

Spatial Modeling of Measurement Error in
Exposure to Air Pollution

by

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Dissertation submitted in partial fulfillment of the requirements for the degree of
Doctor of Philosophy in the Department of Statistical Science
in the Graduate School of Duke University
2010

ABSTRACT
(Statistics)

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Abstract

In environmental health studies air pollution measurements from the closest monitor are commonly used as a proxy for personal exposure. This technique assumes that air pollution concentrations are spatially homogeneous in the neighborhoods associated with the monitors and consequently introduces measurement error into a model. To model the relationship between maternal exposure to air pollution and birth weight, we build a hierarchical model that accounts for the associated measurement error. We allow four possible scenarios, with increasing flexibility, for capturing this uncertainty. In the two simplest cases, we specify one model with a constant variance term and another with a variance component that allows the uncertainty in the exposure measurements to increase as the distance between maternal residence and the location of the closest monitor increases. In the remaining two models, we introduce spatial dependence in these errors using spatial processes in the form of random effects models. We detail the specification for the exposure measure to reflect the sparsity of monitoring sites and discuss the issue of quantifying exposure over the course of a pregnancy. The model is illustrated using Bayesian hierarchical modeling techniques that relate pregnancy outcomes from the North Carolina Detailed Birth Records to air pollution data from the U.S. Environmental Protection Agency.

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Introduction

1.1 Background and Motivation

The association between maternal exposure to air pollution and adverse health outcomes has been extensively investigated. Researchers have shown that increased levels of air pollution have been linked to significant increases in both mortality and morbidity (Dockery *et al.*, 1993; Schwartz, 1994, 1999; Hoek *et al.*, 2001). Studies have also shown that exposure to air pollution may not affect all individuals in a population the same way or even at the same rate (Woodruff *et al.*, 1997; Brunekreef and Holgate, 2002; Bell *et al.*, 2008; Currie *et al.*, 2009). Based on these disparities in the potential health impact, much emphasis has been placed on *at risk* sub-populations including elderly individuals, infants and children, and pregnant women (NRC, 1998). This dissertation directly addresses some well-known challenges in modeling exposure assessment, and introduces new modeling approaches implemented on the effects of air pollution on pregnancy outcomes.

When trying to assess the relationship between air pollution exposure and its effect on pregnancy outcomes, difficulty lies in trying to calculate an accurate

personal exposure measure throughout the gestational period. Traditional proximity models often involve using air pollution measurements from fixed site monitoring stations as a proxy for personal exposure (Bobak, 2000; Dugandzic *et al.*, 2006; Bell *et al.*, 2007; Hansen *et al.*, 2008). Building models based on the assumption that air pollution levels are spatially homogeneous across large surface areas, like counties or cities, can bias the estimation of the health risk. The problems associated with exposure measurement error are well known and correcting this issue is often quite difficult due to the unavailability of accurate estimates of personal exposure.

Without exact personal exposure measurements, statistical modeling techniques are used to account for the measurement error inherent in air pollution exposure studies. Some of these approaches make use of geo-referenced data for the locations of the monitoring stations. Exposure predictions can be computed using kriging methods, inverse-distance weighting, or other statistical exposure prediction models (Mulholland *et al.*, 1998; Jerrett *et al.*, 2001; Gryparis *et al.*, 2007). An obvious advantage when using these statistical techniques is the removal of the assumption that personal exposure is constant over an entire region for all study participants. This, in turn, is expected to reduce the exposure measurement error and increase the accuracy of the resulting model inference.

In environmental health effects studies using geographically referenced data, Bayesian hierarchical models are particularly well-suited for modeling the exposure-response relationship while capturing spatial association and uncertainty. Combined with spatial statistics, Bayesian hierarchical models have given researchers the ability to incorporate complex models involving multiple layers into their analyses. The use of Bayesian methods and Markov chain Monte Carlo (MCMC)

techniques can alleviate some of the computational challenges presented by large datasets and complicated models.

In the current work, we model the relationship between maternal exposure to air pollution and birth weight on the State of North Carolina. We use a Bayesian hierarchical model that reflects the exposure-response relationship and places emphasis on accounting for the associated measurement error. Unlike traditional methods which assume that monitored exposure measures represent personal exposure, we add uncertainty to the model in four different ways:

1. A random normal error model with constant variance
2. An error model with non-constant variance
3. A spatial random effects model with homogeneous variance
4. A spatial random effects model with non-constant variance.

All four models use an original approach for attempting to capture the uncertainty incurred from using the estimates from the closest monitor. The first two proposed models are non-spatial and do not require the specification of a covariance function. These two models differ based on the construction of the variance specification. In the random error model, the variance is constant while in the second model, uncertainty is dependent on the distance between maternal residence and the location of the closest monitor (space), and the duration of the pregnancy (time). The remaining two models mirror the first two but include spatial process dependence in the form of random effects.

1.2 Personal Exposure

Research has shown that exposure to air pollution during pregnancy may elevate the risk of adverse birth outcomes. Because poor birth outcomes are important indicators of infant and childhood health and development, and accurate personal exposure assessment is extremely critical. Exposure prediction models such as land use regression (LUR) models and interpolation models have been developed with the use of geographic information systems (GIS) tools and geo-statistical techniques (Jerrett *et al.*, 2005). These models attempt to address some of the limitations associated with using monitoring station data as proxies for personal exposure.

Both LUR models and interpolation models are limited by data collection problems, as the models are based upon the locations of sparse monitoring stations. Interpolation to areas further away from any monitors can be unreliable and can introduce large errors in the generated pollution surfaces (Jerrett *et al.*, 2005). Scientists have realized the need to develop more sophisticated pollution surfaces that incorporate spatial methodology (Kaiser *et al.*, 2002; Huerta *et al.*, 2004).

There are many factors that need to be considered when modeling personal exposure. As previously mentioned, ambient concentration levels may not be spatially homogenous, and proximity models do not take this fact into account. There are several other sources that can affect the spatial patterns of the pollutants including weather and other meteorological conditions, as well as the chemical composition of the pollutants themselves. Much effort has been made to gain a better understanding of the underlying spatial distribution of the pollution measurements in order to build accurate personal exposure models (Christakos and

Serre, 2000; Kyriakidis and Journel, 2001; Diem, 2003; Gilbert *et al.*, 2005; Lindley and Walsh, 2005).

It has been well-documented that models using air pollution measurements from fixed site monitoring stations as a proxy for personal exposure suffer from well-established problems associated with measurement error (Zeger *et al.*, 2000; Gryparis *et al.*, 2009). With limited data availability, using these exposure measurements is necessary in order to better understand the relationship between air pollution exposure and human health. Although we are restricted to the air pollution data from the monitoring stations, we present methodology for building a measurement error model that adjusts for the incurred uncertainty.

Exposure to air pollution during pregnancy is an important regulatory and public health issue. Models that fail to account for the exposure error can lead to problems with estimation and inference of parameters. This study addresses the measurement error problems connected with using monitoring station data by adding suitable uncertainty which is propagated into a hierarchical birth weight regression model.

1.3 Thesis Outline

This thesis uses Bayesian hierarchical modeling techniques to address the issues surrounding exposure misclassification in the study of maternal exposure to air pollution and birth weight. The main objective is to gain a better understanding of the relationship between air pollution exposure and birth outcomes. We model this relationship by using statistical methods that incorporate both spatial modeling techniques and methods that account for the associated exposure measurement error.

Chapter 2, gives a brief overview of modeling air pollution and pregnancy outcomes. We discuss the challenges that come from investigating this exposure-response relationship and focus mainly on the measurement error problem. With individual level maternal and infant health data from the North Carolina Detailed Birth Records (NCDBR) and air pollution monitoring station data from the U.S. Environmental Protection Agency (USEPA), we begin with an exploratory analysis of these two combined datasets. We explore how ambient exposure measures from monitoring stations connect to pregnancy outcomes in order to understand how to incorporate the different estimates of exposure (e.g., cumulative, episodic, extremes) in the exposure-response relationship. We specify a linear relationship between average air pollution exposure and birth weight, adjusted for standard covariates. We explore how robust the air pollution and birth weight relationship is to different air pollution measurements that vary by spatial resolution. We include exposure as a continuous measure, a categorical variable, and with a piece-wise linear spline function. We compare the output across all three exposure specifications.

Chapter 3, accounts for the uncertainty related to using a local measure of air pollution exposure based upon monitoring station data. We describe the hierarchical model specification with four possible scenarios, each with increasing flexibility, for capturing this uncertainty. For comparability, we first develop a simple model with a random independent normal error structure. The second model incorporates an error term with a non-constant variance component to model the unobserved true exposure measurement. We construct the distribution for the error terms such that the variance depends on the Euclidean distance between the maternal residence and the location of the closest monitor. We define

the variance such that the uncertainty in the exposure measurement increases as the distance between the maternal residence and the closest monitoring station increases.

Building on the assumption that the error terms are spatially varying, the final two models incorporate the spatial association among the error terms using spatial processes. We introduce spatial dependence in the errors in the form of random effects models. Similar to the first two non-spatial models, we build the two spatial models such that one has a constant variance and the other has a non-homogenous variance. We detail the specification for the exposure measure to reflect the sparsity of monitoring sites and discuss the issue of quantifying exposure over the course of a pregnancy.

Chapter 4, uses the birth record data from the NCDBR and air pollution data from the USEPA to build the hierarchical measurement error models. Using birth weight as the continuous outcome variable, we model the relationship between air pollution exposure averaged over the entire pregnancy and birth weight. We account for the associated measurement error using the four error models described in Chapter 3. We compare the results from all four hierarchical models with those from the simple least squares regression model.

Chapter 5, generalizes the modeling techniques from Chapter 3. We illustrate the methodology required for handling exposure metrics other than average exposure. Examples of other metrics can include a discrete measure of the number of days above a certain threshold or the number of consecutive days above that threshold. We view these metrics as functions of the predicted exposure. With careful construction, we show that the model can systematically accommodate other measures of air pollution exposure. We illustrate these generalized models

and summarize the results of our analyses. And finally, Chapter 6 concludes the dissertation with a brief discussion and directions for future work.

Air Pollution and Birth Weight Models

Air pollution exposure has been identified as a major environmental concern across the world. Many epidemiological studies have been conducted to investigate the effect of maternal exposure to air pollution on adverse pregnancy outcomes (Bobak, 2000; Ha *et al.*, 2001; Chen *et al.*, 2002; Dugandzic *et al.*, 2006; Bell *et al.*, 2007). Results of these studies have shown that exposure to air pollution may elevate the risk of adverse health outcomes, including mortality (Dockery *et al.*, 1993; Schwartz, 1994; Bell *et al.*, 2004), cardiovascular and respiratory morbidity (Dominici *et al.*, 2006) and pregnancy outcomes (Pope III *et al.*, 1995; Schulz *et al.*, 2005; Pope III and Dockery, 2006; Bell *et al.*, 2007). A more interesting fact surrounding these results is that the increases in mortality and morbidity seen in some of these studies occur with pollution levels at or below federal air quality standards (Dockery and Pope III, 1994; Brunekreef *et al.*, 1995; Gray *et al.*, 2009).

Focusing on the susceptible subgroup of pregnant women, evidence shows that exposure to air pollution may elevate the risk of adverse birth outcomes, including

low birth weight (LBW), preterm delivery (PTD), and small for gestational age (SGA) (Ritz *et al.*, 2000; Vassilev *et al.*, 2001; Lee *et al.*, 2003; Yang *et al.*, 2003; Lin *et al.*, 2004; Mannes *et al.*, 2005; Parker *et al.*, 2005). Evidence also shows that survivors of LBW, PTD, and SGA are at an increased risk for both short-term neonatal morbidity and long-term health effects (Hack *et al.*, 1995; Lemons *et al.*, 2001). Such effects include mental retardation (Lorenz *et al.*, 1998), severe vision loss (Crofts *et al.*, 1998; Lorenz *et al.*, 1998), deafness, learning disabilities (Resnick *et al.*, 1999; Saigal *et al.*, 2000), motor impairment (Ross *et al.*, 1990), and cerebral palsy (Kuban and Leviton, 1994), as well as hypertension, cardiovascular disease, and type-2 diabetes in adulthood (Osmond and Barker, 2000; Ashdown-Lambert, 2005). Exploring the effect of air pollution on the susceptible subgroup of pregnant women is important to policy makers and, more generally, the overall health of the nation (NRC, 1998, 2004).

Many researchers recognize that it is challenging to assess personal air pollution exposure during pregnancy. There are numerous methodological issues that arise when estimating the association between exposure and maternal health (Ritz and Wilhelm, 2008). In particular, we need to know how to introduce exposure into a statistical model, i.e., should it be cumulative, episodic, extremes, or exceedances. Other considerations for the model include the window of susceptibility, exposure assessment, classification, and, of course, the modeling technique to be used. If possible, it is important to understand and incorporate the spatial structure of the exposure measurements within the statistical models used. And finally, we also need to take into account the measurement error associated with estimating exposure to prevent misclassification of exposure estimates (Zeger *et al.*, 2000).

While several studies suggest that air pollution may be associated with

adverse birth outcomes, difficulty lies in trying to determine how ambient levels of exposure connect to personal levels of exposure. Due to the long term health impacts associated with air pollution's negative effect on maternal and child health, as well as the potential regulatory implications, it is imperative to use models that adequately reflect the uncertainty associated with exposure measurements. We attempt to better understand the relationship between maternal exposure to air pollution and birth outcomes by using statistical models that incorporate both spatial modeling techniques and methods for evaluating the associated measurement error. Understanding and addressing these environmental health issues on this vulnerable subgroup of pregnant women has been identified as a high priority task by the USEPA (NRC, 1998). Without proper modeling and measurement techniques of air pollution exposure, we risk using inaccurate results as the basis to make policy decisions that may negatively impact healthy pregnancies and birth outcomes.

2.1 Modeling Air Pollution and Birth Weight

Epidemiologists and policy makers are often interested in the effect of particulate air pollution on susceptible populations (NRC, 1998); thus pregnant women are of particular concern. Since the National Research Council (NRC) identified at risk subpopulations as a high priority research task, several studies have been conducted to better examine the effects of PM exposure and adverse pregnancy outcomes (Resnick *et al.*, 1999; Ritz *et al.*, 2000; Rogers *et al.*, 2000; Chen *et al.*, 2002; Rogers and Dunlop, 2006; Bell *et al.*, 2007). In the last of four reports produced by the NRC in 2004, the group determined that more research needs to be done in order to clarify uncertainties about impacts of maternal exposure

to PM on pregnancy and to understand how environmental factors can affect pregnancy outcomes (NRC, 2004).

The biological mechanisms by which air pollutants may influence birth weight and fetal growth are still unclear. Fetal health is influenced by maternal, placental, and fetal factors. Studies suggest that maternal exposure to air pollution may lead to placental inflammation, which impairs placental function, and chronic inflammation which may in turn result in growth restriction (Lee *et al.*, 2003). Data also suggest that fetuses may be more prone to genetic damage and may process toxicants less efficiently than adults (Perera *et al.*, 1999). Perera *et al.* (1999) propose that increased DNA adducts in the fetus relative to the mother could result in lower levels of detoxification enzymes and decreased DNA repair efficiency in the fetus. Similar to tobacco use during pregnancy, exposure to air pollution may affect maternal respiratory function or susceptibility to infections (Tabacova *et al.*, 1998) or may impair umbilical blood flow (Vorherr, 1982). The prenatal period is a critical window of vulnerability, and exposure to air pollution may affect fetal growth and the development of organ systems (Dejmek *et al.*, 1999; Selevan *et al.*, 2000). All these factors can influence PTD and intra-uterine growth restriction (IUGR), which may in turn lead to lower birth weight (Slama *et al.*, 2008).

The number of studies investigating the association of maternal exposure to air pollution and adverse pregnancy outcomes is growing worldwide (Glinianaia *et al.*, 2004). Studies have been conducted in various countries including the Czech Republic (Bobak, 2000), China (Wang *et al.*, 1997), South Korea (Ha *et al.*, 2001), Brazil (Gouveia *et al.*, 2004), Australia (Hansen *et al.*, 2006), Canada (Liu *et al.*, 2003b; Dugandzic *et al.*, 2006) and several location within the United States

(Chen *et al.*, 2002; Bell *et al.*, 2007). Although many of these studies have shown a negative association between air pollution and birth outcomes, the traditional techniques that are used for exposure assessment may actually misclassify exposure because of the way the exposure variable is measured and modeled (Thomas *et al.*, 1993; Zeger *et al.*, 2000; Dominici *et al.*, 2003).

Many of these studies are limited to sparsely located monitoring station data and average measurements are calculated from monitoring stations within city or county limits, or postal codes (Bobak, 2000; Dugandzic *et al.*, 2006; Bell *et al.*, 2007; Hansen *et al.*, 2008). Using measurements based on residing either within a certain geographic area or proximity to a monitoring station as a proxy for personal exposure assumes that air pollution levels are spatially homogeneous across the defined geographic regions. Although lacking in precision, this method of estimating exposure for an individual or a population has traditionally been used in air pollution and health effects studies (Dockery *et al.*, 1993; Samet *et al.*, 2000; Pope III *et al.*, 2002) as collection of accurate personal level exposures is often difficult and expensive.

Measuring human exposure to air pollution is quite challenging. It has been shown that exposure measurements from monitoring stations do not accurately represent personal exposure estimates (Goldstein, 1979; Lioy *et al.*, 1990; Mage and Buckley, 1995; Ozkaynak *et al.*, 1996; Janssen *et al.*, 1997, 1998; Haran *et al.*, 2002) and using these measurements as surrogates for true exposure without adjusting for the associated measurement error can possibly lead to inaccurate results (Thomas *et al.*, 1993; Zeger *et al.*, 2000). In using methods that fail to account for measurement error, scientists and policy makers could be making decisions on potentially invalid inferences.

Although we understand the limitations associated with using monitoring station data, we recognize that without actual personal exposure data available, station data can be useful for exploratory purposes. In fact, station data may be the only available source of exposure information. It is also worth mentioning that since the information from monitoring stations is used for regulatory and other policy related purposes, any results generated from the use of this data can also be valuable to policy makers.

Other challenges in exposure modeling, particularly for estimating exposure during a specified time period, include trying to determine how exposure should be calculated. Using daily averages dilutes information on days that were above a certain threshold. Averages of exposure for days that were consistently moderate compared to days that were mostly low with occasional high peaks may be exactly the same but may have different effects on pregnancy outcomes. Assessing exposure at various gestational periods is quite common, with some of these exposure windows including certain trimesters, the entire pregnancy and the last 4-6 weeks of gestation. These different and sometimes overlapping windows are an attempt to determine what the important period during pregnancy to measure is. Further research is still needed in order to determine the critical exposure window that should be used in an exposure-birth weight model (Sram *et al.*, 2005).

The NRC determined that more research needs to be done to:

1. Understand how environmental factors can affect adverse pregnancy outcomes
2. Clarify uncertainties about impacts of maternal exposure to particulate matter on pregnancy

3. Develop estimates of measurement error that can be incorporated into statistical models (NRC, 2004).

Our work focuses on these three concerns.

2.2 Exposure Measurement Error

The exposure measurement error problem arises from the assumption that the measured level of pollution observed from one or more central monitoring stations is the actual personal exposure measurement for an individual or population. Epidemiologists have recognized that it is extremely difficult and expensive to accurately measure personal exposure to air pollution and are also aware that ignoring measurement error can produce misleading conclusions (Thomas *et al.*, 1993; Mage and Buckley, 1995; Zeger *et al.*, 2000). As a result, the USEPA and the Committee on Research Priorities for Airborne Particulate Matter identified the development of sophisticated statistical methods designed to systematically address measurement error in estimating adverse health effects from particulate matter as a high priority task (NRC, 1998). These new methods should attempt to reduce the errors and biased estimates associated with personal exposure misclassification in health risk assessment studies (Brauer *et al.*, 2002).

Measurement error is an inherent limitation to environmental studies that involve modeling the relationship between air pollution exposure and adverse health outcomes. Rarely is it possible to measure air pollution exposure accurately. Studies have shown that measurement error in a single covariate can affect the relationship between the response variable and other covariates that may not be measured with error (Greenland, 1980; Brenner, 1993). The measurement error incurred when using exposure variables that are surrogates for true personal

exposure can lead to biased estimates in regression coefficients and measures of relative risk that usually tend towards the null value (Gilks *et al.*, 1996; Armstrong, 1998; Zeger *et al.*, 2000). In addition to biased estimates, exposure error can also reduce the power of a study, making it more difficult to find significant associations or threshold levels, should they exist (Cakmak *et al.*, 1999; Carrothers and Evans, 2000; Brauer *et al.*, 2002).

2.2.1 Classical Error and Berkson Error

There are two distinct versions of error models for air pollution studies that use individual level surrogate measurements as estimates for true personal exposure. Both models attempt to describe the relationship between a particular outcome Y and the true but unobserved exposure measurement X for each individual. Instead of having the true value X for each individual, there is the observed surrogate measure Z of X . The differences between the Classical and Berkson error models occur when describing the relationship between the true unobserved measurement X and the observed surrogate measurement Z . The classical error modeling uses a hierarchical specification to combine information about three relationships (Gilks *et al.*, 1996; Molitor *et al.*, 2006), namely

1. The disease model which measures the association between the outcome Y and the true unobserved personal exposure measurement X .
2. The measurement model which models the association between the observed exposure measurements Z and the unobserved exposure measurements X .
3. The exposure model which models the distribution of the unobserved exposure X .

Under the classical error model assumptions, the measurement model states that the surrogate measure Z is randomly distributed around the true value X with the property $E[Z|X] = X$. Although this is the most common error model used to adjust exposure measurement error, it makes assumptions that can lead to underestimating of the the regression coefficient associated with the true unobserved exposure measurement (Navidi *et al.*, 1994; Zeger *et al.*, 2000; Dominici *et al.*, 2000, 2003). Other methods have been developed to quantify and account for the exposure measurement bias (Carroll *et al.*, 1995; Zidek *et al.*, 1996; Dominici *et al.*, 2000).

In the Berkson error model, the measurement model assumes that the true exposure measurement X is randomly distributed around the observed value Z with the property that $E[X|Z] = Z$. With a disease model that is linear in X , unbiased parameter estimates are produced; see Armstrong (1990) and Thomas *et al.* (1993) for details. Another important consequence with the Berkson error model is that the need to specify the marginal distribution of the observed exposure Z is completely eliminated, producing a more parsimonious hierarchical model (Gilks *et al.*, 1996). The Berkson error model is most appropriate when a group of individuals is assigned the same approximate exposure measurement (Thomas *et al.*, 1993; Armstrong, 1998).

2.2.2 Accounting for Measurement Error

Several methods of correcting for measurement errors have been explored in epidemiological studies (Thurigen *et al.*, 2000). Measurement error correction schemes vary based on the modeling techniques used e.g., Bayesian or frequentist, as well as the properties of the measurement error model that are considered, e.g.,

classical or Berkson, and additive or multiplicative (Carroll, 1989; Armstrong, 1990; Thomas *et al.*, 1993). Some of these techniques, while accounting for measurement error, may also introduce different types of biases (Zidek *et al.*, 1996; Armstrong, 1998; Zeger *et al.*, 2000).

Building a hierarchical measurement error model with a spatial component is easily handled in a Berkson environment. The Berkson error model specifies the distribution of the true unobserved exposure X as being dependent on the observed exposure measurement Z . At this stage, the spatial component can be incorporated in the model, and the true exposure X can be directly specified into the disease model. This model is desirable because it provides an unbiased estimate of the regression coefficient associated with the true exposure measurement X while accounting for the spatial variability of the error terms.

In a time-series study, Cakmak *et al.* (1999) use a multiplicative classical error model where $Z = X\epsilon$, and the error terms have unit expectation. With this model, the estimates for the variance of the error terms capture different amounts of measurement error. In another time-series study, Dominici *et al.* (2000) use a hierarchical Berkson error model to account for the measurement error in an air pollution and mortality study. They use a linear regression model for the error specification: $X = a_0 + a_1Z + \epsilon$. Thomas *et al.* (1993) discuss other statistical methods for adjusting for exposure measurement error. In the specification of the distribution of the true exposure measure, the authors suggest the use of either a parametric form of X that closely resembles that of Z or a non-parametric likelihood estimation technique.

Regression calibration has also been explored in multiple logistic regression, linear, and nonlinear models (Armstrong, 1985; Rosner *et al.*, 1989; Carroll *et al.*,

1994, 1995). In recent environmental health effects studies, Bayesian hierarchical models have been used to address the measurement error problem (Dominici *et al.*, 2000; Richardson and Best, 2003). Longitudinal studies have been considered as another alternative for addressing the measurement error problem (Liu *et al.*, 2003a; McBride *et al.*, 2007). These studies allow a small subset of the study population to wear personal monitoring devices to give accurate measures of exposure to pollution. Combining these now observed true exposure estimates and other relevant environmental covariates, models can be built that relate this true exposure measure to the ambient monitored pollution measures. A limitation to these studies occurs when these exposure models are based on a small sample size and are used to interpolate personal exposure for an entire population.

In addition to incorporating measurement error in exposure-response models, it has been recognized that the error associated with estimating the true exposure of an individual from the observed measurement at a fixed monitoring site varies with spatial location (Zeger *et al.*, 2000; Molitor *et al.*, 2007). Some studies recognize the need to incorporate this spatial component in model-building (Crooks *et al.*, 2009). Instead of focusing only on modeling both the unobserved “true” personal exposure and the measured exposure in order to eventually express the relationship between the true unobserved exposure and the disease or outcome (Zeger *et al.*, 2000; Molitor *et al.*, 2006, 2007), some studies view the measurement error problem as a spatial misalignment problem. With the locations of the monitoring stations being fixed, the covariates and outcomes can be viewed as being measured at different locations, which leads to spatial misalignment in the health effects analysis (Peng and Bell, 2008; Gryparis *et al.*, 2009).

Although several studies suggest that air pollution exposure may be associated

with adverse birth outcomes, assessing air pollution exposure during pregnancy remains challenging. There are numerous methodological issues that arise when estimating the association between exposure and maternal health. The focus of this work is to overcome some of these challenges.

2.3 Data

2.3.1 AQS Data and Particulate Matter

The USEPA sets national ambient air quality standards (NAAQS) for six common air pollutants, called criteria pollutants. The pollutants are particulate matter (PM), ground-level ozone, carbon monoxide, sulfur oxides, nitrogen oxides (NO_x), and lead. There are two sizes of particulate matter, PM_{10} and $PM_{2.5}$. Coarse PM, less than or equal to 10 micrometers in diameter (PM_{10}), are inhalable particles that can travel through the nose and throat into the lungs, where they can enter the bloodstream and cause adverse health effects (USEPA, 2006b). PM_{10} is composed mostly of larger primary particles emitted directly in the atmosphere through both anthropogenic and natural sources. These sources can include traffic-related emissions such as tire and brake lining materials, direct emissions from industrial, agricultural and mining operations, as well as spores, pollen and bacteria. Fine PM with a diameter of 2.5 micrometers or less ($PM_{2.5}$), is a combination of respirable fine solids produced chiefly by combustion processes and by atmospheric reactions of various gaseous pollutants such as volatile organic compounds (VOCs), sulfur dioxide (SO_2), and NO_x (USEPA, 2006a).

The current short term federal standard for $PM_{2.5}$ is 35 micrograms per cubic meter ($\mu g/m^3$) of air averaged over 24 hours. The long term standard of $PM_{2.5}$ is an annual mean of $15.0 \mu g/m^3$ averaged over a three-year period for each monitor

(USEPA, 2005). In October 2006, the USEPA rescinded the $50 \mu\text{g}/\text{m}^3$ annual standard for PM_{10} , citing a lack of association between long-term exposure to current ambient levels of PM_{10} and adverse health effects (USEPA, 2006a). Consequently, there is currently no annual standard for PM_{10} . At the same time, the USEPA retained the short term federal standard for PM_{10} of 150 micrograms per cubic meter ($\mu\text{g}/\text{m}^3$) of air averaged over 24 hours (not to be exceeded more than once per year on average over 3 years) at each monitor.

The air quality in North Carolina is regulated using a sparse network of monitoring sites. It is important to note that these sites were established for regulatory purposes and not for health effects studies. As a result, many of the monitoring stations are intentionally placed closer to major cities and roadways. Figure 2.1 shows the locations of the PM_{10} and $PM_{2.5}$ monitors in the state. Most of the PM monitors are located along the I-40, I-85 and I-95 corridors.

The air pollution datasets for PM_{10} and $PM_{2.5}$ were obtained from the Air Quality System (AQS) data available from the USEPA for 1999-2002. Preliminary analyses used births between the years of 2000-2002, and air pollution exposures from 1999-2002, since exposures for some 2000 births would have occurred in 1999. The AQS data contained the daily 24-h average concentration ($\mu\text{g}/\text{m}^3$) for PM_{10} and $PM_{2.5}$. There were between 27 and 37 active PM_{10} monitors and between 37 and 41 active $PM_{2.5}$ monitors in North Carolina during 1999-2002. The monitoring stations recorded pollution measurements either every day, every 3 days, or every six days.

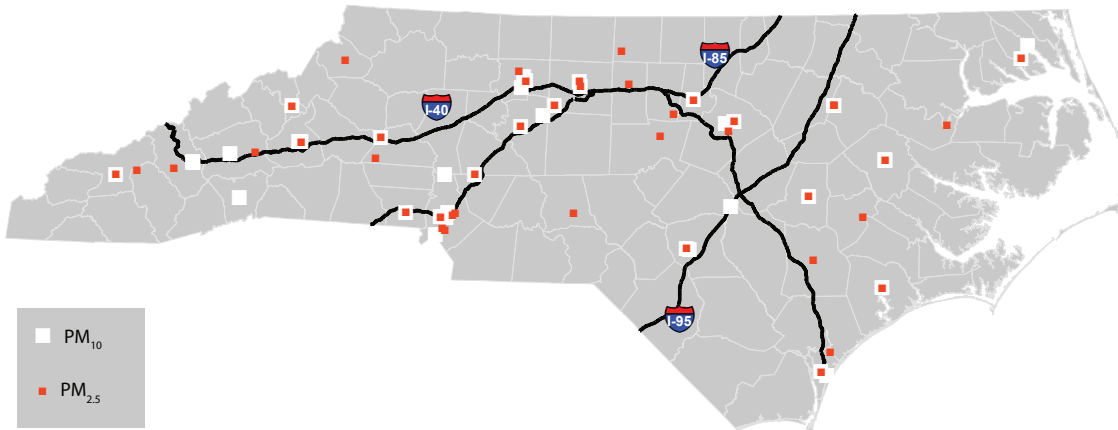


FIGURE 2.1: Locations of the PM_{10} and $PM_{2.5}$ monitors in North Carolina.

2.3.2 NCDBR

The NCDBR data were obtained from the North Carolina State Center for Health Statistics. The NCDBR data contain information on both birth outcomes and parental demographics for all registered births in North Carolina for the years 2000-2002 ($n=350,754$). The recorded birth information in the NCDBR used in this study included gestational age (weeks), infant sex, birth weight, and year of birth. The maternal characteristics recorded in the NCDBR included residential address, age, marital status, education, race and ethnicity, alcohol and tobacco use, plurality, birth order, and the trimester in which prenatal care began.

To link births from the NCDBR to the air pollution data, we street geocoded the residential addresses in the dataset at the individual record level (all spatial data management was performed using ArcGIS 9.2 produced by ESRI, Redlands, CA). The total births successfully geocoded using the maternal residence at the time of delivery in North Carolina can be seen in Figure 2.2. We excluded multi-fetal births (3.3%) and infants characterized by congenital anoma-

lies (0.9%). These exclusions were chosen in order to focus on those pregnancies that could reasonably be expected to go to term and deliver at a normal birth weight. Women under age 15 and over age 44 years (0.3%), or those with reported alcohol consumption (0.6%) were also excluded. As 95% of the women in the dataset self-declared as non-Hispanic white, non-Hispanic black, or Hispanic, we excluded other races/ethnicities due to the small sample size for these groups. We excluded births with gestation less than 32 and greater than 44 weeks (2.2%), birth weight less than 1000 g and greater than 5500 g (1.0%), impossible birth weight and gestation combinations (0.1%) (Alexander *et al.*, 1996), and mothers with any missing data on covariates (1.0%), leaving 259,962 cases.

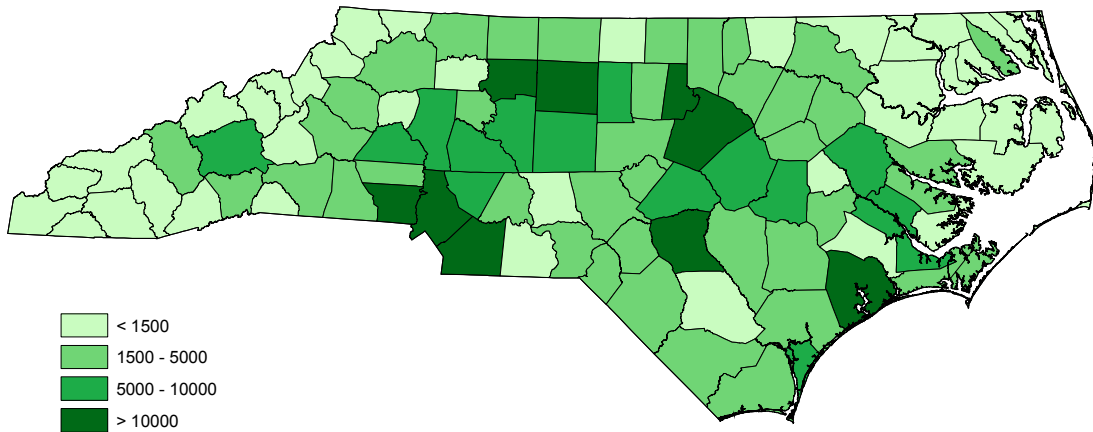


FIGURE 2.2: Total geocoded births by county for 2000-2002

2.4 Preliminary Analyses

This sensitivity analysis compared birth weight regression results using exposure metrics for PM_{10} and $PM_{2.5}$ at various spatial resolutions from 2000-2002 in North Carolina. We evaluate how robust the air pollution and birth weight relationship is to different air pollution measurements. This will serve as preliminary analyses

for the more complicated models described in Chapter 3. For comparability to other studies, we use air pollution metrics based on county averages for the entire state. We then use buffering schemes associated with proximity models of 20, 10 and 5 km radii and compare how these different exposure metrics affect the birth weight model. For the county level model, we focused on women who lived in a county with an active monitoring station whereas for the proximity models, we used only women within a 20-, 10-, and 5-km buffer of a monitoring station. A map of North Carolina with the locations of the PM_{10} and $PM_{2.5}$ monitors and the distance buffers can be seen in Figure 2.3.

2.4.1 Exposure Assessment

To estimate air pollution exposure for the proximity models, each mother's residence at the time of delivery was linked to the closest active monitoring station. The weeks of exposure were calculated based on the actual weeks of pregnancy as recorded in the NCDBR. As birth date and gestational age were supplied as part of the NCDBR data, we calculated the number of weeks of gestation from the delivery date to determine an estimated date of conception for each woman in the study. We note that gestational age is reported as a clinical estimate of the number of completed weeks of gestation and is also a source of potential measurement error.

Average maternal exposure was calculated for each pollutant separately by averaging the weekly data of the closest monitoring station for each trimester of the pregnancy. The trimester variable was constructed based on the following categorization: 1-13 weeks of gestation, 14-26 weeks of gestation, and 27 weeks of gestation until birth. Exposure estimates averaged over the entire pregnancy

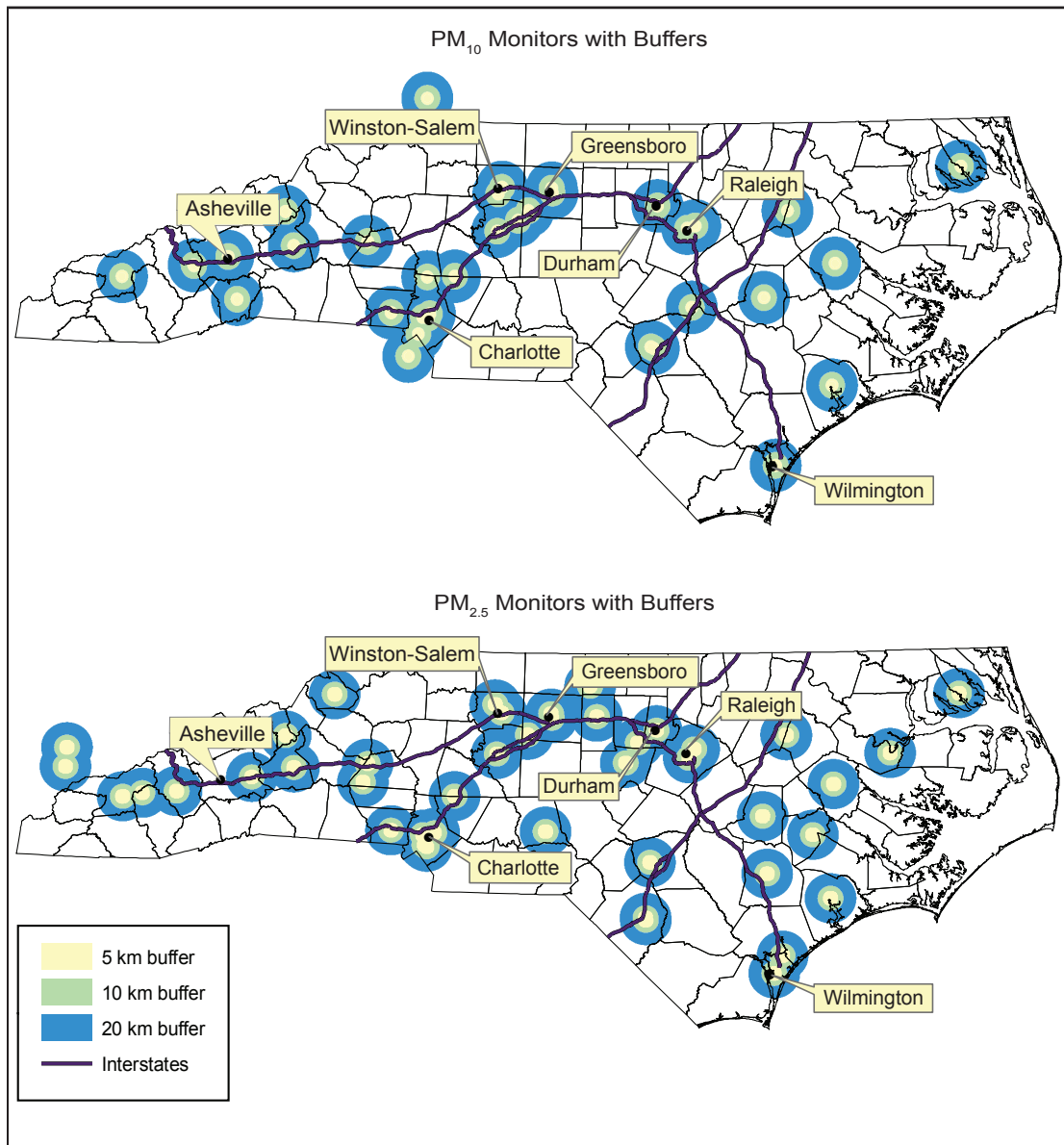


FIGURE 2.3: Distance Buffers for PM_{10} and $PM_{2.5}$ monitors

were also calculated for each pollutant. We constructed this cumulative exposure measure using average concentration measures over specified pregnancy windows as averages take into account the variable length of pregnancy associated with each mother in the study.

The AQS data were not available for every day and week of the years 1999-2002. For each birth, the completeness of the exposure dataset was identified by taking the number of weeks of gestation and dividing it by the number of AQS concentration values for that birth. If the birth had more than 75% of the data and there was no more than one consecutive missing concentration value for that birth, then the average of the concentrations for the weeks before and after the missing value were used as a proxy for the exposure concentration during that week. If there was more than one consecutive missing value for a birth, then that birth was not included in the dataset because a sufficient proxy for the two weeks or more of missing air quality data was not available. After all exclusion criteria, exposure estimates were calculated for 195,141 mothers for at least one of the pollutants of interest.

2.4.2 Regression Model

Multiple linear regression modeling was used to determine the association between exposure to the pollutants of interest, PM_{10} and $PM_{2.5}$, and birth weight. Using birth weight as a continuous outcome variable, we controlled for gestational age (32-34, 35-36, 37-38, 39-40, 41-42, 43-44 weeks) maternal race/ethnicity (non-Hispanic black, non-Hispanic white or Hispanic), maternal education (<9, 9-11, 12, 13-15, >15 years), maternal age (15-19, 20-24, 25-29, 30-34, 35-39, 40-44 years), trimester prenatal care began, tobacco use during pregnancy (yes or no), marital status (married or unmarried), year of birth, firstborn (yes or no), and infant sex (male or female) in separate models for PM_{10} and $PM_{2.5}$. The exposure estimates were considered as continuous variables. We then examined the exposure response relationship with county-wide estimates and estimates for mothers within

20, 10, and 5 km of a monitoring station.

A baseline model without the air pollution variables was constructed to examine which of the standard covariates mentioned above affect birth weight in the sample. We constructed separate models for PM_{10} and $PM_{2.5}$ due to the high correlation between the two pollutants ($r \sim 0.7$). For comparability to previous studies, we constructed models using all three trimester exposure estimates in the same model, as well as models with a pregnancy-long estimate (Maisonet *et al.*, 2001; Glinianaia *et al.*, 2004; Salam *et al.*, 2005). All risk factors considered were observed as being associated with birth weight in recent literature (Bobak, 2000; Maroziene and Grazuleviciene, 2002; Liu *et al.*, 2003b; Dugandzic *et al.*, 2006; Bell *et al.*, 2007).

2.4.3 *Non-Linear Models in Exposure*

In addition to using the continuous measure of exposure, we also introduce exposure as a categorical variable and, alternatively, with a piecewise linear spline function. Research has shown that higher levels of exposure may affect birth weight at a different rate than lower levels of exposure (Wang *et al.*, 1997; Yang *et al.*, 2003; Wilhelm and Ritz, 2005; Ritz *et al.*, 2007). We construct these two additional measures of exposure as the relationship between exposure and birth weight may not necessarily be explained by a single regression line.

For the categorical measure, the exposure estimates were divided into tertiles to correspond with low (< 33 rd percentile), medium (33rd to < 67 th percentile) and high (≥ 67 th percentile) levels of exposure. Exposure corresponding to low levels was used as the referent category in order to compare changes in birth weight for infants in the two highest exposure categories with those in the lowest exposure

category. One criticism of using such a categorical analysis is the inherent loss of information that occurs when collapsing the data into these three specified bins. However, we view the work in this chapter as primarily exploratory.

To make use of the information contained within each category, we also fit a piece-wise continuous function on the exposure measure. This alternative to the categorical analysis is suggested by Greenland (1995). We use a piecewise linear spline with predetermined knots c_1 , and c_2 , placed on the first and second tertiles of the data. Similar to the construction used for the categorical measure, we divided the range of exposure into three parts and fit separate slopes for each piece. This allows the level of the covariate to vary across the three continuous measures of exposure. Applying this approach to the data, we let X_i represent the average PM concentration during the entire pregnancy of each mother and Y_i denote the birth weight response variable. The piecewise linear spline model is defined by

$$\begin{aligned}
 Y_i &= \beta_0 + \mathbf{W}^T \boldsymbol{\beta}_W + \beta_{X_1} X_i + \epsilon, & X_i \leq c_1 \\
 &= \beta_0 + \mathbf{W}^T \boldsymbol{\beta}_W + \beta_{X_1} X_i + \beta_{X_2} (X_i - c_1) + \epsilon, & c_1 < X_i \leq c_2 \\
 &= \beta_0 + \mathbf{W}^T \boldsymbol{\beta}_W + \beta_{X_1} X_i + \beta_{X_2} (X_i - c_1) + \beta_{X_3} (X_i - c_2) + \epsilon, & X_i > c_2
 \end{aligned}$$

where $\boldsymbol{\beta}_W$ and β_X are unknown parameters, \mathbf{W}^T is a vector of personal covariates that affect birth weight, and $\epsilon_Y \sim N(0, \sigma_Y^2)$ is a random normal error term.

Using the exposure estimates summarized over the entire pregnancy, we fit the models with these alternative exposure measures for both pollutants. We compare all the models using the standard measures of model fit. We calculate the empirical coverage of the distribution, the root mean squared error (RMSE), and the R-squared statistic (R^2).

2.4.4 Summary of Results

Our analysis included estimating pollution exposures for sample populations at the county level, and within the 20-, 10-, and 5- km radial buffers surrounding the monitors. At the county level, there were 195,141 observations with the restrictions described above and 167,851, 110,555, and 56,043 births at 20, 10 and 5 km, respectively. Table 2.1 shows the summary statistics for each of the four sample populations (county and 20, 10, and 5 km buffers). Among the 195,141 county-level births, the mean birth weight was 3,368 g, and the prevalence of LBW was 5.4%. Approximately 11% of mothers reported smoking during pregnancy. Most of the mothers were non-Hispanic white (61%), married (68%), and with more than a high school education (52.8%).

The descriptive characteristics of the mothers living within 20 and 10 km of a monitoring station are similar to those in the county level dataset. Some maternal demographics change with proximity to the monitoring station, including maternal race/ethnicity, maternal education, and marital status. Moving from 20 km away to 5 km away from a monitoring station increases the non-Hispanic black population by approximately 14% and Hispanic population by 6.2%. There is also a decrease in the mothers with more than a high school education, as well as those who are married, as residence gets closer to a monitor. This suggests that monitors tend to be located in areas with lower socioeconomic status. The incidence of LBW increases from 5.2% at 20 km to 6.3% at the 5 km buffer.

The means \pm standard deviations (SD) along with the interquartile range (IQR) are shown in Tables 2.2 and 2.3 for the county level and 20 km models, respectively. Tables 2.2 and 2.3 also show the 25th, 50th and 75th percentiles of the average exposure of both pollutants by exposure period.

Table 2.1: Summary statistics of the study population.

	20 km	10 km	5 km	County
Total Births	167,851	110,555	56,043	195,141
Mean birth weight(g) \pm SD	3372 \pm 528.4	3353 \pm 530.5	3311 \pm 531.9	3368 \pm 530.9
% LBW	5.2	5.6	6.3	5.4
Mean gestation (wks)	38.9 \pm 1.6	38.9 \pm 1.6	38.9 \pm 1.7	38.9 \pm 1.6
% Male	50.9	51.0	50.7	51.0
% Firstborn	42.8	43.3	42.3	42.9
<i>% Prenatal Care Began</i>				
First Trimester	86.2	84.6	81.2	86.0
Second Trimester	10.8	12.0	14.6	11.0
Third Trimester	1.7	2.0	2.5	1.7
None	0.7	0.9	1.2	0.8
Unknown	0.6	0.5	0.5	0.5
<i>% Race/ Ethnicity</i>				
NHW	61.7	52.9	41.9	61.1
NHB	25.7	32.2	39.4	26.1
HISP	12.6	14.9	18.8	12.8
<i>% Maternal Education</i>				
< 9 years	5.5	6.6	9.0	5.7
9-11 years	13.8	15.1	19.2	13.9
12 years	27.5	28.0	29.3	27.7
13-15 years	22.3	21.5	19.5	22.3
> 15 years	31.0	28.8	23.0	30.5
<i>% Maternal Age</i>				
15-19 years	10.6	11.6	13.9	10.8
20-24 years	25.4	27.4	30.3	25.7
25-29 years	26.8	26.3	25.2	26.9
30-34 years	24.7	23.0	20.1	24.4
35-39 years	10.7	9.9	8.9	10.5
40-44 years	1.8	1.7	1.6	1.8
% Tobacco Use	11.2	10.7	11.4	10.9
% Married	68.4	63.1	54.0	68.2

Summary statistics of the PM_{10} and $PM_{2.5}$ averages for the 10 and 5 km models (not shown) were similar to the results at the 20 km level. For the 10 km buffer there were 75,111 and 86,573 observations for PM_{10} and $PM_{2.5}$, respectively. At the 5 km level there were 35,212 and 42,782 observations for PM_{10} and $PM_{2.5}$

Table 2.2: County level summaries of $PM_{10}(n = 178, 356)$ and $PM_{2.5}(n = 174, 933)$ by pregnancy period.

Exposure Period	Pollutant	Mean \pm SD	IQR	Quartiles		
				25%	50%	75%
Trimester 1	PM_{10}	19.6 ± 5.5	5.5	16.2	17.8	21.8
	$PM_{2.5}$	13.5 ± 1.5	1.9	12.5	13.7	14.3
Trimester 2	PM_{10}	25.1 ± 5.3	7.3	21.0	24.3	28.3
	$PM_{2.5}$	15.3 ± 1.7	2.1	14.5	15.6	16.6
Trimester 3	PM_{10}	26.5 ± 5.2	7.9	22.6	25.7	30.5
	$PM_{2.5}$	18.2 ± 2.8	3.1	16.8	18.3	19.9
Entire Pregnancy	PM_{10}	23.7 ± 4.9	4.8	20.7	22.7	25.5
	$PM_{2.5}$	15.7 ± 1.6	1.6	15.0	15.7	16.6

Table 2.3: 20 km level summaries of $PM_{10}(n = 117, 279)$ and $PM_{2.5}(n = 134, 232)$ by pregnancy period.

Exposure Period	Pollutant	Mean \pm SD	IQR	Quartiles		
				25%	50%	75%
Trimester 1	PM_{10}	23.0 ± 5.4	7.2	19.0	22.5	26.2
	$PM_{2.5}$	15.0 ± 3.0	4.2	12.7	12.5	16.8
Trimester 2	PM_{10}	22.6 ± 4.9	6.6	19.1	22.4	25.6
	$PM_{2.5}$	14.4 ± 2.6	3.9	12.7	14.4	16.7
Trimester 3	PM_{10}	22.4 ± 4.9	6.4	19.0	22.3	25.4
	$PM_{2.5}$	14.6 ± 2.6	3.9	12.3	14.3	16.5
Entire Pregnancy	PM_{10}	22.6 ± 3.8	3.8	20.5	22.2	24.3
	$PM_{2.5}$	14.7 ± 1.7	2.2	13.7	14.9	15.9

respectively.

Average values of PM_{10} ($PM_{2.5}$) concentration levels were approximately 22.7 (14.3) $\mu g/m^3$. The $PM_{2.5}$ average is below the NAAQS annual mean of 15 $\mu g/m^3$, and there is currently no annual PM_{10} standard in North Carolina. The correlations between PM_{10} and $PM_{2.5}$ during each trimester remain relatively consistent with $r \sim 0.7$. The correlation between PM_{10} and $PM_{2.5}$ exposure during the entire pregnancy was 0.63. Table 2.4 shows the correlation coefficients among

trimester exposures for PM_{10} and $PM_{2.5}$ at the county-level. Similar correlations were obtained at the 20-, 10-, and 5-km level.

Table 2.4: Pearson correlation coefficients between trimester pollution estimates at the county level.

PM_{10}	Trimester			$PM_{2.5}$	Trimester			
	1	2	3		1	2	3	
	1	1			1	1		
Trimester	2	0.44	1	Trimester	2	0.23	1	
	3	0.16	0.42	1	3	-0.08	0.24	1

In all of the baseline models with no air pollution estimates, the standard covariates carried the expected signs with positive correlation between birth weight and longer gestation (>40 weeks), male sex, more than a high school level education and higher parity; and negative correlation between birth weight and tobacco use during pregnancy, unmarried status, less than high school education, minority race groups, firstborns, mothers younger than 24 years and older than 40 years, and mothers who started prenatal care later in pregnancy. All covariates were statistically significant ($p < .001$) and were included in the models with pollution estimates.

The significant findings in the results are consistent for PM_{10} and $PM_{2.5}$. In the multiple regression models for the county level measure of air pollution exposure, PM_{10} and $PM_{2.5}$ exposure in the third trimester and during the entire pregnancy were negatively associated with birth weight (Figures 2.4 and 2.5). An IQR increase in PM_{10} and $PM_{2.5}$ during the entire gestational period was associated with a reduction in birth weight by 5.3 g (95% CI: 3.3 - 7.4) and 4.6 g (95% CI: 2.3 - 6.8), respectively. Similarly, exposure during the third trimester was associated with a reduction in birth weight for PM_{10} (7.1 g, 95% CI: 1.0 -

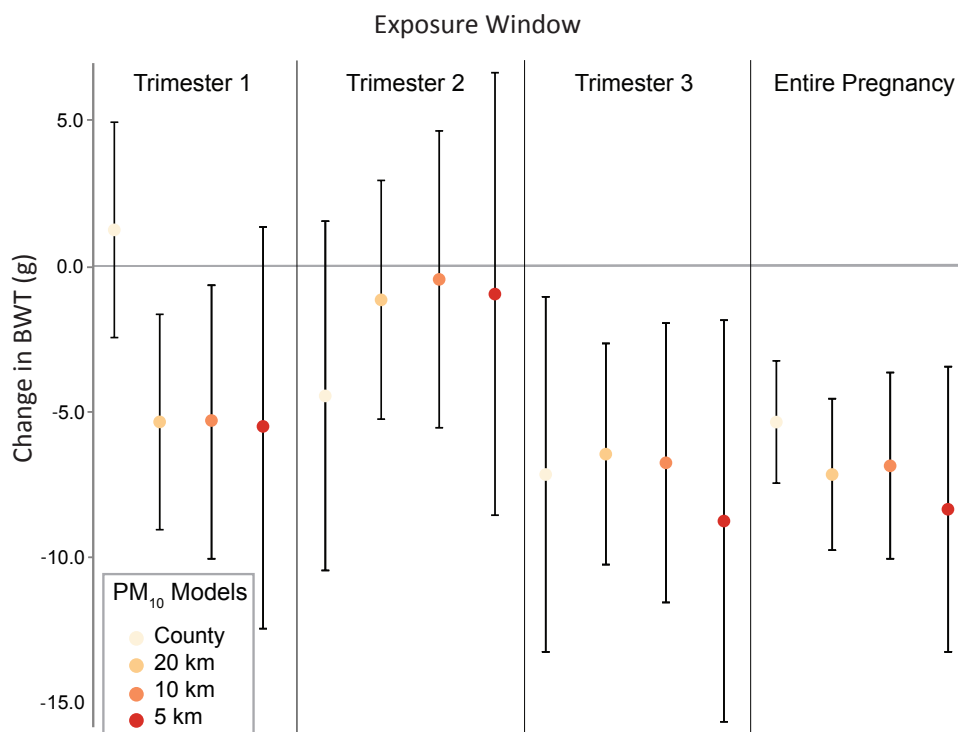


FIGURE 2.4: Changes in birth weight (g) in PM_{10} models

13.2) and $PM_{2.5}$ (10.4 g, 95% CI: 6.4 - 14.4). Similar to Bell *et al.* (2008); Aguilera *et al.* (2009) and Darrow *et al.* (2009), we report changes in birth weight per IQR increase of the pollutant as unit changes in the pollutant may not be sensible for all pollutants.

Proximity models for 20, 10, and 5 km distances showed results similar to the county level models (Figures 2.4 and 2.5). During the entire gestational period, there were birth weight reductions between 7 and 8 g for PM_{10} and 7 and 10 g for $PM_{2.5}$ per IQR increase in each pollutant.

Exposure during the third trimester showed significant results similar to the county level models for both pollutants. $PM_{2.5}$ showed birth weight reductions in the second trimester at 20 and 10 km but not 5 km or the county level model. A

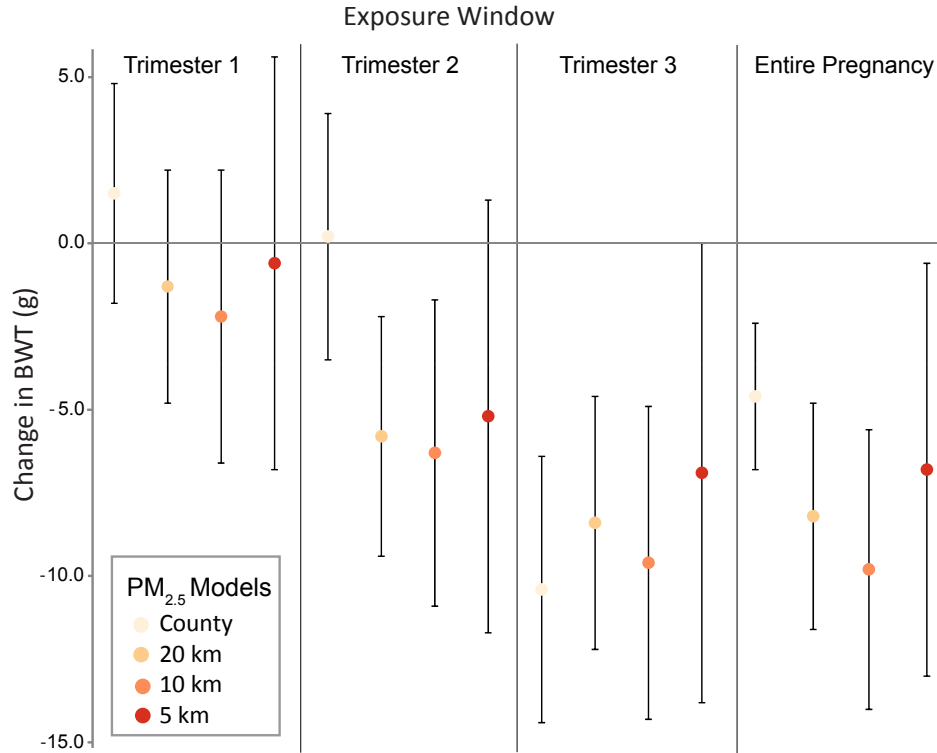


FIGURE 2.5: Changes in birth weight (g) in $PM_{2.5}$ models

similar phenomenon is seen for PM_{10} during the first trimester.

The categorical analysis showed that over the course of the entire pregnancy, higher levels of pollution are worse with regard to birth weight than lower level. During the entire pregnancy, a dose-response relationship can be seen for higher levels of PM_{10} and $PM_{2.5}$ (Figures 2.6 and 2.7). The highest levels of PM_{10} exposure ($\geq 23.4 \mu g/m^3$) during the entire pregnancy are associated with reductions in birth weight of 22 - 25 g while medium levels ($21.1 - 23.4 \mu g/m^3$) see reductions of between 12 and 18 g when compared to low levels ($\leq 21.1 \mu g/m^3$) of exposure (Figure 2.6). Comparatively, in the $PM_{2.5}$ models, the highest levels of exposure ($\geq 15.5 \mu g/m^3$) during the entire pregnancy are associated with reductions in birth weight of 13 - 18 g while medium levels ($14.1 - 15.5 \mu g/m^3$) see

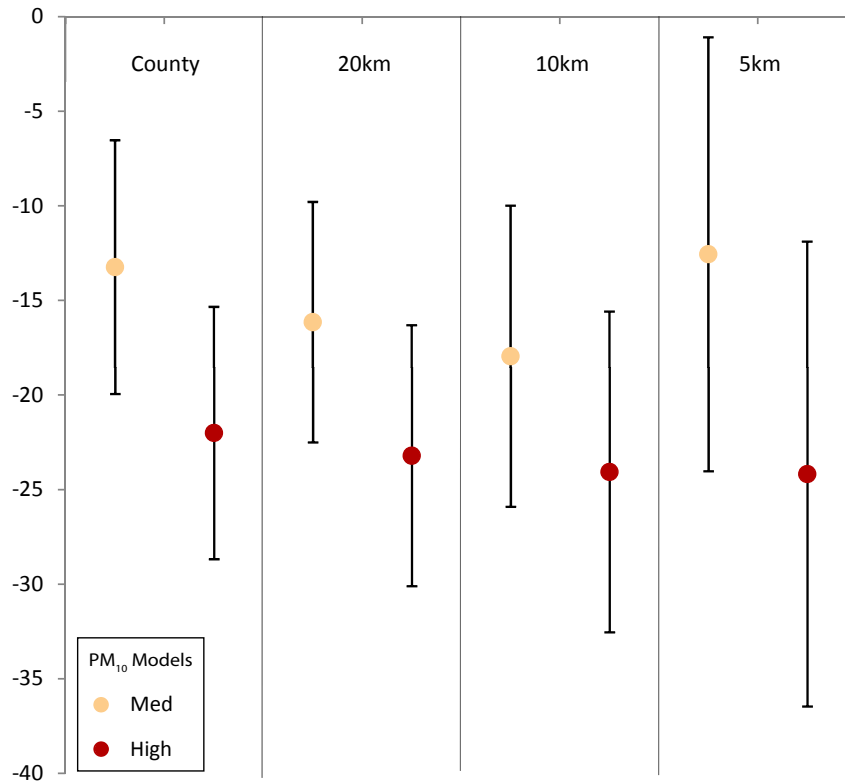


FIGURE 2.6: Changes in birth weight (g) with categorical exposure in PM_{10}

reductions of between 6 and 8 g when compared to low levels ($\leq 14.1 \mu g/m^3$) of exposure (Figure 2.7).

The piecewise spline model produced similar results to the categorical analysis. Figures 2.8 and 2.9 show plots of maternal exposure averaged over the course of the entire pregnancy and the reduction in birth weight using the results from the spline model at the 20-km level. A simple F-test to compare the piecewise linear spline model with regression model containing a single continuous exposure measure showed that the spline function did not provide a better fit for the data ($p=0.51$).

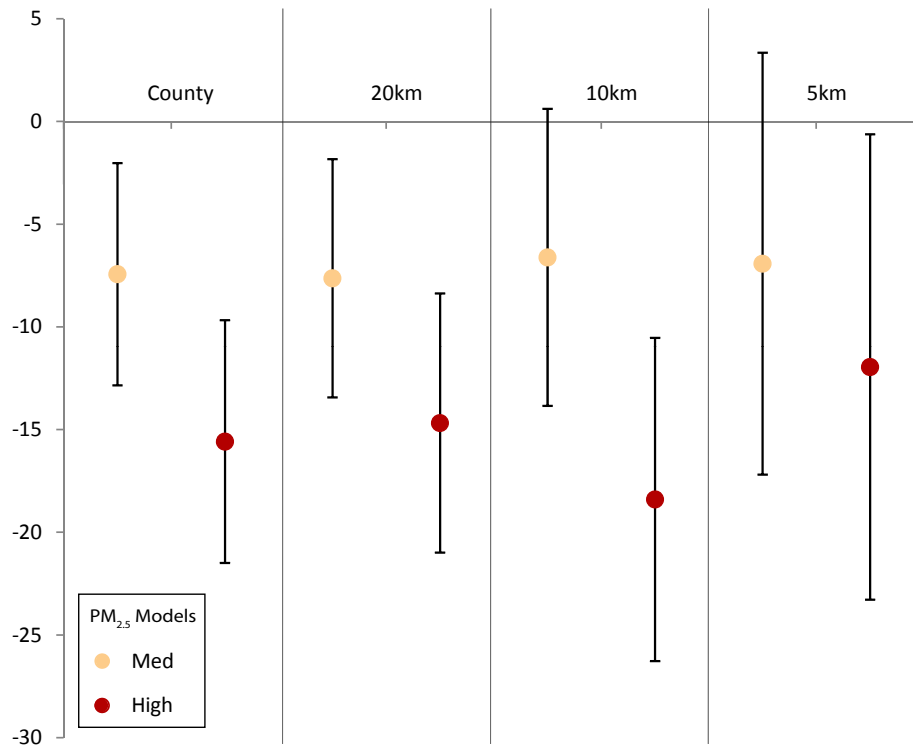


FIGURE 2.7: Changes in birth weight (g) with categorical exposure in $PM_{2.5}$

We see very little change in model fit across the models with continuous pollutant measures compared to the models with categorical measures and the spline function. Figure 2.10 shows the values of the R^2 statistic and the RMSE for all the models. The red bars correspond to the linear model with the continuous exposure measure. The blue and green bars correspond to the models with categorical exposure and linear spline, respectively. The figures show that there almost no change in the R^2 value and little to no change in the RMSE.

Exposure to air pollution during pregnancy is an important public health issue. Despite North Carolina's consistent attainment of federal air quality standards,

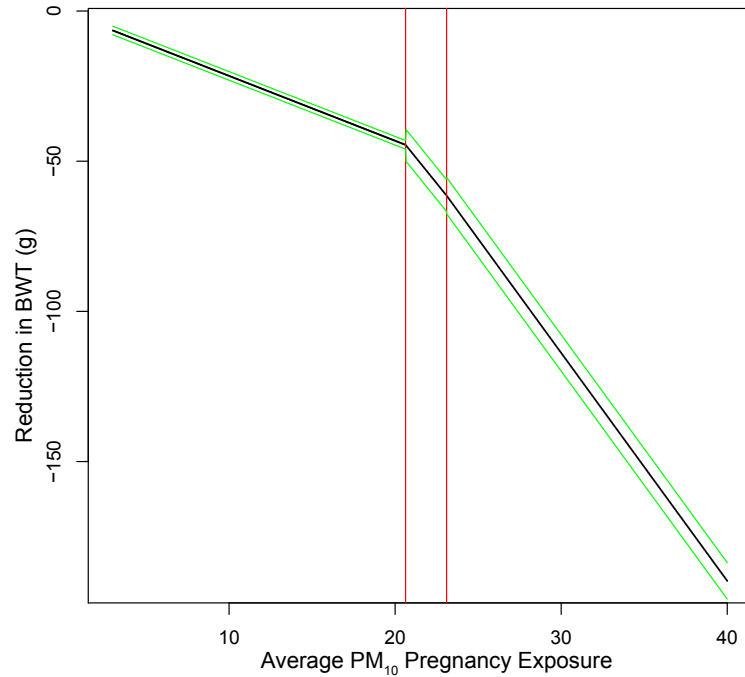


FIGURE 2.8: PM_{10} results from piece-wise linear spline model

we still see a stable and negative association between both pollutants and birth weight. The county level model produced consistent results with the proximity model for estimating reductions in birth weight during the entire pregnancy and in the third trimester for both PM_{10} and $PM_{2.5}$. There were some differences in the first trimester for PM_{10} and the second trimester for $PM_{2.5}$. In both cases, there was a reduction in birth weight at the 20 km and 10 km level but not at the county level or the 5 km level.

In the presence of potential measurement error, it is important to determine whether these various measurements affect the exposure-response relationship. County level models assume that air pollution exposure is spatially homogeneous

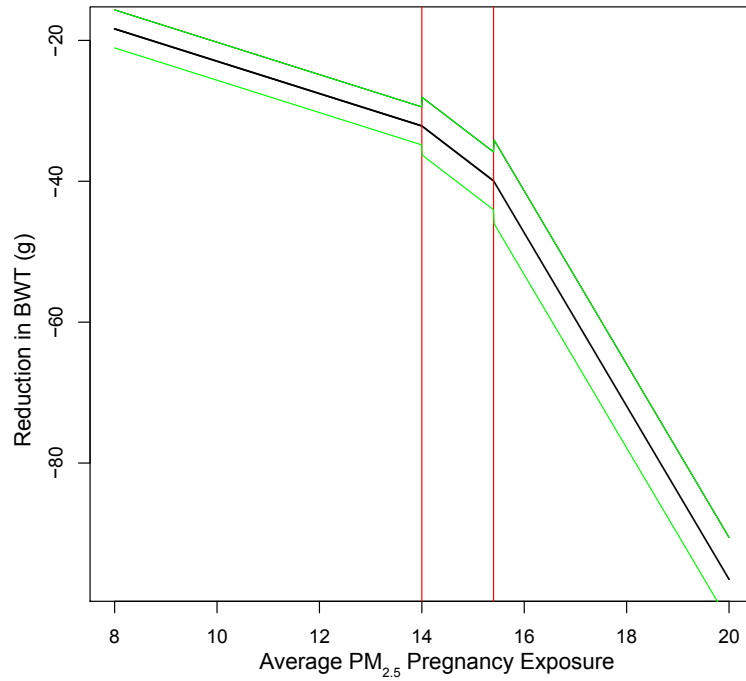


FIGURE 2.9: $PM_{2.5}$ results from piece-wise linear spline model

over a larger surface area than city-wide or neighborhood level models. If air pollution concentrations are heterogeneous, with variability that increases as distance from the pollution source increases, then the associated measurement error may also be larger in exposure measurements based on large geographic regions. This misclassification in the pollution concentration could underestimate the true effects of air pollution exposure in the above results.

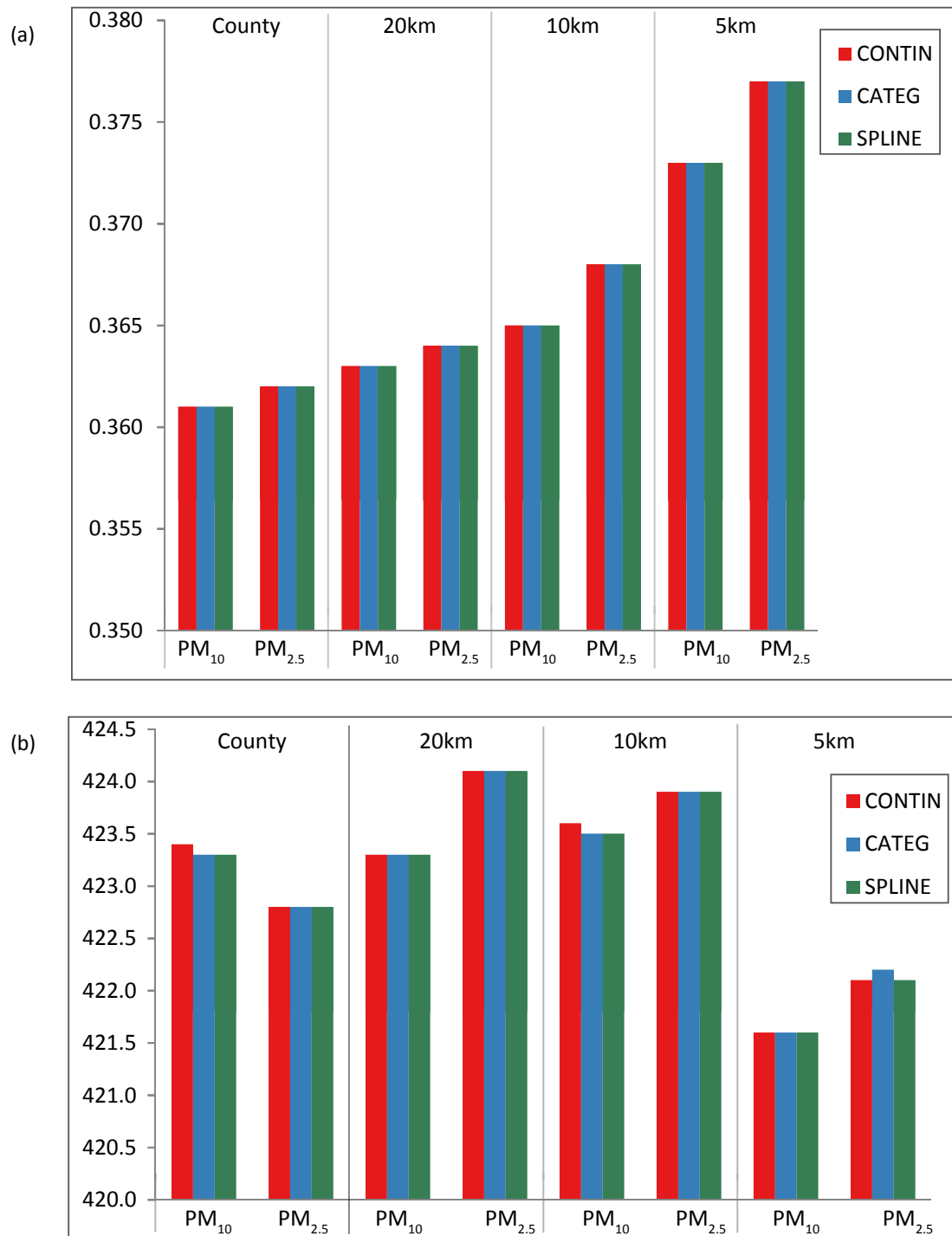


FIGURE 2.10: (a) R^2 and (b) RMSE for exposure entered as continuous, categorical and spline measures

Hierarchical Measurement Error Model

3.1 Measurement Error Modeling

The use of Bayesian methods to account for measurement error is not new. A recent study by Crooks *et al.* (2009) uses a Bayesian hierarchical model to investigate interpolation error on the relationship between ambient PM exposure and cardiovascular health. Crooks *et al.* (2009) interpolate the ambient exposure measures for the study participants using spatial techniques. This produces posterior distributions for both the predicted values of the pollutants and their associated standard errors. These estimates are used as parameters in the distribution of the ‘true’ exposure measurement. The authors show how the interpolation error affects the exposure-response relationship. The authors showed that the significance of the observed associations are robust to the inclusion of measurement error, but the magnitude of the effects is not.

Dominici *et al.* (2000) build a hierarchical regression model to investigate the relationship between exposure to PM_{10} and mortality. Having personal data from

five sites outside the Baltimore area, as well as exposure data from fixed monitoring sites, the authors build a model to relate ambient exposure measures to personal exposure measures. This model is used to produce personal exposure measurements for subjects at a new Baltimore site which are then used in the multi-stage relative-risk model. This study makes the assumption that the linear relationship between the monitored ambient exposure and personal exposure measures from California, New Jersey, Massachusetts and the Netherlands is translatable to Maryland.

Gryparis *et al.* (2009) examined the association between levels of ambient PM and birth weight while regarding the measurement error as a spatial misalignment problem. The misalignment is produced in the different spatial locations of the monitoring stations that measure ambient exposure and the health data that measures the outcome. The authors consider several approaches for handling the misalignment errors and compare the performance of these approaches with different spatial models. They also rely on meteorological conditions, traffic activity, and other temporal factors to make exposure predictions, which showed that spatial variability exists in the exposure measurements.

In a recent article by Peng and Bell (2008), an alternative approach involving spatial misalignment has been presented. Peng and Bell (2008) use a spatial-temporal model to quantify the spatial misalignment error. The authors use a two-stage hierarchical Bayesian model for estimating the cardiovascular risk associated with PM components. Using monitored measurements from neighboring counties, the authors build an underlying pollution process to provide an average county-wide daily exposure measure. With both the county level data and the interpolated county level measure, the spatial misalignment error and variance

can be estimated. Results showed that the spatial misalignment error variance depended on the number of monitors within a county.

Much of the recent work in exposure modeling in measurement error studies includes the use of Bayesian hierarchical models. Richardson and Best (2003) illustrate the use of Bayesian hierarchical models in investigating environmental-health relationships with particular attention being given to exposure measurement error. With the use of personal exposure monitors and other meteorological covariates, McBride *et al.* (2007) use hierarchical techniques to build a model for personal $PM_{2.5}$ exposure. Other personal exposure models such as the probabilistic NAAQS Exposure Model (pCNEM), Community Multi-scale Air Quality (CMAQ), and Comprehensive Air Quality model with Extensions (CAMx) have also been developed to estimate air pollution exposure. These exposure simulators use a combination of stochastic modeling, and personal and environmental characteristics to predict personal exposure (Zidek *et al.*, 2003, 2007).

There are several other relevant approaches to account for the impact of measurement error in exposure models (Richardson and Gilks, 1993; Sheppard and Damian, 2000; Heid *et al.*, 2004; Sheppard *et al.*, 2005; Burstyn, 2010). Ivy *et al.* (2008) use inverse distance weighting in a recent time-series study. Bell (2006) explores various approaches including inverse distance weighting and kriging. Regression calibration methods (Strand *et al.*, 2006), kriging (Leem *et al.*, 2006; Finkelstein *et al.*, 2003) and land use regression models (Briggs *et al.*, 1997; Gilbert *et al.*, 2005) are also used as spatial interpolation techniques. Schwartz and Coull (2003) and Zeka and Schwartz (2004) use non-Bayesian hierarchical modeling for a multiple city study examining the effects of air pollution exposure and mortality. All of these approaches are limited by the use of central monitoring sites to

measure personal exposure.

We use hierarchical, Bayesian, and spatial techniques to model the relationship between adverse pregnancy outcomes and maternal exposure to ambient air pollution, while accounting for the uncertainty attributed to the effects of measurement error. We extend the approaches used by Dominici *et al.* (2000) and Brauer *et al.* (2002), by including both spatial and non-spatial error terms, as well as constant and non-homogeneous variances. With this technique, there are two possibilities that will cause the variability of the exposure measure to increase. The first occurs as the distance between the monitoring station and the residence location increases and the second occurs for shorter gestational ages (see Section 3.4.1 below).

The model is formulated in three stages. First, we model the relationship between the birth weight response variable and average personal exposure in North Carolina, along with other personal covariates. True personal exposure is viewed as an unobserved covariate and is treated as a random variable. The second stage of the model uses the observed ambient exposure measurements from monitoring stations across the state and the modeled error terms to predict the true unobserved average exposure reading. In the final stage, we model the error terms. The error terms are constructed using multiple approaches, including independent errors, non-constant variance errors and spatial error terms. A directed acyclic graph of the model is shown in Figure 3.1. We combine the information on the disease model, the measurement model, and the spatially varying error terms using Bayesian hierarchical modeling techniques similar to the multilevel structure in Dominici *et al.* (2000) and Molitor *et al.* (2006, 2007).

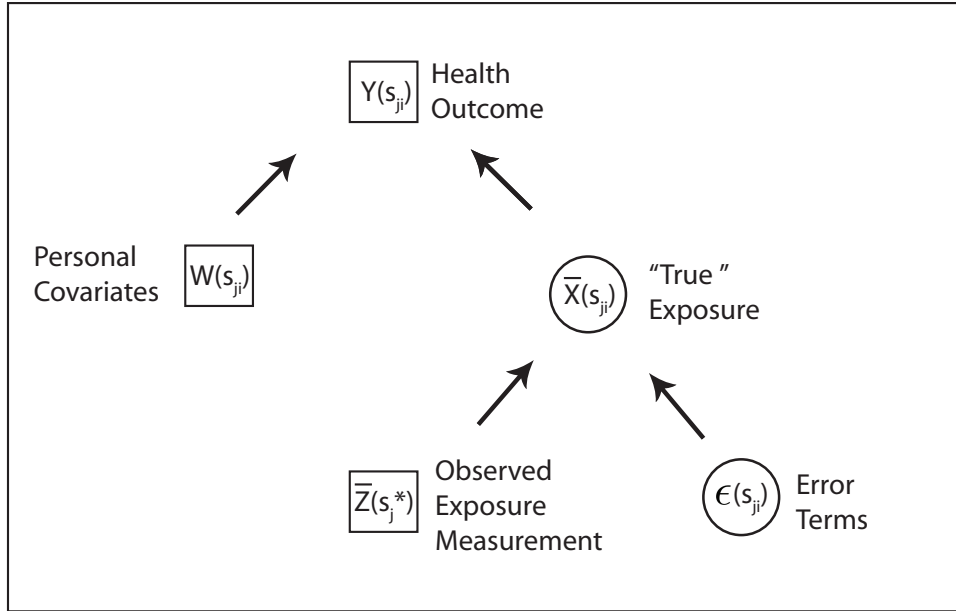


FIGURE 3.1: Directed acyclic graph (DAG) of the hierarchical model

3.2 Disease Model

In this section, we describe the disease model. We use the AQS and NCDBR data described in Chapter 2 and now account for the effects of the measurement error in both the pollutants.

Let s_1^*, \dots, s_m^* denote the locations of the monitoring stations. We partition the state of North Carolina into j polygons so that each polygon j has a set of associated residences, where $j = 1, \dots, J$. The polygons are constructed such that all residences within polygon j are closer to monitoring station j than any other monitoring station in the state. The induced Voronoi tessellations for the PM_{10} and $PM_{2.5}$ monitoring stations are show in Figure 3.2.

Define s_{ji} as the residence at the time of delivery for individual i , whose closest monitor is s_j^* , for all $i = 1, \dots, n$. $Y(s_{ji})$ is the observed birth weight response,

and we consider $Y(s_{ji})$ as the continuous outcome variable. Here we focus on average exposure and define $\bar{X}(s_{ji}, t_i)$ as the true but unobserved average personal exposure level for a mother residing at location s_{ji} . $\bar{X}(s_{ji}, t_i)$ is averaged over time t_i , where $\{t_1, \dots, t_n\}$ corresponds to the length of the entire pregnancy for each mother.

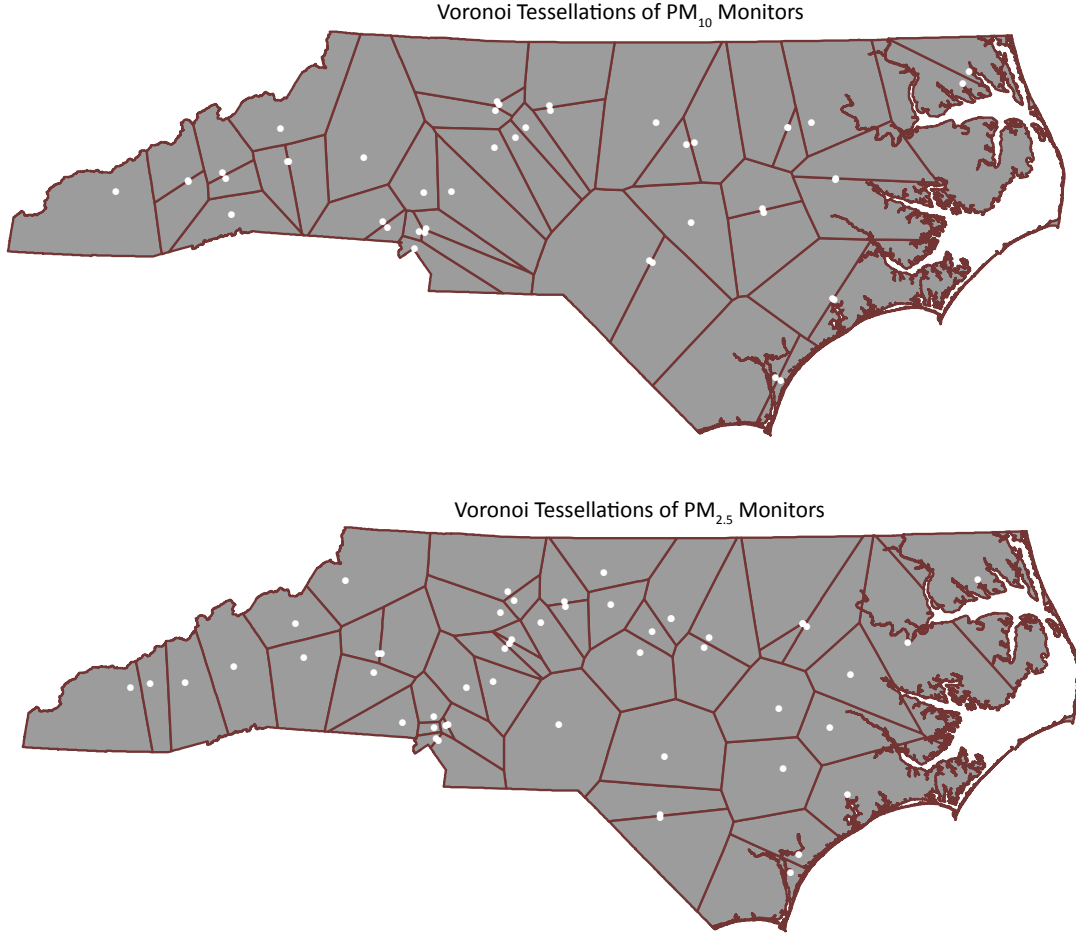


FIGURE 3.2: Veronoi tessellations for PM_{10} and $PM_{2.5}$ monitors

The disease model for $Y(s_{ji})$ is given by:

$$Y(s_{ji}) = \beta_0 + \mathbf{W}^T(s_{ji}) \boldsymbol{\beta}_W + \bar{X}(s_{ji}, t_i) \beta_X + \epsilon_Y(s_{ji}) \quad (3.1)$$

for $i = 1, \dots, n$ and $j = 1, \dots, J$ where β_0 represents the intercept term, β_W and β_X are unknown parameters, $\mathbf{W}^T(s_{ji})$ is a vector of personal covariates that affect birth weight, and $\epsilon_Y(s_{ji})$ is an error term that follows a normal distribution with mean zero and variance σ_Y^2 . The covariates included in $\mathbf{W}^T(s_{ji})$ are the ones used in the linear regression models in Chapter 2.

Equation 3.1 models the relationship between birth weight and maternal exposure to ambient PM along with relevant personal covariates. In practice, the observed ambient measure of air pollution at the county level or from the closest monitoring station would be used. Instead of using this surrogate measure of average personal exposure obtained from the monitoring stations, the true but unobserved average personal exposure measure $\bar{X}(s_{ji}, t_i)$ is used as the predictor. We are especially interested in the parameter β_X which can be interpreted as the effect for the true average personal exposure measure, $\bar{X}(s_{ji}, t_i)$.

3.3 Measurement Model

In the second stage of this multilevel model, we calculate estimates of personal PM exposure based on site specific exposure measurements. We work in the Berkson error environment for two reasons. Tosteson *et al.* (1989) show that measurement error of this type is appropriate for personal exposure measurements obtained from fixed monitoring sites. The second reason is for ease of computation as classical-error models require the specification of the marginal distribution for the observed exposure $\bar{Z}(s_j^*, t_i)$ (Gilks *et al.*, 1996). This step becomes unnecessary with this multilevel specification.

Let $\bar{Z}(s_j^*, t_i)$ be the average exposure measurements from the fixed site monitor s_j^* , over the specified period t_i . We assume that $\bar{Z}(s_j^*, t_i)$ is a surrogate measure

for $\bar{X}(s_{ji}, t_i)$. Using a simple linear specification, we model the relationship of $\bar{X}(s_{ji}, t_i)$ given $\bar{Z}(s_j^*, t_i)$ as

$$\bar{X}(s_{ji}, t_i) = \bar{Z}(s_j^*, t_i) + \epsilon_X(s_{ji}, s_j^*, t_i). \quad (3.2)$$

Equation 3.2 uses the observed measurements $\bar{Z}(s_j^*, t_i)$ and the spatially varying error terms $\epsilon_X(s_{ji}, s_j^*, t_i)$ to predict the true unobserved exposure $\bar{X}(s_{ji}, t_i)$ in an additive Berkson error environment. We assume that the error terms $\epsilon_Y(s_{ji})$ in (3.1) are independent of the measurement errors, $\epsilon_X(s_{ji}, s_j^*, t_i)$. A consequence of the specification of this measurement model is that $Y(s_{ji})$ is conditionally independent of $\bar{Z}(s_j^*, t_i)$ given $\bar{X}(s_{ji}, t_i)$. The third stage of the model requires specification of the measurement error terms $\epsilon_X(s_{ji}, s_j^*, t_i)$. Although a more general specification than (3.2) might be preferred, we are limited to the monitoring station data provided by the USEPA and as a consequence have no validation data available to help with calibration.

3.4 Error Model

The error terms in (3.2) are assumed to capture the unmodeled spatial variability in the observed personal exposure measurements. We allow four possible scenarios for capturing this uncertainty. These four models differ based on the variance and the spatial dependence structure. Figure 3.3 illustrates the four model possibilities. In Model I, the measurement errors take on a normal distribution with a constant variance term. Using a random error term in the measurement model has been considered in classical error models by Molitor *et al.* (2006); Dominici *et al.* (2000) and Cakmak *et al.* (1999) and in Berkson error models by Gryparis *et al.* (2009). Model II specifies an updated error term with a non-constant variance

that is constructed as a function of the length of each mother’s pregnancy t_i , and the distance between the maternal residence s_{ji} and the monitoring station s_j^* .

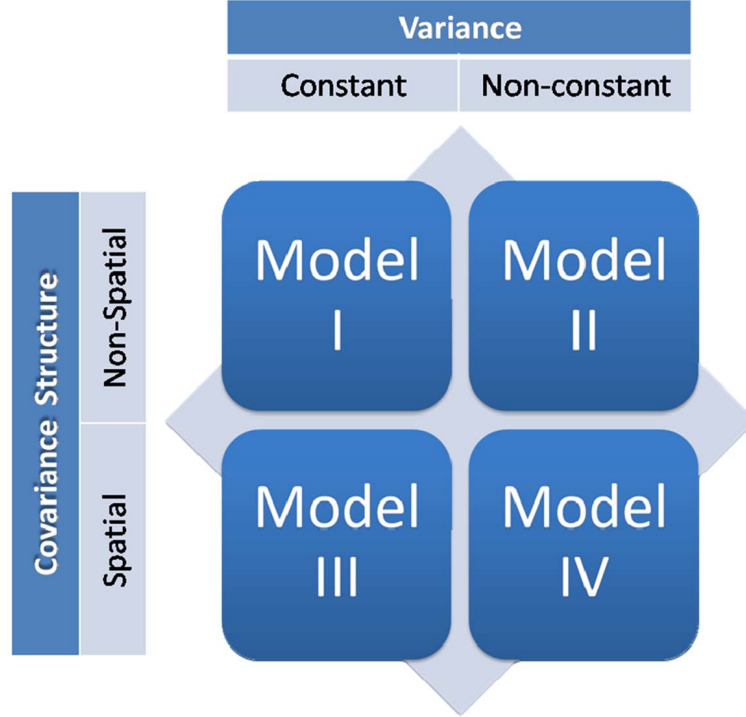


FIGURE 3.3: Variance/Covariance Structure of Error Models

Models III and IV mirror the first two models but now have spatial dependence in the distribution of the error terms. We use random effects to capture the associated spatial measurement error for each mother. In Model III, the random effects have a standard constant variance term. In Model IV, we specify an error term with a variance that is a function of the length of each mother’s pregnancy t_i , and the distance between s_{ji} and s_j^* . Similar to Model II, shorter pregnancies and mothers further away from the monitoring station are expected to have higher levels of uncertainty in this model specification. We assign a spatial random effect to each census tract to ease the computational burden. These random effects are

intended to capture the spatial similarity in the measurement error between census tracts and are specified conditionally, given all of their neighbors. These models are referred to as conditional autoregressive (CAR) models (Besag *et al.*, 1991; Banerjee *et al.*, 1993).

We now more explicitly detail the error models.

3.4.1 Model I: Random Error

The random error term ϵ_X represents the deviations associated in the relationship between the true exposure measurement $\bar{X}(s_{ji}, t_i)$ and the observed monitoring station measurement $\bar{Z}(s_j^*, t_i)$. Here, we assume that ϵ_X has a normal distribution with mean zero and a constant variance σ_ϵ^2 , given by

$$\epsilon_X \sim N(0, \sigma_\epsilon^2). \quad (3.3)$$

By using σ_ϵ^2 as the associated error variance, this measurement error model assumes that the variation associated with the measurement error is homogeneous across all locations.

3.4.2 Model II: Non-constant Variance

In Model II, we specify the mean spatial error structure as

$$\bar{\epsilon}_X(s_{ji}, s_j^*, t_i) \sim N\left(0, \frac{\sigma_\epsilon^2}{t_i} \exp(\phi |s_{ji} - s_j^*|)\right) \quad (3.4)$$

where ϕ is an unknown range parameter representing the rate at which the variance increases as distance from monitoring station increases, and $\frac{\sigma_\epsilon^2}{t_i}$ is the scaled variance with weights that depend on the length of the entire pregnancy. With this manner of model specification, longer gestational periods will provide more

measured pollution values and reduce some of the uncertainty in the mean spatial error. The parameter ϕ is used to characterize the rate of growth of the variability.

Through the specification in Equation 3.4, the average true exposure measurement depends on the average monitored pollution values, as well as an average error term constructed from the distance between the residence and the monitoring station and the length of the pregnancy. Note that here we have defined error terms whose uncertainty depends on the distance between s_{ji} and s_j^* . However, there is no spatial process as there is no covariance function.

3.4.3 Model III: Random Effects

We believe that the measurement errors in exposure should be spatially associated in the sense that if two mothers live near to each other we would expect that their measurement errors in exposure would tend to be similar. To capture the spatial similarity in the measurement error, we include spatial random effects. The use of random effects is potentially beneficial as they allow us to account for the underlying spatial dependence in the error terms.

The random effects are introduced to capture the spatial similarity in the measurement error between census tracts. Individual level random effects for each mother are preferable but impractical. With over 100,000 women in both the PM_{10} and $PM_{2.5}$ datasets and the necessary matrix inversion required for model updating, individual level effects proved computationally intensive. To ease the computational burden, we assign a spatial random effect to each census tract.

There are 1,563 census tracts in North Carolina. The variability in average birth weight by census tract is shown in Figure 3.4. From 3.4, we notice that the

census tracts in North Carolina have irregular shapes and sizes.

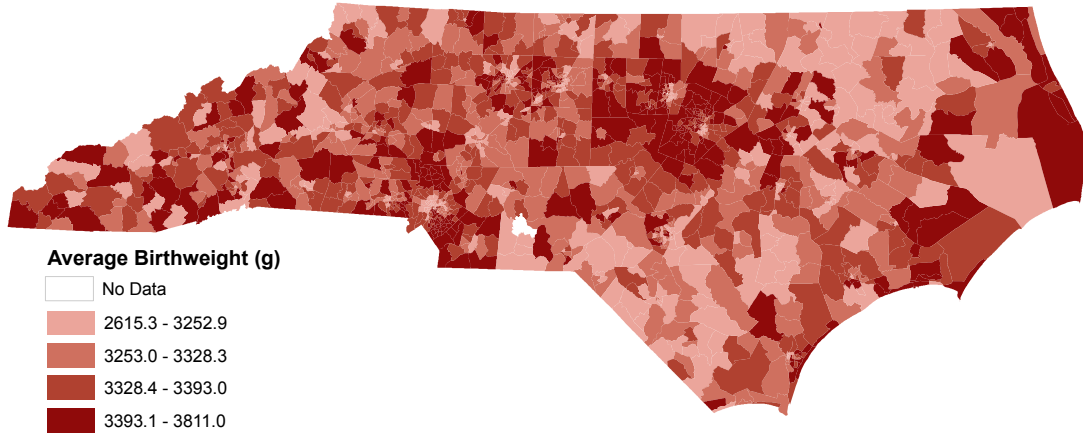


FIGURE 3.4: Average birth weight quartiles for NC census tracts, 2000-2002

The census tract level random effects are specified conditionally, given all of their neighbors and use a CAR structure (Besag *et al.*, 1991; Banerjee *et al.*, 1993). Let w_k denote the spatial random effect for census tract k . We write the measurement model in (3.2) as

$$\bar{X}(s_{ji}, t_i) = \bar{Z}(s_j^*, t_i) + w_{k_i}$$

where w_{k_i} is the deviation of $\bar{Z}(s_j^*, t_i)$ for census tract k , with $w_{k_i} = w_k$ if individual i is in census tract k .

The conditional distribution of the area-specific random effects is given by

$$w_k | w_{-k} \sim N\left(\frac{\sum_l \delta_{kl} w_l}{\sum_l \delta_{kl}}, \frac{\sigma_w^2}{\sum_l \delta_{kl}}\right) \quad (3.5)$$

where $\delta_{kl} = 1$ if tract l is contiguous with tract k and 0 otherwise, and σ_w^2 is the spatial variance component.

3.4.4 Model IV: Non-constant Variance Random Effects

For the last model we combine the ideas from Models II and III. We write the measurement model in (3.2) as

$$\bar{X}(s_{ji}, t_i) = \bar{Z}(s_j^*, t_i) + \sqrt{\frac{\exp(\phi|s_{ji} - s_j^*|)}{t_i}} w_{k_i} \quad (3.6)$$

where ϕ is a measure of the rate at which the variance will decrease and w_{k_i} is the census tract random effect with the CAR structure previously described in Equation 3.5. Notice that the variance in Equation 3.6 depends on the distance between s_{ji} and s_j^* , as well as the length of gestation t_i in a similar manner to Equation 3.4.

3.5 Bayesian Procedures

The multilevel model is described through the disease model in stage 1, the measurement model in stage 2, and the four possibilities for the error model in the third and final stage. The Bayesian hierarchical modeling is completed with prior specifications for the unknown parameters β_0 , $\boldsymbol{\beta}_W$, β_X , σ_Y , σ_ϵ , and ϕ . Typically, vague normal priors centered at zero with inflated variances are adopted for the regression coefficients, and noninformative inverse gamma priors are assumed for the variance parameters. We use empirically driven priors to overcome identifiability problems with jointly estimating σ_Y^2 , σ_ϵ^2 , and ϕ ; see Zhang (2004) and Sahu *et al.* (2006) for details and examples.

The regression coefficients, β_0 , $\boldsymbol{\beta}_W$, and β_X were assigned normal priors centered at the OLS estimates with large variances (10^4). Inverse gamma priors were used for the variance parameters σ_Y and σ_ϵ . For σ_Y and σ_ϵ we used $\text{IG}(\nu, \eta)$,

where $\nu = 2$ and $\eta = 0.5 * MSE$. This prior specification was centered on the residual mean square error term from the OLS regression analysis in Chapter 2. In the models with the non-homogeneous variance component, Models II and IV, a discrete uniform prior is used for ϕ with $\phi \sim U(0, 1)$.

We generate samples from the posterior distribution via MCMC method Gibbs sampling. We ran two separate chains starting from different initial values. We performed sensitivity analyses with various values for the hyperparameters and the results yielded very robust posteriors. The MCMC algorithm was run for 2,000 burn-in iterations followed by another 20,000 iterations. With only linear terms in the model, chains of 20,000 iterations were sufficient for convergence. As all of the models being fit are linear and expected to be well-behaved, we assess convergence by visual plots of posterior means of the parameters. We computed summaries of the posterior distribution for all parameters of interest.

4

Application to Birth Weight

We illustrate the performance of the four measurement error models described in Section 3.4 using the NCDBR data and AQS data for PM_{10} and $PM_{2.5}$. A description of these two datasets is given in Chapter 2. We restricted the dataset to include singleton births characterized by no congenital anomalies or reported alcohol consumption. Further restrictions included only women between ages 15 and 44 years who self-declared as non-Hispanic white, non-Hispanic black, or Hispanic. Births with gestation less than 32 and greater than 44 weeks, birth weight less than 1000g and greater than 5500g, unlikely birth weight and gestation combinations (Alexander *et al.*, 1996), and mothers with any missing data on covariates were excluded. Approximately 5% of the women in this restricted dataset lived further than 50 km away from a monitoring station. We removed these women from the dataset, due to the increased uncertainty associated with this small group.

After restricting the PM_{10} and $PM_{2.5}$ datasets, there were 171,415 and 195,848

subjects, respectively. The number of the births by census tract for PM_{10} can be seen in Figure 4.1, with births occurring in 1,389 census tracts. Figure 4.2 shows the number of observations in each census tract for the $PM_{2.5}$ dataset with births occurring in 1,464 census tracts.

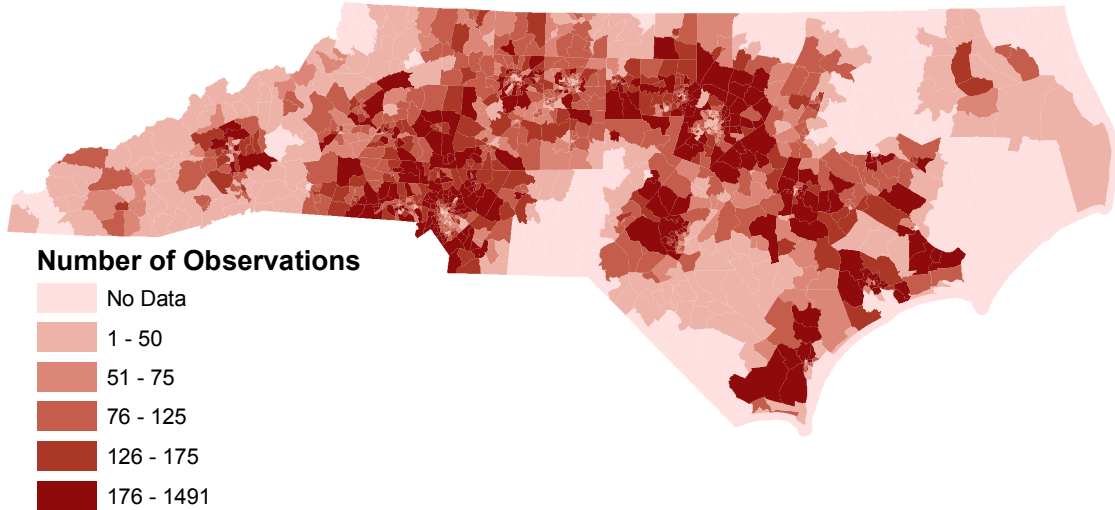


FIGURE 4.1: Number of observations by census tract in PM_{10} dataset

We use individual level covariates in all the models and are interested mainly in the β_X coefficient of the unobserved true PM concentration levels. This term represents the effect estimate of exposure on birth weight during the entire pregnancy. In all the models, birth weight is a continuous outcome variable and is measured in grams. The individual level covariates include gestational age (weeks), maternal race/ethnicity (non-Hispanic black, non-Hispanic white, or Hispanic), maternal education (< 9, 9-11, 12, 13-15, > 15 years), maternal age (15-19, 20-24, 25-29, 30-34, 35-39, 40-44 years), trimester prenatal care began (None, first, second, third), tobacco use during pregnancy (yes or no), marital status (married or unmarried), year of birth, firstborn (yes or no), and infant sex (male or female). The

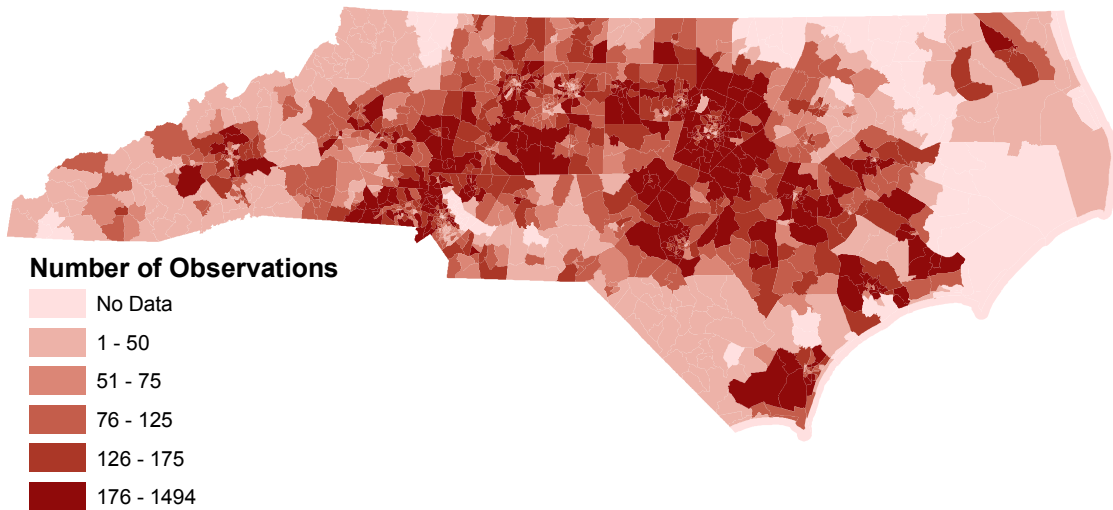


FIGURE 4.2: Number of observations by census tract in $PM_{2.5}$ dataset

Bayesian hierarchical models are fit with MCMC method Gibbs sampling.

4.1 Model Results

Table 4.1 shows the ordinary least squared (OLS) results with point estimates and 95% confidence intervals for PM_{10} and $PM_{2.5}$ obtained by using the monitored estimates as measures of personal exposure. These results prove to be similar to those in the preliminary analysis from Chapter 2. From Table 4.1 we can see that there is still a negative correlation between birth weight and exposure to both PM_{10} and $PM_{2.5}$ during the entire pregnancy.

4.2 Validation

To compare the fit of the spatial models, we computed estimates of model performance: the deviation information criteria (DIC), the root mean square predictive error (RMSE), and the empirical coverage of the 95% predictive intervals. For the

Table 4.1: OLS Results for NCDBR data.

	PM_{10}	$PM_{2.5}$
	Estimate (95% C.I.)	Estimate (95% C.I.)
Gestation (wks)	170.9 (169.67,172.20)	170.12 (169.64,171.98)
Male	127.91 (123.86,131.97)	128.44 (124.65,132.23)
Smoker	-199.26 (-205.89,-192.63)	-196.32 (-202.41,-190.23)
Not Married	-33.84 (-39.36,-28.32)	-32.73 (-37.88,-27.58)
<i>Maternal Education</i>		
< 9 years	-47.26 (-58.03,-63.21)	-48.77 (-58.73,-38.80)
9-11 years	-32.97 (-39.93,-26.01)	-32.57 (-38.99,-26.14)
12 years		
13-15 years	25.39 (19.56,31.22)	25.64 (20.17,31.11)
> 15 years	29.89 (23.59,36.19)	30.36 (24.45,36.26)
<i>Race/ Ethnicity</i>		
NHW		
NHB	-172.21 (-177.71,-166.72)	-177.39 (-182.53,-172.25)
HISP	-70.93 (-78.65,-63.21)	-67.85 (-75.11,-60.60)
<i>Maternal Age</i>		
15-19 years	-29.92 (-38.48,-21.36)	-31.08 (-39.02,-23.13)
20-24 years	-22.90 (-28.75,-17.04)	-23.68 (-29.15,-18.20)
25-29 years		
30-34 years	14.36 (8.51,20.21)	10.91 (5.42,16.40)
35-39 years	4.76 (-2.98,12.49)	2.42 (-4.79,9.64)
40-44 years	-30.78 (-47.09,-14.47)	-30.93 (-46.12,-15.74)
Firstborn	-125.95 (-130.45,-121.44)	-125.44 (-129.66,-121.21)
<i>Year of Birth</i>		
2000		
2001	-12.00 (-16.85,-7.14)	-11.66 (-16.26,-7.06)
2002	-20.51 (-25.57,-15.44)	-21.54 (-26.68,-16.39)
<i>Prenatal Care</i>		
None	-40.27 (-64.61,-15.93)	-40.14 (-62.59,-17.69)
First Trimester		
Second Trimester	-22.58 (-29.36,-15.81)	-19.51 (-25.72,-13.31)
Third Trimester	-37.96 (-53.28,-22.63)	-40.99 (-54.81,-27.16)
PM Exposure	-2.26 (-2.84,-1.69)	-4.60 (-5.84,-3.36)

RMSE and the empirical coverage of the 95% predictive intervals, we used a hold out dataset of 17,142 and 19,585 random subjects for PM_{10} and $PM_{2.5}$, respectively. To show how the spatial measurement error models improve the predictive

performance, we also included results from an ordinary least squares (OLS) model with no spatial error corrections.

Across all four of the measurement error models, results for the included covariates were comparable to the OLS results. Estimates for the β_X coefficient of all models for PM_{10} and $PM_{2.5}$ are reported in Table 4.2. For the OLS models, we report the 95% confidence intervals, and for the Bayesian hierarchical models we report 95% credible intervals. Table 4.2 also reports the width of the 95% credible and confidence intervals, the RMSE and the empirical coverage of the 95% confidence or credible intervals.

Table 4.2: Results for PM models.

	Model	$\hat{\beta}_X$ (95% C.I.)	C.I. Width	RMSE	Coverage (%)
PM_{10}	OLS	-2.26 (-2.84, -1.69)	1.15	423.8	92.8
	Model I	-2.27 (-2.67, -1.87)	0.80	423.6	93.2
	Model II	-2.27 (-2.67, -1.87)	0.79	421.8	93.8
	Model III	-2.03 (-2.52, -1.57)	0.95	419.0	93.2
	Model IV	-2.26 (-2.59, -1.93)	0.66	395.2	96.4
$PM_{2.5}$	OLS	-4.60 (-5.84, -3.36)	2.48	423.3	94.2
	Model I	-4.60 (-5.44, -3.76)	1.68	423.2	94.6
	Model II	-4.59 (-5.43, -3.76)	1.67	425.0	95.0
	Model III	-4.44 (-5.27, -3.36)	1.64	418.8	94.8
	Model IV	-4.46 (-5.17, -3.74)	1.43	387.5	96.7

Table 4.2 shows that the β_X coefficient is significant in all models for both PM_{10} and $PM_{2.5}$. The β_X coefficients remain relatively constant across all the models with the exception of a change in Model III for both PM_{10} and $PM_{2.5}$. In Models I-IV we see that the width of the credible intervals is smaller than the confidence intervals from the OLS model.

From Table 4.2, we see that accounting for the spatial uncertainty in the models improves the predictive performance of the models. Adding the spatial

random effects reduces the RMSE for both pollutants in Models III and IV, with Model IV having the tightest credible intervals, the lowest RMSE, and the highest empirical coverage of all the models.

4.3 Spatial Random Effects

In Figures 4.3 and 4.4, respectively, we present maps of the posterior means of the spatial random effects obtained for the PM_{10} Models III and IV. For both maps the lower values are represented by the lighter shades and larger expected spatial effects are given by darker shades. The maps produce smoothed spatial patterns of the random effects with Model IV providing more smoothing compared with Model III. Spatial maps of the corresponding posterior standard errors of the spatial random effects are shown in Figures 4.5 and 4.6.

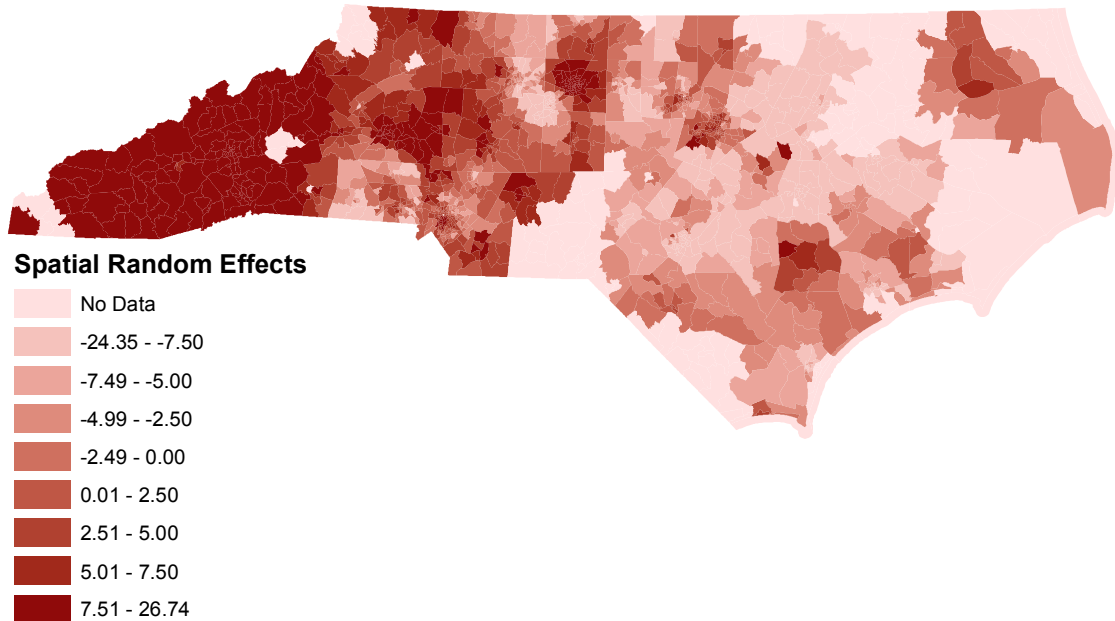


FIGURE 4.3: Posterior mean of spatial random effects for PM_{10} Model III

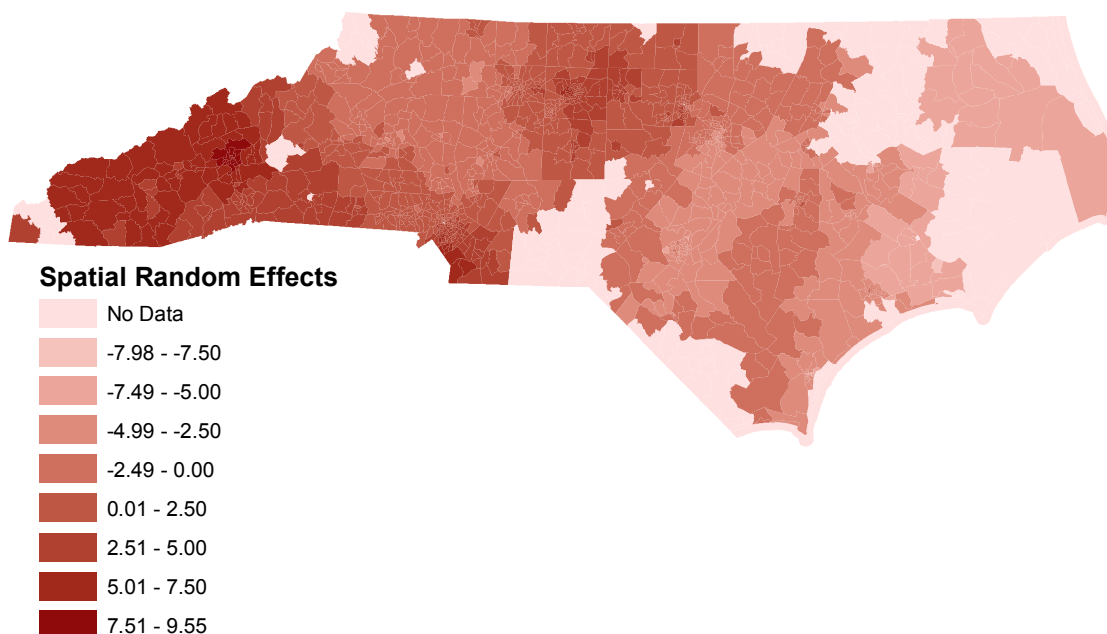


FIGURE 4.4: Posterior mean of spatial random effects for PM_{10} Model IV

Much of the similarities between Figures 4.3 and 4.4 lies in the mountains of North Carolina, located on the Western side of the state. The most likely cause of this similarity is due to the fact that this part of the state has the fewest PM_{10} monitors. As the random effects represent the variability associated with the exposure measurements, we see the similarity in uncertainty where there are fewer monitoring stations. There are some distinct differences in the spatial structure for the random effects between the two models. Model III, the model with the constant variance, has more extreme positive and negative values for the spatial random effects, than those observed for Model IV. The range of the spatial random effects is from -24.4 to 26.7 in Model III and -8.0 to 9.5 in Model IV.

In Figures 4.7 and 4.8, respectively, we present maps of the posterior means of the spatial random effects obtained for the $PM_{2.5}$ Models III and IV. Spatial maps of the corresponding posterior standard errors of the spatial random effects

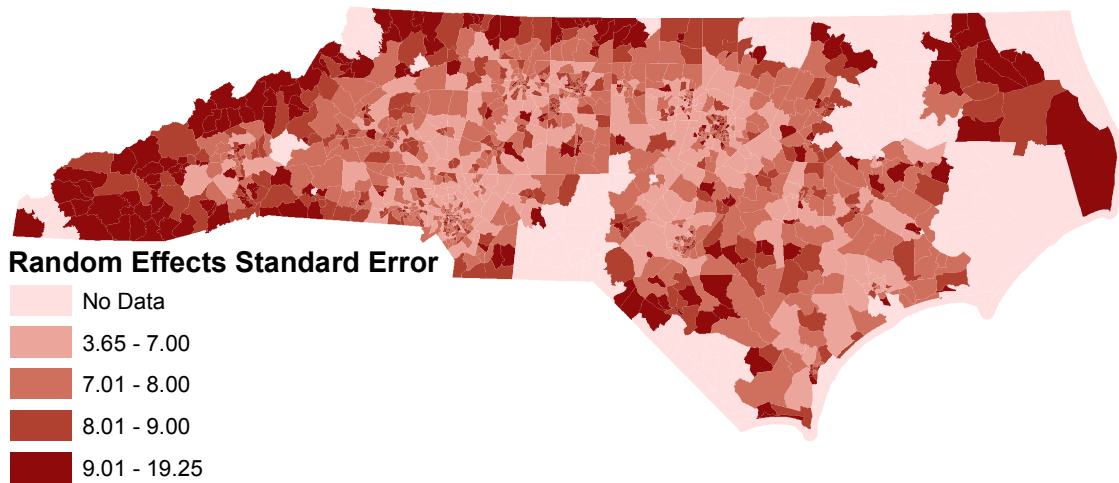


FIGURE 4.5: Posterior standard error of spatial random effects for PM_{10} Model III

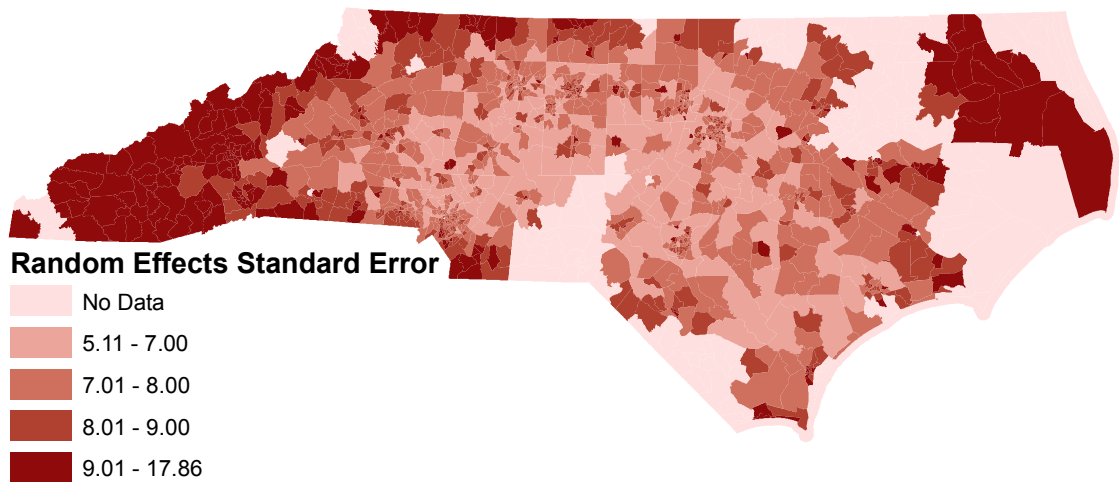


FIGURE 4.6: Posterior standard error of spatial random effects for PM_{10} Model IV

are shown in Figures 4.9 and 4.10. We see fewer differences between Models III and IV for the random effects in the $PM_{2.5}$ dataset.

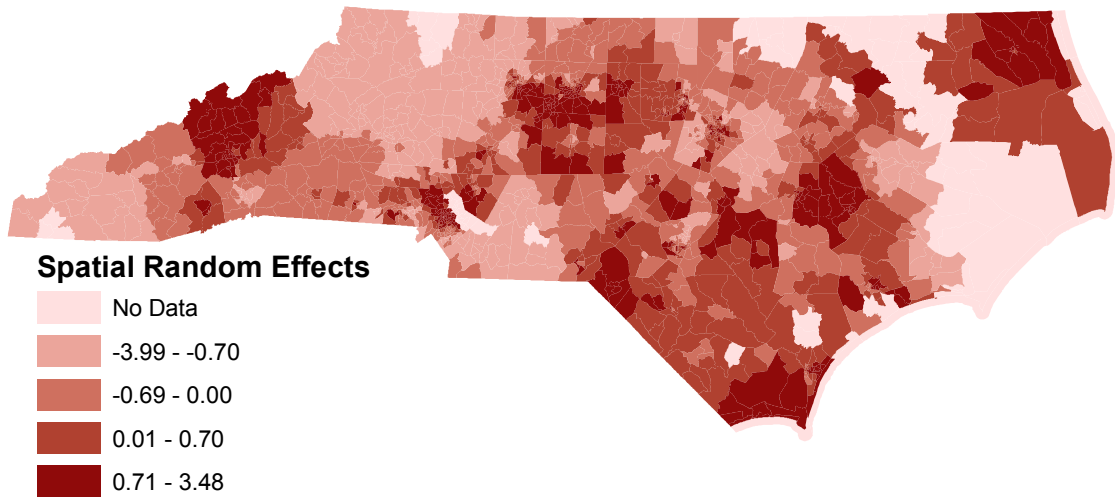


FIGURE 4.7: Posterior mean of spatial random effects for $PM_{2.5}$ Model III

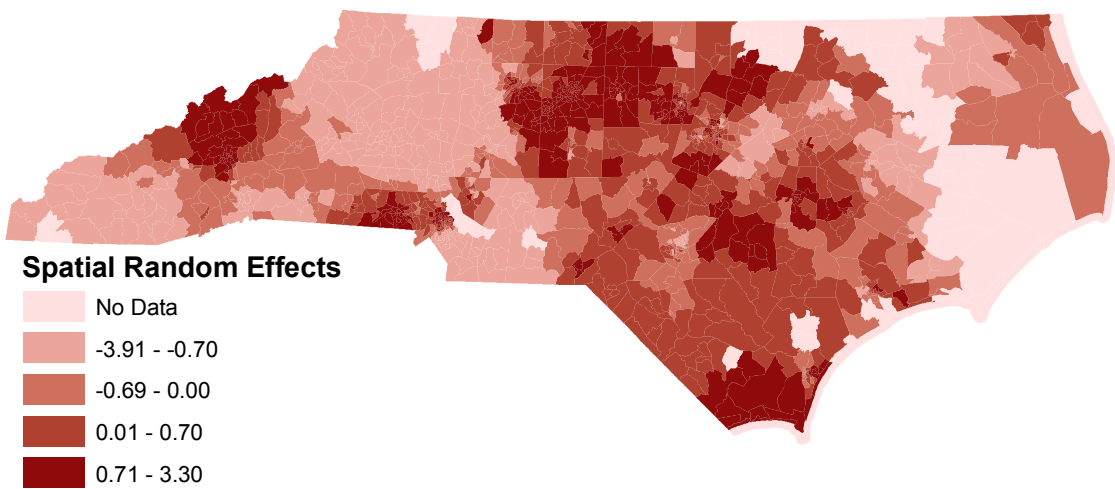


FIGURE 4.8: Posterior mean of spatial random effects for $PM_{2.5}$ Model IV

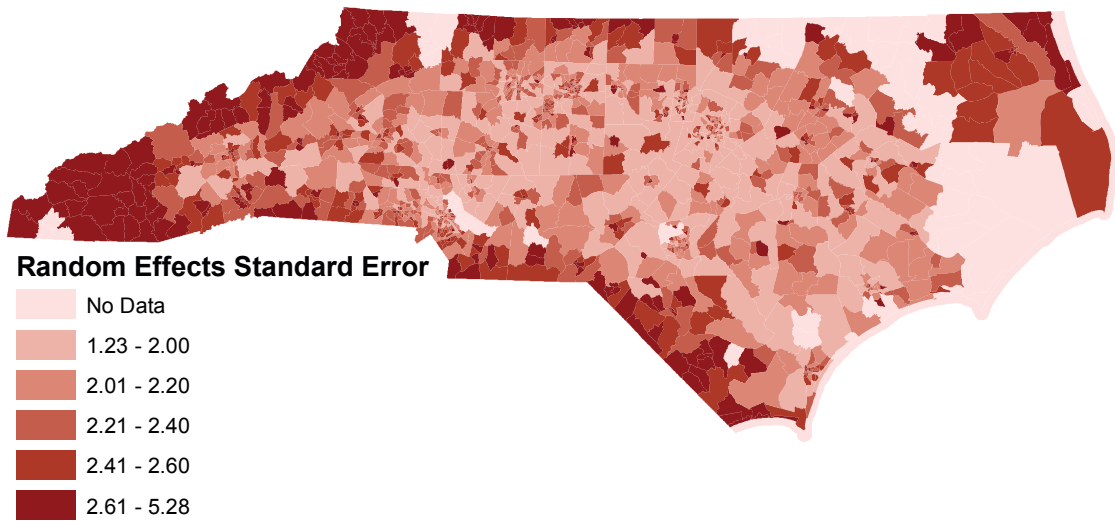


FIGURE 4.9: Posterior standard error of spatial random effects for $PM_{2.5}$ Model III

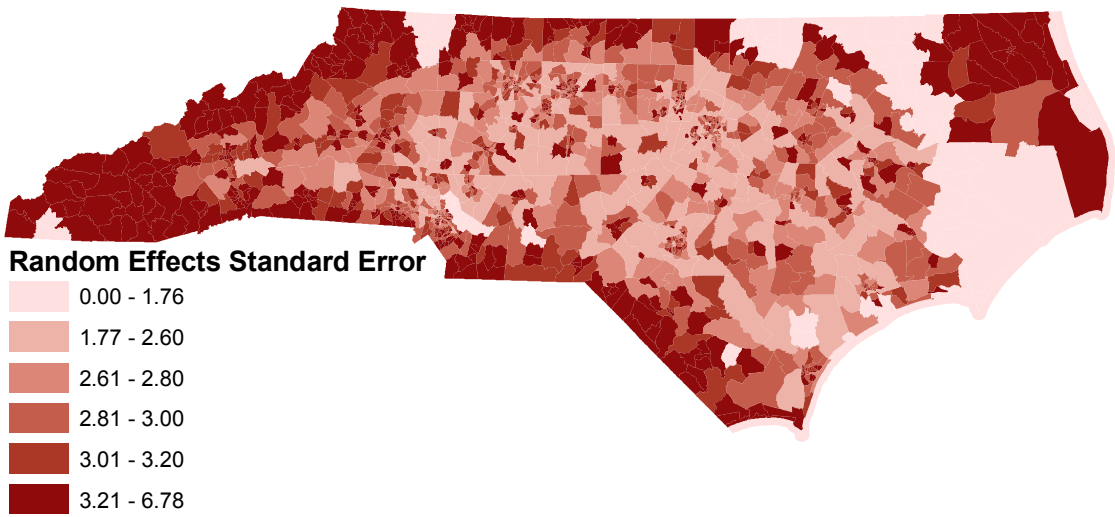


FIGURE 4.10: Posterior standard error of spatial random effects for $PM_{2.5}$ Model IV

We note that across all four years of air pollution data used, there are always more active $PM_{2.5}$ monitors than PM_{10} monitors. Particularly in 2001 there were

29 PM_{10} monitors and 38 $PM_{2.5}$ monitors while in 2002 there were 27 PM_{10} monitors and 37 $PM_{2.5}$ monitors.

We now present maps of the posterior means of the imputed air pollution exposure measurements by census tract.

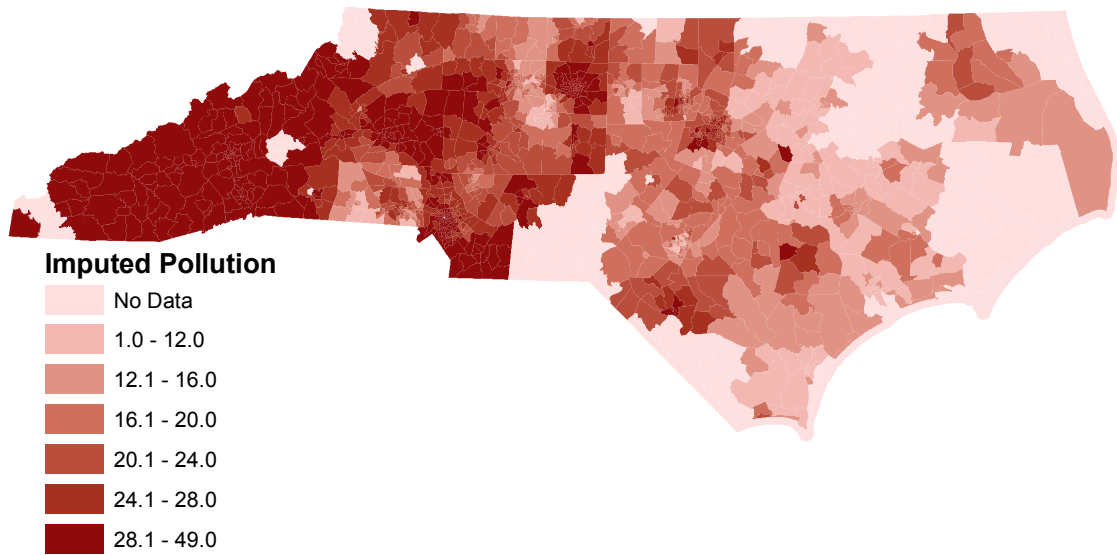


FIGURE 4.11: Expected average PM_{10} values at the census tract level in Model III

Figures 4.11 and 4.12 show the average imputed PM_{10} values for Models III and IV, respectively and Figures 4.13 and 4.14 show the average imputed $PM_{2.5}$ values for Models III and IV, respectively.

For each mother, we have calculated her true exposure measure as a function of the observed measurements from the monitoring station closest to her and the corrected error terms in the form of random effects from Models III and IV. We then took the average values across each census tract to produce the maps in Figures 4.11 - 4.14.

We can see more spatial heterogeneity in Figure 4.12 on the western side of the

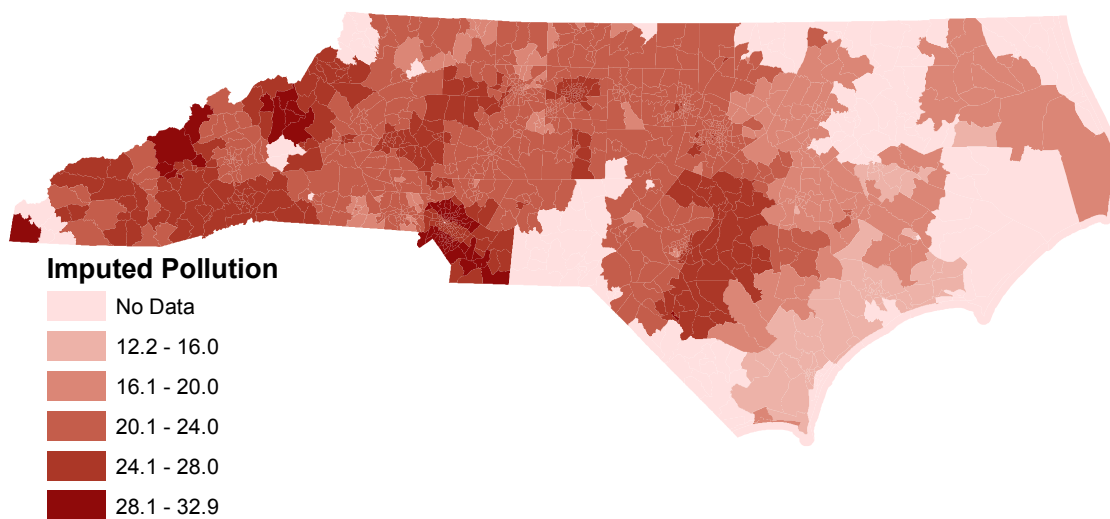


FIGURE 4.12: Expected average PM_{10} values at the census tract level in Model IV

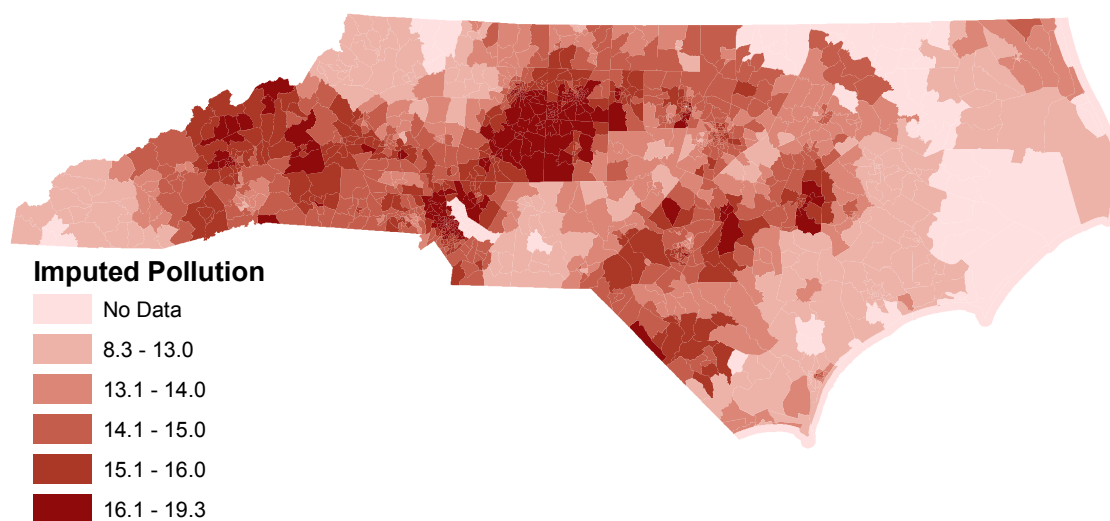


FIGURE 4.13: Expected average $PM_{2.5}$ values at the census tract level in Model III

state when compared to Figure 4.11. Adding information based on distance from the station and length of pregnancy improved the fit of the model and also added

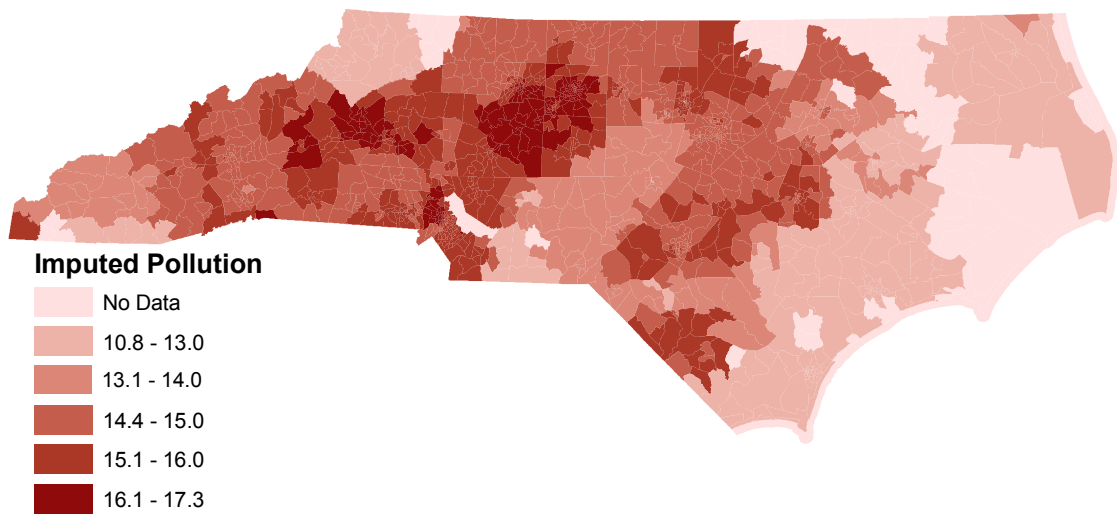


FIGURE 4.14: Expected average $PM_{2.5}$ values at the census tract level in Model IV

some spatial variation to the areas with fewer PM_{10} monitoring stations. We see very little difference between Models III and IV for $PM_{2.5}$ which is supported by the results in Table 4.2.

A Generalized Measurement Error Model

5.1 Exposure Metrics

We have explored the relationship between average exposure over various windows of pregnancy and birth weight. We recognize that using average values will not allow us to differentiate between consistently moderate levels of exposure and low levels of exposure with occasional peaks. We consider using exposure measures of air pollution other than averages to investigate whether effects of extreme levels of pollution contribute to adverse pregnancy outcomes. By generalizing the hierarchical measurement error model, we can now implement these new metrics into the model specification.

To describe the generalized model, we begin with the first stage of the hierarchical model: the disease model as described in Equation 3.1. We relate personal ambient exposure to birth weight using the following model:

$$Y(s_{ji}) = \beta_0 + \mathbf{W}^T(s_{ji}) \boldsymbol{\beta}_W + g(\{X(s_{ji}, t_i)\})\beta_X + \epsilon_Y(s_{ji}), \quad i = 1, \dots, n, \quad (5.1)$$

where $\boldsymbol{\beta}_W$ and β_X are the unknown parameters, $\mathbf{W}^T(s_{ji})$ is a vector of personal

covariates that affect birth weight, and $\epsilon_Y(s_{ji}) \sim N(0, \sigma_Y^2)$ is a random normal error term. For each individual i , the function g is carried out over the set of unobserved exposure readings, $\{X(s_{ji}, t_i)\}$ over the duration of the pregnancy t_i . The function g can now be a sum, the count of days above a threshold or any function of interest.

The second stage specification relates the set of unobserved exposure readings, $\{X(s_{ji}, t_i)\}$, to the observed ambient exposure readings as follows:

$$\{X(s_{ji}, t_i)\} = \{Z(s_j^*, t_i) + \epsilon_X(s_{ji}, s_j^*, t_i)\}. \quad (5.2)$$

In Equation 5.2 we take the modeled error term and add the value to each of the observed ambient concentrations. In this manner the error is specifically attributed to the exposure measurements $Z(s_j^*, t_i)$ and not just to the function of the measurements. This is a more flexible measurement error process than that described in Chapter 3. With this multilevel specification of the generalized model, we avoid having to use the delta approximation method for the variance of $g(\{X(s_{ji}, t_i)\})$.

For the final stage of the model, we can now use any of the error constructions given in Chapter 3. For illustration we give the details for the average exposure metric that was used in the previous analyses, as well as other metrics based on the number of days an individual was above a threshold λ .

5.1.1 Average Exposure Metric

Assume that the function g represents an average concentration measure of personal exposure. Using Equation 5.2, we can represent this metric by:

$$\bar{X}(s_{ji}, t_i) = \frac{1}{t_i} \sum \{X(s_{ji}, t_i)\} \quad (5.3)$$

$$= \bar{Z}(s_j^*, t_i) + \epsilon_X(s_{ji}, s_j^*, t_i). \quad (5.4)$$

The expression in Equation 5.4 is the same expression given in the previous hierarchical model (Equation 3.2).

5.1.2 Exceedance Exposure Metric

Assume that the function g represents the proportion of days over a certain threshold λ . We use proportion to account for different gestational lengths with individual pregnancies. We use this metric to give a measure of the *amount* of poor air quality a mother is exposed to. We explore the hypothesis that exposure to higher levels of pollution may have a more harmful effect on birth weight. An example of an appropriate choice for λ could be the NAAQS set for NO_2 by the USEPA. We define the metric as:

$$g(\{X(s_{ji}, t_i)\}) = \frac{1}{t_i} \sum \mathbf{1}_{(\{X(s_{ji}, t_i)\} > \lambda)}$$

where $\mathbf{1}_{(\{X(s_{ji}, t_i)\} > \lambda)}$ is an indicator of the number of days personal exposure was above λ . Replacing $\{X(s_{ji}, t_i)\}$ with Equation 5.2, we get

$$g(\{X(s_{ji}, t_i)\}) = \frac{1}{t_i} \sum \mathbf{1}_{(\{Z(s_j^*, t_i) + \epsilon_X(s_{ji}, s_j^*, t_i)\} > \lambda)}.$$

In addition to considering the number of days exposure was above a threshold we could also consider a metric that takes into account the magnitude of the

concentration values, as well as the duration of these high air pollution days. We define such a metric by

$$g(\{X(s_{ji}, t_i)\}) = \frac{1}{t_i} \sum [\mathbf{1}_{\{\{X(s_{ji}, t_i)\} > \lambda\}} \times (\{X(s_{ji}, t_i)\} - \lambda)].$$

This metric gives the amount of total exposure above the threshold λ .

The previous applications analyzed the ambient pollutants PM_{10} and $PM_{2.5}$. We turn our attention now to models that are illustrated using the criteria pollutant nitrogen dioxide (NO_2). The detailed daily measurements of NO_2 provided by the AQS data makes this pollutant suitable for applications requiring a more temporally resolved exposure measure. We develop a template for the hierarchical measurement error model to allow for functions of the modeled exposure measure beyond average concentration levels. These other exposure metrics can now be considered when analyzing the relationship between maternal exposure to air pollution and birth weight.

5.2 NO_2 and Birth Weight

NO_2 , like PM_{10} and $PM_{2.5}$, is another criteria pollutants monitored by the USEPA. Sources of NO_2 include vehicle emissions from cars and trucks and industry emissions from powerplants and mechanical equipment. As a result of these sources, elevated levels of NO_2 are observed near high-traffic roadways (Rijnders *et al.*, 2001; Rotko *et al.*, 2001; Ramrez-Aguilar *et al.*, 2002). Other contributors of NO_2 include environmental tobacco smoke, gas stoves, and kerosene heaters. Both indoor and outdoor sources of NO_2 exposure have been linked to a number of adverse effects primarily associated with the respiratory system (Blomberg *et al.*, 1997; Monn, 2001; Latza *et al.*, 2009).

Several studies have shown a relationship between maternal exposure to NO_2 and adverse birth outcomes. Bell *et al.* (2007) showed that NO_2 exposure during the entire pregnancy was associated with a decrease in birth weight and Mannes *et al.* (2005) showed a reduction in birth weight during all three trimesters. Ha *et al.* (2001) showed a birth weight reduction during the first trimester of exposure and increased odds for LBW during the first and third trimester. Other outcomes including SGA, PTD, sudden infant death syndrome and IUGR have also been associated with NO_2 exposure during pregnancy (Liu *et al.*, 2003a,b; Ritz *et al.*, 2006; Liu *et al.*, 2007; Darrow *et al.*, 2009).

Modeling exposure during pregnancy is plagued by the fact that it is still unclear how exposure may affect pregnancy outcomes. The key issue of whether exposure should be measured as chronic or extreme exposures is important when characterizing the exposure measurement. With the detailed temporal resolution given by NO_2 , we develop exposure metrics to investigate both chronic and peak estimates of exposure. These estimates can then be used in the regression models or the measurement error models described in Chapter 3.

5.3 Summary of NO_2 Data

The NO_2 dataset is taken from the AQS data provided by the USEPA for 1999-2003. There were 3 active monitoring stations for the NO_2 data in North Carolina; 2 of which were located in Charlotte and the third in Winston-Salem. The stations provided measurements on a daily scale for the mothers in the study. The average NO_2 levels were approximately 0.016 ppm, which is well below the current long term federal standard of 0.053 ppm. Concentration levels over the study time period had minimal temporal variation (standard deviation = 0.002) and a short

range from 0.01 to 0.02 ppm.

We linked the NCDBR data with the NO_2 dataset and ran preliminary models to assess the exposure-birth weight relationship. We employed the exclusion criteria used for the merged PM datasets and calculated average trimester and pregnancy estimated of NO_2 exposure. Our final sample size consisted of $n=34,522$ women. We ran linear regression models using the same covariates as those used in the PM models and the results are shown in Table 5.1. Preliminary analyses of NO_2 showed a reduction in birth weight during the first and third trimesters by 25.1 g (95% CI: 11.78 - 38.6) and 16.35 g (95% CI: 9.58 - 23.1), respectively and a reduction of 12 g (95% CI: 3.18 - 21.87) during the entire pregnancy. Reductions are reported per IQR increase in NO_2 .

5.4 Metrics Results with NO_2 Data

We ran OLS regression and hierarchical measurement error models with the NO_2 data. We present the results for the number of days above the third quartile of average NO_2 exposure. The results for the β_X coefficient of the exceedance metric for all the models is given in Table 5.2 along with the RMSE and the empirical coverage of the 95% predictive interval.

Across all four of the measurement error models, the β_X coefficients were consistent and comparable to the OLS results. For the OLS models, we report the 95% confidence intervals and for the Bayesian hierarchical models we report 95% credible intervals. Similar to the PM results, Models I-IV show that the width of the credible interval is smaller than the confidence intervals from the OLS model. Adding the spatial random effects to Models III and IV reduces the RMSE for both pollutants. In the hierarchical models, the DIC is the same for

Table 5.1: OLS Results for NO_2 data.

	Estimate (95% C.I.)
Gestation (wks)	168.99 (166.21,171.77)
Male	120.621 (117.84,123.40)
Smoker	-185.77 (-202.28,-169.26)
Not Married	-37.53 (-50.03,-25.03)
<i>Maternal Education</i>	
< 9 years	-30.25 (-51.41,-9.09)
9-11 years	-34.48 (-50.30,-18.65)
12 years	
13-15 years	22.07 (7.69,36.44)
> 15 years	18.74 (3.95,33.53)
<i>Race/ Ethnicity</i>	
NHW	
NHB	-176.41 (-188.88,-163.94)
HISP	-70.06 (-86.21,-53.91)
<i>Maternal Age</i>	
15-19 years	-27.07 (-46.69,-7.45)
20-24 years	-25.66 (-39.39,-11.92)
25-29 years	
30-34 years	15.09 (2.17,28.02)
35-39 years	28.15 (11.69,44.61)
40-44 years	-52.39 (-84.22,-20.57)
Firstborn	-123.08 (-133.09,-113.08)
<i>Year of Birth</i>	
2000	
2001	-9.38 (-23.77,5.02)
2002	-16.65 (-31.73,-1.57)
2003	-25.51 (-42.97,-8.06)
<i>Prenatal Care Began</i>	
None	-44.25 (-89.76,1.25)
First Trimester	
Second Trimester	1.54 (-13.79,16.88)
Third Trimester	-61.22 (-98.54,-23.90)
NO_2 Exposure	-4457.79 (-1131.70,-7783.87)

Models I and II (DIC=536,871) and again for Models III and IV (512,064).

Table 5.2: Results for β_X in NO_2 models with exceedance metric

Model	$\hat{\beta}_x$ (95% C.I.)	C.I. Width	RMSE	Coverage (%)
OLS	-0.28 (-0.50, -0.07)	0.43	423.8	90.7
Model I	-0.29 (-0.43, -0.13)	0.30	422.8	91.7
Model II	-0.28 (-0.43, -0.14)	0.29	421.3	92.3
Model III	-0.29 (-0.44, -0.13)	0.31	416.8	94.3
Model IV	-0.29 (-0.44, -0.13)	0.31	419.0	95.7

6

Conclusion and Future Work

We propose a flexible modeling technique that allows us to incorporate measurement error when estimating the effects of air pollution exposure on birth weight in situations where exact measures of personal exposure are unavailable. We introduce error both spatially and non-spatially, and with a constant variance or a more sensible option of a variance that places more uncertainty on those residing farther away from the monitoring station. The birth weight response variable depends on imputed exposure predictors constructed from the error terms and exposure measurements from monitoring stations, and on individual level maternal and fetal characteristics.

The hierarchical measurement error models are illustrated with the use of the NCDBR and AQS datasets. We also develop a more generalized version of the hierarchical model that can accommodate exposure metrics other than average concentration levels. In the current analysis we use birth weight as the health endpoint and criteria pollutants PM_{10} , $PM_{2.5}$ and NO_2 as exposure variables. The

modeling framework can certainly be extended to future investigations of other health outcomes and pollutants.

Our findings support the growing body of literature which shows evidence that maternal exposure to air pollution has a negative association with birth weight. All models in our analyses showed a negative correlation between air pollution exposure and birth weight with $PM_{2.5}$ having a larger effect on birth weight than PM_{10} . While our findings are similar to other air pollution and birth weight studies, unlike other studies, we do not assume that the exposure readings from the monitors located near the mother's residence are exact measures of personal exposure. We acknowledge the limitation that monitoring station data provides only crude estimates of outdoor exposure.

In our analysis, we compare five models. We use the monitored exposure measurement in a standard regression model. We then construct four hierarchical models: one with a constant variance, another with a variance term that was a function of each mother's gestational period and the distance of her residence from the monitoring station and spatial models with constant and non-constant variances. Although the models yielded estimates of β_X that were similar to each other, the measurement error models produced tighter credible intervals for the parameter of interest. Model prediction was also improved by use of the measurement error terms.

The common problem with trying to study the effects of maternal exposure to air pollution is the limitation of having to use observed exposure measurements collected from a small number of sources. This work addresses the issue by attempting to better understand the relationship between maternal exposure to air pollution and birth outcomes in North Carolina, with the use of statistical

models that incorporate Bayesian hierarchical modeling techniques to account for the associated measurement error.

The current research could be extended in different applications. For the PM analysis our work calculated average weekly exposure as daily data was unavailable for most of the monitoring stations. The stations measured PM daily, every three days, or every six days. We can further extend the computational methods from the measurement error model to impute the missing days of air pollution data. Similar to the exposure error imputation, we would use the available exposure measures as surrogates for the missing days of data. The missing data would be accounted for by assuming that each missing measurement is a function of the closest daily measure and an error term that increases as the time from the nearest recorded measurement increases. This missing data error term is now incorporated into a temporal component of the model and is independent of the exposure measurement error.

In trying to understand the effects of air pollution on human health, we realize that people are generally not exposed to one pollutant at a time. We also recognize that many of these pollutants are correlated with each other. Adding more pollutants to the models could allow us to explore the potential confounding of multiple pollutants.

Other more complicated error models can be considered for the distribution of the spatial structure. For example, a process convolution model could be used as an alternative to the random effects model given in Model IV. The choice for Model IV was based on comparability with Models II and III. In the process convolution model, we define the second stage as follows

$$\bar{X}(s_{ji}, t_i) = \bar{Z}(s_j^*, t_i) + \sqrt{\frac{\sigma_\epsilon^2}{t_i} \exp(\phi |s_{ji} - s_j^*|)} w(s_{ji}) \quad (6.1)$$

where

$$w(\mathbf{s}) = \sum_{j=1}^J l(\mathbf{s} - \mathbf{s}_j^*) z(\mathbf{s}_j^*). \quad (6.2)$$

If we model each $z(\mathbf{s}_j^*)$ as independent draws from a standard normal $N(0,1)$ distribution, we can show that $w(\mathbf{s})$ is a Gaussian process through kernel convolution with

$$E(w(\mathbf{s})) = 0$$

$$Var(w(\mathbf{s})) = \sum_{j=1}^M l^2(\mathbf{s} - \mathbf{s}_j^*)$$

$$Cov(w(\mathbf{s}), w(\mathbf{s}')) = \sum_{j=1}^M l(\mathbf{s} - \mathbf{s}_j^*) l(\mathbf{s}' - \mathbf{s}_j^*).$$

To get the $Var(w(\mathbf{s}))$ to be 1, we scale $l(\mathbf{s} - \mathbf{s}_j^*)$ so that $\sum_{j=1}^M l^2(\mathbf{s} - \mathbf{s}_j^*) = 1$. Let

$$l(\mathbf{s} - \mathbf{s}_j^*) = k_j(\mathbf{s} - \mathbf{s}_j^*) / \sqrt{\sum_{j=1}^M k_j^2(\mathbf{s} - \mathbf{s}_j^*)}$$

where $k_j(\mathbf{s} - \mathbf{s}_j^*)$ decreases as $|\mathbf{s} - \mathbf{s}_j^*|$ increases.

There are some techniques for handling computation on large spatial datasets that should be mentioned. Some include replacing the process $w(\mathbf{s})$ with an approximation that corresponds to realizations in a lower dimensional subspace using kernel convolutions, moving averages, low rank-splines or basis functions (Higdon,

1998; Wikle and Cressie, 1999; Lin *et al.*, 2000; Kamman and Wand, 2003; Ver Hoef *et al.*, 2004). Alternatively, other approaches involve approximating the likelihood (Stein, 1999; Fuentes, 2007; Paciorek, 2007) or approximating the process model by a Markov random field (Rue and Tjelmeland, 2002; Rue and Held, 2006).

Another useful example is proposed by Banerjee *et al.* (2008). Their method uses predictive process models to facilitate computation. This eliminates the need to consider choices of kernels or basis functions and instead builds upon already established kriging ideas. The predictive process model takes the high dimensional process $w(\mathbf{s})$ and projects it onto a lower dimensional subspace generated from realizations of the original process $w(\mathbf{s})$. Implementing this modeling technique uses knot configuration to produce the predictive process $\tilde{w}(\mathbf{s})$ that is derived from the original $w(\mathbf{s})$.

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Biography

Simone Colette Gray was born in San Fernando, Trinidad and Tobago on November 22, 1981. In December of 2001 she graduated from Palm Beach Atlantic University with a Bachelor of Science in Mathematics. She later received a Master of Science degree in Mathematical Sciences from the University of Miami in 2004. From August 2004 to August 2005, she taught Mathematics at North Port High School in Sarasota, FL. During this time she also married Jarvis Gray in July of 2005, just one month before enrolling in the doctoral program at Duke University. In 2008, she was awarded a CDC fellowship (Award #1R36EH000379-01) for her dissertation research. Under the direction of Alan Gelfand and Marie Lynn Miranda, she worked on measurement error models associated with air pollution and pregnancy outcomes (Gray *et al.* (2009)).