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SOIL ARSENIC AND LEAD CONCENTRATIONS AND PRETERM BIRTH: INVESTIGATING RACIAL DISPARITIES, SOURCES, NEIGHBORHOOD EFFECTS, AND SPATIAL PATTERNS

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DEDICATION

To my son, Cole…you are one of the main reason I decided to pursue my PhD, and my primary source of motivation during the entire process. Ray Bradbury wrote in the unfortunately titled novel *Something Wicked This Way Comes*, “She’s immortal. She has a son.” My immortality comes not only from being your mother, but also from the research that I have done because of you. Thank you, Boo Bear.

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ABSTRACT

Preterm birth, generally defined as birth at <37 weeks of gestation, is an important public health issue that has multiple risk factors related to characteristics of both the mother and her environment. The purpose of this dissertation was to examine potential sources of spatially interpolated (kriged) environmental concentrations of arsenic (As) and lead (Pb) in residential soils and preterm birth in a Medicaid population of mothers giving birth in South Carolina (SC) from 1996-2001. The first objective was to investigate if a racial disparity existed for estimated soil As and Pb concentrations, after adjusting for proximal and distal sources of these metals (including distance and direction to industrial facilities) in a subset of SC Medicaid mothers living in areas of SC where soil samples were collected and analyzed for these metals. The second objective was to test the hypothesis that estimated soil As and Pb concentrations were associated with increased odds of early (<34 weeks) and late (34-36 weeks) preterm births in the same subset of SC Medicaid mothers, after adjusting for individual and neighborhood level risk factors, and examine if measure of neighborhood deprivation and racial residential segregation modified these associations. The third objective was to examine if early and all preterm births, aggregated at the county level, varied spatially and/or temporally in SC for all Medicaid mothers giving birth from 1996-2001 in Bayesian models.

For the first objective, black mothers had significantly higher estimated As and Pb soil concentrations than white mothers in the study population (adjusted betas were 0.12 and 0.22 for As and Pb, respectively; all $p<0.006$), and proximal sources of metals (e.g.,

percent of Census block group are covered by roads) were more strongly associated with estimated soil As and Pb concentrations than composite As and Pb releases from industrial facilities categorized by distance from and direction to Census block groups in which maternal residences were located.

For the second objective, estimated soil concentration of neither As nor Pb were associated with increased odds of early or late preterm birth after adjusting for maternal and neighborhood level risk factors. Only individual level covariates were associated with these birth outcomes, and associations were stronger for early as compared to late preterm births. Neighborhood deprivation and racial residential segregation were not associated with either early or late preterm birth in adjusted models, nor did they modify the main associations of interest.

Results from the final objective showed that Bayesian models including spatial and temporal parameters had a better fit, for both early and all preterm births, than those only containing temporal parameters, in the aggregate spatial-temporal analysis at the county level for all SC Medicaid mothers. Some counties in SC had significant risk of early and all preterm births over multiple years, and aggregate county measures of maternal demographics and conditions during pregnancy were associated with increased risk of early and all preterm births by both county and year.

These findings indicate the importance of proximal, historic metal sources to current residential soil concentrations, as well as the racial disparity in soil As and Pb concentrations in the studied locations of SC. They also show that accounting for the distance and direction to industrial facilities releasing these metals does not impact the racial disparity, or estimated residential soil As and Pb concentrations. In addition, odds

of early and late preterm births were not associated with estimated residential soil As and Pb concentrations, and only maternal risk factors were significantly associated with these outcomes in the study population. Finally, taking into account the spatial relationship between counties in SC improved risk estimates of early and all preterm births at the county level for Medicaid mothers in SC. These finding have implications in the areas of environmental justice, environmental contaminant risk assessment, environmental epidemiology, maternal and child health epidemiology, and spatial epidemiology.

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CHAPTER 1

INTRODUCTION

Statement of Problem

Preterm birth, defined as birth at <37 weeks of gestation, is a significant public health problem in the United States (US), with a reported 2010 prevalence of 12% (MOD, 2013). For that same year, the prevalence of preterm birth in South Carolina (SC) was 14.2% (MOD, 2013). Early preterm birth (<34 weeks of gestation) accounted for 3.5% and 4.5% of births in the US and SC, respectively, in 2010 (MOD, 2013). Risk factors for preterm birth are numerous, and can be grouped into three general categories. Maternal factors can include age, race/ethnicity, SES, and amount of stress, as well as smoking, alcohol use, and drug use during pregnancy (Chen et al., 2011; Chien et al., 2011; Clausson et al., 1998; Di Renzo et al., 2011; Erickson et al., 2001; Meis et al., 1998; Menon et al., 2011; Misra et al., 2010; Ofori et al., 2008; Savitz and Murnane, 2010; Sparks, 2009; Zeitlin et al., 2001). This category can also include medical conditions of both the mother and fetus. Neighborhood factors relate to where the mother lives, and can include neighborhood measures of SES, racial residential segregation, crime, socioeconomic status (SES) and, neighborhood deprivation (Bell et al., 2006; Mason et al., 2009; Messer et al., 2006a, 2006b; O’Campo et al., 2008). Environmental factors are associated with characteristics of both the mother and where she lives, and includes the presence of contaminants in soils or water (Miranda et al., 2009; Myers et al., 2010; Pathak et al., 2010; Torres-Sanchez et al., 1999), and in air pollution (Miranda et al., 2009; Malmqvist et al., 2011); these environmental factors pose a potential exposure risk to mothers, and contaminants with a long residence time in the environment are of special concern. Preterm birth can be an indicator of numerous future negative health outcomes throughout the life course (Kajantie et al., 2010; Keijzer-Veen et al., 2010; Norman, 2010; Skilton et al., 2011), with neurological disorders most common (Denouden et al., 1990; Fawke, 2007; Geldof et al., 2012; Jungmann, 2006; Wood et al., 2005). Given these, decreasing the prevalence of preterm birth is one of the main maternal, infant, and child health objectives for Healthy People 2020 (US DHHS, 2013).

Numerous studies have identified racial disparities in preterm birth, particularly between non-Hispanic white and non-Hispanic black (further referred to as white and black) mothers (Kramer et al., 2010b; Kramer and Hogue, 2009; Landrine and Corral, 2009; Menon et al., 2011; Paul et al., 2008; Schempf et al., 2011). This disparity persists even after controlling for well-known risk factors for preterm birth, including SES, maternal infection during pregnancy, and previous preterm birth. In SC alone, the 2010 prevalence of preterm birth for black mothers was 19%, almost 1.5 times the prevalence for white mothers (12%; MOD, 2013). The racial disparity is even more pronounced for early preterm birth, with prevalence of 2.6% for white mothers and of 5.3% for black mothers in SC in 2010 (MOD, 2013). Racial disparities have also been observed for neighborhood measures (Do, 2009; Farmer and Ferraro, 2005) and for environmental concentrations of both arsenic (As) and lead (Pb; Aelion et al., 2012, 2013; Gee and Payne-Sturges, 2004; Hicken et al., 2011). Unfortunately, most studies cannot fully explain (through adjustment of additional measures/variables) the observed racial disparity for preterm birth, and for exposure to metals in the environment, like As and Pb.

When examining racial disparities in preterm birth, as well as exposures to As and Pb in soils, both individual level and neighborhood level risk factors should be considered, as individual risk factors alone do not fully explain racial disparities. Therefore, it makes sense to utilize methodological techniques that can correctly assess risk factors at multiple levels. Hierarchical linear modeling (HLM), has been employed extensively with respect to birth outcomes (Auger et al., 2009; Bell et al., 2006; Culhane et al., 2002; Diez Roux and Mair, 2010; Kramer et al., 2010a; Mason et al., 2009; Messer et al., 2010, 2012; Nkansah-Amankra et al., 2010a, 2010b). However, no studies have evaluated associations of both individual and neighborhood characteristics, along with concentrations of metals in soils, and preterm birth outcomes using this technique. Likewise, no studies have investigated racial disparities in the potential for exposure to As and Pb in soils using this methodology.

While HLM can be used to describe disparities in terms of place, as this method accounts for individuals living in the same “neighborhood”, this type of modeling does not account for spatial relationships among the neighborhoods. Diez-Roux and Mair (2010) suggested that more advanced spatial methods are necessary in neighborhood research. As a result, numerous recent publications (Cech et al., 2007; English et al., 2003; Gray et al., 2011; South et al., 2012; J. Tu et al., 2012; W. Tu et al., 2012; Wu et al., 2004) have examined birth outcomes using spatial methods, though few have investigated preterm birth using spatial models (South et al., 2012).

Literature Review

Preterm birth: a significant public health problem

Preterm birth is an important public health problem in the US for a variety of reasons. First and foremost, preterm birth is associated with a number of health effects that may continue throughout life. In a review of preterm birth-associated morbidity and mortality into adulthood, Saigal and Doyle (2008) noted that while children born at 32-36 weeks of gestation often have better outcomes than those born very preterm (at <32 weeks of gestation), negative neurological and behavioral effects are still extremely common in later preterm birth children. Second, the prevalence of preterm birth in the US far exceeds that of most industrialized nations. The 2010 prevalence rate (per 100 live births) in the US was 12%, while the prevalence rates in Australia, Canada, the United Kingdom, and France were all <8% (MOD Global Action Report, 2013). Third, the medical cost of care for preterm infants in the US far exceeds that of full term infants. Russell et al. (2007), using national hospitalization data from 2001, found that preterm and low birth weight infants, who only accounted for 8% of all infant hospital deliveries, transfers, and readmissions that year were responsible for almost half ($4.8 billion) of all infant hospitalization costs. Average cost per stay was $14,500 more, and average length of stay was 10 days longer for preterm/low birth weight infants as compared to infants with no complications. Given these, preventing preterm birth is extremely important for the health of individuals from infancy through adulthood.

About one third of preterm births are medically indicated; determination is based on the type of complication present, and the risks and benefits to both the mother and infant (ACOG, 2013). The other two-thirds (65-70%) of preterm births are spontaneous and due to premature labor and/or the premature rupture of membranes (PROM; Goldenberg et al., 2008). Additionally, multiple biological pathways can play a role (Romero et al., 2006), and it can be difficult to fully assess all of these pathways. Therefore, it is important to identify risk factors that can be determined before or in early pregnancy in order to prevent spontaneous preterm births.

The bulk of literature on preterm birth risk factors has focused on maternal or host factors. Goldenberg et al. (2008) noted that preterm birth is now considered a multi-mechanistic syndrome that can be linked to a variety of causes. One main cause is the presence of infections, such as bacterial vaginosis or sexually transmitted infections (STI) during pregnancy (Bastek et al., 2011; French et al., 2006; Hitti et al., 2007; Mann et al., 2010; Petit et al., 2012; Randis, 2010). It is thought that these types of infections can trigger immune responses, which can ultimately lead to spontaneous preterm birth. Additionally, genetic susceptibility to preterm birth may occur through infection (Himes and Simhan, 2008), which may also corroborate the increased risk for preterm birth if a mother previously gave birth to a preterm infant, or if she was born preterm herself (Hsieh et al., 2005; Varner and Esplin, 2005). Other specific maternal risk factors associated with preterm birth include maternal demographics (e.g., race and SES; Culhane and Goldenberg et al., 2011; Kramer et al., 2010b; Kramer and Hogue, 2009; Landrine and Corral et al., 2009; Menon et al., 2011; Paul et al., 2008; Schempf et al., 2011) and maternal behaviors such as smoking during pregnancy (Baba et al., 2012; McCowan et al., 2009) alcohol use during pregnancy (Patra et al., 2011), illegal drug use during pregnancy (Almario et al., 2009; Gouin et al., 2011), poor diet (Haugen et al., 2008; Mikkelsen et al., 2008), and lack of leisure-time physical activity (Domingues et al., 2009).

Social determinants of health and the racial disparity in preterm birth

Social determinants of health include any social conditions which may impact an individual's health and specific health outcomes (Braveman et al., 2011; Link and Phelan, 1995). While most research focuses on proximate causes of disease, social conditions are considered more distal or "upstream". These social determinants of health may indirectly impact an individual's health and are considered fundamental causes of disease (Braveman et al., 2011; Link and Phelan, 1995; Phelan et al., 2010). Unfortunately, black and other minority individuals often live in neighborhoods of lower SES due to persistent racial residential segregation or unfair housing practices, and generally have less wealth, less access to health care, and a lower quality of education as compared to white individuals (Adler and Rehkopf, 2008; Braveman, 2006). These social determinants of health can inflict a disproportionate amount of stress on black individuals, which may potentially explain some of the racial disparities that exists for numerous health outcomes, including preterm birth. Both Culhane et al. (2002) and Dolan (2010) found that black mothers reported experiencing more stress than white mothers during pregnancy; additionally, stress itself is also a risk factor for preterm birth (Kramer et al., 2011). This example illustrates the importance of social determinants of health with respect to the racial disparity in preterm birth, and indicates that they may be important risk factors to examine for this outcome.

Neighborhood preterm birth risk factors and the role of place

To investigate the relationships between social health determinants and preterm birth, as well as other outcomes of interest, neighborhood characteristics are often used as proxy measures. The most common neighborhood unit in the preterm birth literature is the US Census tract, mainly due to the availability of desirable variables at that level. Neighborhood research has shown that direct US census measures such as income (Auger et al., 2009; Diez Roux et al., 2001; Kaufman et al., 2003), education (Auger et al., 2011; Diez Roux et al., 2001; Messer et al., 2008), employment (Grady, 2006; Messer et al., 2008), proportion of rental units (Grady, 2006), and proportion of different race/ethnicities (Diez Roux and Mair, 2010; Landrine and Corral, 2009) have been associated with preterm birth. Researchers have also developed measures based on factor analysis of numerous Census variables, such as the neighborhood deprivation index (NDI; Mason et al., 2009; Messer et al., 2006a, 2006b), and have also incorporated measures of racial residential segregation into models as proxy measures for social determinants of health (Grady, 2006; Kramer et al., 2010b). While limitations are associated with the use of geopolitical boundaries, the data associated with these boundaries can still provide researchers with information on the neighborhood where an individual lives. Therefore, the neighborhood, and its associated data, can encompass social determinants of health, most of which are difficult to measure directly.

Environmental risk factors for preterm birth and racial disparities in environmental exposures

One aspect of where an individual lives, which is often neglected in neighborhood studies of preterm birth (i.e., those examining neighborhood measures of SES, crime or deprivation), is the presence of environmental contaminants, even though exposure to a variety of these contaminants have been found to be associated with preterm birth. These include compounds in air pollution (Malmqvist et al., 2011; Miranda et al., 2009; Wu et al., 2004), pesticides (Miranda et al., 2009; Pathak et al., 2010; Stillerman et al., 2008), organic compounds (Miranda et al., 2009; Stillerman et al., 2008), and metals like Pb (Andrews et al., 1994; Baghurst et al., 1999; Bellinger et al., 1991; Jelliffe-Pawlowski et al., 2006; Miranda et al., 2009; Torres-Sanchez et al., 1999; Wu et al., 2004) and As (Myers et al., 2010). Environmental contaminants are, therefore, an important exposure risk that is an undeniable part of one's neighborhood. They are also intrinsically tied to social determinants of health (Bircher and Kuruvilla, 2014; Prochaska et al., 2014).

Racial disparities in exposure to environmental contaminants have been recognized for years, prompting a 1994 presidential executive order aimed at bringing environmental justice to low income and minority populations (Brulle and Pellow, 2006). However, despite legislation, disparities still persist. Lead (Pb), a common anthropogenic metal found throughout the environment with a number of associated negative health effects, has been found in the US in higher concentrations in black individuals as compared to whites, (Hicken et al., 2011; Jones et al., 2009; Kaplowitz et al., 2010) and in soils of locations where the majority proportion of the population is black (Aelion et al., 2012, 2013; Campanella and Mielke, 2008). Arsenic (As), while generally found in low concentrations in soils in the US, has still also been measured in higher concentrations in black individuals (Caldwell et al., 2009), and in soils with a higher proportion of black individuals in the population (Aelion et al., 2012). Exposure routes vary for As and Pb, but can include inhalation of air pollution or contaminated dust and soil, as well as ingestion of contaminated dust, soils, or water. Given the complex nature of describing the risk of preterm birth when considering maternal/host risk factors, neighborhood measures as proxies for social determinants of health, and exposure to environmental contaminants, it is necessary to employ multilevel modeling techniques that can take into account risk factors at these different levels.

Neighborhood modeling for preterm birth: place versus space

When considering neighborhoods in a statistical model, there are two potential modeling options: taking place into account and/or space into account (Arcaya et al., 2012). HLM generally takes only place into account, and is used in the majority of preterm birth neighborhood research (Luke, 2004); it accounts for individuals residing within the same geographic or geopolitical boundary the researchers choose. However, HLM does not take into account the spatial relationship among neighborhood units unless specific spatial parameters are included. Without these, one may be potentially excluding information that could explain some of the variation observed in a model not taking space into account. Therefore, spatial multilevel models provide an important extension to the traditional HLM preterm birth neighborhood research methods, especially considering preterm birth prevalence is known to vary spatially at the national, state, and county levels (Miranda et al., 2009; South et al., 2012; Warren et al., 2012). Bayesian statistical models can additionally offer flexibility in spatial modeling due to the inherent dependence between observations (Bhat et al., 2011; Smith et al., 2010; Warren et al., 2012).

Scope of Study

The overall objectives of this research were to examine if black mothers had higher estimated soil As and Pb concentrations at their residences than white mothers, examine if estimated concentrations of these metals in soils were associated with increased odds of preterm birth, and investigate spatial and temporal relationships of preterm birth, all within a high-risk Medicaid population of mothers (low income and high minority composition) from SC. The first step was to investigate the racial disparity in potential for exposure to As and Pb in soils using estimated soil concentrations of these metals at maternal residences within a Medicaid population of mothers in SC, controlling for individual and neighborhood SES measures, and anthropogenic sources of As and Pb. The next step was to investigate associations between estimated soil As and Pb concentrations (as a surrogate for maternal exposure), and preterm birth (divided into early and late preterm birth categories) in this same population. Both of these steps involved implementation of HLM using both individual level and US Census 2000 block group level risk factors to assess associations between the main outcomes and exposures. The third step was to compare early to all preterm birth (aggregated at the county level) in all SC Medicaid mothers using temporal and/or spatial Bayesian models, and compare spatio-temporal and temporal only models for these outcomes.

Specific Aims and Research Questions

Specific Aim 1: Investigate the existence of a racial disparity in estimated soil As and Pb concentrations at maternal residences in a Medicaid population of mothers in SC.

- Research Question (RQ) 1.1: After controlling for both individual and neighborhood SES measures, will black mothers have higher estimated concentrations of As and Pb in soils at their maternal residence as compared to white mothers?
- RQ 1.2: After additionally controlling for known sources of As and Pb in soils in SC (including distance, directionality, and outputs from industrial point sources, age of homes, and road coverage), will black mothers have higher estimated As and Pb in soils at their residences as compared to white mothers in the study population?
- RQ 1.3: If observed, will the racial disparity in estimated soil As or Pb concentrations be modified by neighborhood deprivation at the US Census 2000 block group level in the study population?

Specific Aim 2: Examine associations between estimated soil As and Pb concentrations at maternal residences and categorical early (<34 weeks of gestation) and late (34-36 weeks of gestation) preterm births, as well as continuous weeks of gestation, in a Medicaid population of mothers in SC.

- RQ 2.1: After controlling for known individual and neighborhood level preterm birth risk factors, are estimated soil As and Pb concentrations associated with increased odds of early and/or late preterm births in the study population?
- RQ 2.2: Is the association between either estimated soil As or Pb concentrations and early and/or late preterm births modified by racial residential segregation (proxied by the isolation index) at the US Census 2000 block group level in the study population?

- RQ 2.3: Is the association between either estimated soil As or Pb concentrations and early and/or late preterm birth modified by neighborhood deprivation at the US Census 2000 block group level in the study population?

Specific Aim 3: Examine early preterm births and all preterm birth in SC Medicaid mothers using temporal and spatial Bayesian models at the county level.

- RQ 3.1: Do early and/or all preterm births, aggregated at the county level, vary spatially and/or temporally in SC Medicaid mothers by county, after adjusting for aggregated and county level preterm birth risk factors?
- RQ 3.2: After accounting for the spatial relationship between counties, temporality, and preterm birth risk factors, does a racial disparity (as measured by the proportion of black study population mothers within a county) exist with respect to early and/or all preterm births in this study population?
- RQ 3.3: Are risk factors for early and all preterm births in spatial/temporal models different?

Significance of Study

Specific Aim 1

This study was one of the first to examine the existence of a racial disparity in estimated soil As and Pb concentrations at maternal residences using HLM in a Medicaid population of mothers, while controlling for known sources of As and Pb in the environment and both individual and neighborhood measures of SES. This is also, to our knowledge, one of the first studies to take into account both distance to and direction from industrial facilities for categorization of industrial releases. If there is a racial disparity in estimated soil As and Pb concentrations after controlling for anthropogenic sources, and both distance to and direction from these sources, this may indicate that there are other reasons why black (or white) mothers live in areas with higher estimated soil As and Pb concentrations. This may be related to proxy measures of social determinants of health, such as neighborhood deprivation, or other neighborhood SES measures. Therefore, investigating if the disparity in either estimated As or Pb soil concentrations varies by neighborhood SES measures may elucidate the importance of social determinants of health to racial disparities of environmental contaminants, and the potential for exposure.

Specific Aim 2

While individual level maternal risk factors, individual level environmental exposures, and neighborhood level risk factors for preterm birth have been investigated independently in the literature, little is known about how environmental exposures to metals in soils like As and Pb can impact odds of early and late preterm births after adjusting for maternal and neighborhood risk factors. Additionally, Burris et al. (2011) specifically recommended examining environmental exposures whenever investigating birth outcomes. Modification of the association between both early and late preterm birth, and estimated soil As or Pb concentrations by either racial residential segregation or neighborhood deprivation, were also examined. These analyses may help further explain how neighborhood measures can impact the association between environmental contaminants and preterm birth, and may elucidate if preterm birth risks are different for this low income, high percentage minority population of Medicaid mothers.

Specific Aim 3

This study was the first to examine early and all preterm births in SC Medicaid mothers in spatial and temporal aggregate Bayesian models at the county level. Given that national and regional spatial variability in preterm birth that has been reported (Miranda et al., 2009), it makes sense to add spatial parameters to models at more local levels, such as the county level. Bayesian analysis also offers advantages over frequentist analysis, including the ability to apply prior belief about distributions of parameters that are being estimated in the model. Differences in risk factors for early and all preterm birth in the Medicaid study population were also examined; it was also investigated if a racial disparity was present for early and/or all preterm births in spatial/temporal models, and if spatio-temporal models of these outcomes are a better fit for the data than temporal only models.

Study Outline

This dissertation is divided into six chapters. The first chapter provides the aims of the research, including research questions, as well as the scope and significance of the research. The second chapter provides the methodology for each aim. The third, fourth, and fifth chapters contain Specific Aims 1, 2 and 3, respectively. The final chapter contains a summary of the manuscript findings, public health implications, future research directions, and limitations.

CHAPTER 2

METHODS

Study Background

The population and associated data sets used for this study are from a retrospective cohort study initiated in 2006, which aimed to examine associations between maternal exposure to residential soil metal concentrations and both intellectual disability (ID) and developmental delay (DD) in children in a Medicaid population of mother-child pairs. For the retrospective cohort study, information on mothers (and their children) who were enrolled in Medicaid during pregnancy in South Carolina (SC) from 1996-2001 was obtained from both SC birth certificates and Medicaid billing records (Kim et al., 2009, 2010; Liu et al., 2010; McDermott et al., 2011, 2014a, 2014b; Zhen et al., 2008, 2009). Medicaid is a federal assistance program that is run by the state, and which offers insurance coverage to medically verified pregnant women throughout pregnancy and up to 60 days postpartum (SC DHHS, 2013). For current pregnancy enrollment, women must be at or below 185% of the poverty level, which is equivalent to an income of $3,631 per month for a family of four (SC DHHS, 2013). Presently, approximately half of all women that give birth in SC are enrolled in Medicaid (SC DHEC, 2013). Additionally, coverage can continue for children up to age 19 if the family is at or below 200% of the poverty level (SC DHHS, 2014).

All singleton children born to Medicaid mothers, and without known cause of ID/DD, have been followed from their birth (in 1996-2001) through 2011 to document

ID and DD diagnoses from service files (Liu et al., 2010; McDermott et al., 2011, 2014a, 2014b; Zhen et al., 2008, 2009). The maternal addresses for these mothers at each month of pregnancy were geocoded using ArcGIS software (ESRI, 2013) by the SC Revenue and Fiscal Affairs Office (SC RFA). Using these geocoded addresses, and the ID and DD diagnoses, Bayesian local likelihood cluster analysis (Zhen et al., 2008) was used to identify nine areas in SC that had a significantly higher ID and/or DD prevalence rate than the state background rate (~3.5%) for all Medicaid mothers. Two areas were also identified to serve as control locations (prevalence was not significantly higher than the state background rate. All nine case locations contained a gradient of risk, however, and details of all 11 areas, including ID/DD prevalence rates, area (in km^2), and date sampled for soils, are shown in Table 2.1.

A regular 120-node grid was laid out over each of the 11 sampling areas; distances between grid nodes ranged from 0.5 km in the smaller sampling areas up to 3 km in the largest sampling area. Single grab surface soil samples (~25 g) were collected as close to each grid node as possible (with sampling locations recorded using a GPS device), and soil samples were analyzed for nine metals (including total As and Pb) using inductively coupled plasma optical emission spectroscopy (ICP-OES) by an independent environmental laboratory. Arsenic and Pb concentrations were reported in mg/kg dry weight. The soil sampling protocol and analytical details have been described elsewhere, (Aelion and Davis, 2007; Aelion et al., 2008, 2009a, 2009b, 2012, 2013, 2014; Davis et al., 2009, 2014). Arsenic and Pb were chosen for this research because both have been shown to be associated with preterm birth in other studies, and both had relatively few numbers of non-detects as compared to other metals examined. After soil metal concentration results were received from the lab, these concentrations (in conjunction with their geocoded sampling location) were used to spatially interpolate (krige) soil metal concentrations at each mother's geocoded address during each month of pregnancy by the SC RFA (Liu et al., 2010; McDermott et al., 2011). Kriging model details can be found in Zhen et al. (2008, 2009). For this dissertation, only kriged soil As and Pb concentrations at the mother's residence at month 6 of pregnancy were used as a surrogate for maternal exposure. This month was chosen as it maximized the size of the study population, and also captured most mothers prior to the occurrence of a preterm birth. The spatially interpolated soil As and Pb concentrations were chosen as surrogates of exposure due to the retrospective nature of the study, lower analytical costs as compared to biomarkers, the fact that soil and biological concentrations of these metals have been found to be correlated in other studies (Díaz-Barriga et al., 1993; Hinwood et al., 2004; Thornton et al., 1990), and because soil is considered a relevant route of exposure to metals in soils (Calderón et al., 2003; Caussy et al., 2003).

Study Population

This Medicaid population is considered high-risk for preterm birth because of the low income requirements for coverage, and due to its high proportion of minority mothers. For Specific Aim 3, the study population consisted of all mothers who gave birth while enrolled in Medicaid in SC from 1996-2001. For Specific Aims 1 and 2, the study population consisted of a subset of the entire SC Medicaid population for this same time period; specifically, those mothers that were living in one of the 11 sampling areas at month 6 of pregnancy (10.1% of all Medicaid moms after exclusions/restrictions).

These are the only mothers with estimated soil As and Pb concentrations at their residence at month 6 of pregnancy. For all aims, mothers were excluded if information on any of the following variables was missing or unknown: mother's race, mother's age, baby birth weight, baby gender, and gestational age (~1.3% of mothers). Mothers were also linked to the US Census 2000 block group in which their residence at month 6 of pregnancy was located for Specific Aims 1 and 2, and their county of residence during month 6 of pregnancy for Specific Aim 3; if this linkage was not possible, they were also excluded from any analyses. The study population was also restricted to only black and white mothers, and did not include mothers with babies that had improbable birth weights (<500 g; n=39) or gestational ages (<21 weeks; n=15). All analyses were also restricted to a mother's first baby temporally, if she had more than one child while enrolled in Medicaid in SC from 1996-2001. Additional sources of data included the SC Department of Social Services (SC DSS), and the US Census Bureau (US Census 2000 Summary File 3; US Census, 2002).

Specific Aim 1

Variables

For Specific Aim 1, the main outcomes of interest were estimated As and Pb soil concentrations at the mother's geocoded address during month 6 of pregnancy (in mg/kg). These outcomes were modeled as continuous concentrations, and were modeled separately given that concentrations of these metals were highly correlated ($r = 0.71$, $p<0.0001$). The main exposure of interest was maternal race, dichotomized and restricted to only black and white mothers, with white mothers serving as the reference level.

At the individual level, both maternal education (dichotomized to less than a high school education and at or above a high school education) and receipt of food stamps during pregnancy were included. A high school diploma or greater and no receipt of food stamps during pregnancy served as the reference levels for these variables. At the neighborhood (US Census 2000 block group) level, the neighborhood deprivation index (NDI) as described by Messer et al., (2006b) was calculated. This index takes into account a variety of US Census measures, including education, poverty, unemployment, and income, at the neighborhood level of analysis, and higher values indicate more deprivation. Given many of these variables are highly correlated, using the NDI should avoid multicollinearity among US Census 2000 block group SES measures in the analysis. The NDI was dichotomized to below, and at or above the median; values below the median served as the reference level. To proxy proximal sources of As and Pb, two different measures were chosen. Percent block group area covered by roads was estimated based on total road length and average road width from a TIGER road file (US Census, 2013). Home age (block group median year home built subtracted from the year 2000) was also calculated. Percent coverage of roads served as a proxy measure of historic use of leaded gasoline, while home age proxied historic use of residential leaded paint. Both were treated as continuous measures.

While both percent of coverage by roads and home age may proxy potential sources of environmental Pb (and As to some extent), more distal anthropogenic sources of both As and Pb in the environment were also examined. Using the Environmental Protection Agency (EPA) Toxics Release Inventory (TRI), all facilities with emissions of As and/or Pb from 1996-2011 were identified (US EPA, 2013), and the average annual on-site releases of both As and Pb (in thousands of pounds) were calculated. Facility locations were mapped in ArcMap (ESRI, 2013) and both the distance to, and directionality of TRI facilities to US Census 2000 block group centroids in which mothers resided was determined. For each distance and/or direction category of interest, average annual releases from As- or Pb-emitting facilities within that category were summed. Thus, how composite annual on-site releases of As and Pb impact estimated soil As and Pb concentrations at the mother's block group of residence during month 6 of pregnancy categorized by distance only, direction only, and distance/direction was able to be examined. Additional details on variables used and data sources are available in Chapter 3.

Statistical methods

For all Specific Aim 1 analyses, SAS Version 9.4 was used (SAS Institute, 2010). The first step was to assess all exposures for multicollinearity, using both outcomes. After this analysis, it was determined that home age should not be included in any models due to its collinearity with multiple exposures. For the continuous As and Pb outcomes, PROC MIXED was used; maximum likelihood estimation was implemented, and the intercept was allowed to vary by neighborhood (US Census 2000 block group). The crude model contained only the main exposure of interest (mother's race). Model 1 contained other individual level risk factors/confounders. Model 2 further contained the NDI and Model 3 further added percent roads. Model 4 contained an interaction term between maternal race and the NDI. The best fit model was then identified using a backwards elimination procedure, and variables were only retained if they remained significant ($p<0.05$) or changed the main effect estimate (maternal race) by more than 10% after removal. To examine the impact of TRI average annual on-site releases on estimated soil As and Pb concentrations, composite annual on-site As and Pb TRI categorized by distance only, direction only, and distance/direction combined, were examined individually in the best fit models previously identified for each outcome of interest. Additional methodological details for Specific Aim 2 are available in Chapter 3.

Specific Aim 2

Variables

The main outcome of interest for Specific Aim 2 was preterm birth, which was divided into two categories: births of <34 weeks of gestation (early preterm) and births from 34-36 weeks of gestation (late preterm). Births at >36 weeks of gestation were considered term births and used as the reference category. The continuous outcome of weeks of gestation was also examined; both birth categories and weeks of gestation were based on the clinical estimates of gestation on birth certificates. The main exposures of interest were estimated soil As and Pb concentrations (in mg/kg), which were continuous and modeled separately for the categorical and continuous birth outcomes. Other examined risk factors for preterm birth were at both the individual and neighborhood level, and determination of inclusion of them in models was based on observation of a significant crude association with either soil As or Pb estimated concentrations. This was to help prevent unnecessary adjustment. Individual level risk factors that were examined included maternal race, maternal education, and receipt of food stamps during pregnancy (the same as from Specific Aim 1), parity (number of previous children), baby gender (dichotomized to male and female), mother’s age, and month of pregnancy that prenatal care began (dichotomized to starting within the first trimester, or starting after the first trimester). Behaviors and conditions during pregnancy were also examined, including smoking during pregnancy (yes or no), and presence of pregnancy-related hypertension (included diagnoses of gestational hypertension, preeclampsia, and eclampsia). Infection was also examined, and was dichotomized based on the presence or absence of any one of the following conditions: bacterial urinary tract infection, genital herpes, gonorrhea, chlamydia, trichomoniasis, chorioamnionitis, candidiasis, cervicitis, or pelvic inflammatory disease. Data sources for the majority of maternal demographics, conditions, and behaviors during pregnancy were from a combination of birth certificates and Medicaid billing records.

Neighborhood level risk factors at the US Census 2000 block group level included if the majority (>50%) of the block group population lived in urban areas (dichotomized), and the continuous NDI that was calculated for Specific Aim 1. Racial residential segregation was also examined, and the isolation index (Massey and Denton, 1988) was chosen to proxy this social determinant of health. The isolation index was calculated using the following formula:

$$ {}_{x}P^{*}_{x} = \Sigma[x_i/X]*[x_i/t_i] \qquad (1) $$

where x_i = total black population of the US Census 2000 block group, X = total black population (total number) of the US Census 2000 tract, and t_i = total population of the US Census 2000 block group. Values range from 0-1, with values closer to 1 suggesting more isolation. Additional details on data sources and variables used (including reference levels) are located in Chapter 4.

Statistical methods

For all Specific Aim 2 analyses, SAS Version 9.4 was used (SAS Institute, 2010). The first step was to assess all exposures for multicollinearity, using both outcomes; no variables were identified that posed a collinearity issue. For the categorical preterm birth outcome, PROC GLIMMIX was used with a cumulative logit link function, a multinomial distribution to account for the multiple birth categories, and Laplace’s estimation. For the weeks of gestation outcome, PROC MIXED was used with maximum likelihood estimation. For both outcomes, the intercept was allowed to vary by neighborhood (block group). The crude models included only As or Pb, as these were the main exposures of interest, and were modeled separately. Model 1 further included all other individual level risk factors. Model 2 further included all neighborhood level risk factors, and Model 3 additionally included interaction terms between As or Pb concentrations and both racial residential segregation (isolation index) and the NDI. This same method was followed for both outcomes of interest (categorical birth and continuous weeks of gestation), and best fit models for both outcomes were determined as for Specific Aim 1. Additional methodological details are available for Specific Aim 2 in Chapter 4.

Specific Aim 3

Variables

For Specific Aim 3, the main outcome of interest was the estimated risk of preterm birth at the SC county level for all mothers in SC giving birth while enrolled in Medicaid from 1996-2001. Early preterm births were defined as <34 weeks (as in Specific Aim 2) and all preterm births were defined as <37 weeks of gestation. This analysis was done at the aggregate county level because, due to privacy concerns, access to the actual geocoded address of mothers during month 6 of pregnancy was not allowed. Without this information, the spatial relationship among individuals could not be examined and, therefore, the spatial relationship among counties was instead assessed. Additionally, the county level was chosen as birth counts at the US Census 2000 block group and tract were too low to ensure valid results. Individual level risk factors were aggregated to the county level, and included proportion of study population mothers that were black, mean mother's age, proportion of mothers with less than a high school education, proportion of mothers beginning prenatal care after the first trimester, proportion of mothers receiving food stamps, and proportions of mothers with other risk factors for preterm birth (infection, pregnancy-associated hypertension, alcohol use during pregnancy, tobacco use during pregnancy, and previous preterm birth). The mean county NDI (as calculated from Specific Aim 1), and the county percentage of the population that was urban were also included as neighborhood level risk factors. To account for the spatial relationship between counties, the number of adjacent neighbors for each county was determined, and a neighborhood weight matrix was created using row standardized weights (Bivand et al., 2015). Additional variable details are located in Chapter 5.

Statistical methods

For Specific Aim 3, both R Version 3.1.1 (R Core Team, 2014) and WinBUGS 14 (Lunn et al., 2000) were used for all statistical analyses, and SAS Version 9.4 (SAS Institute, 2010) was used to prepare the county level data set. The standardized ratios (SR) for both early and all preterm births (observed to expected early or all preterm births) by year were first calculated by county, and 95% confidence intervals for these SRs were also calculated using the Poisson exact method. Crude spatial/temporal Bayesian Poisson models were then examined for both birth outcomes to identify significant risk factors (based on 95% credible interval not containing 1). Only significant exposures for each outcome were included in adjusted spatial/temporal and temporal only models; however, maternal race was included regardless of significance. The deviance information criterion (DIC) values from crude and adjusted spatio-temporal and adjusted temporal only models were compared to determine the best fit model for each birth outcome. Additional methodological details, including prior distributions and initial values, are available in Chapter 5.

Table 2.1 Sampling area characteristics.

Sampling Area	Case or Control[a]	Month/Year Sampled	Approximate Area (km^2)	ID[b] Prevalence	DD[c] Prevalence
Area 1	Control	06/2006	490	0.023	0.16
Area 2	Case	12/2006	120	0.037	0.20
Area 3	Case	07/2007	100	0.017	0.51
Area 4	Case	11/2007	130	0.041	0.24
Area 5	Case	04/2008	60	0.052	0.21
Area 6	Case	07/2008	90	0.12	0.36
Area 27	Case	07/2010	100	0.081	0.21
Area 23	Case	12/2010	80	0.072	0.30
Area 22	Case	01/2011	110	0.052	0.17
Area 31	Case	06/2011	80	0.051	0.23
Area 99	Control	10/2011	100	0.037	0.17

[a] Case: ID/DD prevalence rate significantly ($p<0.05$) higher than the state background rate for all SC Medicaid mothers; Control: ID/DD prevalence rate not significantly higher than state background rate

[b] ID: intellectual disability

[c] DD: developmental delay

CHAPTER 3

ARSENIC AND LEAD IN SOILS: INVESTIGATING POTENTIAL SOURCES AND RACIAL DISPARITIES AMONG PREGNANT WOMEN IN SOUTH CAROLINA

Abstract

Exposure to arsenic (As) and lead (Pb) has been associated with adverse health outcomes, and high-risk populations can be disproportionately exposed to these metals in soils. The objectives of this study were to examine whether racial disparities (between non-Hispanic black and white mothers) were present in estimated soil As and Pb concentrations at residences in South Carolina (SC) Medicaid mothers during pregnancy, and determine if the disparities persisted after controlling for anthropogenic sources of these metals including composite annual releases categorized by distance and direction of the residence block group from industrial facilities. Arsenic and Pb soil concentrations were kriged at maternal residences in 11 SC locations, and covariates included maternal and Census block group level SES measures. Distance and direction from EPA Toxics Release Inventory (TRI) facilities to block groups in which mothers resided were also identified. Consistent racial disparities were observed for estimated residential soil As and Pb concentrations, though the disparity was stronger for Pb (betas from adjusted models 0.12 and 2.2 for As and Pb, respectively, all $p<0.006$). Road coverage in block groups was more closely associated with estimated soil As and Pb concentrations than facility releases, regardless of distance/direction. These findings suggest that non-

Hispanic black mothers in this study population had elevated residential As and Pb soil concentrations, after adjusting for SES, and that historic inputs from leaded gasoline contributed more to current soil As and Pb concentrations than more recent industrial releases.

Introduction

Exposure to metals in soils has the potential to impact human health, and metals such as arsenic (As) and lead (Pb) are pervasive and long-lived in this environmental medium (Aelion et al., 2014; Nriagu and Pacyna, 1988). While As occurs naturally in the environment, elevated soil concentrations are often due to inputs from anthropogenic sources, such as mining, smelting, and other industrial activities (Hinwood et al., 2004; Luo et al., 2008). Arsenic can also leach into soils from chromated copper arsenate (CCA) treated wood (Mielke et al., 2010; Shalat et al., 2006), which was routinely used in residential areas until the early 2000s. In contrast, the presence of Pb in soils is most often the result of anthropogenic inputs, especially in residential locations. Soil Pb concentrations are strongly associated with the historic use of leaded gasoline (Datko-Williams, 2014; Kayhanian, 2012) and lead-based paints (Mielke et al., 2008; Mielke and Reagan, 1998), as well as industrial practices (Landsberger et al., 1999; Luo et al., 2009).

Arsenic or Pb exposure can elicit neurological (Ahamed et al., 2008; Bellinger, 2008; Llop et al., 2013; Mukherjee et al., 2005; Naujokas et al., 2013; Pabello and Bolivar, 2005), and cardiovascular impacts (Balakumar and Kaur, 2009; Kim et al., 2008; Moon et al., 2013; Poreba et al., 2011), as well as adverse reproductive outcomes (Ahamed et al., 2009; Ahmad et al., 2001; Ahmed et al., 2011; Jelliffe-Pawlowski et al., 2006; Myers et al., 2010; Mukherjee et al., 2005; Torres-Sanchez et al., 1999; Yang et al., 2003). Contaminated soils can become a component of household dust (Hinwood et al., 2004; Petrosyan et al., 2004), and the contribution of soil to house dust can range from a third up to 50% (Calabrese and Stanek, 1992; StellaLevinson, 2008). Since household dust can then be inadvertently ingested or inhaled (Caussy et al., 2003), monitoring As and Pb soil contamination, especially in residential areas, can be important for preventing exposure in these settings.

High-risk populations, such as those of racial/ethnic minorities and lower socioeconomic status (SES), are often disproportionately exposed to As and Pb in soils (Aelion et al., 2012, 2013; Calderón et al., 2003; Calderon et al., 2004; Campanella and Mielke, et al., 2008; Diawara et al., 2008; Mielke et al., 1999) and, therefore, they are potentially more susceptible to any associated health impacts. This may result from living in neighborhoods located on prior industrial sites, or in close proximity to industries and/or high volume roadways (McClintock, 2012; Pellow, 2000). This highlights the importance of examining neighborhood features when assessing high-risk populations and their potential exposure to environmental contaminants like As and Pb.

This study used environmental sampling to examine the presence of a racial disparity in estimated soil As and Pb concentrations at the residences of mothers during pregnancy who gave birth while enrolled in the South Carolina (SC) Medicaid program from 1996-2001 (Aelion et al., 2008, 2009a, 2009b, 2012, 2013, 2014; Davis et al., 2009, 2014; McDermott et al, 2011, 2014a, 2014b; Liu et al., 2010; Zhen et al., 2008, 2009), after controlling for individual and neighborhood level SES measures. It was hypothesized that non-Hispanic black mothers would have higher estimated soil As and

Pb concentrations at their residence relative to non-Hispanic white mothers, after controlling for individual SES measures. Since individual SES may not fully explain the disparity in estimated soil As and Pb concentrations for the study population, it was also hypothesized that neighborhood deprivation (a composite measure of US Census SES indicators, with higher values indicating more deprivation) would be positively associated with higher concentrations of both As and Pb, and that neighborhood deprivation would modify the association between estimated soil As and Pb concentrations and maternal race. It was hypothesized that non-Hispanic black mothers living in neighborhoods with higher deprivation (as compared to non-Hispanic black mothers in neighborhoods with lower deprivation) would have higher estimated soil As and Pb concentrations in their neighborhoods. Given these assumptions, additional analyses were performed to evaluate whether the racial disparity in estimated soil As and Pb concentrations would be attenuated in neighborhoods with more deprivation.

Proximal and distal sources of As and Pb were also expected to impact concentrations in residential soils; if racial/ethnic minorities live at locations in closer proximity to more sources, then their residential soil metal concentrations may be higher. Sources investigated included road coverage and median home age (proximal), as well as composite annual releases of As and Pb from facilities (distal) in SC, categorized by both distance to and direction from maternal residences. It was hypothesized that releases from facilities would be positively associated with estimated soil As and Pb concentrations at maternal residences in the path of prevailing winds (i.e., southwest of facilities releasing As and Pb into the atmosphere in SC), and that the racial disparity in potential exposure to As and Pb in soils would no longer be apparent after accounting for these sources of

As and Pb in the analysis. It was also hypothesized that associations would be stronger for releases from facilities located in closer proximity to maternal residences. Associations between soil metal concentrations and distance from industrial facilities have been observed (Aelion et al. 2008a; Bermudez et al., 2009; Douay et al., 2007), but, to our knowledge, no studies have examined the relationship between soil metal concentrations and industrial releases categorized by both the direction and distance from industrial sources of metal emissions.

Methods

Study Design and Population

This study utilized data sets from a retrospective cohort study initiated in 2006 that examined associations between maternal exposure to residential soil metal concentrations and both intellectual disability (ID) and developmental delay (DD) among children in a Medicaid population of mothers giving births to singletons (Kim et al., 2009, 2010; Liu et al., 2010; McDermott et al., 2011, 2014a, 2014b; Zhen et al., 2008, 2009). For the retrospective cohort study, information on mothers and children in SC who were enrolled in Medicaid during pregnancy from 1996-2001 was obtained from SC birth certificates, Medicaid billing records, and the SC Department of Social Services (SC DSS). United States (US) Census 2000 block group level data for SC were also utilized.

Eleven areas in SC were selected for sampling based on prevalence of ID/DD in SC Medicaid mothers for the time period of interest, and nine of these areas had an elevated prevalence that was significantly higher than then statewide background prevalence (3.5%) for all Medicaid mothers (Zhen et al., 2008). The areas were identified using Bayesian local-likelihood cluster analysis of geocoded maternal residences during month of pregnancy (Zhen et al., 2008, 2009), ranged in size from 60-490 km^2 (mean of 130 km^2) and were sampled for soils from 2006 to 2011. The exact geographic locations of the maternal addresses and sampling areas are undisclosed to protect participant confidentiality.

In each of the 11 areas, a regular 120-node grid was laid out and single grab surface soil samples of approximately 25 g were collected as close to each grid node as possible; the geographic location of each sample was also obtained using a GPS device. Soil sample locations were selected to maximize the probability of collecting undisturbed native soil with no visible contamination or previous development. Samples were analyzed for total As and Pb using inductively coupled plasma optical emission spectroscopy (ICP-OES) by an independent environmental laboratory. Both the soil sampling protocol and metals analyses procedures have been previously described (Aelion et al., 2008, 2009a, 2009b, 2012, 2013, 2014; Davis et al., 2009, 2014); concentrations were reported in mg/kg dry weight. These measured soil metal concentrations (and their geocoded sampling locations) were then used to spatially interpolate soil metal concentrations at each mother's geocoded address by month of pregnancy using the ordinary kriging method; kriging methodological details are described in detail in Zhen et al., (2008, 2009).

Mothers were excluded if they were missing maternal age, maternal race, baby birth weight, baby gender and gestational age (~1.3% of mothers). Mothers were also excluded if their infant had an improbable clinical estimates of gestation (<21 weeks, n=15) or birth weight (<500 g, n=39). The analysis was restricted to only non-Hispanic black and non-Hispanic white (henceforth referred to as black and white) mothers, to mothers whose residence at month 6 of pregnancy was spatially linked with the US Census 2000 block group in which the residence was located, and to only the first birth of a mother (temporally) if she gave birth to more than one child during the study period. Additionally, maternal education was imputed for mothers missing this data (14%) using the maximum likelihood method (Alison, 2012).

Variables

Estimated soil As and Pb concentrations at the mother's address at month 6 of pregnancy were used as the main outcome variables of interest for characterization of potential for environmental exposure to these metals. Maternal race was the main independent variable, with white mothers set as the reference category. Individual and neighborhood level measures of SES were included as covariates in the statistical models. At the individual level, maternal education was dichotomized to less than a high school education or a high school diploma or above (reference category) and utilization of food stamps during pregnancy (from SC DSS records) was also examined, with the reference category being no food stamp receipt during pregnancy.

The neighborhood deprivation index (NDI) was derived from US Census 2000 block group data as a contextual measure of SES (Messer et al., 2006b). A principal component analysis (PCA) was performed on 20 US Census 2000 variables identified at the block group level. After identifying 10 variables with factor loadings greater than or equal to the median (proportion of the population with less than a high school education, proportion of population unemployed, proportion of households renter-occupied, proportion of households crowded, proportion of female headed households with dependent children, proportion of households in poverty, proportion of households with an income less than $30,000 per year, proportion of households on public assistance, proportion of households with no car, and proportion of the population identifying as non-Hispanic black), PCA was performed again, and the factor loadings of these variables were weighted by their PCA communality estimates. The NDI was dichotomized using the median (4.8) for mothers in the study population.

Percent of block group area covered by roads (henceforth referred to as percent roads) was calculated by estimating the percentage of each block group’s area covered by roads based on road length and average width (Aelion et al., 2013). This measure was used as a proxy for historic use of leaded gasoline, and was modeled as a continuous variable. The block group median year home built was also calculated by subtracting each block group’s median home age from the year 2000. This measure was used to proxy the historic residential use of Pb-based paint.

To determine block group distance to and direction from sources of atmospheric emissions, all Environmental Protection Agency (EPA) Toxics Release Inventory (TRI) facilities with As (n=21) and/or Pb (n=192) emissions between 1996 and 2011 were identified (US EPA, 2013; Figure 3.1). Total annual on-site releases (in thousands of pounds) were obtained for each metal and averaged for the number of years that each facility reported releases from 1996 to 2011. The bulk of on-site As and Pb releases were to air (fugitive and stack emissions), though on-site surface (land) releases were also included in the calculation. The latitude and longitude of these facilities were mapped in ArcMap Version 10.2 (ESRI, 2013).

From each facility, the straight-line distance to the centroid of each mother's block group was determined. Since the actual location of the maternal residence was not known due to a confidentiality agreement, the block group centroid was utilized for distance measures. Using these distances, all As- and Pb-emitting TRI facilities were categorized into four distance categories from each block group in which a study population mother resided: ≤5 km, 6-10 km, 11-20 km, and >20 km. For direction, the latitude and longitude coordinates (in decimal degrees) of each TRI facility were subtracted from the coordinates of each block group centroid. Then, depending on the sign of these values, the direction of the facility from the block group centroid was assigned to one of the following categories: northeast (NE), northwest (NW), southeast (SE), or southwest (SW).

After determining the distance and direction of each block group centroid from As- and Pb-emitting TRI facilities, the average annual releases were summed for facilities categorized within each hypothesized distance, direction, or distance/direction category to create a composite estimate of all releases for As-or Pb-emitting facilities within each distance and/or direction category. If there were no TRI facilities in that specific distance, direction, or distance/direction category for a study individual, the composite annual release was set to 0 thousand pounds/year.

Statistical Analyses

Estimated soil As and Pb concentrations were modeled individually with each main risk factor of interest in bivariate analyses using analysis of variance for categorical variables and simple linear regression for continuous variables. Collinearity of variables was examined using regression analysis with collinearity and variance inflation factors

(VIF) options (a value of ≥10 was used as a cutoff for to identify variables that may have posed a collinearity issue), as well as simple correlations between variables. Based on these analyses, block group median home age was excluded from further analyses due to its collinearity with percent roads and other exposures.

To test all hypotheses, hierarchical linear modeling (HLM) was used to account for multiple maternal residences within a given block group. As the main outcomes were continuous, maximum likelihood estimation and Satterthwaite's method for determination of degrees of freedom were used, and the slope of the intercept was allowed to vary by block group (random intercept). The crude model contained only the maternal race variable with either estimated soil As or Pb concentration as the outcome. Model 1 further included maternal education and the food stamps variable, and Model 2 was additionally adjusted for NDI. Model 3 was additionally adjusted for the proximal metal source measure percent roads. For Model 4, to investigate the potential modifying role of NDI, an interaction term between maternal race and NDI was added. A backward selection process was used on the full model (Model 4) for both estimated As and Pb concentrations to identify the best fit model for both outcomes. Variables were removed from the model based on the highest p-value until all variables had p-values of <0.05. However, variables were retained, regardless of p-value, if the maternal race parameter change after removal was >10%.

To examine the impact of composite TRI facility releases on estimated residential soil As and Pb concentrations, only the hypothesized direction of interest (SW) was investigated (individually or combined with distances categories). We first compared mean estimated soil As and Pb concentrations between study population mothers living in block groups within TRI facility distance and/or direction categories and study population mothers who did not. To investigate the final two hypotheses, HLM was again used to model each metal outcome predicted by either As and Pb composite annual releases from TRI facilities by distance only, direction only, and distance and direction combined. Each distance/direction category was evaluated in separate models (Models 5-13), and all models were additionally adjusted for all parameters that were retained in the best fit models for estimated As and Pb concentrations after the backward selection. SAS Version 9.4 (SAS Institute, 2010) was used for all statistical analyses and a p-value of 0.05 was used to determine statistical significance.

Results

Estimated residential soil As and Pb concentrations ranged from 0.22-26.6 mg/kg and 1.5-286 mg/kg among study participants, respectively. Mean concentrations were 4.9 mg/kg for As and 58.2 mg/kg for Pb (Table 3.1). Estimated concentrations of these metals were also highly correlated with each other in this study population ($r = 0.71$, $p<0.0001$; data not shown). Comparisons of estimated soil As and Pb concentrations in relation to exposures of interest are shown in Tables 3.1 and 3.2. The majority of the study population identified as black, had at least a high school diploma, and received food stamps during pregnancy (Table 3.1). When stratified by maternal race or education, mean estimated soil As and Pb concentrations were significantly higher among black mothers, as well as for mothers who were not high school graduates (Table 3.1). While mean estimated soil As concentrations were higher for mothers who received food stamps during pregnancy ($p<0.0001$), mean estimated soil Pb concentrations were not different among mothers stratified by receipt of food stamps during pregnancy (Table 3.1). Mean estimated soil concentrations of both As and Pb were also elevated among mothers living in block groups at or above the median NDI value ($p<0.0001$). While 66% of black mothers lived in block groups with NDI values at or above the median, less than one-fourth (21%) of white mothers did (data not shown). For all categorical maternal risk factors, the largest differences in mean estimated soil As and Pb concentrations were between black and white mothers, followed by mothers stratified by NDI values. Estimated soil As and Pb concentrations were also positively associated with more road coverage and higher median age of homes within block groups (Table 3.2).

Study population Medicaid mothers were also compared to all Medicaid mothers under the same exclusion and restriction criteria (Appendix A, Table A.1). Mothers in the study population were more likely to be black, not have a high school diploma or higher, and have received food stamps during pregnancy (Appendix A, Table A.1). Though the study population was stratified at the median NDI of 4.8, only 29% of all Medicaid mothers lived in block groups with this NDI (Appendix A, Table A.1). Block groups in which study population mothers resided at month 6 of pregnancy also had significantly higher mean percent roads and median age of homes (Appendix A, Table A.2).

Parameter estimates for all variables included in crude models, Models 1-3, and the best fit models, are shown in Table 3.3A for As and 3.3B for Pb. For As, the racial disparity was significant in the crude model, as well as Models 1-3 (Table 3.3A). The average estimated soil As concentration at the mother’s residence was 0.12-0.13 mg/kg higher for black as compared to white mothers, after adjusting for all other covariates of interest. Lower maternal education was consistently associated with higher estimated As concentrations at the mother's residence (Table 3.3A); mothers without a high school education had estimated residential soil As concentrations ~0.8 mg/kg higher than mothers with at least a high school diploma, after adjusting for other risk factors. Receipt of food stamps during pregnancy was not significantly associated with As concentrations in any model (Table 3.3A). Residential estimated soil As concentrations were 1.2 mg/kg higher for mothers in block groups with NDI values at or above the median in Model 2 relative to those below the median (Table 3.3A), but this parameter estimate did not remain significant after adjustment of percent roads. The percentage of roads within block groups was positively associated with estimated soil As concentrations in Model 3 (Table 3.3A); for every one percent increase in road coverage in a block group, average estimated soil As concentrations were 0.38 mg/kg higher at maternal residences after adjustment. The interaction term between maternal race and NDI was not significant (β = 0.029, p = 0.8) in Model 4 (data not shown). The best fit model for the estimated soil As concentration outcome contained maternal race, maternal education, and percent roads (Table 3.3A).

For estimated soil Pb concentrations, maternal race parameter estimates were significant in all models, and the racial disparity was stronger than that for As, with black mother's residences having average estimated soil Pb concentrations 2.1-2.3 mg/kg higher than white mothers (Table 3.3B). Neither maternal education nor receipt of food stamps predicted soil Pb concentrations in any model (Table 3.3B). As with As, the NDI also predicted soil Pb concentrations in Model 2; mothers living in block groups with NDI values greater than or equal to the median had estimated soil Pb concentrations almost 10 mg/kg higher than mothers in block groups with NDI values at below the median; however, NDI did not predict soil Pb in Model 3 (Table 3.3B). The interaction term between NDI and maternal race was also not significant (β = -1.2, p = 0.3) for estimated soil Pb concentrations (data not shown). For Pb, the best fit model contained only maternal race and percent roads (Table 3.3B).

Mean estimated soil As concentrations were significantly higher for mothers residing in block groups in the SW direction from As-emitting TRI facilities, compared to mothers that did not, as well as for mothers living in block groups within 11-20 km of facilities and mothers living in block groups in the SW direction at distances of both 11-20 and >20 km (Figure 3.2A). However, estimated soil As concentrations were significantly lower for mothers living in close proximity (≤5 and 6-10 km) to As-emitting TRI facilities compared to those that did not, regardless of direction; this was also true at the combined distance and direction category of SW direction and ≤5 km (Figure 3.2A). Mean estimated soil Pb concentrations were significantly higher for mothers living in block groups within 6-20 km of Pb-emitting TRI facilities compared to those that did not, as well as for distances of 11-20 km combined with the SW direction (Figure 3.2B). As with As, mean estimated soil Pb concentrations were significantly lower for mothers residing in block group located within 5 km of Pb-emitting TRI facilities (Figure 3.2B).

Parameter estimates from mixed models including As and Pb composite annual releases from TRI facilities categorized by distance and direction (Models 5-13) are shown in Table 3.4. For As, all significant parameter estimates were in the negative direction, suggesting lower estimated residential soil As concentrations were associated with higher composite annual facility As releases for that corresponding distance and/or direction category (Table 3.4). This was also true of parameter estimates for composite annual Pb TRI facility releases, with the majority of estimates in the negative direction and only two being statistically significant (Table 3.4). Maternal race parameter estimates remained as statistically significant in all models for both As and Pb (Table 3.4), and were similar in magnitude to estimates from crude models and Models 1-3 (Tables 3.3A-B).

Discussion

A consistent racial disparity in estimated residential soil As and Pb concentrations was observed in this study; the disparity remained significant after controlling for maternal or neighborhood demographics, and proximal and distal sources of these metals. This suggests that black mothers in the study population were more likely to live at locations with higher soil concentrations of both As and Pb, which may mean they could be at increased risk for exposure. However, estimated soil concentrations of both As and Pb were generally low in these sampling areas, and differences between black and white mothers were less than 2.5 mg/kg for both metals in adjusted models. Additionally, the estimated concentrations reported for residential locations in the current study are similar to those reported in studies of background As and Pb concentrations in both SC and the US. Canova (1999) reported ranges of 0-210 mg/kg and 0-200 mg/kg for As and Pb, respectively. Shacklette and Boerngen (1984) reported much lower ranges (0-4.1 mg/kg for As and ≤10 mg/kg for Pb.

Even so, other studies have documented racial disparities in soil Pb concentrations (Campanella and Mielke, 2008; Diawara et al., 2008; Mielke et al., 1999), though mean soil concentrations of Pb reported in these studies were much higher than in the sampling areas examined in this study (5 and 58 mg/kg for As and Pb, respectively), most likely due to more potential sources of this metal in those locations. For example, in Pueblo, CO, Diawara et al. (2006) reported an average soil Pb concentration of 87.8 mg/kg, and higher soil Pb concentrations were associated with higher US Census block population percentages of Hispanics (the main minority group in this state). Mielke et al. (1999) reported median soil Pb concentrations of 120 mg/kg in New Orleans, LA, and the US Census 1990 tract population percentage of blacks was 60% in tracts categorized as high metal (soil Pb concentrations ≥316 mg/kg), compared to just 36% in tracts categorized as low metal. Davis et al. (2014) reported associations between soil Pb concentrations within all of the sampling areas utilized in the current study and US Census 2000 block group population percentages of non-Hispanic blacks; however, that study used measured soil Pb concentrations and Census data. An aggregate analysis at the US Census 2000 block group level using a subset (only four of the 11) of the sampling areas and study population examined in the current study also reported an association between percentage of black study population mothers and mean block group Pb concentrations (Aelion et al., 2012). This study also used the measured Pb concentrations rather than kriged.

Racial disparities in exposure to As in soils are less well studied than those for Pb, but have been examined by a subset of authors of the current study (Aelion et al., 2012; Davis et al., 2014), as well as by Diawara et al. (2006). Aelion et al. (2012) examined a subset of the sampling areas used in the current study and found that block groups with increased percentages of black mothers had mean soil As concentrations at the block group level that were elevated relative to whites in two of four study areas examined. Davis et al. (2014) reported that soil As concentrations were not associated with the US

Census 2000 block group percentages of non-Hispanic blacks; however, Davis et al. (2014) did not examine the racial disparity in soil As concentrations of the study population used in the current study. Soil As concentrations measured by Diawara et al. (2006) were higher than what was reported for estimated As soil concentrations in this study (average of 12.6 mg/kg), and blocks with higher soil As concentrations had higher block population percentages of Hispanics.

In the models that included the interaction term between maternal race and NDI, the interaction term was not significant for either the As or Pb outcome. Therefore, in this study population, the racial disparity in estimated soil As and Pb concentrations at maternal residences was not modified by block group NDI. The neighborhood deprivation index (NDI) was also not retained in the best fit models for either As or Pb. This may be related to the fact that this study's population was more homogeneous than populations examined in other studies that have also looked at neighborhood deprivation. For example, the study population in Messer et al. (2006b) included over 200,000 mothers from Pennsylvania, Maryland, Michigan, and North Carolina, and Messer et al. (2006a) examined over 13,000 mothers from North Carolina. Additionally, the study population examined by Ma et al. (2014) included mothers from all over SC. In all of these studies, all births within the study areas were examined for the time period of interest, not just a subset of mothers giving birth while enrolled in Medicaid (as in this study). Additionally, the study population chosen for this study was based on prevalence of ID and DD in the study areas, suggesting population homogeneity on risk factors associated with this outcome. The variability of NDI calculated for all block groups in SC as part of the current study was higher than the variability of just those block groups in which study population mothers resided at month 6 of pregnancy (data not shown). While comparison of NDI values is difficult between studies as values are standardized, Ma et al. (2014) and Messer et al. (2006a, 2006b) all included 6 of the 10 same variables that were included in the NDI calculation for this study.

It was also of note that the best fit models for As and Pb were different, even though kriged concentrations of these metals were highly correlated in this sampling locations. Estimated soil Pb concentrations were associated with road coverage (a proxy for historic leaded gasoline use) in the study areas, whereas estimated soil As concentrations were associated with maternal SES measures as well as road coverage. Given that As in soils may originate from both natural and anthropogenic sources in these sampling areas (Aelion et al., 2013; Davis et al, 2009), the observed associations between As and SES measures may potentially be related to the homogeneity with regard to SES in the study population. Further investigation of the association between soil As and Pb concentrations and other individual level SES measures may help elucidate the findings of the current study related to maternal education and estimated soil As concentrations.

In models examining composite annual releases from As and Pb emitting facilities categorized by distance, direction, and combined distance/direction to block groups, the racial disparity in estimated soil As and Pb concentrations persisted in both As and Pb models. All significant distance, direction, and distance/direction combined parameter estimates were also in a negative direction. This suggests that not only were residential estimated soil As and Pb concentrations not positively associated with composite annual releases, but also that these distal releases (as well as the more proximal releases) did not greatly impact the magnitude of the racial disparity in either estimated soil As or Pb concentrations. Additionally, mean estimated soil As and Pb concentrations were lower for mothers living in block groups within close distances (or containing) As- or Pb-emitting TRI facilities. This could be related to atmospheric residences times of air emissions. However, more information would be needed to confirm this hypothesis.

Percent roads, a proxy for historic car exhaust emissions, was associated with estimated soil concentrations of both As and Pb in all models, and percent road parameter estimates were much greater than those for distance, direction, or distance/direction combined composite annual release variables. While releases from these TRI facilities are ongoing, and leaded gasoline has been phased out in the US, our findings show that the long-term historic use of leaded gasoline within residential areas of SC has the potential to currently impact human health. Regardless of the environmental source of As or Pb, however, black mothers in this study population, on average, lived in areas with higher soil As and Pb concentrations. These findings could be specific to the locations where samples were collected, but may reflect environmental inequality of residences of black mothers throughout SC. Investigating other social health determinants, such as racial residential segregation, may provide additional insight on why black mothers in the study populations lived in locations with higher estimated soil As and Pb concentrations.

It is acknowledged that this study has several limitations. For one, the study areas were chosen based on prevalence of ID/DD, which limits the generalizability of these results to the general population of mothers in SC. Also, any health behaviors or outcomes related to ID/DD prevalence may be higher in this population and should be considered with respect to the outcome investigated; this was confirmed by comparisons between study population mothers and all Medicaid mothers in SC for the same time period and under the same restriction/exclusion criteria. Additionally, given the observed importance of historical releases of metals (e.g., leaded gasoline) to current soil concentrations of these metals, examining locations of not only TRI facilities, but also historical facilities that may have emitted As and/or Pb by distance and direction may be warranted. Another uncertainty is that estimated soil As and Pb concentrations at maternal residences were used rather than measured soil concentrations at maternal residences; however, kriging is well-documented as an acceptable method for estimation of soil concentrations for a variety of contaminants, and is based on actual concentrations measured at known locations. Simplified methods for determining distance and direction from facilities, and for calculating composite annual releases from facilities, were used. Given the limitations associated with the confidentiality agreement (not knowing the actual maternal residence locations) and that this is the first time, to our knowledge, that facilities releases have been examined by both distance and direction in relation to locations of soil samples measured for metal concentrations, more refined analyses, including angular directions or a different categorization method, may be needed to effectively characterize the contribution of TRI emissions to As or Pb concentrations in residential soils.

Conclusions

Statistically significant racial disparities were observed in this study, with higher estimated concentrations of soil As and Pb at maternal residences for black mothers as compared to white mothers in this study population. These persisted after controlling for individual level and neighborhood level demographics, as well as possible sources of these metals in SC. The disparity was larger for Pb than for As. Percent block group area covered by roads was associated with elevated residential soil concentrations of both As and Pb in all adjusted models, and was more strongly associated with these metals in soils than composite annual TRI facility releases categorized by distance and/or direction. The results suggest the importance of both individual and neighborhood level characteristics to concentrations of these metals in residential soils.

Table 3.1 Mean estimated soil arsenic (As) and lead (Pb) concentrations (standard deviation) for maternal and neighborhood (United States Census 2000 block group) variables and p-values for differences in estimated soil As and Pb concentrations by category.

	No. mothers (%)	Soil As (mg/kg)		Soil Pb (mg/kg)	
		Mean (SD)	P-value[a]	Mean (SD)	P-value[a]
Study Population	8,108 (100)	4.9 (4.2)	NA[d]	58.2 (57.2)	NA
Race					
Black	5,252 (65)	5.6 (4.6)	<0.0001	64.4 (60.7)	<0.0001
White	2,856 (35)	3.5 (2.9)		46.8 (48.1)	
Education					
≥ High school	5,463 (67)	4.7 (4.2)	<0.0001	56.9 (58.0)	0.003
< High school	2,645 (33)	5.2 (4.3)		60.9 (55.4)	
Food stamps[b]					
Food stamps	4,837 (60)	5.2 (4.5)	<0.0001	58.7 (56.9)	0.33
No food stamps	3,271 (40)	4.4 (3.7)		57.4 (57.7)	
NDI[c]					
NDI < 4.8	4,046 (50)	3.5 (3.0)	<0.0001	46.5 (51.8)	<0.0001
NDI ≥ 4.8	4,062 (50)	6.3 (4.7)		69.8 (59.9)	

[a] P-values for comparisons of mean As and Pb concentrations via analysis of variance

[b] Mother received food stamps during pregnancy

[c] NDI: neighborhood deprivation index; standardized composite measure of 10 US Census 2000 block group variables (break in categories at median)

[d] NA: not applicable

Table 3.2 Means (standard deviation) and ranges of continuous neighborhood (United States Census 2000 block group) variables, parameter estimates (standard errors), and p-values for crude associations with estimated soil arsenic (As) and lead (Pb) concentrations.

		As		**Pb**	
	Mean (SD)	**Parameter estimate (SE)**	**P-value**[a]	**Parameter estimate (SE)**	**P-value**[a]
Percent roads (%)[b]	5.8 (3.4)	0.66 (0.08)	<0.0001	7.2 (0.17)	<0.0001
Age of home (years)[c]	33 (13)	0.16 (0.003)	<0.0001	1.8 (0.05)	<0.0001

[a] P-values for association between either As or Pb concentrations and continuous neighborhood level variables via simple linear regression analysis

[b] Percent of US Census 2000 block group area estimated to be covered by roads

[c] 2000 – US Census 2000 block group median year home built

Table 3.3A Parameter estimates (standard error) and p-values for risk factors of estimated soil arsenic (As) concentrations.

	Maternal race[a]	**Maternal education**[b]	**Food stamps**[c]	**NDI**[d]	**Percent roads**
Crude[e]	0.13 (0.04) <0.0001	NA[j]	NA	NA	NA
Model 1[f]	0.12 (0.04) 0.003	0.085 (0.03) 0.01	0.058 (0.03) 0.09	NA	NA
Model 2[g]	0.12 (0.04) 0.006	0.084 (0.03) 0.01	0.057 (0.03) 0.09	1.2 (0.28) <0.0001	NA
Model 3[h]	0.12 (0.04) 0.006	0.084 (0.03) 0.01	0.058 (0.03) 0.09	0.17 (0.29) 0.57	0.38 (0.04) <0.0001
Best Fit Model[i]	0.13 (0.04) 0.001	0.089 (0.03) 0.007	NA	NA	0.39 (0.04) <0.0001

[a] Non-Hispanic white mothers are the referents

[b] Mothers with less than a high school education are the referents

[c] Mothers who did not receive food stamps during pregnancy are the referents

[d] NDI: neighborhood deprivation index; categorized at median; mothers at/above referents

[e] Contains maternal race variable only

[f] Additionally adjusted for maternal education and food stamps

[g] Additionally adjusted for block group NDI

[h] Additionally adjusted for block group percent coverage of roads

[i] Best fit model after backwards selection process

[j] NA: not applicable

Table 3.3B Parameter estimates (standard error) and p-values for risk factors of estimated soil lead (Pb) concentrations.

	Maternal race[a]	**Maternal education[b]**	**Food stamps[c]**	**NDI[d]**	**Percent roads**
Crude[e]	2.2 (0.60) 0.0003	NA[j]	NA	NA	NA
Model 1[f]	2.3 (0.62) 0.0002	0.51 (0.48) 0.29	-0.29 (0.50) 0.57	NA	NA
Model 2[g]	2.2 (0.62) 0.0003	0.51 (0.48) 0.29	-0.29 (0.50) 0.56	9.4 (4.0) 0.02	NA
Model 3[h]	2.2 (0.62) 0.0004	0.50 (0.48) 0.30	-0.29 (0.50) 0.56	-5.4 (4.2) 0.29	5.3 (0.59) <0.0001
Best Fit Model[i]	2.1 (0.60) 0.0006	NA	NA	NA	5.0 (0.54) <0.0001

[a] Non-Hispanic white mothers are the referents

[b] Mothers with less than a high school education are the referents

[c] Mothers who did not receive food stamps during pregnancy are the referents

[d] NDI: neighborhood deprivation index; categorized at median; mothers at/above referents

[e] Contains maternal race variable only

[f] Additionally adjusted for maternal education and food stamps

[g] Additionally adjusted for block group NDI

[h] Additionally adjusted for block group percent coverage of roads

[i] Best fit model after backwards selection process

[j] NA: not applicable

Table 3.4 Parameter estimates (standard errors) for average composite annual releases of arsenic (As) and lead (Pb) from Environmental Protection Agency (EPA) Toxics Release Inventory (TRI) facilities categorized by distance and/or direction, and maternal race in As and Pb best fit models.

	As models[a]		**Pb models[a]**	
	Distance and/or direction	Maternal race	Distance and/or direction	Maternal race
Distance only				
≤5 km	-1.8×10^{-6} (3.0×10^{-6})	**0.13 (0.04)**	-0.0003 (0.0002)	**2.1 (0.60)**
6-10 km	-1.8×10^{-6} (2.1×10^{-6})	**0.13 (0.04)**	-0.00002 (0.00004)	**2.1 (0.60)**
11-20 km	**-2.4×10^{-6} (1.1×10^{-6})**	**0.13 (0.04)**	-0.00007 (0.00005)	**2.1 (0.60)**
>20 km	**2.2×10^{-6} (5.6×10^{-6})**	**0.13 (0.04)**	0.00005 (0.00003)	**2.1 (0.60)**
Direction only				
SW	**-8.8×10^{-7} (1.3×10^{-7})**	**0.14 (0.04)**	**-0.00003 (6.3×10^{-6})**	**2.1 (0.60)**
Distance/direction combined				
SW,≤5	-1.8×10^{-6} (3.0×10^{-6})	**0.13 (0.04)**	-0.0001 (0.0003)	**2.1 (0.60)**
SW,6-10	-2.3×10^{-6} (3.0×10^{-6})	**0.13 (0.04)**	0.0002 (0.0002)	**2.1 (0.60)**
SW,11-20	-2.7×10^{-6} (3.0×10^{-6})	**0.13 (0.04)**	0.0001 (0.0002)	**2.1 (0.60)**
SW,>20	**-8.3×10^{-7} (1.3×10^{-7})**	**0.14 (0.04)**	**-0.00003 (6.3×10^{-6})**	**2.1 (0.60)**

[a] Models additionally adjusted for maternal education (As models only) and block group percent coverage of roads

Bold indicates significant estimate (p<0.05)

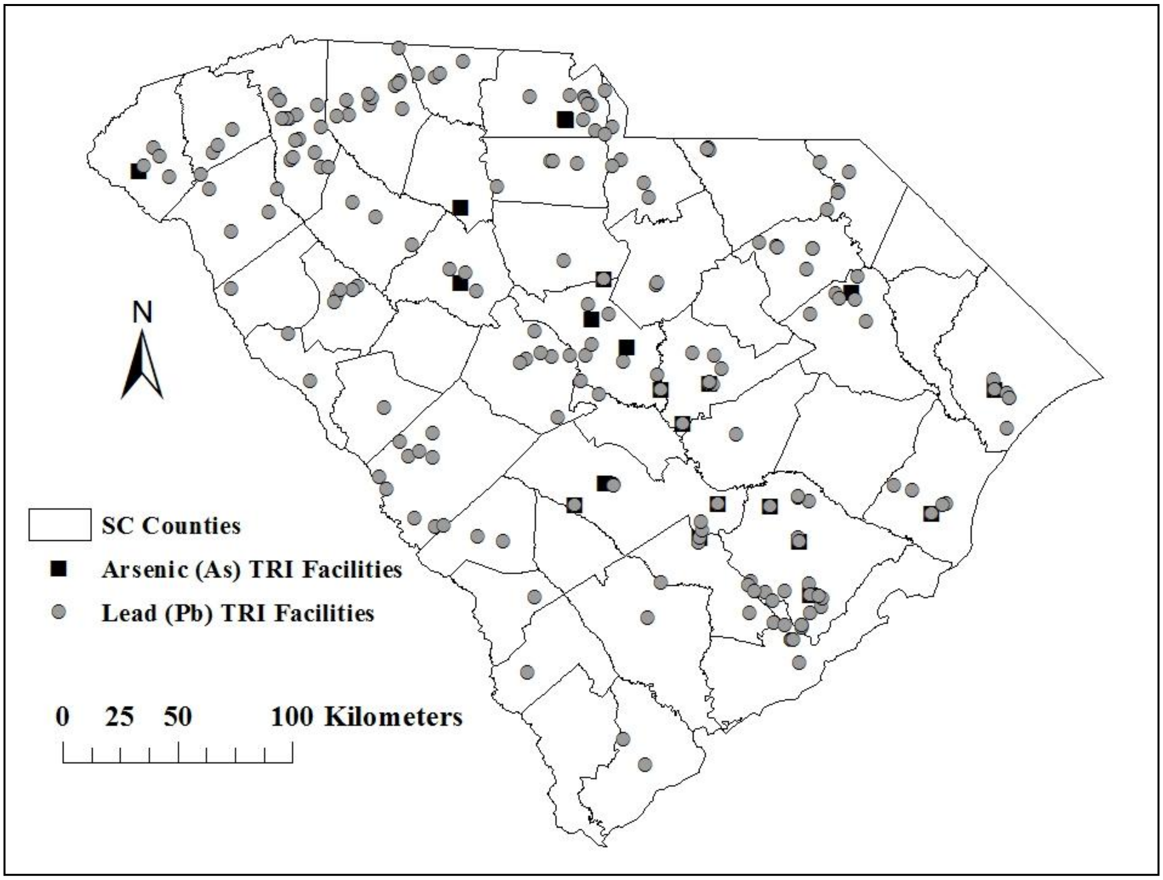

Figure 3.1 Locations of arsenic- (As) and lead- (Pb) emitting Environmental Protection Agency (EPA) Toxics Release Inventory (TRI) facilities reporting releases in South Carolina from 1996-2011.

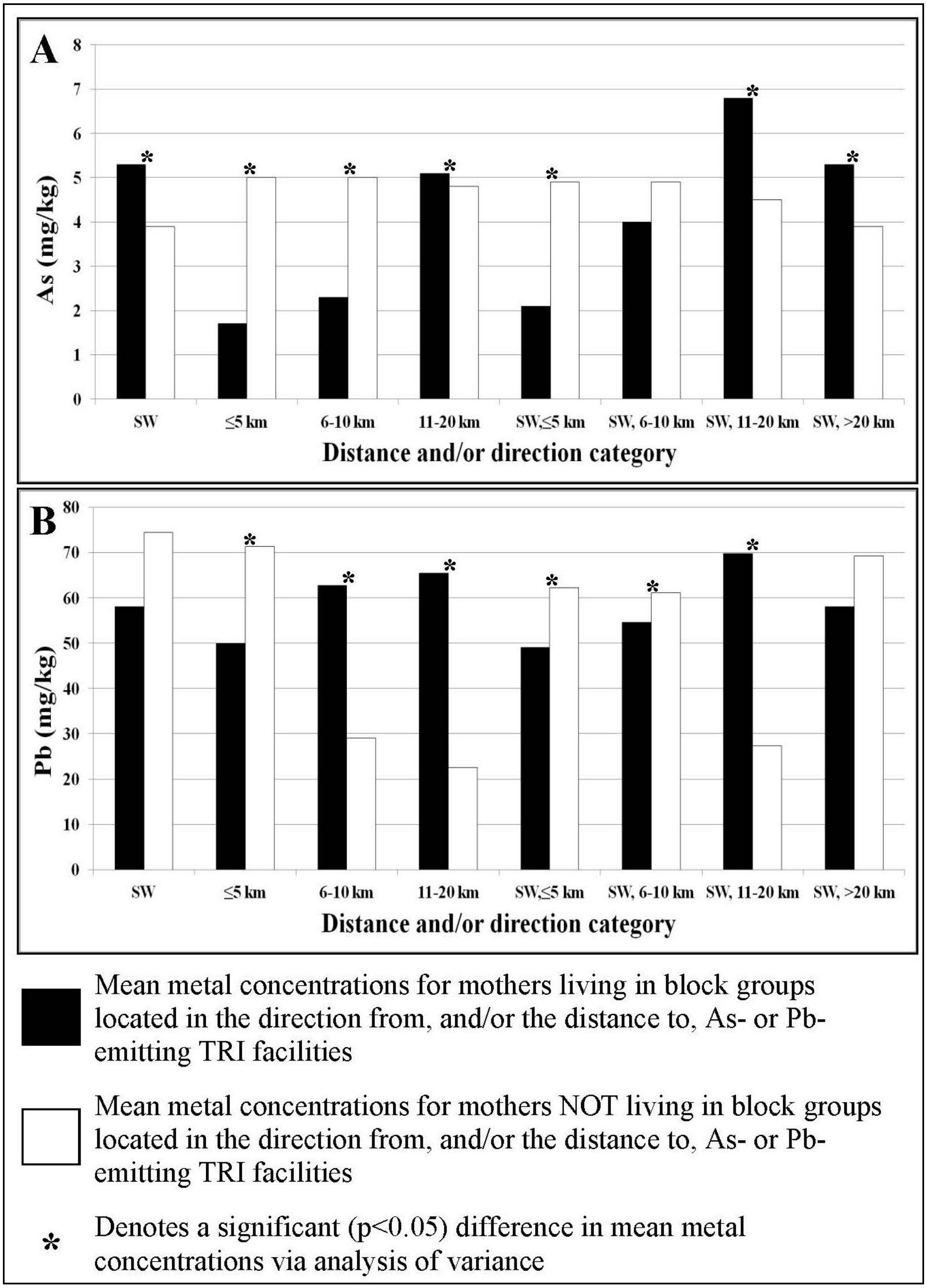

Figure 3.2A-B Comparisons of mean estimated soil A) arsenic (As) and B) lead (Pb) concentrations at maternal residences categorized by block group centroid distance and/or direction from As- or Pb-emitting Toxics Release Inventory (TRI) facilities.

CHAPTER 4

ASSOCIATIONS BETWEEN SOIL ARSENIC AND LEAD CONCENTRATIONS AND EARLY AND LATE PRETERM BIRTHS IN MOTHERS FROM SOUTH CAROLINA

Abstract

Associations between soil concentrations of arsenic (As) and lead (Pb), which were estimated at maternal residences using ordinary kriging, and early (<34 weeks of gestation) and late (34-36 weeks of gestation) preterm births in South Carolina (SC) Medicaid mothers (n=8,108) giving birth from 1996-2001 were investigated using birth certificate, Medicaid billing record, and Census 2000 data. Both maternal and neighborhood risk factors were controlled for, and effect modification of neighborhood deprivation and racial residential segregation were also examined. The prevalence of early and late preterm births in the study population was 3.2% and 7.6%, respectively. In crude models, As was significantly associated with both early (OR = 1.03, 95% CI: 1.01, 1.06) and late (OR = 1.03, 95% CI: 1.01, 1.04) preterm births, and Pb with weeks of gestation ($\beta = -0.001$, $p = 0.04$). However, these associations did not remain significant in models adjusted for individual level risk factors. Measures of neighborhood deprivation and racial residential segregation were not associated with early or later preterm birth in models, and these measures did not modify the association between estimated As and Pb soil concentrations these birth outcomes. However, recognized maternal risk factors (e.g., presence of infection) were significant, and were associated with higher odds of early as compared to late preterm births. While limited variability in our exposure and

neighborhood measures may have impacted our findings, further investigation of the role of potential exposure to soil As and Pb in both early and late preterm births is potentially warranted.

Introduction

Preterm birth, generally defined as birth at <37 weeks of gestation, is an important public health problem. In the United States (US), the 2010 preterm birth prevalence was 12% (Martin et al., 2012); for South Carolina (SC) in that same year, the prevalence was 14.2%, or 1.2 times higher (MOD, 2013). While late preterm birth rates (34-36 weeks of gestation) have declined in recent years in both the US and SC, early preterm birth (<34 weeks of gestation) rates have remained relatively unchanged (Martin et al., 2012). In SC from 2008-2012, late preterm birth prevalence rates fell from 8.3% to 7.9%, while early preterm birth rates remained steady at ~3.4% (SC DHEC, 2013). Risk factors for preterm birth are numerous, though research has focused on maternal demographics, behaviors, and health conditions during pregnancy (ACOG, 2001; Almario et al., 2009; Clausson et al., 1998; Dolan, 2010; Mann et al., 2010; Randis, 2010).

Exposure to environmental contaminants, including pesticides (Miranda et al., 2009; Pathak et al., 2010; Stillerman et al., 2008), metals (Sexton, 2012; Wigle et al., 2008), and those in air (Malmqvist et al., 2011; Miranda et al., 2009) have also been implicated in preterm birth. Metals are particularly important, as many are ubiquitous and relatively stable in the environment (Aelion et al., 2014; Marty and Blaisdell, 2000). More specifically, maternal exposure to both arsenic (As) and lead (Pb) has been found to be associated with preterm birth in geographically diverse populations (Andrews et al., 1994; Burris et al., 2011; Myers et al., 2010; Torres-Sanchez et al., 1999).

In addition to environmental exposures, social conditions of one's neighborhood also impact an individual's health outcomes (Braveman et al., 2011; Link and Phelan, 1995; Phelan et al., 2010). Neighborhood-level conditions, such as racial residential segregation, deprivation (a composite measure of different neighborhood aspects), education, and wealth, have all been implicated with respect to preterm birth (Bell et al., 2006; Kaufman et al., 2003; Mason et al., 2009; Messer et al., 2006a, 2008; O'Campo et al., 2008). Risk for preterm birth is higher in poor, predominately minority, and racially segregated neighborhoods, and these associations are often independent of a mother's individual risk factors (Diez Roux and Mair, 2010). Additionally, higher concentrations of metals such as arsenic (As) and lead (Pb) have also been measured in similar populations (low SES and high minority; Aelion et al., 2012, 2013; Campanella and Mielke, 2008; Diawara et al., 2006). These neighborhood measures have also been found to act as effect modifiers in associations between environmental exposures and birth outcomes (Bellinger, 2000; Limousi et al., 2014).

The main objective of this study was to examine associations between estimated soil concentrations of As and Pb at maternal residences and both early and late preterm births in a Medicaid population of mothers in SC, after controlling for individual and neighborhood level risk factors. Secondly, proxy measures of racial residential segregation (the isolation index) and neighborhood deprivation (the neighborhood deprivation index, or NDI) were investigated to determine if they were associated with early or late preterm birth in the study population, and if these neighborhood measures modified the relationships between As and Pb and preterm birth. It was hypothesized that if neighborhoods with higher deprivation and more isolation have higher concentrations of these metals in soils, then these neighborhood measures could modify the association between metal concentrations and early and late preterm birth. This investigation is novel in that most studies on preterm birth that examine the potential for exposure to environmental contaminants like As and Pb do not control for maternal medical and behavioral risk factors, nor do they take neighborhood characteristics into account. In addition, most studies examining these exposures do not investigate individuals living in residential, relatively uncontaminated locations. However, low level exposure to both of these metals has been found to be detrimental to human health (McDermott et al., 2011; Moon et al., 2013; Xie et al., 2013).

Methods

Study Design

This study utilized data sets from a retrospective cohort study initiated in 2006 examining associations between potential maternal exposure to metals in residential soils and both intellectual disability (ID) and developmental delay (DD) outcomes in children within a Medicaid population of mother-child pairs. For the retrospective cohort study, information on mothers and children who were enrolled in Medicaid during pregnancy in SC from 1996-2001 was obtained from SC birth certificates, Medicaid billing records, SC Department of Social Services (SC DSS) files, and the US Census 2000 (Kim et al., 2009, 2010; Liu et al., 2010; McDermott et al., 2011, 2014a, 2014b; Zhen et al., 2008, 2009). Medicaid, a federal assistance program that is managed by individual states, offers insurance coverage to income qualifying, medically verified pregnant women throughout pregnancy and up to 60 days postpartum; current pregnancy enrollment requires women and their families to be at 185% of the poverty level or less (SC DHHS, 2013). Currently, approximately half of all women who give birth in SC are enrolled in Medicaid (SC DHEC, 2013).

From 2006 to 2011, 11 areas in SC were selected for and sampled based on the prevalence of ID/DD in SC Medicaid mothers, with nine of the areas having an ID/DD prevalence that was significantly above the statewide average for all Medicaid mothers (3.5%, Zhen et al., 2008). These areas were identified using Bayesian local-likelihood cluster analysis (Zhen et al., 2008, 2009), were based on the geocoded locations of maternal residences by month of pregnancy, and were located throughout SC. Of the 11 locations, five were considered urban, five rural, and one was mixed urban/rural (US Department of Commerce, 2002); additional sampling area details are provided in Table 4.1. A confidentially agreement precludes release of the actual geographical locations of the sampling areas, and did not allow for sampling at the actual locations of maternal residences.

In each of the sampling areas, a rectangular-shaped region (median area of 100 km^2) was identified and a regular 120-node grid was laid out; distances between grid nodes ranged from 0.5-3 km (Aelion et al., 2012, 2013, 2014; Davis et al., 2014). Single grab surface soil samples (~25 g) were collected as close to each grid node as possible and geographic coordinates of the sample location were recorded using a GPS device. Soil samples were analyzed for nine metals, including total As and Pb, using inductively coupled plasma optical emission spectroscopy (ICP-OES) by an independent environmental laboratory (Aelion et al., 2007, 2008, 2009a, 2009b, 2012, 2013, 2014; Davis et al., 2009, 2014). All concentrations were reported in mg/kg dry weight and non-detects were set to ½ the minimum detection limit for that analysis. These measured soil metal concentrations, along with their corresponding geocoded sampling location, were then used to krige concentrations at each mother's geocoded address by month of pregnancy. Kriging is a spatial interpolation method that computes values at missing locations using weighted (based on covariance values) averages from nearby locations. For this study, only As and Pb kriged concentrations at the mother's residence at month 6 of pregnancy were used, and detailed kriging methodology is available in Zhen et al. (2008, 2009).

Study Population

The study population was composed of mothers of singletons who gave birth while enrolled in Medicaid from 1996-2001, and who were living in one of 11 areas sampled for soil metal concentrations at month 6 of pregnancy. Choosing this month maximized the study population because: 1) most mothers would be aware of their pregnancy and have enrolled in Medicaid, and 2) most mothers would be captured before they had experienced a preterm birth. Mothers were excluded if they were missing maternal age, maternal race, baby birth weight, baby gender and gestational age (~1.3% of mothers). Mothers were excluded if their infant had either an improbable clinical estimate of gestation (<21 weeks, n=15), or an improbable birth weight (<500 g, n=39). The analysis was restricted to only black and white mothers, to mothers whose residence at month 6 of pregnancy was spatially linked with the US Census 2000 block group in which the residence was located, and to only the first birth of a mother (temporally), if she gave birth to more than one child during the study period. Maternal education was imputed for mothers missing this data (14%) using the maximum likelihood method (Allison, 2012). Figure 4.1 presents a flow chart of steps used to reach the final study population of mother-child pairs (n=8,108).

Variables

The main outcome of interest was preterm birth, which was divided into early preterm births (<34 weeks of gestation) and late preterm births (34-36 weeks of gestation); term births (≥37 weeks of gestation) were the reference group. Calculations were based on the clinical estimate of gestation from birth certificates. The continuous outcome of weeks of gestation was also examined. The main exposures of interest were kriged As and Pb soil concentrations (in mg/kg); these were modeled as continuous measures.

Individual level risk factors were obtained from SC birth certificates, Medicaid billing records, and SC DSS records, and were chosen based on a significant ($p<0.05$) crude association with As and/or Pb concentrations. All variables that were identified were also assessed for collinearity, which included examination of variance inflation factor (VIF) values (a value of ≥10 was used as a cutoff for to identify variables that may have posed a collinearity issue), and the proportion of variance of the estimate accounted for by each principal component for all variables in a multiple regression model with continuous weeks of gestation as the outcome (proportion of variance >0.5 to two or more variables). Variables obtained from birth certificates were maternal race (white mothers the reference level), maternal age (continuous), maternal education (coded as less than high school diploma or equivalent and at or above a high school diploma, with a high school diploma or higher the reference level), parity (ordinal), baby gender (female gender the reference level), adequate prenatal care (coded as beginning within or after the first trimester, with first trimester prenatal care the reference level), and tobacco use during pregnancy (yes versus no, with no tobacco use the reference level). Medicaid billing records, along with birth certificates, were also utilized to identify mothers with the presence of any one of the following infections during pregnancy: bacterial urinary tract infection, genital herpes, gonorrhea, chlamydia, trichomoniasis, chorioamnionitis, candidiasis, cervicitis, and pelvic inflammatory disease; mothers with no reported infection were the reference level. Mothers who received food stamps during pregnancy were identified using data from the SC DSS, and mothers that did not receive food stamps during pregnancy were set as the reference level.

Initially, 20 neighborhood (US Census 2000 block group) level variables were examined to generate each block group’s NDI as described by Messer et al. (2006b). A principal component analysis (PCA) was run on these 20 variables to determine factor loadings. Based on the median loading for the first factor (0.4991), the following 10 variables with loadings greater than or equal to the median were retained: proportion of the population with less than a high school education, proportion of population unemployed, proportion of households renter-occupied, proportion of households crowded, proportion of female headed households with dependent children, proportion of households in poverty, proportion of households with an income less than $30,000 per year, proportion of households on public assistance, proportion of households with no car, and proportion of the population identifying as non-Hispanic black. The PCA was then rerun, each of the variables was weighted by their communality (covariance) estimates, and all were summed to create a continuous NDI variable. Block groups were designated as majority urban if >50% of the population of the block group lived in urbanized areas or urbanized clusters, and block groups that did not have a majority urban population was set as the reference level (US Census, 2002).

A measure of racial residential segregation, the isolation index, was calculated using a formula described by Massey and Denton (1988). The isolation index (as calculated here) is a weighted average of each block group's population of non-Hispanic blacks, and represents the probability of non-Hispanics blacks living in the same Census tract. The formula used was:

$$ {}_{x}P^{*}_{x} = \Sigma[x_i/X]*[x_i/t_i] \qquad (1) $$

where x_i = total non-Hispanic black population of the US Census 2000 block group, X = total non-Hispanic black population (total number) of the US Census 2000 tract, and t_i = total population of the US Census 2000 block group. Values range from 0-1, with values closer to 1 suggesting more isolation (i.e., more segregation). While Massy and Denton's (1988) example formula used metropolitan statistical area (MSA) population as the denominator and studies have focused on segregation at this geographic level (Bell et al., 2006; Kramer et al., 2010a), measuring segregation at smaller geographic levels (like the Census tract or block group) has been implemented in research of rural areas (Lichter et al., 2007). Given our sampling locations were both urban and rural, and, therefore, not all located within an MSA, it made sense to investigate isolation at a level that was comparable for all sampling locations.

Statistical Analyses

SAS Version 9.4 (SAS Institute, 2010) was used for all statistical analyses, and hierarchical modeling was used to account for individuals living in the same US Census 2000 block group. All variables were first compared individually by birth category to examine if these variables were significantly associated with birth category. An analysis of variance was used for continuous variables and a chi-square test of independence was used for categorical variables; given the three birth categories, a test of trend was also examined for both categorical and continuous exposures.

For all models with the categorical birth outcome, PROC GLIMIX was used, with a cumulative logit link function, a multinomial distribution for the multiple birth categories, and Laplace's estimation. For models with the continuous weeks of gestation outcome, PROC MIXDED was used with maximum likelihood estimation and Satterthwaite's method for determination of degrees of freedom; for both categorical and continuous outcomes, the slope of the intercept was allowed to vary by Census block group (random intercept). Given that As and Pb soil concentrations were highly correlated in the data set (0.67, $p<0.0001$), it was decided to model these exposure separately. Three models were then run for each of the birth outcome measures (categorical and continuous). Model 1 included all individual level risk factors. Model 2 further included the NDI, isolation index, and if the block group population was majority urban, and Model 3 further included interactions between either As and Pb concentrations with both the NDI and isolation index. A backwards selection process was then run on Model 3 for each main exposure to determine the best fit models for the outcomes; this was done for estimated soil As and Pb concentrations separately. A p-value of 0.05 was used to determine statistical significance.

Results

The median (range) of kriged As and Pb concentrations at the mother's residence at month 6 of pregnancy was 4.3 (0.22-26.6 mg/kg) and 38.4 mg/kg (1.5-286 mg/kg), respectively. The percentages of early and late preterm births in the study population were 3.2% and 7.6%, respectively. Percentages of early and late preterm births for all other Medicaid mothers giving birth in SC while enrolled in Medicaid from 1996-2001 (also restricted to first babies, n=71,821) were similar to what was observed in the study population (3.0 and 7.1%, respectively). Compared to other SC Medicaid mothers, study population mothers were significantly more likely to be black ($p<0.001$), have less than a high school diploma or equivalent ($p<0.0001$), receive food stamps during pregnancy ($p<0.0001$), report that they did not use tobacco during pregnancy ($p<0.0001$), and start prenatal care in the first trimester ($p<0.0001$; Appendix B, Table B.1). Additionally, study population mothers were more likely to live in block groups with a majority urban population ($p<0.0001$), and with higher average NDI and isolation indices (all p-values <0.0001; Appendix B, Table B.2).

Comparisons of all risk factors for preterm birth categories are shown in Tables 4.2 (categorical variables) and 4.3 (continuous variables). Significant differences by birth category were observed for maternal race, beginning prenatal care within the first trimester, and infection (Table 4.2). For continuous variables, mean maternal age and NDI values for mothers with early preterm births was significantly higher than those for term birth mothers (Table 4.3). The test of trend was significant for maternal race, beginning prenatal care within the first trimester, infection, and both the NDI and isolation indices (all p-values <0.03).

Odds ratios (OR) and 95% confidence intervals (95% CI) for associations between birth categories and As and Pb concentrations in Models 1-3 are shown in Tables 4.4A and 4.4B. Only As was significantly associated with preterm birth in crude models, and was significant for both early and late preterm births (Table 4.4A). For every 1 mg/kg increase in estimated soil As concentrations at the mother's residence at month 6 of pregnancy, the odds of early and late preterm birth were 1.03 times higher (95% CI: 1.01, 1.06) than for term birth. After adjusting for other risk factors, the association between As and birth categories did not remain significant. The OR estimate for Pb was null in all models (Table 4.4B).

Neither the NDI nor isolation index was significantly associated with odds of either early or late preterm birth in As or Pb models (Tables 4.4A and 4.4B). However, the OR estimates for the isolation index did follow a pattern of note. For late preterm birth in As models, the OR estimates were 1.00 and 1.11 for Models 2 and 3, respectively; however, the isolation index was protective for early preterm birth (OR estimates of 0.58 and 0.49 for Models 2 and 3, respectively; Table 4.4A). This pattern was similar for Pb models (Table 4.4B). Interactions between metal concentrations and both the NDI and isolation index were insignificant in Model 3 for both As and Pb exposures (data not shown).

In Models 1-3, beginning prenatal care after the first trimester was associated with increased odds of early preterm birth for As (Model 3 OR = 1.41, 95% CI: 1.07, 1.85) and Pb (Model 3 OR = 1.42, 95% CI: 1.08, 1.87). Maternal age was also associated with increased odds of early preterm birth for both As (Model 3 OR = 1.05, 95% CI: 1.02, 1.08) and Pb (Model 3 OR = 1.05, 95% CI: 1.02, 1.07) in Models 1-3. Maternal race was significantly associated with preterm birth in As and Pb Models 1-3, and OR estimates were higher for early as compared to late preterm birth. For example, in Model 3 for As, the odds of early preterm birth for black mothers, after adjusting for additional risk factors, was 1.63 (95% CI: 1.15, 2.32); for late preterm births, the OR estimate was 1.61 (95% CI: 1.28, 2.02). Presence of infection was also associated with increased odds of both early and late preterm births in Models 1-3 for As and Pb. Similar to maternal race, the infection OR estimates for early preterm birth were higher (Pb Model 3 OR = 1.86, 95% CI: 1.41, 2.45) than for late preterm birth (Pb Model 3 OR = 1.26, 95% CI: 1.04, 1.54). In adjusted models, OR estimates for significant risk factors for early and late preterm births were similar in both As and Pb models, suggesting limited impact of these main exposure measures on explaining variation of preterm birth in the study population, after adjusting for maternal risk factors. Best fit models for both As and Pb exposures and the categorical preterm birth outcomes additionally included maternal race, presence of infection, adequacy of prenatal care, and maternal age (data not shown).

In models examining the continuous weeks of gestation outcome, results were similar to associations observed for the categorical preterm birth variable (Table 4.5). Higher As concentrations were significantly negatively associated with weeks of gestation in the crude model (-0.019; p = 0.002); the same was true for the crude Pb model though the estimate was smaller (-0.00095, p = 0.04). For As in the crude model, a 10 mg/kg increase in estimated soil concentrations was associated with a gestation decrease of ~1 day; for Pb, a 100 mg/kg increase in estimated soil concentrations was associated with a gestation decrease of only 0.67 days.

Neighborhood level covariates were not significant in either As or Pb Models 2 and 3, and the size and direction of parameter estimates were variable (Table 4.5). However, the interaction between NDI and Pb was significant in Model 3 ($\beta = -0.00044$; $p = 0.046$). This suggests that the association between weeks of gestation and estimated soil Pb concentrations was modified by block group NDI. For As and Pb in Models 1-3, maternal race, maternal age, and presence of infection were significantly associated with weeks of gestation (data not shown). Mothers who were black, or who were diagnosed with an infection during pregnancy, gave birth on average 2-3 days sooner than mothers who were white and who were not diagnosed with an infection during pregnancy, after adjusting for other individual level risk factors. Older mothers were also significantly more likely to give birth sooner, but parameter estimates were small in models (data not shown). The best fit model for As additionally contained maternal race, maternal age, maternal education, receipt of food stamps, presence of infection, and the isolation index; for Pb, the best fit model contained maternal race, maternal age, receipt of food stamps, the isolation index, and majority urban block group population (data not shown).

Discussion

A statistically significant association between either As or Pb estimated soil concentrations and preterm birth categories or weeks of gestation was not observed for the study population, after adjusting for individual level risk factors. The exposures of interest were only associated with preterm birth in crude models; higher As soil concentrations were associated with increased odds of both early and late preterm birth, and higher estimated concentrations of either soil As or Pb were associated with decreased weeks of gestation. For both outcomes, however, effect estimates were small in magnitude. While associations between As and Pb exposure and preterm birth have been examined in other studies (Ahmad et al., 2001; Andrews et al., 1994; Burris et al., 2011; Myers et al., 2010; Torres-Sanchez et al., 1999), exposure and outcome measures differ from those that were investigated in the current study. In addition, reported associations have been inconsistent.

For As, studies have generally focused on chronic or high concentration exposure to naturally occurring As in water. In Bangladesh, Ahmad et al. (2001) observed a significantly higher mean number of preterm births in a village exposed to high As concentrations in well water, as compared to an unexposed village ($p=0.018$), as well as in women exposed to high concentrations of drinking water for ≥15 years compared to those exposed to high As concentrations for a shorter period of time ($p=0.02$). However, Mukherjee et al. (2005), Myers et al. (2010), and Yang et al. (2003) did not observe higher means or rates of preterm birth in exposed populations of mothers using similar water As exposure measures in India, China, and Taiwan, respectively. None of these studies controlled for any additional preterm birth risk factors other than maternal demographics, indicating that their results may be different if adjusting for the risk factors used in the current study.

In studies examining the role of Pb in preterm birth, maternal blood, cord blood, and placental samples have commonly been analyzed for Pb, and results have, as with As, been inconsistent. Jelliffe-Pawlowski et al. (2006) reported increased odds (OR = 3.2) of preterm birth in California mothers with prenatal blood Pb concentrations ≥10 µg/dL, and McMichael et al. (1986) observed a preterm birth risk ratio of 4.4 for mothers with blood Pb concentrations >14 µg/dL who were living near a Pb smelter in Australia, as compared to mothers with blood Pb concentrations ≤8 µg/dL. Torres-Sanchez et al. (1999) found that odds of preterm birth were higher for Mexican mothers with cord blood Pb concentrations ≥5.1 µg/dL, though only in primiparous mothers, while Sowers et al. (2002) did not observe a significant association between maternal blood Pb concentrations and weeks of gestation in a Medicaid population of mothers in New Jersey. Again, the majority of these studies controlled only for maternal demographics, not maternal conditions or behaviors during pregnancy as in the current study.

Even though research has shown that associations between As and Pb exposure and preterm birth are variable, human exposure to As and Pb can induce oxidative stress, which is thought to be one potential mechanism that can result in preterm birth. Ahamed et al. (2009) found significantly higher levels of placental oxidative stress markers in a population of Indian mothers giving birth preterm as compared to mothers giving birth at term, and reported that placental Pb concentrations were significantly correlated with levels of oxidative stress markers. While Ahmed et al. (2011) observed that As concentrations in cord blood and placental tissue were associated with oxidative stress markers in mothers, they did not examine relations of either As concentrations or oxidative stress markers with gestational age. Though oxidative stress markers were not measured in the study population, further examination of the role of As and Pb exposures as causative agents of oxidative stress, and effects on preterm birth, is warranted.

Other important factors in this study relate to the exposure measures, and ranges of the estimated As and Pb soil concentrations. While a biological exposure measure for these metals is generally preferred, studies have shown that biological and environmental concentrations of these metals are often correlated. For example, urinary As concentrations measured in a population exposed to As in soils due to mining in Australia were modestly correlated (r = 0.39), though the correlation coefficient was stronger (r = 0.64) when they limited the sample to just those with individuals with soil As concentrations >100 mg/kg (Hinwood et al., 2004). In New Orleans, LA, USA, soil and blood Pb concentrations in children were found to be associated in numerous studies (Mielke et al., 1997, 2007; Zahran et al., 2011). Soil concentrations may also underestimate the potential for exposure, as soil contaminants can accumulate in household dust over time. This can result in higher contaminant concentrations in indoor dust as compared to outdoor soils. Zota et al. (2011) looked at soil and dust Pb concentrations at ~60 homes in Ottawa County, OK, USA, and found that dust As and Pb concentrations were higher than soil As and Pb concentration in approximately half of the homes. In Pb contaminated soils of Torreón, Mexico, due to smelter activities, the median soil Pb concentration was 374 µg/g; in comparison, the median Pb dust concentrations was 1,902 µg/m^2 (Soto-Jimenez and Flegal, 2011). Therefore, estimated soil As and Pb concentrations may underestimate potential exposure to the mothers in the study population, and this may have contributed to both the null and small effect estimates in this study.

An additional byproduct of kriging, which provided the estimated soil As and Pb concentrations used in the current study, is smoothing of estimates across the spatial area of interest. This may have reduced the variability in exposure measures, which could also potentially explain these null findings. A subset of authors (Aelion et al., 2008a, 2008b, 2012, 2013; Davis et al., 2009, 2014) of this current paper utilized the actual measured soil As and Pb concentrations from these 11 sampling areas rather than the kriged concentrations. In these studies, reported ranges of both soil As (0.1 to 64.5 mg/kg) and Pb (0.81 to 2,760 mg/kg) concentrations were much greater than the ranges of estimated soil As and Pb concentrations at maternal residences at month 6 of pregnancy for the study population in the current study. Other studies examining As and Pb soil concentrations in SC reported smaller ranges of concentration, potentially due to fewer samples collected and analyzed. For example, Shacklette and Boerngen (1984) reported soil As concentrations ranging from 0-4.1 mg/kg, and Pb concentrations of ≤10 mg/kg, while Canova (1999) reported ranges of 0-210 mg/kg and 0-200 mg/kg for soil As and Pb, respectively. Given the spatial variability inherent in soil metal concentrations (Aelion et al., 2014), using measured soil concentrations at the location where exposure would most likely occur (i.e., at maternal residences) would be optimal.

The neighborhood measures (NDI, isolation, and majority urban) were not associated with preterm birth categories in any models in this study, and only NDI was different for birth categories in the crude analysis. Additionally, neither NDI nor the isolation index modified the association between estimated soil As and Pb concentrations and birth outcomes. The method employed for choosing sampling locations may have limited the variability of these measures within the study population; the coefficient of variation of both the NDI and isolation index for all SC block groups was greater than for those block groups that contained study population mothers; this suggests limited variability in both measures for study population mothers. Additionally, many studies examining the isolation index consider values ≤0.3 to be very low (Bell et al., 2006; Mendez et al., 2014), and the mean isolation index (0.21) for the study population in the current study was within this category. While comparisons between NDI values are more difficult as they are standardized, the US Census variables that were used to calculate the NDI can be compared. Compared to three other studies where the NDI was examined, proportion of the populations with less than a high school diploma, proportion of the population unemployed, proportion households headed by females with dependent children, proportion of households in poverty, proportion of households with income <$30,000 per year, and proportion of households on public assistance were included in all NDI calculations (Ma et al., 2014; Messer et al., 2006a, 2006b). In contrast, proportion of the population identifying as non-Hispanic black was only included in the NDI calculation for the current study. Additionally variability of the NDI in the study population was less than that of all block groups in SC. This limited variation in both the isolation index and the NDI may have also impacted the ability to observe a significant effect modification between these exposures and outcomes, though they have been observed in other studies (Bellinger, 2000; Limousi et al., 2014).

Well-known risk factors for preterm birth, including maternal race and age, starting prenatal care after the first trimester, and infection, were all strongly associated with early and late preterm births in this study. For all risk factors, ORs and parameter estimates were greater for early preterm birth, suggesting these risk factors may be especially important for those births at <34 weeks. In a report on a California case-control study of very preterm birth (categorized as <34 weeks for non-Hispanic black mothers and <32 weeks for non-Hispanic white mothers), preliminary results showed that case black mothers were significantly more likely to be diagnosed with bacterial vaginosis or chlamydia (p<0.01) than case white mothers, and that 12% of case black mothers began prenatal care after the first trimester as compared to 3.4% of white mothers (Kharrazi et al., 2012). Kramer and Hogue (2009) also reported on these particular risk factors in a review of racial disparities of very preterm births.

It is acknowledged that there are several limitations to this study. This is a special population that is potentially more homogenous that the general population of mothers in SC; therefore, these results may be less generalizable. Also, this subset of Medicaid mothers was different than all Medicaid mothers in SC with respect to some risk factors/covariates examined, most likely due to how the sampling areas were selected. Exposure to As or Pb was also not directly measured, and spatially interpolated estimates of metal concentrations at the maternal residence were used. Unfortunately, privacy concerns did not allow sampling at the maternal residence, and obtaining biological samples was not feasible given the retrospective nature of the study. These exposure limitations may have contributed to the null findings with respect to Pb soil concentrations and both early and late preterm births, as well as the lack of significance of both As and Pb estimated soil concentrations in adjusted models. However, findings of a significant association between As and both early and late preterm births, and Pb and weeks of gestation, in crude models deserves further attention, and should be investigated using more direct exposure measures.

Conclusions

In this study population, soil As and Pb concentrations were not associated with increased odds of early or late preterm births, after adjusting for additional individual and neighborhood level risk factors. These null findings may be attributable to the exposure measure or study population characteristics, and further studies in this high-risk population throughout SC should examine more accurate environmental (e.g., measured As and Pb concentrations in composite soil samples at the maternal residence) or biological (e.g., maternal blood or fingernails) measures of As and Pb. None of the neighborhood measures predicted early or late preterm birth, which may be due to limited variation of these measures within the study population. Some maternal risk factors were significant risk factors for early and late preterm births, with larger estimates for early preterm birth. These findings do indicate that further examination of exposure to As and Pb using additional exposure measures, in this and in other study populations, in larger geographic areas, and in areas with more variation in neighborhood measures may be warranted.

Table 4.1 Sampling area type, date sampled, and approximate area.

Sampling Area	Case or Control[a]	Month/Year Sampled	Approximate Area (km^2)
Area 1	Control	06/2006	490
Area 2	Case	12/2006	120
Area 3	Case	07/2007	100
Area 4	Case	11/2007	130
Area 5	Case	04/2008	60
Area 6	Case	07/2008	90
Area 27	Case	07/2010	100
Area 23	Case	12/2010	80
Area 22	Case	01/2011	110
Area 31	Case	06/2011	80
Area 99	Control	10/2011	100

[a] Case: Intellectual disability (ID) and/or developmental delay (DD) prevalence rate significantly ($p<0.05$) higher than the state background rate for all SC Medicaid mothers; Control: ID/DD prevalence rate not significantly higher than state background rate

Table 4.2 Number (percent) of mothers for categorical variables by preterm birth category, and p-values of category comparisons.

	Early preterm birth (n=255)		**Late preterm birth (n=617)**		**Term birth (n=7,236)**		**P-value[a]**
	Yes	No	Yes	No	Yes	No	
Mother non-Hispanic black	191 (75)	64 (25)	452 (73)	165 (27)	4,609 (64)	2,627 (36)	<0.0001**
Mother completed high school	172 (67)	83 (33)	403 (65)	214 (35)	4,888 (67)	2,348 (32)	0.52
Received food stamps	155 (61)	100 (39)	382 (62)	235 (38)	4,300 (59)	2,936 (41)	0.45
Male baby	130 (51)	125 (49)	292 (47)	325 (53)	3,500 (48)	3,736 (52)	0.62
Pregnancy tobacco use	40 (16)	215 (84)	92 (15)	525 (85)	1,205 (17)	6,031 (83)	0.50
First trimester prenatal care	173 (68)	82 (32)	458 (74)	159 (26)	5,419 (75)	1,817 (25)	0.04**
Infection[b]	81 (32)	174 (68)	151 (24)	466 (76)	1,409 (19)	5,827 (81)	<0.0001**
Majority population urban[c]	227 (89)	28 (11)	547 (89)	70 (11)	6,350 (88)	886 (12)	0.68

[a] Chi-square test of independence

[b] Includes bacterial urinary tract infection, genital herpes, gonorrhea, chlamydia, trichomoniasis, chorioamnionitis, candidiasis, cervicitis, and pelvic inflammatory disease

[c] Mother's residence at month 6 of pregnancy was located in a block group where >50% of the population lived in urban areas

**Denotes significant difference ($p<0.05$)

Table 4.3 Mean (standard deviation) for continuous variables by preterm birth category, and p-values of category comparisons.

	Early preterm birth (n=255)	**Late preterm birth (n=617)**	**Term birth (n=7,236)**	**P-value[a]**
Maternal age	23.6 (6.0)	22.7 (5.7)	22.6 (5.4)	0.008**
Parity	0.9 (1.3)	0.8 (1.2)	0.8 (1.1)	0.17
NDI[b]	5.5 (2.4)	5.4 (2.4)	5.2 (2.4)	0.008**
Isolation index	0.22 (0.18)	0.22 (0.19)	0.21 (0.19)	0.11

[a] Analysis of variance

[b] NDI: neighborhood deprivation index; composite measure based on 10 United States Census 2000 block group variables

**Denotes significant difference at the $p<0.05$ level

Table 4.4A Odds ratios (95% confidence interval) for arsenic (As), the neighborhood deprivation index (NDI) and the isolation index in the crude model, and Models 1-3, for preterm birth categories[a].

	Early preterm birth			**Late preterm birth**		
	As	**NDI**	**Isolation**	**As**	**NDI**	**Isolation**
Crude[b]	1.03 (1.01, 1.06)**	NA[f]	NA	1.03 (1.01, 1.04)**	NA	NA
Model 1[c]	1.01 (0.99, 1.04)	NA	NA	1.01 (0.99, 1.03)	NA	NA
Model 2[d]	1.02 (0.99, 1.05)	1.04 (0.96, 1.11)	0.58 (0.24, 1.36)	1.02 (0.99, 1.04)	0.98 (0.94, 1.03)	1.00 (0.57,1.75)
Model 3[e]	1.02 (0.99, 1.06)	1.05 (0.97, 1.14)	0.49 (0.19, 1.30)	1.02 (0.99, 1.04)	0.98 (0.93, 1.03)	1.11 (0.61, 2.04)

[a] Term births are the reference group

[b] Includes only estimated soil As concentrations

[c] Further includes all individual level covariates (maternal race, maternal education, maternal age, parity, receipt of food stamps, baby gender, pregnancy tobacco use, adequacy of prenatal care, and infection)

[d] Further includes all block group level covariates (NDI, isolation index, and majority urban)

[e] Further includes interactions of As with NDI and the isolation index

[f] NA: not applicable

**Denotes significant difference at $p<0.05$

Table 4.4B Odds ratios (95% confidence interval) for lead (Pb), the neighborhood deprivation index (NDI) and the isolation index in the crude model, and Models 1-3, for preterm birth categories[a].

	Early preterm birth			Late preterm birth		
	Pb	**NDI**	**Isolation**	**Pb**	**NDI**	**Isolation**
Crude[b]	1.00 (1.00, 1.00)	NA[f]	NA	1.00 (1.00, 1.00)	NA	NA
Model 1[c]	1.00 (0.99, 1.00)	NA	NA	1.00 (1.00, 1.00)	NA	NA
Model 2[d]	1.00 (0.99, 1.00)	1.04 (0.97, 1.12)	0.57 (0.24, 1.36)	1.00 (1.00, 1.00)	0.99 (0.94, 1.04)	1.00 (0.57, 1.74)
Model 3[e]	1.00 (0.99, 1.00)	1.04 (0.97, 1.12)	0.57 (0.23, 1.43)	1.00 (1.00, 1.00)	0.98 (0.93, 1.03)	1.05 (0.58, 1.90)

[a] Term births are the reference group

[b] Includes only estimated soil Pb concentrations

[c] Further includes all individual level covariates (maternal race, maternal education, maternal age, parity, receipt of food stamps, baby gender, pregnancy tobacco use, adequacy of prenatal care, and infection)

[d] Further includes all block group level covariates (NDI, isolation index, and majority urban)

[e] Further includes interactions of Pb with NDI and the isolation index

[f] NA: not applicable

**Denotes significant difference at $p<0.05$

Table 4.5 Parameter estimates (standard error) for arsenic (As), lead (Pb), the neighborhood deprivation index (NDI), and the isolation index in crude models and Models 1-3 for the continuous weeks of gestation outcome.

	As models			**Pb models**		
	Pb	**NDI**	**Isolation**	**Pb**	**NDI**	**Isolation**
Crude[a]	-0.019 (0.0061)**	NA[e]	NA	-0.00095 (0.00045)**	NA	NA
Model 1[b]	-0.0056 (0.0061)	NA	NA	-0.00029 (0.00044)	NA	NA
Model 2[c]	-0.0071 (0.0067)	0.0013 (0.015)	0.15 (0.17)	-0.0003 (0.00045)	-0.0017 (0.014)	0.14 (0.17)
Model 3[d]	0.00062 (0.016)	0.022 (0.022)	-0.13 (0.29)	0.0014 (0.001)	0.028 (0.021)	-0.039 (0.28)

[a] Includes only As or Pb concentrations

[b] Further includes all individual level covariates (maternal race, maternal education, maternal age, parity, receipt of food stamps, baby gender, pregnancy tobacco use, prenatal care, and presence of infection)

[c] Further includes all block group level covariates (NDI, isolation index, and majority urban)

[d] Further includes interactions of As with NDI and the isolation index

[e] NA: not applicable

**Denotes significant difference at $p<0.05$

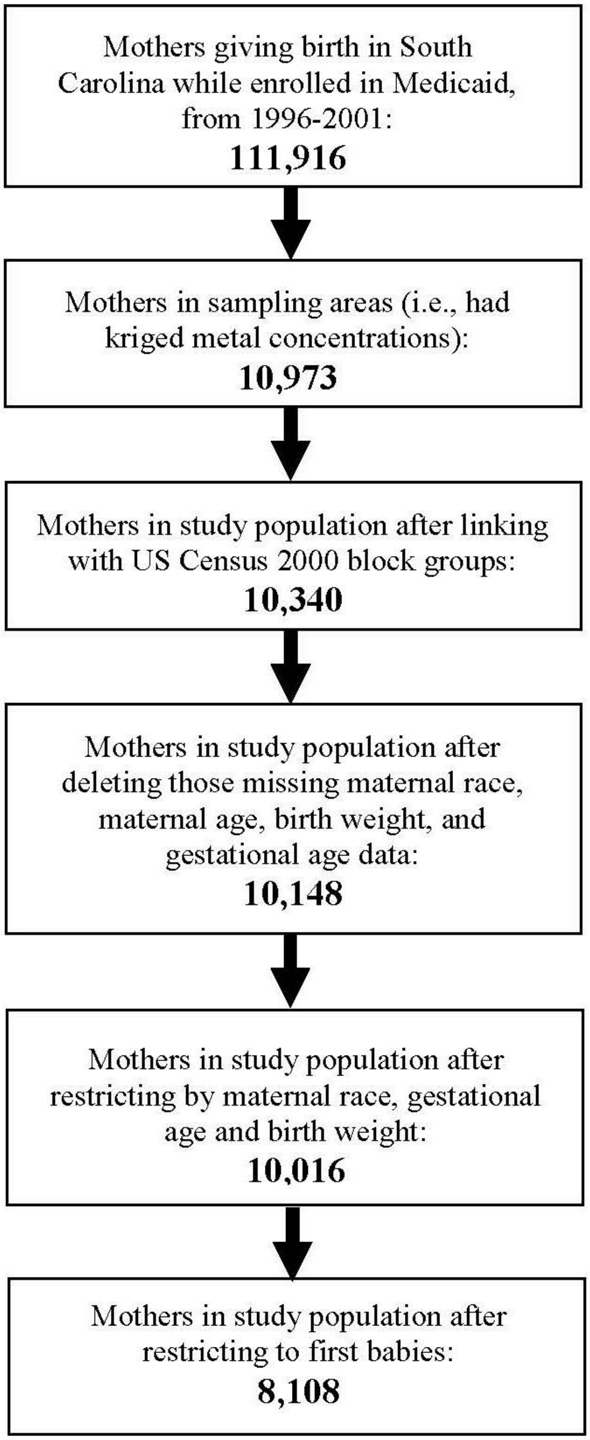

Figure 4.1 Schematic of data linkages, exclusions, and restrictions utilized to finalize study population (n=8,108)

CHAPTER 5

EXAMINING SPATIAL AND TEMPORAL PATTERNS OF EARLY AND ALL PRETERM BIRTHS IN MOTHERS FROM SOUTH CAROLINA USING BAYESIAN METHODS: AN EXPLORATORY ANALYSIS

Abstract

The objectives of this study were to examine early and all preterm birth risk in a Medicaid population of mothers in South Carolina (SC), who gave birth from 1996-2001, in adjusted spatio-temporal Bayesian models, and test the hypothesis of the existence of a racial disparity for these outcomes within this study population. Study population counts of early and all preterm births by year and county in SC were calculated, along with proportions and means of maternal demographics, maternal behaviors during pregnancy, medical conditions during pregnancy, and neighborhood measures at the county level. Poisson crude spatio-temporal, adjusted spatio-temporal, and adjusted temporal models were all used to estimate risk for early and all preterm birth outcomes separately. In comparison of goodness of fit, the adjusted spatio-temporal models for both early and all preterm births were better than the temporal only adjusted models. A racial disparity for early preterm births was identified in the adjusted spatio-temporal Bayesian model; other significant exposures of these outcomes included maternal age, pregnancy hypertensive disorders, and receipt of food stamps during pregnancy. Additionally, certain SC counties had significantly higher adjusted risk of early and all preterm births for consecutive years. Overall, these preliminary findings indicate that adjusting for the spatial relationship

between SC counties in this study population provides better estimates of early and all preterm birth risk for the study population, and the racial disparity in early preterm birth persists after taking the spatial relationship into account.

Introduction

Preterm birth is generally defined as a birth occurring at <37 weeks of gestation, and is considered an important public health issue. The preterm birth prevalence was 11.6% in the United States (US) for 2012 and has been decreasing since 2006, when the prevalence was 12.8% (Martin et al., 2013). However, the prevalence of early preterm birth (<34 weeks of gestation) has remained relatively constant in the US at ~3.4% (Hamilton et al., 2013). In South Carolina (SC), the preterm birth prevalence in 2012 was higher than the national average (13.7%), as was the early preterm birth prevalence (4.4%; MOD, 2013). Preterm births are associated with increased hospitalization rates and costs for infants (Russell et al., 2007), as well as increased infant morbidity and mortality (Fawke, 2007; Kajantie et al., 2010, Norman, 2010; Saigal and Doyle, 2008); therefore, decreasing the prevalence of preterm births in both the US and SC is a public health priority. This is especially true for early preterm births, as infant hospitalization costs, and both infant morbidity and mortality are much higher for those born at earlier weeks of gestation (Russell et al., 2007).

Risk factors for early and all preterm births are similar, and include maternal demographics (Chen et al., 2011; Chien et al., 2011; Clausson et al., 1998; Dolan, 2010), behaviors (Almario et al., 2009; Baba et al., 2012; Patra et al., 2011) and medical conditions during pregnancy (Mann et al., 2010; Petit et al., 2012). Neighborhood (usually defined by a geopolitical boundary such as US Census block, block group, or tract) level risk factors, like crime, deprivation, and other neighborhood measures of socioeconomic status (SES) have also been implicated in preterm births (Bell et al., 2006; Kaufman et al., 2003; Mason et al., 2009; Messer et al., 2006a, 2008; O'Campo et al., 2008). Given the importance of neighborhood risk factors with regard to birth outcomes like preterm birth, it is important to evaluate these associations using models that can best account for neighborhood relationships, including those between individuals living within the same neighborhood as well as between the neighborhoods themselves.

Generally, neighborhood level research of birth outcomes implements hierarchical linear modeling (HLM); this methodology allows the researcher to take into account mothers living in the same neighborhood. In other words, HLM treats mothers living in the same neighborhood as clustered and living within the same place. However, this type of modeling does not take into account the spatial relationship between the neighborhoods themselves unless spatial parameters are included. However, recent studies examining birth outcomes have begun to include spatial parameters in modeling. For example, South et al. (2012) identified hotspots in Hamilton County, Ohio, USA, with high percentages (≥16%) of preterm births using spatial interpolation and compared the attributable risk of different risk factors for preterm births in these hotspots to spatial areas with average or low percentages of preterm birth. Areas with higher percentages of preterm birth had higher risk-adjusted percentages of attributable cases of preterm birth for some risk factors, including chronic hypertension (1.1% versus 0.1%) and previous preterm birth (5.6% versus 3.5%). Warren et al. (2012) examined the association between exposure to air pollution during pregnancy and preterm birth using a spatial-temporal model in Texas, USA; they found that exposure to ozone and other pollutants during the first and second trimester was associated with increased risk of preterm birth. Given that birth outcomes can vary over time as well as space, as can the risk factors for these birth outcomes, it makes sense to investigate both the spatial and temporal variation of these exposures and outcomes. Warren et al. (2012) implemented Bayesian statistical methods, which also may be advantageous for modeling health outcomes in spatial and/or temporal models.

Bayesian statistics allow the researcher to use their prior beliefs, along with the data, to examine associations of interest. All unknown parameters in the model are treated as random variables with their own distributions; after running repeated simulations, one can produce credible intervals for these parameters. Given the dependence inherent in models containing both spatial and temporal parameters, Bayesian methods can offer more flexibility and ease of analysis as compared to more traditional statistical methodologies for spatio-temporal models.

The objectives of this study were to examine if risks of both early and all preterm births varied spatially (at the county level) and/or temporally in Bayesian models in a population of mothers from SC who had a singleton live birth in 1996-2001 while enrolled in Medicaid. This exploratory analysis sought to examine if significant risk factors were different for early and all preterm birth risks modeled in separate spatial-temporal models, and to investigate the existence of a racial disparity (represented by the proportion of black Medicaid mothers within a county) in risks of both early and all preterm births in spatio-temporal models. While other studies have examined preterm births in spatio-temporal models, this is one of the first to control for a variety of individual level (maternal demographics, maternal behaviors, and maternal health conditions during pregnancy) and county level (neighborhood deprivation and urbanicity) risk factors for preterm birth. Most previous studies examining spatio-temporal models of preterm birth have only examined maternal or infant demographics as risk factors.

Methods

Study Population

The study population consisted of mothers giving birth while enrolled in Medicaid in SC from 1996-2001. Medicaid, a federal assistance program that is managed by individual states, offers insurance coverage to income qualifying, medically verified pregnant women throughout pregnancy and up to 60 days postpartum (SC DHHS, 2013). Currently, approximately half of all women who give birth in SC are enrolled in Medicaid (SC DHEC, 2013). Data from birth certificates for these mothers were linked with Medicaid billing records and SC Department of Social Services (SC DSS) records by the South Carolina Revenue and Fiscal Affairs Office (SC RFA). For this study, the population was additionally restricted to only non-Hispanic black and non-Hispanic white mothers (henceforth referred to as black and white), and to only the first birth of a mother (temporally) if she gave birth to more than one child while enrolled in Medicaid from 1996-2001. Mothers were also excluded if their infant had a missing or improbable birth weight (<500 g) or clinical estimate of gestation (<21 weeks), if they were missing information on baby gender, maternal age, and maternal race, and if their residence at month 6 of pregnancy could not be spatially linked with the US Census 2000 block group in which that residence was located. The total study population size was 79,929 mothers.

Variables

The main outcomes of interest were risk ratios of early and all preterm births within the study population. These were initially calculated from counts of early and all preterm births in the study population by county in SC (Figure 5.1) for each year in the period 1996-2001. The main exposure of interest was the proportion of the study population by county that was black. Other risk factors that were aggregated for the individuals in the study population to the county level and examined in this study were: proportion of mothers who received food stamps during pregnancy, proportion of mothers with less than a high school diploma, mean mother's age, proportion of mothers diagnosed with a hypertensive disorder (pregnancy-associated hypertension, preeclampsia, and eclampsia) during pregnancy, proportion of mothers diagnosed with an infection (includes bacterial urinary tract infection, genital herpes, gonorrhea, chlamydia, trichomoniasis, chorioamnionitis, candidiasis, cervicitis, and pelvic inflammatory disease) during pregnancy, proportion of mothers reporting alcohol consumption during pregnancy, proportion of mothers reporting tobacco use during pregnancy, proportion of mothers with a previous preterm birth, and proportion of mothers who began prenatal care after the first trimester. All aggregate measures were from birth certificate data except for proportion of mothers receiving food stamps during pregnancy (from SC DSS).

Two variables related to the maternal US Census 2000 block group of residence were also calculated and aggregated to the county level. These were the neighborhood deprivation index (NDI) and percent of the block group population living in urban areas or urbanized clusters. The NDI calculation was described in detail by Messer et al.

(2006b). Briefly, 20 US Census 2000 variables at the block group level were identified and a principal component analysis (PCA) was performed on these variables. After identifying variables (n=10) with factor loadings greater than or equal to the median, PCA was performed again on these 10 variables, and the values of these variables were weighted by the PCA communality estimates. The percent of the block group population living in urban areas and urbanized clusters is a US Census variable available at the block group level. For both of these neighborhood variables, the means were calculated by county. Additionally, unlike maternal aggregated variables, these were not available for every year during the 1996-2001 study period (i.e., did not change temporally).

Statistical Methods

The first step was to calculate the standardized ratio (SR) of the observed to expected rate of early and all preterm births by county and year for the study population. This was based on the counts of early and all preterm births, and the total number of births to study population mothers within each county by year. It was standardized by the county-specific preterm birth rates. This SR was calculated by year and county, and 95% confidence intervals for these ratios were calculated using a Poisson exact method. This was to identify SC counties by year that had significantly higher crude risk of early and all preterm births. Results from the Potthoff-Whittinghill test of homogeneity were also examined to determine if higher risk for either early or all preterm births for any regions in SC were present for the study population. This test is used as an initial indicator of spatial clustering (Potthoff and Whittinghill, 1966).

The data sets for spatio-temporal models all contained the following variables: spatial weights (based on number of adjacent neighbors for each county), number of counties (N=46), number of years (T=6), spatial and temporal parameters, and expected counts of either early or all preterm births by county and year. There were two spatial parameters (one of which was specifically based on the spatial weights for each county), and one temporal parameter. We first investigated a crude Poisson spatio-temporal model (no exposures) as a reference model for comparison of deviance information criteria (DIC) values, a goodness of fit measure for Bayesian models. For the DIC, lower values indicate better fit.

Individual Poisson spatio-temporal models were then examined for both early and all preterm births, each containing only one of the exposures of interest (12 separate models each for early and all preterm births). After identifying the significant individual exposures for both early and all preterm births, all statistically significant exposures for each outcome were included in separate (for each outcome) adjusted Poisson spatio-temporal models. However, since the proportion of mothers who were black by county was the main exposure of interest, this variable was included regardless of significance in individual models. Finally, the same separate adjusted models for early and all preterm births were examined in a temporal only Poisson model, which did not include the two spatial parameters. DIC values were also calculated for both the adjusted spatio-temporal and temporal only models.

The initial values and all prior distributions used for parameters in Bayesian Poisson spatio-temporal and temporal models are shown in Table 5.1. Prior distributions are required for all parameters of interest, and hyperpriors are the distributions of parameters within prior distributions. For the spatial weights parameter (v), the prior distribution of this parameter is conditional on the spatial weights. For the temporal parameter (δ), times 2-6 are dependent on the prior distribution for the previous year. The posterior distribution for the outcome of interest (early or all preterm births) was a Poisson distribution. An example of coding for a spatio-temporal Poisson model is shown in Appendix C.

All data sets and maps were created, and ratios and confidence intervals calculated using R Version 3.1.1 (R Core Team, 2014). For the spatio-temporal and temporal modeling, the program WinBUGS 14 (Lunn, et al., 2000) was called through R. For each model, 10,000 iterations were run using the Markov Chain Monte Carlo (MCMC) sampling algorithm, Gibbs sampler, with 2,000 burn-in iterations. After running all spatio-temporal models of interest, the two spatial parameters were removed from both early and all preterm birth models to see if DIC values were lower for models without spatial parameters. DIC comparisons were made for models with the same outcome (either early or all preterm births) only. Significance of parameters in Bayesian Poisson models was based on the 95% credible interval not containing 1 (for risk ratios) or 0 (for the mean parameter estimates). 95% credible intervals, risk ratios, and mean parameter estimates were all calculated from the 8,000 MCMC model simulation results for each individual spatio-temporal or temporal only model.

Results

Figures 5.2 and 5.3 show crude SRs for early (Figure 5.2) and all (Figure 5.3) preterm births by year for Medicaid mothers in SC. Intervals were based on even breaks for SRs, calculated separately for early and all preterm births. The majority of counties were in the lowest interval of SRs for both early and all preterm births, and only in 1998 were any counties in the highest intervals (Calhoun county for early preterm birth, and McCormick county for all preterm births; Figures 5.2 and 5.3). For early preterm birth, seven counties had significantly elevated SRs: Richland (1996), Union (1996), Charleston (1997 and 2001), Georgetown (1997), Calhoun (1998), Greenville, (1999), and Orangeburg (2000), with only Charleston having multiple years of significantly more observed as compared to expected early preterm births (Figure 5.2). The highest significant SRs for early preterm birth ranged from 1.35 to 1.90. Results from the Potthoff-Whittinghill test indicate a potential spatial cluster for early preterm births in 1997 only.

There were more counties (n=9) with significantly elevated SRs for all preterm births as compared to SRs for early preterm birth, and more counties with significant SRs for multiple years (Figure 5.3). These were Charleston (1996, 1997, 2000), Laurens (1996), Richland (1996, 1997, 1998, 1999), Newberry (1997, 1998), McCormick (1998), Greenville (1999), Saluda (2000), Dillon (2001) and Williamsburg (2001) counties. Charleston, Richland, and Newberry counties all had significantly higher observed as compared to expected all preterm births for multiple years (Figure 5.3). Significant SRs ranged from 1.20 to 1.73. The Potthoff-Whittinghill test was significant for all years except 2001, suggesting spatial clustering of all preterm births for 1996-2000 in the study population.

For early preterm births, two significant exposures in individual exposure spatio-temporal models were identified; these were proportion of mothers diagnosed with a hypertensive disorder during pregnancy and mean mother’s age. Mean and median parameter estimates (calculated from the 8,000 MCMC simulation iterations), as well as the 95% credible intervals, are shown in Table 5.2. Higher risk of early preterm birth was associated with higher proportions of mothers with hypertensive disorders of pregnancy, and older mothers. Converted to risk ratios, for every one unit increase in proportion of mothers by county and year with pregnancy hypertensive disorders, the risk for early preterm births was 16.4 times higher; for older mother, every one unit increase in mean maternal age by year and county was associated with a 1.09 times higher risk of early preterm birth. The main variable of interest, proportion of mothers who were black, did not predict early preterm birth in the individual exposure spatio-temporal model (Table 5.2).

Three significant exposures for all preterm births were identified in individual exposure spatio-temporal models. Higher risk of all preterm births was associated with higher proportions of black mothers and mothers receiving food stamps, and with older mothers (Table 5.2). Converted to risk ratios, every one unit increase in proportion of black mothers, proportion of mothers receiving food stamps, and mean maternal age was associated with a 1.45, 1.03, and 1.79 times higher risk of all preterm births, respectively.

Figures 5.4 and 5.5 show estimated risk ratios by county for early (Figure 5.4) and all (Figure 5.5) preterm births in SC Medicaid mothers based on separate adjusted spatio-temporal models for each outcome. Risk ratio intervals are the same as for Figures 5.2 and 5.3 (crude SRs). For each year, three or less counties had significantly higher risk of early preterm births, and the majority of counties were in the lowest risk ratio interval (Figure 5.4). Only Richland county had a higher risk of early preterm birth for multiple years (Figure 5.4). In the adjusted spatio-temporal model, estimates for both proportion of mothers with hypertensive disorders during pregnancy and proportion of black mothers were significant (Table 5.3). Adjusted estimates were similar to those from the individual exposure spatio-temporal models for these risk factors. The spatial parameter estimate for only one county was significant in the early preterm birth adjusted spatio-temporal model. The DIC value for the adjusted early preterm birth spatio-temporal model was lower than the DIC value for the crude spatio-temporal model, indicating better model fit for the adjusted spatio-temporal model (Table 5.4).

For all preterm births, 3-4 counties exhibited significantly increased risk for multiple years (Figure 5.5). In the adjusted spatio-temporal model, both mean mother's age and proportion of mothers receiving food stamps were significant exposures for all preterm births (Table 5.3). As with early preterm births, exposure estimates from adjusted spatio-temporal models were similar to those from the individual exposure models. No spatial parameter estimates were significant. As with early preterm birth, the DIC value for the adjusted spatio-temporal model was lower than for the crude spatio-temporal model for all preterm births (Table 5.4).

In the adjusted temporal only models for early and all preterm births, proportion of mothers that were black, and mean mother's age were both significant risk factors for the two birth outcomes (Table 5.3). The risk was slightly higher for all preterm births (converted risk ratio of 1.92) than early preterm birth (converted risk ratio of 1.52) for every one unit increase in proportion of study population mothers that were black. For mean mother's age, the estimates were more similar. DIC values for adjusted temporal only models for both outcomes were higher than the DIC values for the crude models (Table 5.4); this suggests that the adjusted spatio-temporal models were the best fit for both early and all preterm births for the study population.

Discussion

This is one of the first studies to examine early and all preterm births with Bayesian spatio-temporal modeling, and one of the first to additionally investigate aggregate individual health behaviors and conditions during pregnancy for the study population, as well as neighborhood risk factors for preterm birth. It is known that Bayesian estimates are much smoother than the raw SRs, due to the simulation of data to produce estimates and the prior distributions that are given to the model parameters and outcome. This is apparent in results from this study; estimated county risk ratios of early and all preterm births from the Bayesian models were all in the lowest two SR intervals, which was not the case for the SR maps for either outcome. Bayesian modeling also took into account significant exposures of early and all preterm births, while the crude SR estimates do not. Given that preterm birth has multiple risk factors, it makes sense to control for these risk factors to obtain the most valid estimates for early and all preterm birth risk in the study population. While the maps of early and all preterm birth SRs (Figures 5.2 and 5.3) can help researchers initially see what the risk of these outcomes are within an area, the estimates provided in the adjusted Bayesian spatio-temporal and temporal models are a more accurate representation of early and all preterm births in this Medicaid population of mothers for the time period of interest. Not only are the Bayesian model estimates smoothed over the geographic area of interest, but they also reduce the instability of estimates for small populations per geographic unit.

Based on results from the spatio-temporal and temporal models for early and all preterm births in the study population, it appears that the adjusted spatio-temporal models for both preterm birth outcomes were a better fit for the study population data than the adjusted temporal models, based on DIC values. This was the case even though fewer counties had significant risk ratios for either early or all preterm births in the adjusted spatio-temporal models. While the spatial parameters themselves were not significant (based on 95% credible intervals) in either the early or all preterm birth models, it does appear that taking these spatial parameters into account makes for better prediction of the risk of early and all preterm births in the study population, as DIC values were lower. The same counties also consistently had significantly higher risk for both early and all preterm births in the study population.

In the individual exposure spatio-temporal models, the proportion of mothers who were black was only significant for all preterm births. However, in the adjusted spatio-temporal models, this exposure was only significant for early preterm births. This suggests a potential racial disparity for early preterm births in the study population after accounting for the spatial relationship between counties. For all preterm births, the disparity was only significant in the individual exposure and the adjusted temporal model. Other studies have also documented a stronger racial disparity for earlier preterm births (Kharrazi et al., 2012; Kramer and Hogue, 2009), though not using spatial models. Besides proportion of mothers who were black by county, aggregate study population measures of conditions during pregnancy (proportion of mothers with a pregnancy hypertensive disorders), maternal demographics (mean mother's age), and maternal SES (proportion of mothers who received food stamps during pregnancy) were also significantly associated with early and/or and all preterm births in spatio-temporal models. Neighborhood conditions were not significant exposures of either outcome in spatio-temporal models, possibly due to the homogeneity of this Medicaid population with respect to residence location within counties.

In this study, there was overlap of counties that had significant increases in the estimated adjusted risk ratios for both early and all preterm births in spatio-temporal models; specifically, Richland and Charleston counties both had significantly higher risk of early and all preterm births for all years. These locations have many similarities; they are both well-established urban centers in SC so it is likely that populations have similar demographic characteristics and risk factors. While mothers who are high-risk for preterm birth may also be referred to hospitals in these counties due to the SC perinatal regionalization system, this study used mother's residences to aggregate by county, not birth hospital. Also, given early preterm births are a subset of all preterm births, it is not surprising that there is overlap in locations with high risk of both outcomes. There is also the likelihood of similar environmental factors (e.g., air pollution from industry and car exhaust) in these counties, which have also been examined with respect to the preterm birth outcome (Warren et al., 2012). However, further studies are needed to identify what similarities between these locations may be responsible for the significantly higher estimated risk for both early and all preterm births for the study population in both counties.

By knowing where spatial clusters of higher risk of early and all preterm births are, further study within the actual cluster locations can potentially result in a better understanding of why the spatial cluster exists. This could include targeted investigations of populations in those areas (e.g., case-control or cohort studies). These locations could also be the target of educational programs or interventions to reduce that birth outcome.

For example, Stopka et al. (2014) used spatial clustering to identify locations in California with significantly higher density of women eligible for Women, Infants, and Children (WIC) services but who were not receiving those services; this information can inform potential policy changes to focus efforts in these locations to increase WIC enrollment. With respect to the preterm birth outcome, Padilla et al. (2013) found spatial clustering of preterm births in Lillie and Lyon, France, which was associated with an SES deprivation measure. The results from the current exploratory study includes counties with significant risk of early and all preterm births in SC for the study period based on adjusted spatio-temporal models, and these specific counties could be examined on a lower geographic scale (e.g., Census tracts or block groups) to hone in on where preterm birth risk is higher. This could be more conducive for interventions and educational programs.

This study does have limitations. For one, the study population consisted of only Medicaid mothers. Specific income requirements are necessary for enrollment into Medicaid. Therefore, the locations of significant risk of early and all preterm births in this study population are not necessarily generalizable to the general population of mothers in SC. Further studies should examine all mothers giving birth in SC for a time period of interest. Additionally, the time period of the study included mothers giving birth from 1996-2001; it would be beneficial to do a similar analysis using a more recent cohort of mothers to see if spatial patterns hold over time. We also included eclampsia within the calculation of the proportion of mother with hypertensive disorders during pregnancy. Development of this condition is an indicator for preterm delivery but more than half of all mothers with eclampsia (n=576) were diagnosed with either preeclampsia or pregnancy-associated hypertension and would have been included in the proportion anyway.

Conclusions

These results suggest that the risk estimates of early and all preterm births in the study population in models adjusting for the spatial relationship between counties in SC are a better fit for the study population than models that do not. This exploratory analysis provides further evidence to support the inclusion of spatial parameters in models of health outcomes. In addition, the racial disparity in early preterm births within the study population persisted after controlling for maternal risk factors as well as the spatial relationship between counties. Certain counties in SC also had significantly higher risk of early and all preterm births in adjusted spatio-temporal models for multiple years of the study period. Further research is needed at a smaller geographic scale, and potentially with other exposures, to examine why higher risk of early and all preterm births was observed in these counties of SC.

Table 5.1 Initial values and prior distributions for all parameters in Bayesian Poisson spatio-temporal and temporal models.

Parameter	**Prior distribution type (mean and standard deviation)**	**Initial values**
Betas[a]	Normal (0, 0.00001)	0
Spatial parameter (*u*)	Normal (0, *u* precision parameter)	0 (all counties)
Spatial weights parameter (*v*)	CAR[c] Normal (spatial weights)[d]	0 (all counties)
Temporal parameter (δ)	Normal (0, δ precision parameter) for t=1[e]	0 (all years)
u precision parameter[b]	Gamma (0.1, 0.1)	0.00001
v precision parameter[b]	Gamma (0.1, 0.1)	0.00001
δ precision parameter[b]	Gamma (0.01, 0.01)	0.00001

[a] All betas, including intercept and exposures, had the same prior distributions and initial values

[b] Precision parameters are parameters within prior distributions

[c] CAR: conditional autoregressive

[d] Prior distribution is dependent on spatial weights of counties in data set

[e] Prior distributions for times 2-6 dependent on the previous year

Table 5.2 Mean and median exposure parameter estimates, and 95% credible intervals for early and all preterm births in individual exposure spatio-temporal models[a].

	Early preterm birth			All preterm births		
	Mean estimate	Median estimate	95% Credible interval	Mean estimate	Median estimate	95% Credible interval
Black mothers[b]	0.52	0.53	-0.00022, 1.0	0.37	0.37	0.11, 0.65
Pregnancy hypertension[c]	2.8	2.8	0.49, 5.0	NA[f]	NA	NA
Mother's age[d]	0.089	0.067	0.019, 0.18	0.034	0.035	0.0083, 0.050
Receipt of food stamps[e]	NA	NA	NA	0.58	0.57	0.19, 0.99

[a] All exposures in table were significant based on 95% credible intervals, except for proportion of black mothers for the outcome of early preterm births

[b] Proportion of mothers who were black by county and year in the study population

[c] Proportion of mothers diagnosed with a pregnancy-related hypertensive disorder by county and year in the study population

[d] Mean mother's age by county and year in the study population

[e] Proportion of mothers that received food stamps during pregnancy by county and year in the study population

[f] NA: not applicable

Table 5.3 Significant mean exposure parameter estimates (95% credible interval) for adjusted spatio-temporal and adjusted temporal only models of early and all preterm births.

	Early preterm birth		**All preterm births**	
	Spatio-temporal	Temporal only	Spatio-temporal	Temporal only
Black mothers[a]	0.52 (0.003, 1.07)	0.42 (0.19, 0.64)	NA[e]	0.65 (0.46, 0.85)
Pregnancy hypertension[b]	2.93 (0.70, 5.06)	NA	NA	NA
Mother's age[c]	NA	0.05 (0.006, 0.09)	0.04 (0.001, 0.07)	0.04 (0.02, 0.07)
Receipt of food stamps[d]	NA	NA	0.52 (0.05, 0.90)	NA

[a] Proportion of mothers who were black by county and year in the study population

[b] Proportion of mothers diagnosed with a pregnancy-related hypertensive disorder by county and year in the study population

[c] Mean mother's age by county and year in the study population

[d] Proportion of mothers that received food stamps during pregnancy by county and year in the study population

[e] NA: not applicable

Table 5.4 Deviance information criteria (DIC) values for crude spatio-temporal, adjusted spatio-temporal, and adjusted temporal models for early and all preterm births.

	Early preterm births	**All preterm births**
Crude model[a]	1231.54	1637.39
Adjusted spatio-temporal model[b]	1228.67	1633.00
Adjusted temporal model[c]	1275.03	1693.09

[a] Crude model contained only the expected counts of early or all preterm births.

[b] Adjusted spatio-temporal models additionally contained both spatial and temporal parameters; the early preterm birth model was additionally adjusted for proportion of the study population who were black, proportion of the study population diagnosed with hypertensive disorders during pregnancy, and mean maternal age (all by county and year); the all preterm birth model was additionally adjusted for proportion of the study population who were black, proportion of mothers receiving food stamps during pregnancy, and mean maternal age (all by county and year)

[c] Adjusted temporal models contained temporal parameters only; early and all preterm birth models were additionally adjusted for all maternal exposures from the adjusted spatio-temporal models

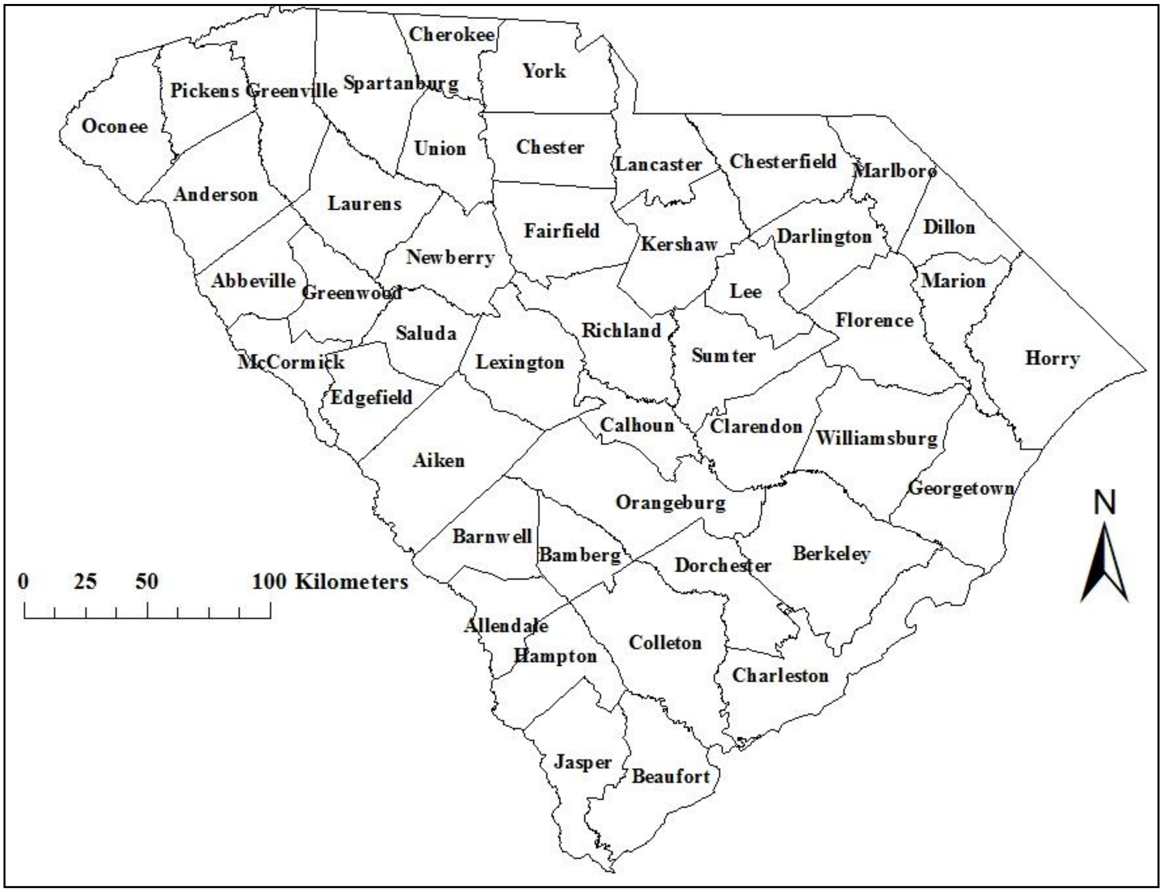

Figure 5.1 South Carolina (SC) county names and locations

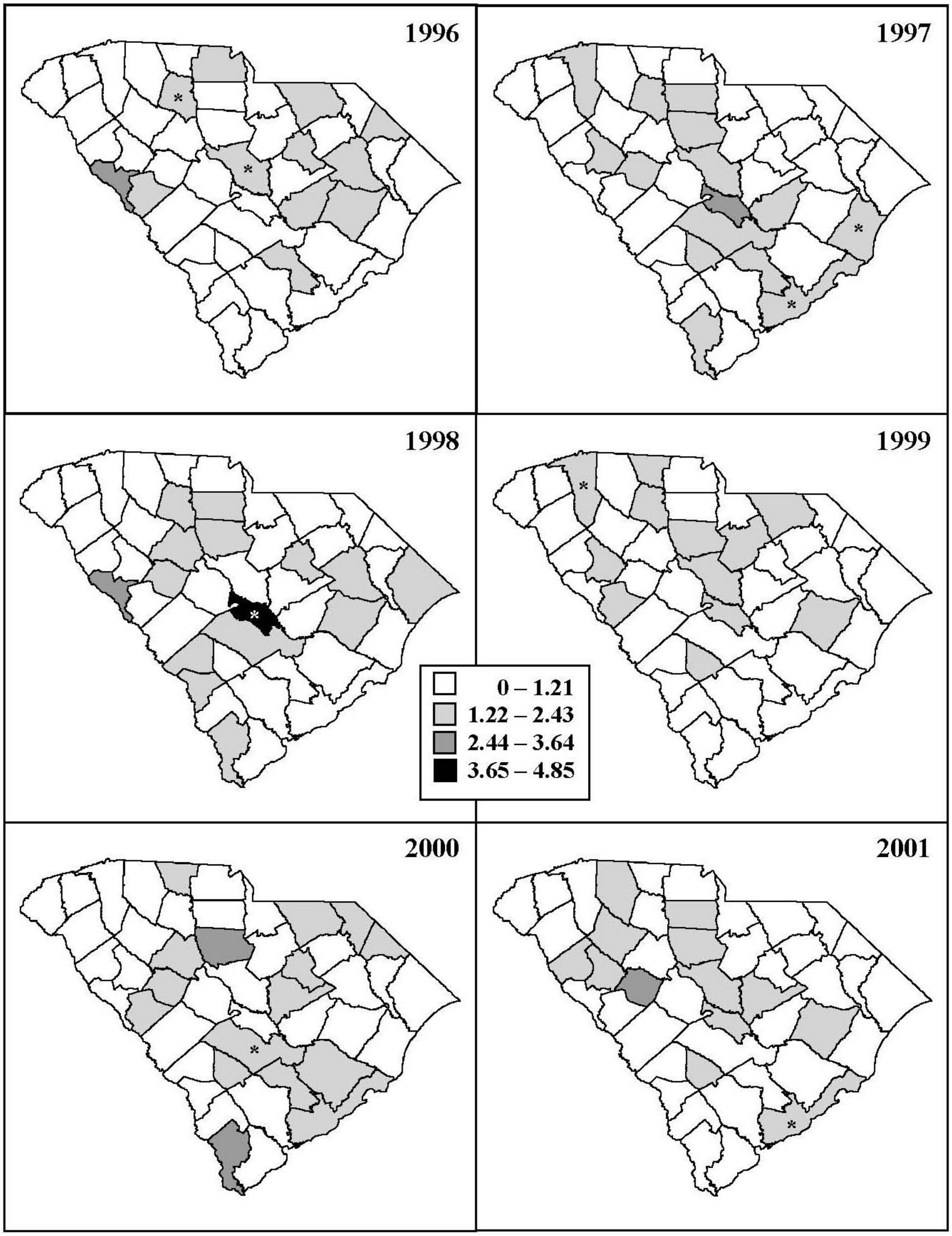

Figure 5.2 Crude standardized ratios (SR) of observed to expected early preterm births by county and year (categorized into even intervals) for Medicaid mothers in South Carolina (SC), 1996-2001

*Denotes significant SR (95% confidence interval does not contain 1)

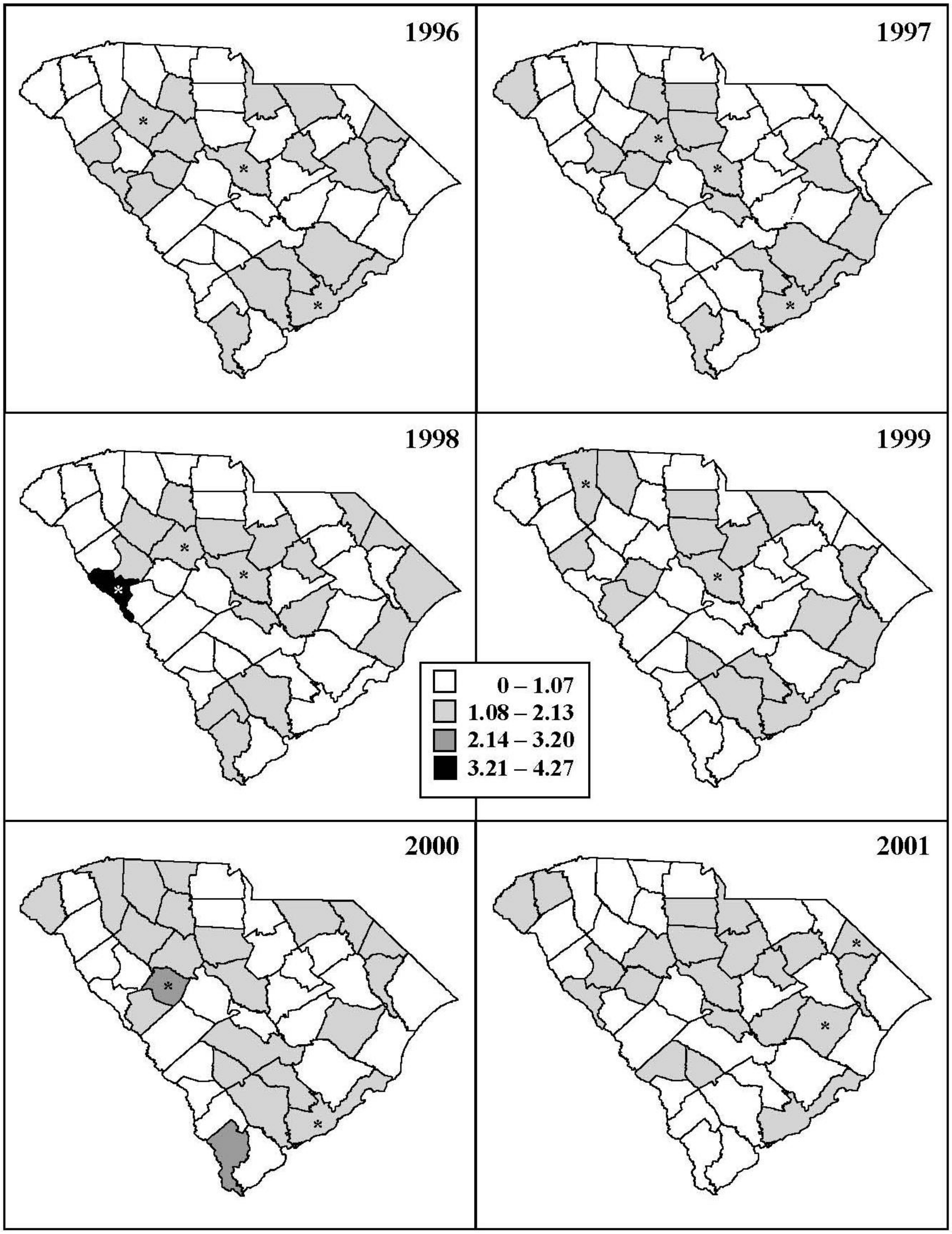

Figure 5.3 Crude standardized ratios (SR) of observed to expected all preterm births by county and year (categorized into even intervals) for Medicaid mothers in South Carolina (SC), 1996-2001

*Denotes significant SR (95% confidence interval does not contain 1)

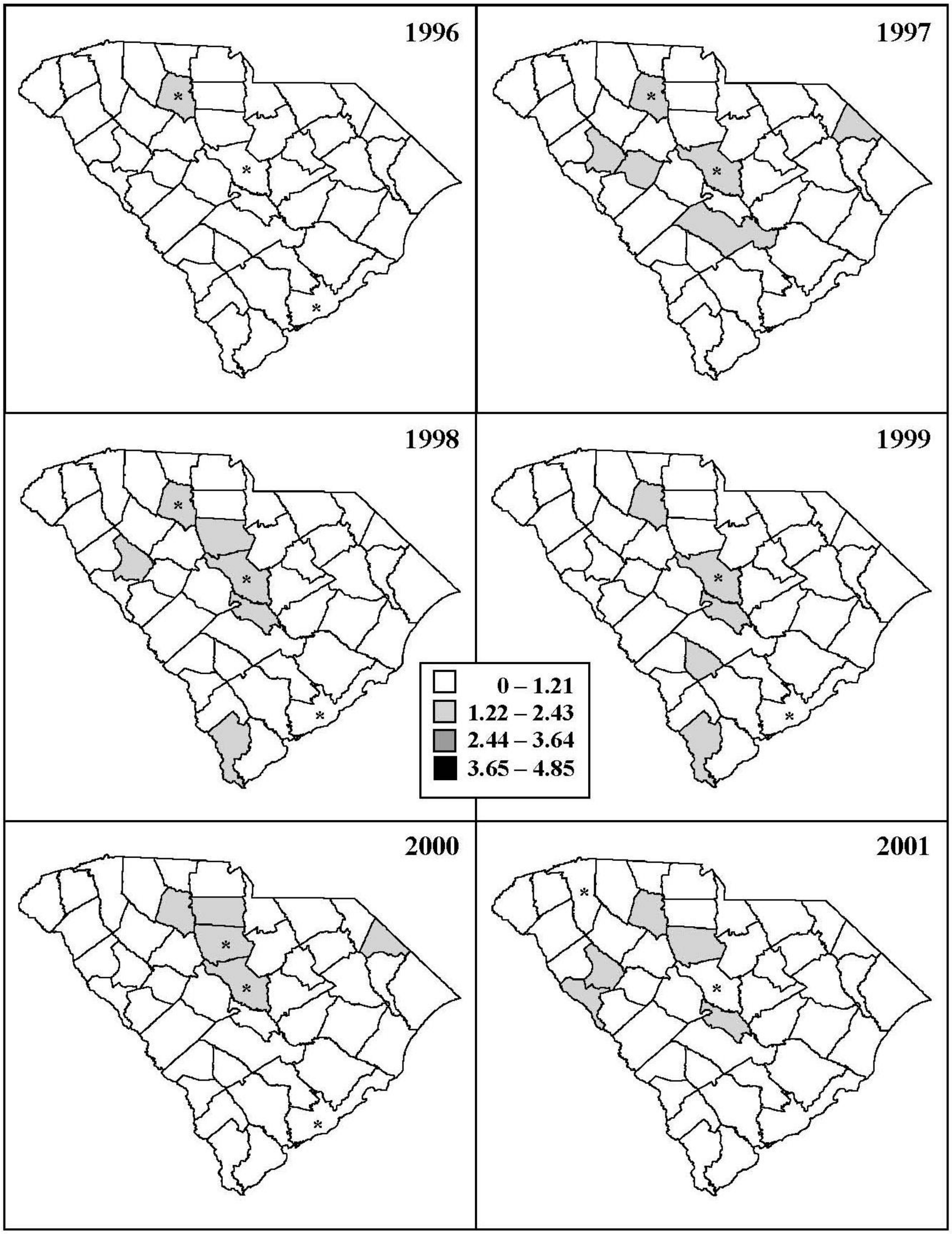

Figure 5.4 Estimated risk ratios (RR) of early preterm birth by county and year (categorized by intervals from Figure 5.2) for Medicaid mothers in South Carolina (SC), 1996-2001, from Bayesian Poisson spatio-temporal model adjusted for maternal race, pregnancy hypertensive disorders, and mother's age
*Denotes significant RR (95% credible interval does not contain 1)

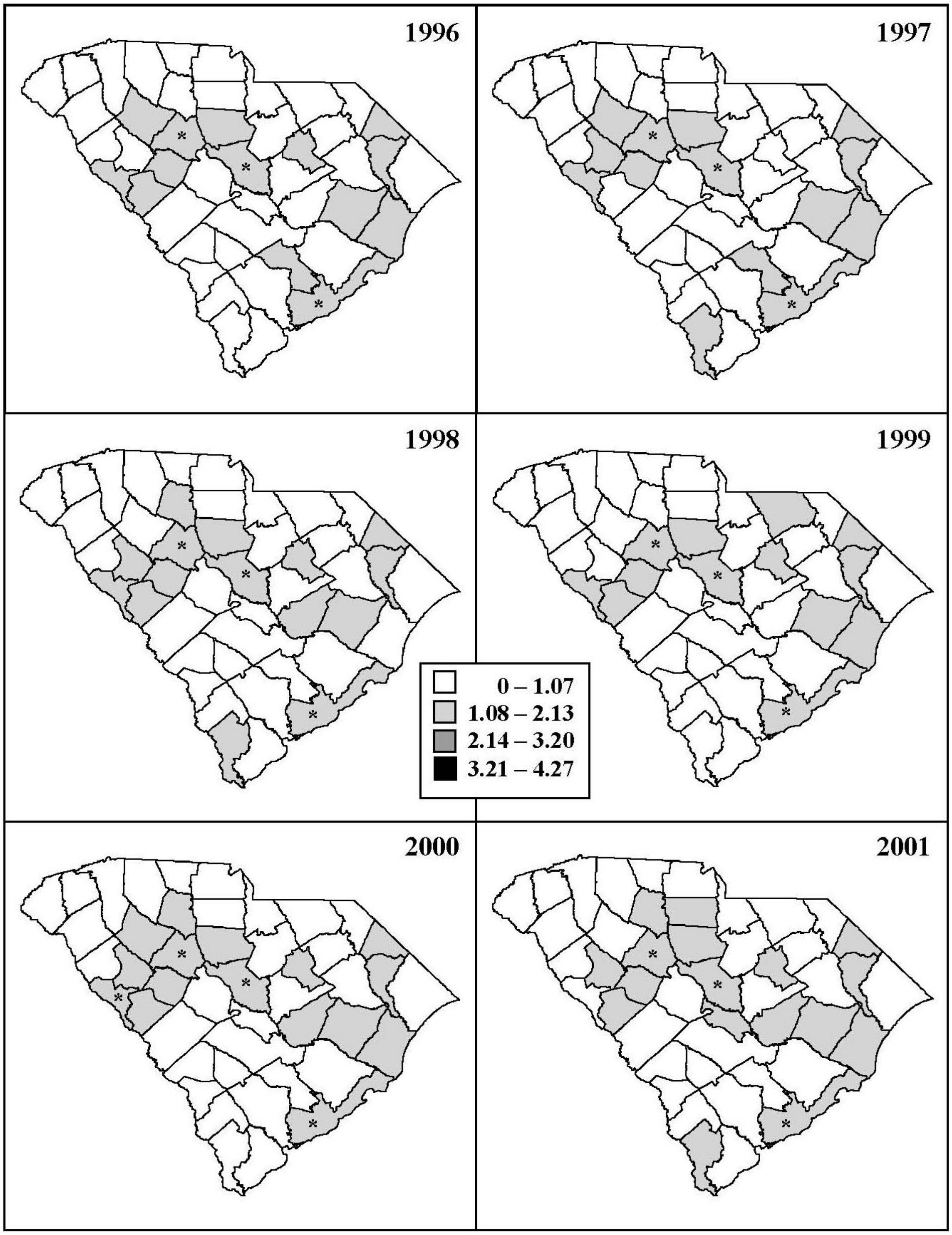

Figure 5.5 Estimated risk ratios (RR) of all preterm births by county and year (categorized into intervals from Figure 5.3) for Medicaid mothers in South Carolina (SC), 1996-2001, from Bayesian Poisson spatio-temporal model adjusted for maternal race, receipt of food stamps, and mother's age
*Denotes significant RR (95% credible interval does not contain 1)

CHAPTER 6

SUMMARY

An individual's health outcomes are impacted by both social and physical characteristics of the neighborhood in which they reside. Many environmental studies of the associations between metals, such as arsenic (As) and lead (Pb), and health outcomes are often limited to contaminated locations with high potential for exposure. The importance of exposure to low concentrations of metals to health outcomes, particularly in utero, is being recognized (Feki-Tounsi et al., 2013; Hinhumpatch et al., 2013; Needleman, 2009; O'Bryant et al., 2011; Xie et al., 2013; Zhu et al., 2010), and additional studies in residential areas are needed.

Residential soil As and Pb concentrations were analyzed as part of a previous retrospective cohort study investigating the associations of low concentrations of soil metals in residential areas of black and white mothers enrolled in Medicaid during pregnancy (from 1996-2001) in South Carolina (SC), and potential associations with intellectual disabilities in children (Aelion et al., 2008, 2009a, 2009b, 2012, 2013, 2014; Cai et al., 2011; Davis et al., 2009, 2014; Kim et al., 2009, 2010; Liu et al., 2010; McDermott et al., 2011, 2014a, 2014b; Onicescu et al., 2014; Zhen et al., 2008, 2009). This dissertation used those data, as well as additional birth certificate, Medicaid billing, SC Department of Social Services (SC DSS), and United States (US) Census 2000 data to examine the social and physical characteristics of the neighborhoods in which the women lived, and their pregnancy outcomes.

Specific Aim 1 investigated whether a racial disparity in soil As and Pb concentrations persisted after controlling for distance and direction of residences from industrial facilities. Specific Aim 2 examined associations between estimated soil As and Pb concentrations and both early and late preterm births of the mothers, after controlling for maternal risk factors, as well as neighborhood measures of neighborhood deprivation and racial residential segregation as effect modifiers. Finally, for Specific Aim 3, aggregate Bayesian spatio-temporal models of early and all preterm births were examined at the county level to investigate whether preterm birth varied spatially for all Medicaid mothers in SC for this time period, after adjusting for aggregated risk factors for preterm birth. Although spatial models have been used to examine birth outcomes (Ball and Pereira, 2013; Ross et al., 2013; Warren et al., 2012), the potential benefits of a Bayesian analysis have been established, especially for spatial models (Law and Chan, 2011; Reich et al., 2014; Wasserman et al., 2004). This research is one of the first to examine a Bayesian spatio-temporal model of preterm birth which allows for investigation of how preterm birth is impacted by the characteristics of one's own county of residence, and nearby counties and their characteristics.

Interpretation of Findings

Specific Aim 1

The findings from this aim supported the hypothesis that black mothers in the study population had significantly higher estimated residential soil concentration of both As and Pb in study areas of SC as compared to white mothers, after adjusting for maternal and neighborhood measures of SES. This is especially important for this pregnant population, as both mothers and their children may potentially be at increased risk for exposure to these metals in soils. While mean differences in estimated soil As and Pb concentrations between black and white mothers were not large in magnitude, the importance of low-level exposures to these metals cannot be discounted and has been examined in other studies for various outcomes (Bräuner et al., 2014; Cabral et al., 2012; Gong et al., 2011; Krishnan et al., 2012; McFarlane et al., 2013). Therefore, these differences between black and white mothers in the study population may be relevant to their health. It was also observed that proximal sources of these metals (percent roads) were positively associated with estimated soil As and Pb concentrations. Significant associations between these concentrations and more distal composite annual industrial releases (categorized by distance and/or direction) of As and Pb from facilities reporting to the Environmental Protection Agency's (EPA) Toxics Release Inventory (TRI) were, however, not observed. Finally, the neighborhood deprivation index (NDI) did not modify the racial disparity in estimated residential As or Pb concentrations, nor did it remain in the best fit model for either metal.

Regardless of source, estimated residential As and Pb concentrations were higher for black mothers than for white mothers, suggesting environmental inequality with regards to potential for exposure for the study population. Environmental inequality has been documented for Pb in soils (Downs et al., 2010; Lambert et al., 2006; McClintock, 2012; Mielke et al., 2007; Morrison et al., 2014), and, to a lesser extent, As (Diawara et al., 2006; Lambert and Lane, 2004; Lambert et al., 2006) in other locations. Because the locations sampled as part of this study were physically and geologically representative of SC (e.g., included urban and rural areas and areas with different types of land use), the fact that the disparity persisted (and the estimate size did not change) after controlling for SES and sources of these metals may suggest that this disparity could persist in the general SC population of mothers.

In this study population, there was no significant effect modification of NDI on the racial disparity in estimated soil As and Pb concentrations. While it was hypothesized that the disparity would be smaller for mothers living in neighborhoods with more deprivation, this was not observed. Additionally, the NDI was not retained in the best fit model for either metal. The role of NDI in the racial disparity of environmental contaminants has not been examined in other studies, though these data suggest little impact. However, the role of neighborhood deprivation as an effect modifier of environmental exposures and health outcomes has been examined. Lovasi et al. (2014) found that environmental exposure to polycyclic aromatic hydrocarbons was associated with lower childhood cognitive test scores after adjusting for neighborhood deprivation measures, though no effect modification of the neighborhood measures on the association of interest was reported. In contrast, Limousi et al. (2014) observed an increased risk of small for gestational age (SGA) infants for mothers exposed to nitrates in drinking water living in less deprived areas compared to those with more deprivation, which they attributed to the presence of more risk factors in less deprived areas, which could compete with the exposure risk factor of interest.

It was also determined that proximal (percent roads) rather than distal (composite industrial facility releases) sources of As and Pb were more strongly associated with both estimated soil As and Pb concentrations in study areas. Percent roads proxy historic use of leaded gasoline and indicate that these inputs still pose a threat to public health for those populations with increased potential for exposure, and the link between historic leaded gasoline use and current soil concentrations has been established in other studies (Ayrault et al., 2014; Morton-Bermea et al., 2011; Wagner and Langley-Turnbaugh, 2008). Both As and Pb are long-lived in the environment, so these concentrations should remain stable for a long period of time (Aelion et al., 2014). Additionally, estimated soil As and Pb concentrations were highly correlated in the study population, which could be due to potential residential sources of As (e.g., historic use of As-containing pesticides or use of chromated copper arsenate (CCA) treated wood on residential structures) being more common in areas with more percent road coverage. However, further investigation of these sources would be needed to verify this, and to examine additional hypotheses related to the co-occurrence of As and Pb in soils of SC.

Recent composite annual industrial releases from As- and Pb-emitting TRI facilities did not impact estimated residential soil As and Pb concentrations, regardless of distance and direction. While these null results were not what were hypothesized, there are some potential explanations. For one, the atmospheric conditions and atmospheric dispersal may dilute these As and Pb TRI facility releases to an extent that their impact on nearby soils may be minimal. Atmospheric dispersion models generally examine distances of ~5 km or less (El-Fadel and Abi-Esber, 2012; Mohan et al., 1995; Sharan et al., 1996), which is much greater than the majority of facility distances from block groups containing maternal residences. Also, release rules and regulations have changed over time and are much stricter now than in the past. Thus, current soil As and Pb concentrations may be associated more with the distance and direction of releases from historical facilities as compared to the locations of existing facilities.

Specific Aim 2

The results from Specific Aim 2 did not support the hypothesis that estimated soil As and Pb concentrations (a proxy for potential exposure) were associated with increased odds of early or late preterm births in the study population, after controlling for additional risk factors. Associations between As and Pb exposure and preterm birth have been investigated in other studies (Andrews et al., 1994; Burris et al., 2011; Myers et al., 2010; Torres-Sanchez et al., 1999), most of which focused on populations with high exposure (e.g., occupational, nearby industrial sources, etc.). Additionally, there has been little consistency in the literature with respect to the impact of exposure to these metals and preterm birth. For example, Myers et al., 2010 did not observe a significant association between maternal As exposure through drinking water and preterm birth in a population in Inner Mongolia, China, though Mukherjee et al. (2005) and Ahmad et al. (2001) observed associations for this form of As exposure and preterm birth in India and Bangladesh, respectively. Similar inconsistencies for results of Pb exposure and preterm birth were reported in a review by Gardella (2001). While a biological mechanism for induction of preterm birth through oxidative stress has been identified for these metals (Ahamed et al., 2009; Ahmed et al., 2011), numerous types of maternal conditions, behaviors, and exposures can also induce oxidative stress. Therefore, identification of As- and Pb-specific oxidative stress markers through prospective studies of preterm birth is needed to help verify the role of As and Pb with respect to this birth outcome. Gene-environment interactions related to As and Pb exposure and oxidative stress may also be important (Shachar et al., 2013).

While estimated soil As and Pb concentrations did not remain significantly associated with increased odds of early and late preterm birth in adjusted models, well-known maternal risk factors were associated with preterm births, and associations varied for early and late preterm births. The adjusted odds ratios for early preterm birth were higher than for late preterm birth for both black mothers and mothers with an infection during pregnancy. Additionally, beginning prenatal care after the first trimester and maternal age were significantly associated with increased odds of only early preterm births in the study population. This suggests that these risk factors may be especially important for early preterm births, which have higher incidences of infant morbidity and mortality than late preterm births (Ananth et al., 2013; Baron et al., 2012; Barros et al., 2012). Differences in risk factors for early and late preterm birth have also been observed in other studies (Goldenberg et al., 2008; Kramer and Hogue, 2009; Saigal and Doyle, 2008). However, these other studies generally did not additionally adjust for neighborhood characteristics, nor did they examine environmental exposures.

Associations between neighborhood measures (NDI, racial residential segregation as the isolation index, and majority urban) and birth outcomes have been observed in other studies (Bell et al., 2006; Kramer et al., 2010b; Mason et al., 2009; Messer et al., 2006a), but were not observed in this research for early or late preterm births, or weeks of gestation. It should be noted that only 30% of the US Census 2000 block groups (neighborhood unit of measure) in SC contained study population mothers, and coefficients of variation for both NDI and the isolation index were greater for all block groups in SC (53.1% and 118.3%, respectively) than for block groups where study population mothers residences were located at month 6 of pregnancy (46.5% and 89.9%, respectively). These findings suggest limited variability of neighborhood measures in the study population block groups, which may have contributed to the null findings in this study with respect to birth outcomes.

In addition, neither NDI nor isolation modified the association between estimated soil As and Pb concentration and early or late preterm births. While it was thought that ORs between preterm birth categories and estimated soil As and Pb concentrations would be lower in neighborhoods with more deprivation and more isolation, this was not observed. As stated above, this could possibly be due to the homogeneity of our study population, which may have attenuated the effect of these neighborhood characteristics on preterm births. Mendez et al. (2014) calculated the isolation index for mothers in Philadelphia, PA; only 25% of their study population (n=3,462) had isolation index values ≤0.3, compared to 77% of our study population. Using this same break point in a population of over 400,000, Bell et al. (2006) reported that only 4.8% of their study population lived in areas with isolation indices ≤0.3. This indicates a very low isolation index for the majority of mothers in our study population. For NDI, comparisons between studies are more difficult since these values are standardized, and the numbers of variables included in the composite measure can vary based on principal component analysis (PCA) results. For example, Messer et al. (2006a) included only eight variables in their NDI, while Messer et al. (2006b) included nine variables.

Specific Aim 3

Based on results from Specific Aim 3, the adjusted Bayesian models for both early and all preterm births that included both spatial and temporal parameters were a better fit than the temporal-only adjusted Bayesian model, based on comparisons of deviance information criteria (DIC) values. Taking the spatial relationship between counties into account in the model provided better estimates of risk of early and all preterm birth for Medicaid mothers in SC that gave birth from 1996-2001. In the adjusted spatio-temporal models, the racial disparity (measured by proportion of black study population mothers by county) was significant only for early preterm births. Mean maternal age was a significant risk factor for both early and all preterm births. In addition, proportion of mothers with hypertensive disorders during pregnancy was significant for early preterm births and proportion of mothers who received food stamps during pregnancy was significant for all preterm births. Neighborhood deprivation was not associated with early or all preterm births in these adjusted models. In this aim, as well as for Specific Aim 2, neighborhood conditions were not significantly associated with preterm birth in this Medicaid population of mothers.

This exploratory analysis is one of the first studies to examine spatio-temporal models of preterm birth, and to have the ability to adjust for numerous maternal demographics, maternal behaviors during pregnancy, and maternal disorders and conditions during pregnancy aggregated to the county level. While the geographic unit of analysis (county) was large, the results suggest that taking into account spatial relationships between geographic areas, at least for the preterm birth outcome, is warranted. Of note was that the same two urban counties in SC consistently had higher risk of early and all preterm births for the study time period in the adjusted spatio-temporal Bayesian models. The general populations in these counties are similar, so there may be similar risk factors associated with preterm births for these study populations by county. Further research is needed to identify potential causes of the increased risk of early and all preterm births in these locations for mothers enrolled in Medicaid, and targeted interventions and educational programs developed to reduce behaviors and conditions that drive preterm birth rates.

Public Health Implications

The results from this dissertation have public health implications in a variety of areas. Preterm birth is an ongoing public health issue, and early preterm birth rates have remained constant for the recent past. The effects of environmental contaminants on human health have been known for a long period of time. Additionally, a racial disparity that spans geographic locations has also been long observed for both the preterm birth outcome and environmental exposure to As and Pb, as have associations of neighborhood measures with these exposures and outcomes. Therefore, the findings from this dissertation could be useful in a variety of public health setting to impact not only these, but additional health outcomes and risk factors.

Results from Specific Aim 1 confirmed the existence of a racial disparity between black and white mothers with respect to estimated soil As and Pb concentrations for study population mothers. Additional studies in the same sampling areas using US Census 2000 demographic data have also produced the same results (Aelion et al., 2013; Davis et al., 2014). While the differences in mean estimated soil As and Pb concentrations were not very large in magnitude, these results may be indicative of environmental injustice within these sampling areas with respect to where mothers of different races/ethnicities are living, and deserve further attention. Additionally, other environmental contaminants may be important in these areas that were not examined in this study give the co-occurrence of environmental contaminants from similar sources.

For Specific Aim 2, the observation of significant crude associations between estimated As concentrations and both early and late preterm births, and both estimated soil As and Pb concentrations with weeks of gestation may be suggestive of the potential risk of exposure to these metals and preterm birth. Interventions or educational programs could be based on additional exposure measures to target high-risk populations. For example, pregnant mothers of children with elevated blood Pb levels could be informed of the risks to the developing fetus related to environmental, household, and occupational Pb exposure to hopefully reduce any negative health outcomes to both mother and child.

Results from Specific Aim 3, as mentioned previously, suggest spatial clustering of early and all preterm births by county for the Medicaid study population. The locations of these clustered could be examined on a lower geographic scale to identify any particular preterm birth risk factors that may be more prevalent within these locations. Based on this information, the at-risk population could be targeted to reduce preterm birth outcomes.

Future Research

To expand upon the findings from these three aims, future research should utilize a general study population, examine biological exposure measures in prospective studies, potentially with repeated measures, and examine preterm births in a spatio-temporal model on a smaller geographical scale (e.g., US Census tracts or block groups). This future research should add to the literature in the areas of racial disparities in exposure to metals, sources of anthropogenic metals in the environment, exposure to metals and associations with preterm birth, and the role of neighborhoods in the preterm birth outcome in models with and without spatial parameters.

The study population was limited to Medicaid mothers giving birth from 1996-2001, to only the first births of these mothers if they gave birth more than once during the time period, and, for Specific Aims 1 and 2, to mothers in areas where soil samples were collected for analysis of As and Pb. Choosing a more representative and diverse population of mothers from SC through prenatal care providers (prospective) or through all birth certificate records (retrospective) would provide more variability in the neighborhood measures if mothers are selected from a larger geographic scale, especially with respect to Specific Aims 1 and 2. It would also allow for spatial modeling of preterm birth at a lower geographic scale (e.g., US Census tracts or block groups) for Specific Aim 3, as the study population size would be larger. Results from these studies would also be more generalizable to other, similar populations.

Soil and biological concentrations of both As and Pb are correlated; however, soil metal concentrations measured at only one time during pregnancy cannot address exposure timing. Recruiting mothers into a prospective study where biological samples are obtained and analyzed for As and Pb at multiple times during pregnancy will provide researchers with a “gold standard” for exposure, and allow them to track exposure throughout the course of pregnancy. In addition to these direct exposure measures, environmental samples collected at the maternal residence during pregnancy (e.g., soil, water, dust) at the same time as biological samples are collected could provide information on potential exposure routes. These features would add greatly to the literature on environmental exposure and potential impact on birth outcomes.

Study Limitations

The major limitations of this dissertation work are related to the lack of direct exposure estimates, and the study population. Specific Aims 1 and 2 used the estimated soil As and Pb concentrations at the mother's residence during month 6 of pregnancy. Due to privacy restrictions associated with the retrospective study from which the data for this dissertation were obtained, soil could not be collected at the actual location of the mother's residence. Therefore, soil samples were collected on a regular grid and spatially interpolated (kriged) at the geocoded maternal residence (Zhen et al., 2008, 2009). The method that was used to spatially interpolate soil As and Pb concentrations is widely accepted for this purpose, these estimated concentrations are still an estimate and not measured values. Actual measured concentrations of As and Pb in these locations had a greater range than kriged concentrations (see Chapter 4), and may have contributed to the null findings in Specific Aim 2. A greater limitation is that these concentrations do not represent actual exposure to the mothers, nor do they include other potential exposure routes. Even so, they have been employed as a proxy for exposure for Aims 1 and 2.

Mothers in this study were identified in a previous research study based on spatial clusters of intellectual disability (ID) and developmental delay (DD) in children born to these mothers who gave birth while enrolled in Medicaid from 1996-2001 (Zhen et al., 2008, 2009). These mothers are different with respect to race/ethnicity and SES compared to the general population of SC and therefore, results are not generalizable to the entire population of mothers in SC. Additionally, these data are 10+ years old, so prevalence of risk factors, including behaviors and conditions during pregnancy, and the general prevalence of preterm births in this study population may not reflect what would be measured in a more current cohort of SC Medicaid mothers. Additionally, the spatial clusters of higher risk of preterm birth (from Specific Aim 3) may not currently be present.

Data sources are also a limitation; the majority of measures used in this dissertation work were from birth certificate data, which has limitations with respect to behaviors and conditions during pregnancy. Data from medical record abstraction would be the most valid, but birth certificate data are highly utilized by researchers examining a variety of different health outcomes. Also, US Census 2000 data were used as they were temporally closest to the time period in which the mothers in the data set were enrolled in Medicaid in SC and gave birth. However, more recent US Census data are available and are likely more representative of the current neighborhood (US Census block group) conditions in SC.

Finally, limitations were associated with the data analyses. For Specific Aim 1, distance and direction were investigated by categorizing the numerous As- and Pb-emitting TRI facilities into specific distance, direction, and distance/direction combined categories. However, there are additional ways to quantify distance and direction that could be employed in a study where geocoded maternal residences are known. For Specific Aims 1 and 2, the neighborhood unit of analysis was the US Census block group; other geographical boundaries could have been chosen that may have been more representative of a mother’s neighborhood. For Specific Aim 3, a Bayesian approach was used. One of the biggest limitations associated with this methodology is the choice of priors used for parameters, as changing these can greatly impact model results.

Conclusions

Results of this dissertation research show the importance of proximal, historical sources of As and Pb, and a racial disparity in distribution of estimated soil As and Pb in residential areas of study population mothers. They also indicated that industrial point sources of these metals, regardless of distance and direction to block groups of maternal residence, were not associated with estimated soil As and Pb concentrations in the study locations. Associations between soil metals and both early and late preterm births did not remain significant after adjustment for maternal and neighborhood level risk factors, suggesting minimal increased risk for the Medicaid mothers in residential areas with higher estimated soil metal concentrations. Results also emphasize the importance of inclusion of spatial parameters in models of birth outcomes. Further investigations should examine more direct measures of exposure in a more generalizable population of mothers, and spatial parameters of birth outcomes at lower geographic levels to further assess spatial relationships.

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APPENDIX A

SUPPLEMENTARY TABLES ASSOCIATED WITH CHAPTER 3

Table A.1 Comparisons between study population mothers and all Medicaid mothers giving birth from 1996-2001 for categorical variables examined in Chapter 3[a].

	Study population (n=8,108)		**All Medicaid mothers (n=71,821)**		**P-value[b]**
	Yes	No	Yes	No	
Mother non-Hispanic black	5,252 (65)	2,856 (35)	36,659 (51)	35,162 (49)	<0.0001**
Mother high school graduate	5,463 (67)	2,645 (33)	50,880 (71)	20,841 (29)	<0.0001**
Received food stamps	4,837 (60)	3,271 (40)	38,797 (54)	33,024 (46)	<0.0001**
NDI below the median (4.8)	4,062 (50)	4,046 (50)	20,604 (29)	51,217 (71)	<0.0001**

[a] Both study population and all Medicaid mothers restricted by maternal race, gestational age, birth weight, to first baby temporally, and to mothers spatially linked to block group in which maternal residence at month 6 was located

[b] Chi-square test of independence

**Denotes significant differences at the p<0.05 level

Table A.2 Comparisons between study population mothers and all Medicaid mothers giving birth from 1996-2001 for continuous variables examined in Chapter 3[a].

	Study population (n=8,108)	**All Medicaid mothers (n=71,821)**	**P-value[b]**
Percent roads (%)	5.8 (3.4)	3.4 (2.6)	<0.0001**
Median age of home (years)	32.8 (12.6)	25.4 (45.5)	<0.0001**

[a] Both study population and all Medicaid mothers restricted by maternal race, gestational age, birth weight, to first baby temporally, and to mothers spatially linked to block group in which maternal residence at month 6 was located

[b] Analysis of variance

**Denotes significant difference at the p<0.05 level

APPENDIX B

SUPPLEMENTARY TABLES ASSOCIATED WITH CHAPTER 4

Table B.1 Comparisons of study population mothers to all Medicaid mothers giving birth from 1996-2001 for categorical variables examined in Chapter 4[a].

	Study population (n=8,108)		**All Medicaid mothers (n=71,821)**		**P-value[b]**
	Yes	No	Yes	No	
Mother non-Hispanic black	5,252 (65)	2,856 (35)	36,659 (51)	35,162 (49)	<0.0001**
Mother completed high school	5,463 (67)	2,645 (33)	50,880 (71)	20,841 (29)	<0.0001**
Received food stamps	4,837 (60)	3,271 (40)	38,797 (54)	33,024 (46)	<0.0001**
Male baby	4,186 (52)	3,922 (48)	36,776 (51)	35,045 (49)	0.47
Pregnancy tobacco use	1,337 (16)	6,771 (84)	14,529 (20)	57,292 (80)	<0.0001**
First trimester prenatal care	6,050 (75)	2,058 (25)	52,024 (72)	19,797 (28)	<0.0001**
Infection[c]	1,641 (20)	6,467 (80)	14,407 (20)	57,414 (80)	0.70
Majority population urban[d]	7,124 (88)	984 (12)	42,087 (59)	29,734 (41)	<0.0001**

[a] Both study population and all Medicaid mothers restricted by maternal race, gestational age, birth weight, to first baby temporally, and to mothers spatially linked to block group in which maternal residence at month 6 was located

[b] Chi-square test of independence

[c] Includes bacterial urinary tract infection, genital herpes, gonorrhea, chlamydia, trichomoniasis, chorioamnionitis, candidiasis, cervicitis, and pelvic inflammatory disease

[d] Mother's residence at month 6 of pregnancy was located in a block group where >50% of the population lived in urban areas

**Denotes significant differences at the $p<0.05$ level

Table B.2 Comparisons between study population mothers and all Medicaid mothers giving birth from 1996-2001 for continuous variables examined in Chapter 4[a].

	Study population (n=8,108)	**All Medicaid mothers (n=71,821)**	**P-value[b]**
Maternal age	22.6 (5.4)	22.7 (5.4)	0.21
Parity	0.81 (1.1)	0.77 (1.1)	0.004**
NDI[c]	5.2 (2.4)	4.0 (1.8)	<0.0001**
Isolation index	0.21 (0.16)	0.15 (0.16)	<0.0001**

[a] Both study population and all Medicaid mothers restricted by maternal race, gestational age, birth weight, to first baby temporally, and to mothers spatially linked to block group in which maternal residence at month 6 was located

[b] Analysis of variance

[c] NDI: neighborhood deprivation index; composite measure based on 10 United States Census 2000 block group variables

**Denotes significant difference at the p<0.05 level

APPENDIX C

EXAMPLE BAYESIAN POISSON SPATIO-TEMPORAL MODEL CODE (FROM WINBUGS 14)

```
model
{
for(i in 1:N)
{
for (t in 1:T)
{

Y[i,t] ~ dpois(mu[i,t])
log(mu[i,t])<-
log(expt[i,t])+beta1+beta2*aa[i,t]+beta3*fs[i,t]+beta4*momage[i,t]+u[i]+v[i]+delta[t]

RR[i,t]<-exp(beta1+beta2*aa[i,t]+beta3*fs[i,t]+beta4*momage[i,t]+u[i]+v[i]+delta[t])

}
RR1[i] <- RR[i,1]
RR2[i] <- RR[i,2]
RR3[i] <- RR[i,3]
RR4[i] <- RR[i,4]
RR5[i] <- RR[i,5]
RR6[i] <- RR[i,6]

u[i] ~ dnorm(0, precu)

}
v[1:N] ~ car.normal(adj[], weights[], num[], precv)
for(k in 1:sumnum){weights[k]<-1}

delta[1] ~ dnorm(0,precdelta)
for (t in 2:T) {
delta[t]~dnorm(delta[t-1], precdelta)
}

beta1 ~ dnorm(0,1.0E-5)
beta2 ~ dnorm(0,1.0E-5)
beta3 ~ dnorm(0,1.0E-5)
beta4 ~ dnorm(0,1.0E-5)
```

```
precu ~ dgamma(0.1, 0.1)
precv ~ dgamma(0.1, 0.1)
precdelta ~ dgamma(0.01, 0.01)
sigmau<-1/precu
sigmav<-1/precv
sigmadelta<-1/precdelta
}
```