratogens: Hazards, Tools and Clues. In *Embryos, Genes and Birth Defects*, ed. P. Thorogood. Chichester, England; New York: John Wiley & Sons.

Buescher, P., M. Roth, D. Williams, and C. Goforth. 1991. An evaluation of the impact of maternity care coordination on Medicaid birth outcomes in North Carolina. *Am J Pub Health* 81:1625-1629.

Byron-Scott, R., E. Haan, A. Chan, C. Bower, H. Scott, and K. Clark. 1998. A population-based study of abdominal wall defects in South Australia and Western Australia. *Paediatr Perinat Epidemiol* 12 (2):136-51.

Calzolari, E., F. Bianchi, H. Dolk, M. Milan, M. Lechat, P. Leurquin, S. Goyens, G. Astolfi, S. Volpato, S. Ayme, A. Calabro, M. Clementi, R. Tenconi, M. Cornel, A. Cuschieri, S. Garciaminaur, E. Garne, Y. Gillerot, J. Goujard, D. Hansenkoenig, M. Roulleaux,

P. J. Howard, Z. Johnson, D. F. Lillis, N. C. Nevin, V. Nelen, T. Pexieder, A. Pierini, C. Stoll, and D. H. Stone. 1995. Omphalocele and Gastroschisis in Europe - A Survey of 3-million Births 1980-1990. *American Journal of Medical Genetics* 58 (2):187-194.

Canfield, M. A., M. A. Honein, N. Yuskiv, J. Xing, C. T. Mai, J. S. Collins, O. Devine, J. Petrini, T. A. Ramadhani, C. A. Hobbs, and R. S. Kirby. 2006. National estimates and race/ethnic-specific variation of selected birth defects in the United States, 1999-2001. *Birth Defects Res A Clin Mol Teratol* 76 (11):747-56.

Canfield, M. A., T. A. Ramadhani, P. H. Langlois, and D. K. Waller. 2006. Residential mobility patterns and exposure misclassification in epidemiologic studies of birth defects. *J Expo Sci Environ Epidemiol* 16 (6):538-43.

Carmichael, S. L., V. Nelson, G. M. Shaw, C. R. Wasserman, and L. A. Croen. 2003. Socio-economic status and risk of conotruncal heart defects and orofacial clefts. *Paediatr Perinat Epidemiol* 17 (3):264-71.

Castilla, E. E., H. Campana, and J. S. Camelo. 2000. Economic activity and congenital anomalies: an ecologic study in Argentina. ECLAMC ECOTERAT Group. *Environ Health Perspect* 108 (3):193-7.

Castilla, E. E., P. Mastroiacovo, and I. M. Orioli. 2008. Gastroschisis: International epidemiology and public health perspectives. *American Journal of Medical Genetics Part C: Seminars in Medical Genetics* 148C (3):162-179.

Clark, J. D., P. A. Mossey, L. Sharp, and J. Little. 2003. Socioeconomic status and orofacial clefts in Scotland, 1989 to 1998. *Cleft Palate Craniofac J* 40 (5):481-5.

Collins, K. 2006. State can't prove birth defect link. *The News & Observer*, May 24, 2006.

Croen, L. A., G. M. Shaw, L. Sanbonmatsu, S. Selvin, and P. A. Buffler. 1997. Maternal residential proximity to hazardous waste sites and risk for selected congenital malformations. *Epidemiology* 8 (4):347-54.

Curry, J. I., P. McKinney, J. G. Thornton, and M. D. Stringer. 2000. The aetiology of gastroschisis. *British Journal of Obstetrics and Gynaecology* 107 (11):1339-1346.

Diego, M. A., N. A. Jones, T. Field, M. Hernandez-Reif, S. Schanberg, C. Kuhn, and A. Gonzalez-Garcia. 2006. Maternal psychological distress, prenatal cortisol, and fetal weight. *Psychosom Med* 68 (5):747-53.

Diez Roux, A. V. 2001. Investigating neighborhood and area effects on health. *Am J Public Health* 91 (11):1783-9.

———. 2004. Estimating neighborhood health effects: the challenges of causal inference in a complex world. *Soc Sci Med* 58 (10):1953-60.

Dolk, H., M. Vrijheid, B. Armstrong, L. Abramsky, F. Bianchi, E. Garne, V. Nelen, E. Robert, J. E. Scott, D. Stone, and R. Tenconi. 1998. Risk of congenital anomalies near hazardous-waste landfill sites in Europe: the EUROHAZCON study. *Lancet* 352 (9126):423-7.

Draper, E. S., J. Rankin, A. M. Tonks, K. R. Abrams, D. J. Field, M. Clarke, and J. J. Kurinczuk. 2008. Recreational drug use: a major risk factor for gastroschisis? *Am J Epidemiol* 167 (4):485-91.

Draper, G. J. 1997. The analysis of registry data in relation to various different types of hypothesis regarding the geographical distribution of disease. *Cent Eur J Public Health* 5 (2):90-2.

Drongowski, R. A., R. K. Smith, Jr., A. G. Coran, and M. D. Klein. 1991. Contribution of demographic and environmental factors to the etiology of gastroschisis: a hypothesis. *Fetal Diagn Ther* 6 (1-2):14-27.

Dubos, R. J. 1965. *Man adapting*. New Haven,: Yale University Press.

Emch, M., and M. Ali. 2002. Spatial Cluster Analysis for Etiological Research and Identification of Socio-environmental Risk Factors In *Geographic Information Systems and Health Applications*, eds. O. Khan and R. Skinner, 172-187. Hershey, PA: Idea Group Publishing.

EPA. 1997. Profile of the Textile Industry, ed. Office of Enforcement and Compliance Assistance: US EPA.

———. 2008. *National Pollution Discharge Elimination System (NPDES)*. EPA 2005 [cited 12/1 2008]. Available from http://cfpub.epa.gov/npdes/.

———. 2008. Better assessment science integrating point and nonpoint sources: BASINS 4.0. EPA, Washington, D.C.

EPA, and Horizon Systems. 2008. National Hydrography Dataset Plus (NHD Plus).

Erickson, J. D., W. M. Cochran, and C. E. Anderson. 1979. Parental occupation and birth defects. In *Contributions to Epidemiology and Biostatistics*, eds. M. A. Klingberg, J. A. C. Weatherall and C. Papier, 107-117. Basel: Karger.

Farrow, A., K. M. Shea, and R. E. Little. 1998. Birthweight of term infants and maternal occupation in a prospective cohort of pregnant women. The ALSPAC Study Team. *Occup Environ Med* 55 (1):18-23.

Feldkamp, M., J. Reefhuis, J. Kucik, S. Krikov, A. Wilson, C. Moore, J. Carey, and L. Botto. 2008a. Case-control study of self reported genitourinary infections and risk of gastroschisis: findings from the national birth defects prevention study, 1997-2003. *Bmj* 336:1420-1423.

Feldkamp, M. L., S. C. Alder, and J. C. Carey. 2008. A case control population-based study investigating smoking as a risk factor for gastroschisis in Utah, 1997-2005. *Birth Defects Res A Clin Mol Teratol* 82 (11):768-75.

Feldkamp, M. L., and L. D. Botto. 2008. Developing a research and public health agenda for gastroschisis: how do we bridge the gap between what is known and what is not? *Am J Med Genet C Semin Med Genet* 148C (3):155-61.

Feldkamp, M. L., J. C. Carey, and T. W. Sadler. 2007. Development of gastroschisis: review of hypotheses, a novel hypothesis, and implications for research. *Am J Med Genet A* 143 (7):639-52.

Feldkamp, M. L., J. Reefhuis, J. Kucik, S. Krikov, A. Wilson, C. A. Moore, J. C. Carey, and L. D. Botto. 2008b. Case-control study of self reported genitourinary infections and risk of gastroschisis: findings from the national birth defects prevention study, 1997-2003. *Bmj* 336 (7658):1420-3.

Fell, D. B., L. Dodds, and W. D. King. 2004. Residential mobility during pregnancy. *Paediatr Perinat Epidemiol* 18 (6):408-14.

Field, T., M. Hernandez-Reif, M. Diego, B. Figueiredo, S. Schanberg, and C. Kuhn. 2006. Prenatal cortisol, prematurity and low birthweight. *Infant Behav Dev* 29 (2):268-75.

Fielder, H. M., C. M. Poon-King, S. R. Palmer, N. Moss, and G. Coleman. 2000. Assessment of impact on health of residents living near the Nant-y-Gwyddon landfill site: retrospective analysis. *Bmj* 320 (7226):19-22.

Forand, S. P., T. O. Talbot, C. Druschel, and P. K. Cross. 2002. Data quality and the spatial analysis of disease rates: congenital malformations in New York State. *Health Place* 8 (3):191-9.

Forrester, M. B., and R. D. Merz. 1999. Epidemiology of abdominal wall defects, Hawaii, 1986-1997. *Teratology* 60 (3):117-23.

———. 2006. Comparison of trends in gastroschisis and prenatal illicit drug use rates. *Journal of Toxicology and Environmental Health-Part a-Current Issues* 69 (13):1253-1259.

Garry, V. F., M. E. Harkins, L. L. Erickson, L. K. Long-Simpson, S. E. Holland, and B. L. Burroughs. 2002. Birth defects, season of conception, and sex of children born to pesticide applicators living in the Red River Valley of Minnesota, USA. *Environ Health Perspect* 110 Suppl 3:441-9.

Goldbaum, G., J. Daling, and S. Milham. 1990. Risk factors for gastroschisis. *Teratology* 42 (4):397-403.

Gordon, D. 2003. Area-Based Deprivation Measures - a U.K. Perspective. In *Neighborhoods and health*, eds. I. Kawachi and L. F. Berkman, 179-207. New York; Oxford: Oxford Univerisity Press.

Haddow, J. E., G. E. Palomaki, and M. S. Holman. 1993. Young maternal age and smoking during pregnancy as risk factors for gastroschisis. *Teratology* 47 (3):225-8.

Hobel, C. J., A. Goldstein, and E. S. Barrett. 2008. Psychosocial stress and pregnancy outcome. *Clin Obstet Gynecol* 51 (2):333-48.

Hougland, K. T., A. M. Hanna, R. Meyers, and D. Null. 2005. Increasing prevalence of gastroschisis in Utah. *J Pediatr Surg* 40 (3):535-40.

Hoyme, H. E., M. C. Jones, and K. L. Jones. 1983. Gastroschisis: abdominal wall disruption secondary to early gestational interruption of the omphalomesenteric artery. *Semin Perinatol* 7 (4):294-8.

Hunter, J. M. 1974. *The geography of health and disease : papers of the first Carolina Geographical Symposium (1974)*. Chapel Hill: University of North Carolina at Chapel Hill, Dept. of Geography.

Juice Analytics. *Excel Geocoding Tool v2* 2006 [cited 7/1/2008]. Available from http://www.juiceanalytics.com/writing/excel-geocoding-tool-v2.

Kawachi, I., and L. F. Berkman. 2003a. Introduction. In *Neighborhoods and Health*, eds. I. Kawachi and L. F. Berkman, 1-19. Oxford; New York: Oxford University Press.

———. 2003b. *Neighborhoods and Health*. Oxford ; New York: Oxford University Press.

Khoury, M. J., W. Stewart, A. Weinstein, S. Panny, P. Lindsay, and M. Eisenberg. 1988. Residential mobility during pregnancy: implications for environmental teratogenesis. *J Clin Epidemiol* 41 (1):15-20.

Kozer, E., S. Nikfar, A. Costei, R. Boskovic, I. Nulman, and G. Koren. 2002. Aspirin consumption during the first trimester of pregnancy and congenital anomalies: A meta-analysis. *American Journal of Obstetrics and Gynecology* 187 (6):1623-1630.

Krieger, N., J. T. Chen, P. D. Waterman, D. H. Rehkopf, and S. V. Subramanian. 2003. Race/ethnicity, gender, and monitoring socioeconomic gradients in health: a comparison of area-based socioeconomic measures—The Public Health Disparities Geocoding Project. . *Am J Public Health* 93:1655-1671.

Krieger, N., J. T. Chen, P. D. Waterman, M.-J. Soobader, S. V. Subramanian, and R. Carson. 2003. Choosing area based socioeconomic measures to monitor social inequalities in low birth weight and childhood lead poisoning: The Public Health Disparities Geocoding Project (US). *Journal of Epidemiology and Community Health* 57:186-199.

Krieger, N., P. Waterman, K. Lemieux, S. Zierler, and J. W. Hogan. 2001. On the wrong side of the tracts? Evaluating the accuracy of geocoding in public health research. *Am J Public Health* 91 (7):1114 - 1116.

Kulldorff, M. 1997. A spatial scan statistic. *Communications in Statistics: Theory and Methods* 26:1481-1496.

———. *SaTScan User Guide for version 7.0* 2006 [cited 9/30/2008]. Available from http://www.satscan.org/techdoc.html.

Kulldorff, M., W. F. Athas, E. J. Feurer, B. A. Miller, and C. R. Key. 1998. Evaluating cluster alarms: a space-time scan statistic and brain cancer in Los Alamos, New Mexico. *Am J Public Health* 88 (9):1377-80.

Kulldorff, M. & Information Management Services, Inc. (2006). SaTScanTM v7.0: Software for the spatial and space-time scan statistics. [cited 9/30/2008]. Available from http://www.satscan.org/.

Kulldorff, M., and N. Nagarwalla. 1995. Spatial disease clusters: detection and inference. *Stat Med* 14 (8):799-810.

Lam, P. K., and C. P. Torfs. 2006. Interaction between maternal smoking and malnutrition in infant risk of gastroschisis. *Birth Defects Research Part a-Clinical and Molecular Teratology* 76 (3):182-186.

Lam, P. K., C. P. Torfs, and R. J. Brand. 1999. A low pregnancy body mass index is a risk factor for an offspring with gastroschisis. *Epidemiology* 10 (6):717-21.

Laughon, M., R. Meyer, C. Bose, A. Wall, E. Otero, A. Heerens, and R. Clark. 2003. Rising birth prevalence of gastroschisis. *J Perinatol* 23 (4):291-3.

Lin, S., J. P. Munsie, M. L. Herdt-Losavio, E. Bell, C. Druschel, P. A. Romitti, and R. Olney. 2008. Maternal asthma medication use and the risk of gastroschisis. *Am J Epidemiol* 168 (1):73-9.

Lovasi, G., J. Weiss, R. Hoskins, E. Whitsel, K. Rice, C. Erickson, and B. Psaty. 2007. Comparing a single-stage geocoding method to a multi-stage geocoding method: how much and where do they disagree? *International Journal of Health Geographics* 6 (1):12.

Macintyre, S., and A. Ellaway. 2003. Neighborhoods and Health: An Overview. In *Neighborhoods and health*, eds. I. Kawachi and L. F. Berkman, 20-42. Oxford; New York: Oxford University Press.

Macintyre, S., A. Ellaway, and S. Cummins. 2002. Place effects on health: how can we conceptualise, operationalise and measure them? *Soc Sci Med* 55 (1):125-39.

Marshall, E. G., L. J. Gensburg, D. A. Deres, N. S. Geary, and M. R. Cayo. 1997. Maternal residential exposure to hazardous wastes and risk of central nervous system and musculoskeletal birth defects. *Arch Environ Health* 52 (6):416-25.

Martinez-Frias, M. L., J. Salvador, L. Prieto, and J. Zaplana. 1984. Epidemiological study of gastroschisis and omphalocele in Spain. *Teratology* 29 (3):377-82.

Mattix, K. D., P. D. Winchester, and L. R. Scherer. 2007. Incidence of abdominal wall defects is related to surface water atrazine and nitrate levels. *J Pediatr Surg* 42 (6):947-9.

May, J. M. 1958. *The ecology of human disease*. New York,: MD Publications.

Mayer, J. D. 2000. Geography, ecology and emerging infectious diseases. *Soc Sci Med* 50 (7-8):937-52.

Mayer, J. D., and M. S. Meade. 1994. A Reformed Medical Geography Reconsidered. *Professional Geographer* 46 (1):103-106.

Meade, M. S. 1977. Medical geography as human ecology: the dimension of population movement. *The Geographical Review* 67 (4):379-393.

Meade, M. S., and R. Earickson. 2000. *Medical geography*. 2nd ed. New York: Guilford Press.

Meade, M. S., and M. Emch. 2009. *Medical geography*. 3rd ed. New York: Guilford Press.

Messer, L. C., L. C. Vinikoor, B. A. Laraia, J. S. Kaufman, J. Eyster, C. Holzman, J. Culhane, I. Elo, J. G. Burke, and P. O'Campo. 2008. Socioeconomic domains and associations with preterm birth. *Soc Sci Med* 67 (8):1247-57.

Meyer, J. D., G. H. Nichols, N. Warren, and S. Reisine. 2008. Maternal occupation and risk for low birth weight delivery: assessment using state birth registry data. *J Occup Environ Med* 50 (3):306-15.

Morris, S. E., A. O. Thomson, L. Jarup, C. de Hoogh, D. J. Briggs, and P. Elliott. 2003. No excess risk of adverse birth outcomes in populations living near special waste landfill sites in Scotland. *Scott Med J* 48 (4):105-7.

National Birth Defects Prevention Network (NBDPN). 2005. Birth Defects Surveillance Data from Selected States, 1998-2002. *Birth Defects Res A Clin Mol Teratol* 73:759-852.

———. 2007. Birth Defects Surveillance Data from Selected States, 2000-2004. *Birth Defects Res A Clin Mol Teratol* 79:874-942.

NIOSH. 1985. Summaries of Current Intelligence Bulletins produced by NIOSH July 1985 *MMRW* 34 (Suppl. 2):33S-49S.

North Carolina State Center for Health Statitistics (NC SCHS). 2006. *North Carolina Birth Defects Monitoring Program*. North Carolina State Center for Health Statistics 2005 [cited October 2006]. Available from http://www.schs.state.nc.us/SCHS/bdmp.

Oakes, J. M. 2004. The (mis)estimation of neighborhood effects: causal inference for a practicable social epidemiology. *Soc Sci Med* 58 (10):1929-52.

Olshan, A. F., P. A. Baird, and K. H. Lo. 1991. Socioeconomic Status and the Risk of Birth Defects. *American Journal of Epidemiology* 134:778-779.

Opitz, J. M., and T. J. Pysher. 2008. Invited editorial comment: further reflections on gastroschisis. *Am J Med Genet C Semin Med Genet* 148C (3):192-8.

Penman, D. G., R. M. Fisher, H. R. Noblett, and P. W. Soothill. 1998. Increase in incidence of gastroschisis in the South West of England in 1995. *British Journal of Obstetrics and Gynaecology* 105 (3):328-331.

Penz, H., G. Menardi, and C. Brezinka. 1998. Omphalocele and gastroschisis in Tirol - Incidence and epidemiology 1985-1996. *Gynakologisch-Geburtshilfliche Rundschau* 38 (4):216-221.

Rankin, J., E. Dillon, and C. Wright. 1999. Congenital anterior abdominal wall defects in the north of England, 1986-1996: occurrence and outcome. *Prenat Diagn* 19 (7):662-8.

Roeper, P. J., J. Harris, G. Lee, and R. Neutra. 1987. Secular rates and correlates for gastroschisis in California (1968-1977). *Teratology* 35 (2):203-10.

Root, E. D., R. E. Meyer, and M. E. Emch. 2009. Evidence of localized clustering of gastroschisis births in North Carolina, 1999-2004. *Soc Sci Med* 68 (8): 1361-1367.

Salihu, H. M., Z. Y. Aliyu, B. J. Pierre-Louis, F. A. Obuseh, C. M. Druschel, and R. S. Kirby. 2004. Omphalocele and gastroschisis: Black-White disparity in infant survival. *Birth Defects Res A Clin Mol Teratol* 70 (9):586-91.

Salihu, H. M., M. N. Shumpert, M. Slay, R. S. Kirby, and G. R. Alexander. 2003. Childbearing beyond maternal age 50 and fetal outcomes in the United States. *Obstet Gynecol* 102 (5 Pt 1):1006-14.

Schmidt, A. I., S. Gluer, K. Muhlhaus, and B. M. Ure. 2005. Family cases of gastroschisis. *J Pediatr Surg* 40 (4):740-1.

Schneider, K., C. Hafner, and I. Jäger. 2004. Mutagenicity of textile dye products. *Journal of Applied Toxicology* 24 (2):83-91.

Shaw, G. M., and L. H. Malcoe. 1992. Residential mobility during pregnancy for mothers of infants with or without congenital cardiac anomalies: a reprint. *Arch Environ Health* 47 (3):236-8.

Shaw, G. M., C. R. Wasserman, C. D. O'Malley, V. Nelson, and R. J. Jackson. 1999. Maternal pesticide exposure from multiple sources and selected congenital anomalies. *Epidemiology* 10 (1):60-6.

Steingraber, S. 1997. *Living downstream: a scientist's personal investigation of cancer and the environment*. Reading, Mass.: Addison-Wesley Publishing.

Stothard, K. J., P. W. Tennant, R. Bell, and J. Rankin. 2009. Maternal overweight and obesity and the risk of congenital anomalies: a systematic review and meta-analysis. *Jama* 301 (6):636-50.

Swartz, C. H., R. A. Rudel, J. R. Kachajian, and J. G. Brody. 2003. Historical reconstruction of wastewater and land use impacts to groundwater used for public drinking water: exposure assessment using chemical data and GIS. *J Expo Anal Environ Epidemiol* 13 (5):403-16.

Tarboton, D. G. 1997. A New Method for the Determination of Flow directions and Contributing Areas in Grid Digital Elevation Models. *Water Resources Research* 33 (2):309-319.

———. 2006. *Terrain Analysis Using Digital Elevation Modesl (TauDEM)* 2005 [cited October 2006]. Available from http://hydrology.neng.usu.edu/taudem.

Tarboton, D. G., and D. P. Ames. 2001. Advances in the mapping of flow networks from digital elevation data. Paper read at World Water and Environmental Resources Congress, at Orlando, FL.

Torfs, C., C. Curry, and P. Roeper. 1990. Gastroschisis. *J Pediatr* 116 (1):1-6.

Torfs, C. P., R. E. Christianson, D. M. Iovannisci, G. M. Shaw, and E. J. Lammer. 2006. Selected gene polymorphisms and their interaction with maternal smoking, as risk factors for gastroschisis. *Birth Defects Res A Clin Mol Teratol* 76 (10):723-30.

Torfs, C. P., and C. J. Curry. 1993. Familial cases of gastroschisis in a population-based registry. *Am J Med Genet* 45 (4):465-7.

Torfs, C. P., E. A. Katz, T. F. Bateson, P. K. Lam, and C. J. R. Curry. 1996. Maternal medications and environmental exposures as risk factors for gastroschisis. *Teratology* 54 (2):84-92.

Torfs, C. P., P. K. Lam, D. M. Schaffer, and R. J. Brand. 1998. Association between mothers' nutrient intake and their offspring's risk of gastroschisis. *Teratology* 58 (6):241-250.

Torfs, C. P., E. M. Velie, F. W. Oechsli, T. F. Bateson, and C. J. R. Curry. 1994. A population-based study of Gastroschisis - Demographic, Pregnancy, and Life-style Risk-Factors. *Teratology* 50 (1):44-53.

Vrijheid, M., H. Dolk, D. Stone, L. Abramsky, E. Alberman, and J. E. Scott. 2000. Socioeconomic inequalities in risk of congenital anomaly. *Arch Dis Child* 82 (5):349-52.

Wall, A., and R. Meyer. 2006. Birth Defects in North Carolina, 15. Raleigh: North Carolina Birth Defects Monitoring Program, State Center for Health Statistics.

Waller, D. K., G. M. Shaw, S. A. Rasmussen, C. A. Hobbs, M. A. Canfield, A. M. Siega-Riz, M. S. Gallaway, and A. Correa. 2007. Prepregnancy obesity as a risk factor for structural birth defects. *Arch Pediatr Adolesc Med* 161 (8):745-50.

Wasserman, C. R., G. M. Shaw, S. Selvin, J. B. Gould, and S. L. Syme. 1998. Socioeconomic status, neighborhood social conditions, and neural tube defects. *Am J Public Health* 88 (11):1674-80.

Werler, M. M., A. A. Mitchell, and S. Shapiro. 1992a. Demographic, reproductive, medical, and environmental factors in relation to gastroschisis. *Teratology* 45 (4):353-60.

———. 1992b. First trimester maternal medication use in relation to gastroschisis. *Teratology* 45 (4):361-7.

Werler, M. M., J. E. Sheehan, and A. A. Mitchell. 2002. Maternal medication use and risks of gastroschisis and small intestinal atresia. *American Journal of Epidemiology* 155 (1):26-31.

White, F. M., F. G. Cohen, G. Sherman, and R. McCurdy. 1988. Chemicals, birth defects and stillbirths in New Brunswick: associations with agricultural activity. *Cmaj* 138 (2):117-24.

Williams, J. R., F. E. Alexander, R. A. Cartwright, and R. J. Q. McNally. 2001. Methods for eliciting aetiological clues from geographically clustered cases of disease, with application to leukaemia-lymphoma data. *Journal of the Royal Statistical Society: Series A (Statistics in Society)* 164 (1):49-60.

Williams, L. J., J. E. Kucik, C. J. Alverson, R. S. Olney, and A. Correa. 2005. Epidemiology of gastroschisis in Metropolitan Atlanta, 1968 through 2000. *Birth Defects Research Part a-Clinical and Molecular Teratology* 73 (3):177-183.

Williams, T. 2008. Animal models of ventral body wall closure defects: a personal perspective on gastroschisis. *Am J Med Genet C Semin Med Genet* 148C (3):186-91.

Wilson, J. P., and J. C. Gallant. 2000. *Terrain Analysis: Principles and Applications*. New York: Wiley.

Wilson, R. D., and M. P. Johnson. 2004. Congenital abdominal wall defects: an update. *Fetal Diagn Ther* 19:385-398.

Womersley, J., and D. H. Stone. 1987. Epidemiology of facial clefts. *Arch Dis Child* 62 (7):717-20.