SPATIAL AND TEMPORAL PATTERNS OF GASTROINTESTINAL ILLNESS AND THEIR RELATIONSHIP WITH PRECIPITATION ACROSS THE STATE OF NORTH CAROLINA

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ABSTRACT

Jenna M. Hartley: Spatial and temporal patterns of gastrointestinal illness and their relationship with precipitation across the state of North Carolina
(Under the direction of J. Jason West and Charles E. Konrad)

The quality of drinking water quality in the United States is among the best in the world. Nonetheless, pathogens are present in source waters that are used for drinking water. Water in general and floodwaters specifically can spread pathogens within watersheds by mobilizing pathogens in the environment and transporting them. Previous research has identified a positive association between gastrointestinal illness and meteorological variables, including heavy precipitation. This study analyzes patterns of gastrointestinal illness and their relationship with various demographic variables and precipitation across the state of North Carolina. Results show the strongest demographic relationships between poverty indicators and disease. Moreover, this study identifies increases in the rate of gastrointestinal illness after periods of heavy rainfall. Several geographical clusters of high disease occurrence are identified at the county level, with seven counties across the state showing 300% and greater increases in average rates of ED admissions after heavy rainfall.

To my husband Keith.

ACKNOWLEDGEMENTS

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AGI	Acute gastrointestinal illness, including specified and non-specified causes for illness, as derived from the ICD-9-CM codes 1.00-9.00 (specified gastrointestinal illness) and 589.89 (non-specified, noninfectious gastrointestinal illness, including acute gastrointestinal illness)
ArcGIS	A geographic information system (GIS) for working with maps and geographic information
CISA	Carolinas Integrated Science Assessments, South Carolina
ED	Emergency Department
EPA	Environmental Protection Agency
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification. A set of standardized codes used to describe diagnoses of morbidity in hospitals.
IPCC	Intergovernmental Panel on Climate Change
NC	North Carolina
NC DETECT	North Carolina's statewide syndromic surveillance system, which is funded by the North Carolina Division of Public Health (NC DPH) Federal Public Health Emergency Preparedness Grant and managed through collaboration between NC DPH and the University of North Carolina at Chapel Hill's Department of Emergency Medicine's Carolina Center for Health Informatics
RUCC	Rural-Urban Continuum Codes; a classification system of level of rurality
SDWIS	Safe Drinking Water Information System, maintained by the U.S. EPA
SERCC	Southeast Regional Climate Center, Chapel Hill, NC

CHAPTER 1: ACUTE GASTROINTESTINAL ILLNESS AND DIARRHEA

Introduction: Gastrointestinal Illness and Diarrhea

One of the targets of the United Nations' 2015 Millennium Development Goals was to "halve, by 2015, the proportion without sustainable access to safe drinking water and basic sanitation" (United Nations, 2008). Now in 2015, assessments of our progress have been made. Between 1990 and 2015, progress was made, as 2.6 billion people gained access to improved sources of water (United Nations, 2015). However, the United Nations reports that there are still 2.4 billion people that use unimproved sanitation facilities (United Nations, 2015), which can contribute to disease burdens in those communities (DeFelice, Johnston, & MacDonald Gibson, 2015). Diarrhea and gastrointestinal illness are illnesses that are often associated with poor drinking water and sanitation (Patz, Vavrus, Uejio, & McLellan, 2008). Despite uncertainties associated with all estimates of disease burdens, one detailed literature review has concluded that the median number of global annual deaths from diarrhea is 2.5 million people, which, although high, shows a decrease over four consecutive decades (Kosek, Bern, & Guerrant, 2003). Even with the decrease in mortality from diarrhea, illnesses associated with the consumption of contaminated or inadequately treated water are still a global public health concern (Murphy et al., 2015b).

Fortunately, the amount of drinking water-related illnesses in developed countries such as the United States is much lower than in developing countries (Murphy et al., 2015a). The quality of drinking water in the United States (US) ranks among the best in the world (Tinker et al., 2010). This high quality and the lower rates of drinking water-related illnesses are due in part to the improvement of the municipal water and sewer systems in the United States during the twentieth century (DeFelice et al., 2015). The improvements in these United States' public systems served as highly influential public health advances that helped contribute to decreased rates of infant mortality, child mortality, and total mortality during the twentieth century (DeFelice et al., 2015). However, drinking water is still responsible for a portion of all cases of acute gastrointestinal illness (AGI) in developed countries such as the United States (Murphy et al., 2015a).

The short period of time that it takes for most enteric and acute gastrointestinal illnesses, including diarrhea, to run their course makes them largely underreported in clinical records, both in the United States and globally (Drayna, McLellan, Simpson, Li, & Gorelick, 2010; Murphy et al., 2015b). However, research suggests that drinking water contributes an estimated 4.3-16.4 million cases of gastrointestinal illness (GI) in the United States annually (Colford et al., 2006; Messner et al., 2006; Tinker et al., 2010). Despite great efforts and many resources devoted to maintaining safe drinking water in the United States, there are still pathogens present in source waters that are used for drinking water purposes (Tinker et al., 2010) and there is some evidence to suggest that developed countries with established municipal and sewer systems are not entirely immune to diseases of this type (Murphy et al., 2015a). Users of private wells and small water systems may be at an increased risk of AGI (Murphy et al., 2015b). In the United States, private wells that are shallow may be especially prone to contamination (Richards et al., 1996). Gastroenteritis, diarrhea, and AGI, the disease outcomes of this study, are the primary diseases associated with contaminated water exposure (Patz et al., 2008). In 2003 and 2004, gastroenteritis (referred heretofore as gastrointestinal illness) was noted in 48% and 68% of reported recreational and drinking water outbreaks, respectively (Patz et al., 2008).

Disease Burden

Waterborne diseases are one of the major contributors to global disease burden and mortality (Pruss-Ustun, et al., 2014). Waterborne and foodborne disease outbreaks also contribute to significant morbidity in the United States. In 2002, there were 1,330 water-related disease outbreaks (Socolovschi, et al., 2011). In the cases associated with recreational water, bacteria were responsible for the most outbreaks (32%), parasites (mainly *Cryptosporidium*) accounted for 24%, and viruses accounted for 10% (Lowe, Ebi, & Forsberg, 2013). In drinking water outbreaks, bacteria were also the most responsible for outbreaks (29%, with *Campylobacter* as the most common bacteria), followed by parasites and viruses, which accounted for 5% each (Lowe et al., 2013).

Waterborne pathogens are associated with high rates of AGI and a small but significant number of deaths (Portier, Thigpen, Carter, & Dilworth, 2010). Waterborne diseases may cause as many as 900,000 cases and 900 deaths to occur annually in the United States (Bennet, Homberg, & Rogers, 1987). Gastroenteritis remains the primary disease associated with food and water exposure (Lowe et al., 2013). It has been estimated that up to 19 million cases of AGI may be due to contamination of public drinking water systems (Colford et al., 2007; Messner et al., 2006; Reynolds, Mena, & Gerba, 2008). Children under the age of five and the elderly show the highest levels for risk of waterborne disease infection (Teschke et al., 2004), and often have higher incidence of waterborne disease following heavy rainfall (Wade et al., 2004). The symptoms often associated with AGI range from mild to acute and include nausea, vomiting, and diarrhea (Rose et al., 2000).

Pathways to Human Exposure: Overview

Humans may be exposed to contaminated waters via a number of routes, one being consumption of contaminated water or consumption of crops that have been treated with fertilizers or have taken up contaminants from soils (Boxall et al., 2008). Exposure may also occur as a result of the inhalation of particulates or volatiles or as a result of direct contact with contaminated water bodies or agricultural soils (Boxall et al., 2009). Direct contact with contaminated floodwaters via walking or swimming can also cause illness (Greenough et al., 2001; Malilay, 1997). Ear, nose, and throat, respiratory, and gastrointestinal illnesses are frequently associated with recreational swimming in both fresh and oceanic waters (Lowe et al., 2013). Swimmers have a greater risk of contracting gastrointestinal illnesses than non-swimmers, and this risk has been shown to increase with prolonged exposure (Lowe et al., 2013). Heavy runoff after severe rainfall can also contaminate recreational waters, increasing the risk of human health impacts with higher bacterial counts (Lowe et al., 2013). This association has been found to be most closely associated at the beaches that are closest to rivers (Lowe et al., 2013).

The largest waterborne disease outbreak ever to impact the United States occurred in 1993 in Milwaukee, Wisconsin, and was a result of outdated combined sewer system infrastructure (MacKenzie et al., 1994). In the wake of the heaviest rainfall the region had received in over 50 years, a parasitic *Cryptosporidium* outbreak occurred as the combined sewer system sent sewage directly into local surface waters (MacKenzie et al., 1994). The *Cryptosporidium* infections affected more than 400,000 people and caused over 100 deaths (MacKenzie et al., 1994). Symptoms of that outbreak included severe diarrhea that lasted from several days to a week (MacKenzie et al., 1994). Similarly, *Cryptosporidium* transmission in humans has been linked to agricultural areas where manure is applied to land as a fertilizer (Lake et al., 2007). Waterborne disease outbreaks from the contamination of water supplies either with sewage or animal waste continue to be an important public health concern (Crowther, Kay, & Wyer, 2002).

Pathways to Human Exposure: The impact of Heavy Rains on Drinking and Recreational Water Contamination

Just as the 1993 *Cryptosporidium* outbreak followed the heavy rainfall event in Milwaukee (MacKenzie et al., 1994), over 60% of waterborne disease outbreaks have been shown to be preceded by precipitation events above the 90th percentile (Curriero, Patz, Rose, & Lele, 2001). After heavy precipitation events, floodwaters can contain over 100 types of disease-causing bacteria, viruses, and parasites (Batterman et al., 2009; Domino, Fried, Moon, Olinick, & Yoon, 2003; Rose et al., 2000). Moreover, a storm surge can infiltrate human infrastructure from the sea, and/or the build-up of agricultural waste, human waste, and chemicals can subsequently mix with freshwater sources. The rate and effect to which runoff of storm water can happen depends on multiple variables, such as slope, vegetation, flow rate, infiltration rate, and rainfall intensity (Sterk, Schijven, de Nijs, & de Roda Husman, 2013).

In some older cities, like Milwaukee, the contamination leading to such waterborne disease outbreaks can be attributed to combined sewer systems, wherein during an overflow event, floodwaters and sewage waters can be sent directly into local surface waters (MacKenzie et al., 1994). Typically, when this type of overflow event due to heavy rains occurs in a community, the contaminated water gets flushed into the local waterways, thus impacting the community via the water treatment plant. This flushing of water may overwhelm or decrease the efficiency of the sewage disposal infrastructure (Patz et al., 2008). Furthermore, heavy rainfall can promote manure-borne oocyst transportation of protozoan pathogens (Sterk et al., 2013).

When the water volume exceeds the containment capacity of the water treatment plant, the overburden is typically discharged directly into surface water bodies (Patz et al., 2008). The cities with combined sewer systems are the most at risk from the threat of water contamination and include more than 700 communities throughout the nation (EPA, 2011). Combined sewer systems are designed to collect both sanitary sewage and storm water (Patz et al., 2008). These systems then transport the sewage and storm water to a wastewater treatment plant, where they are all treated (Patz et al., 2008). When these systems are overwhelmed by heavy rainfall, they overflow and send a mixture of storm water and untreated raw sewage directly into surface waters and local waterways (Curriero et al., 2001). The excessive rainfall can cause the untreated sewage in combined systems to breach the dam (sometimes called weir) and then to be mixed directly with the storm water that is released into surface waters (Figure 1, EPA 2004).

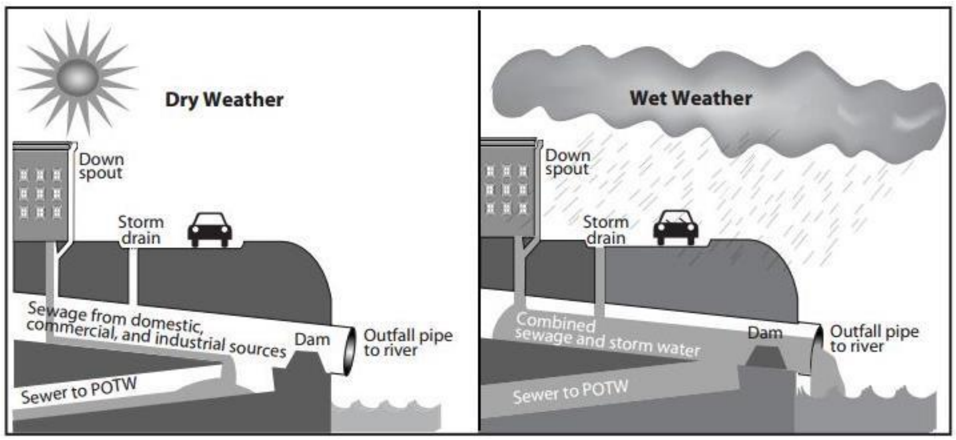


Figure 1. Schematic of a combined sewer system that discharges directly to surface waters during wet weather and heavy rainfall. Image from: US EPA. 2004. *Report to Congress: Impacts and Control of CSOs and SSOs. EPA 833-R-04-001.*

Obviously, this risk varies greatly depending on each individual system and regional differences. For example, more than 2.5 inches of rainfall in one day in the Chicago area will send raw sewage into Lake Michigan, whereas .25 of an inch in Indianapolis can send raw sewage into surface waters (Hayhoe & Wuebbles, 2008). Regardless of regional variations, the national toll of combined sewer systems is grand: each year, overflows from combined sewer systems can send over

850 billion gallons of stormwater and sewage into local waterways (EPA, 2004). This can be particularly dangerous for communities with recreational facilities along the surface waters and coastal beaches where people swim. At the time of writing, the majority of the communities served by combined sewer systems were concentrated in the Midwest and the Northeast, and there were no combined sewer systems in North Carolina (EPA, 2004, Figure 2).

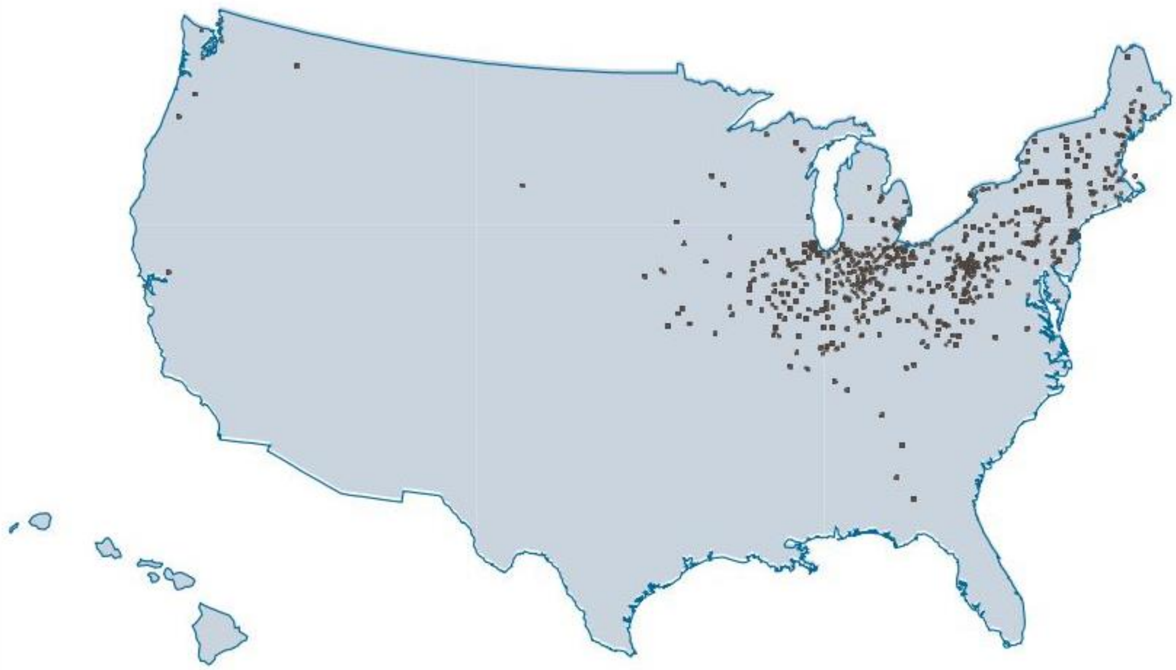


Figure 2. National distribution of communities served by Combined Sewer Systems in the United States. Heaviest concentrations are in the Northeast and the Great Lakes regions. Image from: US EPA. 2004. *Report to Congress: Impacts and Control of CSOs and SSOs. EPA 833-R-04-001.*

Heavy precipitation and waterborne disease outbreaks are not merely an issue for the future: as can be evidenced by the 1993 Milwaukee outbreak, heavy rainfall events are occurring now. In a study that collected and analyzed 83 peer-reviewed papers on waterborne diseases and heavy rainfall events, the authors concluded that heavy rainfall and flooding were the most commonly reported events preceding an outbreak (Cann, Thomas, Salmon, Wyn-Jones, & Kay, 2013; Curriero et al., 2001). Although the literature suggests that rainfall alone is not predictive of an outbreak, heavy rainfall may increase the potential for disease exposure, which could lead to an increase in the potential risk to public health. In sum, the issue of disease as a result of contaminated water is absolutely one that merits further research. In fact, the United States Environmental Protection Agency (EPA) stated in 1990 that "microbial contamination from pathogens represents the greatest remaining risk to drinking-water supplies" (Macler & Merkle, 2000).

Links between precipitation and gastrointestinal illness, AGI, and diarrhea

After a heavy rainfall event, floodwaters can be contaminated with over 100 types of disease-causing agents (Batterman et al., 2009). These disease-causing agents can come in many different forms, including viruses, bacteria, and protozoans (Drayna et al., 2010). The majority of the viral agents (e.g. rotavirus, norovirus, enterovirus, calcivirus, and adenovirus) that can cause gastrointestinal illness, AGI, and diarrhea have incubation times from 1-7 days (American Academy of Pediatrics, 2006; Drayna et al., 2010). Bacterial causes of gastrointestinal illness, AGI, and diarrhea are much less common, but have similar incubation times to viral agents (Drayna et al., 2010). Examples of bacterial causes of gastrointestinal illness, AGI, and diarrhea include *Campylobacter sp., Salmonella sp.,* and *Echerichia coli sp*. Protozoans have longer incubation periods than 7 days and tests for protozoans are typically run within water treatment plant facilities to determine their presence in the water (Drayna et al., 2010). Nonetheless, protozoans have been found to cause AGI, with *Giardia* and *Cryptosporidium* being the leading examples. Given the similarity between the incubation periods for the majority of the waterborne disease-causing agents listed above, scientists have used a lag period of 1-7 days from the date of rainfall to associate exposure from rainfall with illness (Drayna et al., 2010).

Escherichia coli (E. coli), which is a type of bacterium that typically originates in the intestines of humans and some other mammals, can also cause gastrointestinal illness (Batterman et al., 2009). *E. coli* has been found in storm water at concentrations of 100 to 500 times higher than the maximum water quality standards in Lake Michigan after heavy rains (McLellan et al., 2007). After five days of heavy rain Walkerton, Ontario in 2000, high concentrations of *E. coli* in the water supply also caused over 2,300 cases of illness and seven deaths (Auld, MacIver, & Klaasen, 2004). Once considered only a foodborne pathogen, *E. coli* continues to be linked to waterborne disease. In fact, the largest reported outbreak of *E. coli* 0157:H7 occurred at a fairground in New York State in September of 1999 and it was linked to contaminated well water (Curriero et al., 2001). Furthermore, the unusually heavy rainfall linked to this outbreak was preceded by a drought (Curriero et al., 2001; Patz et al., 2000). Several articles document increases in diarrhea or outbreaks following dry periods, which might suggest an interaction between the accumulation of pathogens in the environment during dry periods (referred to as the "concentration effect") followed by rain events that can then spread the accumulated pathogens (Adkins et al., 1987; Carlton et al., 2014; Effler et al., 2001; Nicholas, Lane, Asgari, Verlander, & Charlett, 2009; Smith et al., 1989; Willocks et al., 1998).

In addition to *E. coli,* other bacteria are frequently associated with waterborne disease outbreaks. *Vibro sp.* are one of the most-frequently associated waterborne bacteria with heavy precipitation (Schwab, 2007). *Vibrio* are ubiquitous, heterotrophic bacteria (Schwab, 2007) and its genus includes three significant human pathogens: *Vibrio cholera, Vibrio parahaemolyticus,* and *Vibrio vulnificus* (Schwab, 2007). According to leading scientists, "all three species have been demonstrated to have human health impacts on a global scale and are considered to be emerging or re-emerging human pathogens" (Colwell, 1996). *Vibrio cholorae* is found frequently in the United States' East

Coast estuaries (Shope, 1991) and could therefore be a future threat to some eastern United States' watersheds, such as those in the state of North Carolina.

Temperature is a limiting factor for *Vibrio* (Shope, 1991). Total *Vibrio* abundance is typically high in the summer and low (sometimes undetectable) in the winter months or when temperatures fall below 10-12ºC (Shope, 1991). Salinity is also a limiting factor for *Vibrio* growth, and mesohaline waters are optimal for growth (Schwab, 2007). Very high or very low salinities have been shown to be detrimental to *Vibrio* growth and development (Schwab, 2007).

The consequences of increased *Vibrio* exposure to humans in a climate that is projected to be warmer, wetter, and potentially less saline (due to increased precipitation, increased valley-glacier melt into surface water bodies, and increased continental-glacier melt into oceans) could be significant. Scientific observations have raised questions about the ecological response of total *Vibrio,* which could see major changes in a warming climate. Although one species may not seem like much, even small increases in risk, if left unchecked, could represent substantial impacts to the global burden of disease.

It has been well-documented that water in general and floodwaters specifically can spread pathogens within watersheds (Curriero et al., 2001; Dorner, Anderson, Slawson, Kouwen, & Huck, 2006; Ferguson, Husman, Altavilla, Deere, & Ashbolt, 2003). Excessive rainfall can mobilize pathogens in the environment and contribute to an increase in runoff from livestock or other agricultural fields, as well as transport them into rivers, coastal waters, and wells (Semenza et al., 2009). Waterborne disease outbreaks in the U.S. are clustered in key watersheds and associated with heavy precipitation (Patz et al., 2008).

The Safe Drinking Water Act and the Clean Water Act have emphasized the need to focus on the watershed to better protect water quality and public health (Rose et al., 2000). Rainfall and runoff have been associated with individual outbreaks of waterborne disease caused by fecal-oral pathogens (Rose et al., 2000). Fecal-oral pathogens, which originate from human or animal wastes, include the following: bacteria (*Escherichia coli (E. coli), Campylobacter, Salmonella,* and *Shigella)*, viruses (Norwalk virus, small round structured viruses, and hepatitis A virus), and protozoa (*Cryptosporidium* and *Giardia)* (Rose et al., 2000). Rose et al. (2000) also confirmed a statistically significant relationship between precipitation events and waterborne disease outbreaks originating from groundwater sources (Rose et al., 2000). In brief, there is mounting evidence that heavy precipitation and runoff events add to the risk of waterborne disease outbreaks (Curriero et al., 2001).

Connection to Climate Change

During the 20th century, greenhouse gas concentrations have increased significantly (IPCC, 2013; Nicholls & Cazenave, 2010). The burning of fossil fuels has been a major contributor to this rise in greenhouse gas concentrations, and there is increasing scientific data to support that the human-caused (anthropogenic) emissions of greenhouse gases are having a noticeable impact on the climate of the Earth (Houghton, 2009). Global temperatures have been observed as having increased 0.6ºC and global sea levels have risen 10-20cm (Houghton, 2009). This anthropogenic influence on climate is expected to increase during the 21st century and beyond (IPCC, 2013).

The importance of this association between rainfall and gastrointestinal illness, AGI, and diarrhea is underscored by the fact that global climate change will increase overall hydroclimatic variability, which includes increases in the frequency, intensity, and excessive rainfall, storm surges, floods, and drought (Cann et al., 2013; Drayna et al., 2010; Patz et al., 2000 & 2008). Different pressure and temperature patterns, caused by climate change and global warming, could also shift the geographic distribution of when and where extreme weather-related events occur (IPCC, 2013).

This regional and geographic hydroclimatic variability can make specific projections of future climate change impacts difficult (IPCC, 2013). In the United States, data show that downpours averaged less than 8 percent of the total annual precipitation at the beginning of the twentieth century and that they had increased to 10 percent of the total at the end of the century (Rose et al., 2000).

This meteorological variability is not unique to the present, as it can also be observed in climate reconstructions of the past. Scientists are still trying to find trends and patterns regarding historical extreme weather-related events. According to the most recent IPCC report (the Assessment Report Five, often referred to as the AR5, released in 2013/2014), regional trends in precipitation extremes since the middle of the 20^{th} century are varied. Nonetheless, there are some distinct weather patterns that can be extracted from long-term data despite the regional variation. It is likely that since 1951, there have been increases in the number of heavy precipitation events in more regions than there have been decreases (Trenberth, 2011). However, Trenberth also acknowledges that there are strong regional and subregional variations in these trends and that not all regions of the United States will experience a wetter and rainier future (Trenberth, 2011).

It would be remiss to not mention the large-scale oceanic circulation patterns and their impact on weather and storms. Alexander (2009) found that changes in large-scale circulation patterns have substantial influence on precipitation extremes globally. Changes to these large-scale patterns, while not the direct subject of this study, could absolutely have an impact on future storms and precipitation events. Westra et al. (2013) showed that trends in the wettest day of the year indicate more increases than would be expected by chance (Westra, Alexander, & Zwiers, 2013). In short, scientists have suggested that the overall trend of past weather could predict that future weather will be of a wetter and rainier overall nature, however these trends could have regional variability (Alexander, 2009; Trenberth, 2001; Westra et al., 2013).

With the expectation of meteorological changes that could include an increase in precipitation in at least some parts of the United States, the US National Assessment on the Potential Consequences of Climate Variability and Change has stated that "determining the role of weather in the incidence of waterborne disease outbreaks is a priority public health research issue for this country" (Curriero et al., 2001).

Overall Objectives of the Study

The overall objective of this study is to uncover spatial and temporal patterns of diarrheal disease across the state of North Carolina and to determine if those patterns are related to socioeconomic, demographic, and/or meteorological factors. North Carolina is a good study area for multiple reasons. The state has distinct geographic variation that includes mountains, piedmont, and coastal areas, which can contribute to variations both in meteorology as well as variations in the incidence of gastrointestinal illness, AGI, and diarrhea across the state. In addition to geographic variability, there is a wide range of variation in the demographic and socioeconomic statuses across the state of North Carolina (Sugg et al., 2015). Some of these variations may also be associated with incidence of disease across the state.

Although waterborne disease outbreaks are frequently associated with heavy precipitation events, this study will establish North Carolina baseline levels for diarrheal disease infections that may not be classified as "outbreaks," but can still be associated with rainfall trends and patterns. As such, we hope that the results of this study may be able to inform health officials in specific counties of a potential increase in number of waterborne disease infections given a particular set of meteorological variables. Ideally, once the given meteorological parameters for risk increase have been determined, this could be used as real-time information to guide better prevention and controls to limit the impacts or magnitudes of contamination events for the state (Patz et al., 2008). Furthermore, this study contributes to a larger field of work both across the United States (Curriero et al., 2001; DeFelice et al., 2015; Drayna et al., 2010; Tinker et al., 2010; Patz et al., 2008, among others), in Canada (Murphy et al., 2015a and 2015b), and internationally (United Nations, 2015) that attempts to pin down the true burden of diarrheal disease in various regions.

CHAPTER 2: METHODS

Data Sources and IRB Exemption

Data sources for this study include the NC DETECT (North Carolina Disease Event Tracking and Epidemiologic Collection Tool), the United States Bureau of Census including the American Community Survey (ACS), a previously-published study that determined drinking water sources (private or community systems) at the county-level for the state of North Carolina (Luh et al., 2015), and weather stations maintained by the National Weather Service and Federal Aviation Administration (FAA) and the U.S. Forest Service (USFS) as well as stations in the North Carolina Environment and Climate Observing Network (NC ECONET). This research project was approved as exempted research by the University of North Carolina Institutional Review Board (IRB) (Study number 15-1158).

Health Data

Incidence of gastrointestinal illness, AGI, and diarrhea in North Carolina was determined using Emergency Department (ED) visit data from NC DETECT (North Carolina Disease Event Tracking and Epidemiologic Collection Tool), and the methodology for the data extraction emulated a previous study on heat-related illness in North Carolina (Sugg, Konrad, & Fuhrmann, 2015). NC DETECT is North Carolina's statewide syndromic surveillance system, which is funded by the North Carolina Division of Public Health (NC DPH) Federal Public Health Emergency Preparedness Grant and managed through collaboration between NC DPH and the University of

North Carolina at Chapel Hill's Department of Emergency Medicine's Carolina Center for Health Informatics.

NC DETECT was created in 2004 to "address the need for early event detection in North Carolina" (www.ncdetect.org) and includes ED visit data, EMS data and poison center call data, as well as pilot data from various sources. This study utilized the ED visit data available in NC DETECT. In 2005, the state of North Carolina mandated that all civilian hospitals electronically report ED visit data to the state for public health surveillance (www.ncdetect.org). NC DETECT began collecting ED visit data shortly thereafter, and reached nearly full reporting compliance (92% of ED visits captured) from all North Carolina hospitals in 2007 (Sugg et al., 2015). By 2008, all North Carolina State Emergency Departments were reporting ED visit data to the NC DETECT system and 99% of all ED visits were reported (Lippman, Fuhrmann, Waller, & Richardson, 2013; Sugg et al., 2015). In total, 122 North Carolina hospitals (as of October 2014, Figure 3) report daily to NC DETECT, which allows for statewide coverage of ED visits (Sugg et al., 2015). It should be noted that NC DETECT does exclude ED visit data from three North Carolina hospitals, including two federally-operated military hospitals (Womack Army Hospital at Fort Bragg in Cumberland County, NC and the Naval Hospital at Camp Lejeune in Onslow County, NC) and one Indian Health Service hospital (Cherokee Indian Hospital located in Swain County, NC) (Sugg et al., 2015).

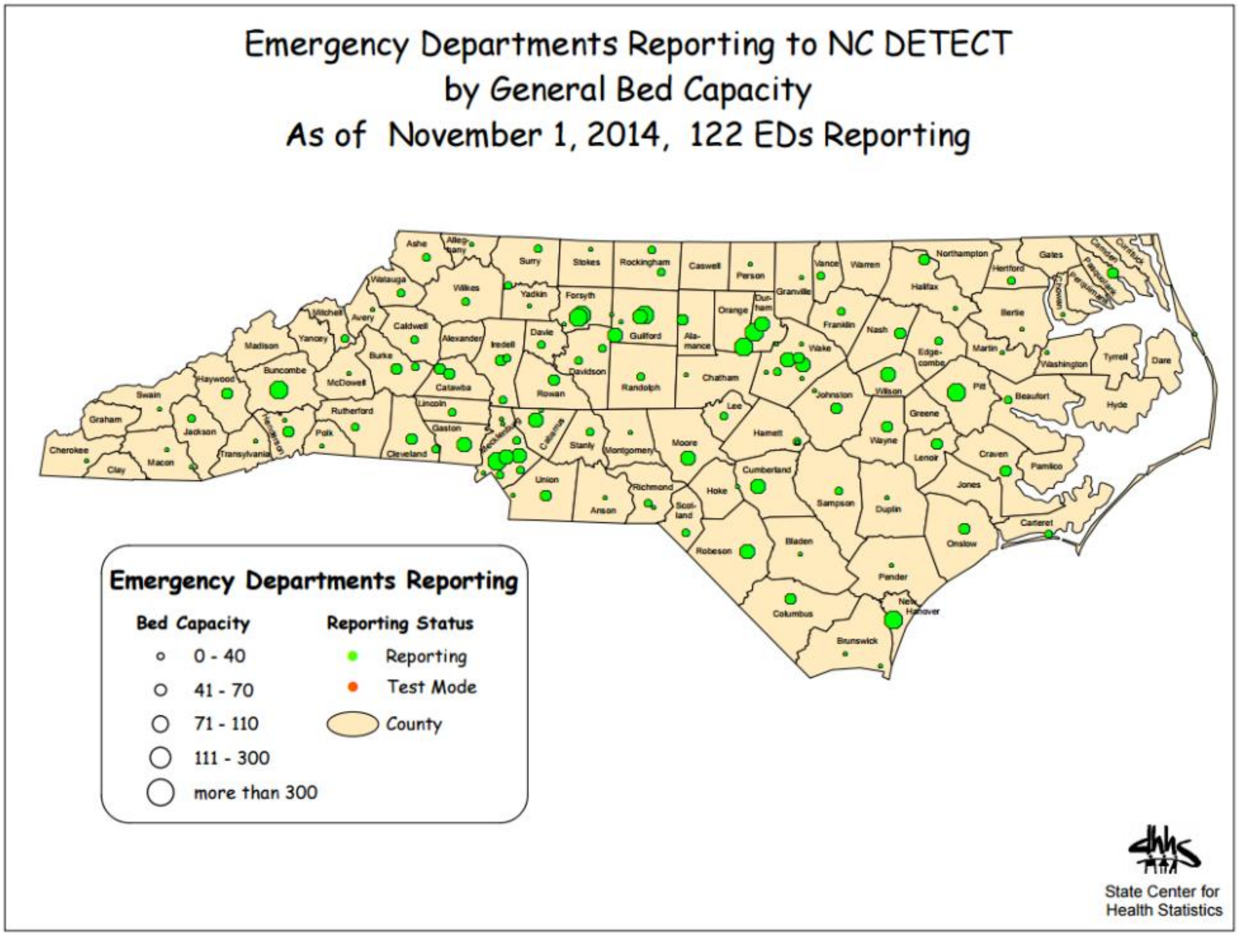


Figure 3. Map of all North Carolina Emergency Departments that report to NC DETECT, as of November 1, 2014. (www.ncdetect.org)

When the ED visits are reported to NC DETECT, the reason for patient admission is coded via ICD-9-CM code into the NC DETECT database upon patient discharge. For the purpose of this study, we followed a version of the case definition for gastrointestinal illness from previous literature and used the ICD-9-CM codes (*International Classification of Diseases, 9th Revision, Clinical Modification*) shown in Table 1. Heretofore, we will use the term "gastrointestinal illness" and/or "gastrointestinal disease" interchangeably as an umbrella term to describe results for all of the ICD-9-CM codes utilized in this study (Table 1). We chose to exclude nausea with vomiting (787.01-787.03) as well as abdominal pain (789.0) in our case definition to increase the specificity of the case definition. Following existing literature (Tinker et al., 2010), we included non-infectious gastrointestinal illness (558.9) due to the fact that research has shown that some cases of actual gastrointestinal illness cases are misclassified into this diagnostic code (Gangarosa, Glass, Lew, & Boring, 1992; Hoxie, Davis, Vergeront, Nashold, & Blair, 1997; Schwartz, Levin, & Hodge, 1997; Tinker et al., 2010). Furthermore, some care providers may choose not to run specific tests on intestinal infectious diseases (codes 001-009) (Tinker et al., 2010) due to cost, time constraints, or other reasons, meaning that actual intestinal infections that could be specified (e.g. norovirus, *salmonella*, etc.) get coded instead as "non-specified."

Table 1. ICD-9-CM codes utilized in this study, including examples from each code.

ICD-9-CM Diagnosis Code	Disease	Examples (incomplete list)
001-009	**Intestinal infectious diseases**	• *Cholera* (001) • *Salmonella* (003) • *Giardiasis* (007.1) • *Cryptosporidosis* (007.4) • *Campylobacter* (008.43) • Norovirus (008.63) • *Rotavirus* (008.61)
558.9	**Gastroenteritis, noninfectious, unspecified**	• Acute gastroenteritis • Enteritis • Gastroenteritis
787.91	**Diarrhea, not otherwise specified**	• Diarrhea, noninfectious • Nausea, vomiting and diarrhea

Emergency Department (ED) visit data have been used as a uniform sentinel for community-wide events of gastrointestinal illness in similar contexts before (Drayna et al., 2010; Tinker et al., 2009) and thus provide a framework to follow in this North Carolina-based study. In addition to providing the ICD-9-CM code that describes the reason for each ED visit, NC DETECT ED data also provide linked details such as time of visit as well as patient information such as age, gender, county of residence and ZIP code of residence for the patient. Each visit can be linked to as many as 11 ICD-9-CM diagnoses codes. Similar to the heat-related illness studies after which this study was modeled (Lippman et al., 2013; Sugg et al., 2015), ED visits containing at least one code from Table 1 were used to calculate the incidence of gastrointestinal illness in North Carolina during the study period, regardless of if those codes were categorized as primary or secondary codes.

Due to the fact that the NC DETECT data is only ED visits, the data could be skewed based on multiple factors, such as gender [many ED data studies have found that, in general, women frequent the Emergency Department more often than men, (Agency for Healthcare Research and Quality, 2011)] and severity of illness (Lowe et al., 2003). Other limitations with ED data could include, but are not limited to, a lack of individual data regarding disease etiology, clinical course, drinking water source and habits, and recreational water exposures (Drayna et al., 2010). Furthermore, considering that ED data itself can present an underestimation of the true incidence of disease (Drayna et al., 2010), all 11 possible codes (both primary and secondary diagnoses codes) were utilized in order to capture a larger proportion of ED visits. In this North Carolina-based study over a five-year period (2008-2012), the resulting dataset contains a total of 660,891 ED visits for the ICD-9-CM codes shown in Table 1.

Demographic Data

Demographic data was collected from the public records of the United States Bureau of Census via Social Explorer, a web-interface that provides users with data from the US Census and the American Community Survey, among other data elements (www.socialexplorer.com). Age- and gender-specific estimates of the North Carolina population by both ZIP code and county were obtained and extracted from the United States Bureau of Census. The 2010 census-based population estimates were used as denominators in the estimation of gastrointestinal illness ED visits per 100,000 person years (modeled after Sugg et al., 2015). Corresponding to the 2010 US Census age categories, all 660,891 cases were divided into 12 age categories in order to obtain the rates for different age groups and demographic groups (i.e. under 5, 5 to 9, 10 to 14, 15 to 17, 18 to 24, 25 to 34, 35 to 44, 45 to 54, 55 to 64, 75 to 84, and over 85).

In addition to age and gender, we assessed whether other measures of demographic and socioeconomic character factor into the incidence of gastrointestinal illness. We chose to determine if there were associations between gastrointestinal illness in North Carolina counties with the following elements: percentage of the population living in poverty (divided into two age categories by the U.S. Census Bureau: under 18 and 18 to 64), average number of people per household, urban vs. rural counties, drinking water source, and the type, level, and percentage of health insurance coverage. All of the information for the above elements was collected from the 5-year estimates in the American Community Survey for 2008-2012 at the county level (methodology modeled after Sugg et al., 2015; data from United States Census Bureau 2006-2010).

Drinking water source data by county for the state of North Carolina were obtained from a previous study conducted at the University of North Carolina at Chapel Hill through the Gillings School of Global Public Health (Luh et al., 2015). The authors of that study calculated the proportion of the county population serviced by different water technology types (Luh et al., 2015). In order to do so, they assumed that the only two water technology types in the United States were domestic self-supply (private wells) and community piped water systems as defined by the United States Environmental Protection Agency (EPA) (Luh et al., 2015; USEPA 2012).

For starters, they estimated the number of people on private wells for the year 2005 via the United States Geological Survey's National Water Information System (Luh et al., 2015). We recognize that there could be discrepancies in this information since the private well information provided by Luh et al. (2015) is from 2005 and our study runs from 2008-2012. However, we assumed that the variation in the percentage of the population using self-supplied vs. community water systems from 2005-2008 would not be so great as to egregiously skew the results for the study. Secondly, Luh et al. (2015) obtained county-level information on the number of people on very small, small, medium, large, and very large community piped water systems in 2010 from the U.S. EPA Safe Drinking Water Information System (SDWIS) (Luh et al., 2015; USEPA, 2012), wherein the size categories are determined based on the size of the population served (Luh et al., 2015). We were given access to this North Carolina county-level drinking water-source data in early November 2015 to include in our study.

Meteorological Data

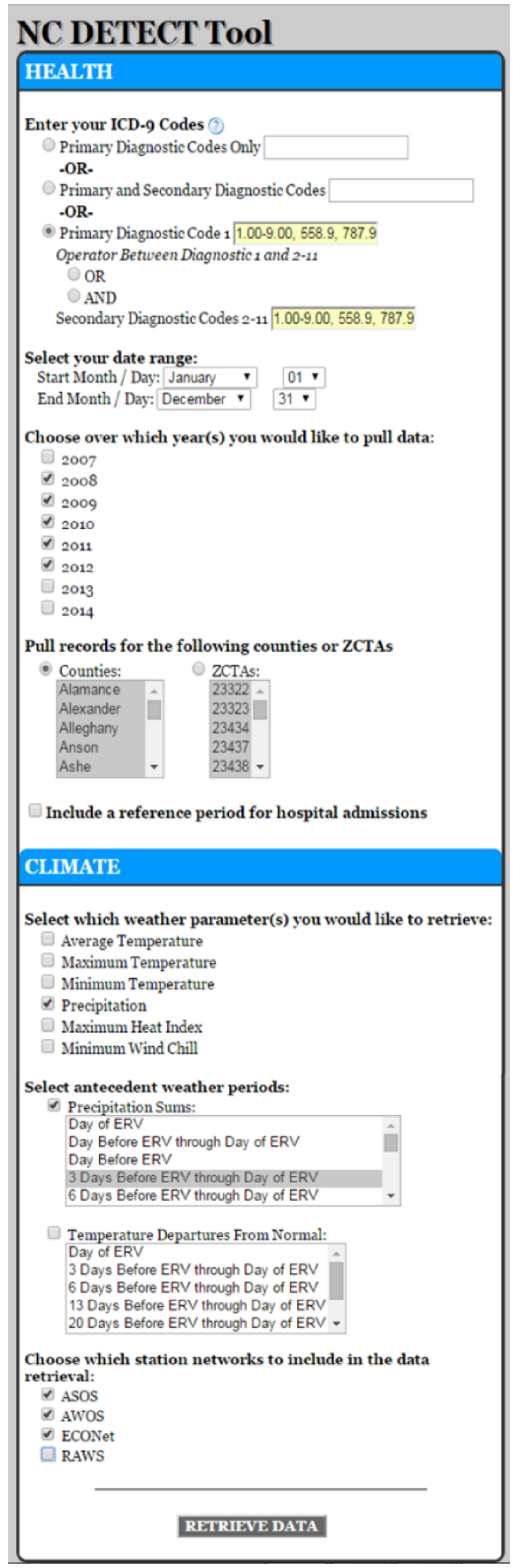
Meteorological data was obtained through the Climate-Health Toolbox which includes a feature using NC DETECT ED visit data. The Climate-Health Toolbox was designed by and is a product of the Southeast Regional Climate Center (SERCC). The Climate-Health Toolbox was constructed and continues to be operated and maintained by the North Carolina State Climate Office (NC SCO). The toolbox has access to weather stations maintained by the National Weather Service and Federal Aviation Administration and the U.S. Forest Service (USFS) as well as stations in the North Carolina Environment and Climate Observing Network (ECONET). Along with the ED visit data, the antecedent precipitation for each ED visit was made available by features within the Climate-Health Toolbox (Figure 2). The toolbox can provide weather variables (precipitation and temperature) within a range of days (up to 90 days) prior to an Emergency Department visit. For this study, cumulative totals for the 3 days prior to each ED visit and 10 days prior to each ED visit were selected so as to capture any precipitation that occurred prior to the visit within the accepted lag period in the existing literature (Drayna et al., 2010; Tinker et al., 2010). We chose for the precipitation data available within the NC DETECT Climate-Health Toolbox to pull from the following weather networks: the Automated Surface Observing System (ASOS), the Automated Weather Observing System (AWOS), and the North Carolina Environment and Climate Observing Network (ECONET). In total, there are 113 of these stations across the 100 counties in North Carolina (Sugg et al., 2015). The patient's county of residence was utilized to determine which weather station to assign to each ED visit. If nearby weather stations were missing precipitation data or not functioning at the time of the ED visit, the closest weather station with available data was assigned to the ED visit.

Within the Climate-Health Toolbox, the ZIP code of the patient's residential address was utilized to determine which weather station to assign to the ED visit. The nearest weather station was identified using the center of the patient's ZIP code area to determine the shortest distance to a station. This was based on the Euclidean distance using the great circle distance formula:

$$D = R \cos^{-1} [\sin l_1 \sin l_2 + \cos l_1 \cos l_2 \cos (m_2 - m_1)]$$

where D is the distance (km) between the ED patient's residence and the weather station, R is the mean earth radius, l_1 and l_2 are latitudes (rad) of the ED patient's residence and the weather station, respectively, and m_1 and m_2 are the longitudes (rad) of the ED patient's residence and the weather station, respectively (Cao, Weinreb, & Xu, 2004; Sugg et al., 2015).

Figure 4. Features of the NC DETECT Climate-Health Toolbox. This example shows how information for this study was retrieved from the NC DETECT ED visit database and the North Carolina weather station networks. (www.sercc.com/ncdetect)



Once the meteorological data was extracted from the NC DETECT Climate-Health Toolbox, we isolated the information just to examine a 3-day lag and a 10-day lag for the purpose of this study. An example for the Climate-Health Toolbox parameters of a "lag period" is that, using a 3-day lag as an example: a 3-day lag is the sum of all of the precipitation that occurred three days before the ED visit up until the day of the visit, including the precipitation data from the date of the visit itself. Similarly, a 10-day lag represents the sum of all of the precipitation beginning ten days prior to the ED visit and including all of the days leading up to visit and the precipitation data from the date of the visit itself. We recognize that there are limitations associated with this definition, including the following: 1) other lag periods may capture a different relationship and 2) the precipitation can occur in the hours after a patient enters the emergency room. The module in the NC DETECT Climate-Health Toolbox that estimates precipitation for each visit is still under development, and as such the tool is currently being updated based on feedback from studies like this one. Future studies will be able to use this module to explore a wider range of precipitation lags and therefore identify the one that best captures the relationship.

Using the 3-day and the 10-day lag periods, heretofore referred to together as simply the "lag periods," the population of ED visits was then split into two samples based on the amount of precipitation (Table 2). Precipitation values that were unreasonably high were excluded, and the remaining values were binned into two groups: 1) Heavy: Greater than 2" of rain and 2) Light: Less than 2" of rain. Although extreme precipitation values such as those excluded have occurred in the past, they were excluded due to the fact that their occurrence was highly unlikely during the study period. Furthermore, the light rainfall group does include days with and cumulative totals of zero precipitation, which is why there are far more light cases throughout the study overall.

Table 2. Definitions of "heavy precipitation" for this study given 3-day and 10-day lag periods.

Lag period	Precipitation threshold	Threshold in which precipitation considered to be in error
3-day	**0.00" - 2.00"**	Any values greater than 15.00"
10-day	**0.00" - 2.00"**	Any values greater than 25.00"

The following information was calculated for each lag period and precipitation group:

1) Cases per county over the entire study period (2008-2012)
2) The average cases per county
3) The average rate of ED visits per county per 100,000 person-years
4) The proportional difference between the heavy and light precipitation groups
5) The average rate of ED visits across the entire state per 100,000 person-years

Cases per county over the entire study period were derived by using a Pivot Table in Excel that summed the cases per county from the originally-extracted data, which was already sorted based on the given lag period of interest. Using that cases per county information, the average cases per county was calculated (e.g., the cases per county were divided by how many days the condition (heavy or light) was observed). The information regarding how many days in the study period had observations of heavy or light precipitation, given both lag periods, was provided by the North Carolina State Climate Office (SCO). The leap days both in 2008 and in 2012 were taken into account when measuring the number of days in the 5-year study period that the certain conditions were observed.

Next, the rate of average ED visits per county per 100,000 person-years was calculated by dividing the average cases per county values by the population per county (based on the U.S. Census data) and then multiplying by 100,000. These values, although still in 100,000 person-years, are smaller than previous values throughout the study for 100,000 person-years due to the fact that the *average* number of cases per county was divided by the population whereas earlier calculations were made by dividing *total* number of cases per county by the population of respective county. The rates of average ED visits per county per 100,000 person-years were mapped for both lag periods and precipitation groups using the ArcMap product within ArcGIS10.2. The map scales for each lag period are the same; to see maps with natural breaks used to delineate contour values (Jenks), refer to Appendix 3.4.

Proportional differences between the two rates of average ED visits per county per 100,000 person years for the rain thresholds (heavy vs. light) were then determined. These proportional differences were calculated for the heavy and light rates within each given lag period. Proportional rates were determined simply by dividing the heavy rates by the light rates. Those proportional differences were then mapped for both the lag periods using ArcGIS10.2 to show whether or not average ED visits per county per 100,000 person-years were higher after heavy rain totals. Furthermore, we hypothesized that counties with the biggest proportional increases could be related to waterborne disease vulnerability. T-tests for both lag periods were also carried out to determine the statistical significance of the proportional differences results.

Lastly, the rate of average ED visits per county per 100,000 person-years was weighted by each county's population. In order to do so, the aforementioned rate (rate of average ED visits per county per 100,000 person-years) was multiplied by the county population and then divided by the total population for all of the state of North Carolina. These values were summed across all of the counties to arrive at the total rate for the state of North Carolina given different lag periods and precipitation thresholds.

Geographic Data

North Carolina has distinct physical geographical regions (e.g. mountains, piedmont, and coastal plain) that are hypothesized to contribute to variations in the incidence of gastrointestinal illness across the state. In addition to geographic variability, there is a wide range of variation in the demographic and socioeconomic statuses across the state of North Carolina (Sugg et al., 2015). Some of these variations may also be associated with incidence of gastrointestinal illness across the state. We chose to ascertain the rurality of North Carolina counties in this study and did so using the Rural-Urban Continuum Codes (RUCC) provided by the United States Department of Agriculture, Economic Research Service (USDA, 2013). According to the Rural-Urban Continuum Codes, rurality is measured based on metropolitan vs. nonmetropolitan areas, and then population size per county. The Rural-Urban Continuum Codes are developed for the entire United States and the specific qualifications for each code are listed below in Table 3. We chose to investigate rurality because we suspected that there might be an association between runoff from livestock and agriculture into surface waters in more rural areas.

Table 3. Rural-Urban Continuum Codes and descriptions (USDA, 2013).

Code	Description
Metro counties:	
1	Counties in metro areas of 1 million population or more
2	Counties in metro areas of 250,000 to 1 million population
3	Counties in metro areas of fewer than 250,000 population
Nonmetro counties:	
4	Urban population of 20,000 or more, adjacent to a metro area
5	Urban population of 20,000 or more, not adjacent to a metro area
6	Urban population of 2,500 to 19,999, adjacent to a metro area
7	Urban population of 2,500 to 19,999, not adjacent to a metro area
8	Completely rural or less than 2,500 urban population, adjacent to a metro area
9	Completely rural or less than 2,500 urban population, not adjacent to a metro area

Mapping of Spatial Patterns

Spatial patterns of incidence of gastrointestinal illness across the state of North Carolina were assessed at the county and ZIP code level. Gastrointestinal disease rates per 100,000 person-years were mapped using the ArcGIS 10.2 product within ArcMap. Maps expressing rates in 100,000 person-years were made using the "Jenks method," a classification method proposed by George Jenks and collaborators in the 1970s (Jenks and Caspall, 1971; Jenks, 1977). The "Jenks method," sometimes referred to as the Jenks optimization method or the Jenks natural breaks classification method, is a method of data classification that determines the best arrangement of values into different classes (Chen et al., 2013). This is accomplished by minimizing each class' average deviation from the class mean and simultaneously maximizing each class' deviation from the means of the other groups (Chen et al., 2013).

The 2008-2012 incidence rates per 100,000 person-years using the "Jenks method" was utilized as the uniform standard for comparison and/or serves as the baseline map for all other maps. As a result, different years, age groups, and various socioeconomic factors can all be compared to the uniform standard. Unless otherwise noted, the rates on the maps are based off of the 5-year study period uniform standard.

Statistical Analyses

The overarching objective of this study was to document patterns of gastrointestinal illness in space and time and determine how these patterns relate to socioeconomic, demographic factors and precipitation. Within that overarching objective, we hoped to identify relationships between heavy precipitation and incidence rates of gastrointestinal illness. Various statistical analyses were performed in this study to quantify the geographic variability of illness and assess the nature of its relationships with certain socioeconomic and demographic factors. These analyses are described below.

T-tests were used to ascertain the statistical significance of differences in rates of gastrointestinal disease across different groups (e.g. cases associated with heavy vs. light precipitation). Correlations were calculated to assess the strength of relationship between different variables in the study. Correlations were identified using the Microsoft Excel 7 program, specifically, the "CORREL (R_1, R_2)" function within the Data Analysis Toolbox. The CORREL function produces the correlation coefficient of data in arrays R_1 and R_2. Similarly, correlation matrices were also developed and produced in the Microsoft Excel 7 program.

Moran's I provides a measure of the degree of spatial autocorrelation and was used to investigate the statistical significance of geographic variations in the occurrence of gastrointestinal disease. *Moran's I* has been widely used in the analyses of geographic differences in health variables (Getis & Ord, 1992).

CHAPTER 3: RESULTS

Introduction

Emergency Department, meteorological, and population data were all analyzed in order to assess the spatial and temporal patterns of gastrointestinal disease across the state of North Carolina. Results are conveyed in the form of maps, correlation matrices, correlograms, as well as summary tables and charts.

Descriptions of temporal patterns

Gastrointestinal illness Emergency Department visits show one spike for total counts around 10:00am and another spike around 7:00pm (Figure 5). The 10:00am spike in Emergency Department visits coincides with reported visit escalations at that time for all Emergency Departments (Partin, 2010). The 7:00pm spike coincides with evidence from existing literature which notes that approximately 60% of national Emergency Department visits occur after business hours (defined as Monday through Friday, 8:00am-5:00pm) (National Hospital Ambulatory Medical Care Survey, 2011). Gastrointestinal disease shows a distinct seasonal pattern, with a maximum peak in total counts during the winter months and a minimum in counts during the summer months (Figure 6). Daily counts of disease over the study period display the same trend (Figure 7); this winter peak signal for diarrheal disease is consistent with existing literature (Kilgore, Holman, Clarke, & Glass, 1995; Zapikan et al., 1976) and follows the "pronounced winter peak" signal for norovirus (Hall et al., 2013).

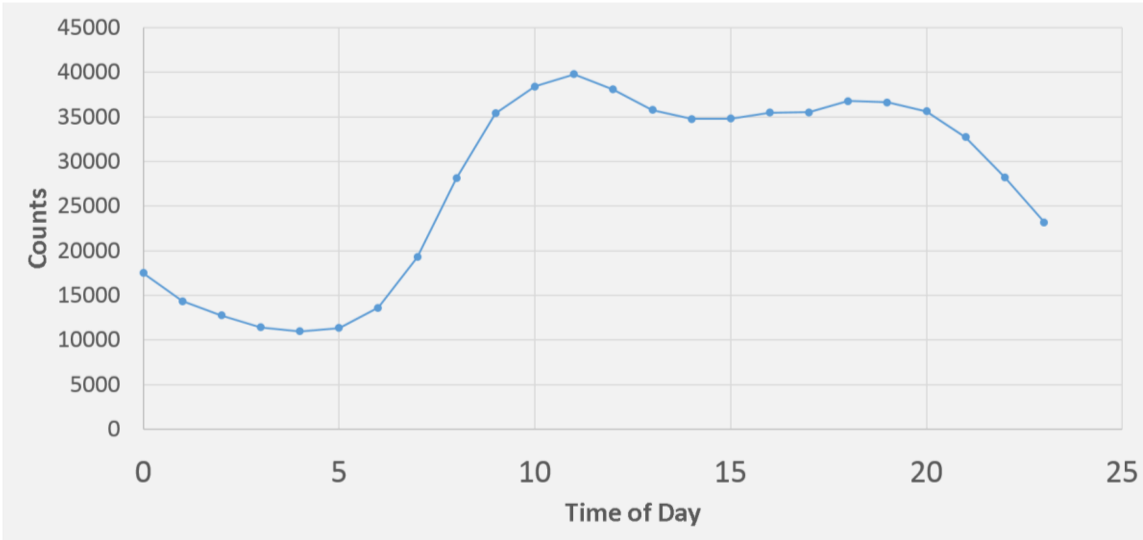


Figure 5. ED visits for gastrointestinal illness, AGI, and diarrhea in North Carolina from 2008-2012, separated by time of day.

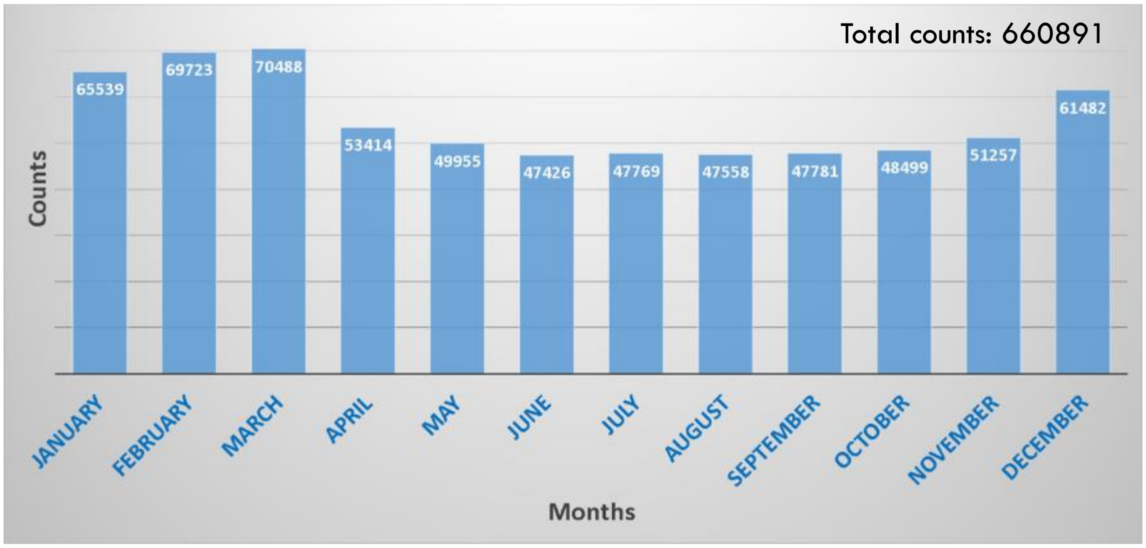


Figure 6. Total Counts of gastrointestinal illness, AGI, and diarrhea in North Carolina from 2008-2012, separated by month of year.

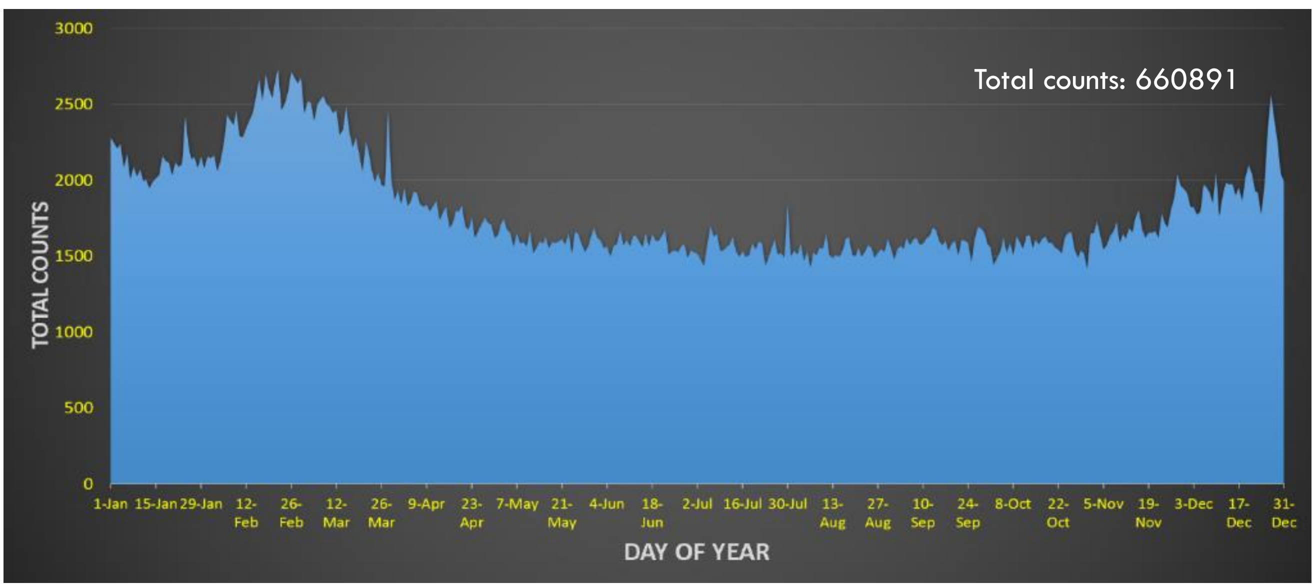


Figure 7. Total Counts of gastrointestinal illness, AGI, and diarrhea in North Carolina from 2008-2012, separated by day of year.

Spatial patterns

The incidence rates per 100,000 person-years of gastrointestinal illness ED visits by county are presented in Figure 8. The highest rates of gastrointestinal illness were found in the following counties using the "Natural Breaks" (Jenks) method, shown West to East (Figure 8): McDowell (2,856.6), Anson (2972.4), Halifax (2,966.5), and Chowan (2,586.4) counties.

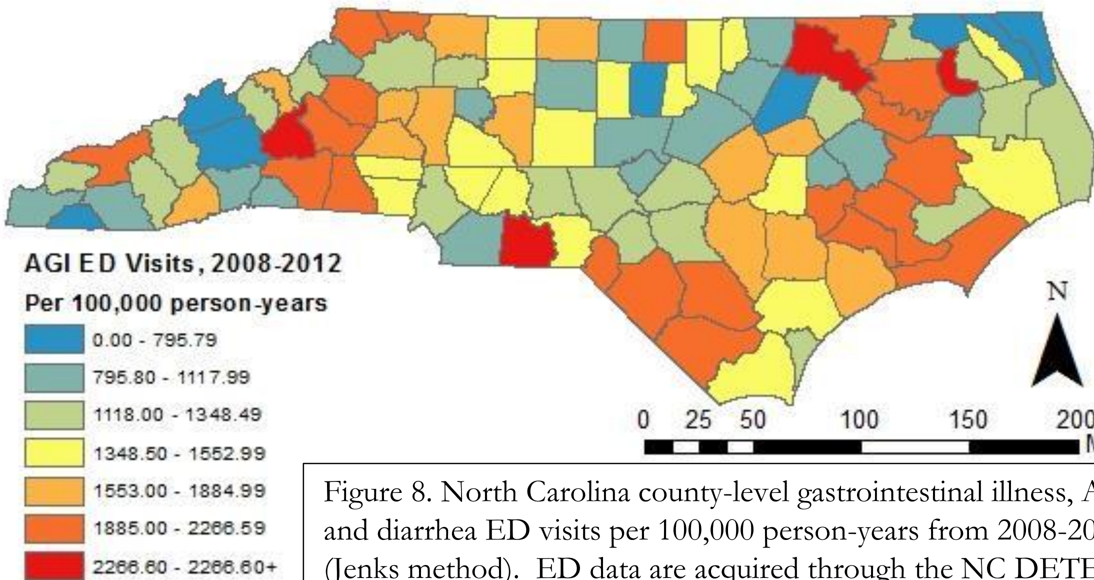


Figure 8. North Carolina county-level gastrointestinal illness, AGI, and diarrhea ED visits per 100,000 person-years from 2008-2012 (Jenks method). ED data are acquired through the NC DETECT.

Spatial autocorrelation tests for the overall county-level "Natural Breaks" map were run using the *Moran's I* calculation and results show that at a 95% confidence interval, there is no significant clustering at the county level (Figure 9). To examine spatial patterns over time, county-level maps for all individual years were made using a standard set of values for Natural Breaks; those can be found in Appendix 3.1.

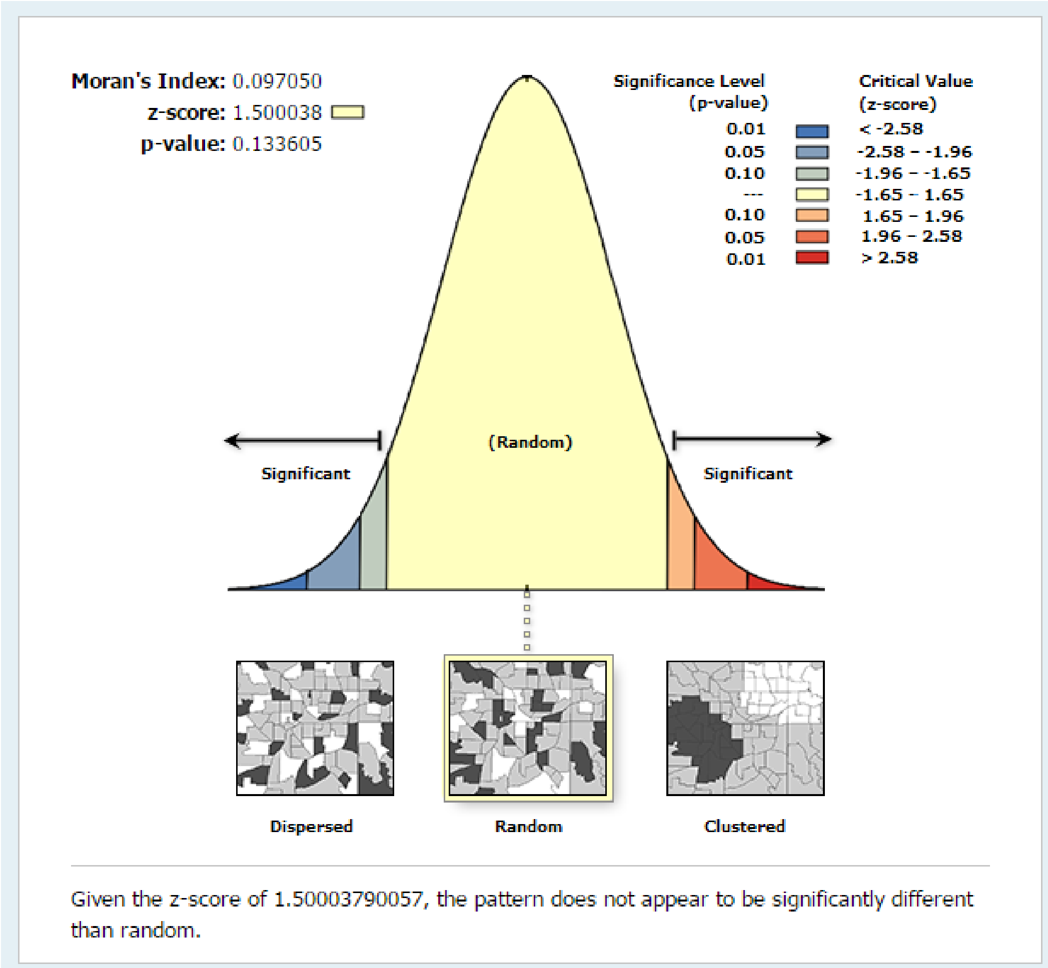


Figure 9. Spatial autocorrelation analysis of the county-level map (Figure 7) for gastrointestinal illness ED visits per 100,000 person-years from 2008-2012. Given the z-score and p-value for the map, the pattern does not appear to be significantly different from random.

When broken into quantiles (20 counties in each quantile) as opposed to natural breaks, incidence rates for gastrointestinal illness can be seen in more condensed areas of the state, despite a lack of statistical clustering (Figure 10). However, the .133 p-value does show that the value is right on the edge of being statistically significant at the 95% confidence interval, and therefore a smaller-scale of observation, such as a map made at the ZIP code level, could show significant clustering. To examine spatial patterns over time, county-level maps made using a quantiles for all individual years in the study period can be found in Appendix 3.2.

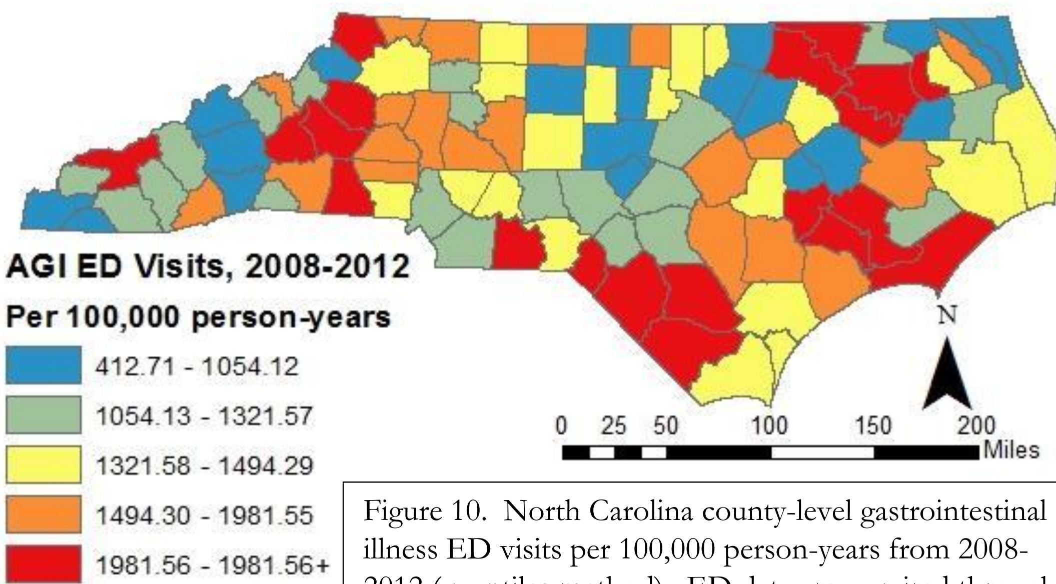


Figure 10. North Carolina county-level gastrointestinal illness ED visits per 100,000 person-years from 2008-2012 (quantiles method). ED data are acquired through the NC DETECT.

A mapping of the patterns of gastrointestinal illness at the ZIP code level reveals a clustering in the pattern of incidence rates (Figure 12, which is revealed in the *Moran's I* calculation) (Figure 11). The z-score indicates that there is a less than 1% likelihood that the clustered pattern could be the result of random chance (Figure 12). Although the statistical significance for clustering is highest at the ZIP code level, many of the calculations for this study were made at the county level (e.g. see the Study limitations portion of the Discussion section). The clustering of high rates at the ZIP code level is found largely in rural areas in the coastal plain as well as in scattered pockets in the Piedmont and the North Carolina mountains (Figure 11).

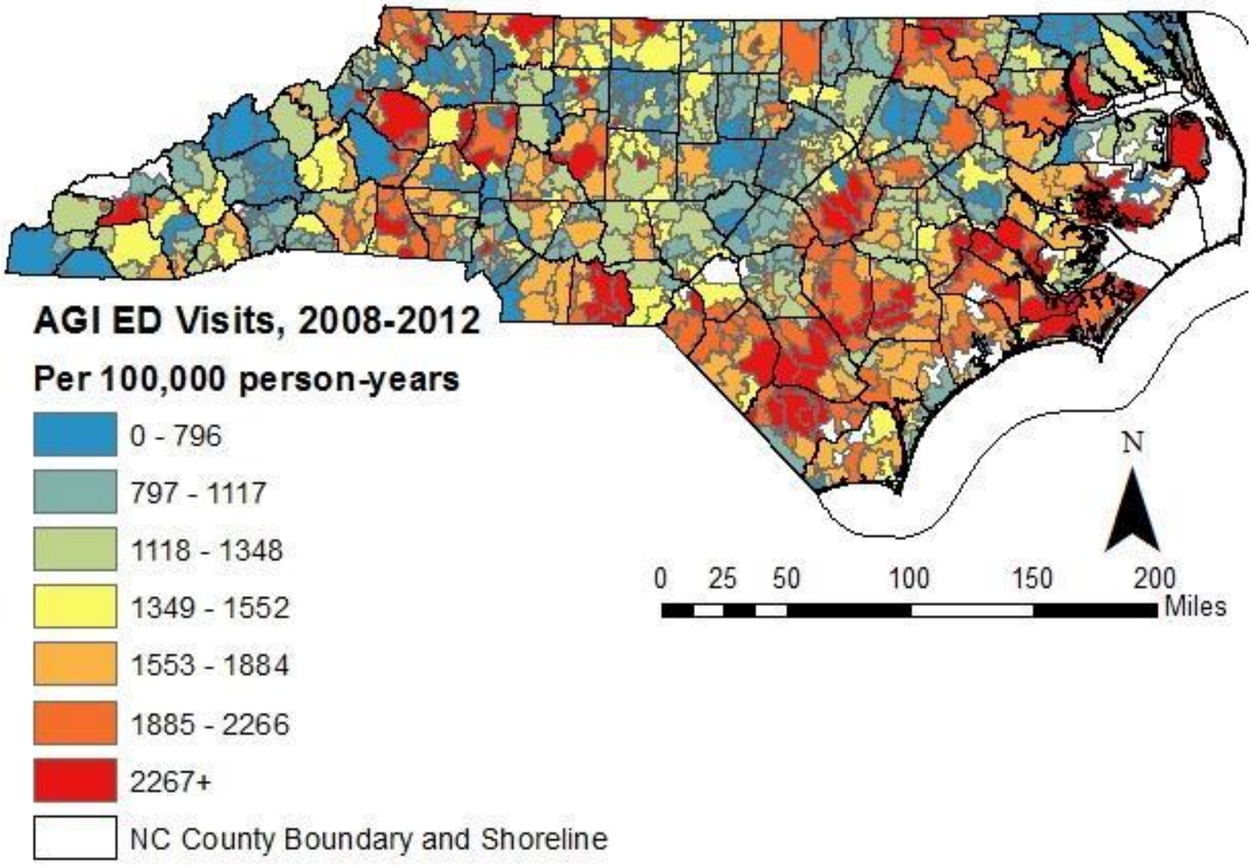


Figure 11. North Carolina ZIP code-level gastrointestinal illness ED visits per 100,000 person-years from 2008-2012. ED data are acquired through the NC DETECT. Data not available for ZIP code areas that are blank. The East coast blank areas are North Carolina sounds (Albemarle and Pamlico) and show no data due to being bodies of water.

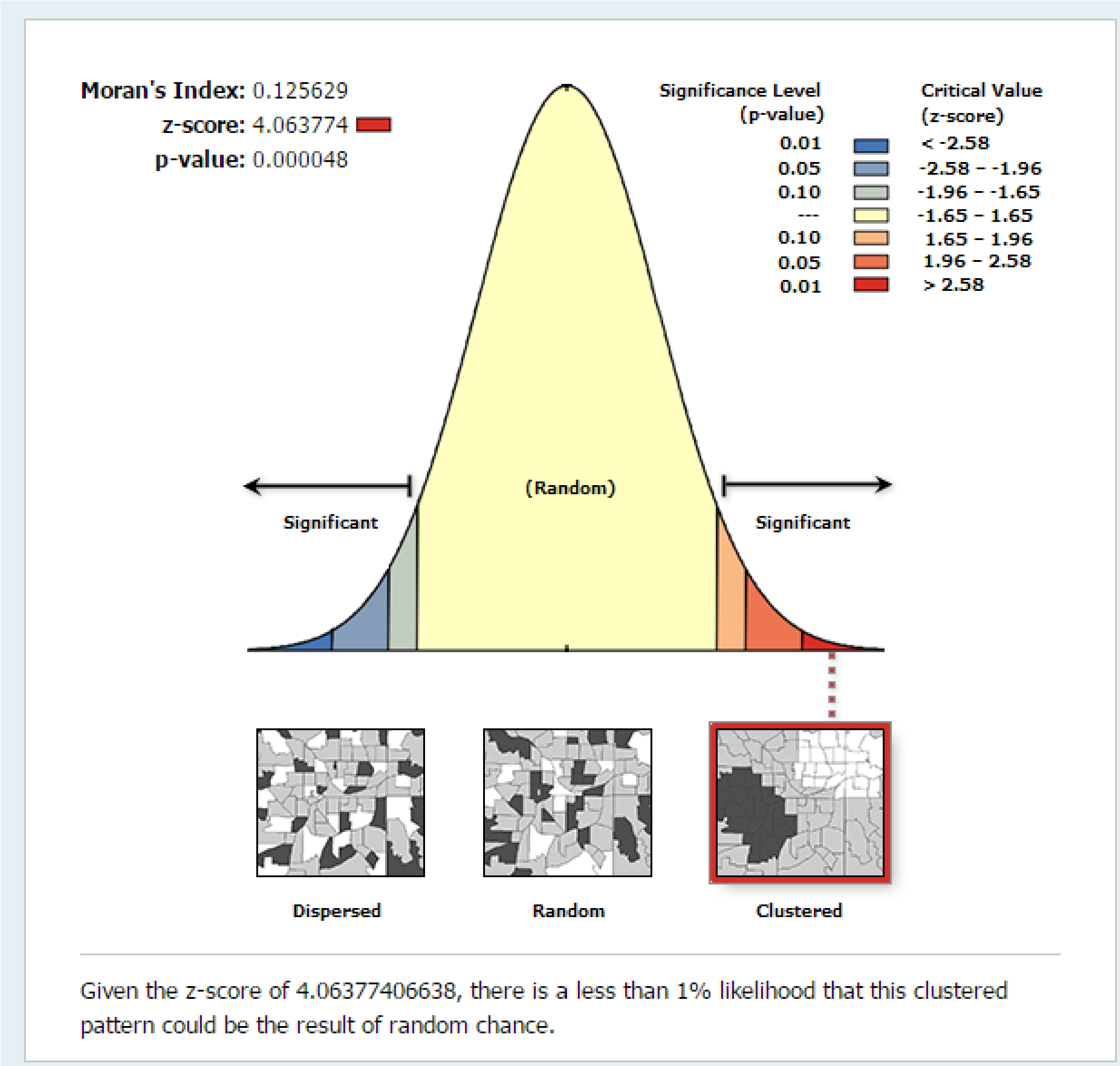


Figure 12. Spatial autocorrelation analysis of the ZIP code-level map (Figure 11) for gastrointestinal illness ED visits per 100,000 person-years from 2008-2012. Given the z-score and p-value for the map, the pattern does show that there is less than a 1% likelihood that the clustered pattern could be the result of random chance.

Efforts were made to assess the effect of norovirus, an endemic disease that occurs year-round but has a pronounced winter peak and that may have a large influence on the geographic patterns of gastrointestinal illness (Hall et al., 2013). Despite causing an average of 400,000 emergency department visits in the United States each year and being recognized as “the leading cause of epidemic acute gastroenteritis across all age groups," norovirus has been poorly directly associated with respect to disease incidence (Hall et al., 2013). In the United States, there is currently no public health reporting requirement for individual cases of norovirus (Hall et al., 2013). CalciNet, which is an outbreak surveillance network for norovirus in the United States, was launched in March 2009 in an effort to "develop and improve standardized typing of norovirus outbreaks" (Vega et al., 2011). Although all 50 states have the laboratory capacity for testing norovirus, unfortunately for this study, as of 2011, North Carolina was not a participating state in CalciNet (Vega et al., 2011).

For this study, very few cases of norovirus were actually clinically diagnosed (just under 200 cases over the entire 5-year study period, or 0.29% of the total 660,891 cases). In fact, 45 counties in the state did not have any clinically diagnosed cases of norovirus during the entire study period. Nonetheless, we suspected that cases of undiagnosed norovirus could have affected some of the winter rates for our diseases in question. Figure 13 reveals the geographic patterns of clinically diagnosed norovirus. Counties within the two highest brackets of incidence values include (from West to East): Alleghany, Cabarrus, Union, Robeson, Edgecombe, and Beaufort counties) (Figure 13). The county in red is Allegheny County (Figure 13), which is a county that does not show up in the highest bracket consistently for other factors, and could therefore possibly show a norovirus outbreak or simply more clinical diagnoses of norovirus in that county (Figure 13). Lastly, norovirus incidence rates from laboratory testing are much lower than that for gastrointestinal illness, but that is due partially to the fact that there is currently no norovirus reporting requirement and as such, fewer laboratory tests are performed for norovirus (Hall et al., 2011).

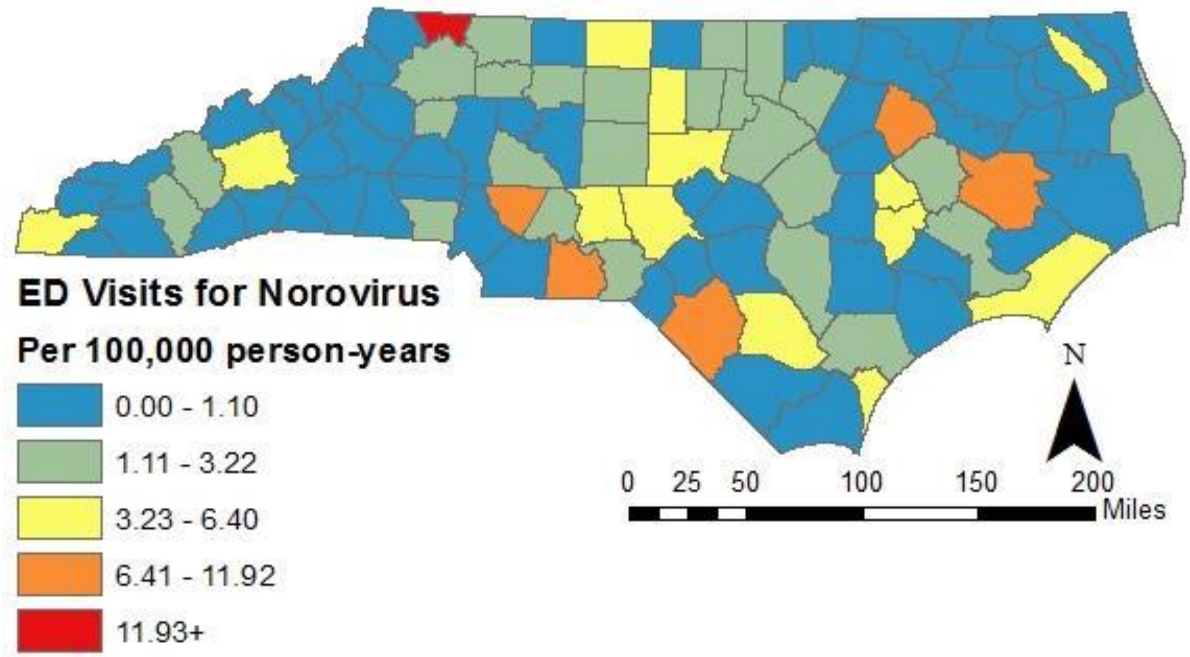


Figure 13. Incidence of Norovirus across the state of North Carolina per 100,000 person-years, split by Natural Breaks (Jenks). Data from NC DETECT.

Seasonal maps were made to see if the geographical patterns during the cool season (October – March), when norovirus incidence is high, are different from the warm season (April – September), when bacterial agents may play a greater role for gastrointestinal illness. Hereafter, we refer to the former as "high viral" season where the rates are higher (e.g. Figure 6) and the latter as the "non-viral" season. The geographic patterns of disease incidence are very similar across the two seasons (Figure 14). As is expected, the signal for gastrointestinal illness is stronger in the high viral season; however, there are still some counties in the low-viral season that show high rates of gastrointestinal illness incidence, such as (from West to East) Caldwell, Anson, Robeson, Columbus, Halifax, Craven, and Chowan counties (Figure 14). The higher incidence rates in these counties could merit further investigation as to the potential sources of gastrointestinal illness increases there during the low-viral season (Figure 14).

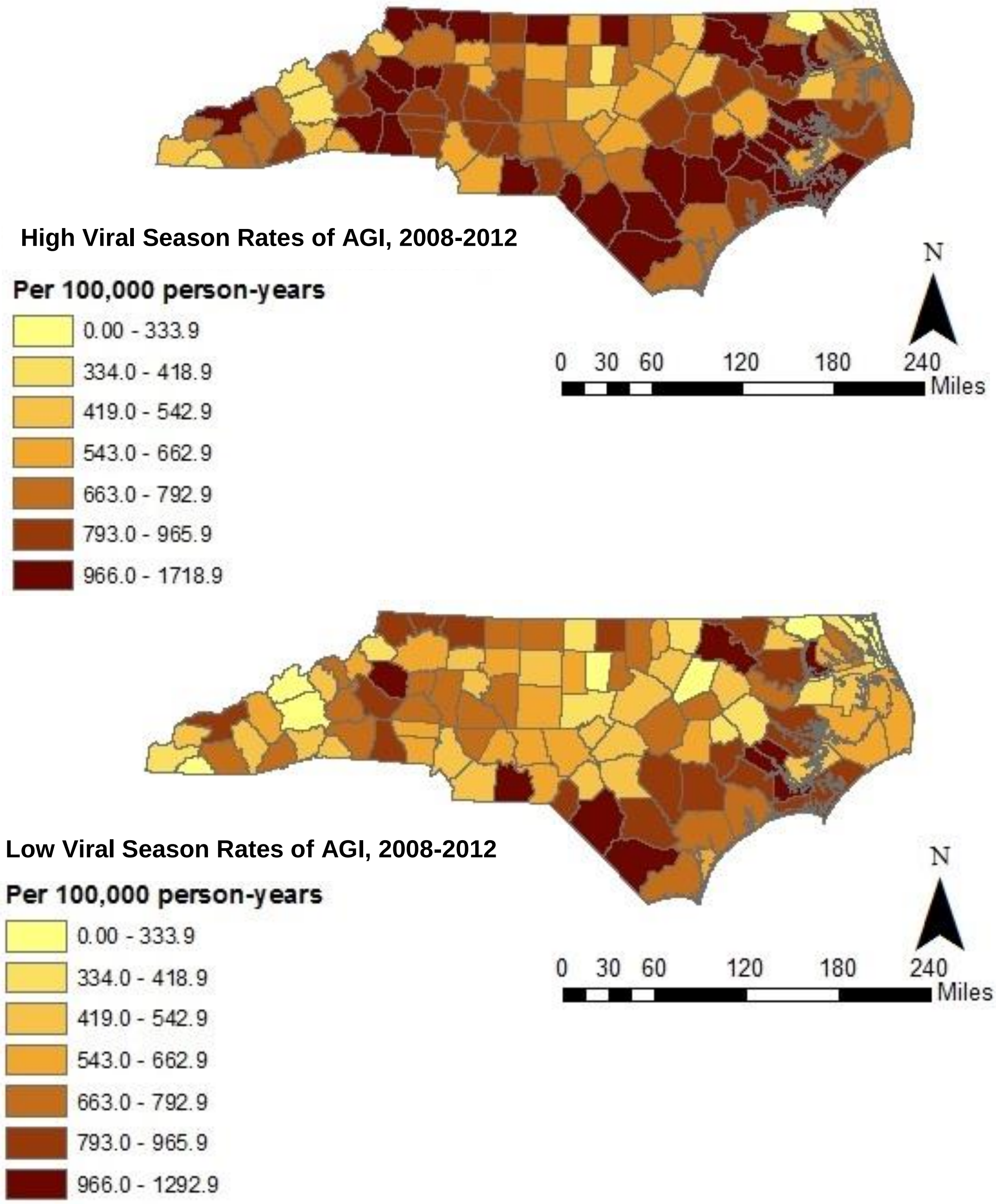


Figure 14. High Viral vs. Low-Viral Season Maps: county-level maps for gastrointestinal illness ED visits per 100,000 person-years from 2008-2012.

Demographic patterns

Demographic information results display information gathered in terms of gender and age, both from NC DETECT and the US Census. Additional information gathered at the county-level from the US Census included average household size, poverty status, urban or rural, proportion of residents using specific sources of drinking water, and health insurance status. As is consistent with existing literature regarding the use of the ED for all causes (Agency for Healthcare Research and Quality, 2011), more women than men visited the ED for gastrointestinal illness, as women comprised roughly 60% of the visits for gastrointestinal visits, while men accounted for only 40%. This study also supports existing literature that children under the age of five and the elderly show the highest levels for risk of waterborne disease infection (Teschke et al., 2004), as those two age groups show the highest incidence rates for gastrointestinal disease in this study (Figure 15).

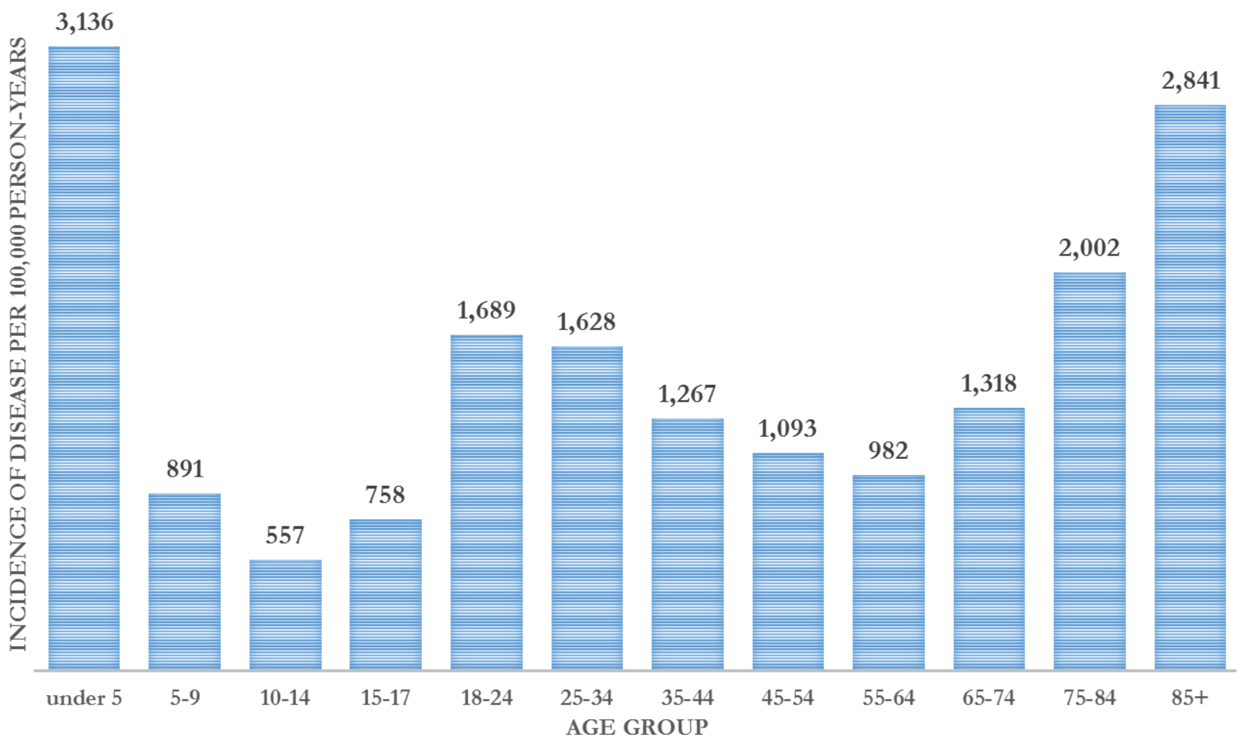


Figure 15. Incidence of gastrointestinal illness in North Carolina from 2008-2012 per 100,000 person-years, split by age group. Data from the US Census and NC DETECT.

The geographic patterns of gastrointestinal disease at the county level are similar across gender (Figure 16). Age group maps using a standardized scale show a wide range of variation among incidence rates of gastrointestinal illness across age groups and geographic counties, with the under 5 and over 85 age groups reflecting the highest incidence rates of disease (Appendix, 3.2). Maps generated with more specific breakdowns (natural breaks) for age groups that showed some of the highest rates (under 5, 18-24, 35-34, and over 85) also show county level spatial incidence rates (Appendix 3.3).

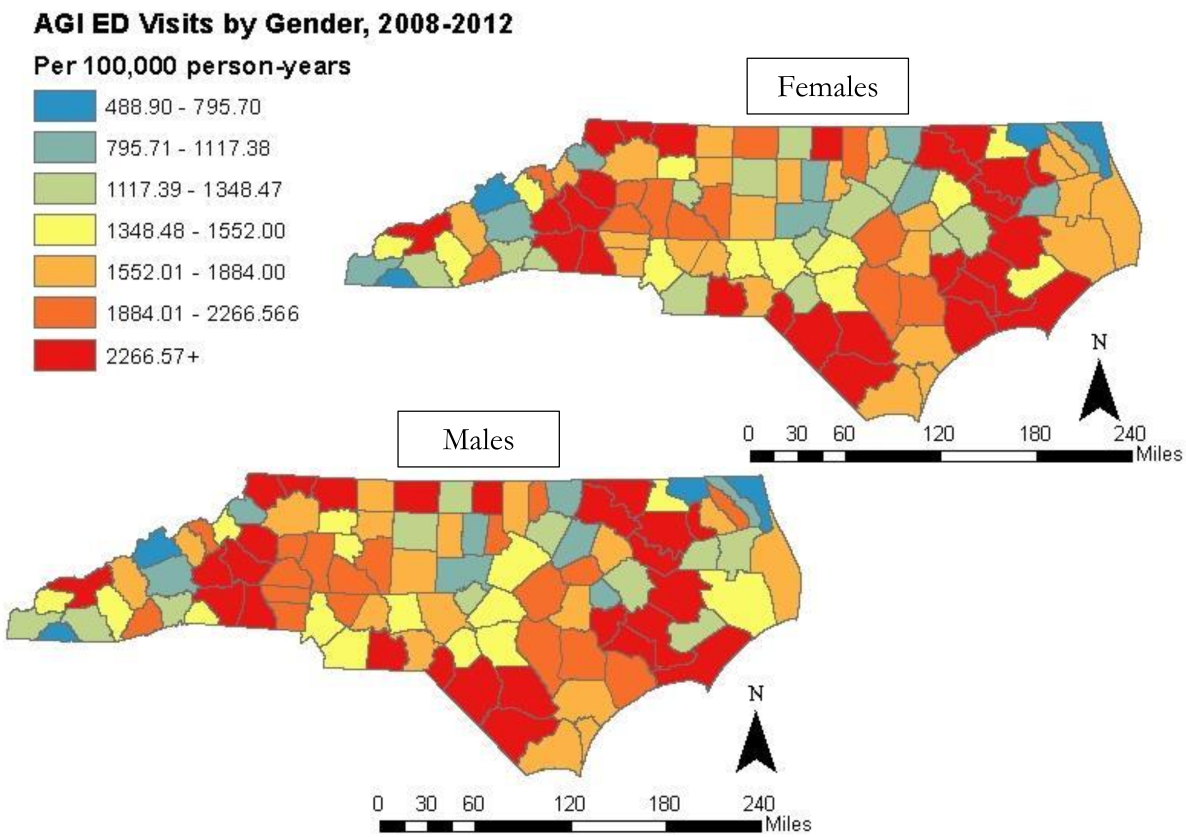


Figure 16. Gender maps for incidence of diarrheal disease, 2008-2012. Data from NC DETECT.

A map of the state for average household size within each county shows that there are some distinct geographic pockets across the state with larger average household sizes (Figure 17). This measure was selected since it could be a confounding factor for the spread of disease, specifically diarrheal disease, within homes that have more people per household. Although all of the counties in the highest disease bracket show average household sizes of 2.5 or greater, not all of the counties in the Sandhills within the second-highest disease bracket show this association (Figure 17).

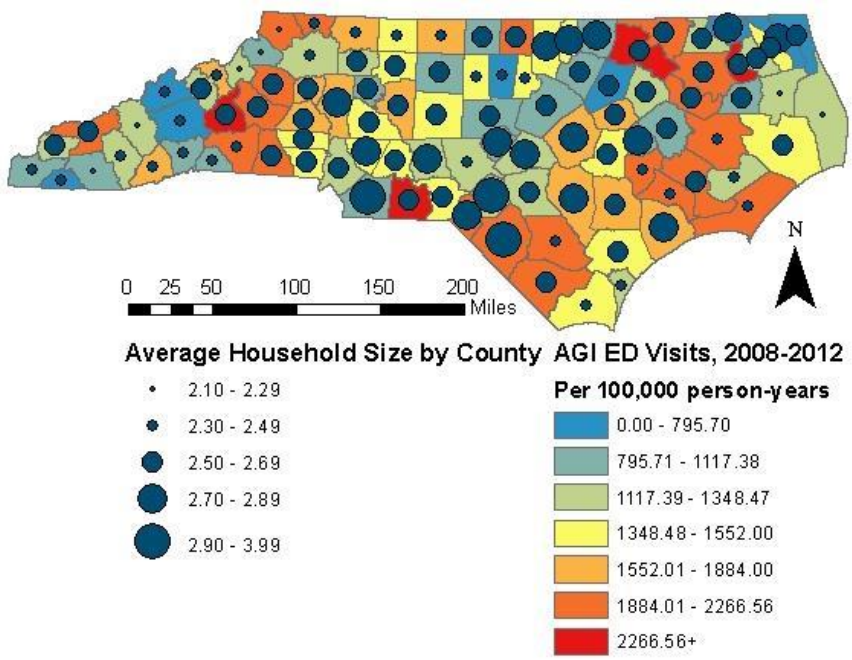


Figure 17. Average household size and the incidence of gastrointestinal illness ED visits per 100,000 person-years from 2008-2012. Data from NC DETECT and the US Census American Community Survey, 2008-2012.

Poverty shows much variation across the state but is especially clustered in the Coastal Plain and the Sandhills (Figure 18). Many of these counties (Anson, Halifax, Robeson, Columbus, Bladen, etc.) also display relatively high rates of gastrointestinal illness (Figure 18). Correlations for these variables at the end of this section reveal that some of the strongest relationships exist between poverty and incidence rates of disease (Table 4).

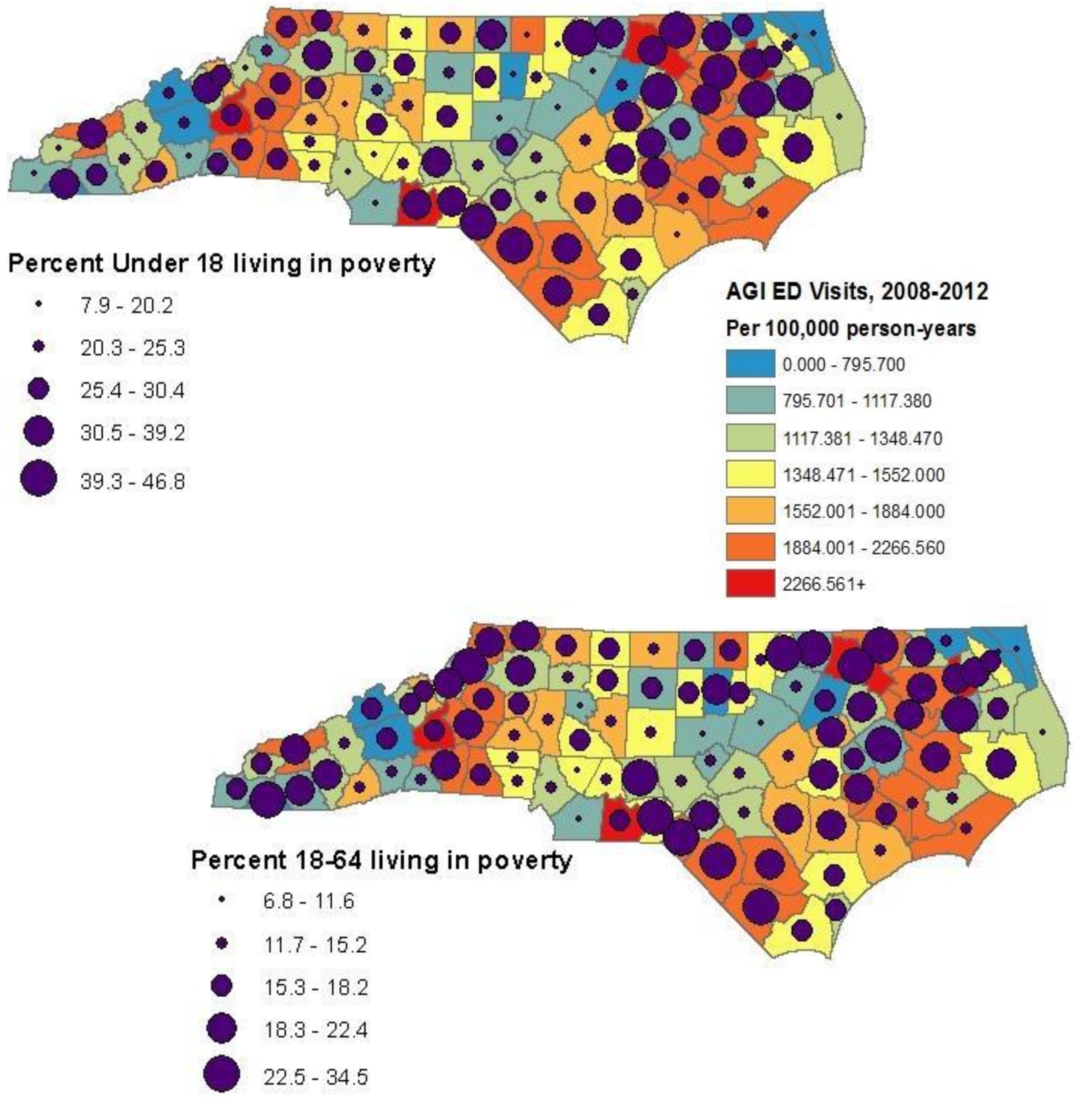


Figure 18. Percent of the population under the age of 18 (top) and between the ages of 18-64 (bottom) within each county that are living in poverty. Note that the two charts have different scales. The purple information overlays the incidence of gastrointestinal illness ED visits per 100,000 person-years from 2008-2012. Data from NC DETECT and the US Census American Community Survey, 2008-2012.

A rural and urban county-level map made utilizing the 2013 Rural-Urban Continuum Codes (RUCC) shows the urban and rural counties in North Carolina that could factor into incidence levels of gastrointestinal illness. Many, although not all, of the counties that are especially rural also display relative high rates of gastrointestinal illness (e.g. compare Figures 8 and 19).

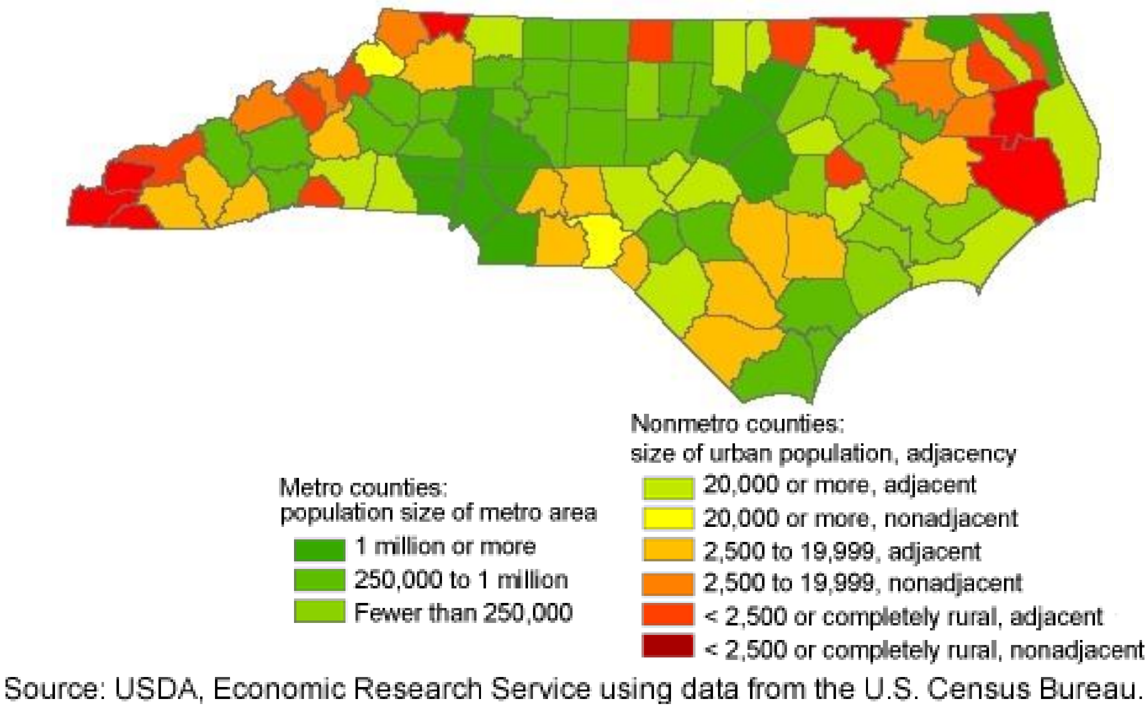


Figure 19. Rural-urban continuum codes the state of North Carolina (right). The rural-urban continuum codes (RUCC) were developed by the USDA, Economic Research Service using data from the U.S. Census Bureau.

Drinking water source maps for the state of North Carolina (Figure 20) show the proportion of the population in counties that use self-supplied drinking water, small or very small community systems, and medium, large, or very large community systems. The counties with the highest proportions of self-supplied drinking water are in the mountains region, which do not show the highest rates of gastrointestinal disease incidence. McDowell County is one of the four counties within the highest bracket for gastrointestinal disease incidence, and it has a 0.59-0.86 proportion of the population with self-supplied drinking water (Figure 20), but three of the other four highest disease-bracket counties have high proportions of their populations on community water systems (Figure 20).

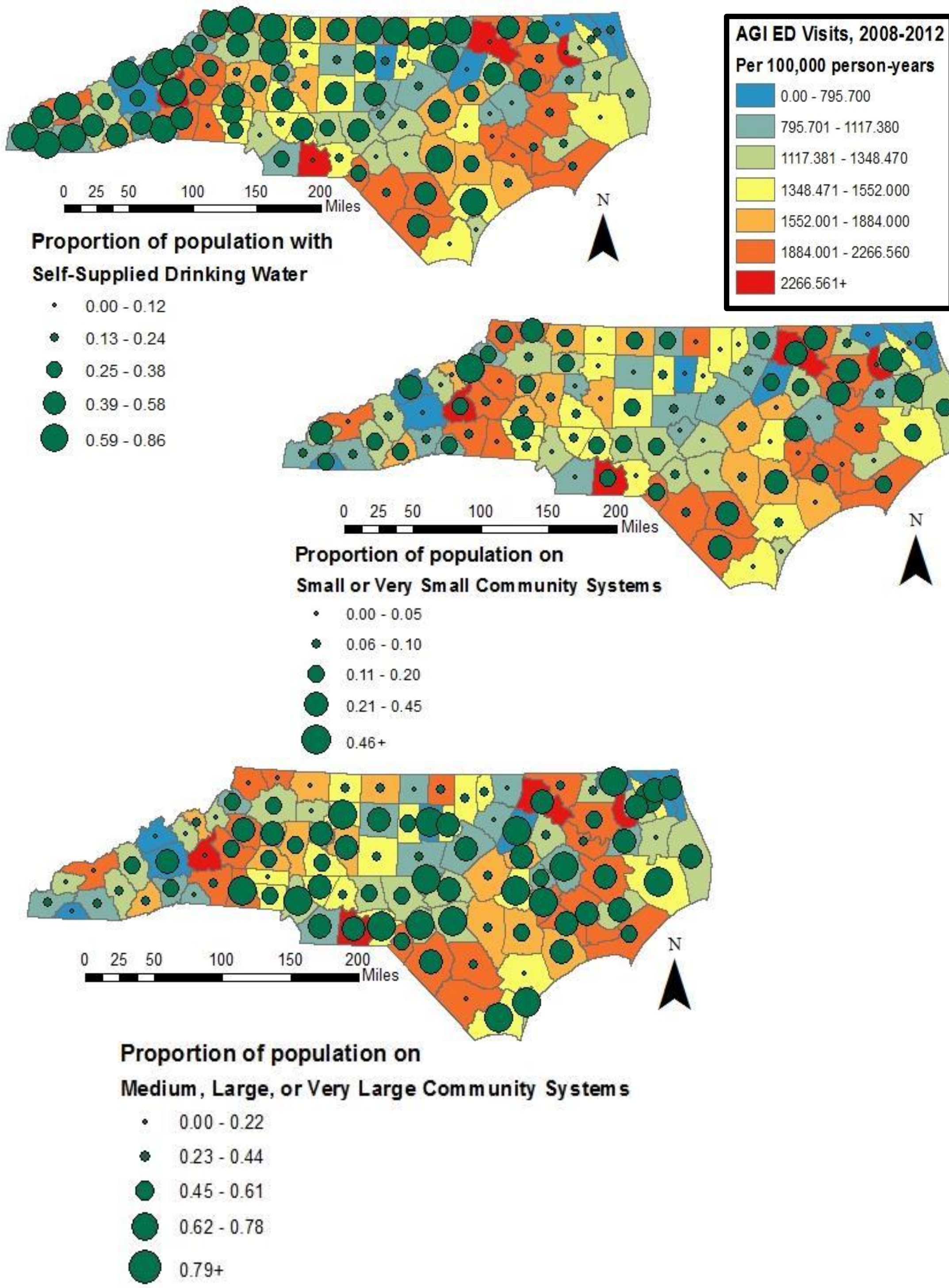


Figure 20. Proportion of the population in each county using self-supplied drinking water (top), on small or very small community water systems (middle) and on medium, large, and very large systems (bottom). Note that while the underlying scale for gastrointestinal illness visits per 100,000 person-years is the same for each map, the proportion values have different scales for each map. Data from Luh et al., 2015.

The last demographic factor that was analyzed for a spatial signal was the patient's health insurance status. Counties were spatially mapped with high percentages of the population without health insurance or that only have public health insurance. The spatial pattern of insurance status seems to closely resemble the spatial pattern for poverty status (e.g. compare Figures 18 and 21).

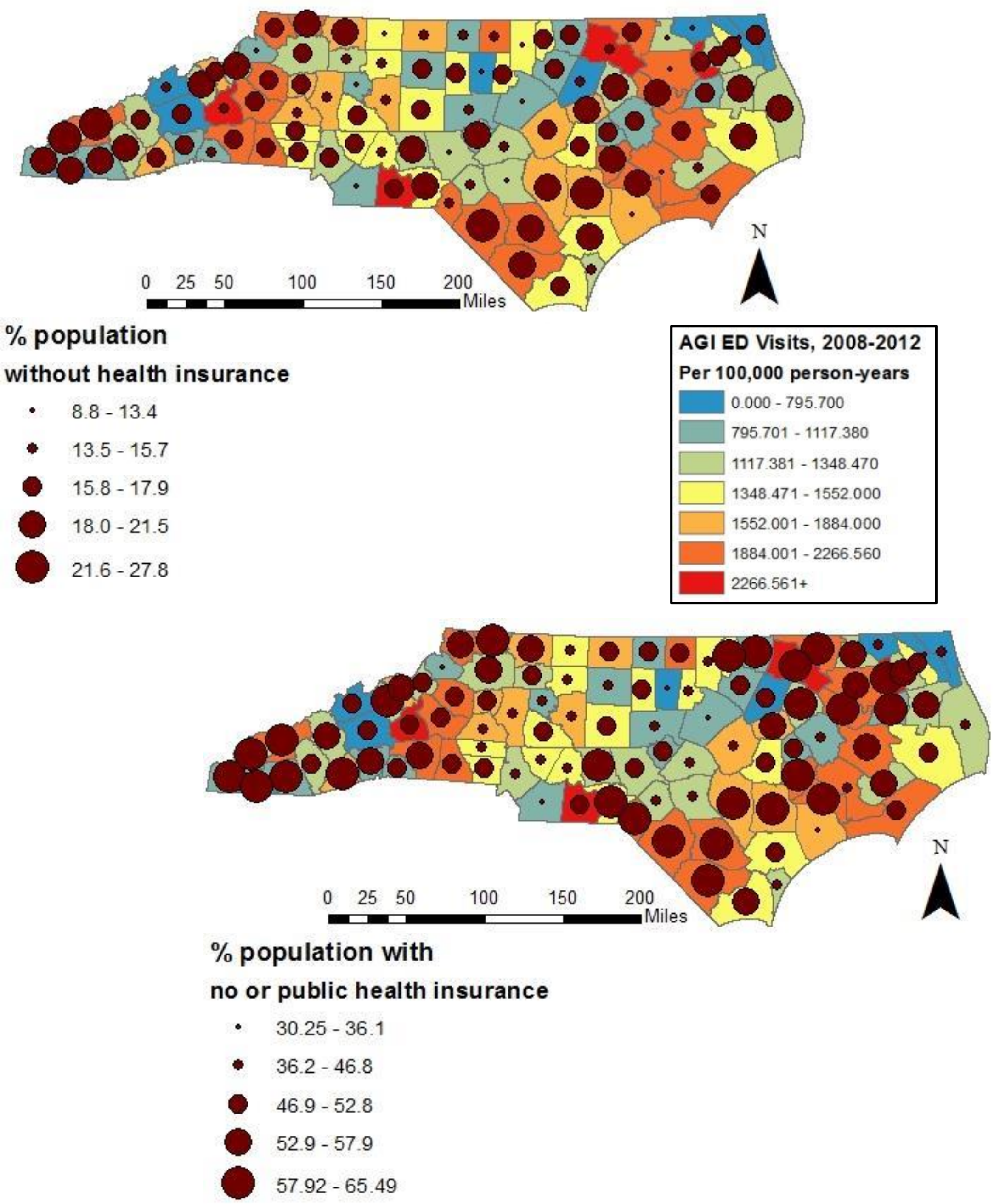


Figure 21. Percentage of the population in each county without health insurance (top), and without or only with public health insurance (bottom). Note that while the underlying scale for gastrointestinal illness ED visits per 100,000 person-years is the same for each map, the % population values are different scales for each map. Data from US Census American Community Survey, 2008-2012.

A correlation matrix supports the spatial results for demographic variables (Table 4). The only strong association with rates of gastrointestinal illness ED visits and a demographic variable is with the cluster of variables that relate to poverty, which includes percent of the population without health insurance or with only public health insurance (Table 4). The highest association (.40) within this poverty cluster is for the percent of the population under the age of 18 living in poverty (Table 4). The association for percent of the population aged 18-64 living in poverty is slightly lower, with a correlation rate of .24 (Table 4). The second-highest association (.35) is with the percent of the population that either has no health insurance or only public health insurance (Table 4). Surprisingly, there is a negative correlation (-0.06) between rates and the proportion of the population on self-supplied drinking water. Also surprisingly, there are identical correlation rates for rates in the high-viral and low-viral seasons (Table 4).

Table 4. Correlation Matrix for Rates of gastrointestinal illness per 100,000 person-years and demographic variables. A * represents statistical significance.

Key for abbreviations in Correlation Matrix:

Rates: Gastrointestinal illness ED visits per 100,000 person-years

Pov.=Poverty

DW: Source of Drinking Water, value is proportion of population of county

Self: proportion of population of county that is on self-supplied drinking water

S, VS: proportion of population of county that is on small or very small community drinking water systems

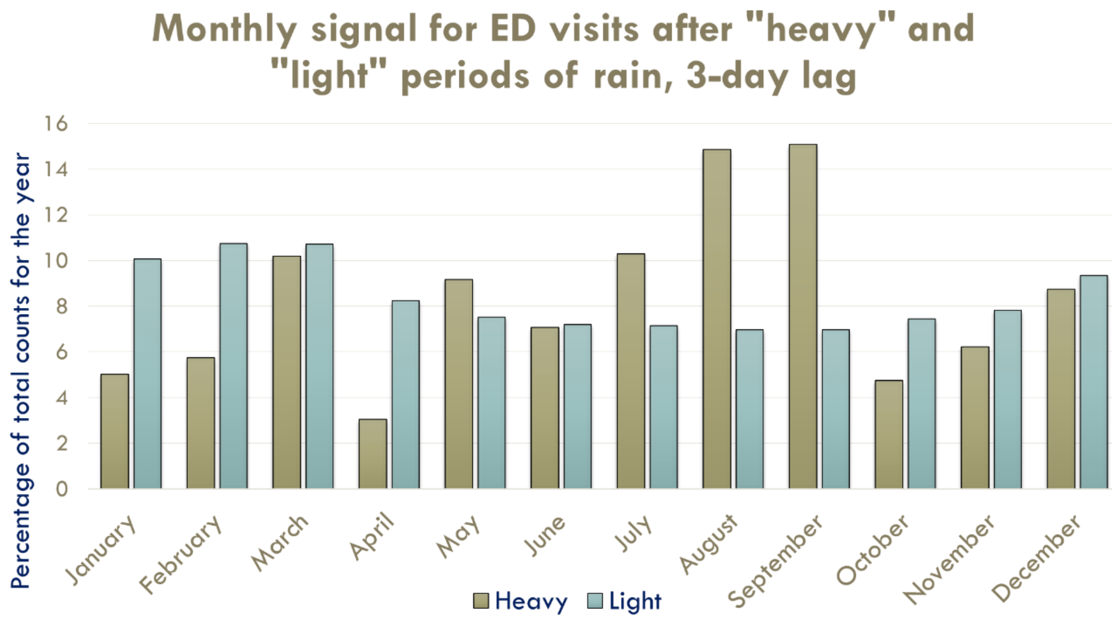
M, L, VL: proportion of population of county that is on medium, large, or very large community drinking water systems

	Rates	Avg. Hshold. Size	% Pov: Under 18	% Pov: 18-64	High-Viral Season	Low-Viral Season	DW: Self	DW: S, VS	DW: M, L, VL	% No Health Ins.	% No or Public Health Ins.
Rates	1.00										
Avg. Hs. Size	0.02	1.00									
% Pov.: Under 18	*0.40	0.06	1.00								
% Pov.: 18-64	*0.24	-0.11	*0.71	1.00							
High-Viral	*0.96	0.00	*0.42	*0.26	1.00						
Low-Viral	*0.96	0.00	*0.36	*0.23	*0.97	1.00					
DW: Self	-0.06	-0.17	0.01	0.02	-0.09	-0.07	1.00				
DW: S,VS	0.04	-0.24	*0.25	*0.22	0.07	0.01	0.10	1.00			
DW: M, L, VL	0.03	*0.25	-0.12	-0.11	0.05	0.06	-0.89	-0.54	1.00		
% No HealthIns	*0.23	-0.16	*0.40	*0.38	*0.27	*0.24	*0.21	*0.30	-0.31	1.00	
% No or Public HealthIns	*0.35	-0.18	*0.73	*0.53	*0.38	*0.35	*0.29	*0.30	-0.38	*0.63	1.00

Precipitation patterns

Monthly patterns of ED visits following light vs. heavy rain events display distinct patterns (Figure 22). The monthly pattern for all cases, regardless of precipitation totals, shows a winter peak for cases of gastrointestinal illness (Figure 6). Similarly, the monthly distribution of cases after light rainfall closely follows the overall pattern for all cases (Figure 6, 22), which is due to the fact that the light cases represent the vast majority of overall cases during the study period. The monthly pattern for heavy rainfall, however, shows peak admissions rates in the months of July, August, and September for both lag periods, with a spike in November for the 10-day lag period (Figure 22).

The foundation of this summer spike in visits after heavy rainfall events could be multi-faceted. For starters, it could be attributed to the meteorological trend of higher overall rainfall in North Carolina during those months, or it could be attributed to an increase in bacterial and protozoan pathogens in the water during these times. Furthermore, recreational bathing and swimming also increases during the summer months, and as such, swimmers and bathers could be increasingly exposed to disease-causing pathogens, many of which are naturally occurring (Fewtrell & Kay, 2015). In addition to these potential factors, pathogens present in surface waters that end up in ocean waters or surface waters following heavy precipitation events could contribute to the increase in visits during the summer months. Although more statistical analysis and further research is necessary to accurately investigate the cause behind this summer season spike following heavy rain events, it is clear that higher proportions of visits after heavy rainfall exist for the state of North Carolina during the summer is months (Figure 22).



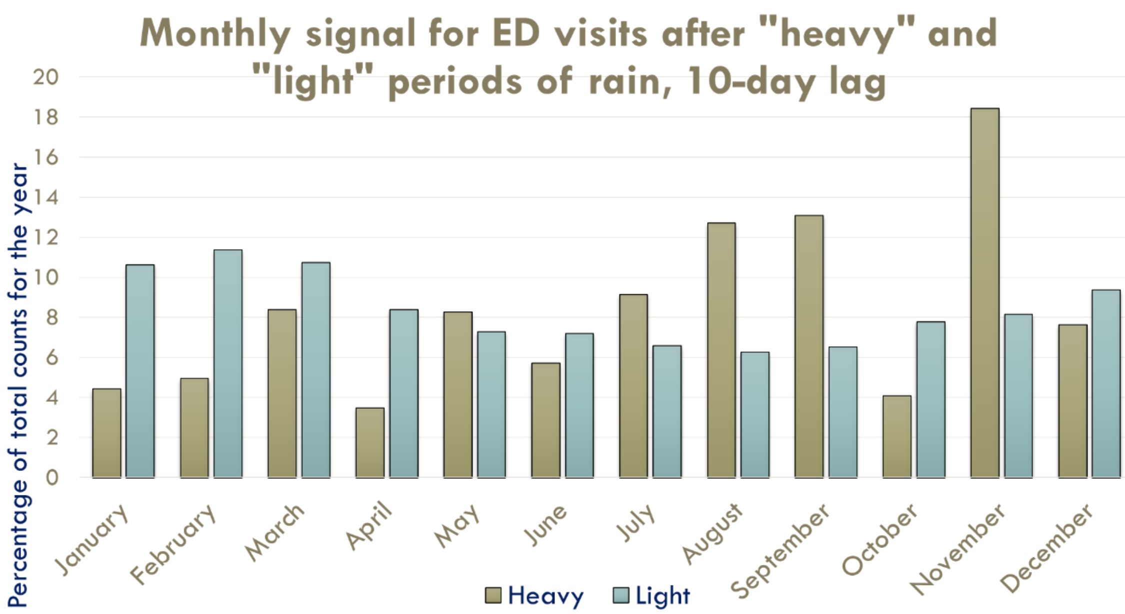


Figure 22. Monthly distributions of ED visits for gastrointestinal illness after periods of heavy and light rain as a proportion of total visits for the year. Charts shown for 3-day lag (top) and 10-day lag (bottom).

Across the entire state, the average number of admissions per day is significantly higher after periods of heavy rainfall ($p<.01$) and this is especially the case for the 3-day lag period. These results support our hypothesis that heavy precipitation amounts can contribute to an increase in Emergency

Department visits for gastrointestinal illness. The spatial patterns in disease rates for both lag periods are nearly identical, but there is much county-to-county variability in the rates. Only slightly more than half (52%) of the counties show increased rate of gastrointestinal admission rates. This suggests that the influence of heavy precipitation is confined to particular regions of the state. Interestingly, there are counties that show higher admission rates after heavy precipitation that do not have demographic factors that are associated with high rates gastrointestinal disease overall (e.g. Swain, Lee, and Johnston Counties) (Figures 23, 24). It should be noted that although the light maps for both the 3-day and the 10-day lag periods (Figures 23, 24) appear different from the overall map showing incidence of disease (Figure 8), the light maps are still a representation of disease events as a whole. Although there is less gradation in the light maps than the overall disease incidence map (Figure 8), the light maps still capture the majority of disease occurrence since the light values include all of the cumulative totals of zero precipitation, and therefore a large number of the overall cases throughout the study period.

The maps of the proportional rates for both lag periods suggest a clustering pattern (Figures 23, 24), and indeed *Moran's I* spatial autocorrelation examinations indicate spatial clustering that has less than a 1% likelihood to be the result of random chance. The cluster in the east central portion of the state is especially noteworthy. Lee County, for example, has the highest increase in the 10-day lag with a proportional difference of 6.91 (or a 591% increase). In the 3-day lag period window, there are four counties that show proportional differences with increases over 500%: Johnston (6.19, or 519%), Lee (6.21, or 521%), Chatham (6.71, or 571%), and Harnett (6.71, or 571%) counties, suggesting increased vulnerabilities in these counties after heavy rainfall. Although these county-level proportional difference maps could certainly be valuable to county leaders and members, we believe that ZIP code level analyses for proportional differences between heavy and light rainfall events might more clearly elucidate the pattern of local to regional scale vulnerability in these counties.

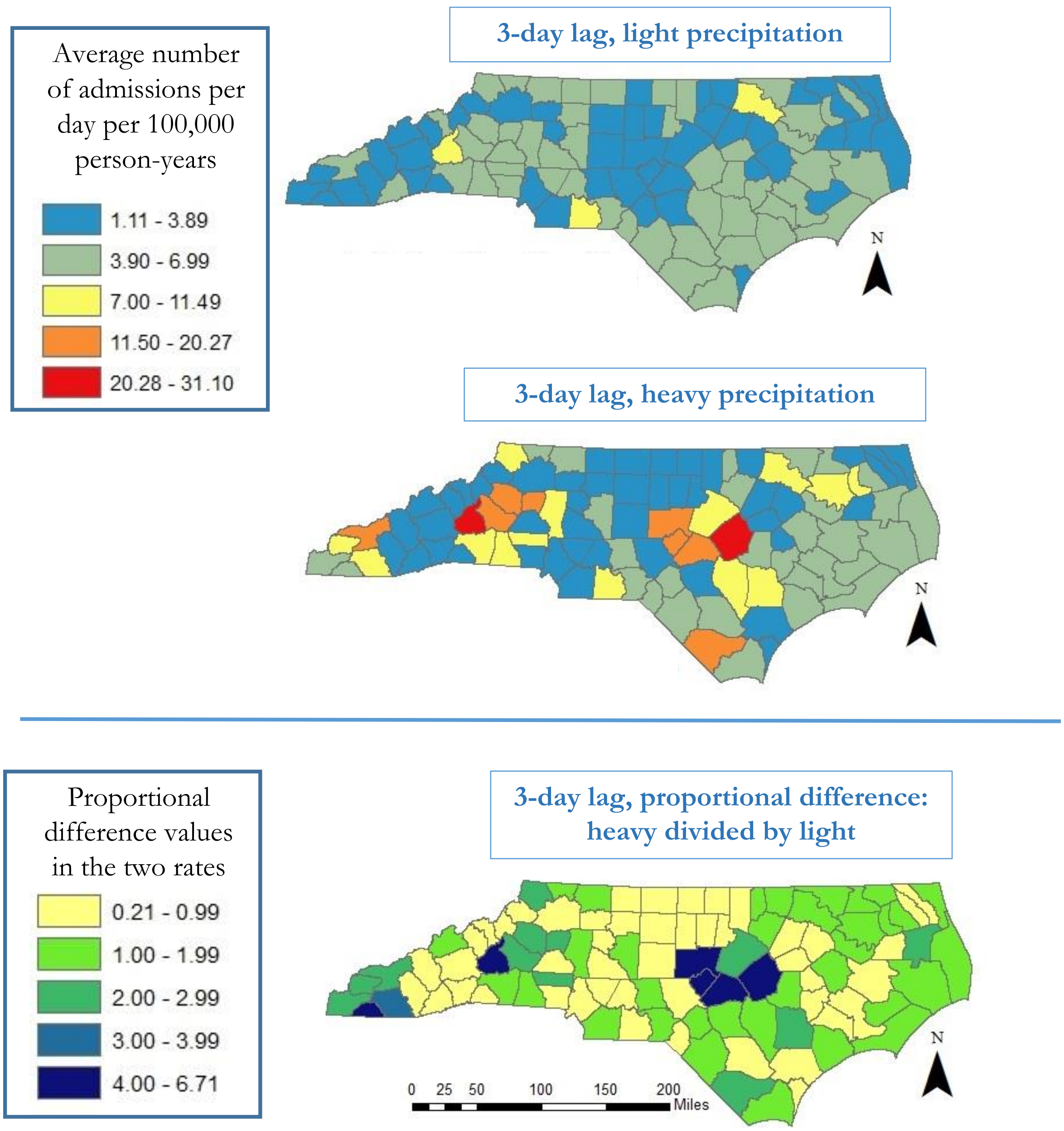


Figure 23. The rate of admissions per day per county for light and heavy precipitation over a 3-day lag period (top) and the proportional difference values in the two rates (bottom).

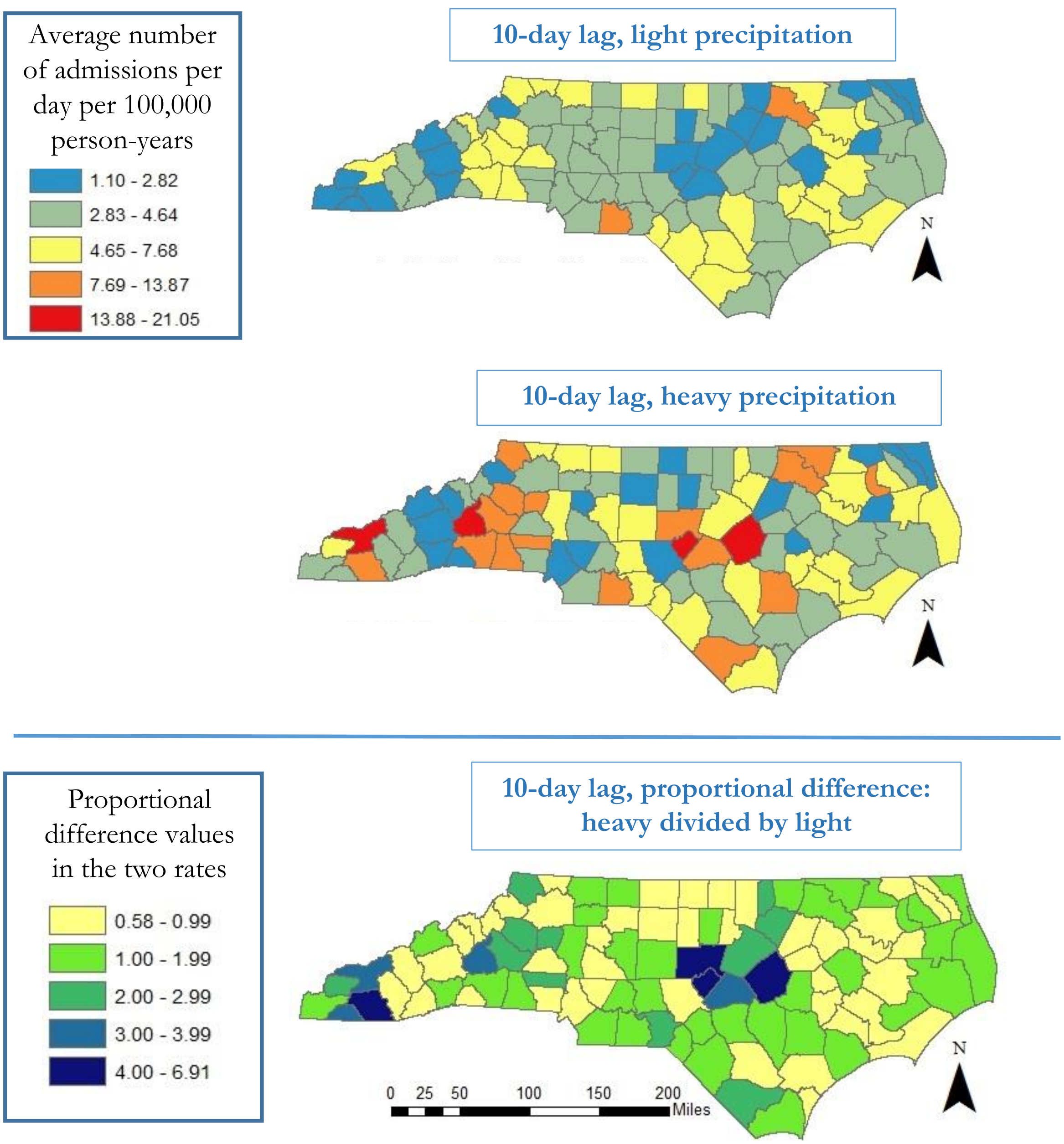


Figure 24. The rate of admissions per day per county for light and heavy precipitation over a 10-day lag period (top) and the proportional difference values in the two rates (bottom).

The highest-bracket counties show several commonalities (Table 5). Five out of seven of these counties are rural with a high proportion of the population that has self-supplied drinking water. Moreover, only 2 out of 7 of these counties are in the top two brackets in regards to poverty status.

Table 5. Comparisons of high-bracket counties for proportional differences in heavy vs. light precipitation and other demographic factors.

Demographic Factor	Number of counties, percentage of counties
Considered "non-metropolitan" or "rural" (Fig. 19)	5/7, 71%
In the top-two brackets for poverty status, any age group (Fig. 18)	2/7, 29%
In the top-two brackets for largest average household size (Fig. 17)	3/7, 43%
With a 39% or greater proportion of the population on self-supplied drinking water (Figure 20)	5/7, 71%

The areas with the greatest proportional differences in admissions after heavy vs. light rain loosely match North Carolina watershed and river drainage basins (Figure 25). For example, while counties within the French Broad River Basin and the Roanoke River Basin show decreases in average admissions per day per county after heavy rainfall events, other counties show increases in admissions after heavy rainfall events, such as the counties in the Catawba, Lumber, and Cape Fear River Basins (Figure 25). As a result of this geographical connection, the unique factors to each specific watershed and the methods of watershed management could be investigated in more detail to extrapolate differences in some of these geographic pockets. The geographic pocket that occupies the Cape Fear River Basin with 300% increases in average admissions rates per day in some of the counties, for example, lies south of one of the most rapidly-urbanizing areas of the United States within Wake County (Figure 25). Perhaps new hypotheses could be developed in response to these connections with land cover, watershed management, and urbanization, especially for the Cape

Fear River Basin county-cluster which has a cluster of some of the highest increases in rates across the entire state, in order to investigate more localized signals of admissions rates after heavy rainfall.

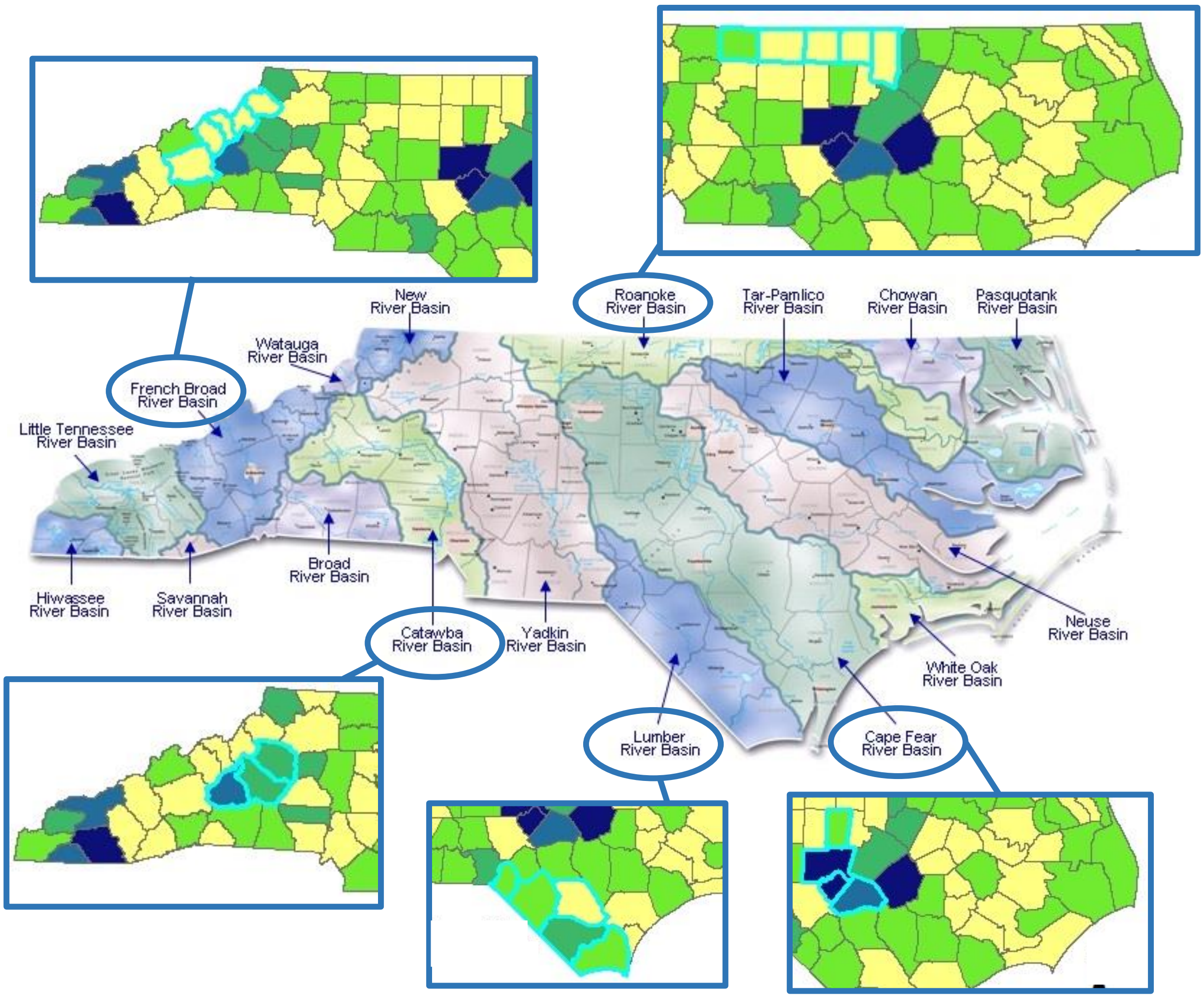


Figure 25. Map of North Carolina river drainage basins (from www.learnnc.org) that align with highlighted portions of the state from the 10-day lag proportion map (from Figure 24).

CHAPTER 4: DISCUSSION AND CONCLUSIONS

This study investigated the association between heavy rainfall, defined as rainfall totals over 2 inches within either a 3-day or a 10-day lag period, and incidence of gastrointestinal illness in North Carolina from 2008-2012. The effects of heavy rainfall on human health have been studied extensively; however, the majority of these studies are confined to a locale (e.g. cities or metropolitan areas). To our knowledge, no study of gastrointestinal disease has yet been conducted statewide across North Carolina. Unlike previous studies, this study examined the gastrointestinal illness burden for the state of North Carolina, the role of certain demographic factors in disease burden, and whether or not rainfall totals greater than 2" had an impact on that disease burden. In addition, this study investigated the spatial patterns of gastrointestinal illness across the entire state of North Carolina, allowing for investigation into the relationships with various demographic variables.

Results did show statistically significant correlations with a few of those demographic variables. Poverty and a lack of health insurance had the strongest relationships with disease rates across the State, with the highest correlation value existing between children under 18% living in poverty and disease rates of gastrointestinal illness (0.40).

Across the entire state, the average number of gastrointestinal disease admissions per day was found to be significantly higher after periods of heavy rainfall. This relationship was identified for both lag periods in the study but was especially the case for the 3-day lag period. A significant geographic clustering was revealed in the spatial patterns with several clusters of counties displaying exceptionally high proportional differences between heavy and light precipitation. These counties included Clay, Macon, and McDowell counties in the West and Chatham, Lee, Johnston, and Harnett in the Piedmont. Furthermore, maps of proportional differences in average ED visits per day per county per 100,000 person-years show that 52% of North Carolina counties experienced an increase in ED visits for gastrointestinal illness following heavy rainfall. Some of those counties even experienced increases greater than 200% and up to 591%. Such information could guide public health employees and officials in those counties to examine and investigate potential causes for the increase in gastrointestinal illness following heavy rainfall in their counties.

Like other studies before it, this study supports the suggestion that there is potentially a waterborne component of disease transmission in the population (Drayna et al., 2010). As was said by K.F. Cann and echoed by many other scientists (Drayna et al., 2010; Patz et al., 2008), "it is important to establish the current impact of such events on public health and to allow future predictions, aid policy formulation, and improve adaptive capacity," (Cann et al., 2013). Finally, as global climate change is predicted to lead to an increase in extreme weather-related and precipitation events, it becomes increasingly imperative to determine the role of weather in the incidence of waterborne disease (Patz et al., 2000). A better understanding of the impact that heavy rainfall events and water-related events have on disease incidence is a public health priority and an important public health step towards finding ways to prevent and mitigate the risk of disease (Drayna et al., 2010).

Study Limitations

First of all, and perhaps most importantly, there are understood limitations associated with using ED visit data for these types of studies. Multiple scientists have suggested that ED data show an underrepresentation of the true burden of gastrointestinal disease (Drayna et al., 2010; Tinker et al., 2010) for multiple reasons, including any of the following alone or in combination: (1) ED physicians may fail to properly document and diagnose the symptoms of gastrointestinal illness, , (2) there are some health care providers and Emergency Departments that are not within the NC DETECT network and therefore those cases are non-reported to this study (e.g. the two federal military hospitals in Cumberland and Onslow County or urgent care providers) (3) it has been suggested that the nature of gastrointestinal illness is such that people might not seek medical care, therefore those that did not seek care were not captured within this study, (4) only cases that are severe enough to require a trip to the emergency department are captured in this study, and it has been shown that the population that chooses to attend the emergency department may be of lower socioeconomic status than the general population (Tinker et al., 2010; Walls, Rhodes, & Kennedy, 2002), and lastly, (5) the intentional exclusion of certain ICD-9-CM codes, such as the codes for abdominal pain (789.0) and nausea with vomiting (787.01) makes it impossible to capture patients with gastrointestinal illness that show these symptoms but not the other symptoms captured within the codes of our study.

Secondly, we chose to analyze two lag periods after rainfall, a 3-day lag period as well as a 10-day lag period. Previous literature proposes that a 6 to 9-day lag window is ideal to capture the majority of waterborne pathogens when the travel time of water in the distribution system is accounted for (Chin, 2000; Tinker et al., 2010). On the shorter end of the lag spectrum, literature suggests that a 24-48 hour lag window is appropriate to capture the short incubation periods of enteric viruses (Chin, 2000; Tinker et al., 2010). Although our 3-day lag and our 10-day lag likely captured much of the same information that would have been captured by a 2-day lag or a 9-day lag, we cannot be certain that such is the case.

Thirdly, weather stations and therefore the associated precipitation data were located based on the ZIP code of each patient. In an unknown number of cases, the patient may or may not work or spend the majority of their day within the same ZIP code as their residence. Therefore, exposure to something outside of their ZIP code of residence could alter the results of this study. Furthermore, due to the existence of microclimates and the variability of precipitation, the possibility does exist that the precipitation patterns in the county where the patient spends the majority of their day could vary from the precipitation patterns in their ZIP code of residence.

Future Research

There is much work that can be done in continuation of this study. In investigating the basics of gastrointestinal illness in North Carolina and precipitation patterns, it quickly became clear that this topic is highly complex, which is part of what makes it so fascinating. There are demographic, geographic, meteorological, and other variables that can be investigated in much more depth than were completed in this preliminary study. We propose that future work in continuation of this study examine multiple elements:

1) The role of runoff from agriculture, with a focus on the nature of this agriculture (e.g. livestock versus plants) and the diversity of agriculture across the state of North Carolina.

2) Analyses of water quality in the regions identified to have higher rates after heavy precipitation, especially before and after periods of heavy rainfall in some of the counties that show highest increases in proportional rates (e.g. the "pocket" within the Cape Fear River Basin).

3) Analyses at the ZIP code as opposed to the county level, as significant clustering in the disease rates was found at the ZIP code level.

4) Detailed examination of areas of high gastrointestinal illness after heavy rain and their relationship with: a) management activities in the watershed and b) soil or geologic differences that impact runoff and/or infiltration rates.

5) Broader exploration of relationships between precipitation and disease rates using other lag periods and threshold definitions for heavy rainfall.

6) Identification of spatial and temporal clusters of disease occurrence (i.e. outbreaks) within the study period (e.g. norovirus, perhaps from the CalciNet outbreak surveillance network). Single outbreaks could be responsible for the majority of cases and may not be limited to our heavy rainfall threshold; therefore, better identification of such outbreaks could reveal different patterns in disease occurrence.

7) More rigorous statistical analyses of differences, such as risk differences.

8) Increased investigation of antecedent weather parameters, such as antecedent drought or dryness followed by heavy rains.

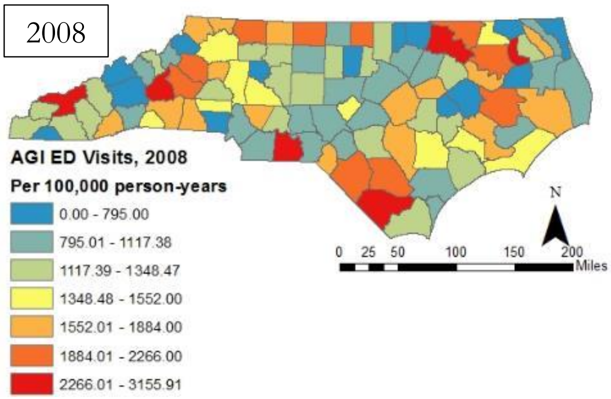
9) Use of other sources of data and new technologies, such as localized Google-search analytics and/or records of sales of diarrhea-related medicines at pharmacies and grocery stores, in order to supplement the ED visit data with additional data that can also track illness in a geographic way.

In summary, there is much future work that can continue to be done for a study of this nature in North Carolina, and we have great hopes that this study has merely laid the groundwork for further public health work to be built upon in the future.

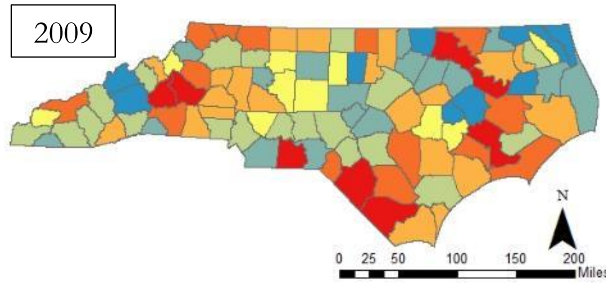
APPENDIX 3.1: ANNUAL VARIATION MAPS, NATURAL BREAKS

Appendix 3.1. Annual variation across North Carolina State, separated by Natural Breaks (Jenks). The scale for all five years is the same standard scale, shown left. The standard scale is the average for the entire 5-year study period (2008-2012).

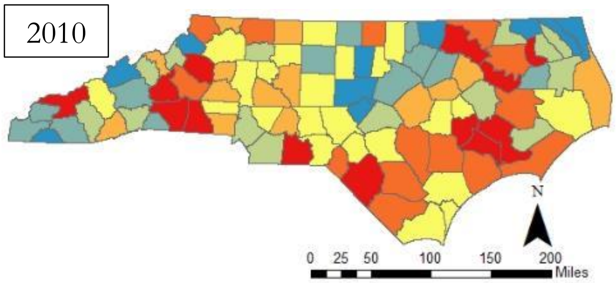
2008



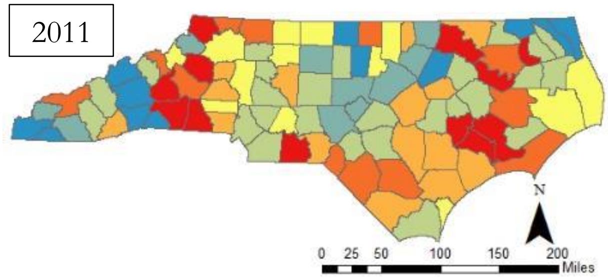
2009



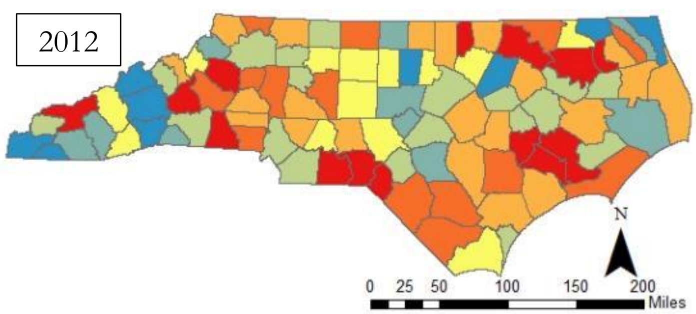
2010



2011

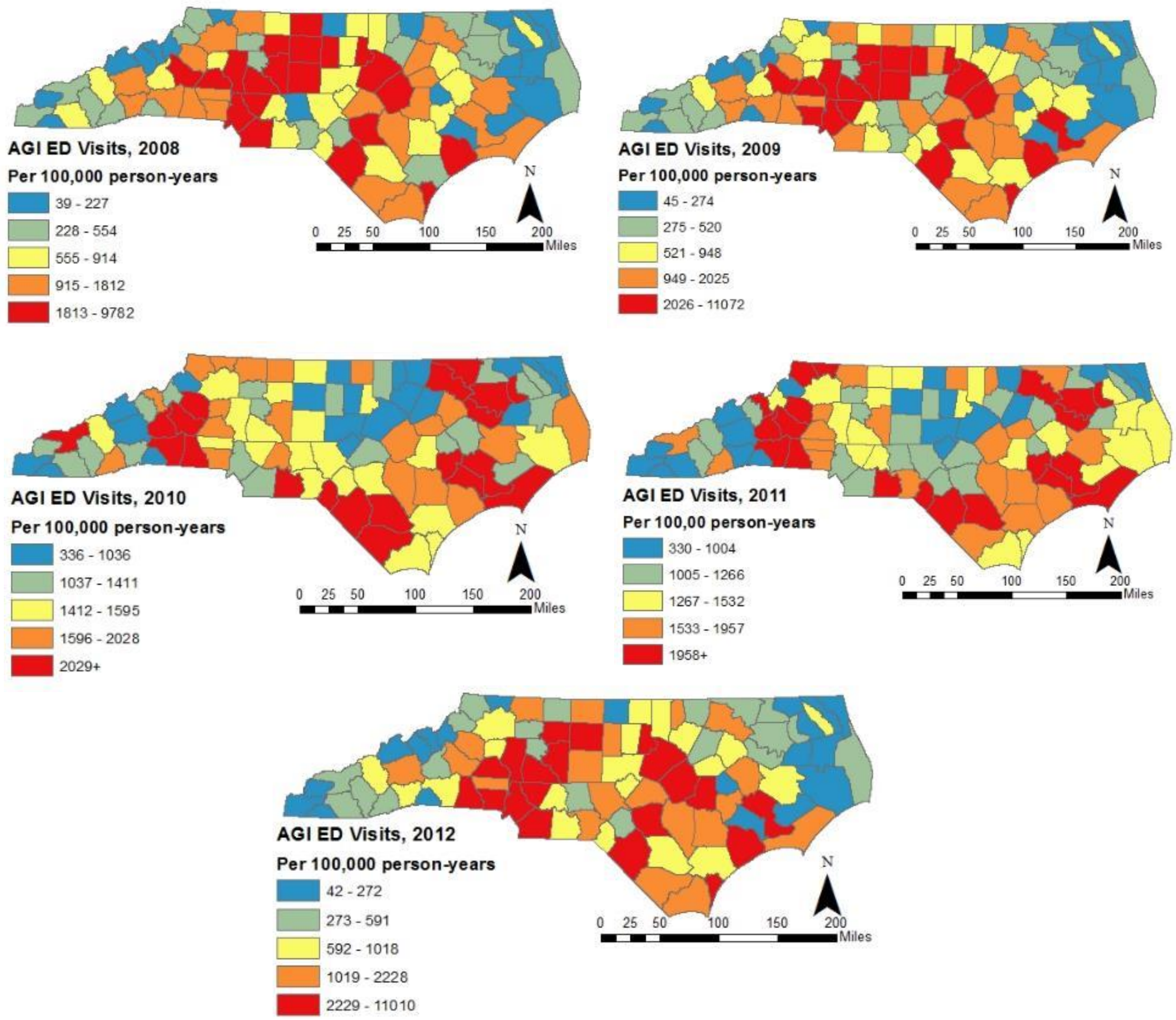


2012



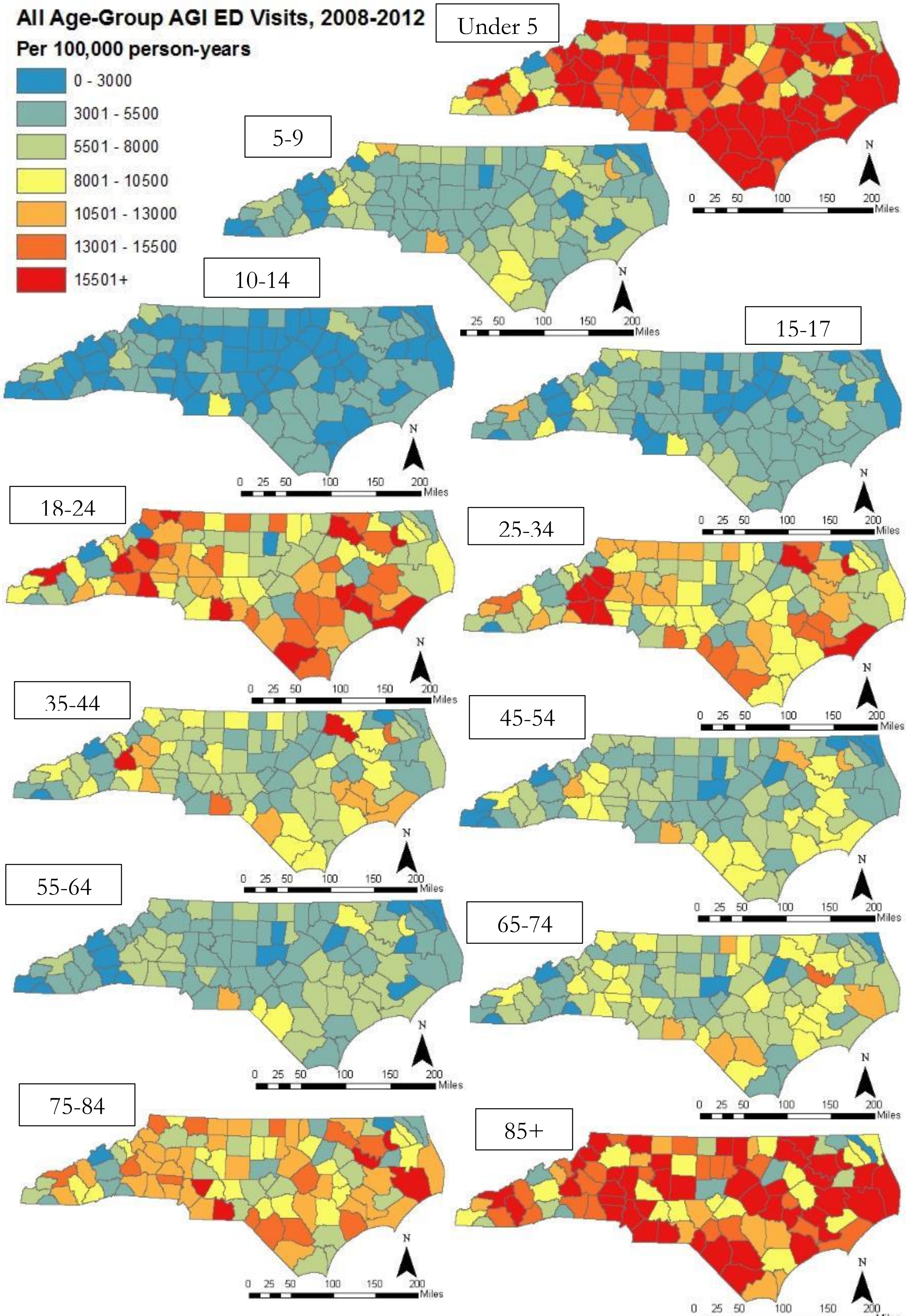
APPENDIX 3.2: ANNUAL VARIATION MAPS, SPLIT BY QUANTILES

Appendix 3.2. Annual variation across North Carolina State, separated by quantiles (20 out of North Carolina's 100 counties per category). Separate quantile scales can be seen accompanying each annual map.



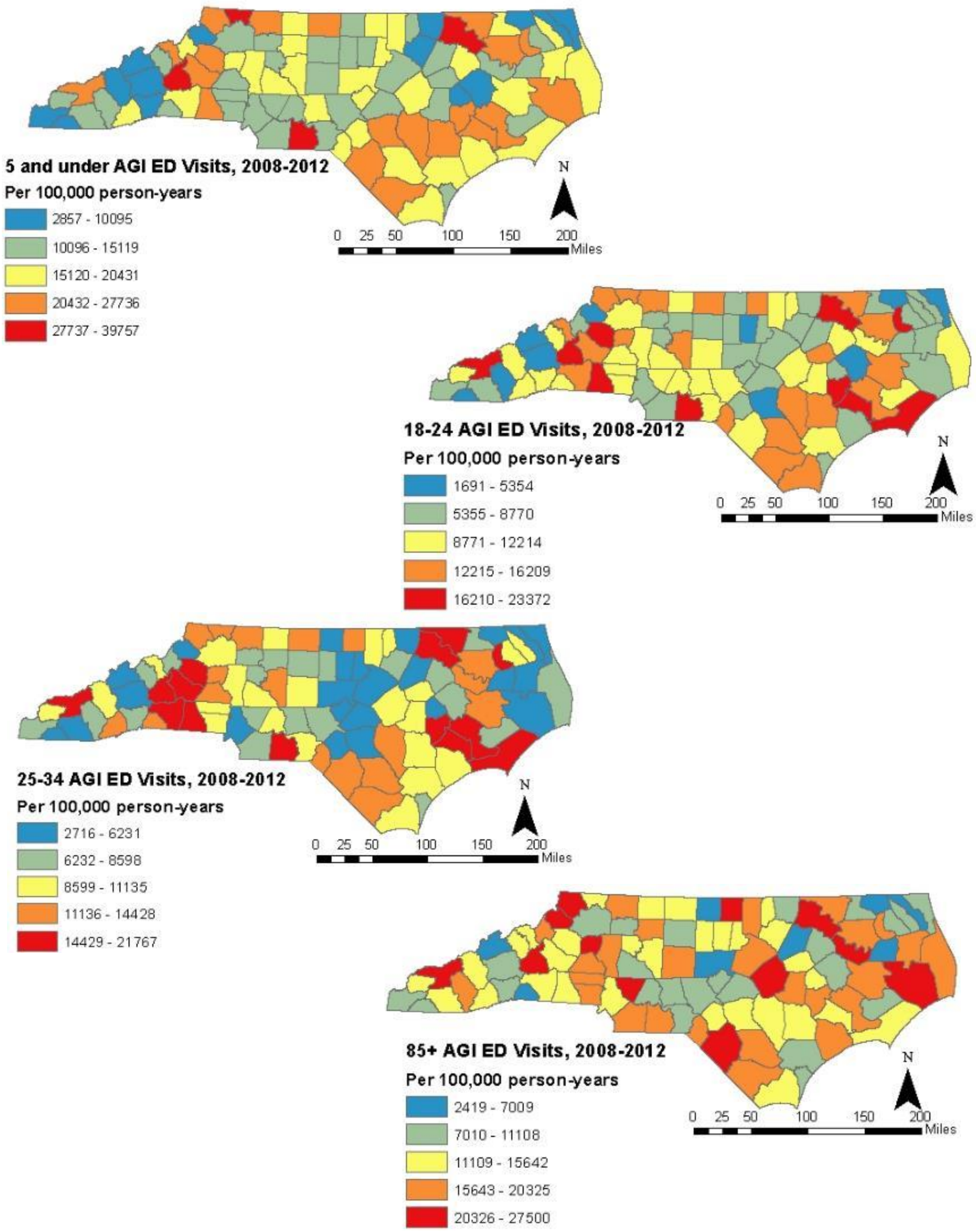
APPENDIX 3.3: AGE-GROUP MAPS OF ALL AGE GROUPS, SPLIT BY STANDARDIZED SCALE (SEE NEXT PAGE)

Appendix 3.3. Age-group maps for incidence of diarrheal disease, 2008-2012.



APPENDIX 3.4: AGE-GROUP MAPS OF SPECIFIC AGE GROUPS, EACH SPLIT BY NATURAL BREAKS (JENKS)

Appendix 3.4. Age-group variation for selected age groups with high incidence rates of gastrointestinal illness across North Carolina State, separated by natural breaks. Separate scales can be seen accompanying each age-group map.



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