This Page Intentionally Left Black

AN ABSTRACT OF THE DISSERTATION OF

Eric S. Coker for the degree of Doctor of Philosophy in Public Health presented on March 2, 2016.

Title: Examination of Multiple Air Pollutant Exposure, the Food Environment, and Low Birth Weight in Los Angeles, County.

Abstract approved: _____

John T. Molitor

Exposure to urban outdoor air pollution is ubiquitous and low birth weight represents an important health disparity in the United States. While previous research suggests that exposure to outdoor air pollutants are associated with term low birth weight, few studies have evaluated the effects of multipollutant outdoor air exposures or whether there is a spatial patterning to such associations. In addition, populations living in neighborhoods with poor air quality and high neighborhood deprivation may be more likely to reside in neighborhoods that are also characterized by adverse food environments.

The first study investigated the overall association between fine particulate matter ($PM_{2.5}$) air pollution with term low birth weight (TLBW) in urban Los Angeles County. This first study also applies spatial multilevel modeling to explore spatial patterns in the exposure response relationship between $PM_{2.5}$ and TLBW. The results from the first study indicates that higher exposure to $PM_{2.5}$ is associated with a higher odds of TLBW and that the exposure response exhibits spatial dependence.

The second study examines joint exposure to multiple outdoor air pollutants in Los Angeles County, including $PM_{2.5}$, nitrogen dioxide [NO_2], and nitrogen oxide [NO]. The second study showed that multipollutant profiles with elevated exposure to NO_2, NO, and $PM_{2.5}$ are associated with increased log odds of TLBW, and that multipollutant profiles characteristic of primary traffic emissions impart the greatest increased odds of TLBW.

In the third study I examine the association between the neighborhood food environment and TLBW, and explore whether this relationship may be modified by air pollution exposure. In

this study I also explore how the food environment clusters with other area-level TLBW risk factors, including income and greenness, and how exposure profiles for these area-level factors combine to impart risk of TLBW. This study found a higher odds of TLBW among mothers who resided in neighborhoods with reduced availability of more healthy food stores and increased availability of less healthy food stores. This study did not find that the food environment works as an effect modifier of $PM_{2.5}$, however, the data provided evidence to suggest that the food environment may influence the magnitude of the association between $PM_{2.5}$ and TLBW (but not the strength of the relationship). Furthermore, I identify neighborhoods with clustering of poor food environments, low socioeconomic status, and low greenness, which are associated with an elevated prevalence of TLBW.

Examination of Multiple Air Pollutant Exposure, the Food Environment, and Low Birth Weight in Los Angeles, County

by
Eric S. Coker

A DISSERTATION

submitted to

Oregon State University

in partial fulfillment of
the requirements for the
degree of

Doctor of Philosophy

Presented March 2, 2016
Commencement June 2016

Doctor of Philosophy dissertation of Eric S. Coker presented on March 2, 2016

APPROVED:

Major Professor, representing Public Health

Co-Director of the School of Biological and Population Health Sciences

Dean of the Graduate School

I understand that my dissertation will become part of the permanent collection of Oregon State University libraries. My signature below authorizes release of my dissertation to any reader upon request.

Eric S. Coker, Author

ACKNOWLEDGEMENTS

I hold a great deal of admiration and gratitude towards Dr. John Molitor for his guidance and encouragement during my dissertation work. I feel fortunate to have worked with and received knowledgeable advice from such a brilliant researcher. We spent hours upon hours in his office together hammering out complex and very detailed statistical analyses that often stretched the bounds of my creativity and understanding. Dr. Molitor showed the patience and commitment that any advisee could hope for. I similarly hold a great deal of gratitude for the efforts and guidance I received from Dr. Molly Kile, both early on in my PhD career and into the present. Dr. Kile provided me with the early guidance that helped ground me in sound environmental epidemiological approaches and further helped to develop my skills in this field. Dr. Kile also gave me sage advice at critical times during my pursuit of a PhD. I also want to acknowledge Dr. Ellen Smit who helped me develop my survey data analysis and epidemiologic skills. In addition, thank you to my PhD committee members for your feedback and sincerely placed encouragement. I also owe a great deal of gratitude to my collaborators and co-authors, especially those at UCLA and UC Berkeley, for your thorough reviews of our work together, and thank you for entrusting me with such a rich dataset with which to work with. And thank you to the administrative staff at OSU for your timely email reminders and the hard work you do every day to ensure this campus and its professors and students operate effectively.

Finally, to my family and friends, thank you so much for being the support that I needed at any time, day or night, to get through this process. Most especially to my wife, Irene; thank you for giving me the time and space to complete this 'all-consuming' work and for dealing with my long work nights that sometimes went into the wee hours of the morning. Your encouragement, sense of humor, patience and love saw me through this process. And thank you to my son, Elisha Mukisa (aka Mookie) for making me laugh and to help me forget about dissertation work for a while. Thank you to my Mother, Anita, for giving me the foundation to pursue such a lofty goal. Without the loving support of my family and friends this would not be possible.

CONTRIBUTION OF AUTHORS

Dr. John Molitor, Dr. Molly Kile, Dr. Ellen Smit, Dr. Beate Ritz, Dr. Mike Jerret, Dr. JoKay Ghosh, Dr. Silvia Liverani, and Dr. Virgillio Gomez provided substantial contributions to the conception, design and interpretation of the data as well as the critical review and editing of the manuscripts. Dr. Bernardo Beckerman, Dr. Mike Jerret, Dr. Beate Ritz, and Dr. Jo Kay Ghosh all contributed in providing the air pollution estimates. Dr. Beate Ritz and Dr. Jo Kay Ghosh contributed towards collected the birth record data. Dr. Arthur Li contributed towards cleaning and managing the air pollution and birth record data.

TABLE OF CONTENTS

TABLE OF CONTENTS (Continued)

Page

LIST OF FIGURES

Figure Page

LIST OF FIGURES (Continued)

Figure Page

LIST OF TABLES

LIST OF APPENDICES

LIST OF APPENDIX FIGURES

LIST OF APPENDIX TABLES

LIST OF ABBREVIATIONS AND ACRONYMS

ACS	American Community Survey
BYM	Besag-York-Molly
CAR	conditional autoregressive
CDC	Centers for Disease Control and Prevention
CT	census tract
ERS	Economic Research Service
ESRI	Economic and Social Research Institute
FARA	Food Access Research Atlas
g	grams
GIS	Geographic Information System
glm	generalized linear model
INLA	Integrated Nested Laplace Approximation
IQR	interquartile range
IUGR	intrauterine growth restriction
LA	Los Angeles
LBW	low birth weight
LMi	Local Moran's I
LUR	Land Use Regression
$\mu g/m^3$	micrograms per meter cubed
mRFEI	modified retail food environment index
NDVI	normalized differential vegetation index
NO_2	Nitrogen Dioxide
NO	Nitrogen Oxide
NOx	Nitrogen Oxides
O_3	ozone
OR	Odds Ratio
PM	particulate matter
$PM_{0.1}$	particulate matter with aerodynamic diameter <0.1µm
$PM_{2.5}$	particulate matter with aerodynamic diameter <2.5µm
ppb	parts per billion
R	software environment for statistical computing
R-INLA	Integrated Nested Laplace Approximation for R
SES	socioeconomic status
SNAP	Supplemental Nutritional Assistance Program
Stata	Data Analysis and Statistical Software
TLBW	term low birth weight
U.S.	United States
USDA	United States Department of Agriculture
USEPA	United States Environmental Protection Agency
WIC	Special Supplemental Nutrition Program for Women, Infants, and Children

Chapter 1 - INTRODUCTION

Environmental Health and Joint Assessment of Risk

There is increased need in the field of environmental health to evaluate health risks as they relate to cumulative (or aggregate) exposures to multiple different environmental stressors (National Research Council (U.S.) et al., 2009). In the US EPA's 2003 report entitled, "Framework for Cumulative Risk Assessment", cumulative risk is defined as "the combined risk from aggregate exposures to multiple agents or stressors." In order to appropriately apply this cumulative risk framework the US EPA stresses that "multiple agents or stressors" must be assessed and that "agents or stressors" are not merely chemical but can include physical, biological and/or an activity (e.g. food consumption). Furthermore, such a cumulative risk framework emphasizes that risks due to agents or stressors be *combined*, and that the combined risks should not merely be added together but also assessed jointly. The US EPA also states that "an assessment that covers a number of chemicals or other stressors but that merely lists each chemical with a corresponding risk without consideration of the other chemicals present is not an assessment of cumulative risk" (US EPA, 2003). The proposed study is motivated by this cumulative risk framework described by the US EPA and focuses on the assessment of joint exposures to multiple environmental chemical agents (i.e. air pollutants) and stressors (i.e. the food environment and other neighborhood-level factors) and their associations with population level effects on TLBW, an important health disparity.

Increasing evidence indicates the importance of place in terms of the combined exposures related to neighborhood stressors such as the built environment and exposure to environmental pollutants, which have negative consequences for population health and contribute to health disparities. However, the decisive combinations of place-based environmental exposures along

with other correlated neighborhood stressors are not well characterized. For instance, there are many neighborhoods in the United States where disadvantaged racial groups and low income populations lack ready access to nutritious and affordable foods, and the negative impacts on population health are becoming more apparent as research in this area evolves. Despite the evolving literature regarding the relationship between the food environment and human health outcomes, very few studies have evaluated the relationship between the food environment on birth outcomes. Additionally, it has been hypothesized that populations living in poor food environments may live in neighborhoods simultaneously characterized by poor outdoor air quality and socioeconomic disadvantage, yet little research has been conducted to explicitly investigate whether this is true. Moreover, there is a need to better understand exposure to mixtures of air pollutants, especially the spatial patterns of multipollutant exposures and their effects on health. The environmental health studies in my dissertation seeks to help fill these gaps in knowledge regarding the consequences of multiple and joint exposures and also attempts to advance the capacity of public health to apply spatial analysis methods to address such critically important environmental health concerns.

Prenatal Exposures and Birth Outcomes

Prenatal nutritional and environmental toxin exposures occur at a sensitive developmental stage of life whereby high levels of cell proliferation, organ development, and changes in fetal metabolism take place. Such *in utero* exposures have been linked with prenatal and postnatal health outcomes, including spontaneous abortion, infant mortality, preterm birth, and low birth weight (among several others) (Ritz and Wilhelm, 2008a; Selevan et al., 2000). The link between maternal nutrition and adverse birth outcomes is complex, however, since the effects of nutrition during pregnancy may be influenced by a variety of factors, from socioeconomic status (SES), cultural and environmental factors, baseline maternal nutritional status, to multiple nutrient deficiencies. For instance, maternal nutrient effects on birth outcomes have generally been

shown to be most pronounced among lower SES populations, particularly in low income/developing nations. Importantly though, it is not just in lower income developing countries where we see micronutrient deficiencies, mothers in the US are shown to suffer from micronutrient deficiencies that are important for fetal growth and development (Allen, 2005). Therefore, to the greatest extent feasible studies should take these other mediating or confounding factors into account, given such complexities in the association between maternal nutrient intake and adverse birth outcomes (Abu-Saad and Fraser, 2010). Compared to maternal nutrition and birth outcomes research, the link between prenatal air pollution exposures with adverse birth outcomes has been made relatively recently (Abu-Saad and Fraser, 2010; Ritz and Wilhelm, 2008a). By the mid-1990's researchers initiated investigations into exposure to criteria air pollutants and associations with birth outcomes and found significant association for infant mortality, preterm birth and low birth weight (Ritz and Wilhelm, 2008a). Similar to maternal nutrition, the associations of outdoor air pollution on adverse birth outcomes is complex, with area-level factors such as SES (Ponce, 2005a; Zeka et al., 2008), proximity to roadways (Dadvand et al., 2014; Laurent et al., 2014a; Zeka et al., 2008), and the type of air pollutant, shown to influence outdoor air pollution effects on birth outcomes (Bell et al., 2012; Ebisu and Bell, 2012a; Laurent et al., 2014a; Ritz and Wilhelm, 2008a). Given the complex nature in the relationships between area-level factors and exposure to outdoor air pollution, and the potential influence on related birth outcome risks, studies should examine how this interplay of place or joint exposures (chemical or non-chemical) contribute to disparities (geographic or otherwise) in birth outcomes (Morello-Frosch and Shenassa, 2006).

Low Birth Weight

LBW is typically defined as a birth weight below 2,500 grams (g) with full term (>=37 weeks gestation) LBW infants (TLBW) typically considered to be growth restricted (Ritz and Wilhelm, 2008a). Annually in the United States there are more than 300,000 low birth weight (LBW) infants (or ~8% of all births)(World Health Organization and UNICEF, 2004). LBW represents an important source of racial/ethnic and socioeconomic health disparities in the U.S (Foster et al., 2000) and is a major secondary cause of infant mortality (Abu-Saad and Fraser, 2010). LBW is also particularly important from a public health standpoint due to its role in the fetal origins of disease hypothesis (Barker, 1995; Eriksson, 2005). For instance, LBW tied to

undernutrition is considered a risk factor for a variety of diseases later on in childhood and into adulthood including diabetes and cardiovascular diseases (Barker et al., 2002), child and adult pulmonary disorders (den Dekker et al., 2015; Lawlor et al., 2005), and childhood neurologic morbidities (Tandon et al., 2000). Furthermore, LBW infants impose is a significant financial burden in terms of healthcare costs in the US. A study from California indicates that the healthcare costs attributable to lower birth weight is considerable, with neonatal care costs increasing exponentially with lower birth weights (Gilbert et al., 2003).

From a biologic standpoint, the rapid growth of a fetus begins from the period approximately nine weeks post-conception and continues until birth, with various tissue/organ growth that occur at different critical phases of gestation. Fetal growth is dependent on the uptake of nutrients and oxygen and a lack of either of these during critical time windows of gestation can slow the rate of tissue growth, and thus lead to increased risk of low birth weight (Barker, 1995). It is this maternal under nutrition, during middle to late gestation, that is hypothesized to contribute to diseases in adulthood, such as coronary heart disease.

Risk Factors for Low Birth Weight

The constellation of risk factors for LBW occur at both the individual and neighborhood levels. Individual-level risk factors include preterm birth, sex of the infant, maternal status in terms of age, preconception nutrition and prenatal nutrition, existing health status (i.e. pre-eclampsia/eclampsia and hypertension), parity (e.g. nulliparous), sociodemographics (i.e. race/ethnicity and education), smoking, psychosocial stress, and environmental exposures (e.g. air pollution such as particulate matter and NOx), among others (Kannan et al., 2006; WHO, 2014). Operating at the neighborhood-level, research data indicates that neighborhood-level SES (English et al., 2003a; Meng et al., 2013a), greenness (Hystad et al., 2014a; Laurent et al., 2013c; Markevych et al., 2014), and racial/ethnic segregation each contribute as risk factors for TLBW (Vinikoor et al., 2008; Walton, 2009). Additionally, several of these risk factors may act as confounders and/or effect modifiers on determinants of TLBW risks (Kannan et al., 2006; Meng et al., 2013a). In the interest of disease prevention and reducing health disparities it is paramount to identify the modifiable risk factors associated with TLBW. Environmental pollution and the built environment stand out as modifiable conditions for policy makers and researchers to

consider when attempting to reduce health disparities and to ultimately improve population health outcomes overall (Srinivasan et al., 2003).

Air Pollution and Low Birth Weight

Data from several air pollution epidemiologic studies point towards prenatal exposure to outdoor air pollutants as being associated with adverse birth outcomes including reduced term birth weight (Basu et al., 2013; Bell et al., 2012; Brauer et al., 2008; Ebisu and Bell, 2012a; Ghosh et al., 2012a; Kloog et al., 2012; Laurent et al., 2013a; Morello-Frosch et al., 2010a; Padula et al., 2012; Parker et al., 2005; Proietti et al., 2013; C Protano et al., 2012; Ritz and Wilhelm, 2008a; Ritz and Yu, 1999a; Shah and Balkhair, 2011, 2011; Slama et al., 2009; David M Stieb et al., 2012; Wilhelm et al., 2011a; Wilhelm and Ritz, 2003a; Wu et al., 2011). This dissertation focuses on TLBW because of this established link between environmental air pollution exposures with TLBW and the need to examine how joint exposure to multiple different air pollutants and other contextual factors may influence the association between air pollution and TLBW. Moreover, there is currently only a small number of studies that focus on air pollution and TLBW within the context of maternal nutrition, despite the possibility that these two maternal exposures (air pollution and nutrition) act along similar biologic pathways.

The biologic mechanisms underpinning the effects of air pollution on TLBW is still being elucidated. The epidemiologic, clinical and experimental data suggests the following biologic mechanics of air pollution on affecting birth outcomes:

1) systemic oxidative stress (Adamson et al., 2000; Delfino et al., 2009; Donaldson and MacNee, 2001; Elango et al., 2013; Fleischer et al., 2014; Geer et al., 2012; Jedrychowski et al., 2013; Labranche et al., 2012; Mohorovic, 2004; Pedersen et al., 2013; Perera et al., 1998; Ritz and Wilhelm, 2008a; Sørensen et al., 2003; Whyatt et al., 1998),

2) pulmonary and placental inflammation (Bobak, 2000; Brook et al., 2003; Delfino et al., 2009; Elango et al., 2013; Nel et al., 1998; Panagiotakos et al., 2004; Robertson et al., 2012),

3) coagulation of circulating blood (Pekkanen et al., 2000; Peters et al., 1997; Strak et al., 2013),

(4) promotion of endothelial dysfunction (Ambrose and Barua, 2004; Brook et al., 2004, 2003, 2002; Hansen et al., 2007; Holay et al., 2004; Otsuka et al., 2001; Zanobetti et al., 2014b), and

(5) alteration of maternal hemodynamics (i.e. altered systolic or diastolic blood pressure) (Bellavia et al., 2013; Duvekot et al., 1995; Ibald-Mulli et al., 2004; Misra, 1996; Xiong et al., 1999; Zanobetti et al., 2004).

While molecular epidemiologic studies are fewer in number, some studies further suggest various biologic mechanisms by which prenatal air pollution exposure affects birth outcomes, such as DNA methylation facilitated by DNA adducts caused by polycyclic aromatic hydrocarbon (PAH) exposure (Šrám et al., 2005). Recent work by Ghosh et al., (2016) further suggests an epigenomic link with low birth weight by finding CpG sites that were significantly more disrupted by DNA methylation among births in the lowest quintile of the birth weight distribution in comparison to births from the highest quintile of the birth weight distribution.

As the epidemiologic evidence supporting a link between air pollution as a risk factor for TLBW strengthens, especially for $PM_{2.5}$ (Fleischer et al., 2014), such risks may not be equal across different sub-populations (Morello-Frosch and Shenassa, 2006). A variety of factors are likely to contribute to an unequal distribution of health effects from outdoor air pollution. For instance, while concentrations of fine particulate matter ($PM_{2.5}$) are relatively homogenous across a given region, $PM_{2.5}$ is especially likely to exhibit a spatial dependence in terms of variation in different physical (size fractions) and chemical component characteristics (Laurent et al., 2014a; Levy et al., 2013a). Such spatial dependence in $PM_{2.5}$ composition is related to localized emissions patterns and meteorology (among numerous other factors)(Hajat et al., 2013; Molitor et al., 2011; Su et al., 2012). Hence, it follows that the magnitude of effects on health may impose geographic disparities at a population-level (Laurent et al., 2014a; Pirani et al., 2015a; Zanobetti et al., 2014a). As a study by Laurent et al. (2014) in LA County recently showed, different components of $PM_{2.5}$ pollution exhibited strong source-dependent characteristics and thus produced substantial variation in PM-related effects on reductions in term birth weight. Wilhelm et al., (2011) similarly found that the exposure-response between $PM_{2.5}$ and TLBW varied by $PM_{2.5}$ source type (e.g. gasoline versus geologic sources) within LA County. Pedersen et al., (2015) investigated eight European birth cohorts and observed variation

in the exposure-response between $PM_{2.5}$ chemical components, with OR estimates for sulfur $PM_{2.5}$ of 1.24, compared to 1.08 for overall $PM_{2.5}$. Hence we would expect to see that localized intra-urban differences in source-dependent particulate air pollution exposure and health effects patterns should contribute to inequalities with regard to PM-related adverse birth outcome risks (Baxter et al., 2007). Additionally, an array of spatially correlated contextual neighborhood factors and individual factors may contribute to variations in susceptibilities to air pollution, including socioeconomic status (SES), demographics (i.e. racial segregation), exposure to violence (Messer et al., 2006), access to healthy food (Lane et al., 2008), access to green space (Hystad et al., 2014a), housing characteristics (Ghosh et al., 2013a), and psychosocial risk factors (Ghosh et al., 2010a). So it follows that studies investigating the relationship between outdoor air pollutants such as $PM_{2.5}$ ought to consider the spatial dependency in the exposure response relationships.

Spatial dependency in air pollution effects, however, are not accounted for when using standard regression models that rely on fixed covariate effects (Morello-Frosch and Shenassa, 2006). While previous health research has demonstrated the spatial dependency of PM-related chronic health effects such as cardiovascular disease and asthma (Boehm Vock et al., 2014; Choi et al., 2009; Fuentes et al., 2006; Jerrett et al., 2005; Krewski et al., 2009; McConnell et al., 2010; Samoli et al., 2004; Shankardass et al., 2009), to my knowledge no previous study has explicitly modeled the spatial dependency of individual-level $PM_{2.5}$ exposure-response relationships on birth outcomes within an urban area. As such, the first study in this dissertation will not only investigate the overall fixed effects from exposure to $PM_{2.5}$, but will also explore the spatial dependency in the exposure response between $PM_{2.5}$ on TLBW.

Linking Multipollutant Exposures with Health Outcomes

While it is well established that people are exposed to multiple correlated air pollutants simultaneously (Hidy et al., 2011; Mauderly et al., 2010; Molitor et al., 2011), it remains unclear whether specific mixtures of air pollutants (or pollutant profiles) are implicated in health effects (Ebisu and Bell, 2012a; Laurent et al., 2013a; Olsson et al., 2012; Proietti et al., 2013; C Protano et al., 2012; Shah and Balkhair, 2011; Slama et al., 2009; David M Stieb et al., 2012). Meanwhile, regulatory bodies are increasingly being faced with determining management

strategies to reduce the health risks and disparities attributable to multipollutant exposures, yet there is insufficient exposure data and health effects research to provide appropriate guidance in this area (Hidy et al., 2011; Mauderly et al., 2010). As such, it has become increasingly important to better delineate the specific pollutant profiles that are most important within the context of multipollutant health risks (Sun et al., 2013; Vedal and Kaufman, 2011).

According to a review of multipollutant and health effects research (Oakes et al., 2014), there is currently no "gold standard" multipollutant metric or analytic framework for which to evaluate the public health risks associated with multi-pollutant exposures (Oakes et al., 2014). A major epidemiologic and statistical hurdle in our understanding of multipollutant health effects is our inability, as of yet, to determine whether combined exposure to pollutants acts additively or synergistically to contribute to health risks, or even infer which pollutant or combination thereof are in the causal pathway (see for instance Laurent et al., (2014)). Additionally, while there is considerable spatial variation in intra-urban multipollutant concentrations (Levy et al., 2013a), little research exists that explores the spatial patterning of multipollutant exposures or multipollutant health risks (Mauderly and Samet, 2009). Further complicating our lack of understanding regarding multipollutant air exposures and their consequent health risks, as pointed out in the much of the environmental justice literature, is the effects of other geographically correlated environmental, built environment, social and economic factors that coincide with poor air quality in the US. Such correlated contextual exposures may include: environmental stressors aside from air pollution exposures, psychosocial stressors, underlying health status, poverty, built environment factors such as greenness and access to nutritious foods, vulnerable sociodemographic sub-populations, and occupational factors, which are all believed to contribute to health disparities (Marshall, 2008; Molitor et al., 2011; Zou et al., 2014).

Consequently there is a push to move away from a single pollutant approach (Vedal and Kaufman, 2011) and to explore the degree to which pollutant profiles vary over local geographies, and to further evaluate whether health effects differ across these pollutant profiles and across geographies (Hidy et al., 2011). Therefore, a major focus of this dissertation examines spatial patterns in prenatal exposure to multipollutant profiles and birth outcomes, within the context of correlated contextual factors.

Multiple different statistical approaches have recently been proposed to address exposure to pollutant mixtures for assessment in health research. Several of these approaches have been reviewed and described in great detail by Sun et al. (2013), Oakes et al. (2014), and Billionnet et al. (2012). These novel statistical approaches include, but are not limited to: (1) least absolute shrinkage and selection operator regression, (2) Bayesian model averaging, (3) supervised principle component analysis, (4) partial least squares regression, (5) deletion/substitution and addition, (6) classification and regression tree, and (7) cluster analysis. A detailed explanation of each statistical approach is available in Sun et al. (2013) and Billionnet et al. (2012). Within the context of the statistical approach taken in this dissertation research, the following text describes the Bayesian model averaging and clustering approach applied in this study.

Cluster and Bayesian analysis

Cluster analysis partitions explanatory variables into smaller sets of variables (or profiles) and typically relies on distance-based "hard" clustering methods, such as the commonly used k-means algorithm (Austin et al., 2012a; Hartigan and Wong, 1979). The primary advantage gained from employing cluster analysis in the evaluation of multipollutant exposures and health risks relates to mitigation of the well know problems associated with multicollinearity (Dormann et al., 2013a). For instance, the presence of highly correlated covariates (i.e. multicollinearity) in a regression context challenges our ability to infer which covariates are associated with an effect in a given model and is liable to inflate standard errors of regression estimates (Dormann et al., 2013a). Whereas the 'proxy-indicators' of the collinear variables, represented as a profile of covariates into clusters, are more robust to the influences of multicollinearity compared to including the multiple collinear variables in a statistical model (Dormann et al., 2013a).

A disadvantage with the "hard" clustering approach is the arbitrary pre-assignment in the number of clusters for analysis and the need for extensive sensitivity analyses to optimize the cluster number (as done in the k means approach), and the inability to handle uncertainty in terms of cluster assignment for a given profile of covariates (Abubaker and Ashour, 2013; Austin et al., 2012a; Dormann et al., 2013a; Molitor et al., 2010b). Bayesian model averaging (BMA) combined with a clustering approach, on the other hand, is a particularly strong approach because it is better equipped to handle uncertainty for the purposes of cluster assignment (Sun et

al., 2013). Rather than choosing a "hard" clustering with which to partition individual profiles of pollutants, the BMA approach averages over all possible partitions of pollutant-concentration mixture profiles produced by the cluster sampling algorithm, thereby inclusion of uncertainty into "best" cluster assignments (Molitor et al., 2011, 2010b).

This unified process of clustering and model averaging is referred to as a Bayesian mixture model and has been advanced in work by Molitor et al. (2010b) and Pirani et al., (2015). The approach relies on a non-parametric mixture modeling technique that unconstrained (i.e. infinite) by a predetermined number of clusters; thereby allowing a data-driven determination of clusters as opposed to pre-assigning an arbitrary number of clusters as with contemporary "hard" clustering techniques (Austin et al., 2012a; Zanobetti et al., 2014a). The infinite mixture profiles are described by unknown probabilities that are derived from a prior distribution known as the Direchlet process, described in detail elsewhere (Ferguson, 1973; Pirani et al., 2013).

The application of cluster analysis in combination with Bayesian model averaging techniques in air pollution epidemiologic studies is still in its infancy, most especially for modeling multipollutant health risks. The Bayesian mixture modeling framework described above-- also referred to as Bayesian profile regression-- has been employed in several recent publications (Molitor et al., 2014a, 2011, 2010a, 2010b; Pirani et al., 2015a), but only one of these studies examined the association between multiple air pollutant exposure with health risks (Pirani et al., 2015a). Although, a Bayesian model averaging technique has been used in previous studies to establish model covariates to predict pollutant health effects, none of these studies have applied a multipollutant cluster analysis to evaluate health risks (Clyde, 2000; Clyde et al., 2000; Clyde and DeSimone-Sasinowska, 1998; Koop and Tole, 2004; Schwartz and Laden, 2004). A cluster analysis of health effects related to multiple pollutant profiles was conducted in (Qian et al., 2004a) and Zanobetti et al., (2014a), these studies relied on a "hard" clustering framework and did not use a Bayesian approach. Furthermore, for such a complex birth outcome such as birth weight, it is imperative to examine joint chemical exposures since different pollutants are liable to have different biologic effects.

The one study by Pirani et al., (2015) that employed the Bayesian profile regression technique to estimate health risks attributable to multipollutant profiles provided intriguing

results. The authors used the PReMiuM package in R (Liverani et al., 2014) and evaluated the relationship between temporal air pollutant exposure profiles with respiratory mortality in London (UK). The authors were able pinpoint $PM_{2.5}$ component profiles most related with elevated respiratory mortality. The PReMiuM package in R builds off of earlier work by Molitor et al., (2010b) and offers an easily implementable and novel approach to model health risks associated with multiple air pollutant profiles, and therefore provides the statistical framework from which to achieve parts of Aim 1 of this proposal. In using this Bayesian profile regression approach, the second study of this dissertation explores exposure to multiple different air pollutants simultaneously-- in the form of clusters of exposure profiles-- to assess which multipollutant profiles exhibit elevated log odds of TLBW and to determine the spatial patterning of these multipollutant exposure profile TLBW relationships.

Nutrition and Low Birth Weight

Maternal diet during pregnancy must provide sufficient nutrients to attain fetal nutrient requirements for optimal placental and fetal growth. Maternal nutrition is also capable of changing expression of the fetal genome, and animal studies further demonstrate that both undernutrition (Belkacemi et al., 2010) and overnutrition (Wallace et al., 2004, 2003) are capable of inducing reduced placental-fetal blood flows, thus contributing to stunting of the fetus (Wu et al., 2004). Inadequate dietary intake of protein-energy and micronutrients (i.e. iron and folate) during the rapid growth phases of fetal development may be most important with respect to malnutrition's effect on fetal growth. Research data also suggest that micronutrient supplementation (Cogswell et al., 2003), multi-micronutrient supplementation (Shah et al., 2009), and food-supplementation (Buescher et al., 1993) programs can reduce the risk of low birth weight, particularly among low SES populations (Abu-Saad and Fraser, 2010). In addition, inadequate gestational weight gain (GWG) is related to an increase risk of lower birth weight babies (Siega-Riz et al., 2009), and inadequate GWG has been found to be influenced by gestational dietary intake and pre-pregnancy BMI (Chihara et al., 2014; Rasmussen et al., 2009).

It has been hypothesized that nutrition may confound or modify the association between environmental exposures on birth outcomes (Abu-Saad and Fraser, 2010; Erickson and Arbour, 2014; Ritz and Wilhelm, 2008a; Ritz and Yu, 1999b). Kannan et al. (2006) hypothesized a

biologically plausible mechanism for joint effects between nutrition and air pollution exposures on birth outcomes due to the fact that air pollution and nutrition are believed to act on similar etiologic pathways. Some studies have found antagonistic effects of fruit and vegetable derived antioxidants on environmental toxin effects, such as down-regulation of endothelial inflammation associated with environmental pollutants (Hennig et al., 2007a, 2007b, 2005). Observational data suggests that certain micronutrients likely play a role in counteracting oxidative stress; these include fat-soluble carotenoids (Kiokias and Gordon, 2003) and vitamin E, water-soluble vitamin C (Bhagavathy and Sumathi, 2012; Mayne, 2003; Porrini et al., 2002), methyl nutrients such as B-vitamins and folate (Kawashima et al., 2007; Smolková et al., 2004), and trace minerals such as zinc and manganese (Ames, 1999; Modi et al., 2006). While a few epidemiological studies have directly examined effect modification of nutrition on air pollution effects on birth weight, unfortunately such studies are few in number and study finding have been mixed in terms of finding evidence for effect modification (Jedrychowski et al., 2010, 2007; Masters et al., 2007; Pedersen et al., 2013). However, these studies do provide important insights to indicate the importance of evaluating the potential for joint effects between nutrition and air pollution effects on birth outcome risks.

The Food Environment and Health Outcomes

The vast majority of epidemiologic literature relating the food environment to health outcomes have centered on overweight/obesity health effects (Broady and Meeks, 2014; Drewnowski et al., 2012; Dubowitz et al., 2012; Giskes et al., 2011; Hattori et al., 2013; Janevic et al., 2010; Salois, 2012). This body of research has provided data to indicate that, in urban areas, the availability of supermarkets, fast food/takeout restaurants (Dubowitz et al., 2012; Hattori et al., 2013), and convenience stores (Walker et al., 2014), are associated with overweight/obesity status. Since research data in the US indicates that maternal obesity/overweight is related to having a large for gestational age baby, the implication is that an adverse food environment may actually contribute to birth weight in the opposite direction of reduced term birth weight. For instance, previous research findings show that closer distance to supermarkets within a neighborhood is associated with improved diet quality in pregnant women (Laraia et al., 2004) and further distance to supermarkets has been linked with pre-pregnancy weight >200lbs (Janevic et al., 2010). Geospatial analysis has also shown that the prevalence of

fast food retailers is associated with a higher odds of gestational diabetes (Kahr et al., 2015), and gestational diabetes is linked with a higher birth weight for gestational age. While data from several studies indicate that both maternal overweight/obesity status (Bhattacharya et al., 2007; Crane et al., 2009; Frederick et al., 2008) and excessive GWG (Crane et al., 2009; Siega-Riz et al., 2009) are related to a reduced risk of TLBW babies, these relationship are not so clear-cut, particularly with regard to race and pre-pregnancy weight status.

Olafsdottir et al.,(2006) found that overweight women pre-pregnancy were more likely to have inadequate GWG compared to women at a normal pre-pregnancy weight. Seabra et al., (2011) similarly found that overweight/obesity was associated with higher prevalence of inadequate GWG. Importantly, differences in the effect of pre-pregnancy BMI on GWG, by race-ethnicity, have been observed in the US. Headen et al., (2015) used the 1979 USA National Survey of Youth cohort and found that normal weight non-Hispanic Black and Hispanic women had increased risk of inadequate GWG compared to Whites, and only underweight African Americans had increased risk of inadequate GWG compared to underweight Whites. This apparent effect modification was not observed in overweight or obese pregnancies. Liu et al., (2014) found similar evidence of effect modification by race in the relationship between pre-pregnancy weight and GWG. Among women with a BMI<25kg/m^2, Blacks and Hispanics showed a 50% higher odds of inadequate GWG compared to Whites. Research data also suggests effect modification by race in the positive relationship between excessive GWG with an increase in birth weight among women with a pre-pregnancy BMI>30kg/m^2, wherein Blacks (101 g [95% CI: 91, 111]) show a lower increased birth weight compared to Whites (118 g [95% CI: 109, 127]) when comparing excessive GWG to those with adequate GWG.

Despite this array of rather complex research findings, the food environment has been proposed as a neighborhood level mediator of the observed socioeconomic effects on birth outcomes (Erickson and Arbour, 2014; Meng et al., 2013a; Metcalfe et al., 2011). A likely driver behind poor food environments in possibly increasing the risk of having a TLBW baby in the US could be related to its influence on maternal consumption of highly processed foods or fast foods that tend to be low in micronutrients that are essential for optimal fetal growth and development (Goletzke et al., 2015; Institute of Medicine (U.S.) et al., 2005; Laraia et al., 2004; Moodie et al., 2013). Not surprisingly, however, the relatively few number of studies that have examined the

relationship between the food environment on birth outcomes have thus far shown conflicting results (Farley et al., 2006; Lane et al., 2008; Ma et al., 2015).

Neighborhood Food Environments and Birth Weight

A cross-sectional study by Farley et al. (2006) examined census tract-level (N=1,015) density of retail outlets selling food in relation to individual-level birth outcomes (N=105,111) in Louisiana. Data from this study did not find a significant association between food retail outlet density and birth outcomes. The coefficient for supermarket density (stores per 1,000 population) in relation to birth weight and gestational age were -0.24 (SE=0.27) and 0.022 (SE=0.021), respectively. Another study, conducted by Lane et al. (2008), examined the relationship between census-tract level (N=57) distance to supermarkets within 1/2 mile and IUGR. This study found a significant association between supermarket proximity on IUGR with an adjusted OR of 3.38 (95%CI:1.26-9.09) for low food access census tracts compared to high food access census tracts. A recently published study by Ma et al., (2015) examined the association between the food environment on individual birth weight, using neighborhood-level indicators of low food access for 867 census tracts. The unadjusted linear regression in Ma (2015) indicated significantly reduced birth weight in low supermarket access communities. After adjustment for confounders, however, low access tracts had significantly increased birth weight (β=18.7, 95%CI:10.1,27.3). On the other hand, this study also found that the presence of at least two convenience stores within a one-mile buffer was associated with a significantly lower birth weight in the study population (Ma et al., 2015).

One possible explanation behind these conflicting results in previous food environment and birth outcomes research may be related to the variation in the definition of the food environment along with potential misclassification of exposure. Two of these study described above employed a one-dimensional construct for the food environment (only looking at grocery stores). A one-dimensional examination for the food environment may not adequately capture the determinants of neighborhood level food purchasing and consumption behaviors, and may therefore act as a source of bias due to exposure misclassification. Given the lack of health research on this topic, the conflicting evidence from different studies, and the use of one-dimensional constructs to define the food environment, this dissertation uses a multidimensional

framework to define food environments rather than the more narrowly defined proximity based measure of food environment, and relates these to birth outcomes.

Neighborhood food environments and dietary intake

Dietary intake during pregnancy and the types of foods mothers purchase are influenced by a complex set of factors; ranging from individual level behavioral and socioeconomic status to environmental and other socially dynamic factors (Black et al., 2014; Cannuscio et al., 2014). In addition, area-level factors are shown to influence maternal access to and consumption of healthy and nutritious foods, and have further been shown to contribute to birth weight of infants. For instance, birth outcome and maternal and child health studies in developing countries have demonstrated that seasonality in some regions influence both access to nutritious food and birth outcomes (including birth weight and PTB) (Bantje, 1983; Bates et al., 1994; Fulford et al., 2006; Kinabo, 1993; Rayco-Solon et al., 2005; Rousham and Gracey, 1998). Thus it follows that neighborhood-level factors, such as food environments in developed countries, may be an important determinant of birth outcomes. While neighborhood access to healthy and affordable food should not be considered the most precise and direct measure of individual-level dietary intake, data from a number of studies provide evidence that neighborhood food access and food affordability indicators significantly influence individual dietary intake.

Black et al (Black et al., 2014) conducted a review of the literature on the food environment in developed countries and found a trend that better access to healthier foods and less healthy foods were related to better and poorer dietary intake, respectively. Black's review found that overall, proximity to supermarkets tended to be a better predictor of improved dietary intake relative to other indicators such as grocery stores or "green grocers". This review also found that compared to other developed countries, studies conducted in the United States (N=24) generally showed the strongest relationship ($p<0.05$) between the food environment and dietary intake. However, there is a considerable amount of heterogeneity regarding the association of the food environment on dietary intake. Caspi et al. (2012) also conducted an extensive review of the literature on studies that examined the relationship between the food environment and dietary intake. This review similarly found conflicting results. Importantly, authors in this review noted that studies which measured the food environment by incorporating more than one dimension of

the environment tended to find more consistent associations with food intake. The implication here is that defining the food environment based purely on distance to a healthy food stores is insufficient since it ignores other area-level factors such as proximity to fast-food and convenience stores, access to transportation, and the affordability of neighborhood food stores (Caspi et al., 2012). For instance, research data from California finds that spatial proximity of fast-food restaurants near homes and schools are related to dietary intake (Babey et al., 2011).

Poor food environments in Los Angeles County

An examination of the USDA's Food Environment Atlas dataset suggests that poor food environments may be a significant problem in LA County (US Department of Agriculture Economic Research Service, 2014). For instance, year 2007 data indicate that LA County is below California's median for grocery stores per capita (US Department of Agriculture Economic Research Service, 2014) and year 2008 data further indicate that LA County is below California's median number of grocery stores per capita authorized for the federal food subsidy program Women, Infant and Children (WIC). Incidentally, studies have shown that prenatal WIC participation has been associated with reduced risk of LBW babies (Buescher et al., 1993; Reichman and Teitler, 2003). Research from LA indicates that WIC participation reduces food insecurity among pregnant women (Herman et al., 2004), and improved food security during pregnancy has been shown to modify the association between poor maternal health status effects on TLBW (Meng et al., 2013a).

Studies conducted in LA County also indicate that the relationship between the neighborhood food environment and health may be strongly linked with household economic resources. According to an LA County Health Survey of LA County households, there is a strong correlation between increasing household poverty and increasing food insecurity and that this relationship is strongest among households with children (Morier, 2015). Inagami et al. (2009) studied 2,156 adults from 63 LA County neighborhoods and found that the association between the local food environment (as measured by fast food restaurant density) and body mass index was significantly stronger among residents who did not own a vehicle. The implication of this result is that a lack of vehicle ownership in neighborhoods with low access to healthy foods-- but ready access to fast food restaurants-- may be more likely to opt for less healthy foods that

increase obesity risks, since such food options are accessible by means that don't involve use of a vehicle or paying for public transportation. A different study conducted in LA County found that low income, minority and urban communities suffered from markedly reduced access to supermarkets per capita (Shaffer, 2002). Furthermore, another study conducted in LA County found that census tract-level fast-food restaurant density (per roadway-mile) was significantly higher in lower income communities compared to the highest income communities (Inagami et al., 2009). Taken together, these data suggest that LA County is characterized by SES and racial/ethnic disparities in food insecurity and healthy food access.

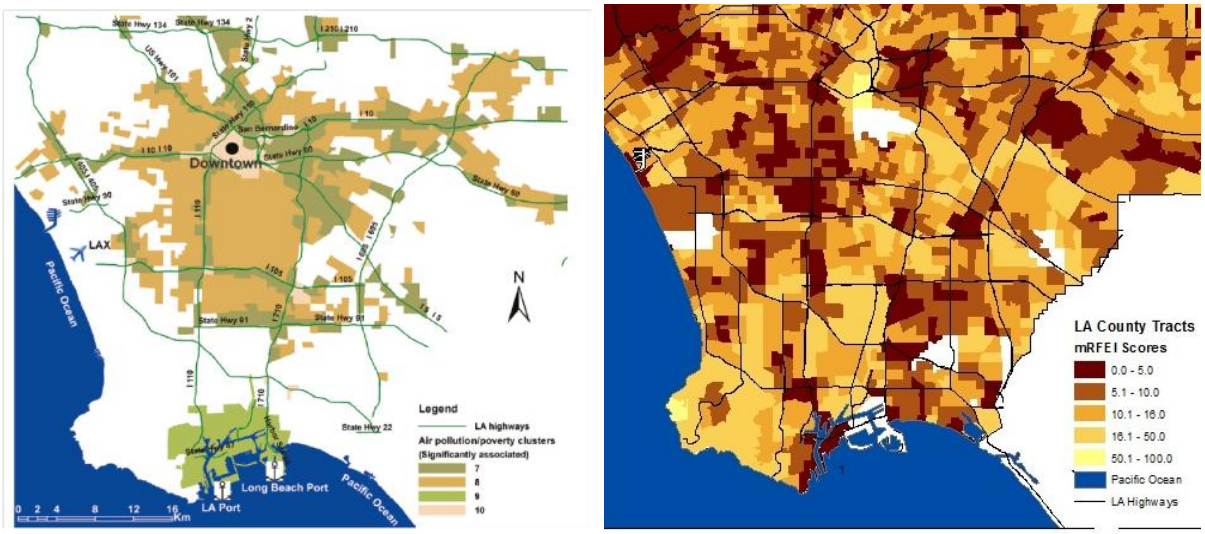
Linking Air Pollution Exposures, Food Environments, and Socioedemographics

Since it has become well established that neighborhood design influences air pollution exposures, there is increased research interest into how specific aspects of the built environment and related community-level stressors may correlate or interact with neighborhood-level air pollution (Marshall et al., 2009). Also, the concept of environmental inequity emphasizes that the distribution of desirable and undesirable environmental characteristics and their health burdens are distributed unevenly between different communities (Hilmers et al., 2012; Larsen and Gilliland, 2008). While only a fraction of the U.S. population lives in so-called food deserts, it is clear that urban residents belonging to racial minority groups and areas of low income are disproportionately burdened in this regard (Ver Ploeg et al., 2012). Currently, however, there is a paucity of research into the neighborhood-level correlation between exposure to poor air quality and poor food environments, or how this combination of neighborhood factors correlate with socio-demographic factors such as racial segregation.

There is sound reason to hypothesize that populations in US that live within socioeconomically disadvantaged neighborhoods are simultaneously exposed to higher levels of air pollution and more adverse food environments, which may have important implications for population health. Multiple lines of evidence indicate that neighborhood deprivation indicators are correlated with both poor food environment neighborhoods (Cummins et al., 2005; Franco et al., 2008; Hilmers et al., 2012; Lamichhane et al., 2013; Larson et al., 2009; Pearce et al., 2007; Richardson et al., 2012) and higher air pollution exposures (Gray et al., 2013; Hajat et al., 2013; Lee et al., 2014; Molitor et al., 2011). Research data further suggests that access to either fast

food restaurants or grocery stores are each influenced by proximity to arterial roads (Hurvitz et al., 2009a; Macintyre et al., 2005) and highways (Block et al., 2004). Likewise, differences in neighborhood air quality are influenced by proximity to arterial roads and highways (Choi et al., 2013). For instance, Kozawa et al. (2009) observed that neighborhoods 150 meters downwind from arterial roadways in the LA area are exposed to significantly higher levels of black carbon, nitric oxide, ultrafine particles, and particle-bound polycyclic hydrocarbons.

The maps of urban LA County presented in Figure 2 suggests substantial spatial overlap between clustering of neighborhood deprivation, exposures to elevated levels of multiple air pollutants, and adverse food environments. The first map (Figure 1.1.a) is from a paper by Molitor et al. (2011) which displays colored areas corresponding to census tracts with high multipollutant exposure profiles associated with clusters of high poverty neighborhoods. The colored census tracts in the second map (Figure 1.1.b) displays the spatial distribution of the CDC's modified retail food environment index (mRFEI) for LA county, with less healthy food environments indicated by darker shaded tracts and more healthy food environments indicated by lighter shaded tracts. These maps depict the strong potential for correlation between high exposure multipollutant profiles, high poverty, and poor neighborhood food environments.



(a) Census tract multipollutant profiles associated with poverty (b) Census tracts mRFEI scores

Figure 1.1. Census tract-level air pollution, deprivation, and food environments in LA County.

Specific Aims

The overall goal of this research is to apply a joint risk framework through investigations into the relationship between TLBW and outdoor air pollution and pollutant mixtures (or pollutant profiles), and between TLBW and the food environment in Los Angeles County, California. To achieve this goal, this research comprises three separate studies. The first study examined the overall relationship between exposure to outdoor $PM_{2.5}$ with TLBW in urban Los Angeles (LA) County, and further explored the within region spatial variation in the pollutant exposure response relationship. The second study used a Bayesian framework to model exposure to multiple pollutants in order to develop pollutant profile clusters, and further relates these pollutant profiles with TLBW within LA County. The third study examined whether the neighborhood environment is related to TLBW, and further explored whether the food environment acts as an area-level confounder or possibly as an effect modifier in the relationships between $PM_{2.5}$ on TLBW.

Specific Aim 1

To determine multiple air pollutant exposure profiles for residents in LA County and examine the relationship between mixed pollutant exposure profiles on TLBW.

Hypothesis 1a. There is a higher prevalence of TLBW with higher exposure during the entire pregnancy to urban outdoor air pollutants ($PM_{2.5}$, NO_2, and NO).

Hypothesis 1b. Air pollution exposure profiles composed of $PM_{2.5}$, NO_2, and NO are clustered by pollutant concentrations within LA County neighborhoods.

Hypothesis 1c. Individual births assigned to pollutant exposure profiles with high exposures to NO_2, NO, and $PM_{2.5}$ are more likely to be TLBW compared to births assigned to low NO_2, NO, and $PM_{2.5}$ pollutant exposure profiles.

Hypothesis 1d. Pollutant profile associations will be non-linear, in that high risk profiles will have high levels for some pollutants and low for others.

Specific Aim 2

To determine the confounding or effect modifying role of neighborhood-level food access on the association between individual-level prenatal exposure to air pollution on TLBW in LA County.

Hypothesis 2a. There is a higher prevalence of TLBW from mothers living in neighborhoods with low access to healthy foods compared to mothers living in neighborhoods with better access to healthy foods.

Hypothesis 2b. The magnitude of association between the food environment with TLBW is significantly larger at higher concentrations of $PM_{2.5}$ air pollution.

Specific Aim 3

To determine whether the geographic variation in air pollution concentrations are associated with poor food environments throughout Los Angeles County.

Hypothesis 3a. Higher concentrations of outdoor air pollutants in LA County are positively associated with census tracts with low access to healthy food retail stores.

Hypothesis 3b. Non-white populations are exposed to both poorer air quality and neighborhoods with low access to healthy food retailers compared to White populations.

Chapter 2 - Modeling Spatial Effects of PM2.5 on Term Low Birth Weight in Los Angeles County

[*]Eric Coker[a],
Jokay Ghosh,
Michael Jerrett[b],
Virgilio Gomez-Rubio[c],
Bernardo Beckerman[b],
Cockburn[d],
Silvia Liverani[e],
Jason Su[b],
Arthur Li[f],
Molly L. Kile[a],
[¥]Beate Ritz[g],
[¥]John Molitor[a]

[a]College of Public Health and Human Sciences, Oregon State University, Corvallis, OR
[b]School of Public Health, University of California, Berkeley, Berkeley, CA
[c]Department of Mathematics, Universidad De Castilla-La Mancha, Albacete, Spain
[d]Preventive Medicine and Spatial Sciences, University of Southern California, Los Angeles, CA
[e]Department of Mathematics, Brunel University, London, United Kingdom
[f]Department of Information Science, City of Hope National Cancer Center, Duarte, CA
[g]School of Public Health, University of California, Los Angeles, Los Angeles, CA
*Corresponding Author, Eric Coker, cokerer@onid.orst.edu
[¥]Equal contribution

Environmental Research
Published in Volume 142, October 2015, pages 354-364

Abstract

Air pollution epidemiological studies suggest that elevated exposure to fine particulate matter ($PM_{2.5}$) is associated with higher prevalence of term low birth weight (TLBW). Previous studies have generally assumed the exposure-response of $PM_{2.5}$ on TLBW to be the same throughout a large geographical area. Health effects related to $PM_{2.5}$ exposures, however, may not be uniformly distributed spatially, creating a need for studies that explicitly investigate the spatial distribution of the exposure-response relationship between individual-level exposure to $PM_{2.5}$ and TLBW. Here, we examine the overall and spatially varying exposure-response relationship between $PM_{2.5}$ and TLBW throughout urban Los Angeles (LA) County, California. We estimated $PM_{2.5}$ from a combination of land use regression (LUR), aerosol optical depth from remote sensing, and atmospheric modeling techniques. Exposures were assigned to LA County individual pregnancies identified from electronic birth certificates between the years 1995-2006 (N=1,359,284) provided by the California Department of Public Health. We used a single pollutant multivariate logistic regression model, with multilevel spatially structured and unstructured random effects set in a Bayesian framework to estimate global and spatially varying pollutant effects on TLBW at the census tract level. Overall, increased $PM_{2.5}$ level was associated with higher prevalence of TLBW county-wide. The spatial random effects model, however, demonstrated that the exposure-response for $PM_{2.5}$ and TLBW was not uniform across urban LA County. Rather, the magnitude and certainty of the exposure-response estimates for $PM_{2.5}$ on log odds of TLBW were greatest in the urban core of Central and Southern LA County census tracts. These results suggest that the effects may be spatially patterned, and that simply estimating global pollutant effects obscures disparities suggested by spatial patterns of effects. Studies that incorporate spatial multilevel modeling with random coefficients allow us to identify areas where air pollutant effects on adverse birth outcomes may be most severe and policies to further reduce air pollution might be most effective.

Research Highlights

- We model the spatial dependency of $PM_{2.5}$ effects on term low birth weight (TLBW).
- $PM_{2.5}$ effects on TLBW are shown to vary spatially across urban LA County.
- Modeling spatial dependency of $PM_{2.5}$ health effects may identify effect 'hotspots'.

- Birth outcomes studies should consider the spatial dependency of $PM_{2.5}$ effects.

Keywords

Air pollution; $PM_{2.5}$; term low birth weight, spatial effects, multilevel modeling

Introduction

Extensive evidence indicates that prenatal exposure to outdoor air pollution is associated with risk of term low birth weight (Brauer et al., 2008; Fleischer et al., 2014; Ghosh et al., 2013b, 2012a; Hyder et al., 2014; Padula et al., 2012; Parker et al., 2011; Ponce, 2005a; Proietti et al., 2013; Ritz and Wilhelm, 2008b; Shah and Balkhair, 2011; David M. Stieb et al., 2012; Wilhelm et al., 2011a; Wu et al., 2011). While TLBW contributes to racial-ethnic and socioeconomic health disparities in the United States, air pollution is thought to be an important place-based factor in the complex geography of and susceptibly to TLBW (Jerrett and Finkelstein, 2005; Morello-Frosch and Shenassa, 2006). It is reasonable to consider, however, that air pollution exposure-response effects on adverse birth outcomes, such as TLBW, vary spatially within an urban setting.

First and foremost, air pollutant mixtures or components of PM air pollution can be autocorrelated spatially within urban environments− depending on local-scale air pollution sources, the intensity of emissions, and meteorology (among other factors)(Hajat et al., 2013; Molitor et al., 2011; Su et al., 2012). As a result, the intrinsic toxicity of $PM_{2.5}$ mixtures is likely to be spatially dependent. For instance, Laurent et al. (2014) found that various components and sources of fine PM air pollution, which exhibit strong spatially varying characteristics, produced statistically significant gradients in PM-related TLBW risk in LA County. Similarly, Wilhelm et al., (2011), found that the exposure-response between $PM_{2.5}$ and TLBW varied by $PM_{2.5}$ source type (e.g. gasoline versus geologic sources) within LA County. Furthermore, (Pedersen et al., 2015) studied eight European birth cohorts and found that the exposure-response between $PM_{2.5}$ was dependent on its chemical composition, with OR estimates for sulfur $PM_{2.5}$ of 1.24, compared to 1.08 for overall $PM_{2.5}$. Such local-scale intra-urban differences in particulate air pollution exposure and health effects patterns may therefore lead to inequalities with regard to PM-related adverse birth outcome risks (Baxter et al., 2007). Further, a wide range of contextual

neighborhood factors and individual factors that are spatially correlated, from socioeconomic status (SES), demographics (i.e. racial segregation), exposure to violence (Messer et al., 2006), access to healthy food (Lane et al., 2008) or green space (Hystad et al., 2014a), housing characteristic, and psychosocial, may contribute to variations in susceptibilities to air pollution that are not fully accounted for in standard regression models relying on fixed covariate effects (Morello-Frosch and Shenassa, 2006). Few studies, however, have been conducted to examine whether there is a spatial patterning − or a "risk-scape" (Morello-Frosch and Shenassa, 2006) − for PM-related birth outcomes. While previous health research has evaluated the spatial dependency of PM-related chronic health effects such as cardiovascular disease and asthma (Boehm Vock et al., 2014; Choi et al., 2009; Fuentes et al., 2006; Jerrett et al., 2005; Krewski et al., 2009; McConnell et al., 2010; Samoli et al., 2004; Shankardass et al., 2009), no studies have modeled the spatial dependency of individual-level $PM_{2.5}$ exposure-response relationships on birth outcomes.

Several recent studies examined the spatial variation in $PM_{2.5}$ effects on TLBW between different countries or between US states. A large collaborative multi-site international study found a substantial degree of heterogeneity in estimates for entire pregnancy exposure-response between study sites, despite the use of similar exposure assessments and statistical models in the studies (Dadvand et al., 2013; Parker et al., 2011). (Hao et al., 2015) found substantial differences between states in the U.S. in terms of the magnitude and direction of effects of $PM_{2.5}$ on TLBW. Another multi-state U.S. study also found that the size of exposure-response estimates for $PM_{2.5}$ and TLBW depended upon study site; with odds ratios ranging from between 0.942 (95% CI: 0.817, 1.09) in Utah to as high as 1.72 (95% CI: 1.55, 1.93) in New York state (per 10-unit increase in $PM_{2.5}$ exposure) (Harris et al., 2014). Additionally, Williams et al. (2007) demonstrated, through implementation of a multilevel linear random coefficient model, that adverse effects on average birth weight in a population varied by census tract due to hazardous air pollution emitting industrial sites. The observed statistically significant differences in effect size between census tracts remained significant even after adjusting for the number of hazardous sites per census tract, individual level confounders, and contextually relevant census tract level confounding factors (Williams et al., 2007).

Despite the recent evidence suggesting that air pollution-related adverse effects on birth weight may vary spatially, no studies have explicitly examined spatial variation in effects within a dense metropolitan region such as LA county, which we are targeting in our paper. Our guiding hypothesis is that modeling of the spatially varying coefficients will show differences in TLBW according to LA County census tracts and thus provide evidence for localized $PM_{2.5}$ exposure response. Specifically, the magnitude of effect will be higher in some census tracts when compared to the global mean exposure-response for all of urban LA County. Our approach goes beyond the commonly employed estimation of an overall average $PM_{2.5}$ effect on birth weight and will allow us to describe a spatially-patterned deviation from the average effects, thus pinpointing potential 'hotspots' within LA County where the magnitude and probability of $PM_{2.5}$ effects are likely to be strongest.

In our paper we utilize an existing land use regression (LUR) $PM_{2.5}$ exposure model within a multi-level Bayesian framework; implemented with spatially-dependent random coefficients. This information may be useful from a policy perspective to create targeted public health interventions for LA County.

Methods

Study Population and Birth Outcomes

Data on infant birth weight were derived from electronic birth certificates provided by the California Department of Public Health, for LA County births between 1/1/1995 and 12/31/2006 (N=1,522,084). The birth records provided information on maternal characteristics such as age, race/ethnicity, education, total number of previous maternal births, and residential address, as well as characteristics of the infant (abnormalities, birth season, gestational age at birth, birth weight and baby's sex). Human subjects research was approved through the University of California, Los Angeles' Office of the Human Subjects Protection Program, the California Committee for the Protection of Human Subjects, and the University of Southern California's Office for the Protection of Research Subjects. Similar to previous studies, we restricted the dataset to singleton births with no recorded abnormalities (Ghosh et al., 2013b, 2012a; Wilhelm et al., 2011a). Additionally, we excluded births with extreme gestational days (less than 140 days or greater than 320 days), births that were not full term (<259 gestation days), and births with

birth weight less than 500g or greater than 5000g due to concerns about recording errors. For our final analyses, we further excluded births without complete information on the full set of study covariates (n=19,017). Finally, since we are interested in estimating within-city spatial variation in $PM_{2.5}$ effects, the spatial analysis further excluded rural sub-region of LA County, thus leaving a final study population of N=1,356,304. A detailed description of methods for geocoding residential addresses are described elsewhere (Goldberg et al., 2008).

$PM_{2.5}$ Exposure Assessment

A $PM_{2.5}$ LUR model developed previously by (Jerrett et al., 2013) was used to estimate individual exposures to $PM_{2.5}$ at each mother's residential address. Such estimates are intended to best represent spatially resolved long-term exposure to annual levels of $PM_{2.5}$ between 1995-2006, rather than pregnancy period-specific exposure. This $PM_{2.5}$ LUR model has been used previously to examine chronic long-term exposure to $PM_{2.5}$ and related health effects over time, in a large cohort study of California adults (Jerrett et al., 2013). This LUR method has been described in previous publications and the reader is referred to (Beckerman et al., 2013a) and Jerrett et al. (2013) for greater detail. Briefly, the predicted concentrations of $PM_{2.5}$ were based on covariate data from the following sources: (1) daily observations of $PM_{2.5}$ air monitoring collected between 1998-2002 at government monitoring sites throughout California, which was supplemented with remotely-sensed $PM_{2.5}$ data covering the time period between 2001-2006 (Beckerman et al., 2013a); (2) data on traffic and road networks from 1990-2001; (3) land use data from the year 2001; (4) population density data from the 2000 US Census; and (5) numerical output from remote sensing modeling coupled with atmospheric modeling (van Donkelaar et al., 2010). A deletion/substitution/addition algorithm was then implemented to develop the final model covariates with a cross-validated R^2 value of 0.65.

Covariates

Since this study is a methodological extension of previous work for the LA County area (Ghosh et al., 2012a; Wilhelm et al., 2011a), we applied similar covariates as in the previous studies to evaluate $PM_{2.5}$ in relation to risk of TLBW. Individual-level covariates were maternal age at delivery (<20 years, 20-24 years, 25-29 years, 30-34 years, ≥35 years), maternal race (non-Hispanic White, non-Hispanic Black, Hispanic, Asian, and Other race), maternal years of

education (< 9 years, 9-12 years, 13-15 years, and ≥ 16 years), parity, gestational days, gestation days-squared (Ghosh et al., 2012a; Wilhelm et al., 2011a) and sex of the infant.

Statistical Analysis

Standard Analysis

While our main objective was to evaluate the spatial dependency of $PM_{2.5}$ effects on TLBW, we initially examined "global" (or L.A. County-wide) associations between $PM_{2.5}$ and TLBW using crude-unadjusted and multivariate adjusted logistic regressions techniques. The intent of implementing a global fixed effects model is to replicate exposure-response relationships between increasing $PM_{2.5}$ exposure and increasing prevalence of TLBW as demonstrated from previous research. The crude and multivariate models were implemented as a generalized linear model (*glm*) using the binomial family with the logistic function in the R statistical computing environment (R-version 3.1.2) (see supplemental materials for code describing the specific models employed in R (Everitt and Hothorn, 2010)). For consistency, the multivariate model utilized same fixed effects covariates as for the multilevel model described below.

Multilevel Spatial Modeling

The focus of the present study was to expand on previous work by implementing a multilevel spatial logistic regression model that would assess whether exposure-response relationships vary within L.A. County. Along with the fixed effects on the covariates, we simultaneously included a random effect coefficient for the census tract-level effect of $PM_{2.5}$ on log-odds of TLBW. The random air pollution effect coefficient is composed of a global intercept plus independent and spatial residual error terms via the Besag-York-Molly (BYM) model (Besag et al., 1991). Because this model includes both spatial and independently structured error terms, the data determined the extent of spatial smoothing employed, without requiring strong assumptions regarding residual spatial dependency. Further, this approach yields both a countywide global mean effect as well as census tract-level random coefficients indicating sub-regional (or census tract) effects of $PM_{2.5}$ on TLBW.

The variance structure of the spatial component of the BYM model requires specification of a spatial zero-one weight matrix of dimension J by J, where J is the number of census tracts. Each element i, j of the weight matrix is one if census tract i and j are adjacent to each other, and zero otherwise. The '*spdep'* package (*spdep* package version 0.5-77 obtained September 30 2014) in R (R. Bivand et al., 2013; Bivand and Piras, 2015) was used to construct this neighborhood weight matrix and we assigned neighbors based on queens adjacency, which is defined as any neighboring census tract with a shared edge or vertex for a given area (i.e. census tract).

In fitting the model, we took advantage of the computational efficiency of Integrated Nested Laplace Approximations (INLA, version 0.0-1420281647) estimation techniques as implemented in the well-established R-INLA package (Rue et al., 2015), which has been used in several recent studies of large dimensions (Bennett et al., 2014; Castelló et al., 2013; Lee et al., 2013; Lee and Mitchell, 2014). The INLA approach avoids the computational burden related to typical Markov Chain Monte Carlo techniques (Gilks et al., 1998a) often used to fit Bayesian spatial models and allows accurate approximations to posterior marginal distributions of the model parameters (Grilli et al., 2014).

In the implementation of our model using R-INLA, the sub-regional-level air pollution effects consist of an overall fixed effect (that represents the overall mean effect) plus spatial and independent random residual effects as defined in the BYM model. (Rue et al., 2014, 2009)(Martino and Rue, 2009a)(Martino and Rue, 2009)(Martino and Rue 2009)(Martino and Rue, 2009). Hence, each Sub-Regional air pollution effect is then obtained as the sum of the overall fixed effect plus spatial and non-spatial census tract-level residual terms via the linear combination feature in R-INLA. This allows us to obtain a posterior distribution for each Sub-Regional-level air pollution effect, β_j, and to examine the spatial distribution of these effects throughout L.A. County.

The full model specification is presented in equations (1) and (2) below. Our first-level logistic-regression model is,

$$\text{logit}(y_i) = V\boldsymbol{\eta}' + \beta_{z_i} x_i \qquad (1)$$

where y_i denotes the logit probability of TLBW for individual i, $V\boldsymbol{\eta}'$ represents individual-level covariates V and associated fixed effect coefficients $\boldsymbol{\eta}'$, β_{z_i} represents sub-regional random effects of exposure, and x_i denotes individual-level $PM_{2.5}$ exposure. Note that $z_i = j$ indicates the census tract j to which individual i belongs, so if, say, individual 3 is in census tract number 12, then $z_3 = 12$, and $\beta_{z_3} = \beta_{12}$. There are therefore $\beta_j, j = 1, \ldots, J$ effects of $PM_{2.5}$ on log-odds of TLBW corresponding to each census tract, j.

We model the effects of $PM_{2.5}$ on TLBW for each census tract, j, as

$$\beta_j = \gamma_0 + S_j + \epsilon_j^{\beta} \qquad (2)$$

where γ_0 is the overall region-wide $PM_{2.5}$ effect, and S_j and ϵ_j^{β} denote spatial and independent residual error terms, respectively, with the restriction $\sum_j S_j = 0$ imposed for indefinability reasons. While the independent error term is defined in the standard way as $\epsilon_j^{\beta} \sim N(0, \sigma_{\beta}^2)$, the spatial error term is defined as,

$$S_{j|k\neq j} \sim N\left(\frac{\sum_{k\neq j} w_{jk} S_k}{\sum_{k\neq j} w_{jk}}, \frac{\tau^2}{\sum_{k\neq j} w_{jk}}\right),$$

where the weights $w_{j,k}$ are elements of the zero-one neighborhood adjacency matrix defined to be equal to one when census tracts i, k are adjacent and zero otherwise. This approach has been successfully employed in a variety of exposure/health association studies. (See, for example, (Molitor et al., 2007).)

Mapping

Estimates of the posterior quantities correspond to the adjusted random air pollution effects from the multilevel model were imported into ArcGIS 10.1 (ESRI, Redlands, CA) and merged with census tract boundary shapefiles to create exposure-response census tract-level 'effect maps'. In addition to mapping the multilevel adjusted census tract mean effects, the R-INLA package includes the 'inla.pmarginal' function that computes probabilities from the

posterior distribution of the marginal random effects as obtained from the linear combinations described above. This enabled us to map the marginal probabilities that a given census tract's random effect coefficient lies above zero, $P(\beta_j > 0)$. Similarly, we mapped the probability that a given census tract's random effect coefficient is above the adjusted global mean effect, $P(\beta_j > \bar{\beta})$. Computation of these probabilities help illustrate where associations between $PM_{2.5}$ and TLBW are most likely to occur (see supplemental materials for requisite R-INLA code needed to obtain posterior probabilities). Thus, our 'effect maps' depict probabilities that the $PM_{2.5}$ census tract-specific exposure response (β_j) lies above zero (or an OR above 1) and the probability that a census tract-specific air pollution effect deviates from the overall average ($P(\beta_j > \bar{\beta})$).

Results

Descriptive Analyses

Between 1995-2006 the overall prevalence of TLBW was 2.1% and the average $PM_{2.5}$ exposure was 17.04 μg/m^3 (interquartile range= 16.25, 18.21). The spatial distribution of $PM_{2.5}$ concentrations indicated that exposures were highest within the urban core of LA County, specifically the southern, eastern, and northwest portions of urban LA (Appendix A, Figure A.1). Risk factors that were associated with TLBW included maternal age, race, level of education, parity, gestation length (days), gestation squared, sex of the infant (Table 2.1), and were adjusted for in the following models.

$PM_{2.5}$ Regression Analyses

Standard Logistic Model

The final statistical analyses included 1,356,304 births from 2,033 LA County census tracts. In unadjusted fixed effects logistic regression, the odds of TLBW was 23.2% higher (OR=1.23 [95%CI: 1.16, 1.30]) per 10 μg/m^3 increase of $PM_{2.5}$. After adjusting for maternal age, race-ethnicity, education, parity, and infant gestation and sex, a 10 μg/m^3 increase in $PM_{2.5}$ exposure remained associated with statistically significant increased odds of TLBW (OR=1.17; 95%CI=1.10-1.24)(Table 2.2). The fully adjusted model results along with the model covariates are provided in detail within the supplementary material (Table A.1, Appendix A).

Multilevel Spatial Model

The multilevel spatial model provides $PM_{2.5}$ coefficients on TLBW at a global county-wide level (Table 2.2) and at the census tract neighborhood level. The overall mean $PM_{2.5}$ exposure-response estimate for our multilevel spatial model was similar in magnitude to the fixed effect logistic regression result ($OR_{spatial}$=1.19 versus OR_{fixed}=1.17, Table 2.2). The two maps presented in Figure 2.1 and Figure 2.3 present the probability that a given census tract's air pollution effect (with outcome on log-odds scale) is above zero (Figure 2.3) and the probability that a given census tract's effect is above the estimated overall mean effect (Figure 2.3), while Figure 2.2 presents the mean $PM_{2.5}$ random effect per census tract.

For the probability effect map in Figure 2.1, the census tracts in dark brown have a >95% probability of an effect that is above zero ($P(\beta_j > 0)$.). Thus, these areas represent census tracts where the $PM_{2.5}$ exposure-response with TLBW is most likely to be positive. The dark brown neighborhoods in Figure 2.3 have a >95% probability for an effect above the county-wide (or "global") mean effect. Hence, these areas represent census tracts that are most likely to exhibit a $PM_{2.5}$ exposure-response that is greater in magnitude compared to the estimated mean exposure-response relationship, which we are considering to be 'hotspots' within the context of our study. The hotspots appear to be concentrated in census tracts within central and south-central LA County (Figure 2.3).

LA Health District Summaries

LA County is composed of 26 health districts created from aggregates of census tract boundaries for the purposes of health assessments. Therefore, to highlight the observed spatial patterns in Figure 2.3, from the posterior distribution of the marginal random effects we calculated and mapped the average probabilities for LA County health districts with respect to tract-level probabilities above the overall mean $PM_{2.5}$ coefficient. These numerical summaries are simply descriptive since they were acquired by calculating the mean tract-level probabilities across health districts. Health districts of LA's urban core, including Central, Compton, Hollywood-Wilshire, Inglewood, South, Southeast, and Southwest health districts, are characterized by the highest probablities for $PM_{2.5}$ random coefficients above the overall county mean $PM_{2.5}$ coefficient (Figure 2.4). Thus the map suggests effect 'hotspots' are concentrated

within these health districts, which are generally lower income and non-white in terms of race-ethnicity (see Appendix A, Figures A.2 and A.3).

Discussion

Key Findings

We applied Bayesian multilevel spatial modeling to examine whether the exposure-response relationship between $PM_{2.5}$ and TLBW varies spatially. Consistent with previous findings from LA County (Ghosh et al., 2012a; Ritz et al., 2007a; Wilhelm et al., 2011a), we observed an overall relationship between increasing $PM_{2.5}$ exposure and increasing risk of TLBW. More important, we observed substantive variations across census tracts within LA County in the exposure-response between $PM_{2.5}$ and TLBW. Higher probabilities for positive $PM_{2.5}$ effects were mostly concentrated in central LA and south central LA sub-regions. Relative to the mean regional $PM_{2.5}$ effect on the log odds of TLBW, several census tracts located in central LA and south-central LA exhibited higher exposure-response relationships in terms of effect size and posterior probabilities for effects above the mean ($P(\beta_j > \bar{\beta})) > 0.95$). These observations suggested that $PM_{2.5}$ related adverse effects on birth weight may be modified by place.

A number of plausible explanations may account for the spatial patterning in the exposure response between $PM_{2.5}$ exposures and TLBW observed in our study. Firstly, regionally varying and spatially correlated neighborhood contextual factors may enhance exposure gradients within an urban setting and other spatially structured individual factors may further create susceptibility to adverse birth outcome by interacting with $PM_{2.5}$. Regionally varying and overlapping aspects of neighborhoods with the potential to enhance exposure to air pollutants or susceptibility to air pollution related health effects may include (but are not limited to): built environment factors (i.e. age of homes, homes set back further from the curb along heavily trafficked roadways) (Ponce, 2005a; Ramachandran et al., 2003); spatially correlated variation in the types of $PM_{2.5}$ sources (e.g. large truck traffic) and thus $PM_{2.5}$ component mixtures (Laurent et al., 2014a; Wilhelm et al., 2011a); the presence of older and higher pollution emitting vehicles, and neighborhood SES (Ponce, 2005a)(Lane et al., 2008)(Lane et al. 2008). For example, (Singer and Harley, 2000) observed that older vehicles tended to emit

higher air pollutant levels relative to newer vehicles within the LA area, and that vehicular emissions tended to be higher in low income areas compared to higher income areas (even for vehicles of the same age). Individual-level differences that display spatial clustering may also partially explain spatial patterns in birth outcomes risks; such as psychosocial (Ghosh et al., 2010b), occupational (Horner and Mefford, 2007; Ritz et al., 2007a), or nutritional factors (Jedrychowski et al., 2010; Lane et al., 2008), as well as individual home environments (i.e. home insulation or access to air conditioning (Ghosh et al., 2013b; Jerrett et al., 2005; Ponce, 2005a)). For instance, (Ritz et al., 2007a) found that parous women in LA without an occupation outside the home during the last 6 weeks of the pregnancy who were highly exposed to traffic-related air pollution had higher odds for preterm birth than exposed parous women working outside the home, illustrating the potential impact of exposure misclassification when sing a home address. In another study we conducted in LA (Ponce, 2005a) individuals' access to health insurance and their race, as well as neighborhood level factors such as SES and the physical environment (i.e. proximity to air pollution-related traffic and winter season) acted in concert to increase susceptibility to adverse pregnancy outcomes across LA county census tracts. Taken together this suggests a rather complex set of individual- and neighborhood-level social, cultural and environmental contributors to adverse birth outcomes that vary over space and may act on different biologic pathways to impair growth of the fetus resulting in TLBW, as suggested by the spatially varying effects estimated in our study.

In addition to spatial clustering of neighborhood and individual determinants and effect measure modifiers for birth outcomes, multi-pollutant mixtures in urban areas may create gradients in effects between Sub-Regions (Levy et al., 2013b; Novák et al., 2014). While multi-pollutant mixtures may be more toxic in terms of birth outcomes, our study did not explicitly account for pollutant mixtures. While inclusion of a spatial random effects term may have mitigated this limitation to some extent − since multiple pollutant profiles have been observed to be clustered spatially (Austin et al., 2012a) − this is an important limitation of this study. Furthermore, it cannot be ruled out that neighborhood-level and individual-level susceptibility and pollutant mixtures co-occur and together contribute to the observed spatially varying effect estimates seen in our study. Within regions of CA, such geographic-based susceptibility may be particularly acute. For instance, countywide studies in three California counties (Alameda, LA

and San Diego) found that, while concentrations of individual pollutants such as diesel PM, NO2, and $PM_{2.5}$ were statistically significantly higher within socioeconomically disadvantaged compared to less disadvantaged communities, when cumulative exposures to diesel PM, NO_2, and $PM_{2.5}$ were considered, the relationship between SES and exposure was stronger (Su et al., 2012). Overlap of environmental and SES risk factors that can enhance neighborhood-level susceptibility has been reported previously (Jerrett and Finkelstein, 2005; Morello-Frosch and Shenassa, 2006).

Spatial Dependency, Air Pollution, and Birth Outcome Studies

A multilevel spatial hierarchical modeling approach is established as a flexible means of addressing spatial structure in the exposure-response relationship between air pollution and health effects (Boehm Vock et al., 2014; Dominici et al., 2000; Lee et al., 2013) and may therefore highlight notable localized effects (Chakraborty, 2012; Dominici et al., 2000; Earnest et al., 2007). A major statistical advantage gained in using this approach to modeling a spatially-structured exposure-response relationship is to maximize statistical power by using data in all sub-regions to inform the analysis, rather than calculating separate regression models for each sub-region (Gelman and Hill, 2006a) . Multilevel modeling approaches which incorporate spatial smoothing allow information from nearby regions to potentially exert more weight and influence compared to distant regions (Banerjee et al., 2004; Zhuoqiong He, 2000).

A strength of our approach is the inclusion of individual-level pollutant effect estimates that are modeled with spatial structure at the census-tract level. Some air pollution and birth outcome studies have accounted for spatial dependency in the residuals, but still assume a global effect due to exposure (Berrocal et al., 2011; Castelló et al., 2013; Thompson et al., 2014; Williams et al., 2007). A spatial correlated autoregressive (CAR) model has been applied by (Berrocal et al., 2011) to examine the effect of CT-level $PM_{2.5}$ on continuous birth weight in North Carolina. An important distinction between the present study and Berrocal et al (2011) is that we applied a spatially structured random air pollution effect term, whereas Berrocal et al (2011) implemented a random intercept and did not explore the possibility of geographic disparities in the PM exposure-response relationship. A study by (Thompson et al., 2014) examined the exceedance probability of very LBW risks in relation to proximity to National

Priorities List Superfund Sites in Texas by modeling the spatially structured error term using Poisson regression. This study, however, used aggregated outcomes for a given geographic area and did not include individual-level air pollution estimates of exposure. A study conducted in Spain that examined municipal-level risks of PTB and LBW with proximity to different types of industries modeled spatially varying effects using Poisson regression with a spatial error term and an unstructured error term (Castelló et al., 2013). A major difference in the Castelló et al. (2013) study is that these researchers, again, used aggregated outcome data and did not relate birth outcomes with individual-level estimates of air pollutant exposures. A study by (Williams et al., 2007) applied a linear hierarchical random effects model with spatially unstructured random coefficients and found substantial variation across census tracts regarding the estimated effects of maternal residential proximity to hazardous air pollution sites for reducing average birth weight. Our results also found varying effects by census tract; however, Williams et al (2007) did not use air pollution estimates but rather the proxy measure of spatial proximity to hazardous air pollution emitting sites and did not apply spatial structure to the random coefficients. While it is clear from these studies that multilevel modeling is capable of revealing important spatial processes regarding air pollution-related reductions in birth weight; our work goes beyond previous findings by not only applying spatial structure to pollutant effects but illustrating spatially varying effects while adjusting for individual level confounders.

Study Limitations

Our study is limited by the presence of unmeasured confounders. Most notably we lack information on maternal smoking or maternal exposure to indoor smoking. However, our previous research (Ritz et al., 2007a) found that adjustment for maternal or household smoking did not alter the strength of air pollution effects on adverse birth outcomes in LA County. Our study also did not account for spatially varying housing characteristics (e.g. age of housing stock, substandard housing, or lack of air conditioning) that could potentially exacerbate gradients in intra-urban exposures; even between neighborhoods with similar ambient PM concentrations (Baxter et al., 2007; Burgos et al., 2013; Clougherty et al., 2011; Jerrett and Finkelstein, 2005; Lv and Zhu, 2013; Meng et al., 2005; Ramachandran et al., 2003; Reid et al., 2009). Additionally, PM-related birth outcome risks may be modified by individual-level or neighborhood-level susceptibility factors that are often spatially patterned, such as SES, racial-

ethnic status, maternal body mass index, maternal nutrition status, and other adverse neighborhood conditions, e.g., poor access to healthy foods or green spaces (English et al., 2003b; Hystad et al., 2014a; Jedrychowski et al., 2010; Kannan et al., 2006; Lakshmanan et al., 2015; Lane et al., 2008; Laurent et al., 2014a; Ponce, 2005a; Schempf et al., 2009).

While the $PM_{2.5}$ LUR estimates in our study best represents the spatial contrasts of chronic exposures at maternal residences throughout LA county, our estimates lacked the temporal resolution to consider exposures during specific pregnancy time periods. This limitation may obscure important biologic differences with regard to birth outcome risks associated with different trimester exposure windows. Studies that have relied upon nearest site monitors for $PM_{2.5}$ estimation (Ghosh et al., 2012a; Wilhelm et al., 2011a) are better equipped to capture the temporal contrasts in maternal exposures, however, these studies lacked the spatial resolution to assess spatially varying effects of $PM_{2.5}$. For instance, while $PM_{2.5}$ may be fairly homogenous over a large region, it is likely that local-scale sources of $PM_{2.5}$ pollution carry greater importance when examining spatially varying TLBW effects (Laurent et al., 2014a, 2013b). Therefore, it was determined that the value in obtaining high spatial resolution was an acceptable temporal tradeoff, given the nature of our research question. Furthermore, we are confident in the ability of our exposure model to assess TLBW risks since our overall fixed effect $PM_{2.5}$ exposure-response estimate was consistent in terms of effect size when compared with previous research findings (Dadvand et al., 2013; Ghosh et al., 2012a; Hyder et al., 2014; Laurent et al., 2014a; David M. Stieb et al., 2012; Wilhelm et al., 2011a). For example, in the present study, we found an OR of 1.03 per *IQR* increase in maternal $PM_{2.5}$ exposure (Table 3.2). Ghosh et al. (2012) estimated maternal $PM_{2.5}$ concentrations, using an inverse distance weighting procedure based on governmental air monitoring stations for the years 2000-2006 in LA County, and found an OR of 1.04 per *interquartile range* (IQR) increase for entire pregnancy $PM_{2.5}$ exposure. Recently, Laurent et al. (2014) estimated an OR of 1.025 per IQR increase in maternal $PM_{2.5}$ exposure for LA County births between 2001-2008. Notably, Laurent et al. (2014) found that gasoline $PM_{2.5}$ exposure imparted the highest risk of TLBW compared to all other sources of $PM_{2.5}$ within LA. In a separate $PM_{2.5}$ and birth outcomes study, (Dadvand et al., 2013) pooled multiple $PM_{2.5}$ and TLBW analyses from seven different country study sites, despite large heterogeneity between the country-specific PM2.5 effect estimates, they estimated a 10%

(95%CI: 3%, 18%) adjusted increased odds of TLBW for a *10-unit* increase in PM2.5 exposure, which is comparable to our finding of a 17% increase per *10-unit* increase in PM2.5 exposure (Table 3.2).

Public Health Implications

Findings from our research is highly relevant to environmental health disparities and regulatory policy. First of all, our study implies that uniform regulatory standards geared towards reducing public health impacts from air pollution may not be sufficiently protective of susceptible sub-populations, and that such policies may need to be spatially tailored to protect these sub-populations. Secondly, our approach could identify 'hotspots' to help guide spatially targeted public health interventions intended to protect susceptible sub-populations from outdoor air pollution health effects (e.g., for example, by installing HEPA filters and air conditioning to reduce indoor exposures). Lastly, while our study found large within-county differences in effect estimates and thus the potential for $PM_{2.5}$ effect 'hotspots', additional data on potential modifying factors by neighborhood (i.e. $PM_{2.5}$ composition or neighborhood food environment) are needed to more fully explain the causes for this apparent spatial variation in the exposure-response relationship between $PM_{2.5}$ and TLBW.

Conclusion

We found that maternal exposure to $PM_{2.5}$ was associated with higher odds of TLBW in LA County. Moreover, our results indicate that the spatial patterning of the exposure-response relationship for $PM_{2.5}$ and TLBW needed to be considered. While previous research conducted in LA County has found variation of pollutant effects on adverse birth outcomes based on neighborhood factors such as SES, our results take these previous findings a step further by identifying neighborhood TLBW 'hotspots' most likely to be affected negatively by air pollution. Also, compared to global effect estimates, our findings suggest the potential value of modeling spatial random air pollution effect coefficients in identifying disproportionately impacted communities as well the relative probability of localized exposure-response estimates. Finally, additional research is needed in hotspot areas to explore which spatially-based factors may help to better understand these differences between neighborhoods.

Acknowledgments

"Research described in this article was conducted under contract to the Health Effects Institute (HEI), an organization jointly funded by the United States Environmental Protection Agency (EPA) (Assistance Award No. R-82811201) and certain motor vehicle and engine manufacturers. The contents of this article do not necessarily reflect the views of HEI, or its sponsors, nor do they necessarily reflect the views and policies of the EPA or motor vehicle and engine manufacturers."

Table 2.1. Demographic Characteristics Overall and by TLBW and Crude Odds Ratios for TLBW (N=1,359,284).

Parameter	Overall (N = 1,359,284)		TLBW Cases (N=27,714)		Non Cases (N=1,331,570)		Crude TLBW
	n	% or mean (95%CI)	n	% (95%CI)	n	% (95%CI)	OR (95%CI)
Gestational Age (days)		Mean = 278.91 (278.92, 278.89)					
Sex of Infant							
Male	688568	50.66 (50.57, 50.74)	11890	42.90 (42.32, 43.49)	676678	50.82 (50.73, 50.90)	1.00
Female	670716	49.34 (49.26, 49.43)	15824	57.10 (56.51, 57.68)	654892	49.18 (49.10, 49.27)	1.38 (1.34, 1.41)
Maternal Age							
<20 years	143265	10.54 (10.49, 10.59)	4090	14.76 (14.34, 15.18)	139175	10.45 (10.40, 10.50)	1.00
20 - 24 years	318122	23.40 (23.33, 23.47)	6959	25.11 (24.60, 25.62)	311163	23.37 (23.30, 23.44)	0.76 (0.73, 0.79)
25 - 29 years	364301	26.80 (26.73, 26.86)	6581	23.75 (23.25, 24.25)	357720	26.86 (26.79, 26.94)	0.63 (0.60, 0.65)
30 - 34 years	322341	23.71 (23.64, 23.79)	5674	20.47 (20.00, 20.95)	316667	23.78 (23.71, 23.85)	0.61 (0.59, 0.64)
≥35 years	211255	15.54 (15.48, 15.60)	4410	15.91 (15.48, 16.35)	206845	15.55 (15.47, 15.60)	0.73 (0.69, 0.76)
Race-Ethnicity							
White	249759	18.37 (18.31, 18.44)	3605	13.01 (12.61, 13.41)	246154	18.49 (18.42, 18.55)	1.00
Hispanic	852886	62.75 (62.66, 662.83)	16260	58.67 (58.09, 59.25)	836626	62.83 (62.75, 62.91)	1.33 (1.28, 1.38)
Black	107237	7.89 (7.84, 7.93)	4175	15.06 (14.65, 15.49)	103062	7.74 (7.69, 7.79)	2.77 (2.64, 2.89)
Asian	94764	6.97 (6.93, 7.01)	2097	7.57 (7.26, 7.88)	92667	6.96 (6.92, 7.00)	1.55 (1.46, 1.63)
Other	54638	4.02 (3.99, 4.05)	1577	5.69 (5.42, 5.97)	53061	3.98 (3.95, 4.02)	2.03 (1.91, 2.15)
Maternal Education							
0-8 years	206487	15.19 (15.13, 15.25)	4194	15.13 (14.71, 15.56)	202293	15.19 (15.13, 15.25)	1.00
9-12 years	666565	49.04 (48.95, 49.12)	14867	53.64 (53.06, 54.23)	651698	48.94 (48.86, 49.03)	1.10 (1.06, 1.14)
13-15 years	232319	17.09 (17.03, 17.15)	4453	16.07 (15.64, 16.51)	227866	17.11 (17.05, 17.18)	0.94 (0.90, 0.98)
≥16 years	253913	18.68 (18.61, 18.75)	4200	15.15 (14.73, 15.58)	249713	18.75 (18.69, 18.82)	0.81 (0.78, 0.85)
Parity							
0	522598	38.45 (38.36, 38.53)	13257	47.84 (47.25, 48.43)	509341	38.25 (38.17, 38.33)	1.00
≥1	836686	61.55 (61.47, 61.64)	14457	52.16 (51.57, 52.75)	822229	61.75 (61.67, 61.83)	0.68 (0.66, 0.69)

Table 2.2. Association Between $PM_{2.5}$ Exposure and TLBW using Standard and Multilevel Spatial Regression Methods (N=1,356,304)

	Standard Model[a]	Spatial Multilevel Model[a]
Exposure	OR (95% CI)[b]	OR (95% CI)[c]
$PM_{2.5}$ (per 10μg/m^3)	1.17 (1.10, 1.24)[d]	1.19 (1.02, 1.39)

[a]Adjusted for sex of the infant, gestation age of infant, gestation age squared, maternal age, maternal race, maternal education level, and parity
[b]OR per interquartile range = 1.03 (95% CI: 1.02, 1.04), IQR=1.96μg/m^3
[c]OR per interquartile range = 1.03 (95% CI: 1.00, 1.07), IQR=1.96μg/m^3
[d]For all of LA County, including rural areas, OR = 1.17 (1.10-1.24)

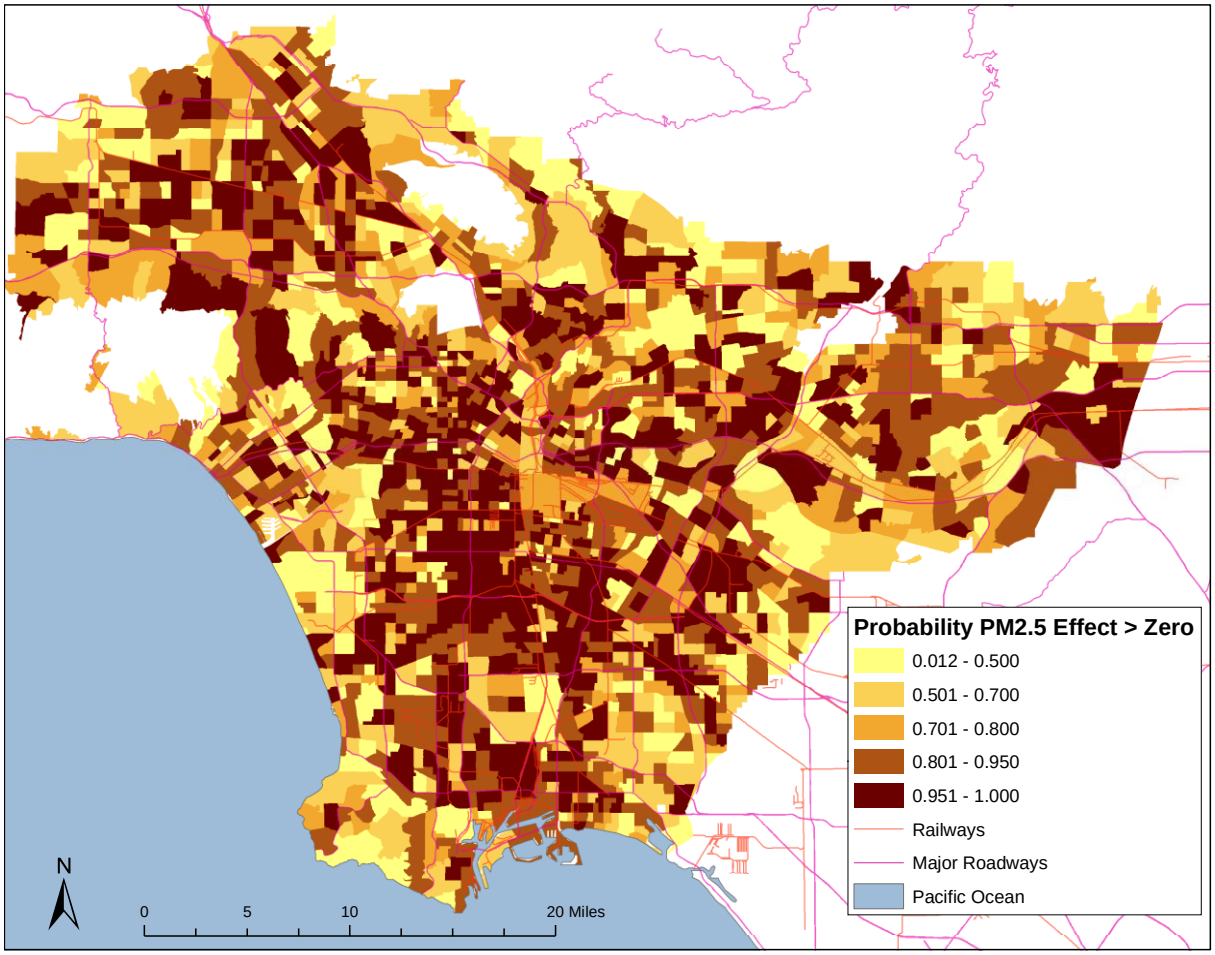


Figure 2.1. Probability Map[a] for Census Tract $PM_{2.5}$ effects for TLBW ($P(\beta_j > 0)$) after adjusting for maternal age, race-ethnicity, education, parity, and infant gestation+gestation squared, and infant sex.

[a] Areas colored white are either rural designated areas or areas outside of LA County.

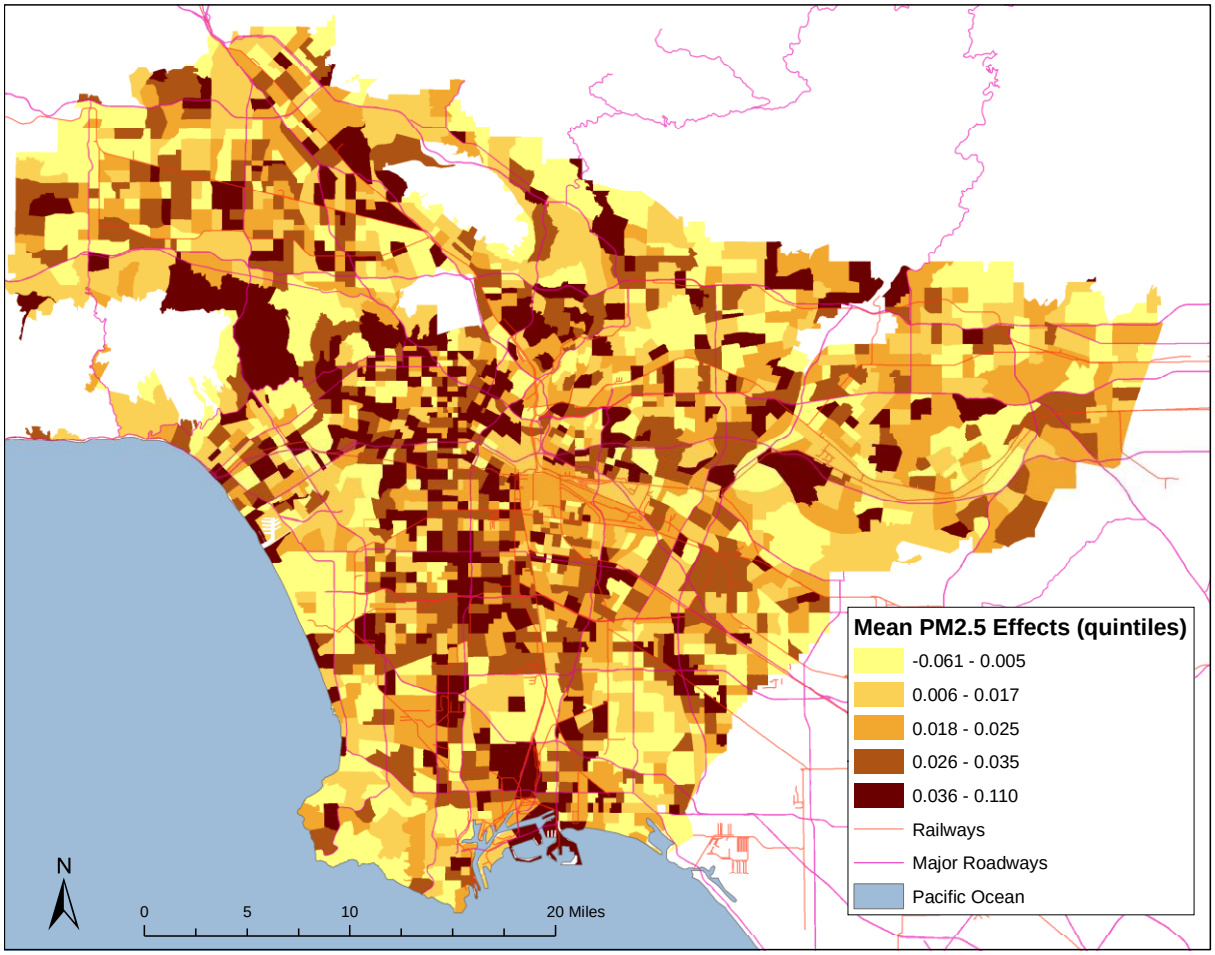


Figure 2.2. Census Tract $PM_{2.5}$ effects for TLBW (mean) after adjusting for maternal age, race-ethnicity, education, parity, and infant gestation+gestation squared, and infant sex.

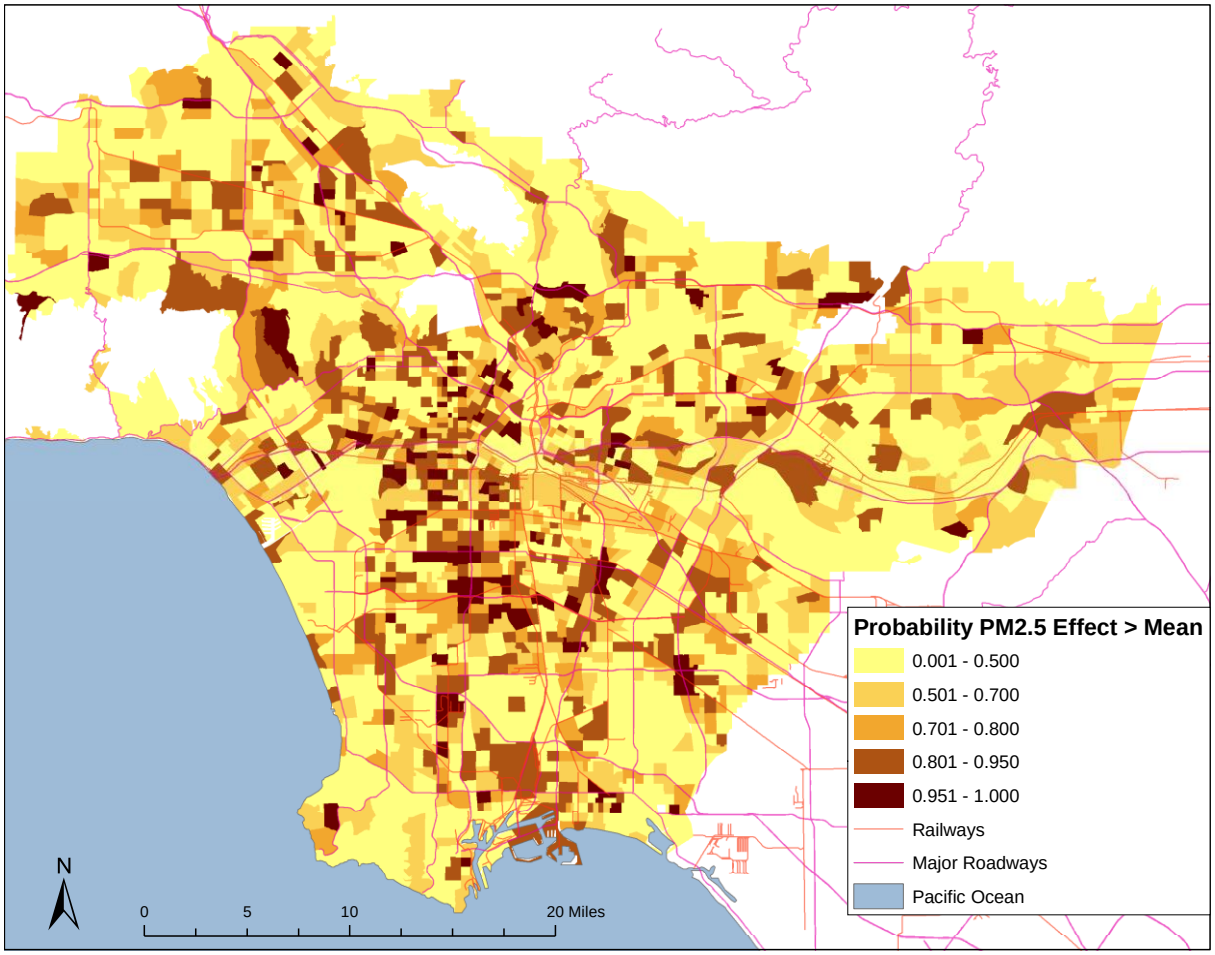


Figure 2.3. Probability Map for Census Tract $PM_{2.5}$ effects for TLBW ($P(\beta_j > \bar{\beta})$) after adjusting for maternal age, race-ethnicity, education, parity, and infant gestation+gestation squared, and infant sex.

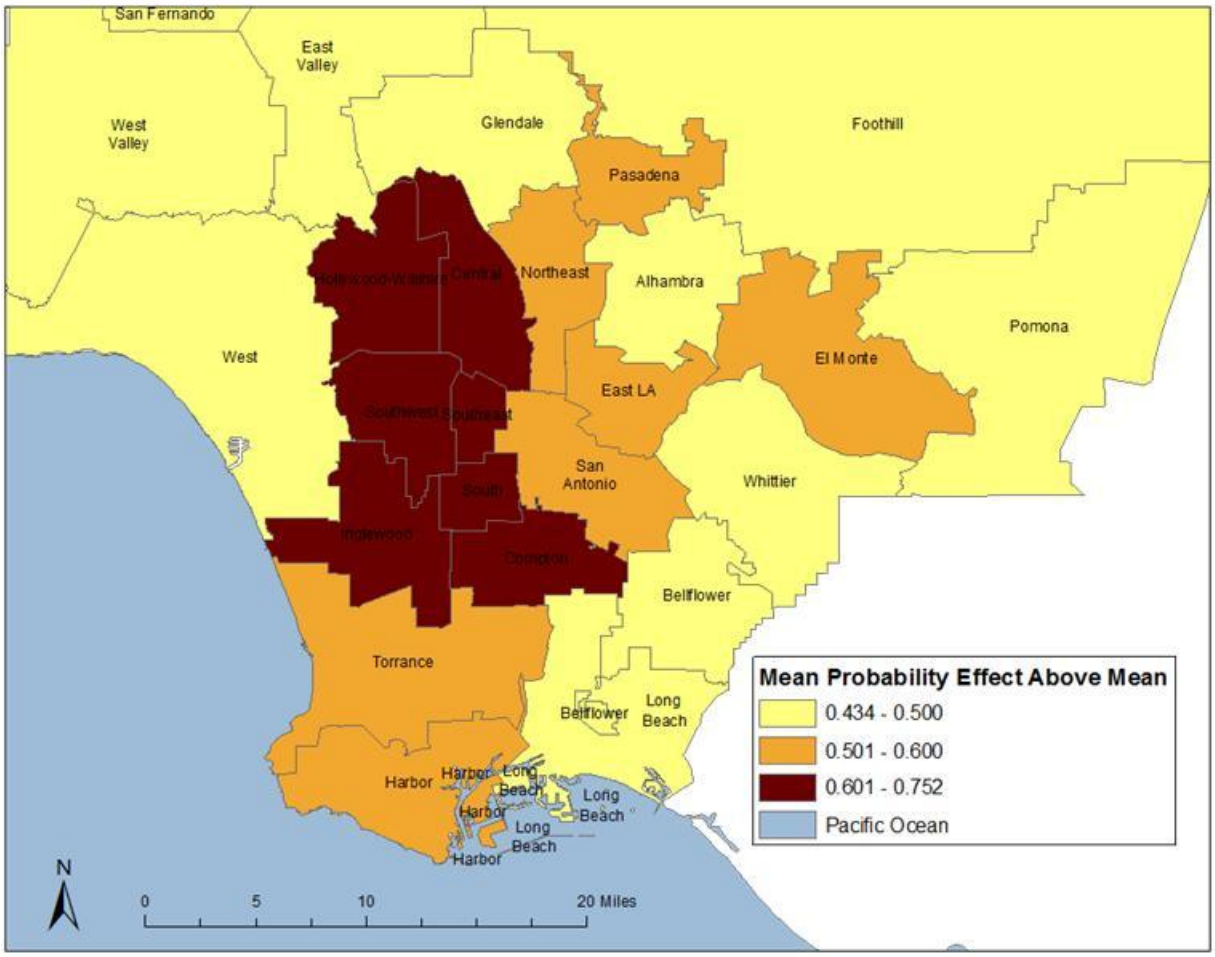


Figure 2.4. Mean Probabilities for Census Tract Random Effect Above Global Mean Effect by LA County Health Districts.

Chapter 3 - Multi-Pollutant Exposure Profiles Associated with Term Low Birth Weight in Los Angeles County

Eric Coker[1]

Silvia Liverani[2]

Jo Kay Ghosh[3]

Michael Jerrett[4]

Bernardo Beckerman[4]

Arthur Li[5]

Beate Ritz[3]

John Molitor[1]

[1]College of Public Health and Human Sciences, Oregon State University, Corvallis, OR

[2]Department of Mathematics, Brunel University, London, UK

[3]School of Public Health, University of California, Los Angeles, Los Angeles, CA

[4]School of Public Health, University of California, Berkeley, Berkeley, CA

[5]Department of Information Science, City of Hope National Cancer Center, Duarte, CA

Environment International

Published in Volume 91, 2016, pages 1-13

Abstract

Research indicates that multiple outdoor air pollutants and adverse neighborhood conditions are spatially correlated. Yet health risks associated with concurrent exposure to air pollution mixtures and clustered neighborhood factors remain underexplored. Statistical models to assess the health effects from pollutant mixtures remain limited, due to problems of collinearity between pollutants and area-level covariates, and increases in covariate dimensionality. Here we identify pollutant exposure profiles and neighborhood contextual profiles within Los Angeles (LA) County. We then relate these profiles with term low birth weight (TLBW). We used land use regression to estimate NO_2, NO, and $PM_{2.5}$ concentrations averaged over census block groups to generate pollutant exposure profile clusters and census block group-level contextual profile clusters, using a Bayesian profile regression method. Pollutant profile cluster risk estimation was implemented using a multilevel hierarchical model, adjusting for individual-level covariates, contextual profile cluster random effects, and modeling of spatially structured and unstructured residual error. Our analysis found 13 clusters of pollutant exposure profiles. Correlations between study pollutants varied widely across the 13 pollutant clusters. Pollutant clusters with elevated NO_2, NO, and $PM_{2.5}$ concentrations exhibited increased log odds of TLBW, and those with low $PM_{2.5}$, NO_2, and NO concentrations showed lower log odds of TLBW. The spatial patterning of pollutant cluster effects on TLBW, combined with between-pollutant correlations within pollutant clusters, imply that traffic-related primary pollutants influence pollutant cluster TLBW risks. Furthermore, contextual clusters with the greatest log odds of TLBW had more adverse neighborhood socioeconomic, demographic, and housing conditions. Our data indicate that, while the spatial patterning of high-risk multiple pollutant clusters largely overlaps with adverse contextual neighborhood cluster, both contribute to TLBW while controlling for the other.

Keywords

air pollution; Bayesian; clustering; low birth weight; pollutant profile; profile regression

Introduction

Evidence has been accumulating that birth outcomes may be particularly sensitive to air pollution mixtures, specifically components related to traffic sources of airborne particulate matter (PM) (Bell et al., 2010; Laurent et al., 2014a; Wilhelm et al., 2011a). While earlier research has linked increased prevalence of term low birth weight (TLBW) with various outdoor air pollutants including NO_2, NO, and $PM_{2.5}$ (Geer, 2014; Ritz and Wilhelm, 2008a), most evidence relied on single pollutant modeling of exposures (Ritz and Wilhelm, 2008a). A number of studies (Brauer and Tamburic, 2009; Ghosh et al., 2012b; Gouveia et al., 2004; Laurent et al., 2014a; Le et al., 2012; Morello-Frosch et al., 2010b; Wilhelm et al., 2011a, 2011b) investigated exposures to multiple pollutants in relation to birth outcomes; however, these studies are limited in assessing which combination of pollutants are most hazardous or how multipollutant health effects vary spatially. Despite there being no single exposure-measure-framework to holistically address the health effects of multipollutant exposures (Oakes et al., 2014), investigating health effects of profiles of multiple pollutants using clustering techniques has recently shown promise (Gu et al., 2012; Molitor et al., 2014b; Papathomas et al., 2010; Pirani et al., 2015b; Qian et al., 2004b; Zanobetti et al., 2014a).

Multipollutant Exposures

Considerable intra-urban spatial variations in outdoor air pollution concentrations exists, and recent research indicates that between-pollutant correlations and $PM_{2.5}$ composition exhibit highly localized spatial patterns to create complex mixtures (Austin et al., 2013, 2012b; Bell et al., 2011; Geer, 2014; Hasheminassab et al., 2014; Houston et al., 2014; Janhäll et al., 2012; Laurent et al., 2014a; Levy et al., 2013b; Molitor et al., 2011; Monn, 2001; Tsai et al., 2015).

Spatially correlated air pollution mixtures correspond to localized sources, such as transportation-related emissions (Laurent et al., 2014a), local industrial activities (Morello-Frosch et al., 2002; Zhu et al., 2011), or small-area commercial land uses (Morello-Frosch et al., 2002, 2001). Factors that combine to determine exposure to spatially correlated pollutants from a particular source are complex and diverse, e.g., traffic-source driven exposures are influenced by traffic volumes and congestion, proximity to traffic, the types of fuel and engines, operating conditions of emitting sources, types of emitting sources, background air pollution levels, local meteorology, chemical reactions between pollutants, and local topographies (Austin et al., 2012b; Boehmer et al., 2013; Cho et al., 2009; Greco et al., 2007; Hu et al., 2012; Janhäll et al., 2012; U.S. EPA, 2008; Zhang and Batterman, 2013).

Correlations across different pollutants hinders our ability to assess their individual or combined health effects, since estimates of effects may become unstable when adjusting for co-pollutants using regression techniques (Mauderly et al., 2010). Correlations between $PM_{2.5}$ concentrations and nitrogen oxides (NO_2 and NO [NO_x]) are typically weak to moderate (Ghosh et al., 2013b; Laurent et al., 2014a; Levy et al., 2013b). However, such correlations can vary spatially (Levy et al., 2013b; Tsai et al., 2015) based upon whether the particulates represent primary $PM_{2.5}$ (particles emitted directly from the source, e.g. fuel combustion (Fine et al., 2008)) or secondary $PM_{2.5}$ (particles formed in the atmosphere (Fine et al., 2008)). Therefore, since some $PM_{2.5}$ components represent "fresh" traffic emissions (i.e. ultrafine PM and black carbon), they can exhibit high correlations with outdoor concentrations of NO_x, as studies of urban air pollution from Asia, Europe, and North America demonstrate (Brauer et al., 2011; Dionisio et al., 2014; Janhäll et al., 2012; Levy et al., 2013b; Tsai et al., 2015; Wang et al., 2014). Furthermore, the spatial variation in between-pollutant correlations also suggests a strong

potential for a unique spatial pattern of multipollutant-related health risks, yet research on this question is lacking.

Contextual Factors

Neighborhood-level "contextual" factors may also affect risk of birth outcomes (English et al., 2003b; Morello-Frosch and Shenassa, 2006). Contextual effects are non-chemical stressors (Lewis et al., 2011) that arise when grouped neighborhood-level factors − such as socio-demographic or built environment (e.g. housing as one component of the built environment) factors − influence health outcomes across populations (Sheppard et al., 2012). Data from Southern California indicates that spatially clustered socioeconomic deprivation and racial segregation correlate with air pollution exposures, including pollutant mixtures (Molitor et al., 2011; Morello-Frosch et al., 2011, 2002; Morello-Frosch and Shenassa, 2006; Su et al., 2012). In addition, compared to newer homes, older homes are shown to have higher indoor air pollution levels within LA County (Spengler et al., 1994). Older housing stock may further correlate with higher poverty, residential racial segregation patterns, substandard housing conditions, and a lack of compliance with building or sanitary codes (Shennassa et al, 2004). Moreover, research from LA County indicate that housing ventilation conditions may be associated with TLBW (Ghosh et al., 2013b).

Air pollution and birth outcomes research studies, however, generally do not account for spatial clustering of multiple neighborhood-level vulnerabilities (i.e. race-ethnicity, poverty, and adverse housing conditions etc.) related to exposure. This may confound multipollutant exposure-response relationships (Geer, 2014; Morello-Frosch et al., 2011; Morello-Frosch and Shenassa, 2006; Ponce, 2005b; Ritz and Wilhelm, 2008a). Given this gap in air pollution and health effects literature, our study includes contextual factors, as clustering covariates, to better

control for highly correlated contextual factors known to influence differential exposures across socio-demographic groups and risk of TLBW.

Study Objectives

The primary objectives of our study are to first identify profiles of exposure to multiple different air pollutants (pollutant profiles) for pregnant women within LA County, and secondly to assess whether and which pollutant profiles relate with elevated prevalence of TLBW. Additionally, our approach identifies pollutant profiles most likely related to primary traffic emissions, based on examination of the spatial patterning of pollutant exposure profiles and well established pollutant source emissions relationships.

Methods

Study Population and Birth Outcomes

Electronic birth certificates from the California Department of Public Health provided the data on baby's birth weight and individual-level covariates for LA County births during the years 2000-2006. Individual data from the birth records included maternal characteristics (age, race and ethnicity, education, total number of previous maternal births, and residential address) and information on the infant and birth (date of birth, abnormalities, birth season, gestational age at birth [as determined by self report of last menstruation], birth weight and baby's sex). The dataset was restricted to singleton births without apparent abnormalities, while births with extreme gestational days (less than 140 days or greater than 320 days) and births with weight less than 500g or greater than 5000g were excluded from the analysis. Such extreme values are likely attributable to recording errors. These data restrictions provided a sample size of 899,554. Finally, we defined TLBW as full-term (≥259 gestation days) infants with a birth weight <2500 grams, which further restricted the study population to term births, to provide a final sample size of 804,726 to assess the relationship between TLBW with neighborhood-level pollutant profile

exposures. Human subjects research was approved through the University of California, Los Angeles' Office of the Human Subjects Protection Program, the California Committee for the Protection of Human Subjects, and the University of Southern California's Office for the Protection of Research Subjects. Geocoding of residential addresses are explained elsewhere (Goldberg et al., 2008).

Exposure Estimation

Two separate land use regression (LUR) models estimated individual-level exposures for $PM_{2.5}$, NO, and NO_2 (Beckerman et al., 2013a, 2013b; Su et al., 2009). LUR estimates were temporally adjusted to derive the entire pregnancy average exposures. LUR exposure predictions for NO and NO_2 were based on traffic volumes, truck routes, road networks, land use data, satellite-derived vegetation greenness and soil brightness, truck route slope gradients, and air monitoring data. NO_2 and NO data were collected during 2-week time periods in Summer of 2006 and Winter of 2007, from over 200 monitoring locations (Su et al., 2009). The $PM_{2.5}$ exposure estimates came from a LUR model that utilized long-term governmental monitoring data of $PM_{2.5}$ measurements collected between 1998 through 2002 (Beckerman et al., 2013b). A machine learning deletion/substitution technique (Beckerman et al., 2013a) assessed as many as 70 covariates to develop the final $PM_{2.5}$ LUR model, such as land use data (i.e. agricultural, barren, all developed land, high-density development, green space, water, and wetland), long-term traffic counts (1990-2001), and road networks from the year 2000 (Beckerman et al., 2013a; Jerrett et al., 2013).

We adjusted LUR exposure estimates temporally to derive "*seasonalized*" values that correspond to each pregnancy time span. For temporal adjustments, we first used daily air monitoring data from LA County between the years 1999-2006, for all monitors to calculate an overall daily average for $PM_{2.5}$, NO_2, and NO_x. Pregnancy time period averages were then

calculated for each pregnancy from these daily averages. As NO was not directly measured by these monitors, we subtracted the NO_2 pregnancy average from the NO_x pregnancy average to derive NO pregnancy time period estimates. Temporal adjustments of the LUR estimates for NO_2 and NO was achieved using the following equation, which is similar in approach to our earlier work (see (Ghosh et al., 2012b)):

$$NO_2\ LUR\ Pregnancy\ Average\ = NO_2\ LUR\ \times \frac{monitor\ station\ pregnancy\ average\ NO_2}{2006\ NO_2\ average\ for\ all\ monitor\ stations}$$

$$NO\ LUR\ Pregnancy\ Average = NO\ LUR\ \times \frac{monitoring\ station\ pregnancy\ average\ NO}{2006\ NO\ average\ for\ all\ monitoring\ stations}$$

Since the $PM_{2.5}$ LUR estimates represent long-term estimates spanning the study time period and some pregnancies began in 1999, we performed seasonal adjustments with the following equation:

$$PM_{2.5}\ LUR\ Pregnancy\ Average = PM_{2.5}LUR \times \frac{monitor\ station\ pregnancy\ average\ PM_{2.5}}{PM_{2.5}\ average\ for\ all\ monitoring\ stations\ (1999-2006)}$$

Such temporal adjustment via region-wide monitoring station ratios has been validated for the purposes of estimating pregnancy exposures in birth outcomes studies (Ross et al., 2013).

All of the available data from the temporally adjusted LUR model estimates (N=899,554) were then averaged over census block groups to develop air pollution exposure profiles at the census block group level. Data aggregation at the census block group-level for individual estimates was performed since we were interested in assessing between neighborhood multipollutant exposure-related TLBW risks. Moreover, implementation of the Bayesian profile regression using individual-level estimates with a dataset as large as ours is not feasible given the current computational limitations of the R PReMiuM package (described below).

Bayesian Profile Regression

We developed the profile clusters using a non-parametric dimension reduction technique known as Bayesian profile regression, based on commonly used Dirichlet process mixture model

methods (Neal, 2000). Profile regression is set in a Bayesian framework using Markov chain Monte Carlo (MCMC) methods. Bayesian profile regression uses covariate values to observe joint patterns within the covariate data. This approach was used in recent studies (Hastie et al., 2013; Molitor et al., 2014b, 2011, 2010b; Papathomas et al., 2012), including environmental epidemiology studies (Papathomas et al., 2010; Pirani et al., 2015b; Vrijheid et al., 2014). This clustering approach is advantageous because it reduces the dimensionality of the covariate data and allows for examining health risks as they relate to joint patterns of exposure, while avoiding the pitfalls of exposure variables that are highly collinear. This approach is also quite flexible because it does *not* rely on setting a total number of allowable clusters, as seen with k-means clustering procedures (Austin et al., 2013, 2012b; Gu et al., 2012). We implemented the profile regression using the PReMiuM package in R (Liverani et al., 2015). Since our interest is in obtaining clustering that best fits the data for sub-regions within the LA County area, we utilized a feature of the PReMiuM package that excludes the outcome variable from the profile regression model (Liverani et al., 2015). We relied on "hard clustering" (Fang et al., 2011) in the sense that a census block group's final allocation is to a single cluster. Cluster allocation is based on the "*best*" clustering derived from the Bayesian averaging process, rather than probabilistic allocation to several different clusters simultaneously (as in fuzzy [or soft] clustering). Briefly, for each census block group, j, a covariate profile is defined as, $x_j = (x_2, x_2, ..., x_p)$, where every covariate, x_p, $p = 1, ..., P$, within each profile signifies a level of exposure for covariate p in region j. The primary model for cluster profiles was defined by a multivariate normal mixture model (Jain and Neal, 2004) that further integrates a Dirichlet process prior into the mixing distribution. For greater details on this Bayesian profile regression approach, the reader is

referred to other recent works (Hastie et al., 2013; Liverani et al., 2015; Molitor et al., 2014b, 2011, 2010b; Papathomas et al., 2012, 2010).

We performed two separate profile regressions to develop a set of two unique profile clusters to fit in the TLBW risk model. The first clustering procedure developed pollutant-only profile clusters. The second clustering procedure developed contextual-only profile clusters. The co-pollutants for our pollutant-only profile regression included average census block group-level concentrations for NO_2, NO, and $PM_{2.5}$. Furthermore, since our LUR estimates were seasonalized and thus provide temporally resolved estimates of exposure for each pregnancy, we also performed pollutant profile regression across different birth seasons and across different birth years. We present the results of these seasonal and yearly pollutant clusters in the supplemental materials (Appendix B, Figures B.1-B.4), however, in this paper we focus on the overall pollutant profiles as described above since the spatial patterning and between-pollutant correlations were very stable across each of these different seasonal and yearly pollutant profile cluster analyses.

The contextual-only exposure profile regression utilized year 2000 U.S. census data and included census block group-level race-ethnicity (percent non-Hispanic White, percent non-Hispanic Black, and percent Hispanic), median household income, and percent of homes built prior to year 1950. Even though our multivariate risk model (described below) adjusts for individual-level maternal race-ethnicity, we included census block group-level racial/ethnic composition as a clustering contextual covariate under the rationale that area-level racial/ethnic composition may act as a contextual risk factor for TLBW separate from an individual's race-ethnicity (Debbink and Bader, 2011). Similarly, while our multivariate model adjusts for maternal education as a marker of individual-level SES, we included census block group level

median household income as a contextual SES variable in the clustering procedure, under the same rationale that area-level SES acts as a contextual risk factor for TLBW independent of individual-level SES (Grady, 2011, 2006). We included the percentage of homes built before 1950 since disparities in housing quality and other housing characteristics correlated with older housing may act as an important contextual risk factor in TLBW risk (Ghosh et al., 2013b; Grady, 2011). Individual mothers were then assigned to both a pollutant cluster and a contextual cluster as determined by which census block group the mother resided in according to their address at time of delivery.

Multilevel Risk Model

Our multilevel logistic regression model was set in a Bayesian framework with pollutant profile clusters and contextual profile clusters used as separate random effects variables in the regression equation, along with spatially structured and unstructured independent error terms fit as additional random effects. The model specification is detailed in turn:

$$\text{logit}(p_i) = \alpha + V\eta' + \gamma_{k[i]}^{pollutant-cluster} + \gamma_{c[i]}^{contextual-cluster} + S_j + \epsilon_j \qquad (1)$$

where p_i denotes the logit of TLBW (y_i =1) for individual i, $V\eta'$ represents the *individual-level* covariate fixed effects, $\gamma_k^{pollutant-cluster} \sim N\left(0, \sigma^2_{pollutant-cluster}\right), k = 1, \dots, 13$ represents the random effects for the pollutant-clusters and $\gamma_c^{contextual-cluster} \sim N(0, \sigma^2_{contextual-cluster}), c = 1, \dots, 14$ represents the contextual cluster random effects. Following Gelman et al., (2006), we use the notation $k[i]$ to denote the pollutant profile group k to which individual i belongs and $c[i]$ to denote the contextual profile group c to which individual i belongs. Thus, each pollutant random error term represents the variation in TLBW prevalence in the pollutant profile clusters and likewise each contextual random error term represents the variation in TLBW in the contextual clusters. In other words, the cluster random effect can be interpreted as measuring the

change in baseline log odds of TLBW for individual *i* in cluster *k*, when all other covariates in the model are set to zero (see (Molitor et al., 2010b).

Regarding the spatial and independent residual error terms, here S_j and ϵ_j denote spatial and independent residual error terms, respectively, with the restriction $\sum_j S_j = 0$ imposed for indefinability reasons. While the independent error term is defined in the standard way as $\epsilon_j \sim N(0, \sigma^2)$, the spatial error term is defined as,

$$S_{j|k\neq j} \sim N\left(\frac{\sum_{k\neq j} w_{jk} S_k}{\sum_{k\neq j} w_{jk}}, \frac{\tau^2}{\sum_{k\neq j} w_{jk}}\right),$$

where the weights $w_{j,k}$ are elements of the zero-one neighborhood adjacency matrix defined to be equal to one when census tracts j, k are adjacent and zero otherwise. This approach implements the Besag-York-Molly (BYM) model (Besag et al., 1991) and has been successfully employed in a variety of exposure/health association studies ((Molitor et al., 2007).

Given the large number of records in the dataset, we "pre-clustered" exposure profiles as described in our clustering section and then used the R-INLA (integrated nested Laplace approximations) package to implement the Bayesian multilevel random effects model described in equation (1) above. R-INLA estimates Bayesian posterior marginal distributions (Rue et al., 2014; Rue and Martino, n.d.) without relying on computationally intensive Markov chain Monte Carlo techniques (Gilks et al., 1998b).

Assessing Uncertainty in Pollutant Random Effects

As our analysis is in a Bayesian framework, with random effects terms for each pollutant cluster and for each contextual cluster, we assessed the uncertainty with respect to the random effect for each cluster on the baseline log odds of TLBW. For instance, we calculated the posterior probability that a specific profile cluster's posterior distribution of baseline log odds for TLBW ($[\text{logit}[\Pr(y_i = 1)] = \theta_k]$) *is above the overall baseline log odds for TLBW (θ)*

(Papathomas et al., 2010). *Said another way, for each cluster we calculate the probability as* $P(\theta_k > \theta)$, with probability values close to 1 indicative of a high probability for a baseline log odds above zero for each cluster (evidence for adverse effect). Conversely, a posterior probability close to zero is indicative of a low probability for a baseline log odds above zero for each cluster (evidence for no adverse effect). The posterior probabilities for each pollutant cluster and for each contextual cluster were then mapped in ArcGIS V.10.1 (Redlands, CA) to investigate the spatial distribution of these clusters effects on the log odds of TLBW. These kinds of probability effect maps are commonly used in Bayesian modeling of spatial effects of exposure (R. S. Bivand et al., 2013; Coker et al., 2015).

Covariates

Individual-level covariates adjusted for were maternal factors including age at delivery (<20 years, 20-24 years, 25-29 years, 30-34 years, ≥35 years), race-ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, Asian, and Other race), highest education level attained (< 9 years, 9-12 years, 13-15 years, and ≥ 16 years), parity, along with infant factors such as gestational days, gestational days squared, and infant sex (male/female).

Characterization of Pollutant Clusters

In order to infer which clusters are most likely affected by near highway traffic emission (or primary emissions) we characterized each pollutant cluster in terms of their respective pollutant ratios, between-pollutant correlations, and maternal residential distance to major highways. Such metrics have shown to be helpful in terms of assessing sources of emissions related to near road vehicle traffic (Austin et al., 2012b; Janhäll et al., 2012; Laurent et al., 2014a; Levy et al., 2013b). Also, since both NO and NO_2 could be highly correlated with $PM_{2.5}$ under certain emissions scenarios, we normalized NO and NO_2 concentration to $PM_{2.5}$ as described in (Austin et al., 2012b). This normalization helps to indicate which pollutant clusters

have elevated NO and NO_2 concentrations, after accounting for their overall relationship with $PM_{2.5}$. We obtained the normalized concentrations by calculating the cluster-specific ratio of NO or NO_2 to $PM_{2.5}$ and dividing by the overall study area ratio of NO or NO_2 to $PM_{2.5}$.

Results

We observed an overall TLBW prevalence of 2.07% (95% CI: 2.04-2.11, n=16,694) for the study population. Our data also showed spatial autocorrelation at the census tract level with respect to prevalence of TLBW (Figure B.5, Appendix B). Average census block group concentrations of NO_2, NO, and $PM_{2.5}$ were 22.49 ppb (interquartile range [IQR]: 19.68, 25.30 ppb), 21.84 ppb (IQR: 16.05, 26.11), and 16.94 $\mu g/m^3$ (IQR: 15.96, 18.18), respectively (Table 3.1).

Pollutant and Contextual Variable Correlations

As indicated in Figure 3.1, there is evidence of strong correlation (*Pearson's r*) for between pollutant concentrations, most notably for NO_2 and NO. The positive correlations between $PM_{2.5}$ and NO_2 and between $PM_{2.5}$ and NO are considerably weaker (Figure 3.1). However, we did find that the between-pollutant correlations for $PM_{2.5}$ and the NO_x species varied widely across LA County (Figure B.7, Appendix Bf). Correlations between our contextual variables and the study pollutants ranged from only weak to moderate (range: -0.53 to 0.54) (Figure 3.1). Correlations between the contextual variables on the other hand were stronger (range: -0.66 to 0.64).

Pollutant clusters

The profile regression identified 13 pollutant profile clusters (P1 - P13) from the 6,280 census block groups from which we had complete air pollution data. Summary statistics for each pollutant overall, and stratified by cluster, are in Table 3.1. These data summaries are color coded to help indicate which exposure profile clusters have either elevated (red), typical (green),

or lowered (blue) pollutant concentrations compared to the overall concentrations. According to pollutant summaries in Table 3.1, the elevated NO_2 clusters are pollutant clusters P3, P7, P9, P10, and P13. The elevated NO pollutant clusters are the same as for NO_2, plus P12. The elevated $PM_{2.5}$ pollutant clusters are clusters P6, P7, P9, P10and P13. Four of the pollutant clusters show elevated levels for all pollutants, including P7, P9, P10, and P13. Whereas pollutant profile clusters P1, P2, P4, P5, and P11 show low levels for all pollutants. We mapped the spatial distributions of pollutant clusters in Figure 3.2. Clusters with high concentrations for all pollutants are mostly within the downtown/metro area of LA and South-Central LA (clusters P7, P9, and P10), and a relatively fewer number of census block groups in the eastern section of the county (P13).

Between pollutant correlations for each pollutant cluster are indicated in Table 3.2 (see Appendix B for the spatial pattern of pollutant correlations). In Figure 3.3 we present the distributions of NO/NO_2 ratios and the normalized NO_2 and normalized NO values for each pollutant cluster, while the median residential distances to major highways throughout the county are shown in Figure 3.4. According to these pollutant and near-highway exposure metrics, mothers residing in pollutant clusters P9 and P10 are most likely exposed to higher levels of primary traffic pollution since these two clusters are characterized by high NO/NO_2 ratios and high normalized NO and NO_2 concentration. Additionally, P9 and P10 are characterized by low correlations between NO and NO_2 (suggestive of near roadway emissions) and elevated $PM_{2.5}$ concentrations. Moreover, clusters P9 and P10 have the shortest median residential distance to major highways (478 meters and 230 meters respectively). Even though pollutant cluster P13 exhibited the highest average $PM_{2.5}$ in addition to elevated NO_2 and NO, this cluster is emblematic of combined high levels of regional sources of $PM_{2.5}$ and secondary particulate

formation from traffic emissions. For instance, compared to all other clusters, P13 shows some of the strongest positive correlation between NO_2 and $PM_{2.5}$, a low NO/NO_2 ratio and low normalized NO and NO_2 levels. AQ6: Yes, Number of CBGs is correct.

Pollutant Cluster Random Effects

For each pollutant cluster, Table 3.3 presents the total number of births, the number of TLBW cases, percent prevalence of TLBW, and the posterior means and 95% credible intervals for the pollutant cluster random effects. The cluster-specific effects represent the variation in the baseline log odds of TLBW, after adjusting for individual-level covariates, contextual cluster random effects, and accounting for spatially structured and unstructured residual error. In Table 3.3 we also present the posterior probability that a pollutant cluster effect is above the overall baseline log odds for TLBW (i.e. probability effect > zero).

Pollutant clusters with the highest probabilities for a random effect above zero are clusters P9 and P10, with probabilities of 94.9% and 91.6%, respectively (Table 3.3). Pollutant cluster P13 showed the next highest probability (77.4%). All other pollutant clusters showed probabilities below 70% for posterior probabilities with effects above zero. Pollutant clusters P1, P2, and P3 showed substantially lower baseline log odds of TLBW (Table 3.3).

Spatial Distribution of Pollutant Cluster Effects

In Figure 3.5 we mapped the posterior probabilities for the pollutant cluster random effects. This map indicates clustering within LA County's urban core of downtown/metro LA, South-Central LA, and parts of east LA County for the pollutant profile clusters associated with the highest probability for increased baseline log odds of TLBW. Furthermore, the census block groups with the largest certainty for elevated TLBW log odds are mostly confined to census block groups near major highways; suggesting that women exposed to air pollution mixtures near highways have the greatest probability of delivering a TLBW baby.

Contextual clusters

The profile regression determined 14 distinct contextual profiles clusters (C1 - C14) and are summarized in Figure 3.6. Since the contextual clusters were developed separtely from the pollutant clusters, these contextual clusters are distinct from the pollutant clusters. Table 3.4 presents a summary of the the contextual profile cluster random effects. Again, these random effects represent the variation in the baseline log odds of TLBW across contextual clusters in our multilevel model. Compared to all other clusters, contextual cluster C6 showed the largest posterior mean effect (0.124) and the highest probability for a baseline log odds above the overall baseline log odds (probability = 99.5%). The income distribution for cluster C6 is significantly below the overall median income for LA County and consists of a significantly lower percentage of Whites. Additionally, we find that cluster C6 has above average percentage of homes older than 1950, percentage of Blacks, and percentage of Hispanics. The next two highest probability contextual clusters are clusters C11 and C14, with elevated baseline TLBW log odds probabilities of 90.2% and 81.6%, respectively. While contextual clusters C11 and C14 have elevated percentages for homes older than 1950 and elevated percentages for Black populations, only C11 has significantly lower median income levels. All other clusters fell below 80% for elevated baseline TLBW log odds probabilities.

We also mapped the spatial distribution of contextual profile cluster effect probabilities in Figure 3.7. This map indicates that contextual profile clusters with the highest probabilities for an elevated baseline log odds of TLBW are mostly in the urban core of LA County (central LA and south central LA). As anticipated, we find a large degree of spatial overlap between pollutant profile clusters with elevated effects on TLBW and contextual profile clusters with elevated effects on TLBW. Despite this spatial overlap, the two types high risk clusters take on distinct spatial patterns from one another.

Fixed Effects Results

In Table 3.5 we summarize each fixed effects estimate and corresponding 95% credible intervals from the multilevel spatial model. Individual-level factors associated with odds of TLBW were female sex, gestational days, and gestational days squared, as well as maternal factors such as parity, age, race-ethnicity, and education level.

Discussion

Our Bayesian profiling approach highlights the varied and distinct spatial patterns of pollutant exposure profiles and how such exposures contribute to TLBW within the context of clustered indicators of socio-demographic and housing. While exposure profile clustering has been used in previous epidemiologic studies (Molitor et al., 2014a; Papathomas et al., 2010; Pirani et al., 2015b; Zanobetti et al., 2014a), no such studies have examined birth outcomes. Our clustering procedure and multilevel analysis provided concentration estimates for pollutants and TLBW risk estimates for place-based air pollution mixtures across LA County that take on a strong spatial structure.

Pollutant Profile Clusters and Effects on TLBW

We find that census block groups adjacent to major highways in the downtown/metro LA, South-Central LA, and parts of eastern LA County show elevated $PM_{2.5}$, NO_2, and NO concentrations. We also find that census block groups in downtown/metro LA, South-Central LA, and east LA County, consistently had the most hazardous air pollution mixtures in relation to prevalence of TLBW.

We also identified profiles of clustered neighborhood contextual factors to show that sub-populations previously shown to be vulnerable to TLBW are concentrated in the downtown/metro area of LA and South-Central LA County. These high risk contextual clusters partially overlapped spatially with the most hazardous air pollution mixtures. Such co-occurrence

of clustered indicators of disadvantage and hazardous air pollution mixtures reinforced the validity in our approach of adjusting for such correlated factors in examining multiple pollutant health effects.

Spatially clustered emissions related to residential proximity to emissions sources may explain why our multilevel analysis of pollutant profile TLBW risks reveals such distinct spatial patterning. Spatial cluster inducing factors may include localized circumstances, such as traffic volumes and congestion, the vehicle fleet (e.g. heavy-duty trucks), and higher exposures to specific primary PM components that result from proximity to PM emissions sources. In our study, the spatial patterning across pollutant profiles of maternal distance to major highways, between pollutant correlations, elevated concentrations of NO and NO_2, and elevated NO/NO_2 ratios suggest that clusters reflective of primary traffic emissions tended to impart the greatest risk of TLBW (i.e. pollutant clusters P9 and P10). For instance our spatial proximity data show that the highest risk pollutant clusters (P9 and P10) are characterized by the smallest median maternal residential distances to major roadways, compared to all other cluster-specific residential distances to highways. In terms of primary traffic emission above background levels, the residential distances for P9 and P10 are consistent with the literature that suggest primary traffic emissions decay to background levels between 115 meters to 570 meters (Karner et al., 2010). In addition, there was clear spatial clustering of higher risk pollutant profiles (P9 and P10) at interchanges where LA's major interstate highways (I-5, I-110, I-710, and I-10) converge in central and south-central areas of LA County. This is suggestive of highly localized traffic and emission patterns that are germane to these major highways and their intersections.

Findings from our study are notably consistent with our earlier studies and other's conducted in LA County that found variation in estimated effects on birth outcomes between

traffic-related sources of air pollution (e.g. traffic-related versus natural background sources) and proximity to major roadways (Laurent et al., 2014a; Ritz et al., 2007b; Wilhelm et al., 2011a; Wilhelm and Ritz, 2005). When juxtaposed with other recent studies (Bell et al., 2011; Coker et al., 2015; Laurent et al., 2014a; Pirani et al., 2015b; Wilhelm et al., 2011a; Zanobetti et al., 2014a), our findings carry the implication that TLBW risks related to spatial patterns in exposure combined with the physical and chemical properties of $PM_{2.5}$ requires further investigation, and further suggests important spatially derived hypotheses. For instance, recent findings by our group showed that the exposure response relationship of $PM_{2.5}$ on TLBW varied spatially across LA County (Coker et al., 2015). Spatially varying effects suggests greater than additive health impacts influenced by (1) the sources of localized emissions, (2) proximity to PM sources (Buonocore et al., 2009; Cho et al., 2009; Greco et al., 2007; Kuhn et al., 2005; Laurent et al., 2014a; Wagner et al., 2012), and (3) the varied pollutant profiles associated with proximity to different emissions sources of $PM_{2.5}$ (Laurent et al., 2014a).

An important limitation of previous studies that attempted to find gradients in TLBW risk associated with various $PM_{2.5}$ components is the inability to pinpoint major sources or components contributing to TLBW risks. Instead, nearly all sources and components imparted a risk of exposure and are correlated. For example, the inherent dependencies between $PM_{2.5}$, $PM_{0.1}$, and various carbonaceous particulates (e.g. organic carbon, black carbon, and elemental carbon), or between $PM_{2.5}$ and sulfates in the exposure model used by Laurent et al. (2014), made it impossible to parse out which fraction sizes, components within $PM_{2.5}$- or combination thereof - are most likely to impart the greatest TLBW risk (Laurent et al., 2014a). A single major source combined with certain spatially determined factors may produce a particular air pollution

mixture that is more hazardous, yet multiple regression techniques struggle to distinguish between them.

The results from ours and a recent study by (Pirani et al., 2015b), show that Bayesian profile regression provides a tangible clustering procedure to develop profiles of exposure to multiple pollutants and simultaneously provide visualization tools. For instance, (Pirani et al., 2015b) studied variations in respiratory mortality across exposure profile clusters using a similar Bayesian profile regression. They found that days with high levels of secondary particulates (e.g. nitrates and sulfates) imparted the highest mortality risk in comparison to all other $PM_{2.5}$ component exposure profiles. Thus, rather than multiple regression models with pollutants and sources being highly correlated (Hampel et al., 2015; Laurent et al., 2014a), our clustering approach could be applied to develop PM-exposure profiles using data on $PM_{2.5}$ components, sources, and size fractions. Furthermore, our spatially-based clustering approach enables identification and mapping of sub-regions that are characterized by the most hazardous PM-source components.

Rather than simply examining gradients in multipollutant health outcome risks devoid of spatial information, our study illustrates the importance in examining the spatial patterning of multipollutant health effects to help bring out the likely causes of apparent non-linear effects. For example, pollutant cluster P9 - reflective of primary traffic $PM_{2.5}$ pollution - was not the only cluster with elevated concentrations for all study pollutants. Cluster P9, however, displayed the highest probability for an estimated effect above zero and the second highest effect estimate size, despite other pollutant clusters displaying higher $PM_{2.5}$ or higher NO and NO_2 concentrations. The only other pollutant cluster with a larger estimated effect size was cluster P10, which was also characteristic of *primary* traffic pollution. Whereas pollutant cluster P13 − reflective of

mostly secondary traffic $PM_{2.5}$ − has a $PM_{2.5}$ concentration 30% higher than P9 and P10. Despite this, the estimated effect size for cluster P13 is lower than P9 and P10. Our approach thus identifies patterns that help explain apparent non linear effects, such as: (1) mapping of cluster effects that exhibited strong spatial patterns related to major roadways, (2) the variations in pollutant metrics such as correlations and pollutant ratios across clusters combined with the spatial patterning of these pollutant metrics, and (3) the influence of residential distance to major roadways. These spatial data provide strong evidence that *primary* traffic emissions uniquely impart the largest effect on TLBW.

Correlated Pollutants and Health Effects Research

Our approach to examining health effects of correlated exposures via exposure profile clusters offers several advantages compared to co-pollutant regression methods. Problems with collinearity within a multivariate regression include inflated variance in regression coefficients, unstable effect estimates, and causal inference challenges (Dormann et al., 2013b; Lin, 2008; Schmidt and Muller, 1978). Several outdoor air pollution studies find that pollutants contribute to a health outcome in single pollutant models; however, mutual adjustment for correlated pollutants can result in no pollutant showing an association (Ebisu and Bell, 2012b) or coefficients flipping sides i.e. opposite in direction from single pollutant models (Kelsall et al., 1997). Furthermore, whether mutual adjustment is necessary − i.e. whether multiple pollutants actually confound each other − cannot be determined in models with highly correlated pollutants. When we analyze our data using a co-pollutant model that includes all pollutants in a multivariate regression model, we find instability of specific pollutant coefficient estimates and increased standard errors (see Table B.1 in the Appendix B). Also, while we find suggestive evidence for a statistically significant interaction between NO and NO_2 in a co-pollutant model (Table B.1, Appendix B), the interpretation is challenging since both pollutants tend to co-vary

and are linked through conversion into one-another by atmospheric chemistry involving ozone. Bayesian profile regression on the other hand harnesses the collinearity of air pollutants to find meaningful patterns of joint exposure that are relevant for determining different health risks across pollutant clusters.

Another important problem with multipollutant modeling is that correlations between pollutants can vary over space (Dionisio et al., 2014; Levy et al., 2013b; Snowden et al., 2015). Spatial variability in pollutant correlations between and within urban communities is challenging because it can lead to exposure measurement error and further calls into question estimating co-pollutant effects reliably. It is also unclear whether results from studies in one particular region are generalizable to others that have different spatial patterns of pollutant correlations. Consistent with previous studies (Dionisio et al., 2014; Levy et al., 2013), we found substantial within county variability in pollutant correlations between our pollutant clusters (Figures S3.6 and S3.7, Supplemental Materials). To some extent our approach overcomes spatial variation in pollutant correlations because we characterized the heterogeneity in pollutant relationships across space, and further relate these exposure profiles to a health outcome. Hence, employing our approach in environmental health studies may better inform policies designed to protect public health since policies can be tailored towards pollution mixtures relevant to a specific area.

Contextual Neighborhood Effects on TLBW

An important aspect to our pollutant clustering approach lies in simultaneously adjusting for clustered neighborhood indicators of disadvantage (i.e. income and race) and older housing. While other contextual factors related to TLBW could have been included in our clustering procedure, it is clear that our clustering variables are highly correlated with other adverse contextual factors (i.e. education, housing values, low social support, neighborhood greenness, violent crimes, etc.) in southern California, and thus likely account for these other contextual

factors (Boggess and Hipp, 2010; Conway et al., 2010; English et al., 2003; Ghosh et al., 2010). Furthermore, since our contextual variables correlate with one another and correlate with pollutants, it was important to separate out the contextual area-level effects from the pollutant profile cluster effects. Despite the spatial similarity between the two different types of clusters in our study, the high risk contextual clusters display a spatial pattern that is distinct from the high risk pollutant clusters, suggesting that these two separate exposure profiles measured different spatial patterns of risk related to their respective variables.

Study Limitations

We lacked data on speciation and tracers for specific sources of $PM_{2.5}$, which limits our ability to attribute a particular air pollution source to effects on TLBW. Despite this limitation, the spatial patterning of our results, supplemented with metrics such as cluster-specific NO/NO_2 ratios and between pollutant correlations, offers strong evidence implicating primary traffic pollution. Another limitation lies in the lack of fine-scale spatial data for other air toxics (i.e. benzene, ozone and carbon monoxide). Since we lack data on other air toxics that correlate with the pollutants considered in our study (Fujita et al., 2011; Ghosh et al., 2012b; Laurent et al., 2014a; C. Protano et al., 2012; Salam et al., 2005; Wilhelm et al., 2011a), we cannot say whether and how these other pollutants may contribute to the observed spatial patterning of TLBW risks. Other limitations include a lack of information on indoor air pollution exposure and time-activity patterns that may influence air pollution exposures, such as information about whether the women worked outside the home (Ritz et al., 2007b) or commuted daily (Zuurbier et al., 2010); all of which can contribute further to exposure misclassification. However, recent findings suggest that maternal outdoor air pollution estimates at the home address are unlikely affected by a lack of time-activity patterns during pregnancy (Ouidir et al., 2015). Finally, while our approach offers several important advantages over previous air pollution profile studies, our

Bayesian approach is currently limited in regards to handling a dataset with high dimensionality, which can only be overcome via future gains in computational efficiencies.

Study Strengths

The primary strength of our study is that we were able to examine exposures to multiple correlated air pollutants and TLBW, mitigating some of the typical problems encountered with correlated exposures. Our study also had a large sample size and used population-wide data for exposure, thus avoiding selection of a study population based on proximity to major sources of air pollution or proximity to central site monitors (Dionisio et al., 2014; Kumar, 2012). Another strength is adjustment for individual-level covariates and contextual factors associated with TLBW, and adjustment for spatial residual confounding at the census tract-level. Another important strength is that we were able to fit a multilevel/hierarchical random effects model for the clustered pollutant profiles and contextual profiles enabling us to look at multiple profile-specific risks, thus avoiding some of the issues related to multiple testing of myriad exposure/SES effects on health (Gelman and Hill, 2006b).

Conclusion

Our Bayesian clustering procedures allowed us to go beyond simple one-at-a-time analyses usually employed to examine marginal effects of individual pollutants on birth outcomes. Further, this spatially distributed *mixtures* approach provides information on the spatial distribution of exposure/SES profiles that pertain to the *levels* of various pollutants and SES factors. Policy analysts can use this information to determine which exposure/SES profiles dominate a particular sub-region of L.A. County, as a starting point for regulatory considerations. In our analyses, we found that neighborhood-level $PM_{2.5}$, NO_2, and NO concentrations were correlated with census block group-level contextual factors throughout LA County; and the nature of these relationships was quite complex and highly spatially variable

across the County. Moreover, the pollutant profile clusters showed a strong spatial contrast with respect to exposure-related TLBW risks. LA County's urban core, south-central urban region, and parts of the eastern-most region of the county exhibited the largest exposures for $PM_{2.5}$, NO_2, and NO, which decreased with distance from major highways. Moreover, the highest concentration pollutant profile clusters imparted the greatest TLBW risks after controlling for other important risk factors, especially those closest to major highways, which suggests near roadway emissions are more important in terms of risk of adverse birth outcomes related to these air pollution profiles.

Acknowledgments

Research described in this article was conducted under contract to the Health Effects Institute (HEI), an organization jointly funded by the United States Environmental Protection Agency (EPA) (Assistance Award No. R-82811201) and certain motor vehicle and engine manufacturers. The contents of this article do not necessarily reflect the views of HEI, or its sponsors, nor do they necessarily reflect the views and policies of the EPA or motor vehicle and engine manufacturers.

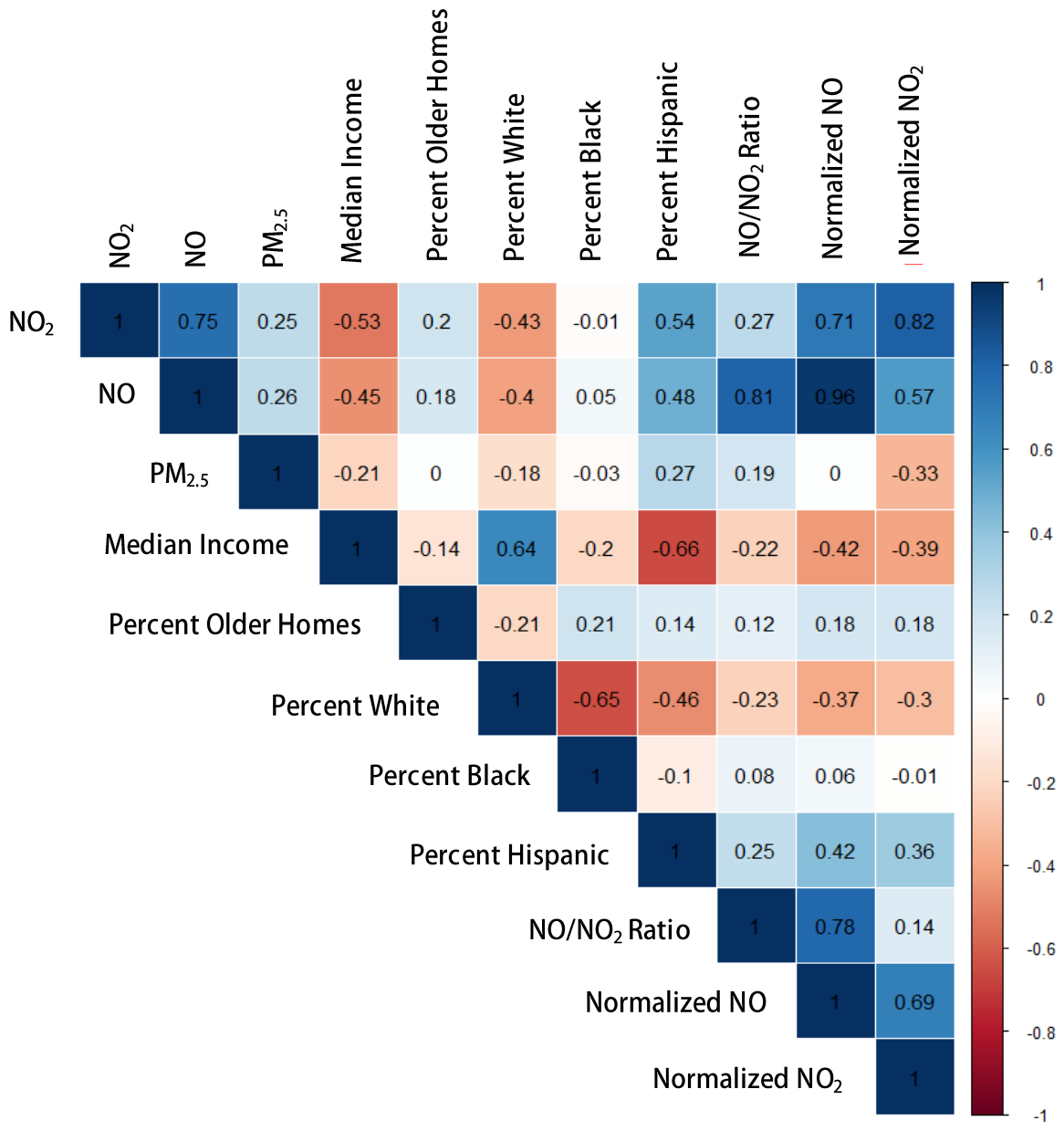


Figure 3.1. Pearson correlation matrix of census block group level averages for air pollutants, contextual variables, and pollutant metrics.

Table 3.1. Summary Statistics of Mean Census Block Group-level Pollutant Concentrations for Pollutant Exposure Profile Clusters.

Pollutant Cluster (Number of Census Block Groups)	$PM_{2.5}$ µg/m^3 (IQR)	NO_2 ppb (IQR)	NO ppb (IQR)
P1 (329)	**13.20 (11.95, 14.55)**	**18.19 (15.58, 20.79)**	**10.99 (9.30, 12.87)**
P2 (242)	**12.83 (12.03, 13.69)**	**21.34 (19.28, 23.2)**	**19.17 (16.07, 21.60)**
P3 (633)	**14.93 (14.58, 15.30)**	**28.14 (26.12, 29.84)**	**29.10 (23.46, 33.90)**
P4 (1399)	**16.91 (16.41, 17.36)**	**23.87 (21.87, 26.17)**	**21.08 (17.35, 24.53)**
P5 (624)	**15.96 (15.27, 16.52)**	**21.94 (20.61, 23.33)**	**23.50 (21.84, 25.21)**
P6 (500)	**18.87 (18.31, 19.41)**	**17.84 (16.12, 19.66)**	**15.46 (13.24, 18.20)**
P7 (1715)	**18.16 (17.79, 18.50)**	**25.63 (24.00, 27.31)**	**29.36 (26.11, 32.57)**
P8 (96)	**16.90 (16.40, 17.18)**	**16.46 (13.23, 18.78)**	**22.34 (16.29, 30.91)**
P9 (513)	**17.66 (17.12, 18.15)**	**31.74 (30.14, 33.27)**	**42.31 (37.57, 46.37)**
P10 (52)	**17.23 (16.84, 17.67)**	**42.51 (39.91, 44.29)**	**74.08 (63.40, 80.79)**
P11 (29)	**10.01 (8.93, 10.83)**	**14.44 (7.44, 16.80)**	**18.67 (10.86, 23.07)**
P12 (52)	**16.87 (16.28, 17.47)**	**16.51 (15.78, 17.42)**	**59.62 (35.43, 83.08)**
P13 (96)	**22.77 (21.89, 23.75)**	**31.39 (29.55, 32.85)**	**30.69 (28.13, 33.10)**
Overall (6,280)	16.88 (15.84, 18.13)	24.41 (21.33, 27.45)	25.99 (19.12, 30.94)

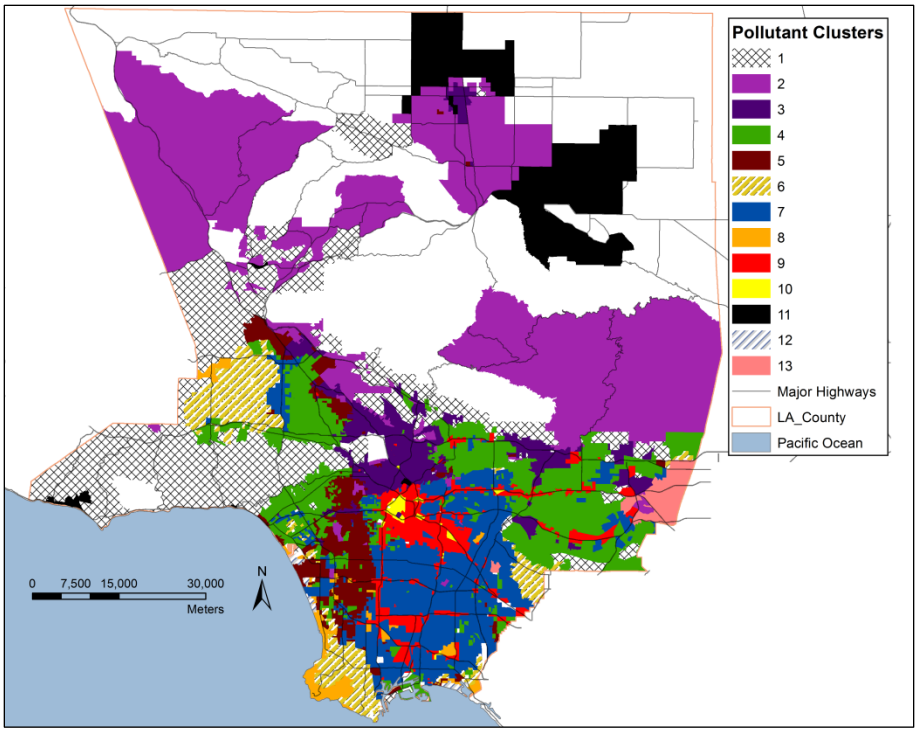


Figure 3.2. Spatial distribution of pollutant exposure profile clusters

Table 3.2. Between pollutant Pearson's correlations for the pollutant exposure profile clusters (P1-P13)[a].

	Pollutant Clusters												
Pollutants	**P1**	**P2**	**P3**	**P4**	**P5**	**P6**	**P7**	**P8**	**P9**	**P10**	**P11**	**P12**	**P13**
NO2~NO	0.86	0.85	0.90	0.88	0.79	0.86	0.73	0.93	0.53	0.15	0.94	0.41	0.75
NO2~$PM_{2.5}$	0.49	0.75	0.24	0.26	-0.42	0.37	0.12	-0.27	0.15	-0.23	0.58	0.40	0.55
NO~$PM_{2.5}$	0.45	0.67	0.33	0.10	-0.14	0.38	-0.11	-0.18	0.23	0.43	0.56	0.30	0.36
PM2.5~NO/NO_2[b]	0.16	0.38	0.36	-0.06	0.32	0.26	-0.27	0.02	0.18	0.54	0.15	0.27	0.14

[a]Overall correlations: NO_2~NO=0.76, NO_2~$PM_{2.5}$=0.25, NO~$PM_{2.5}$=0.26, $PM_{2.5}$~NO/NO_2 ratio=0.19
[b]Correlation between $PM_{2.5}$ concentration and the ratio of NO concentration to NO_2 concentration.

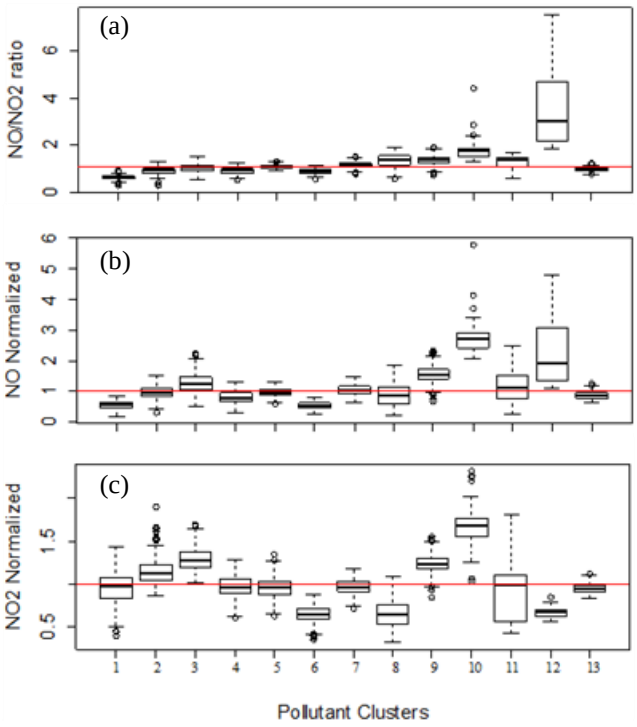


Figure 3.3. Boxplots of (a) NO/NO2 ratios, (b) normalized NO, and (c) normalized NO_2 for each pollutant cluster. The red line indicates the overall average for each of these pollutant metrics.

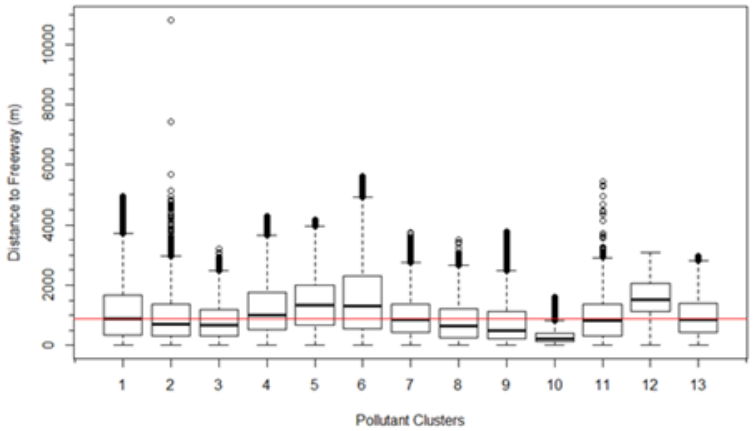


Figure 3.4. Distribution of residential distance to highways among mothers within each pollutant cluster. Redline indicates the overall median for all maternal residential distances (median = 867 meters).

Table 3.3. Prevalence of TLBW for Multipollutant Clusters and Model Results for Multipollutant Exposure Profile Cluster Random Effects (N=804,726).

Cluster	No. Births[a]	No. TLBW	% TLBW[b] (95% CI)	Cluster Effect[c,d] (95% CI)	Probability Effect > 0[e]
P1	29394	431	1.47* (1.33, 1.61)	-0.122 (-0.254, 0.008)	0.033
P2	34263	589	1.72* (1.58, 1.86)	-0.108 (-0.232, -0.015)	0.042
P3	79199	1555	1.96 (1.87, 2.06)	-0.026 (-0.133, 0.081)	0.315
P4	168145	3305	1.97 (1.89, 2.03)	0.006 (-0.093, 0.106)	0.548
P5	66035	1595	2.42* (2.30, 2.53)	0.017 (-0.092, 0.126)	0.619
P6	58164	1067	1.83* (1.73, 1.95)	0.003 (-0.109, 0.115)	0.519
P7	256817	5612	2.19* (2.13, 2.24)	0.019 (-0.080, 0.117)	0.642
P8	7452	113	1.52* (1.25, 1.82)	-0.096 (-0.275, 0.079)	0.141
P9	77336	1824	2.36* (2.25, 2.47)	0.089 (-0.018, 0.195)	0.949
P10	3171	82	2.59 (2.06, 3.20)	0.141 (-0.060, 0.338)	0.916
P11	3491	74	2.12 (1.67, 2.65)	0.043 (-0.168, 0.252)	0.656
P12	3357	51	1.52 (1.13, 1.99)	-0.012 (-0.232, 0.205)	0.459
P13	17902	396	2.21 (2.00, 2.44)	0.055 (-0.087, 0.196)	0.774
Overall	804,726	16,694	2.07 (2.04, 2.11)		

[a]Full term births (>259 days gestation).
[b]Percent prevalence of TLBW without model adjustment.
[c]Adjusted for maternal age, race, education, and parity, infant sex, gestation (days) , gestation-squared, and contextual random effect clusters.
[d]Random effect presented on the log-odds scale.
[e]Probabilities were calculated utilizing the "*inla.pmarginal*" function in INLA.
*TLBW prevalence is significantly (p-value<0.01, two-sided) different from the overall proportion of TLBW (unadjusted).

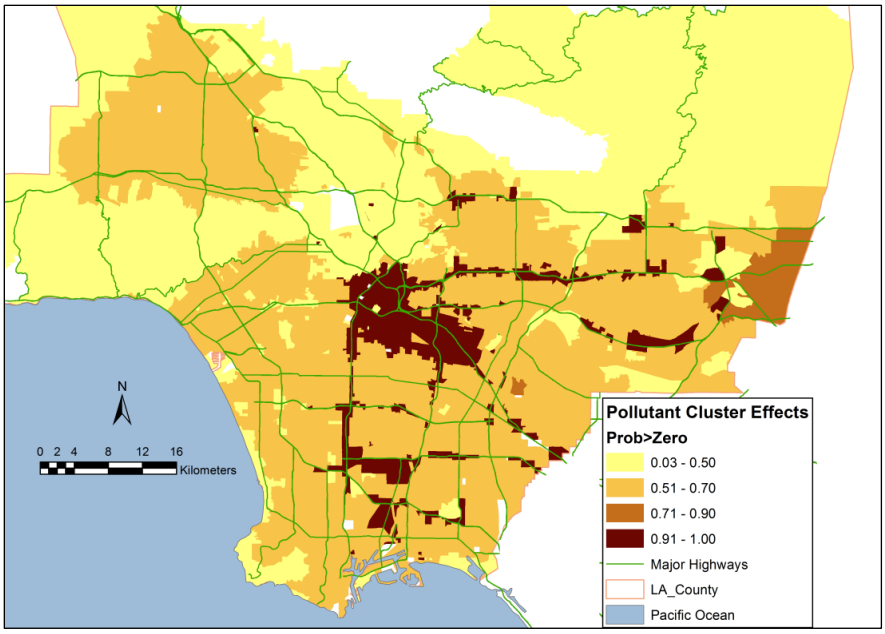


Figure 3.5. Spatial distribution of pollutant profile cluster random effect posterior probabilities.

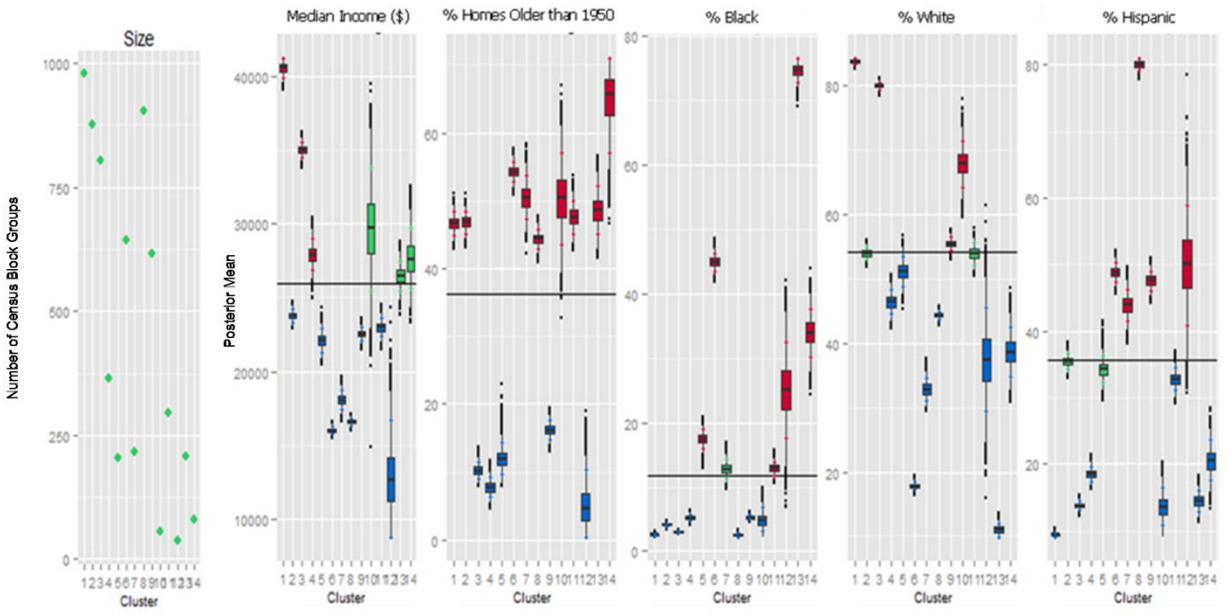


Figure 3.6. Contextual profile clusters: Cluster size (number of census block groups) and posterior distributions for median income, percent older homes, percent black, percent white, and percent Hispanic ($N_{clusters}$=14). Black lines indicates the overall average exposure for a given covariate.

Table 3.4. Prevalence of TLBW for contextual clusters and model results for contextual exposure profile cluster random effects (N=804,726).

Cluster	No. Births[a]	No. TLBW	% TLBW[b] (95% CI)	Cluster Effect[c,d] (95% CI)	Probability Effect > 0[e]
C1	64018	965	1.51* (1.42, 1.60)	-0.09 (-0.19, 0.02)	0.05
C2	95559	1869	1.96 (1.87, 2.05)	-0.03 (-0.12, 0.07)	0.30
C3	76163	1218	1.60* (1.51, 1.69)	-0.08 (-0.18, 0.02)	0.07
C4	39105	787	2.01 (1.88, 2.16)	-0.03 (-0.14, 0.08)	0.31
C5	38084	809	2.12 (1.98, 2.27)	-0.002 (-0.11, 0.11)	0.49
C6	112919	2970	2.63* (2.54, 2.73)	0.12 (0.03, 0.22)	0.99
C7	39738	912	2.30* (2.15, 2.45)	0.03 (-0.08, 0.14)	0.71
C8	165328	3384	2.05 (1.98, 2.12)	0.03 (-0.07, 0.12)	0.71
C9	101455	2040	2.01 (1.93, 2.10)	0.02 (-0.07, 0.14)	0.67
C10	2624	42	1.60 (1.18, 2.16)	-0.08 (0.30, 0.13)	0.22
C11	43403	975	2.25* (2.11, 2.39)	0.07 (-0.04, 0.17)	0.90
C12	963	18	1.87 (1.18, 2.95)	0.07 (-0.31, 0.18)	0.30
C13	18784	538	2.86* (2.64, 3.11)	0.03 (-0.09, 0.15)	0.68
C14	6583	167	2.54* (2.18, 2.95)	0.07 (-0.09, 0.23)	0.82

[a]Full term births (>259 days gestation).
[b]Percent prevalence of TLBW without model adjustment.
[c]Adjusted for maternal age, race, education, and parity, infant sex, gestation (days) , gestation-squared, and pollutant random effect clusters.
[d]Random effect presented on the log-odds scale.
[e]Probabilities were calculated utilizing the "*inla.pmarginal*" function in INLA.
*TLBW prevalence is significantly (p-value<0.01, two-sided) different from the overall proportion of TLBW (unadjusted).

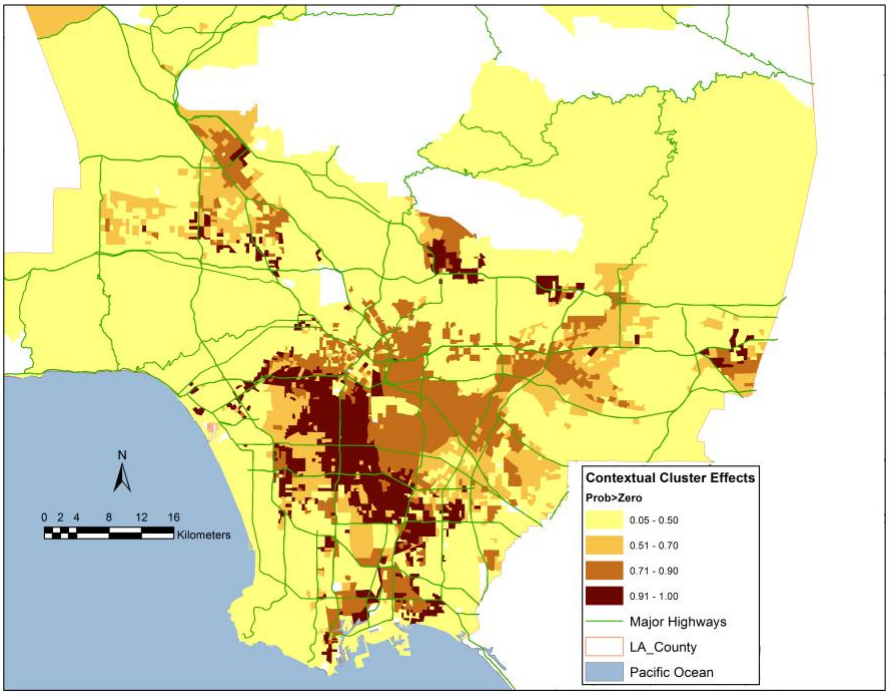


Figure 3.7. Spatial distribution of contextual profile cluster random effect posterior probabilities.

Table 3.5. Fixed Effects Odds Ratios of TLBW for Individual-level Covariates[a] (N=804,726).

Fixed Effects Covariates	Odds Ratio	2.5% Quantile	97.5% Quantile
Infant			
Male (reference)	1		
Female	1.45	1.40	1.49
Parity			
No previous births (reference)	1		
≥1 previous birth	0.59	0.57	0.61
Maternal Age			
<20 years (reference)	1		
20 - 24 years	0.97	0.92	1.03
25 - 29 years	0.90	0.85	0.96
30 - 34 years	0.91	0.86	0.97
≥35	1.06	1.00	1.14
Maternal Education			
0-8 years (reference)	1		
9-12 years	0.90	0.86	0.94
13-15 years	0.75	0.70	0.79
≥16 years	0.66	0.62	0.71
Race/Ethnicity			
Non-Hispanic White (reference)	1		
Hispanic	1.08	1.02	1.15
Non-Hispanic Black	2.16	2.01	2.32
Non-Hispanic Asian	1.42	1.32	1.53
Other	1.81	1.67	1.97
Gestation (days)	0.32	0.30	0.33
Gestation-squared	1.0019	1.0018	1.002

[a] ORs represent covariate fixed effects estimated from the multilevel model. Random effects in this model were pollutant clusters, contextual clusters, a spatial random error term based on adjacent census tracts, and a spatially unstructured random error term

Chapter 4 - The Relationship Between The Neighborhood Food Environment and Term Low Birth Weight in Los Angeles County

Eric Coker[a],

Ellen Smit[a],

John Molitor[a]

[a]College of Public Health and Human Sciences, Oregon State University, Corvallis, OR

Health & Place

Submission Pending

Abstract

Proper nutrition during pregnancy is considered an important determinant towards ensuring a healthy birth weight baby. Neighborhood retail food environments may also influence local food options and food intake among pregnant women and risks of adverse birth outcomes. Using a Bayesian multilevel framework we implemented a multivariate logistic regression model with spatial conditionally autoregressive (CAR) errors to investigate the association between term low birth weight (TLBW) and the modified retail food environment (mRFEI) in Los Angeles (LA) County. We found that an interquartile range (IQR) increase in the mRFEI is associated with a lower adjusted odds of TLBW by 3.44% (95%CI: 0.76%, 6.07%). We also found that mothers residing in tracts with joint exposure to poor food environments (low mRFEI), low socioeconomic status (SES), and low area greenness had the highest log odds of having a TLBW baby. This cross-sectional analysis of LA birth data suggests that an improved neighborhood food environment is protective against TLBW. Since these findings are observational and restricted to LA County, further research into the relationship between the neighborhood food environment and birth outcomes as well as joint exposure to other neighborhood indicators such as SES and greenness is warranted.

Key Words: food environment, low birth weight, $PM_{2.5}$, Bayesian multilevel modeling, birth outcomes

Introduction

Food purchasing habits and food intake are influenced by individual-level factors such as behavioral, exposure to advertisements, socioeconomic, and demographic, to higher level factors such as the neighborhood-level food environment and local food systems (Black et al., 2014; Brown and Brewster, 2015; Cannuscio et al., 2014; Halford et al., 2004; Laraia et al., 2004; Neff et al., 2009; Sobal and Wansink, 2007; Zenk et al., 2014). A wealth of research data suggests that

low access to grocery stores at the neighborhood level and greater access to fast food restaurants and small corner stores are associated with a higher prevalence of overweight or obesity (Broady and Meeks, 2014; Drewnowski et al., 2012; Dubowitz et al., 2012; Giskes et al., 2011; Hattori et al., 2013; Hsieh et al., 2015; Janevic et al., 2010; Koleilat et al., 2012; Langellier, 2012; Salois, 2012). Maternal obesity is linked to adverse reproductive health outcomes such as diabetes, preterm birth, and fetal growth disorders (Marsh and Hecker, 2014), thus investigations into the relationship between the food environment and birth outcomes is warranted.

Despite the relative lack of research investigating community-level food environments on term birth weight (Farley et al., 2006; Lane et al., 2008; Ma et al., 2015), data from the U.S. suggests that differences in proximity to supermarkets is associated with differences in both diet quality during pregnancy (Laraia et al., 2004) and pre-pregnancy weight (Janevic et al., 2010). A greater prevalence of fast food restaurants in neighborhoods has also been linked with greater consumption of fast food during pregnancy and a higher prevalence of gestational diabetes (Dominguez et al., 2014; Kahr et al., 2015).

The few studies that address the relationship between the food environment and birth outcomes have produced inconclusive results (Farley et al., 2006; Lane et al., 2008; Ma et al., 2015). A cross-sectional study in Louisiana by Farley et al., (2006) found that neither supermarket density (per 1,000 population) nor fast-food restaurant density (per 1,000 population) were associated with birth weight (Farley et al., 2006). Another study by Lane et al., (2008) examined the relationship between the neighborhood food environment (defined as a census tract with or without a supermarket within 1/2 mile) and intrauterine growth restriction (IUGR) in Syracuse, New York and found a three times higher adjusted odds (adjusted OR=3.38 (95% CI:1.26-9.09)) of IUGR for census tracts without a supermarket within 1/2 mile. A study

conducted in South Carolina showed that a higher prevalence of convenience stores was associated with lower birth weight in the study population, however, further distance to supermarkets was associated with a higher birth weight (Ma et al., 2015).

In the present study we used the modified retail food environment index (mRFEI) to represent the food environment to investigate the association between the food environment and TLBW. The mRFEI has been used in recent studies to investigate the relationships among socio-demographics (Salinas et al., 2014; Salinas and Sexton, 2015), health outcomes (Adam Drewnowski et al., 2014; A Drewnowski et al., 2014; Koh et al., 2015), and dietary intake (Greer et al., 2014). When examining the relationship between food environments and birth weight, particularly within urban environments, it is important to consider other area-level birth weight risk factors that coincide with poor food environments, since other area-level factors may confound or modify any observed association. For instance, research has shown that the locations of fast food restaurants are dependent on proximity to heavily trafficked roadways (Dunn, 2010; Hurvitz et al., 2009b; Inagami et al., 2009). Outdoor air quality is also partially dependent on heavily trafficked roadways and studies further show that maternal exposure to traffic-related air pollution is associated with a higher prevalence of TLBW (Coker et al., 2015; Ghosh et al., 2012c). Also, in urban envrironments low levels of area-level greenness is linked with impervious surfaces such as roadways, and area-level greenness has been linked with TLBW. Hence, in the present study we assesses the association between the food environment and TLBW while accounting for exposure to air pollution and other area-level factors.

The primary goal of this research is to investigate the relationship between the neighborhood food environment (at the census tract-level) and TLBW in LA County. We also investigate whether the association between the food environment and TLBW is influenced by

exposure to fine particulate matter ($PM_{2.5}$). Additionally, we employ a novel Bayesian profile regression technique to explore whether the TLBW prevalence is associated with clusters of tract-level covariate exposure patterns for the food environment, socioeconomic status (SES), and greenness (controlling for $PM_{2.5}$).

Methods

Study design and population

We used a cross-sectional study design to examine the association between the mRFEI and TLBW in women who gave birth to a full term baby. The study population is comprised of women who resided in LA County at the time of delivery between the years 2004 to 2006 (N=344,244).

Birth data

Birth data were obtained from electronic birth records from the California Department of Health. Access to these data were approved through the University of California, LA Office of the Human Subjects Protection Program, the California Committee for the Protection of Human Subjects, and the University of Southern California's Office for the Protection of Research Subjects. We assessed the birth outcome measure of term (>=37 weeks gestation) low birth weight (<2,500grams (g)). Information on the mother (i.e. race, education attainment, prenatal care attendance, residential address, etc.) and the infant (i.e. sex, presence of any birth defects) were obtained from these records. We restricted the dataset to singleton births lacking any apparent abnormalities. Births with extreme gestational days (<140 days or >320 days) and birth weights (<500g or >5000g) were excluded from analysis, as such values are likely due to recording errors. Geocoding of residential addresses are explained elsewhere (Goldberg et al., 2008).

Modified Retail Food Environment Index

The mRFEI comes from the Center for Disease Control and Prevention's (CDC) data on the food environment. The mRFEI was developed by the CDC to assess the spatial patterns of healthy and unhealthy food environments across the U.S. The mRFEI represents a ratio (multiplied by 100) of healthy food retailers to less healthy food retailers per census tract that ranges between 0-100. Hence, higher mRFEI scores reflect better food environments while lower scores reflect poorer food environments. The equation below indicates how the CDC calculated the mRFEI:

$$\frac{Number\ of\ Healthy\ Food\ Retailers_{census\ tract}}{Number\ of\ Healthy\ Food\ Retailers_{census\ tract} + Number\ of\ Less\ Healthy\ Food\ Retailers_{census\ tract}}$$

CDC defined healthy food retailers as supermarkets, large grocery stores, fruit and vegetable markets, and warehouse clubs, while less healthy food retailers were fast food restaurants and convenience stores (CDC, 2011). CDC utilized the InfoUSA database to obtain data on healthy food retailers (year 2009) and data from the NavTeq database (year 2009) and the Homeland Security Information Program database (year 2008) for data on the less healthy food retailers (CDC, 2011).

Individual-level measures

Infant factors including sex, gestation age (days), gestation squared (days^2), as well as maternal factors such as race/ethnicity, age, parity, education level, number of prenatal care visits, and exposure to outdoor $PM_{2.5}$ were included as covariates. These variables were selected based on prior studies in this population that demonstrated the importance of these variables for TLBW (Coker et al., 2015; Ghosh et al., 2012c; Wilhelm et al., 2011c; Wilhelm and Ritz, 2003a). $PM_{2.5}$ exposure estimates were derived from a land use regression (LUR) model (Beckerman et al., 2013a) that we used in our previous work (Coker et al., 2015). This LUR provides long-term exposure concentration estimates for $PM_{2.5}$ at each maternal residence. Briefly, data for the $PM_{2.5}$ LUR model included long-term regulatory monitoring data of $PM_{2.5}$ measurements (Beckerman

et al., 2013b) along with remotely sensed aerosol optical depth data. A machine learning deletion/substitution method (Beckerman et al., 2013a) tested up to 70 covariates to build the final LUR model, including data on land use (i.e. agricultural, barren, all developed land, high-density development, green space, water, and wetland), long-term traffic counts, and road networks (Beckerman et al., 2013a; Jerrett et al., 2013). Entire pregnancy average exposures for each mother were then calculated by applying a temporal adjustment factor to the LUR estimates. Daily $PM_{2.5}$ air monitoring data from LA County were utilized to compute the temporal adjustment factor.

Area-level measures

Census tract-level covariates were included in the following models to adjust for area-level confounding. They were average normalized differential vegetation index (NDVI) and median household income. These covariates were selected since research data conducted in LA and other regions show that NDVI (or area-level greenness) and median household income are risk factors for lower term birth weight (Gray et al., 2014; Hystad et al., 2014b; Laurent et al., 2013c; Markevych et al., 2014; Zeka et al., 2008). Furthermore, low SES neighborhoods have been correlated with poor neighborhood food environments in the U.S. (Inagami et al., 2009; Shaffer, 2002b). Additionally, NDVI and the food environment may be spatially correlated built environment factors.

Year 2000 U.S. Census data on LA County median household incomes for census block groups was downloaded from the American Fact Finder. Average NDVI was calculated from 250 meter resolution 16-day composite images from the Moderate Resolution Imaging Spectroradiometer (MODIS) as downloaded from the University of Maryland's Global Land Cover Facility database (Carrott et al., 2005). NDVI 16-day composites from January 1, 2005 through December 31, 2005 were averaged for the year 2005 using the Raster Algebra tool in ArcGIS

(version 10.1, Redlands, CA) to obtain a single year NDVI raster surface. The entire year average NDVI raster surface was averaged over census block group boundaries (year 2000 US Census boundaries) using the Zonal Statistics tool in ArcGIS to assign maternal NDVI.

Since mRFEI data are based on census tracts, each subject was assigned to a census tract based on latitude and longitude of their geo-coded residence . Mothers were similarly assigned to a census block group using the residential latitude and longitude. The spatial join tool in ArcGIS was used for maternal census tract and census block group spatial assignments. Data merging between the respective maternal census tract and maternal census block group assignments with the spatially bounded covariate data were performed in the R statistical computing environment (version 3.2.0) by matching on census tracts for the mRFEI data and census block groups for the NDVI and median household income data.

Statistical analysis

Births with complete covariate data resulted in a total of 344,244 full term births for analysis. Summary statistics were computed for the study's health outcome as well as for individual and neighborhood level covariate data (Tables 4.1 and 4.2). We fit two separate multilevel multivariate logistic regression models to estimate the association between the food environment and TLBW. The first model was fit to estimate the main effect of mRFEI on TLBW while controlling for other factors and residual spatial error. The second model tests whether there is a significant multiplicative interaction effect between $PM_{2.5}$ exposure and mRFEI (e.g. mRFEI*$PM_{2.5}$) in the association with TLBW. Covariates included in the models were determined based on *a priori* information drawn from the literature. Since the continuous covariates were on widely different scales, we standardized these covariates to similar scales in order to facilitate interpretation of regression coefficients. The mRFEI was rescaled by dividing each mRFEI observation by 100, while all other continuous covariates were standardized by

subtracting the mean and dividing by the standard deviation for each observation (e.g., [$mean_x$ - x_i] / $std.dev_{x)}$. Each model was fit in R (R version 3.2.0) using the R-INLA package (R-INLA version 0.0.1453319343) in order to implement the multilevel model for Bayesian inference (Martino and Rue, 2009b; Rue et al., 2015).

The multilevel component of the model incorporates spatially structured (CAR) and unstructured (independent and identically distributed [iid]) random effects error terms to account for extra-variability in our response variable (TLBW) not explained by the first-level covariates. The multilevel/hierarchical logistic regression model is presented below in Equation 1.

$$logit(y_i) = \beta_0 + \beta_{mrfei} X_{mrfei,j} + \ldots \beta_i X_i + S_j + \epsilon_j \qquad (1)$$

where y_i is the logit probability of having a TLBW baby for individual i, β_0 is the global intercept, β_{mrfei} is the main effects coefficient for census tract level mRFEI, $X_{mrfei,j}$ is the mRFEI value for census tract j, $\beta_i X_i$ are the additional coefficients and predictors in the model (e.g. NDVI), S_j is the spatially structured residual error term for the j^{th} census tract (with restriction $\sum_j S_j = 0$ for indefinability reasons), and ϵ_j is the independent residual error term for the j^{th} spatial unit. The independent error term is defined in the typical way as $\epsilon_j \sim N(0, \sigma^2)$ and the spatial error term is defined as,

$$S_{j|k\neq j} \sim N\left(\frac{\sum_{k\neq j} w_{jk} S_k}{\sum_{k\neq j} w_{jk}}, \frac{\tau^2}{\sum_{k\neq j} w_{jk}}\right),$$

where the weights $w_{j,k}$ are elements of the zero-one neighborhood adjacency matrix classified equal to one when census tracts j, k are adjacent and zero otherwise. This method employs the Besag-York-Mollé (BYM) model (Besag et al., 1991).

Since several of the covariates in our analysis are defined at the census tract-level (i.e. the food environment, median household income, and NDVI), we also explored how these area-level

contextual factors cluster together throughout LA County and how joint exposures to contextual factors are associated with the odds of TLBW. A Bayesian clustering technique known as Bayesian Profile Regression was used to determine how tract-level mRFEI, median income, and NDVI cluster together numerically, and geographically.

Bayesian profile regression is a modeling approach that is able to flexibly cluster joint patterns of exposure values while handling the uncertainty in these joint patterns in a Bayesian framework. For an in-depth description of this technique, the reader is referred to (Liverani et al., 2015; Molitor et al., 2010c). We implemented the Bayesian profile regression using the R statistical package PReMiuM (version 3.1.2) (Liverani et al., 2015). The statistical output from this analysis provides posterior distributions of the covariate profiles for each cluster, which are drawn from the Markov Chain Monte Carlo (MCMC) simulations.

The profile clusters derived from this clustering analysis were analyzed in a third multilevel model, with the profile clusters included as random effects. Such a modeling framework means that the cluster random effects represent the variation in TLBW explained by the profile clusters, after controlling for individual-level covariates and modeling of spatial residual error (described above). Hence this modeling framework was identical to Equation 1 except that this final model (Model 3) included the random effect implemented as an iid random error term for profile clusters. Another important difference in this final model is that mRFEI, median income quartiles, and NDVI tertiles were not included as typical fixed effects because these area-level variables were captured within the profile cluster random effects. All other fixed effects from Model 1 are however included in this final model. To display the spatial pattern from the results of this secondary analysis we mapped the posterior probability that a given profile cluster has a higher log odds above the baseline log odds of TLBW.

Results

Descriptive statistics

Statistical summaries of individual-level characteristics for the study population are provided in Table 4.1, while area-level variables are summarized in Table 4.2. Supplemental materials Figure C.1 (Appendix C) describes the correlations between mRFEI and the other continuous covariates in our study (i.e. NDVI and median income). The prevalence of TLBW in our study population was 2.13% and the overall average tract-level mRFEI was 11.05 (Table 4.1). Average neighborhood mRFEI among TLBW cases was lower (10.66 [95% confidence interval (CI): 10.51-10.81]) compared to non-cases (11.06 [95% CI: 11.03-11.08]) (Table 4.1). In a univariate analysis we found that the percentage of TLBW was significantly higher (p-value<0.05) among mothers who resided in census tracts with the lowest (less healthy) quartile of mRFEI (2.31% [95% CI: 2.21, 2.41]) compared to mothers who resided in census tracts with the highest (more healthy) quartile mRFEI (1.97% [95% CI: 1.88, 2.07].

We also observed significant differences by race-ethnicity for several important exposures in our study. As indicated in Table 4.3, in comparison to nonHispanic Whites, nonHispanic Blacks and Hispanics have on average significantly lower area-level mRFEI, NDVI, and household incomes, and significantly higher $PM_{2.5}$ exposure.

Multilevel regression model

The estimated coefficients and their corresponding 95% credible intervals for each standardized covariate analyzed in the multilevel logistic regression model are summarized in Figure 4.1. An IQR increase in mRFEI was associated with a 6.48% (95% CI: 3.93%, 8.95%) lower odds (unadjusted) for TLBW. After adjustment for individual and census tract level covariates and accounting for spatial residual error, a higher mRFEI score(per IQR) was associated with a 3.44% (95% credible interval: 0.76%, 6.07%) lower odds for TLBW (adjusted

Odds Ratio = 0.97 [95% credible interval: 0.93, 0.99]). After statistical adjustment, an IQR increase in $PM_{2.5}$ was associated with an odds ratio of 1.02 (95% credible interval: [0.99, 1.04]) for TLBW. An interaction term between $PM_{2.5}$ and mRFEI indicated there was no apparent change in the association between mRFEI and TLBW with a change in $PM_{2.5}$ exposure and vice versa (see Supplemental Materials, Appendix C, Table C.1.).

Profile regression results

The joint patterns of tract-level mRFEI, median household income, and NDVI values resulted in six different profile clusters from the Bayesian profile regression analysis. Figure 4.2 displays these joint patterns across each variables, along with the number of tracts within each profile cluster (or cluster size). The boxplots for each indicator in Figure 4.2 represent the within cluster posterior distributions of the means from the MCMC draws, with the black lines indicating the overall mean for each indicator. As shown in Figure 4.2, two of the profile clusters have low means for mRFEI, NDVI and median income (clusters 3 and 5). Conversely, the two highest income clusters have elevated means for NDVI and mRFEI (clusters 4 and 6). The largest cluster (cluster 1) is about average for all tract-level indicators, while cluster 2 is about average for mRFEI and elevated for NDVI and income. A map of the geographic pattern for each cluster is provided in the Supplemental Materials, in Figure C.3 (Appendix C).

The profile cluster random effects estimates from the multilevel logistic regression model (Model 3) are shown in Figure 4.3. According to Figure 4.3, cluster 3 has the largest deviation above the baseline log odds for TLBW (meaning increased log odds) and cluster 5 has the second largest deviation above the baseline log odds for TLBW, while all other clusters showed a deviation below the overall baseline log odds for TLBW. There was a 97.3%

probability that cluster 3 is associated with a higher log odds for TLBW and 77.8% probability that cluster 5 is associated with an elevated log odds for TLBW. In Figure 4.4 we mapped the spatial distribution of the cluster random effect probabilities of elevated log odds for TLBW, overlaid with LA County Health Districts. This map highlights the concentration of the highest risk clusters (cluster 3) being concentrated within the urban core of LA County. The Health Districts with at least a third of their area that includes the highest risk cluster (cluster 3) are the South, Southeast, East LA, Southwest, Inglewood, Compton, and Hollywood-Willshire Health Districts, which comprise nearly half (45%) of cluster 3 tracts. The spatial distribution for the profile clusters are mapped in the supplemental materials in Figure C.3 (Appendix C).

Discussion

Key findings

This large cross-sectional study in LA County observed that mothers residing in neighborhoods (census tracts) with a higher ratio of healthy food retailers to less healthy food retailers (mRFEI) were less likely to have a TLBW baby. We did not observe a multiplicative interaction effect between the food environment with exposure to $PM_{2.5}$ on the association with TLBW, although the effect estimate for $PM_{2.5}$ on TLBW lowered by 10% after including the food environment as main effect in the model. Another important finding from our study is that we observed clustering between the food environment, greenness, and SES across LA County census tracts, and that tract-level profiles with adverse food environments, low greenness, and low SES were associated with a higher log odds of TLBW compared to neighborhoods without such an adverse profile. Importantly, we did not observe spatial variation in the effect of TLBW when fit as a random coefficient.

Interpretation of findings

A plausible mechanism for the food environment to influence risk of adverse birth outcomes such as TLBW is predicated on the rationale that the food environment acts as a built environment determinant of poor prenatal or pre-pregnancy nutrient intake and thereby lowers maternal nutritional status to reduce fetal growth. Since the developing fetus must obtain sufficient nutrients from the mother to attain optimal growth (Barker, 1995), an insufficient maternal diet related to the food environment may play an important role in determining risk of reduced birth weight. Some research conducted in higher income developed countries suggests a link between maternal food insufficiency and reduced birth weight. A study by Meng et al., (2013b) conducted a study in Ontario, Canada found that the effect of maternal health status on TLBW was modified by food insecurity of the mother. Research data from the U.S. has shown that prenatal WIC participation is associated with reduced risk of LBW infants (Buescher et al., 1993; Currie and Rajani, 2014; Hernandez et al., 2010; Reichman and Teitler, 2003). Research conducted in LA further indicates that WIC participation reduces food insecurity among pregnant women (Herman et al., 2004). Moreover, our study is in agreement with studies by Lane et al., (2008) and Ma et al., (2015) who also found a link between the neighborhood food environment and birth weight. Lane et al., (2008) conducted a study in Syracuse, New York and found that infants born to women living in census tracts with low access to a supermarkets had a significantly higher odds of a lower birth weight infant. Ma et al (2015) conducted a study in South Carolina and found that a higher number of convenience stores within a 1-mile buffer of a census tract was associated with a lower birth weight in the population.

Although our study did not find evidence that the food environment acts as a multiplicative effect modifier on the relationship between $PM_{2.5}$ and TLBW (or vice versa), there was evidence to suggest that the magnitude in the association between $PM_{2.5}$ and TLBW is

sensitive to the inclusion of the food environment into the statistical model. For instance, the inclusion of mRFEI in the model lowered the β coefficient for $PM_{2.5}$ by 10.5 % (Table C.1, Appendix C). However, the reverse was not true, in that including $PM_{2.5}$ in the model failed reduce the coefficient estimate for mRFEI substantially (~4% change in the β coefficient) and thus does not suggest that $PM_{2.5}$ is a confounder in the relationship between mRFEI with TLBW. Importantly, the strength of the $PM_{2.5}$ association with TLBW is not impacted after including the food environment into the model, which indicates that air pollution is still important as a risk factor for TLBW even after factoring in the food environment.

We also found evidence for distinct spatial patterning for clustering of area-level indicators including the food environment, SES, and greenness, with profile clusters characterized by poor food environments, low greenness, and low SES located predominantly within the urban core of LA County. These same profile clusters with the most adverse conditions were also characterized with a higher log odds of TLBW, even after adjusting for individual-level maternal and infant characteristics. We also found that on average, nonHispanic Blacks and Hispanics lived in neighborhoods with the poorest food environments, the lowest levels of greenness and median incomes, and had the highest $PM_{2.5}$ exposures (Table 4.3). Importantly, we found that association between the food environment and TLBW was uniform across census tracts and across different racial-ethnic groups (data not shown).

Study implications

Our main finding relates to the food environment and its association with TLBW in LA County. This finding implies that an improvement in the neighborhood food environment may be an important structural intervention at the built environment-level to reduce socioeconomic disparities in birth outcomes. However, since the three studies (including ours) that demonstrate such a link, longitudinal research is needed to substantiate these results. Our study findings also

imply that the food environment may act as an important place-based factor to influence maternal nutrition and thus TLBW, and that it may further act additively with the effects of air pollution on TLBW. To our knowledge this is the first study to explore the association of $PM_{2.5}$ on TLBW within the context of the food environment; as such it requires further investigation to replicate our finding. If this finding is borne out in other research, it also implies that health studies investigating environmental exposure associations birth weight should account for maternal nutritional status. Furthermore, since the area-level factors analyzed in our study exhibit clustering that occurs with a distinct spatial pattern, it implies strong geographic disparities in exposure to these adverse neighborhood conditions.

Strengths and limitations

There are several important limitations to our study however. Firstly, our study is cross-sectional and observational and therefore no causal links may be inferred. While few studies have addressed our main and novel secondary research questions, longitudinal research better served toward establishing a causal link is needed. Importantly our study is unable to directly link mRFEI scores with food purchasing and dietary intake behaviors among individuals in our study population; hence our study is purely ecological in this respect. Nor were we able obtain information on maternal smoking, which is a limitation of our study. Another important limitation is in regards to exposure misclassification as it relates to our estimates of exposure to $PM_{2.5}$ and area-level NDVI. For instance, we assumed that residential address at the time of delivery--used for exposure assignments-- is the same address for the entirety of the pregnancy, which may not be accurate. Also, we assumed that average census block group NDVI values properly characterizes area-level exposure to greenness, which may or may not be the case (Kihal-Talantikite et al., 2013; Markevych et al., 2014). Finally, the use of an index, which incorporates multiple dimensions of the food environment, is also limiting since it may obscure

which specific aspects of less healthy food environments (i.e. fast food versus convenience stores) are contributing to our findings. While each of these limitations do not necessarily invalidate our study findings, it implies that our results should be interpreted with caution.

A major strength of our study is the large sample size from which to assess the relationship between the food environment and TLBW. We were also able to control for a number of individual-level and area-level covariates that may confound our main research question. Another important strength of our study relates to assessing whether the relationship between a ubiquitous air pollutant ($PM_{2.5}$) and TLBW is modified by the neighborhood food environment. Another important strength of this study lies in using a multilevel modeling approach such that we were able to account for some degree of residual confounding related to unobserved spatial processes. Moreover, our study used a novel clustering approach in a multilevel modeling framework to successfully identify sub-regions of LA County most adversely affected by a combination of poor food environments, low greenness, and low SES.

Conclusion

Our analysis of LA birth data suggests women residing in neighborhoods with better food environments are associated with lower odds of TLBW. Our analysis further shows that the food environment attenuates the positive association between $PM_{2.5}$ and TLBW. Since our findings are strictly observational and restricted to LA County, further research into the relationship between the neighborhood food environment and birth outcomes is warranted, including research that discerns the mechanisms by which the food environment may influence pre-pregnancy and prenatal maternal diet.

Acknowledgments

We would like to acknowledge work performed by Beate Ritz and Jo Kay Ghosh to collect birth records data as well as work performed by Michael Jerret and Bernie Beckerman to develop $PM_{2.5}$ estimates used in this study.

Table 4.1. Individual Characteristics overall and stratified by TLBW cases and non-cases (N=344,244).

Individual-level Parameter	Overall (N=344,244) N	Overall (N=344,244) % or mean (SD)	TLBW Cases (N=7,340, 2.13%) n	TLBW Cases (N=7,340, 2.13%) % or mean (SD)	Non Cases (N=336,904, 97.87%) N	Non Cases (N=336,904, 97.87%) % or mean (SD)
Gestational Age (days)		277.94 (9.99)		273.62 (10.49)		278.04 (9.95)
mRFEI[a]		11.05 (6.91)		10.66 (6.75)		11.06 (6.91)
Sex of Infant						
Male	174535	51%	3170	43%	171365	51%
Female	169709	49%	4170	57%	165539	49%
Maternal Age (years)						
<20 years	32660	9%	968	13%	31692	9%
20 - 24	76033	22%	7809	25%	74224	22%
25 - 29	89776	26%	1771	24%	88008	26%
30 - 34	85576	24%	1552	21%	84024	25%
≥35	60199	17%	1240	17%	58959	18%
Race-Ethnicity						
Non Hispanic White	60843	18%	881	12%	59962	18%
Hispanic	216332	63%	4494	61%	211838	63%
Non Hispanic Black	24989	7%	985	13%	24004	7%
Non Hispanic Asian	26767	8%	566	8%	26201	8%
Other	15313	4%	414	6%	14899	4%
Maternal Education						
0-8 years	42154	12%	956	13%	41198	12%
9-12 years	164393	48%	3835	52%	160558	48%
13-15 years	61425	18%	1212	17%	60213	18%
≥16 years	76272	22%	1337	18%	74935	22%
Parity[b]						
Nulliparous	135723	39%	3570	39%	132153	49%
Multiparous	208521	61%	3770	51%	204751	61%
Prenatal Care Visits[c]		12.95 (3.76)		12.61 (4.33)		12.96 (3.74)
$PM_{2.5}$ ($\mu g/m^3$)		17.07 (2.14)		17.14 (2.05)		17.07 (2.14)

[a]mRFEI stands for modified retail food environment index

[b]Parity refers to whether or not the mother has had a previous live birth. Nulliparous and Multiparous refer to no previous births and at least one previous birth, respectively.

[c]Prenatal care visits refers to the number of prenatal care visits attended by the mother throughout the course of the pregnancy.

Table 4.2. Means and standard deviations for area-level variables overall and among TLBW cases and non-cases (N=344,244).

Area-level Parameters	Overall	TLBW Cases	Non Cases
	mean (SD)	**mean (SD)**	**mean (SD)**
mRFEI[a]	11.05 (6.91)	10.66 (6.75)	11.06 (6.91)
NDVI[b]	106.31 (21.17)	104.45 (20.59)	106.35 (21.18)
Median Income ($)	41,628 (20,012)	39,167 (18,673)	41,682 (20,037)

[a]mRFEI, modified retail food environment index; Interquartile Range (IQR) for mRFEI is 7.62.
[b]NDVI, normalized differential vegetation index.

Table 4.3. Food environment scores, PM2.5, NDVI, and Income by maternal race/ethnicity

Race/Ethnicity	**mRFEI (95%CI)**	**PM2.5 - µg/m^3 (95%CI)**	**NDVI (95%CI)**	**Income - $ (95%CI)**
nonHispanic Black	9.91 (9.81, 10.00)*	16.84 (16.81, 16.86)*	103.6 (103.4, 103.8)*	36131 (35933, 36328)*
Hispanic	10.87 (10.84, 10.90)*	17.336 (17.28, 17.344)*	102.8 (102.8, 102.9)*	35880 (35821, 35939)*
nonHispanic White (reference)	11.65 (11.59, 11.71)	16.26 (16.23, 16.28)	117.1 (116.9, 117.3)	59126 (58918, 59334)
nonHispanic Asian	11.74 (11.66, 11.82)	17.08 (17.06, 17.11)*	112.0 (111.7, 112.3)*	50268 (49998, 50538)*
Other (nonHispanic)	11.87 (11.75, 11.98)*	16.82 (16.79, 16.86)*	107.1 (106.8, 107.5)*	47186 (46896, 47478)*

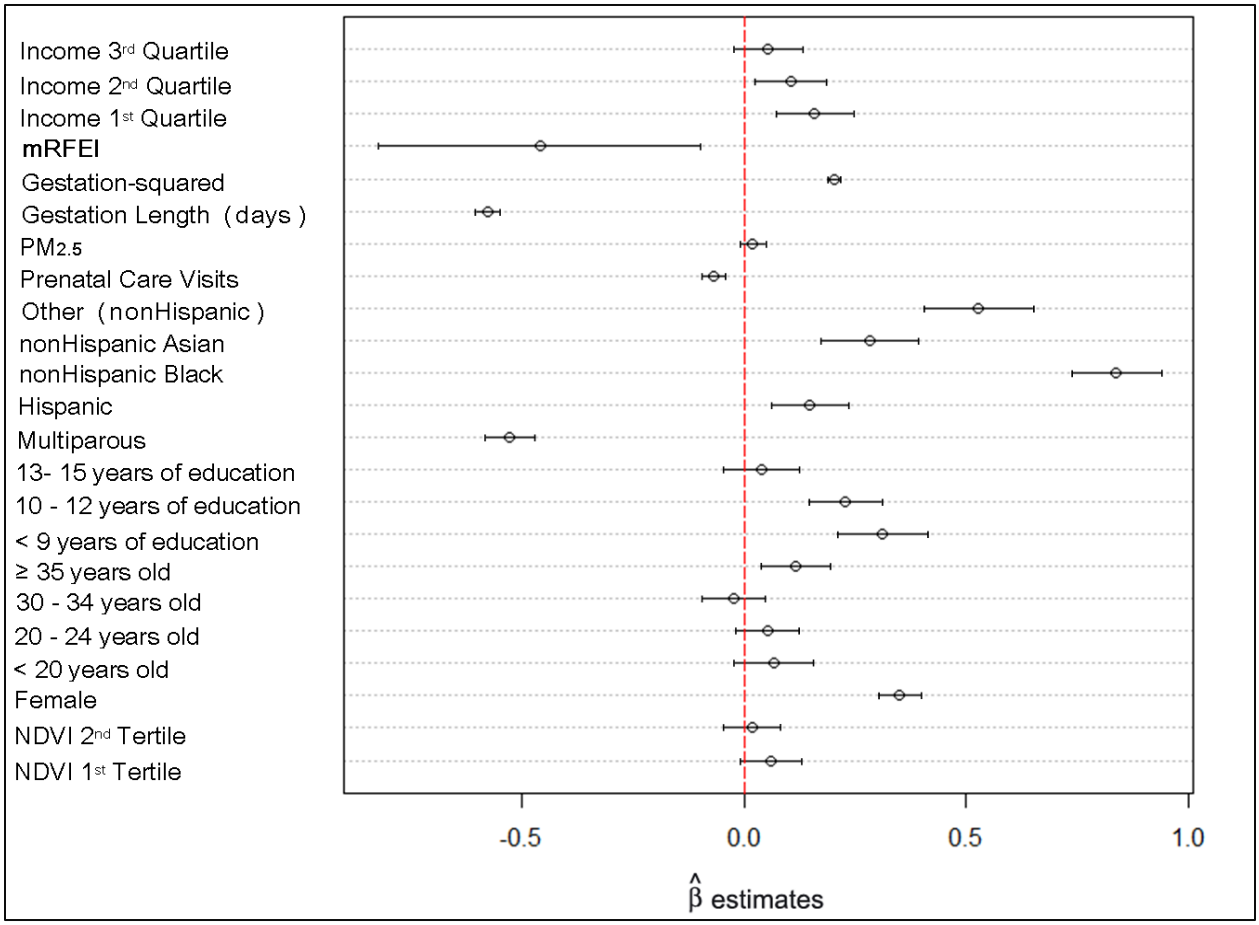


Figure 4.1. Adjusted coefficient estimates (± 95% credible intervals) of every covariate from the multivariate Model 1. For NDVI the reference group is the third quartile (or highest tertile). For sex the reference group is male. For maternal age the reference group is 25-29 years old. For education the reference group is ≥ 16 years of education. For parity the reference group is Nulliparous. For race and ethnicity the reference group is nonHispanic White. Income the reference group is the 4th quartile (or highest quartile). Continuous covariates were analyzed in their standardized forms.

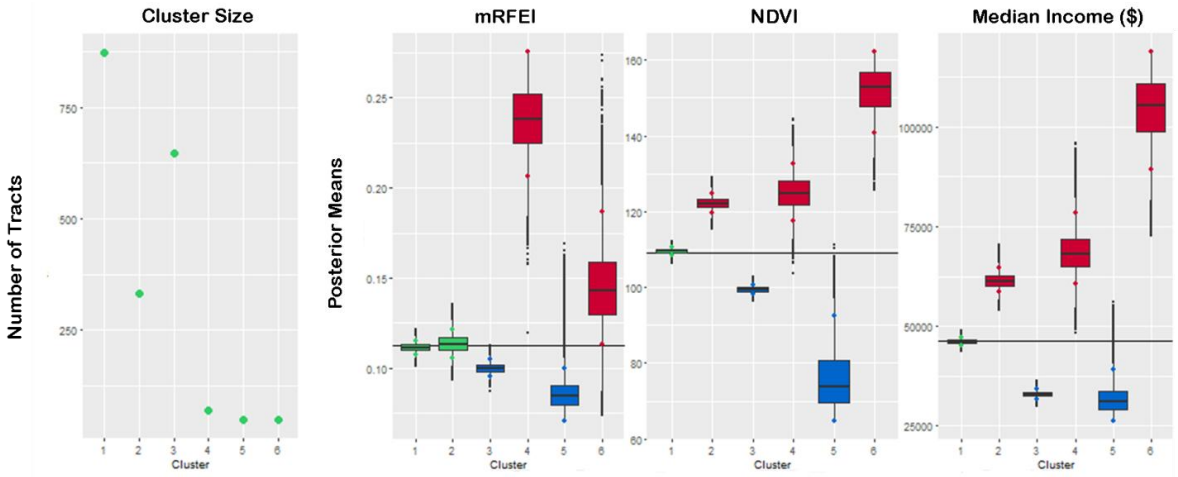


Figure 4.2. Posterior means of mRFEI, NDVI, median income, and number of census tracts for each profile cluster.

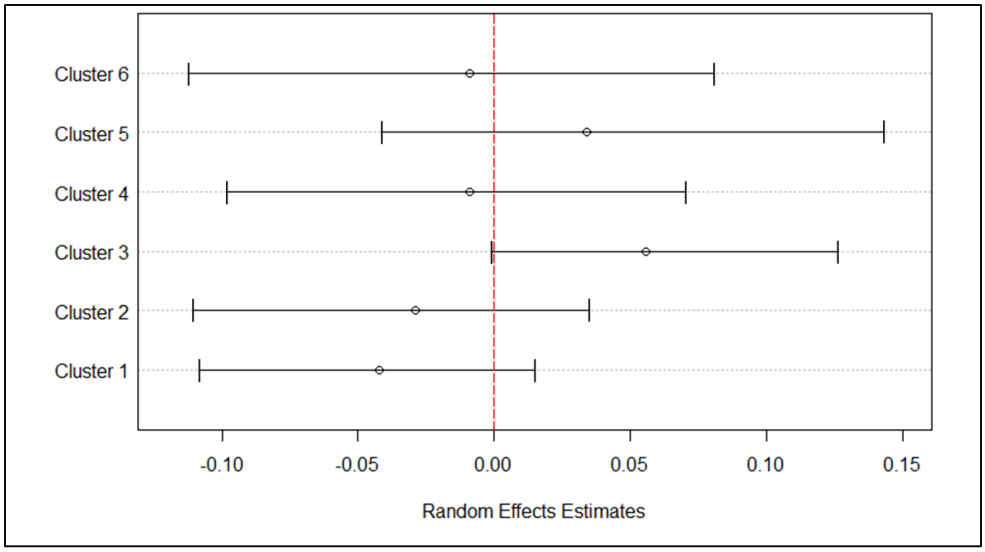


Figure 4.3. Random effects estimates (± 95% credible intervals) for profile clusters (clusters 1-6). The mean effect estimate (represented by the circles) represents the deviation in the log odds of TLBW away from the baseline log odds of TLBW.

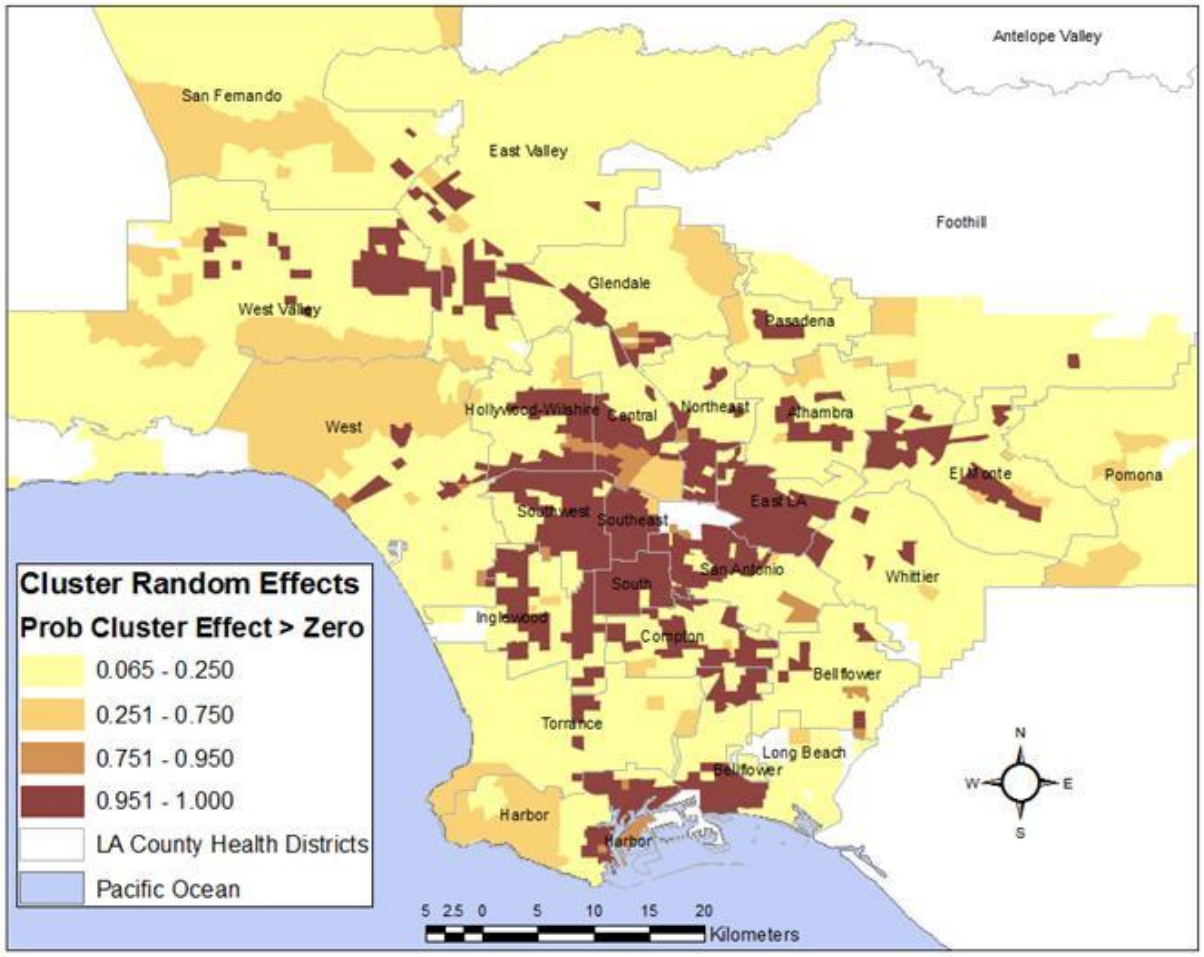


Figure 4.4. Spatial distribution of pollutant profile cluster random effect posterior probabilities.

CHAPTER 5 - SUMMARY AND CONCLUSIONS

Given the vast array of urban neighborhoods with differing characteristics in terms of environmental quality, built environments, demographics, and SES, it is believed that the role of place and its inherent cumulative exposures burden is an important determinant of health disparities. TLBW represent an important health disparity in the U.S. and the neighborhood factors mentioned above have each been associated with the risk of TLBW in previous studies. This dissertation research examines the odds of TLBW using a multilevel and joint exposures framework, and thus goes beyond previous studies that tend to isolate a single exposure or neighborhood characteristic in relation to TLBW. A multilevel and joint exposures frame is likely to reveal the complex nature of disparities of TLBW and disparities in environmental exposures across geographic, SES and racial lines.

The first manuscript used a multilevel Bayesian modeling framework to observe an overall and spatially varying exposure response between $PM_{2.5}$ and TLBW after controlling for individual-level risk factors. In other words, elevated exposure to $PM_{2.5}$ (at the individual-level) showed differing associations in terms of the magnitude and direction of $PM_{2.5}$ effect estimates, dependent upon the census tract and adjacent census tracts where mothers resided. An important aspect of this study, from a population health standpoint, is the mapping of spatially varying effects to help reveal the effect hotspots. Conveying this information to community and governmental stakeholders regarding effect hotspots could help focus air pollution exposure efforts intended to protect against adverse birth outcomes. An important implication from this first study is that latent spatial processes may be interacting with the association between $PM_{2.5}$ on TLBW. Given the spatial dependency of $PM_{2.5}$ composition and emissions sources, in addition to other air pollutants in urban environs, it is plausible that part of the unobserved

spatial processes involved with spatially varying effects are explained by unobserved localized pollutant mixtures (or pollutant exposure profiles). Furthermore, since local multipollutant exposures are likely to correlate spatially with other neighborhood-level stressors, it is also plausible that such neighborhood stressors and adverse built environments play a role in determining these spatially varying effects. For instance, a recent study by Li et al., (2016) found that the spatial variability in air pollution effects in LA County are influenced by census tract-level factors including distance to highways, socioeconomic status, greenness, racial-ethnic composition, and other land use factors. Finally, since this first study suggests strong geographic disparities in $PM_{2.5}$ associations with TLBW, it also implies that population-level TLBW disparities that fall along racial and SES lines may be partially explained by such spatially varying effects. Therefore more research is critically needed to investigate the degree to which spatially varying pollutant effects impact health disparities in the U.S.

The next study employed a Bayesian profile regression technique to identify multipollutant exposure profiles and further observed that multipollutant profiles with high exposure to $PM_{2.5}$, NO_2, and NO are associated with a higher log odds of TLBW. This study also reveals that the high exposure multipollutant profiles that most resembled primary traffic-related $PM_{2.5}$ mixtures were the only high exposure profiles associated with significantly higher odds of TLBW. This second study thus supports finding from the first study in two important ways. Firstly, the second study confirms that the air pollution association with TLBW is likely influenced by place. Secondly, this second study lends support to the concept that different types of $PM_{2.5}$ exposures may well impact the odds of TLBW, which can also be implied from the first study. Moreover, the spatial mapping of these results are consistent with the first study in that

LA County's urban core of central and south-central LA show some of the strongest effects in terms of associations between air pollution and TLBW.

This second study also incorporated contextual factors to examine joint exposure patterns to highly correlated neighborhood-level stressors and their association with the odds of TLBW. This approach reveals the profound role that contextual factors play in determining spatial patterns of TLBW across LA County. For instance, the multilevel analysis demonstrated that sub-regions that were predominantly Black or Hispanic populations and simultaneously exhibited some of the highest levels of older housing stock and lowest median incomes were also characterized by the largest deviations above the baseline log odds for having a TLBW infant. This approach also demonstrates the need to assess multiple dimensions of community-level disadvantage in order to help isolate multipollutant effects, particularly since multipollutant birth outcome effects are spatially dependent.

The primary finding from the third study is that a better neighborhood food environment is associated with a lower odds of TLBW. Since this study question is predicated on a neighborhood built environment indicator (e.g. the food environment), I also incorporated other data at the neighborhood-level, including NDVI (or area greenness) and SES (median income) to control for other contextual factors that may confound neighborhood-level relationships. Results from this study revealed that the exposure response relationship between $PM_{2.5}$ on TLBW was sensitive to adjustment for the food environment, thus suggesting that the food environment is important to consider when examining the association between $PM_{2.5}$ TLBW. Importantly, this third study failed to observe a spatially varying effect in the food environment, whereas the PM2.5 exposure response varied spatially. Because we found that the exposure response for the food environment on TLBW may be spatially uniform while simultaneously influencing the

exposure response of PM2.5 on TLBW, it further suggests that some of the spatially varying effects observed in the first study could potentially be influenced by the food environment. However, further study should explore this important hypothesis.

This final study also identified clustering of neighborhood level factors-- specifically mRFEI, NDVI, median household income-- and portrays the spatial patterning of these exposure profile clusters and their association with TLBW. Similar to study two, this approach reveals the importance of combined exposure to community-level stressors and elements of the built environment in terms of potentially shaping TLBW geographic disparities. Furthermore, much of these community level-stressors and built environment factors represent modifiable conditions that may be amenable to public health interventions that work at a more structural level, as opposed to public health interventions that strictly focus only on individual-level interventions. For instance, combing built environment interventions with individual-level interventions that focus on improving both area-level greenness and food environments and nutrition education may well be needed in low income communities in order to have a positive impact on reducing TLBW disparities. Additionally, given that $PM_{2.5}$ effects on term birth weight may be sensitive place-based factors such as greenness (Li et al., 2016) and the food environment, improvements in air quality may be more likely to net a public health benefit if more structural neighborhood-level interventions are pursued in concert.

Finally, our results support other studies to show that elevated exposure to outdoor air pollution during pregnancy is related to an increase in the odds of TLBW. Our research goes beyond previous study findings, however, in that we learned that air pollutant effects may vary spatially, and that joint exposure to multiple pollutants is likely to play an important role in determining TLBW pollutant risks. Our results also show that the neighborhood food

environment is associated with TLBW, which may represent an important built environment factor for which to target public health intervention in order to reduce disparities in TLBW. One of the more profound conclusions to draw from our study is that adverse environmental and contextual factors tend to cluster together and take on strong spatial characteristics that are likely to drive population health disparities related to SES and race and ethnicity. This last point drives home the larger notion that multilevel joint assessment of risk along with spatial patterning of risk is paramount for future environmental health studies; particularly research that targets vulnerable populations and exposures amenable to public health intervention across multiple levels.

Bibliography

Abubaker, M., Ashour, W., 2013. Efficient Data Clustering Algorithms: Improvements over Kmeans. Int. J. Intell. Syst. Appl. 5, 37–49. doi:10.5815/ijisa.2013.03.04

Abu-Saad, K., Fraser, D., 2010. Maternal Nutrition and Birth Outcomes. Epidemiol. Rev. 32, 5–25. doi:10.1093/epirev/mxq001

Adamson, I.Y., Prieditis, H., Hedgecock, C., Vincent, R., 2000. Zinc is the toxic factor in the lung response to an atmospheric particulate sample. Toxicol. Appl. Pharmacol. 166, 111–119. doi:10.1006/taap.2000.8955

Ambrose, J.A., Barua, R.S., 2004. The pathophysiology of cigarette smoking and cardiovascular disease: an update. J. Am. Coll. Cardiol. 43, 1731–1737. doi:10.1016/j.jacc.2003.12.047

Amegah, A.K., Damptey, O.K., Sarpong, G.A., Duah, E., Vervoorn, D.J., Jaakkola, J.J.K., 2013.

Malaria Infection, Poor Nutrition and Indoor Air Pollution Mediate Socioeconomic Differences in Adverse Pregnancy Outcomes in Cape Coast, Ghana. PLoS ONE 8, e69181. doi:10.1371/journal.pone.0069181

Ames, B.N., 1999. Micronutrient deficiencies. A major cause of DNA damage. Ann. N. Y. Acad. Sci. 889, 87–106.

Auchincloss, A.H., 2009. Neighborhood Resources for Physical Activity and Healthy Foods and Incidence of Type 2 Diabetes Mellitus: The Multi-Ethnic Study of Atherosclerosis. Arch. Intern. Med. 169, 1698. doi:10.1001/archinternmed.2009.302

Auchincloss, A.H., Diez Roux, A.V., Brown, D.G., Erdmann, C.A., Bertoni, A.G., 2008. Neighborhood resources for physical activity and healthy foods and their association with insulin resistance. Epidemiol. Camb. Mass 19, 146–157. doi:10.1097/EDE.0b013e31815c480

Auchincloss, A.H., Mujahid, M.S., Shen, M., Michos, E.D., Whitt-Glover, M.C., Diez Roux, A.V., 2013. Neighborhood health-promoting resources and obesity risk (the multi-ethnic study of atherosclerosis). Obes. Silver Spring Md 21, 621–628. doi:10.1038/oby.2012.91

Austin, E., Coull, B.A., Zanobetti, A., Koutrakis, P., 2013. A framework to spatially cluster air pollution monitoring sites in US based on the PM2.5 composition. Environ. Int. 59, 244–254. doi:10.1016/j.envint.2013.06.003

Austin, E., Coull, B., Thomas, D., Koutrakis, P., 2012a. A framework for identifying distinct multipollutant profiles in air pollution data. Environ. Int. 45, 112–121. doi:10.1016/j.envint.2012.04.003

Austin, E., Coull, B., Thomas, D., Koutrakis, P., 2012b. A framework for identifying distinct multipollutant profiles in air pollution data. Environ. Int. 45, 112–121. doi:10.1016/j.envint.2012.04.003

Babey, S.H., Wolstein, J., Diamant, A.L., 2011. Food environments near home and school related to consumption of soda and fast food. Policy Brief UCLA Cent. Health Policy Res. 1–8.

Banerjee, S., Carlin, B.P., Gelfand, A.E., 2004. Hierarchical Modeling and Analysis for Spatial Data. Chapman & Hall / CRC, Boco Raton, Florida.

Bantje, H., 1983. Seasonal variations in birthweight distribution in Ikwiriri village, Tanzania. J. Trop. Pediatr. 29, 50–54.

Barker, D.J., 1995. The fetal and infant origins of disease. Eur. J. Clin. Invest. 25, 457–463.

Barker, D.J.P., Eriksson, J.G., Forsén, T., Osmond, C., 2002. Fetal origins of adult disease: strength of effects and biological basis. Int. J. Epidemiol. 31, 1235–1239.

Basu, R., Harris, M., Sie, L., Malig, B., Broadwin, R., Green, R., 2013. Effects of fine particulate matter and its constituents on low birth weight among full-term infants in California. Environ. Res. doi:10.1016/j.envres.2013.10.008

Bates, C.J., Prentice, A.M., Paul, A.A., 1994. Seasonal variations in vitamins A, C, riboflavin and folate intakes and status of pregnant and lactating women in a rural Gambian community: some possible implications. Eur. J. Clin. Nutr. 48, 660–668.

Baxter, L.K., Clougherty, J.E., Laden, F., Levy, J.I., 2007. Predictors of concentrations of

nitrogen dioxide, fine particulate matter, and particle constituents inside of lower socioeconomic status urban homes. J. Expo. Sci. Environ. Epidemiol. 17, 433–444. doi:10.1038/sj.jes.7500532

Beckerman, B.S., Jerrett, M., Martin, R.V., van Donkelaar, A., Ross, Z., Burnett, R.T., 2013a. Application of the deletion/substitution/addition algorithm to selecting land use regression models for interpolating air pollution measurements in California. Atmos. Environ. 77, 172–177. doi:10.1016/j.atmosenv.2013.04.024

Beckerman, B.S., Jerrett, M., Serre, M., Martin, R.V., Lee, S.-J., van Donkelaar, A., Ross, Z., Su, J., Burnett, R.T., 2013b. A Hybrid Approach to Estimating National Scale Spatiotemporal Variability of $PM_{2.5}$ in the Contiguous United States. Environ. Sci. Technol. 130617085617008. doi:10.1021/es400039u

Belkacemi, L., Nelson, D.M., Desai, M., Ross, M.G., 2010. Maternal undernutrition influences placental-fetal development. Biol. Reprod. 83, 325–331. doi:10.1095/biolreprod.110.084517

Bellavia, A., Urch, B., Speck, M., Brook, R.D., Scott, J.A., Albetti, B., Behbod, B., North, M., Valeri, L., Bertazzi, P.A., Silverman, F., Gold, D., Baccarelli, A.A., 2013. DNA hypomethylation, ambient particulate matter, and increased blood pressure: findings from controlled human exposure experiments. J. Am. Heart Assoc. 2, e000212. doi:10.1161/JAHA.113.000212

Bell, M.L., Belanger, K., Ebisu, K., Gent, J.F., Leaderer, B.P., 2012. Relationship between birth weight and exposure to airborne fine particulate potassium and titanium during gestation. Environ. Res. 117, 83–89. doi:10.1016/j.envres.2012.05.004

Bell, M.L., Belanger, K., Ebisu, K., Gent, J.F., Lee, H.J., Koutrakis, P., Leaderer, B.P., 2010. Prenatal Exposure to Fine Particulate Matter and Birth Weight: Variations by Particulate Constituents and Sources. Epidemiology 21, 884–891. doi:10.1097/EDE.0b013e3181f2f405

Bell, M.L., Ebisu, K., Peng, R.D., 2011. Community-level spatial heterogeneity of chemical constituent levels of fine particulates and implications for epidemiological research. J. Expo. Sci. Environ. Epidemiol. 21, 372–384. doi:10.1038/jes.2010.24

Bennett, A., Yukich, J., Miller, J.M., Vounatsou, P., Hamainza, B., Ingwe, M.M., Moonga, H.B., Kamuliwo, M., Keating, J., Smith, T.A., Steketee, R.W., Eisele, T.P., 2014. A methodological framework for the improved use of routine health system data to evaluate national malaria control programs: evidence from Zambia. Popul. Health Metr. 12. doi:10.1186/s12963-014-0030-0

Berrocal, V.J., Gelfand, A.E., Holland, D.M., Burke, J., Miranda, M.L., 2011. On the use of a PM2.5 exposure simulator to explain birthweight. Environmetrics 22, 553–571. doi:10.1002/env.1086

Besag, J., York, J.C., Molli'e, A., 1991. Bayesian Image Restoration, with Two Applications in Spatial Statitics (with discussion). Ann Stat Math 43, 1–59.

Bhagavathy, S., Sumathi, P., 2012. Evaluation of antigenotoxic effects of carotenoids from green algae Chlorococcum humicola using human lymphocytes. Asian Pac. J. Trop. Biomed. 2, 109–117. doi:10.1016/S2221-1691(11)60203-7

Billionnet, C., Sherrill, D., Annesi-Maesano, I., GERIE study, 2012. Estimating the health

effects of exposure to multi-pollutant mixture. Ann. Epidemiol. 22, 126–141. doi:10.1016/j.annepidem.2011.11.004

Bivand, R., Hauke, J., Kossowski, T., 2013. Computing the Jacobian in Gaussian Spatial Autoregressive Models: An Illustrated Comparison of Available Methods: Computing the Jacobian in Spatial Autoregressive Models. Geogr. Anal. 45, 150–179. doi:10.1111/gean.12008

Bivand, R., Piras, G., 2015. Comparing Implementations of Estimation Methods for Spatial Econometrics. J. Stat. Softw. 63.

Bivand, R.S., Pebesma, E., Gómez-Rubio, V., 2013. Applied spatial data analysis with R, 2. ed. ed, Use R! Springer, New York, NY.

Black, C., Moon, G., Baird, J., 2014. Dietary inequalities: What is the evidence for the effect of the neighbourhood food environment? Health Place 27C, 229–242. doi:10.1016/j.healthplace.2013.09.015

Block, J.P., Scribner, R.A., DeSalvo, K.B., 2004. Fast food, race/ethnicity, and income. Am. J. Prev. Med. 27, 211–217. doi:10.1016/j.amepre.2004.06.007

Bobak, M., 2000. Outdoor air pollution, low birth weight, and prematurity. Environ. Health Perspect. 108, 173–176.

Boehmer, T.K., Foster, S.L., Henry, J.R., Woghiren-Akinnifesi, E.L., Yip, F.Y., Centers for Disease Control and Prevention (CDC), 2013. Residential proximity to major highways - United States, 2010. Morb. Mortal. Wkly. Rep. Surveill. Summ. Wash. DC 2002 62 Suppl 3, 46–50.

Boehm Vock, L.F., Reich, B.J., Fuentes, M., Dominici, F., 2014. Spatial variable selection methods for investigating acute health effects of fine particulate matter components. Biometrics. doi:10.1111/biom.12254

Brauer, M., Hystad, P., Poplawski, K., 2011. Assessing the spatial representativeness of PM2.5 and O3 Measurements from the National Air Pollutant Surveillance System. Envrionment Canada.

Brauer, M., Lencar, C., Tamburic, L., Koehoorn, M., Demers, P., Karr, C., 2008. A Cohort Study of Traffic-Related Air Pollution Impacts on Birth Outcomes. Environ. Health Perspect. 116, 680–686. doi:10.1289/ehp.10952

Brauer, M., Tamburic, L., 2009. Multi-Pollutant Analysis of Reproductive Outcomes and Air Pollution Using the CMAQ Model: Epidemiology 20, S72–S73. doi:10.1097/01.ede.0000362926.16562.96

Broady, K.E., Meeks, A.G., 2014. Obesity and Social Inequality in America. Rev. Black Polit. Econ. doi:10.1007/s12114-014-9202-1

Brook, R.D., Brook, J.R., Rajagopalan, S., 2003. Air pollution: the “Heart” of the problem. Curr. Hypertens. Rep. 5, 32–39.

Brook, R.D., Brook, J.R., Urch, B., Vincent, R., Rajagopalan, S., Silverman, F., 2002. Inhalation of fine particulate air pollution and ozone causes acute arterial vasoconstriction in healthy adults. Circulation 105, 1534–1536.

Brook, R.D., Franklin, B., Cascio, W., Hong, Y., Howard, G., Lipsett, M., Luepker, R.,

Mittleman, M., Samet, J., Smith, S.C.J., Tager, I., Expert Panel on Population and Prevention Science of the American Heart Association, 2004. Air pollution and cardiovascular disease: a statement for healthcare professionals from the Expert Panel on Population and Prevention Science of the American Heart Association. Circulation 109, 2655–2671. doi:10.1161/01.CIR.0000128587.30041.C8

Brown, D.R., Brewster, L.G., 2015. The food environment is a complex social network. Soc. Sci. Med. 133, 202–204. doi:10.1016/j.socscimed.2015.03.058

Buescher, P.A., Larson, L.C., Nelson, M.D.J., Lenihan, A.J., 1993. Prenatal WIC participation can reduce low birth weight and newborn medical costs: a cost-benefit analysis of WIC participation in North Carolina. J. Am. Diet. Assoc. 93, 163–166.

Buonocore, J.J., Lee, H.J., Levy, J.I., 2009. The Influence of Traffic on Air Quality in an Urban Neighborhood: A Community–University Partnership. Am. J. Public Health 99, S629–S635. doi:10.2105/AJPH.2008.149138

Burgos, S., Ruiz, P., Koifman, R., 2013. Changes to indoor air quality as a result of relocating families from slums to public housing. Atmos. Environ. 70, 179–185. doi:10.1016/j.atmosenv.2012.12.044

Cannuscio, C.C., Hillier, A., Karpyn, A., Glanz, K., 2014. The social dynamics of healthy food shopping and store choice in an urban environment. Soc. Sci. Med. 1982 122, 13–20. doi:10.1016/j.socscimed.2014.10.005

Carrott, M.L., DiMiceli, C.M., Sohlberg, R.A., Townshed, J.R.G., 2005. 250m MODIS

Normalized Difference Vegetation Index, US.Albers.2005001.ndvi - US.Albers.2005353.ndvi, Collection 4. University of Maryland, College Park, MD.

Caspi, C.E., Sorensen, G., Subramanian, S.V., Kawachi, I., 2012. The local food environment and diet: A systematic review. Health Place 18, 1172–1187. doi:10.1016/j.healthplace.2012.05.006

Castelló, A., Río, I., García-Pérez, J., Fernández-Navarro, P., Waller, L.A., Clennon, J.A., Bolúmar, F., López-Abente, G., 2013. Adverse birth outcomes in the vicinity of industrial installations in Spain 2004–2008. Environ. Sci. Pollut. Res. 20, 4933–4946. doi:10.1007/s11356-012-1444-5

CDC, 2011. Children's Food Environment State Indicator Report, 2011. Center for Disease Control and Prevention.

Centers for Disease Control and Prevention, 2011. CDC Health Disparities and Inequalities Report — United States, 2011. MMWR 60, 1–116.

Chakraborty, J., 2012. Cancer risk from exposure to hazardous air pollutants: spatial and social inequities in Tampa Bay, Florida. Int. J. Environ. Health Res. 22, 165–183. doi:10.1080/09603123.2011.628643

Choi, J., Fuentes, M., Reich, B.J., 2009. Spatial–temporal association between fine particulate matter and daily mortality. Comput. Stat. Data Anal. 53, 2989–3000. doi:10.1016/j.csda.2008.05.018

Choi, W., Hu, S., He, M., Kozawa, K., Mara, S., Winer, A.M., Paulson, S.E., 2013.

Neighborhood-scale air quality impacts of emissions from motor vehicles and aircraft. Atmos. Environ. 80, 310–321. doi:10.1016/j.atmosenv.2013.07.043

Cho, S.-H., Tong, H., McGee, J., Baldauf, R., Krantz, Q., Gilmour, M., 2009. Comparative Toxicity of Size-Fractionated Airborne Particulate Matter Collected at Different Distances from an Urban Highway. Environ. Health Perspect. doi:10.1289/ehp.0900730

Clougherty, J.E., Houseman, E.A., Levy, J.I., 2011. Source apportionment of indoor residential fine particulate matter using land use regression and constrained factor analysis: Indoor-source apportionment using LUR and factor analysis. Indoor Air 21, 53–66. doi:10.1111/j.1600-0668.2010.00682.x

Clyde, M., 2000. Model uncertainty and health effect studies for particulate matter. Environmetrics 11, 745–763. doi:10.1002/1099-095X(200011/12)11:6<745::AID-ENV431>3.0.CO;2-N

Clyde, M., DeSimone-Sasinowska, H., 1998. Accounting for model uncertainty in Poisson regression models: particulate matter and mortality in Birmingham, Alabama. Institute of Statistics and Decisions Sciences, Duke University.

Clyde, M., Guttorp, P., Sullivan, E., 2000. Effects Of Ambient Fine And Coarse Particles On Mortality In Phoenix, Arizona. Institute of Statistics and Decision Sciences, Duke University.

Cogswell, M.E., Parvanta, I., Ickes, L., Yip, R., Brittenham, G.M., 2003. Iron supplementation during pregnancy, anemia, and birth weight: a randomized controlled trial. Am. J. Clin. Nutr. 78, 773–781.

Coker, E., Ghosh, J., Jerrett, M., Gomez-Rubio, V., Beckerman, B., Cockburn, M., Liverani, S., Su, J., Li, A., Kile, M.L., Ritz, B., Molitor, J., 2015. Modeling spatial effects of PM2.5 on term low birth weight in Los Angeles County. Environ. Res. 142, 354–364. doi:10.1016/j.envres.2015.06.044

Cummins, S.C.J., McKay, L., MacIntyre, S., 2005. McDonald's restaurants and neighborhood deprivation in Scotland and England. Am. J. Prev. Med. 29, 308–310. doi:10.1016/j.amepre.2005.06.011

Currie, J., Rajani, I., 2014. Within-Mother Estimates of the Effects of WIC on Birth Outcomes in New York City. Natl. Bur. Econ. Res. Working Paper No. 20400.

Dadvand, P., Ostro, B., Figueras, F., Foraster, M., Basagaña, X., Valentín, A., Martinez, D., Beelen, R., Cirach, M., Hoek, G., Jerrett, M., Brunekreef, B., Nieuwenhuijsen, M.J., 2014. Residential Proximity to Major Roads and Term Low Birth Weight: The Roles of Air Pollution, Heat, Noise, and Road-Adjacent Trees. Epidemiology 25, 518–525. doi:10.1097/EDE.0000000000000107

Dadvand, P., Parker, J., Bell, M.L., Bonzini, M., Brauer, M., Darrow, L.A., Gehring, U., Glinianaia, S.V., Gouveia, N., Ha, E., Leem, J.H., van den Hooven, E.H., Jalaludin, B., Jesdale, B.M., Lepeule, J., Morello-Frosch, R., Morgan, G.G., Pesatori, A.C., Pierik, F.H., Pless-Mulloli, T., Rich, D.Q., Sathyanarayana, S., Seo, J., Slama, R., Strickland, M., Tamburic, L., Wartenberg, D., Nieuwenhuijsen, M.J., Woodruff, T.J., 2013. Maternal Exposure to Particulate Air Pollution and Term Birth Weight: A Multi-Country Evaluation of Effect and Heterogeneity. Environ. Health Perspect. 121, 267–373. doi:10.1289/ehp.1205575

Danaei, G., Vander Hoorn, S., Lopez, A.D., Murray, C.J., Ezzati, M., 2005. Causes of cancer in the world: comparative risk assessment of nine behavioural and environmental risk factors. The Lancet 366, 1784–1793. doi:10.1016/S0140-6736(05)67725-2

Debbink, M.P., Bader, M.D.M., 2011. Racial Residential Segregation and Low Birth Weight in Michigan's Metropolitan Areas. Am. J. Public Health 101, 1714–1720. doi:10.2105/AJPH.2011.300152

Delfino, R.J., Staimer, N., Tjoa, T., Gillen, D.L., Polidori, A., Arhami, M., Kleinman, M.T., Vaziri, N.D., Longhurst, J., Sioutas, C., 2009. Air Pollution Exposures and Circulating Biomarkers of Effect in a Susceptible Population: Clues to Potential Causal Component mixtures and mechanisms. Environ. Health Perspect. 117, 1232–1238. doi:10.1289/ehp.0800194

den Dekker, H.T., Sonnenschein-van der Voort, A.M.M., de Jongste, J.C., Anessi-Maesano, I., Arshad, S.H., Barros, H., Beardsmore, C.S., Bisgaard, H., Phar, S.C., Craig, L., Devereux, G., van der Ent, C.K., Esplugues, A., Fantini, M.P., Flexeder, C., Frey, U., Forastiere, F., Gehring, U., Gori, D., van der Gugten, A.C., Henderson, A.J., Heude, B., Ibarluzea, J., Inskip, H.M., Keil, T., Kogevinas, M., Kreiner-Møller, E., Kuehni, C.E., Lau, S., Mélen, E., Mommers, M., Morales, E., Penders, J., Pike, K.C., Porta, D., Reiss, I.K., Roberts, G., Schmidt, A., Schultz, E.S., Schulz, H., Sunyer, J., Torrent, M., Vassilaki, M., Wijga, A.H., Zabaleta, C., Jaddoe, V.W.V., Duijts, L., 2015. Early growth characteristics and the risk of reduced lung function and asthma: A meta-analysis of 25,000 children. J. Allergy Clin. Immunol. doi:10.1016/j.jaci.2015.08.050

Dionisio, K.L., Baxter, L.K., Chang, H.H., 2014. An Empirical Assessment of Exposure

Measurement Error and Effect Attenuation in Bipollutant Epidemiologic Models. Environ. Health Perspect. doi:10.1289/ehp.1307772

Dominguez, L.J., Martínez-González, M.A., Basterra-Gortari, F.J., Gea, A., Barbagallo, M., Bes-Rastrollo, M., 2014. Fast Food Consumption and Gestational Diabetes Incidence in the SUN Project. PLoS ONE 9, e106627. doi:10.1371/journal.pone.0106627

Dominici, F., Samet, J.M., Zeger, S., 2000. Combinine evidence on air pollution and daily mortality from the 20 largest us cities: a hierarchical modelling strategy. J. R. Stat. Soc., A (Statistics in Society) 163, 263–302.

Donaldson, K., MacNee, W., 2001. Potential mechanisms of adverse pulmonary and cardiovascular effects of particulate air pollution (PM10). Int. J. Hyg. Environ. Health 203, 411–415. doi:10.1078/1438-4639-00059

Dong, G.-H., Qian, Z.M., Liu, M.-M., Wang, D., Ren, W.-H., Flick, L.H., Fu, J., Wang, J., Chen, W., Simckes, M., Trevathan, E., 2014. Ambient air pollution and the prevalence of obesity in chinese children: The seven northeastern cities study: Air Pollution and Obesity. Obesity 22, 795–800. doi:10.1002/oby.20198

Dormann, C.F., Elith, J., Bacher, S., Buchmann, C., Carl, G., Carré, G., Marquéz, J.R.G., Gruber, B., Lafourcade, B., Leitão, P.J., Münkemüller, T., McClean, C., Osborne, P.E., Reineking, B., Schröder, B., Skidmore, A.K., Zurell, D., Lautenbach, S., 2013a. Collinearity: a review of methods to deal with it and a simulation study evaluating their performance. Ecography 36, 27–46. doi:10.1111/j.1600-0587.2012.07348.x

Dormann, C.F., Elith, J., Bacher, S., Buchmann, C., Carl, G., Carré, G., Marquéz, J.R.G., Gruber, B., Lafourcade, B., Leitão, P.J., Münkemüller, T., McClean, C., Osborne, P.E., Reineking, B., Schröder, B., Skidmore, A.K., Zurell, D., Lautenbach, S., 2013b. Collinearity: a review of methods to deal with it and a simulation study evaluating their performance. Ecography 36, 27–46. doi:10.1111/j.1600-0587.2012.07348.x

Drewnowski, A., Aggarwal, A., Hurvitz, P.M., Monsivais, P., Moudon, A.V., 2012. Obesity and Supermarket Access: Proximity or Price? Am. J. Public Health 102, e74–e80. doi:10.2105/AJPH.2012.300660

Drewnowski, A., Rehm, C.D., Arterburn, D., 2014. The geographic distribution of obesity by census tract among 59 767 insured adults in King County, WA. Int. J. Obes. 38, 833–839. doi:10.1038/ijo.2013.179

Drewnowski, A., Rehm, C.D., Moudon, A.V., Arterburn, D., 2014. The Geography of Diabetes by Census Tract in a Large Sample of Insured Adults in King County, Washington, 2005–2006. Prev. Chronic. Dis. 11. doi:10.5888/pcd11.140135

Dubowitz, T., Ghosh-Dastidar, M., Eibner, C., Slaughter, M.E., Fernandes, M., Whitsel, E.A., Bird, C.E., Jewell, A., Margolis, K.L., Li, W., Michael, Y.L., Shih, R.A., Manson, J.E., Escarce, J.J., 2012. The Women's Health Initiative: The Food Environment, Neighborhood Socioeconomic Status, BMI, and Blood Pressure. Obesity 20, 862–871. doi:10.1038/oby.2011.141

Dunn, R.A., 2010. The Effect of Fast-Food Availability on Obesity: An Analysis by Gender, Race, and Residential Location. Am. J. Agric. Econ. 92, 1149–1164. doi:10.1093/ajae/aaq041

Duvekot, J.J., Cheriex, E.C., Pieters, F.A., Peeters, L.L., 1995. Severely impaired fetal growth is preceded by maternal hemodynamic maladaptation in very early pregnancy. Acta Obstet. Gynecol. Scand. 74, 693–697.

Earnest, A., Morgan, G., Mengersen, K., Ryan, L., Summerhayes, R., Beard, J., 2007. Evaluating the effect of neighbourhood weight matrices on smoothing properties of Conditional Autoregressive (CAR) models. Int. J. Health Geogr. 6, 54. doi:10.1186/1476-072X-6-54

Ebisu, K., Bell, M.L., 2012a. Airborne PM2.5 chemical components and low birth weight in the northeastern and mid-Atlantic regions of the United States. Environ. Health Perspect. 120, 1746–1752. doi:10.1289/ehp.1104763

Ebisu, K., Bell, M.L., 2012b. Airborne PM_{2.5} Chemical Components and Low Birth Weight in the Northeastern and Mid-Atlantic Regions of the United States. Environ. Health Perspect. doi:10.1289/ehp.1104763

Elango, N., Kasi, V., Vembhu, B., Poornima, J.G., 2013. Chronic exposure to emissions from photocopiers in copy shops causes oxidative stress and systematic inflammation among photocopier operators in India. Environ. Health Glob. Access Sci. Source 12, 78. doi:10.1186/1476-069X-12-78

English, P.B., Kharrazi, M., Davies, S., Scalf, R., Waller, L., Neutra, R., 2003a. Changes in the spatial pattern of low birth weight in a southern California county: the role of individual and neighborhood level factors. Soc. Sci. Med. 56, 2073–2088. doi:10.1016/S0277-9536(02)00202-2

English, P.B., Kharrazi, M., Davies, S., Scalf, R., Waller, L., Neutra, R., 2003b. Changes in the

spatial pattern of low birth weight in a southern California county: the role of individual and neighborhood level factors. Soc. Sci. Med. 56, 2073–2088. doi:10.1016/S0277-9536(02)00202-2

Erickson, A.C., Arbour, L., 2014. The shared pathoetiological effects of particulate air pollution and the social environment on fetal-placental development. J. Environ. Public Health 2014, 901017. doi:10.1155/2014/901017

Everitt, B., Hothorn, T., 2010. A handbook of statistical analyses using R, 2nd ed. ed. CRC Press, Boca Raton.

Fang, H., Johnson, C., Stopp, C., Espy, K.A., 2011. A new look at quantifying tobacco exposure during pregnancy using fuzzy clustering. Neurotoxicol. Teratol. 33, 155–165. doi:10.1016/j.ntt.2010.08.003

Farley, T.A., Mason, K., Rice, J., Habel, J.D., Scribner, R., Cohen, D.A., 2006. The relationship between the neighbourhood environment and adverse birth outcomes. Paediatr. Perinat. Epidemiol. 20, 188–200. doi:10.1111/j.1365-3016.2006.00719.x

Ferguson, T., 1973. A Bayesian Analysis of Some Nonparametric Problems. Ann. Stat. 1, 209–230.

Fine, P.M., Sioutas, C., Solomon, P.A., 2008. Secondary Particulate Matter in the United States: Insights from the Particulate Matter Supersites Program and Related Studies. J. Air Waste Manag. Assoc. 58, 234–253. doi:10.3155/1047-3289.58.2.234

Fleischer, N.L., Merialdi, M., van Donkelaar, A., Vadillo-Ortega, F., Martin, R.V., Betran, A.P., Souza, J.P., O'Neill, M.S., 2014. Outdoor Air Pollution, Preterm Birth, and Low Birth Weight:

Analysis of the World Health Organization Global Survey on Maternal and Perinatal Health. Environ. Health Perspect. doi:10.1289/ehp.1306837

Foster, H.W., Wu, L., Bracken, M.B., Semenya, K., Thomas, J., Thomas, J., 2000. Intergenerational effects of high socioeconomic status on low birthweight and preterm birth in African Americans. J. Natl. Med. Assoc. 92, 213–221.

Franchini, M., Mannucci, P.M., 2012. Air pollution and cardiovascular disease. Thromb. Res. 129, 230–234. doi:10.1016/j.thromres.2011.10.030

Franco, M., Diez Roux, A.V., Glass, T.A., Caballero, B., Brancati, F.L., 2008. Neighborhood characteristics and availability of healthy foods in Baltimore. Am. J. Prev. Med. 35, 561–567. doi:10.1016/j.amepre.2008.07.003

Fuentes, M., Song, H.-R., Ghosh, S.K., Holland, D.M., Davis, J.M., 2006. Spatial association between speciated fine particles and mortality. Biometrics 62, 855–863. doi:10.1111/j.1541-0420.2006.00526.x

Fujita, E.M., Campbell, D.E., Zielinska, B., Arnott, W.P., Chow, J.C., 2011. Concentrations of air toxics in motor vehicle-dominated environments. Res. Rep. Health Eff. Inst. 3–77.

Fulford, A.J.C., Rayco-Solon, P., Prentice, A.M., 2006. Statistical modelling of the seasonality of preterm delivery and intrauterine growth restriction in rural Gambia. Paediatr. Perinat. Epidemiol. 20, 251–259. doi:10.1111/j.1365-3016.2006.00714.x

Geer, L.A., 2014. Identifying exposure disparities in air pollution epidemiology specific to adverse birth outcomes. Environ. Res. Lett. 9, 101001. doi:10.1088/1748-9326/9/10/101001

Geer, L.A., Weedon, J., Bell, M.L., 2012. Ambient air pollution and term birth weight in Texas from 1998 to 2004. J. Air Waste Manag. Assoc. 1995 62, 1285–1295.

Gelman, A., Hill, J., 2006a. Data Analysis Using Regression and Multilevel/Hierarchical Models, 1 edition. ed. Cambridge University Press, Cambridge ; New York.

Gelman, A., Hill, J., 2006b. Data Analysis Using Regression and Multilevel/Hierarchical Models. Cambridge University Press, Leiden.

Ghosh, J.K.C., Wilhelm, M.H., Dunkel-Schetter, C., Lombardi, C.A., Ritz, B.R., 2010a. Paternal support and preterm birth, and the moderation of effects of chronic stress: a study in Los Angeles County mothers. Arch. Womens Ment. Health 13, 327–338. doi:10.1007/s00737-009-0135-9

Ghosh, J.K.C., Wilhelm, M.H., Dunkel-Schetter, C., Lombardi, C.A., Ritz, B.R., 2010b. Paternal support and preterm birth, and the moderation of effects of chronic stress: a study in Los Angeles County mothers. Arch. Womens Ment. Health 13, 327–338. doi:10.1007/s00737-009-0135-9

Ghosh, J.K.C., Wilhelm, M., Ritz, B., 2013a. Effects of Residential Indoor Air Quality and Household Ventilation on Preterm Birth and Term Low Birth Weight in Los Angeles County, California. Am. J. Public Health 103, 686–694. doi:10.2105/AJPH.2012.300987

Ghosh, J.K.C., Wilhelm, M., Ritz, B., 2013b. Effects of Residential Indoor Air Quality and Household Ventilation on Preterm Birth and Term Low Birth Weight in Los Angeles County, California. Am. J. Public Health 103, 686–694. doi:10.2105/AJPH.2012.300987

Ghosh, J.K.C., Wilhelm, M., Su, J., Goldberg, D., Cockburn, M., Jerrett, M., Ritz, B., 2012a. Assessing the Influence of Traffic-related Air Pollution on Risk of Term Low Birth Weight on

the Basis of Land-Use-based Regression Models and Measures of Air Toxics. Am. J. Epidemiol. 175, 1262–1274. doi:10.1093/aje/kwr469

Ghosh, J.K.C., Wilhelm, M., Su, J., Goldberg, D., Cockburn, M., Jerrett, M., Ritz, B., 2012b. Assessing the Influence of Traffic-related Air Pollution on Risk of Term Low Birth Weight on the Basis of Land-Use-based Regression Models and Measures of Air Toxics. Am. J. Epidemiol. 175, 1262–1274. doi:10.1093/aje/kwr469

Ghosh, J.K.C., Wilhelm, M., Su, J., Goldberg, D., Cockburn, M., Jerrett, M., Ritz, B., 2012c. Assessing the Influence of Traffic-related Air Pollution on Risk of Term Low Birth Weight on the Basis of Land-Use-based Regression Models and Measures of Air Toxics. Am. J. Epidemiol. 175, 1262–1274. doi:10.1093/aje/kwr469

Ghosh, J., Mainigi, M., Coutifaris, C., Sapienza, C., 2016. Outlier DNA methylation levels as an indicator of environmental exposure and risk of undesirable birth outcome. Hum. Mol. Genet. 25, 123–129. doi:10.1093/hmg/ddv458

Gilbert, W.M., Nesbitt, T.S., Danielsen, B., 2003. The cost of prematurity: quantification by gestational age and birth weight. Obstet. Gynecol. 102, 488–492.

Gilks, W.R., Richardson, S., Spiegelhalter, D.J., 1998a. Markov chain Monte Carlo in practice. Chapman & Hall/CRC, Boca Raton, Fla.

Gilks, W.R., Richardson, S., Spiegelhalter, D.J. (Eds.), 1998b. Markov chain Monte Carlo in practice. Chapman & Hall, Boca Raton, Fla.

Giskes, K., van Lenthe, F., Avendano-Pabon, M., Brug, J., 2011. A systematic review of

environmental factors and obesogenic dietary intakes among adults: are we getting closer to understanding obesogenic environments?: Environmental factors and obesogenic dietary behaviours. Obes. Rev. 12, e95–e106. doi:10.1111/j.1467-789X.2010.00769.x

Goldberg, D.W., Wilson, J.P., Knoblock, C.A., Ritz, B., Cockburn, M.G., 2008. An effective and efficient approach for manually improving geocoded data. Int. J. Health Geogr. 7, 60. doi:10.1186/1476-072X-7-60

Gonzalez, C.A., Riboli, E., 2010. Diet and cancer prevention: Contributions from the European Prospective Investigation into Cancer and Nutrition (EPIC) study. Eur. J. Cancer 46, 2555–2562. doi:10.1016/j.ejca.2010.07.025

Gouveia, N., Bremner, S.A., Novaes, H.M.D., 2004. Association between ambient air pollution and birth weight in São Paulo, Brazil. J. Epidemiol. Community Health 58, 11–17.

Grady, S.C., 2011. Housing Quality and Racial Disparities in Low Birth Weight: A GIS Assessment, in: Maantay, J.A., McLafferty, S. (Eds.), Geospatial Analysis of Environmental Health. Springer Netherlands, Dordrecht, pp. 303–318.

Grady, S.C., 2006. Racial disparities in low birthweight and the contribution of residential segregation: a multilevel analysis. Soc. Sci. Med. 1982 63, 3013–3029. doi:10.1016/j.socscimed.2006.08.017

Gray, S.C., Edwards, S.E., Miranda, M.L., 2013. Race, socioeconomic status, and air pollution exposure in North Carolina. Environ. Res. 126, 152–158. doi:10.1016/j.envres.2013.06.005

Gray, S.C., Edwards, S.E., Schultz, B.D., Miranda, M.L., 2014. Assessing the impact of race,

social factors and air pollution on birth outcomes: a population-based study. Environ. Health Glob. Access Sci. Source 13, 4. doi:10.1186/1476-069X-13-4

Greco, S.L., Wilson, A.M., Spengler, J.D., Levy, J.I., 2007. Spatial patterns of mobile source particulate matter emissions-to-exposure relationships across the United States. Atmos. Environ. 41, 1011–1025. doi:10.1016/j.atmosenv.2006.09.025

Greer, S., Schieb, L., Schwartz, G., Onufrak, S., Park, S., 2014. Association of the Neighborhood Retail Food Environment with Sodium and Potassium Intake Among US Adults. Prev. Chronic. Dis. 11. doi:10.5888/pcd11.130340

Grilli, L., Metelli, S., Rampichini, C., 2014. Bayesian estimation with integrated nested Laplace approximation for binary logit mixed models. J. Stat. Comput. Simul. 1–9. doi:10.1080/00949655.2014.935377

Gu, J., Pitz, M., Breitner, S., Birmili, W., von Klot, S., Schneider, A., Soentgen, J., Reller, A., Peters, A., Cyrys, J., 2012. Selection of key ambient particulate variables for epidemiological studies — Applying cluster and heatmap analyses as tools for data reduction. Sci. Total Environ. 435-436, 541–550. doi:10.1016/j.scitotenv.2012.07.040

Hajat, A., Diez-Roux, A.V., Adar, S.D., Auchincloss, A.H., Lovasi, G.S., O'Neill, M.S., Sheppard, L., Kaufman, J.D., 2013. Air Pollution and Individual and Neighborhood Socioeconomic Status: Evidence from the Multi-Ethnic Study of Atherosclerosis (MESA). Environ. Health Perspect. doi:10.1289/ehp.1206337

Halford, J.C.., Gillespie, J., Brown, V., Pontin, E.E., Dovey, T.M., 2004. Effect of television

advertisements for foods on food consumption in children. Appetite 42, 221–225. doi:10.1016/j.appet.2003.11.006

Hampel, R., Peters, A., Beelen, R., Brunekreef, B., Cyrys, J., de Faire, U., de Hoogh, K., Fuks, K., Hoffmann, B., Hüls, A., Imboden, M., Jedynska, A., Kooter, I., Koenig, W., Künzli, N., Leander, K., Magnusson, P., Männistö, S., Penell, J., Pershagen, G., Phuleria, H., Probst-Hensch, N., Pundt, N., Schaffner, E., Schikowski, T., Sugiri, D., Tiittanen, P., Tsai, M.-Y., Wang, M., Wolf, K., Lanki, T., 2015. Long-term effects of elemental composition of particulate matter on inflammatory blood markers in European cohorts. Environ. Int. 82, 76–84. doi:10.1016/j.envint.2015.05.008

Hansen, C.S., Sheykhzade, M., Møller, P., Folkmann, J.K., Amtorp, O., Jonassen, T., Loft, S., 2007. Diesel exhaust particles induce endothelial dysfunction in apoE-/- mice. Toxicol. Appl. Pharmacol. 219, 24–32. doi:10.1016/j.taap.2006.10.032

Hao, Y., Strosnider, H., Balluz, L., Qualters, J.R., 2015. Geographic Variation in the Association between Ambient Fine Particulate Matter (PM2.5) and Term Low Birth Weight in the United States. Environ. Health Perspect. doi:10.1289/ehp.1408798

Harris, G., Thompson, W.D., Fitzgerald, E., Wartenberg, D., 2014. The association of PM(2.5) with full term low birth weight at different spatial scales. Environ. Res. 134, 427–434. doi:10.1016/j.envres.2014.05.034

Hartigan, J.A., Wong, J., 1979. A K-Means Clustering Algorithm. J. R. Stat. Soc., C 28, 100–108.

Hasheminassab, S., Daher, N., Saffari, A., Wang, D., Ostro, B.D., Sioutas, C., 2014. Spatial and temporal variability of sources of ambient fine particulate matter (PM_{2.5}) in California. Atmospheric Chem. Phys. 14, 12085–12097. doi:10.5194/acp-14-12085-2014

Hastie, D.I., Liverani, S., Azizi, L., Richardson, S., Stücker, I., 2013. A semi-parametric approach to estimate risk functions associated with multi-dimensional exposure profiles: application to smoking and lung cancer. BMC Med. Res. Methodol. 13, 129. doi:10.1186/1471-2288-13-129

Hattori, A., An, R., Sturm, R., 2013. Neighborhood Food Outlets, Diet, and Obesity Among California Adults, 2007 and 2009. Prev. Chronic. Dis. 10. doi:10.5888/pcd10.120123

Hennig, B., Ettinger, A.S., Jandacek, R.J., Koo, S., McClain, C., Seifried, H., Silverstone, A., Watkins, B., Suk, W.A., 2007a. Using nutrition for intervention and prevention against environmental chemical toxicity and associated diseases. Environ. Health Perspect. 115, 493–495. doi:10.1289/ehp.9549

Hennig, B., Oesterling, E., Toborek, M., 2007b. Environmental toxicity, nutrition, and gene interactions in the development of atherosclerosis. Nutr. Metab. Cardiovasc. Dis. NMCD 17, 162–169. doi:10.1016/j.numecd.2006.01.003

Hennig, B., Reiterer, G., Majkova, Z., Oesterling, E., Meerarani, P., Toborek, M., 2005. Modification of environmental toxicity by nutrients: implications in atherosclerosis. Cardiovasc. Toxicol. 5, 153–160.

Herman, D., Harrison, G., Afifi, A., Jenks, E., 2004. The Effect of the WIC Program on Food Security Status of Pregnant, First-Time Participants. Fam. Econ. Nutr. Rev. 16, 21.

Hernandez, L., Goodman, D., Sappenfield, W., Eibeck, D., Menges, J., 2010. Prenatal WIC Participation and The Effect On Effect on Gestational Weight Gain and Low Birth Weight Among Florida's Medicaid Population. Fla. Dep. Health Div. Fam. Health Serv. Off. Surveill. Eval. Epidemiol. 1–14.

Hidy, G., Brook, J., Demerjian, K., Molina, L., Pennell, W., Scheffe, R., 2011. Technical Challenges of Multipollutant Air Quality. Springer, Dordrecht Heidelberg London New York.

Hilmers, A., Hilmers, D.C., Dave, J., 2012. Neighborhood disparities in access to healthy foods and their effects on environmental justice. Am. J. Public Health 102, 1644–1654. doi:10.2105/AJPH.2012.300865

Holay, M.P., Paunikar, N.P., Joshi, P.P., Sahasrabhojney, V.S., Tankhiwale, S.R., 2004. Effect of passive smoking on endothelial function in: healthy adults. J. Assoc. Physicians India 52, 114–117.

Horner, M.W., Mefford, J.N., 2007. Investigating urban spatial mismatch using job – housing indicators to model home – work separation. Environ. Plan. A 39, 1420–1440. doi:10.1068/a37443

Houston, D., Li, W., Wu, J., 2014. Disparities in exposure to automobile and truck traffic and vehicle emissions near the Los Angeles-Long Beach port complex. Am. J. Public Health 104, 156–164. doi:10.2105/AJPH.2012.301120

Hsieh, S., Klassen, A.C., Curriero, F.C., Caulfield, L.E., Cheskin, L.J., Davis, J.N., Goran, M.I., Weigensberg, M.J., Spruijt-Metz, D., 2015. Built Environment Associations with Adiposity Parameters among Overweight and Obese Hispanic Youth. Prev. Med. Rep. 2, 406–412. doi:10.1016/j.pmedr.2015.05.005

Hurvitz, P.M., Moudon, A.V., Rehm, C.D., Streichert, L.C., Drewnowski, A., 2009a. Arterial roads and area socioeconomic status are predictors of fast food restaurant density in King County, WA. Int. J. Behav. Nutr. Phys. Act. 6, 46. doi:10.1186/1479-5868-6-46

Hurvitz, P.M., Moudon, A.V., Rehm, C.D., Streichert, L.C., Drewnowski, A., 2009b. Arterial roads and area socioeconomic status are predictors of fast food restaurant density in King County, WA. Int. J. Behav. Nutr. Phys. Act. 6, 46. doi:10.1186/1479-5868-6-46

Hu, S., Paulson, S.E., Fruin, S., Kozawa, K., Mara, S., Winer, A.M., 2012. Observation of elevated air pollutant concentrations in a residential neighborhood of Los Angeles California using a mobile platform. Atmos. Environ. 51, 311–319. doi:10.1016/j.atmosenv.2011.12.055

Hyder, A., Lee, H.J., Ebisu, K., Koutrakis, P., Belanger, K., Bell, M.L., 2014. PM2.5 Exposure and Birth Outcomes: Use of Satellite- and Monitor-Based Data. Epidemiology 25, 58–67. doi:10.1097/EDE.0000000000000027

Hystad, P., Davies, H.W., Frank, L., Van Loon, J., Gehring, U., Tamburic, L., Brauer, M., 2014a. Residential Greenness and Birth Outcomes: Evaluating the Influence of Spatially Correlated Built-Environment Factors. Environ. Health Perspect. doi:10.1289/ehp.1308049

Hystad, P., Davies, H.W., Frank, L., Van Loon, J., Gehring, U., Tamburic, L., Brauer, M.,

2014b. Residential Greenness and Birth Outcomes: Evaluating the Influence of Spatially Correlated Built-Environment Factors. Environ. Health Perspect. doi:10.1289/ehp.1308049

Ibald-Mulli, A., Timonen, K.L., Peters, A., Heinrich, J., Wölke, G., Lanki, T., Buzorius, G., Kreyling, W.G., de Hartog, J., Hoek, G., ten Brink, H.M., Pekkanen, J., 2004. Effects of particulate air pollution on blood pressure and heart rate in subjects with cardiovascular disease: a multicenter approach. Environ. Health Perspect. 112, 369–377.

Inagami, S., Cohen, D.A., Brown, A.F., Asch, S.M., 2009. Body Mass Index, Neighborhood Fast Food and Restaurant Concentration, and Car Ownership. J. Urban Health 86, 683–695. doi:10.1007/s11524-009-9379-y

Jain, S., Neal, R.M., 2004. A Split-Merge Markov chain Monte Carlo Procedure for the Dirichlet Process Mixture Model. J. Comput. Graph. Stat. 13, 158–182. doi:10.1198/1061860043001

Janevic, T., Borrell, L.N., Savitz, D.A., Herring, A.H., Rundle, A., 2010. Neighbourhood food environment and gestational diabetes in New York City. Paediatr. Perinat. Epidemiol. 24, 249–254. doi:10.1111/j.1365-3016.2010.01107.x

Janghorbani, M., Momeni, F., Mansourian, M., 2014. Systematic review and metaanalysis of air pollution exposure and risk of diabetes. Eur. J. Epidemiol. doi:10.1007/s10654-014-9907-2

Janhäll, S., Molnar, P., Hallquist, M., 2012. Traffic emission factors of ultrafine particles: effects from ambient air. J. Environ. Monit. 14, 2488. doi:10.1039/c2em30235g

Jedrychowski, W.A., Perera, F.P., Tang, D., Rauh, V., Majewska, R., Mroz, E., Flak, E., Stigter, L., Spengler, J., Camann, D., Jacek, R., 2013. The relationship between prenatal exposure to

airborne polycyclic aromatic hydrocarbons (PAHs) and PAH-DNA adducts in cord blood. J. Expo. Sci. Environ. Epidemiol. 23, 371–377. doi:10.1038/jes.2012.117

Jedrychowski, W., Masters, E., Choi, H., Sochacka, E., Flak, E., Mroz, E., Pac, A., Jacek, R., Kaim, I., Skolicki, Z., Spengler, J.D., Perera, F., 2007. Pre-pregnancy dietary vitamin A intake may alleviate the adverse birth outcomes associated with prenatal pollutant exposure: epidemiologic cohort study in Poland. Int. J. Occup. Environ. Health 13, 175–180.

Jedrychowski, W., Perera, F., Mrozek-Budzyn, D., Flak, E., Mroz, E., Sochacka-Tatara, E., Jacek, R., Kaim, I., Skolicki, Z., Spengler, J.D., 2010. Higher fish consumption in pregnancy may confer protection against the harmful effect of prenatal exposure to fine particulate matter. Ann. Nutr. Metab. 56, 119–126. doi:10.1159/000275918

Jerrett, M., Burnett, R.T., Beckerman, B.S., Turner, M.C., Krewski, D., Thurston, G., Martin, R.V., van Donkelaar, A., Hughes, E., Shi, Y., Gapstur, S.M., Thun, M.J., Pope, C.A., 2013. Spatial Analysis of Air Pollution and Mortality in California. Am. J. Respir. Crit. Care Med. 188, 593–599. doi:10.1164/rccm.201303-0609OC

Jerrett, M., Burnett, R.T., Ma, R., Pope, C.A., Krewski, D., Newbold, K.B., Thurston, G., Shi, Y., Finkelstein, N., Calle, E.E., Thun, M.J., 2005. Spatial Analysis of Air Pollution and Mortality in Los Angeles: Epidemiology 16, 727–736. doi:10.1097/01.ede.0000181630.15826.7d

Jerrett, M., Finkelstein, M., 2005. Geographies of risk in studies linking chronic air pollution exposure to health outcomes. J. Toxicol. Environ. Health A 68, 1207–1242. doi:10.1080/15287390590936085

Jerrett, M., McConnell, R., Wolch, J., Chang, R., Lam, C., Dunton, G., Gilliland, F., Lurmann, F., Islam, T., Berhane, K., 2014. Traffic-related air pollution and obesity formation in children: a longitudinal, multilevel analysis. Environ. Health 13, 49. doi:10.1186/1476-069X-13-49

Kahr, M.K., Suter, M.A., Ballas, J., Ramin, S.M., Monga, M., Lee, W., Hu, M., Shope, C.D., Chesnokova, A., Krannich, L., Griffin, E.N., Mastrobattista, J., Dildy, G.A., Strehlow, S.L., Ramphul, R., Hamilton, W.J., Aagaard, K.M., 2015. Geospatial Analysis of Food Environment Demonstrates Associations with Gestational Diabetes. Am. J. Obstet. Gynecol. doi:10.1016/j.ajog.2015.08.048

Kannan, S., Misra, D.P., Dvonch, J.T., Krishnakumar, A., 2006a. Exposures to airborne particulate matter and adverse perinatal outcomes: a biologically plausible mechanistic framework for exploring potential effect modification by nutrition. Environ. Health Perspect. 114, 1636–1642.

Kannan, S., Misra, D.P., Dvonch, J.T., Krishnakumar, A., 2006b. Exposures to airborne particulate matter and adverse perinatal outcomes: a biologically plausible mechanistic framework for exploring potential effect modification by nutrition. Environ. Health Perspect. 114, 1636–1642.

Karner, A.A., Eisinger, D.S., Niemeier, D.A., 2010. Near-roadway air quality: synthesizing the findings from real-world data. Environ. Sci. Technol. 44, 5334–5344. doi:10.1021/es100008x

Kawashima, A., Madarame, T., Koike, H., Komatsu, Y., Wise, J.A., 2007. Four week supplementation with mixed fruit and vegetable juice concentrates increased protective serum antioxidants and folate and decreased plasma homocysteine in Japanese subjects. Asia Pac. J.

Clin. Nutr. 16, 411–421.

Kelsall, J.E., Samet, J.M., Zeger, S.L., Xu, J., 1997. Air pollution and mortality in Philadelphia, 1974-1988. Am. J. Epidemiol. 146, 750–762.

Kihal-Talantikite, W., Padilla, C.M., Lalloué, B., Gelormini, M., Zmirou-Navier, D., Deguen, S., 2013. Green space, social inequalities and neonatal mortality in France. BMC Pregnancy Childbirth 13, 191. doi:10.1186/1471-2393-13-191

Kinabo, J., 1993. Seasonal variation of birth weight distribution in Morogoro, Tanzania. East Afr. Med. J. 70, 752–755.

Kiokias, S., Gordon, M.H., 2003. Dietary supplementation with a natural carotenoid mixture decreases oxidative stress. Eur. J. Clin. Nutr. 57, 1135–1140. doi:10.1038/sj.ejcn.1601655

Kloog, I., Melly, S.J., Ridgway, W.L., Coull, B.A., Schwartz, J., 2012. Using new satellite based exposure methods to study the association between pregnancy pm2.5 exposure, premature birth and birth weight in Massachusetts. Environ. Health 11, 40. doi:10.1186/1476-069X-11-40

Koh, K., Grady, S.C., Vojnovic, I., 2015. Using simulated data to investigate the spatial patterns of obesity prevalence at the census tract level in metropolitan Detroit. Appl. Geogr. 62, 19–28. doi:10.1016/j.apgeog.2015.03.016

Koleilat, M., Whaley, S.E., Afifi, A.A., Estrada, L., Harrison, G.G., 2012. Understanding the Relationship Between the Retail Food Environment Index and Early Childhood Obesity Among WIC Participants in Los Angeles County Using GeoDa. Online J. Public Health Inform. 4. doi:10.5210/ojphi.v4i1.3936

Koop, G., Tole, L., 2004. Measuring the health effects of air pollution: to what extent can we really say that people are dying from bad air? J. Environ. Econ. Manag. 47, 30–54. doi:10.1016/S0095-0696(03)00075-5

Kozawa, K.H., Fruin, S.A., Winer, A.M., 2009. Near-road air pollution impacts of goods movement in communities adjacent to the Ports of Los Angeles and Long Beach. Atmos. Environ. 43, 2960–2970. doi:10.1016/j.atmosenv.2009.02.042

Krewski, D., Jerrett, M., Burnett, R.T., Ma, R., Hughes, E., Shi, Y., Turner, M.C., Pope, C.A., Thurston, G., Calle, E.E., Thun, M.J., Beckerman, B., DeLuca, P., Finkelstein, N., Ito, K., Moore, D.K., Newbold, K.B., Ramsay, T., Ross, Z., Shin, H., Tempalski, B., 2009. Extended follow-up and spatial analysis of the American Cancer Society study linking particulate air pollution and mortality. Res. Rep. Health Eff. Inst. 5–114; discussion 115–136.

Krukowski, R.A., West, D.S., 2010. Consideration of the Food Environment in Cancer Risk Reduction. J. Am. Diet. Assoc. 110, 842–844. doi:10.1016/j.jada.2010.03.026

Kuhn, T., Biswas, S., Fine, P.M., Geller, M., Sioutas, C., 2005. Physical and Chemical Characteristics and Volatility of PM in the Proximity of a Light-Duty Vehicle Freeway. Aerosol Sci. Technol. 39, 347–357. doi:10.1080/027868290930024

Kumar, N., 2012. Uncertainty in the relationship between criteria pollutants and low birth weight in Chicago. Atmos. Environ. 49, 171–179. doi:10.1016/j.atmosenv.2011.12.001

Labranche, N., El Khattabi, C., Dewachter, L., Dreyfuss, C., Fontaine, J., van de Borne, P., Berkenboom, G., Pochet, S., 2012. Vascular Oxidative Stress Induced by Diesel Exhaust

Microparticles: Synergism With Hypertension. J. Cardiovasc. Pharmacol. 60, 530–537. doi:10.1097/FJC.0b013e318270f1a8

Lakshmanan, A., Chiu, Y.-H.M., Coull, B.A., Just, A.C., Maxwell, S.L., Schwartz, J., Gryparis, A., Kloog, I., Wright, R.J., Wright, R.O., 2015. Associations between prenatal traffic-related air pollution exposure and birth weight: Modification by sex and maternal pre-pregnancy body mass index. Environ. Res. 137, 268–277. doi:10.1016/j.envres.2014.10.035

Lamichhane, A.P., Warren, J., Puett, R., Porter, D.E., Bottai, M., Mayer-Davis, E.J., Liese, A.D., 2013. Spatial patterning of supermarkets and fast food outlets with respect to neighborhood characteristics. Health Place 23, 157–164. doi:10.1016/j.healthplace.2013.07.002

Lane, S.D., Keefe, R.H., Rubinstein, R., Levandowski, B.A., Webster, N., Cibula, D.A., Boahene, A.K., Dele-Michael, O., Carter, D., Jones, T., Wojtowycz, M., Brill, J., 2008. Structural violence, urban retail food markets, and low birth weight. Health Place 14, 415–423. doi:10.1016/j.healthplace.2007.08.008

Langellier, B.A., 2012. The food environment and student weight status, Los Angeles County, 2008-2009. Prev. Chronic. Dis. 9, E61.

Laraia, B.A., Siega-Riz, A.M., Kaufman, J.S., Jones, S.J., 2004. Proximity of supermarkets is positively associated with diet quality index for pregnancy. Prev. Med. 39, 869–875. doi:10.1016/j.ypmed.2004.03.018

Larsen, K., Gilliland, J., 2008. Mapping the evolution of “food deserts” in a Canadian city: Supermarket accessibility in London, Ontario, 1961–2005. Int. J. Health Geogr. 7, 16.

doi:10.1186/1476-072X-7-16

Larson, N.I., Story, M.T., Nelson, M.C., 2009. Neighborhood environments: disparities in access to healthy foods in the U.S. Am. J. Prev. Med. 36, 74–81. doi:10.1016/j.amepre.2008.09.025

Laska, M.N., Caspi, C.E., Pelletier, J.E., Friebur, R., Harnack, L.J., 2015. Lack of Healthy Food in Small-Size to Mid-Size Retailers Participating in the Supplemental Nutrition Assistance Program, Minneapolis–St. Paul, Minnesota, 2014. Prev. Chronic. Dis. 12. doi:10.5888/pcd12.150171

Laurent, O., Hu, J., Li, L., Cockburn, M., Escobedo, L., Kleeman, M.J., Wu, J., 2014a. Sources and contents of air pollution affecting term low birth weight in Los Angeles County, California, 2001–2008. Environ. Res. 134, 488–495. doi:10.1016/j.envres.2014.05.003

Laurent, O., Hu, J., Li, L., Cockburn, M., Escobedo, L., Kleeman, M.J., Wu, J., 2014b. Sources and contents of air pollution affecting term low birth weight in Los Angeles County, California, 2001-2008. Environ. Res. 134, 488–495. doi:10.1016/j.envres.2014.05.003

Laurent, O., Wu, J., Li, L., Chung, J., Bartell, S., 2013a. Investigating the association between birth weight and complementary air pollution metrics: a cohort study. Environ. Health 12, 18. doi:10.1186/1476-069X-12-18

Laurent, O., Wu, J., Li, L., Chung, J., Bartell, S., 2013b. Investigating the association between birth weight and complementary air pollution metrics: a cohort study. Environ. Health 12, 18. doi:10.1186/1476-069X-12-18

Laurent, O., Wu, J., Li, L., Milesi, C., 2013c. Green spaces and pregnancy outcomes in Southern

California. Health Place 24, 190–195. doi:10.1016/j.healthplace.2013.09.016

Lawlor, D.A., Ebrahim, S., Davey Smith, G., 2005. Association of birth weight with adult lung function: findings from the British Women's Heart and Health Study and a meta-analysis. Thorax 60, 851–858. doi:10.1136/thx.2005.042408

Lee, D., Mitchell, R., 2014. Controlling for localised spatio-temporal autocorrelation in long-term air pollution and health studies. Stat. Methods Med. Res. doi:10.1177/0962280214527384

Lee, D., Rushworth, A., Sahu, S., 2013. A Bayesian localised conditional auto-regressive model for estimating the health effects of air pollution. University of Glasgow, University of Southhampton.

Lee, D., Rushworth, A., Sahu, S.K., 2014. A Bayesian localized conditional autoregressive model for estimating the health effects of air pollution. Biometrics. doi:10.1111/biom.12156

Le, H.Q., Batterman, S.A., Wirth, J.J., Wahl, R.L., Hoggatt, K.J., Sadeghnejad, A., Hultin, M.L., Depa, M., 2012. Air pollutant exposure and preterm and term small-for-gestational-age births in Detroit, Michigan: Long-term trends and associations. Environ. Int. 44, 7–17. doi:10.1016/j.envint.2012.01.003

Levy, I., Mihele, C., Lu, G., Narayan, J., Brook, J.R., 2013a. Evaluating Multipollutant Exposure and Urban Air Quality: Pollutant Interrelationships, Neighborhood Variability, and Nitrogen Dioxide as a Proxy Pollutant. Environ. Health Perspect. doi:10.1289/ehp.1306518

Levy, I., Mihele, C., Lu, G., Narayan, J., Brook, J.R., 2013b. Evaluating Multipollutant Exposure and Urban Air Quality: Pollutant Interrelationships, Neighborhood Variability, and Nitrogen

Dioxide as a Proxy Pollutant. Environ. Health Perspect. doi:10.1289/ehp.1306518

Lewis, A.S., Sax, S.N., Wason, S.C., Campleman, S.L., 2011. Non-chemical stressors and cumulative risk assessment: an overview of current initiatives and potential air pollutant interactions. Int. J. Environ. Res. Public. Health 8, 2020–2073. doi:10.3390/ijerph8062020

Lin, F.-J., 2008. Solving Multicollinearity in the Process of Fitting Regression Model Using the Nested Estimate Procedure. Qual. Quant. 42, 417–426. doi:10.1007/s11135-006-9055-1

Liverani, S., Hastie, D., Azizi, L., Papathomas, M., Richardson, S., 2015. PReMiuM : An R Package for Profile Regression Mixture Models using Dirichlet Processes. J. Stat. Softw. 3, 1–29.

Liverani, S., Hastie, D., Azizi, L., Papathomas, M., Richardson, S., 2014. PReMiuM : An R Package for Profile Regression Mixture Models using Dirichlet Processes. Arxiv 13032836v3 3, 1–29.

Lv, J., Zhu, L., 2013. Effect of central ventilation and air conditioner system on the concentration and health risk from airborne polycyclic aromatic hydrocarbons. J. Environ. Sci. China 25, 531–536.

Macintyre, S., McKay, L., Cummins, S., Burns, C., 2005. Out-of-home food outlets and area deprivation: case study in Glasgow, UK. Int. J. Behav. Nutr. Phys. Act. 2, 16. doi:10.1186/1479-5868-2-16

Markevych, I., Fuertes, E., Tiesler, C.M.T., Birk, M., Bauer, C.-P., Koletzko, S., von Berg, A., Berdel, D., Heinrich, J., 2014. Surrounding greenness and birth weight: Results from the

GINIplus and LISAplus birth cohorts in Munich. Health Place 26, 39–46. doi:10.1016/j.healthplace.2013.12.001

Marshall, J.D., 2008. Environmental inequality: Air pollution exposures in California's South Coast Air Basin. Atmos. Environ. 42, 5499–5503. doi:10.1016/j.atmosenv.2008.02.005

Marshall, J.D., Brauer, M., Frank, L.D., 2009. Healthy Neighborhoods: Walkability and Air Pollution. Environ. Health Perspect. 117, 1752–1759. doi:10.1289/ehp.0900595

Martino, S., Rue, H., 2009a. Implementing Approximate Bayesian Inference using Integrated Nested Laplace Approximation: a manual for the inla program.

Martino, S., Rue, H., 2009b. Implementing Approximate Bayesian Inference using Integrated Nested Laplace Approximation: a manual for the inla program.

Masters, E.T., Jedrychowski, W., Schleicher, R.L., Tsai, W.-Y., Tu, Y.-H., Camann, D., Tang, D., Perera, F.P., 2007. Relation between prenatal lipid-soluble micronutrient status, environmental pollutant exposure, and birth outcomes. Am. J. Clin. Nutr. 86, 1139–1145.

Mauderly, J.L., Burnett, R.T., Castillejos, M., Ozkaynak, H., Samet, J.M., Stieb, D.M., Vedal, S., Wyzga, R.E., 2010. Is the air pollution health research community prepared to support a multipollutant air quality management framework? Inhal. Toxicol. 22 Suppl 1, 1–19. doi:10.3109/08958371003793846

Mauderly, J.L., Samet, J.M., 2009. Is There Evidence for Synergy Among Air Pollutants in Causing Health Effects? Environ. Health Perspect. 117, 1–6. doi:10.1289/ehp.11654

Ma, X., Liu, J., Hardin, J.W., Zhao, G., Liese, A.D., 2015. Neighborhood Food Access and Birth Outcomes in South Carolina. Matern Child Health J. doi:10.1007/s10995-015-1818-7

Mayne, S.T., 2003. Antioxidant nutrients and chronic disease: use of biomarkers of exposure and oxidative stress status in epidemiologic research. J. Nutr. 133 Suppl 3, 933S–940S.

McConnell, R., Islam, T., Shankardass, K., Jerrett, M., Lurmann, F., Gilliland, F., Gauderman, J., Avol, E., Künzli, N., Yao, L., Peters, J., Berhane, K., 2010. Childhood Incident Asthma and Traffic-Related Air Pollution at Home and School. Environ. Health Perspect. 118, 1021–1026. doi:10.1289/ehp.0901232

Meng, G., Thompson, M.E., Hall, G., 2013a. Pathways of neighbourhood-level socio-economic determinants of adverse birth outcomes. Int. J. Health Geogr. 12, 32. doi:10.1186/1476-072X-12-32

Meng, G., Thompson, M.E., Hall, G., 2013b. Pathways of neighbourhood-level socio-economic determinants of adverse birth outcomes. Int. J. Health Geogr. 12, 32. doi:10.1186/1476-072X-12-32

Meng, Q.Y., Turpin, B.J., Korn, L., Weisel, C.P., Morandi, M., Colome, S., Zhang, J.J., Stock, T., Spektor, D., Winer, A., Zhang, L., Lee, J.H., Giovanetti, R., Cui, W., Kwon, J., Alimokhtari, S., Shendell, D., Jones, J., Farrar, C., Maberti, S., 2005. Influence of ambient (outdoor) sources on residential indoor and personal PM2.5 concentrations: analyses of RIOPA data. J. Expo. Anal. Environ. Epidemiol. 15, 17–28. doi:10.1038/sj.jea.7500378

Messer, L.C., Kaufman, J.S., Dole, N., Herring, A., Laraia, B.A., 2006. Violent crime exposure

classification and adverse birth outcomes: a geographically-defined cohort study. Int. J. Health Geogr. 5, 22. doi:10.1186/1476-072X-5-22

Metcalfe, A., Lail, P., Ghali, W.A., Sauve, R.S., 2011. The association between neighbourhoods and adverse birth outcomes: a systematic review and meta-analysis of multi-level studies: Neighbourhoods and adverse birth outcomes. Paediatr. Perinat. Epidemiol. 25, 236–245. doi:10.1111/j.1365-3016.2011.01192.x

Misra, D.P., 1996. The effect of the pregnancy-induced hypertension on fetal growth: a review of the literature. Paediatr. Perinat. Epidemiol. 10, 244–263.

Modi, M., Kaul, R.K., Kannan, G.M., Flora, S.J.S., 2006. Co-administration of zinc and n-acetylcysteine prevents arsenic-induced tissue oxidative stress in male rats. J. Trace Elem. Med. Biol. Organ Soc. Miner. Trace Elem. GMS 20, 197–204. doi:10.1016/j.jtemb.2006.02.002

Mohorovic, L., 2004. First two months of pregnancy--critical time for preterm delivery and low birthweight caused by adverse effects of coal combustion toxics. Early Hum. Dev. 80, 115–123. doi:10.1016/j.earlhumdev.2004.06.001

Molitor, J., Brown, I.J., Chan, Q., Papathomas, M., Liverani, S., Molitor, N., Richardson, S., Van Horn, L., Daviglus, M.L., Dyer, A., Stamler, J., Elliott, P., for the INTERMAP Research Group, 2014a. Blood Pressure Differences Associated With Optimal Macronutrient Intake Trial for Heart Health (OMNIHEART)-Like Diet Compared With a Typical American Diet. Hypertension 64, 1198–1204. doi:10.1161/HYPERTENSIONAHA.114.03799

Molitor, J., Brown, I.J., Chan, Q., Papathomas, M., Liverani, S., Molitor, N., Richardson, S., Van

Horn, L., Daviglus, M.L., Dyer, A., Stamler, J., Elliott, P., for the INTERMAP Research Group, 2014b. Blood Pressure Differences Associated With Optimal Macronutrient Intake Trial for Heart Health (OMNIHEART)-Like Diet Compared With a Typical American Diet. Hypertension 64, 1198–1204. doi:10.1161/HYPERTENSIONAHA.114.03799

Molitor, J., Jerrett, M., Chang, C.C., Molitor, N.T., Gauderman, J., Berhane, K., McConnell, R., Lurmann, F., Wu, J., Winer, A., Thomas, D., 2007. Assessing uncertainty in spatial exposure models for air pollution health effects assessment. Env. Health Perspect 115, 1147–53.

Molitor, J., Lechevallier, Y., Saporta, G. (Eds.), 2010a. , in: Proceedings of COMPSTAT'2010. Physica-Verlag HD, Heidelberg.

Molitor, J., Papathomas, M., Jerrett, M., Richardson, S., 2010b. Bayesian profile regression with an application to the National Survey of Children's Health. Biostat. Oxf. Engl. 11, 484–498. doi:10.1093/biostatistics/kxq013

Molitor, J., Papathomas, M., Jerrett, M., Richardson, S., 2010c. Bayesian profile regression with an application to the National Survey of Children's Health. Biostat. Oxf. Engl. 11, 484–498. doi:10.1093/biostatistics/kxq013

Molitor, J., Su, J.G., Molitor, N.-T., Rubio, V.G., Richardson, S., Hastie, D., Morello-Frosch, R., Jerrett, M., 2011. Identifying vulnerable populations through an examination of the association between multipollutant profiles and poverty. Environ. Sci. Technol. 45, 7754–7760. doi:10.1021/es104017x

Monn, C., 2001. Exposure assessment of air pollutants: a review on spatial heterogeneity and

indoor/outdoor/personal exposure to suspended particulate matter, nitrogen dioxide and ozone. Atmos. Environ. 35, 1–32. doi:10.1016/S1352-2310(00)00330-7

Morello-Frosch, R., Jesdale, B.M., Sadd, J.L., Pastor, M., 2010a. Ambient air pollution exposure and full-term birth weight in California. Environ. Health 9, 44. doi:10.1186/1476-069X-9-44

Morello-Frosch, R., Jesdale, B.M., Sadd, J.L., Pastor, M., 2010b. Ambient air pollution exposure and full-term birth weight in California. Environ. Health 9, 44. doi:10.1186/1476-069X-9-44

Morello-Frosch, R., Pastor, M., Porras, C., Sadd, J., 2002. Environmental justice and regional inequality in southern California: implications for future research. Environ. Health Perspect. 110 Suppl 2, 149–154.

Morello-Frosch, R., Pastor, M., Sadd, J., 2001. Environmental Justice and Southern California's "Riskscape": The Distribution of Air Toxics Exposures and Health Risks among Diverse Communities. Urban Aff. Rev. 36, 551–578. doi:10.1177/10780870122184993

Morello-Frosch, R., Shenassa, E.D., 2006. The Environmental "Riskscape" and Social Inequality: Implications for Explaining Maternal and Child Health Disparities. Environ. Health Perspect. 114, 1150–1153. doi:10.1289/ehp.8930

Morello-Frosch, R., Zuk, M., Jerrett, M., Shamasunder, B., Kyle, A.D., 2011. Understanding The Cumulative Impacts Of Inequalities In Environmental Health: Implications For Policy. Health Aff. (Millwood) 30, 879–887. doi:10.1377/hlthaff.2011.0153

Morier, D., 2015. Social Determinants of Health: Rising Food Insecurity in Los Angeles County. County of Los Angeles Public Health, Los Angeles CA.

Mujahid, M.S., Diez Roux, A.V., Morenoff, J.D., Raghunathan, T.E., Cooper, R.S., Ni, H., Shea, S., 2008. Neighborhood Characteristics and Hypertension: Epidemiology 19, 590–598. doi:10.1097/EDE.0b013e3181772cb2

National Research Council (U.S.), National Research Council (U.S.), National Research Council (U.S.), 2009. Science and decisions: advancing risk assessment. National Academies Press, Washington, D.C.

Neal, R.M., 2000. Markov Chain Sampling Methods for Dirichlet Process Mixture Models. J. Comput. Graph. Stat. 9, 249. doi:10.2307/1390653

Neff, R.A., Palmer, A.M., McKenzie, S.E., Lawrence, R.S., 2009. Food Systems and Public Health Disparities. J. Hunger Environ. Nutr. 4, 282–314. doi:10.1080/19320240903337041

Nel, A.E., Diaz-Sanchez, D., Ng, D., Hiura, T., Saxon, A., 1998. Enhancement of allergic inflammation by the interaction between diesel exhaust particles and the immune system. J. Allergy Clin. Immunol. 102, 539–554.

Nolen, J., 2014. State of the Air 2014. American Lung Association, Chicago, IL.

Novák, J., Hilscherová, K., Landlová, L., Čupr, P., Kohút, L., Giesy, J.P., Klánová, J., 2014. Composition and effects of inhalable size fractions of atmospheric aerosols in the polluted atmosphere. Part II. In vitro biological potencies. Environ. Int. 63, 64–70. doi:10.1016/j.envint.2013.10.013

Oakes, M., Baxter, L., Long, T.C., 2014. Evaluating the application of multipollutant exposure metrics in air pollution health studies. Environ. Int. 69, 90–99. doi:10.1016/j.envint.2014.03.030

Olsson, D., Ekström, M., Forsberg, B., 2012. Temporal Variation in Air Pollution Concentrations and Preterm Birth—A Population Based Epidemiological Study. Int. J. Environ. Res. Public. Health 9, 272–285. doi:10.3390/ijerph9010272

Otsuka, R., Watanabe, H., Hirata, K., Tokai, K., Muro, T., Yoshiyama, M., Takeuchi, K., Yoshikawa, J., 2001. Acute effects of passive smoking on the coronary circulation in healthy young adults. JAMA J. Am. Med. Assoc. 286, 436–441.

Ouidir, M., Giorgis-Allemand, L., Lyon-Caen, S., Morelli, X., Cracowski, C., Pontet, S., Pin, I., Lepeule, J., Siroux, V., Slama, R., 2015. Estimation of exposure to atmospheric pollutants during pregnancy integrating space–time activity and indoor air levels: Does it make a difference? Environ. Int. 84, 161–173. doi:10.1016/j.envint.2015.07.021

Padula, A.M., Mortimer, K., Hubbard, A., Lurmann, F., Jerrett, M., Tager, I.B., 2012. Exposure to Traffic-related Air Pollution During Pregnancy and Term Low Birth Weight: Estimation of Causal Associations in a Semiparametric Model. Am. J. Epidemiol. 176, 815–824. doi:10.1093/aje/kws148

Panagiotakos, D.B., Pitsavos, C., Chrysohoou, C., Skoumas, J., Masoura, C., Toutouzas, P., Stefanadis, C., ATTICA study, 2004. Effect of exposure to secondhand smoke on markers of inflammation: the ATTICA study. Am. J. Med. 116, 145–150.

Papathomas, M., Molitor, J., Hoggart, C., Hastie, D., Richardson, S., 2012. Exploring Data From Genetic Association Studies Using Bayesian Variable Selection and the Dirichlet Process: Application to Searching for Gene × Gene Patterns: Searching for Gene × Gene Patterns. Genet. Epidemiol. 36, 663–674. doi:10.1002/gepi.21661

Papathomas, M., Molitor, J., Richardson, S., Riboli, E., Vineis, P., 2010. Examining the Joint Effect of Multiple Risk Factors Using Exposure Risk Profiles: Lung Cancer in Nonsmokers. Environ. Health Perspect. 119, 84–91. doi:10.1289/ehp.1002118

Parker, J.D., Rich, D.Q., Glinianaia, S.V., Leem, J.H., Wartenberg, D., Bell, M.L., Bonzini, M., Brauer, M., Darrow, L., Gehring, U., Gouveia, N., Grillo, P., Ha, E., van den Hooven, E.H., Jalaludin, B., Jesdale, B.M., Lepeule, J., Morello-Frosch, R., Morgan, G.G., Slama, R., Pierik, F.H., Pesatori, A.C., Sathyanarayana, S., Seo, J., Strickland, M., Tamburic, L., Woodruff, T.J., 2011. The International Collaboration on Air Pollution and Pregnancy Outcomes: Initial Results. Environ. Health Perspect. 119, 1023–1028. doi:10.1289/ehp.1002725

Parker, J.D., Woodruff, T.J., Basu, R., Schoendorf, K.C., 2005. Air pollution and birth weight among term infants in California. Pediatrics 115, 121–128. doi:10.1542/peds.2004-0889

Pearce, J., Blakely, T., Witten, K., Bartie, P., 2007. Neighborhood deprivation and access to fast-food retailing: a national study. Am. J. Prev. Med. 32, 375–382. doi:10.1016/j.amepre.2007.01.009

Pedersen, M., Gehring, U., Beelen, R., Wang, M., Giorgis-Allemand, L., Andersen, A.M.N., Basagaña, X., Bernard, C., Cirach, M., Forastiere, F., de Hoogh, K., Gražulevičienė, R., Gruzieva, O., Hoek, G., Jedynska, A., Klümper, C., Kooter, I.M., Krämer, U., Kukkonen, J., Porta, D., Postma, D.S., Raaschou-Nielsen, O., van Rossem, L., Sunyer, J., Sørensen, M., Tsai, M.-Y., Vrijkotte, T.G., Wilhelm, M., Nieuwenhuijsen, M.J., Pershagen, G., Brunekreef, B., Kogevinas, M., Slama, R., 2015. Elemental Constituents of Particulate Matter and Newborn's Size in Eight European Cohorts. Environ. Health Perspect. doi:10.1289/ehp.1409546

Pedersen, M., Schoket, B., Godschalk, R.W., Wright, J., von Stedingk, H., Törnqvist, M., Sunyer, J., Nielsen, J.K., Merlo, D.F., Mendez, M.A., Meltzer, H.M., Lukács, V., Landström, A., Kyrtopoulos, S.A., Kovács, K., Knudsen, L.E.., Haugen, M., Hardie, L.J., Gützkow, K.B., Fleming, S., Fthenou, E., Farmer, P.B., Espinosa, A., Chatzi, L., Brunborg, G., Brady, N.J., Botsivali, M., Arab, K., Anna, L., Alexander, J., Agramunt, S., Kleinjans, J.C., Segerbäck, D., Kogevinas, M., 2013. Bulky DNA Adducts in Cord Blood, Maternal Fruit-and-Vegetable Consumption, and Birth Weight in a European Mother–Child Study (NewGeneris). Environ. Health Perspect. doi:10.1289/ehp.1206333

Pekkanen, J., Brunner, E.J., Anderson, H.R., Tiittanen, P., Atkinson, R.W., 2000. Daily concentrations of air pollution and plasma fibrinogen in London. Occup. Environ. Med. 57, 818–822.

Perera, F.P., Whyatt, R.M., Jedrychowski, W., Rauh, V., Manchester, D., Santella, R.M., Ottman, R., 1998. Recent developments in molecular epidemiology: A study of the effects of environmental polycyclic aromatic hydrocarbons on birth outcomes in Poland. Am. J. Epidemiol. 147, 309–314.

Peters, A., Döring, A., Wichmann, H.E., Koenig, W., 1997. Increased plasma viscosity during an air pollution episode: a link to mortality? Lancet 349, 1582–1587. doi:10.1016/S0140-6736(97)01211-7

Pirani, M., Best, N., Blangiardo, M., Liverani, S., Atkinson, R.W., Fuller, G.W., 2015a. Analysing the health effects of simultaneous exposure to physical and chemical properties of airborne particles. Environ. Int. 79, 56–64. doi:10.1016/j.envint.2015.02.010

Pirani, M., Best, N., Blangiardo, M., Liverani, S., Atkinson, R.W., Fuller, G.W., 2015b. Analysing the health effects of simultaneous exposure to physical and chemical properties of airborne particles. Environ. Int. 79, 56–64. doi:10.1016/j.envint.2015.02.010

Pirani, M., Papageorgiou, G., Best, N., Atkinson, R.W., Fuller, G., 2013. Bayesian Modelling for Estimating Adverse Health Effects of Exposure to Multiple Air Pollutants in a Time Series Framework.

Ponce, N.A., 2005a. Preterm Birth: The Interaction of Traffic-related Air Pollution with Economic Hardship in Los Angeles Neighborhoods. Am. J. Epidemiol. 162, 140–148. doi:10.1093/aje/kwi173

Ponce, N.A., 2005b. Preterm Birth: The Interaction of Traffic-related Air Pollution with Economic Hardship in Los Angeles Neighborhoods. Am. J. Epidemiol. 162, 140–148. doi:10.1093/aje/kwi173

Porrini, M., Riso, P., Oriani, G., 2002. Spinach and tomato consumption increases lymphocyte DNA resistance to oxidative stress but this is not related to cell carotenoid concentrations. Eur. J. Nutr. 41, 95–100. doi:10.1007/s003940200014

Price, J.H., Khubchandani, J., McKinney, M., Braun, R., 2013. Racial/Ethnic Disparities in Chronic Diseases of Youths and Access to Health Care in the United States. BioMed Res. Int. 2013, 1–12. doi:10.1155/2013/787616

Proietti, E., Röösli, M., Frey, U., Latzin, P., 2013. Air Pollution During Pregnancy and Neonatal Outcome: A Review. J. Aerosol Med. Pulm. Drug Deliv. 26, 9–23. doi:10.1089/jamp.2011.0932

Protano, C., Scalise, T., Orsi, G.B., Vitali, M., 2012. A systematic review of benzene exposure during pregnancy and adverse outcomes on intrauterine development and birth: still far from scientific evidence. Ann. Ig. Med. Prev. E Comunità 24, 451–463.

Protano, C., Scalise, T., Orsi, G.B., Vitali, M., 2012. A systematic review of benzene exposure during pregnancy and adverse outcomes on intrauterine development and birth: still far from scientific evidence. Ann. Ig. Med. Prev. E Comunità 24, 451–463.

Qian, Z., Chapman, R.S., Hu, W., Wei, F., Korn, L.R., Zhang, J. (Jim), 2004a. Using air pollution based community clusters to explore air pollution health effects in children. Environ. Int. 30, 611–620. doi:10.1016/j.envint.2003.11.003

Qian, Z., Chapman, R.S., Hu, W., Wei, F., Korn, L.R., Zhang, J. (Jim), 2004b. Using air pollution based community clusters to explore air pollution health effects in children. Environ. Int. 30, 611–620. doi:10.1016/j.envint.2003.11.003

Raaschou-Nielsen, O., Andersen, Z.J., Beelen, R., Samoli, E., Stafoggia, M., Weinmayr, G., Hoffmann, B., Fischer, P., Nieuwenhuijsen, M.J., Brunekreef, B., Xun, W.W., Katsouyanni, K., Dimakopoulou, K., Sommar, J., Forsberg, B., Modig, L., Oudin, A., Oftedal, B., Schwarze, P.E., Nafstad, P., De Faire, U., Pedersen, N.L., Östenson, C.-G., Fratiglioni, L., Penell, J., Korek, M., Pershagen, G., Eriksen, K.T., Sørensen, M., Tjønneland, A., Ellermann, T., Eeftens, M., Peeters, P.H., Meliefste, K., Wang, M., Bueno-de-Mesquita, B., Key, T.J., de Hoogh, K., Concin, H., Nagel, G., Vilier, A., Grioni, S., Krogh, V., Tsai, M.-Y., Ricceri, F., Sacerdote, C., Galassi, C., Migliore, E., Ranzi, A., Cesaroni, G., Badaloni, C., Forastiere, F., Tamayo, I., Amiano, P., Dorronsoro, M., Trichopoulou, A., Bamia, C., Vineis, P., Hoek, G., 2013. Air pollution and lung

cancer incidence in 17 European cohorts: prospective analyses from the European Study of Cohorts for Air Pollution Effects (ESCAPE). Lancet Oncol. 14, 813–822. doi:10.1016/S1470-2045(13)70279-1

Ramachandran, G., Adgate, J.L., Pratt, G.C., Sexton, K., 2003. Characterizing Indoor and Outdoor 15 Minute Average PM 2.5 Concentrations in Urban Neighborhoods. Aerosol Sci. Technol. 37, 33–45. doi:10.1080/02786820300889

Rayco-Solon, P., Fulford, A.J., Prentice, A.M., 2005. Differential effects of seasonality on preterm birth and intrauterine growth restriction in rural Africans. Am. J. Clin. Nutr. 81, 134–139.

Reichman, N.E., Teitler, J.O., 2003. Effects of psychosocial risk factors and prenatal interventions on birth weight: evidence from New Jersey's HealthStart program. Perspect. Sex. Reprod. Health 35, 130–137.

Reid, C., O'Neill, M., Gronlund, C., Brines, S., Brown, D., Diez-Roux, A., Schwartz, J., 2009. Mapping Community Determinants of Heat Vulnerability. Environ. Health Perspect. doi:10.1289/ehp.0900683

Richardson, A.S., Boone-Heinonen, J., Popkin, B.M., Gordon-Larsen, P., 2012. Are neighbourhood food resources distributed inequitably by income and race in the USA? Epidemiological findings across the urban spectrum. BMJ Open 2, e000698. doi:10.1136/bmjopen-2011-000698

Ritz, B., Wilhelm, M., 2008a. Ambient Air Pollution and Adverse Birth Outcomes:

Methodologic Issues in an Emerging Field: AMBIENT AIR POLLUTION AND ADVERSE BIRTH OUTCOMES. Basic Clin. Pharmacol. Toxicol. 102, 182–190. doi:10.1111/j.1742-7843.2007.00161.x

Ritz, B., Wilhelm, M., 2008b. Ambient air pollution and adverse birth outcomes: methodologic issues in an emerging field. Basic Clin. Pharmacol. Toxicol. 102, 182–190. doi:10.1111/j.1742-7843.2007.00161.x

Ritz, B., Wilhelm, M., Hoggatt, K.J., Ghosh, J.K.C., 2007a. Ambient Air Pollution and Preterm Birth in the Environment and Pregnancy Outcomes Study at the University of California, Los Angeles. Am. J. Epidemiol. 166, 1045–1052. doi:10.1093/aje/kwm181

Ritz, B., Wilhelm, M., Hoggatt, K.J., Ghosh, J.K.C., 2007b. Ambient Air Pollution and Preterm Birth in the Environment and Pregnancy Outcomes Study at the University of California, Los Angeles. Am. J. Epidemiol. 166, 1045–1052. doi:10.1093/aje/kwm181

Ritz, B., Yu, F., 1999a. The effect of ambient carbon monoxide on low birth weight among children born in southern California between 1989 and 1993. Environ. Health Perspect. 107, 17–25.

Ritz, B., Yu, F., 1999b. The effect of ambient carbon monoxide on low birth weight among children born in southern California between 1989 and 1993. Environ. Health Perspect. 107, 17–25.

Robertson, S., Gray, G.A., Duffin, R., McLean, S.G., Shaw, C.A., Hadoke, P.W., Newby, D.E., Miller, M.R., 2012. Diesel exhaust particulate induces pulmonary and systemic inflammation in

rats without impairing endothelial function ex vivo or in vivo. Part. Fibre Toxicol. 9, 9. doi:10.1186/1743-8977-9-9

Ross, Z., Ito, K., Johnson, S., Yee, M., Pezeshki, G., Clougherty, J.E., Savitz, D., Matte, T., 2013. Spatial and temporal estimation of air pollutants in New York City: exposure assignment for use in a birth outcomes study. Environ. Health Glob. Access Sci. Source 12, 51. doi:10.1186/1476-069X-12-51

Rousham, E.K., Gracey, M., 1998. Seasonality of low birthweight in indigenous Australians: an increase in pre-term birth or intrauterine growth retardation? Aust. N. Z. J. Public Health 22, 669–672.

Rue, H., Martino, S., n.d. Approximate Bayesian inference for latent Gaussian models using integrated nested Laplace approximations (with discussion). J. R. Stat. Soc.

Rue, H., Martino, S., Chopin, N., 2009. Approximate Bayesian inference for latent Gaussian models by using integrated nested Laplace approximations. J. R. Stat. Soc. Ser. B Stat. Methodol. 71, 319–392. doi:10.1111/j.1467-9868.2008.00700.x

Rue, H., Martino, S., Lindgren, F., Simpson, D., Riebler, A., Krainski, E., 2015. INLA: Functions which allow to perform full Bayesian analysis of latent Gaussian models using Integrated Nested Laplace Approximaxion.

Rue, H., Martino, S., Lindgren, F., Simpson, D., Riebler, A., Krainski, E., 2014. Functions which allow to perform full Bayesian analysis of latent Gaussian models using Integrated Nested Laplace Approximaxion [WWW Document]. URL http://inla.googlecode.com/hg-

history/default/rinla/DESCRIPTION

Rundle, A., Hoepner, L., Hassoun, A., Oberfield, S., Freyer, G., Holmes, D., Reyes, M., Quinn, J., Camann, D., Perera, F., Whyatt, R., 2012. Association of Childhood Obesity With Maternal Exposure to Ambient Air Polycyclic Aromatic Hydrocarbons During Pregnancy. Am. J. Epidemiol. 175, 1163–1172. doi:10.1093/aje/kwr455

Salam, M.T., Millstein, J., Li, Y.-F., Lurmann, F.W., Margolis, H.G., Gilliland, F.D., 2005. Birth outcomes and prenatal exposure to ozone, carbon monoxide, and particulate matter: results from the Children's Health Study. Environ. Health Perspect. 113, 1638–1644.

Salinas, J., Abdelbary, B., Klaas, K., Tapia, B., Sexton, K., 2014. Socioeconomic Context and the Food Landscape in Texas: Results from Hotspot Analysis and Border/Non-Border Comparison of Unhealthy Food Environments. Int. J. Environ. Res. Public. Health 11, 5640–5650. doi:10.3390/ijerph110605640

Salinas, J.J., Sexton, K., 2015. A Border Versus Non-Border Comparison of Food Environment, Poverty, and Ethnic Composition in Texas Urban Settings. Front. Public Health 3. doi:10.3389/fpubh.2015.00063

Salois, M.J., 2012. Obesity and diabetes, the built environment, and the "local" food economy in the United States, 2007. Econ. Hum. Biol. 10, 35–42. doi:10.1016/j.ehb.2011.04.001

Samoli, E., Analitis, A., Touloumi, G., Schwartz, J., Anderson, H.R., Sunyer, J., Bisanti, L., Zmirou, D., Vonk, J.M., Pekkanen, J., Goodman, P., Paldy, A., Schindler, C., Katsouyanni, K., 2004. Estimating the Exposure–Response Relationships between Particulate Matter and

Mortality within the APHEA Multicity Project. Environ. Health Perspect. 113, 88–95. doi:10.1289/ehp.7387

Schempf, A., Strobino, D., O'Campo, P., 2009. Neighborhood effects on birthweight: An exploration of psychosocial and behavioral pathways in Baltimore, 1995–1996. Soc. Sci. Med. 68, 100–110. doi:10.1016/j.socscimed.2008.10.006

Schmidt, P., Muller, E., 1978. The Problem of Multicollinearity in multistage Causal Alienation Model: A COmparison of Ordinary Least Sqares, Maximum Likelihood and Ridge Esimation. Qual. Quant. 12, 267–297.

Schwartz, J., Laden, F., 2004. DOSE, TIME AND DEATH: A BAYESIAN MODEL AVERAGING APPROACH TO ESTIMATING THE ASSOCIATION BETWEEN PARTICLES AND SURVIVAL. Epidemiology 15, S152–S153.

Selevan, S.G., Kimmel, C.A., Mendola, P., 2000. Identifying critical windows of exposure for children's health. Environ. Health Perspect. 108 Suppl 3, 451–455.

Shaffer, A., 2002. "The Persistence of L.A.'s Grocery Gap: The Need for a New Food Policy " by Amanda Shaffer. Occidental College.

Shah, P.S., Balkhair, T., 2011. Air pollution and birth outcomes: A systematic review. Environ. Int. 37, 498–516. doi:10.1016/j.envint.2010.10.009

Shah, P.S., Ohlsson, A., on behalf of the Knowledge Synthesis Group on Determinants of Low Birth Weight and Preterm Births, 2009. Effects of prenatal multimicronutrient supplementation on pregnancy outcomes: a meta-analysis. Can. Med. Assoc. J. 180, E99–E108.

doi:10.1503/cmaj.081777

Shankardass, K., McConnell, R., Jerrett, M., Milam, J., Richardson, J., Berhane, K., 2009. Parental stress increases the effect of traffic-related air pollution on childhood asthma incidence. Proc. Natl. Acad. Sci. U. S. A. 106, 12406–12411. doi:10.1073/pnas.0812910106

Sheppard, L., Burnett, R.T., Szpiro, A.A., Kim, S.-Y., Jerrett, M., Pope, C.A., Brunekreef, B., 2012. Confounding and exposure measurement error in air pollution epidemiology. Air Qual. Atmosphere Health 5, 203–216. doi:10.1007/s11869-011-0140-9

Singer, B.C., Harley, R.A., 2000. A fuel-based inventory of motor vehicle exhaust emissions in the Los Angeles area during summer 1997. Atmos. Environ. 34, 1783–1795. doi:10.1016/S1352-2310(99)00358-1

Slama, R., Thiebaugeorges, O., Goua, V., Aussel, L., Sacco, P., Bohet, A., Forhan, A., Ducot, B., Annesi-Maesano, I., Heinrich, J., Magnin, G., Schweitzer, M., Kaminski, M., Charles, M.-A., cohort study group, E. mother-child, 2009. Maternal Personal Exposure to Airborne Benzene and Intra-Uterine Growth. Environ. Health Perspect. doi:10.1289/ehp.0800465

Smolková, B., Dusinská, M., Raslová, K., McNeill, G., Spustová, V., Blazícek, P., Horská, A., Collins, A., 2004. Seasonal changes in markers of oxidative damage to lipids and DNA; correlations with seasonal variation in diet. Mutat. Res. 551, 135–144. doi:10.1016/j.mrfmmm.2004.02.021

Snowden, J.M., Reid, C.E., Tager, I.B., 2015. Framing Air Pollution Epidemiology in Terms of Population Interventions, with Applications to Multipollutant Modeling: Epidemiology 26, 271–

279. doi:10.1097/EDE.0000000000000236

Sobal, J., Wansink, B., 2007. Kitchenscapes, Tablescapes, Platescapes, and Foodscapes: Influences of Microscale Built Environments on Food Intake. Environ. Behav. 39, 124–142. doi:10.1177/0013916506295574

Sørensen, M., Daneshvar, B., Hansen, M., Dragsted, L.O., Hertel, O., Knudsen, L., Loft, S., 2003. Personal PM2.5 exposure and markers of oxidative stress in blood. Environ. Health Perspect. 111, 161–166.

Spence, J.C., Cutumisu, N., Edwards, J., Raine, K.D., Smoyer-Tomic, K., 2009. Relation between local food environments and obesity among adults. BMC Public Health 9, 192. doi:10.1186/1471-2458-9-192

Spengler, J., Schwab, M., Ryan, P.B., Colome, S., Wilson, A.., Billick, I., Becker, E., 1994. Personal Exposure to Nitrogen Dioxide in the Los Angeles Basin. Air Waste 44, 39–47. doi:10.1080/1073161X.1994.10467236

Šrám, R.J., Binková, B., Dejmek, J., Bobak, M., 2005. Ambient Air Pollution and Pregnancy Outcomes: A Review of the Literature. Environ. Health Perspect. 113, 375–382. doi:10.1289/ehp.6362

Srinivasan, S., O'Fallon, L.R., Dearry, A., 2003. Creating healthy communities, healthy homes, healthy people: initiating a research agenda on the built environment and public health. Am. J. Public Health 93, 1446–1450.

Stieb, D.M., Chen, L., Eshoul, M., Judek, S., 2012. Ambient air pollution, birth weight and

preterm birth: a systematic review and meta-analysis. Environ. Res. 117, 100–111. doi:10.1016/j.envres.2012.05.007

Stieb, D.M., Chen, L., Eshoul, M., Judek, S., 2012. Ambient air pollution, birth weight and preterm birth: a systematic review and meta-analysis. Environ. Res. 117, 100–111. doi:10.1016/j.envres.2012.05.007

Strak, M., Hoek, G., Godri, K.J., Gosens, I., Mudway, I.S., van Oerle, R., Spronk, H.M.H., Cassee, F.R., Lebret, E., Kelly, F.J., Harrison, R.M., Brunekreef, B., Steenhof, M., Janssen, N.A.H., 2013. Composition of PM Affects Acute Vascular Inflammatory and Coagulative Markers - The RAPTES Project. PLoS ONE 8, e58944. doi:10.1371/journal.pone.0058944

Su, J.G., Jerrett, M., Beckerman, B., Wilhelm, M., Ghosh, J.K., Ritz, B., 2009. Predicting traffic-related air pollution in Los Angeles using a distance decay regression selection strategy. Environ. Res. 109, 657–670. doi:10.1016/j.envres.2009.06.001

Su, J.G., Jerrett, M., Morello-Frosch, R., Jesdale, B.M., Kyle, A.D., 2012. Inequalities in cumulative environmental burdens among three urbanized counties in California. Environ. Int. 40, 79–87. doi:10.1016/j.envint.2011.11.003

Sun, Z., Tao, Y., Li, S., Ferguson, K.K., Meeker, J.D., Park, S., Batterman, S.A., Mukherjee, B., 2013. Statistical strategies for constructing health risk models with multiple pollutants and their interactions: possible choices and comparisons. Environ. Health 12, 85. doi:10.1186/1476-069X-12-85

Tandon, A., Kumari, S., Ramji, S., Malik, A., Singh, S., Nigam, V.R., 2000. Intellectual psycho-

educational and functional status of low birth weight survivors beyond 5 years of age. Indian J. Pediatr. 67, 791–796.

Thompson, J.A., Bissett, W.T., Sweeney, A.M., 2014. Evaluating geostatistical modeling of exceedance probability as the first step in disease cluster investigations: very low birth weights near toxic Texas sites. Environ. Health Glob. Access Sci. Source 13, 47. doi:10.1186/1476-069X-13-47

Tonne, C., Melly, S., Mittleman, M., Coull, B., Goldberg, R., Schwartz, J., 2007. A case-control analysis of exposure to traffic and acute myocardial infarction. Environ. Health Perspect. 115, 53–57.

Tsai, M.-Y., Hoek, G., Eeftens, M., de Hoogh, K., Beelen, R., Beregszászi, T., Cesaroni, G., Cirach, M., Cyrys, J., De Nazelle, A., de Vocht, F., Ducret-Stich, R., Eriksen, K., Galassi, C., Gražuleviciene, R., Gražulevicius, T., Grivas, G., Gryparis, A., Heinrich, J., Hoffmann, B., Iakovides, M., Keuken, M., Krämer, U., Künzli, N., Lanki, T., Madsen, C., Meliefste, K., Merritt, A.-S., Mölter, A., Mosler, G., Nieuwenhuijsen, M.J., Pershagen, G., Phuleria, H., Quass, U., Ranzi, A., Schaffner, E., Sokhi, R., Stempfelet, M., Stephanou, E., Sugiri, D., Taimisto, P., Tewis, M., Udvardy, O., Wang, M., Brunekreef, B., 2015. Spatial variation of PM elemental composition between and within 20 European study areas — Results of the ESCAPE project. Environ. Int. 84, 181–192. doi:10.1016/j.envint.2015.04.015

US Department of Agriculture Economic Research Service, 2014. USDA ERS - Food Environment Atlas [WWW Document]. URL http://www.ers.usda.gov/data-products/food-environment-atlas.aspx#.U3lgUbHmapo (accessed 5.19.14).

U.S. EPA, 2008. Idling Vehicle Emissions for Passenger Cars, Light-Duty Trucks, and Heavy-Duty Trucks (No. EPA420-F-08-025). U.S. Environmental Protection Agency, Washington, D.C.

US EPA, 2003. Framework for Cumulative Risk Assessment (No. EPA/630/P-02/001F). U.S. Environm ental Protection Agency, Washington, D.C.

US EPA, n.d. Air Pollution and Cardiovascular Disease | Air Research | Research Priorities | Research | US EPA [WWW Document]. URL http://www.epa.gov/research/airscience/air-cardiovascular.htm (accessed 5.23.14).

van Donkelaar, A., Martin, R.V., Brauer, M., Kahn, R., Levy, R., Verduzco, C., Villeneuve, P.J., 2010. Global Estimates of Ambient Fine Particulate Matter Concentrations from Satellite-Based Aerosol Optical Depth: Development and Application. Environ. Health Perspect. 118, 847–855. doi:10.1289/ehp.0901623

Vedal, S., Kaufman, J.D., 2011. What Does Multi-Pollutant Air Pollution Research Mean? Am. J. Respir. Crit. Care Med. 183, 4–6. doi:10.1164/rccm.201009-1520ED

Ver Ploeg, M., Breneman, V., Dutko, P., Williams, R., Snyder, S., Dicken, C., Kaufman, P., 2012. Access to Affordable and Nutritious Food: Updated Estimates of Distance to Supermarkets Using 2010 Data (ERR-143). US Department of Agriculture, Economic Research Services.

Vinikoor, L.C., Kaufman, J.S., MacLehose, R.F., Laraia, B.A., 2008. Effects of racial density and income incongruity on pregnancy outcomes in less segregated communities. Soc. Sci. Med. 1982 66, 255–259. doi:10.1016/j.socscimed.2007.08.016

Vrijheid, M., Slama, R., Robinson, O., Chatzi, L., Coen, M., van den Hazel, P., Thomsen, C., Wright, J., Athersuch, T.J., Avellana, N., Basagaña, X., Brochot, C., Bucchini, L., Bustamante, M., Carracedo, A., Casas, M., Estivill, X., Fairley, L., van Gent, D., Gonzalez, J.R., Granum, B., Gražulevičienė, R., Gutzkow, K., Julvez, J., Keun, H.C., Kogevinas, M., McEachan, R.R.C., Meltzer, H.M., Sabidó, E., Schwarze, P.E., Siroux, V., Sunyer, J., Want, E., Zeman, F., Nieuwenhuijsen, M.J., 2014. The Human Early-Life Exposome (HELIX): Project Rationale and Design. Environ. Health Perspect. doi:10.1289/ehp.1307204

Wagner, J.G., Morishita, M., Keeler, G.J., Harkema, J.R., 2012. Divergent effects of urban particulate air pollution on allergic airway responses in experimental asthma: a comparison of field exposure studies. Environ. Health 11, 45. doi:10.1186/1476-069X-11-45

Walker, R.E., Block, J., Kawachi, I., 2014. The Spatial Accessibility of Fast food Restaurants and Convenience Stores in Relation to Neighborhood Schools. Appl. Spat. Anal. Policy 7, 169–182. doi:10.1007/s12061-013-9095-6

Wallace, J.M., Aitken, R.P., Milne, J.S., Hay, W.W., 2004. Nutritionally mediated placental growth restriction in the growing adolescent: consequences for the fetus. Biol. Reprod. 71, 1055–1062. doi:10.1095/biolreprod.104.030965

Wallace, J.M., Bourke, D.A., Aitken, R.P., Milne, J.S., Hay, W.W., 2003. Placental glucose transport in growth-restricted pregnancies induced by overnourishing adolescent sheep. J. Physiol. 547, 85–94. doi:10.1113/jphysiol.2002.023333

Walton, E., 2009. Residential segregation and birth weight among racial and ethnic minorities in the United States. J. Health Soc. Behav. 50, 427–442.

Wang, Y., Ying, Q., Hu, J., Zhang, H., 2014. Spatial and temporal variations of six criteria air pollutants in 31 provincial capital cities in China during 2013–2014. Environ. Int. 73, 413–422. doi:10.1016/j.envint.2014.08.016

WHO, 2014. Global Nutrition Targets 2025: Low Birth Weight Policy Brief (Policy Brief). World Health Organization: Department of Nutrition for Health and Development, Switzerland.

Whyatt, R.M., Bell, D.A., Jedrychowski, W., Santella, R.M., Garte, S.J., Cosma, G., Manchester, D.K., Young, T.L., Cooper, T.B., Ottman, R., Perera, F.P., 1998. Polycyclic aromatic hydrocarbon-DNA adducts in human placenta and modulation by CYP1A1 induction and genotype. Carcinogenesis 19, 1389–1392.

Wilhelm, M., Ghosh, J.K., Su, J., Cockburn, M., Jerrett, M., Ritz, B., 2011a. Traffic-Related Air Toxics and Term Low Birth Weight in Los Angeles County, California. Environ. Health Perspect. 120, 132–138. doi:10.1289/ehp.1103408

Wilhelm, M., Ghosh, J.K., Su, J., Cockburn, M., Jerrett, M., Ritz, B., 2011b. Traffic-related air toxics and preterm birth: a population-based case-control study in Los Angeles county, California. Environ. Health 10, 89. doi:10.1186/1476-069X-10-89

Wilhelm, M., Ghosh, J.K., Su, J., Cockburn, M., Jerrett, M., Ritz, B., 2011c. Traffic-Related Air Toxics and Term Low Birth Weight in Los Angeles County, California. Environ. Health Perspect. 120, 132–138. doi:10.1289/ehp.1103408

Wilhelm, M., Ritz, B., 2005. Local variations in CO and particulate air pollution and adverse birth outcomes in Los Angeles County, California, USA. Environ. Health Perspect. 113, 1212–

1221.

Wilhelm, M., Ritz, B., 2003a. Residential proximity to traffic and adverse birth outcomes in Los Angeles county, California, 1994-1996. Environ. Health Perspect. 111, 207–216.

Wilhelm, M., Ritz, B., 2003b. Residential proximity to traffic and adverse birth outcomes in Los Angeles county, California, 1994-1996. Environ. Health Perspect. 111, 207–216.

Williams, B.L., Pennock-Román, M., Suen, H.K., Magsumbol, M.S., Ozdenerol, E., 2007. Assessing the impact of the local environment on birth outcomes: a case for HLM. J. Expo. Sci. Environ. Epidemiol. 17, 445–457. doi:10.1038/sj.jes.7500537

World Health Organization, UNICEF, 2004. Low birthweight: country, regional and global estimates. WHO ; UNICEF, Geneva : New York.

Wu, G., Bazer, F.W., Cudd, T.A., Meininger, C.J., Spencer, T.E., 2004. Maternal nutrition and fetal development. J. Nutr. 134, 2169–2172.

Wu, J., Wilhelm, M., Chung, J., Ritz, B., 2011. Comparing exposure assessment methods for traffic-related air pollution in an adverse pregnancy outcome study. Environ. Res. 111, 685–692. doi:10.1016/j.envres.2011.03.008

Xiong, X., Mayes, D., Demianczuk, N., Olson, D.M., Davidge, S.T., Newburn-Cook, C., Saunders, L.D., 1999. Impact of pregnancy-induced hypertension on fetal growth. Am. J. Obstet. Gynecol. 180, 207–213.

Ying-Ying, M., Babey, S., Pickett, M., Wolstein, J., 2013. Do Air Pollution Exposure and Food

Environment Impact Overweight/Obesity? Presented at the Environment and Health, Environmental Health Perspectives, Basel, Switzerland.

Zanobetti, A., Austin, E., Coull, B.A., Schwartz, J., Koutrakis, P., 2014a. Health effects of multi-pollutant profiles. Environ. Int. 71, 13–19. doi:10.1016/j.envint.2014.05.023

Zanobetti, A., Canner, M.J., Stone, P.H., Schwartz, J., Sher, D., Eagan-Bengston, E., Gates, K.A., Hartley, L.H., Suh, H., Gold, D.R., 2004. Ambient pollution and blood pressure in cardiac rehabilitation patients. Circulation 110, 2184–2189. doi:10.1161/01.CIR.0000143831.33243.D8

Zanobetti, A., Luttmann-Gibson, H., Horton, E.S., Cohen, A., Coull, B.A., Hoffmann, B., Schwartz, J.D., Mittleman, M.A., Li, Y., Stone, P.H., de Souza, C., Lamparello, B., Koutrakis, P., Gold, D.R., 2014b. Brachial Artery Responses to Ambient Pollution, Temperature, and Humidity in People with Type 2 Diabetes: A Repeated-Measures Study. Environ. Health Perspect. doi:10.1289/ehp.1206136

Zeka, A., Melly, S.J., Schwartz, J., 2008. The effects of socioeconomic status and indices of physical environment on reduced birth weight and preterm births in Eastern Massachusetts. Environ. Health 7, 60. doi:10.1186/1476-069X-7-60

Zenk, S.N., Schulz, A.J., Israel, B.A., Mentz, G., Miranda, P.Y., Opperman, A., Odoms-Young, A.M., 2014. Food shopping behaviours and exposure to discrimination. Public Health Nutr. 17, 1167–1176. doi:10.1017/S136898001300075X

Zhang, K., Batterman, S., 2013. Air pollution and health risks due to vehicle traffic. Sci. Total Environ. 450-451, 307–316. doi:10.1016/j.scitotenv.2013.01.074

Zhuoqiong He, D.S., 2000. Hierarchical Bayes estimation of hunting success rates with spatial correlations. Biometrics 56, 360–7. doi:10.1111/j.0006-341X.2000.00360.x

Zhu, X., Fan, Z. (tina), Wu, X., Jung, K.H., Ohman-Strickland, P., Bonanno, L.J., Lioy, P.J., 2011. Ambient concentrations and personal exposure to polycyclic aromatic hydrocarbons (PAH) in an urban community with mixed sources of air pollution. J. Expo. Sci. Environ. Epidemiol. 21, 437–449. doi:10.1038/jes.2011.2

Zou, B., Peng, F., Wan, N., Mamady, K., Wilson, G.J., 2014. Spatial Cluster Detection of Air Pollution Exposure Inequities across the United States. PLoS ONE 9, e91917. doi:10.1371/journal.pone.0091917

Zuurbier, M., Hoek, G., Oldenwening, M., Lenters, V., Meliefste, K., van den Hazel, P., Brunekreef, B., 2010. Commuters' exposure to particulate matter air pollution is affected by mode of transport, fuel type, and route. Environ. Health Perspect. 118, 783–789. doi:10.1289/ehp.0901622

Appendix A: Supplemental Material for Chapter 2

Table A.1. Multivariate Logistic Regression Results for Standard and Multilevel Spatial Models

	Standard Regression Model			**Multilevel Spatial Model**		
	Odds Ratios	Lower 95th Percentile	Upper 95th Percentile	Odds Ratios	2.5% Quantile	97.5% Quanitle
$PM_{2.5}$ (per 10μg/m^3)	1.17	1.10	1.24	1.19	1.02	1.39
Maternal Age						
<20 years	1 (reference)			1 (reference)		
20 - 24 years	.93	0.90	0.97	0.94	0.90	0.98
25 - 29 years	0.87	0.83	0.90	0.87	0.84	0.91
30 - 34 years	0.88	0.84	0.93	0.90	0.86	0.94
≥35 years	1.05	0.99	1.10	1.06	1.01	1.12
Maternal Education						
0-8 years	1 (reference)			1 (reference)		
9-12 years	0.93	0.90	0.96	0.96	0.93	1.00
13-15 years	0.74	0.71	0.77	0.79	0.76	0.83
≥16 years	0.64	0.61	0.68	0.70	0.67	0.74
Maternal Race						
White	1 (reference)			1 (reference)		
Hispanic	1.11	1.06	1.16	1.024	0.978	1.073
Black	2.42	2.31	2.54	2.132	2.012	2.245
Asian	1.44	1.36	1.52	1.394	1.311	1.482
Other	1.87	1.76	1.98	1.764	1.654	1.880
Parity	0.61	0.59	0.62	0.603	0.587	0.620
Gestation age (days)	0.32	0.31	0.33	0.32	0.31	0.33
Gestation squared	1.00194	1.00187	1.002	1.001943	1.00188	1.0019442
Female sex	1.44	1.40	1.47	1.44	1.40	1.47

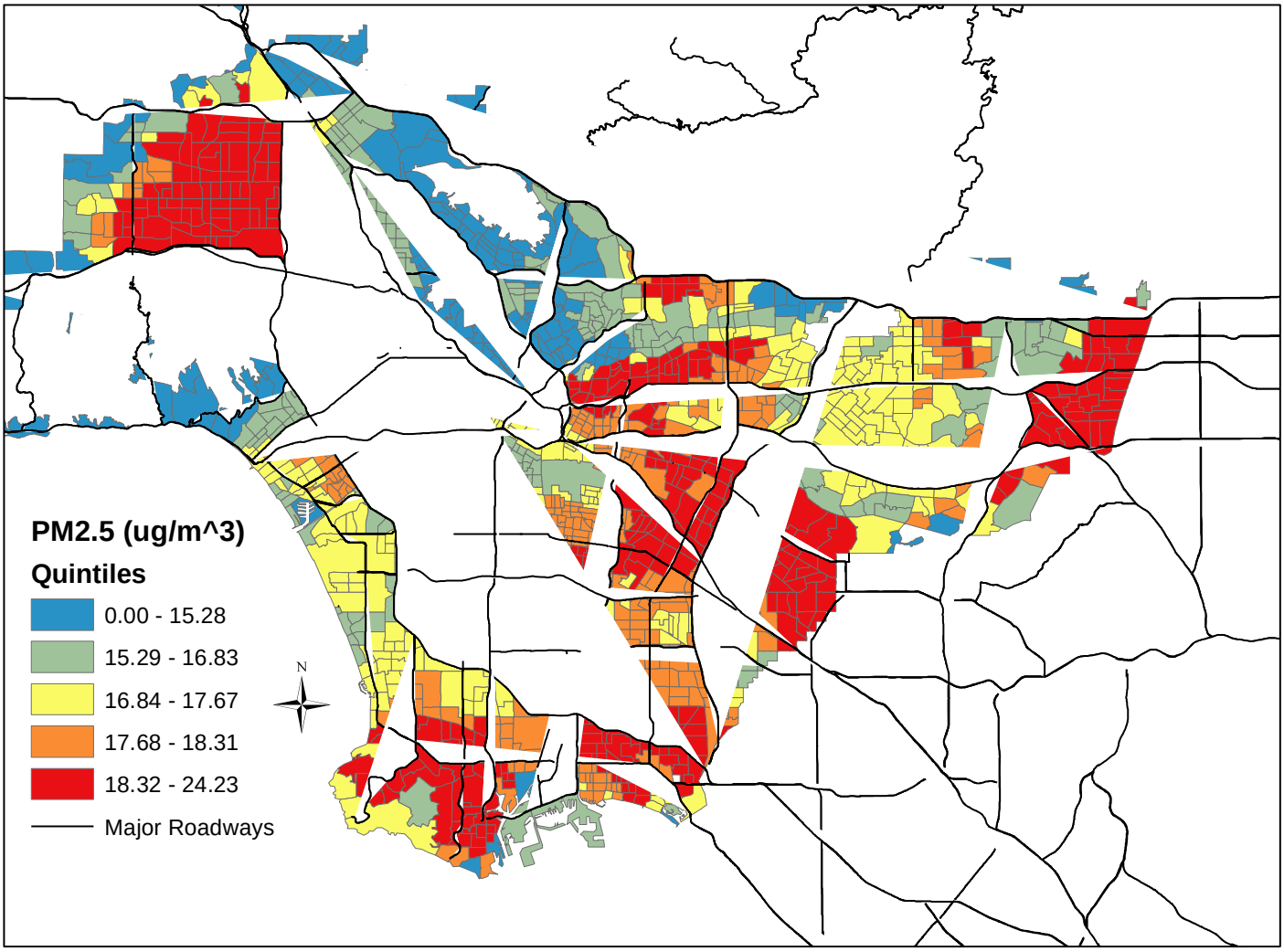


Figure A.1. Spatial Distriubtion of $PM_{2.5}$ Concentrations (in quintiles) throughout urban LA County Census Tracts.

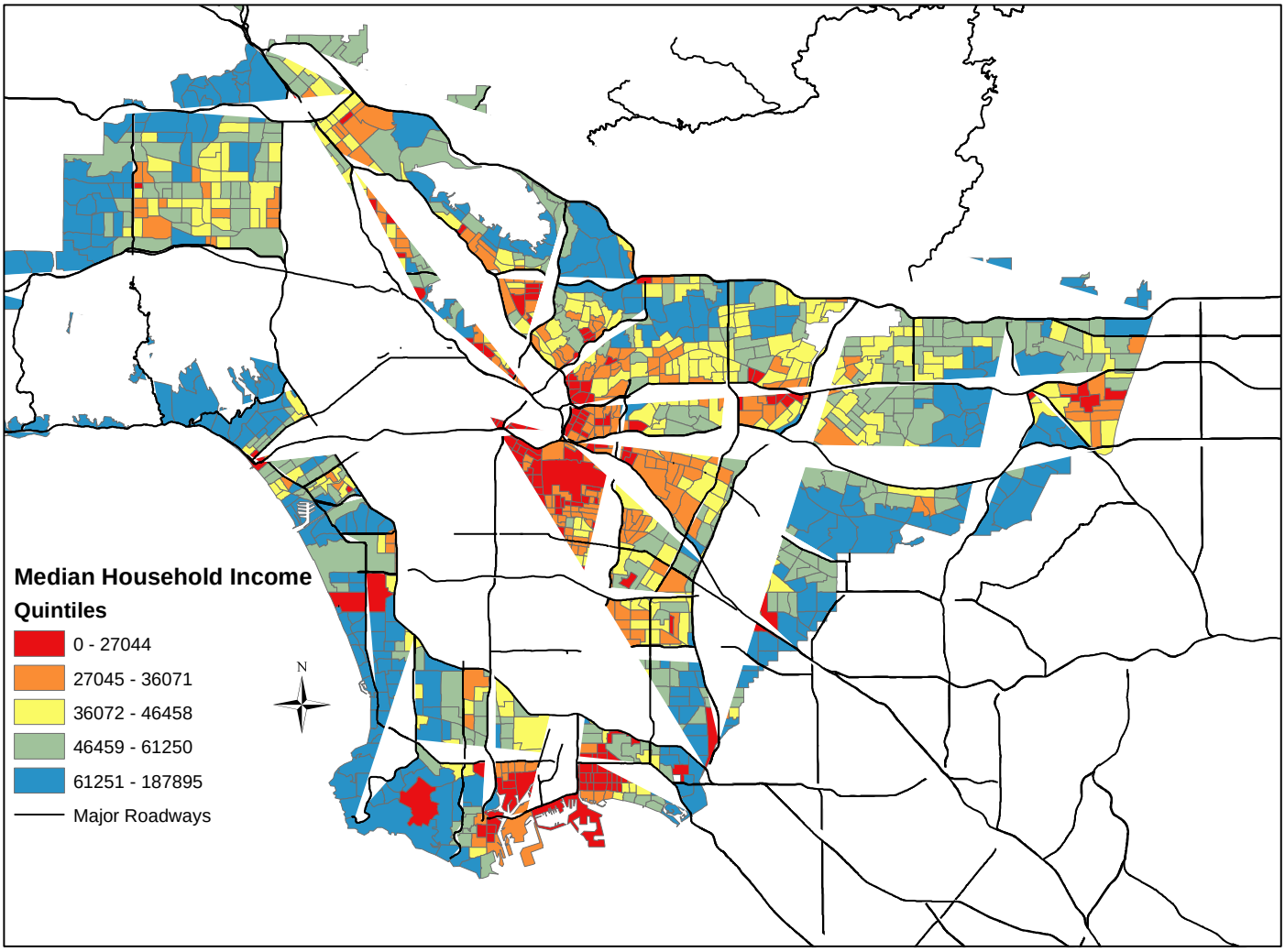


Figure A.2. Spatial Distriubtion of Median Household Income (in quintiles) throughout urban LA County Census Tracts.

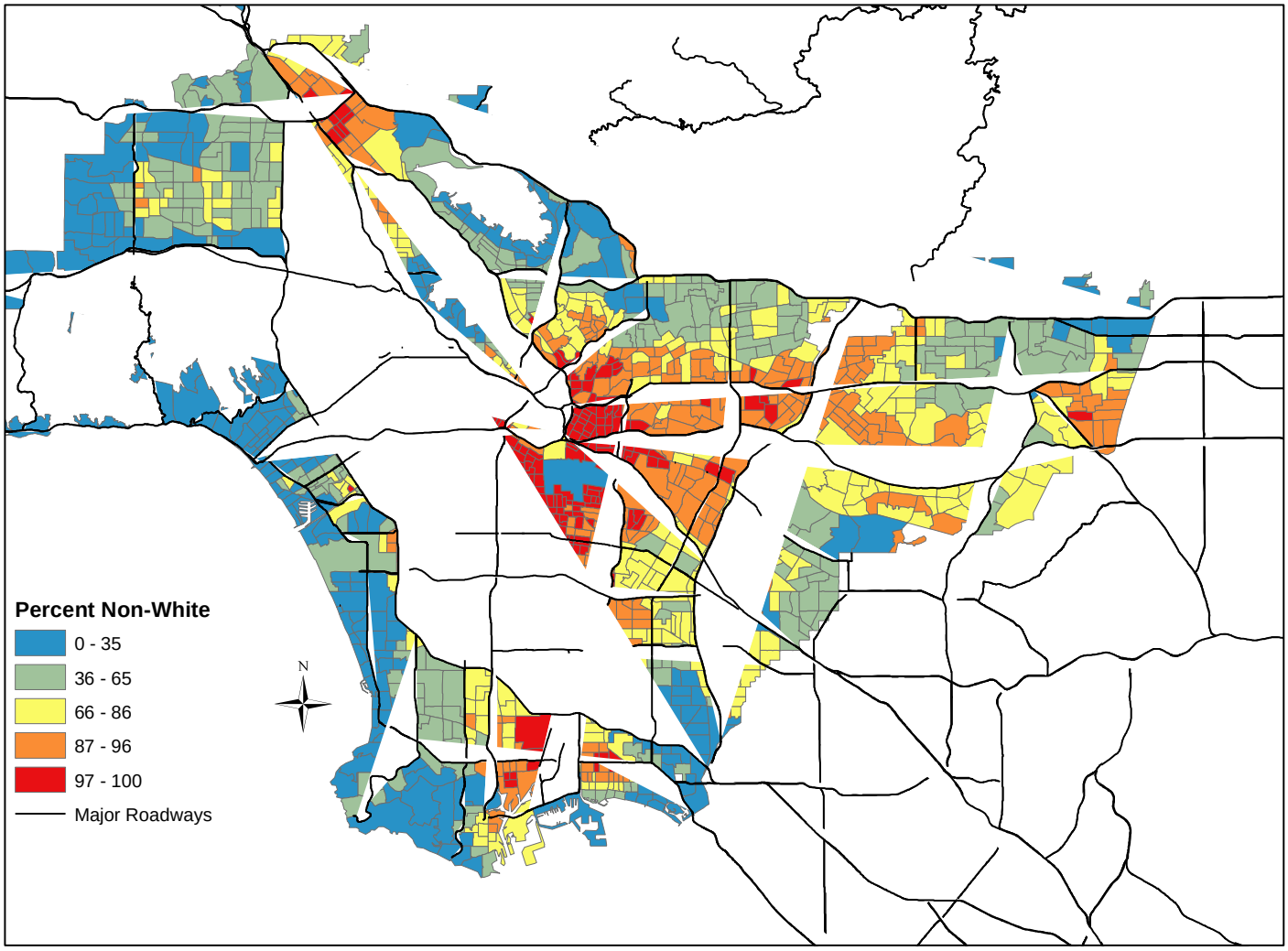


Figure A.3. Spatial Distriubtion of Percent Non-White (in quintiles) throughout urban LA County Census Tracts.

Appendix B - Supplemental Material for Chapter 3

Figure B.1. Between pollutant correlations for different seasons using entire pregnancy average exposure.

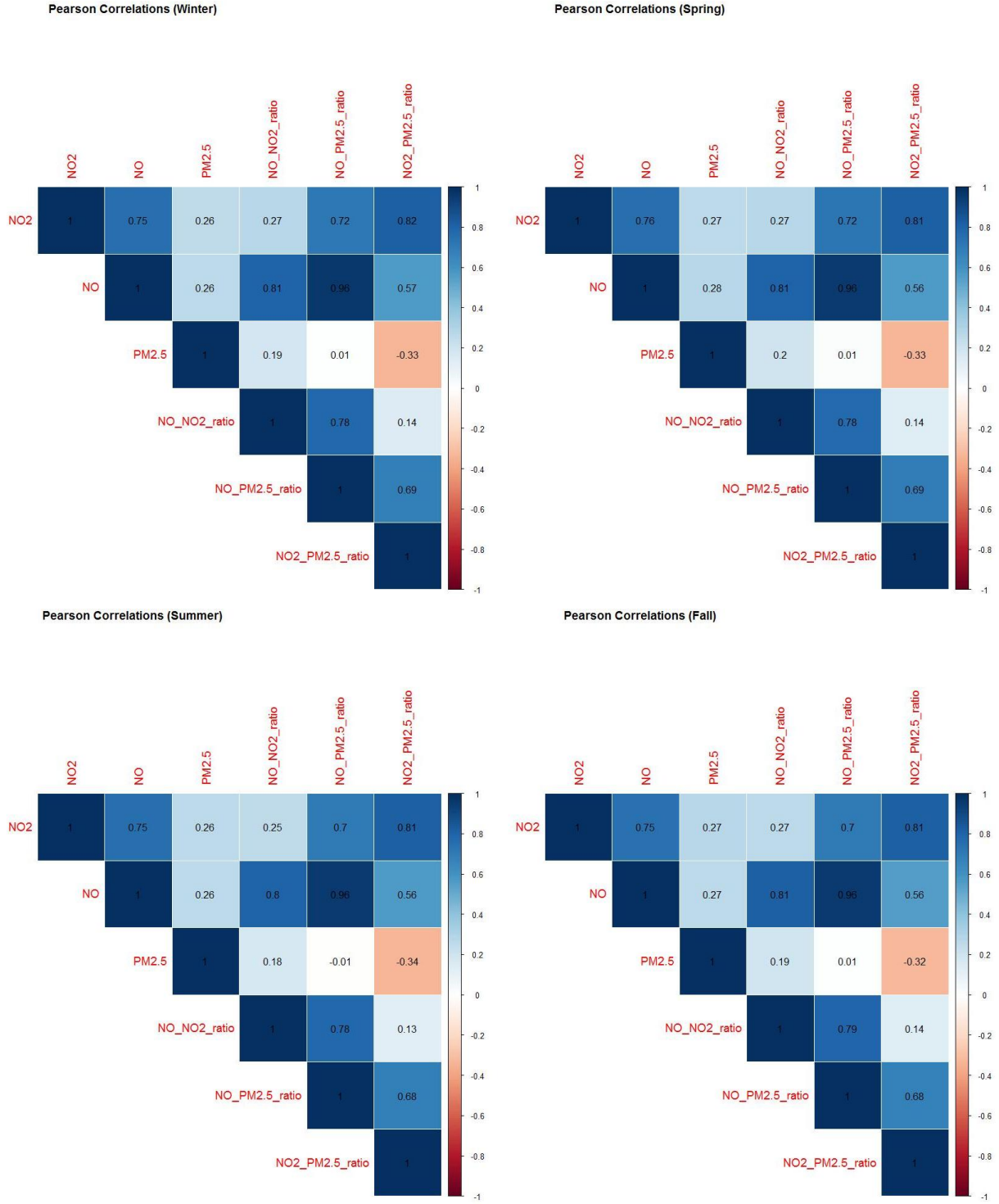


Figure B.2. Spatial patterns of season-specific pollutant clusters.

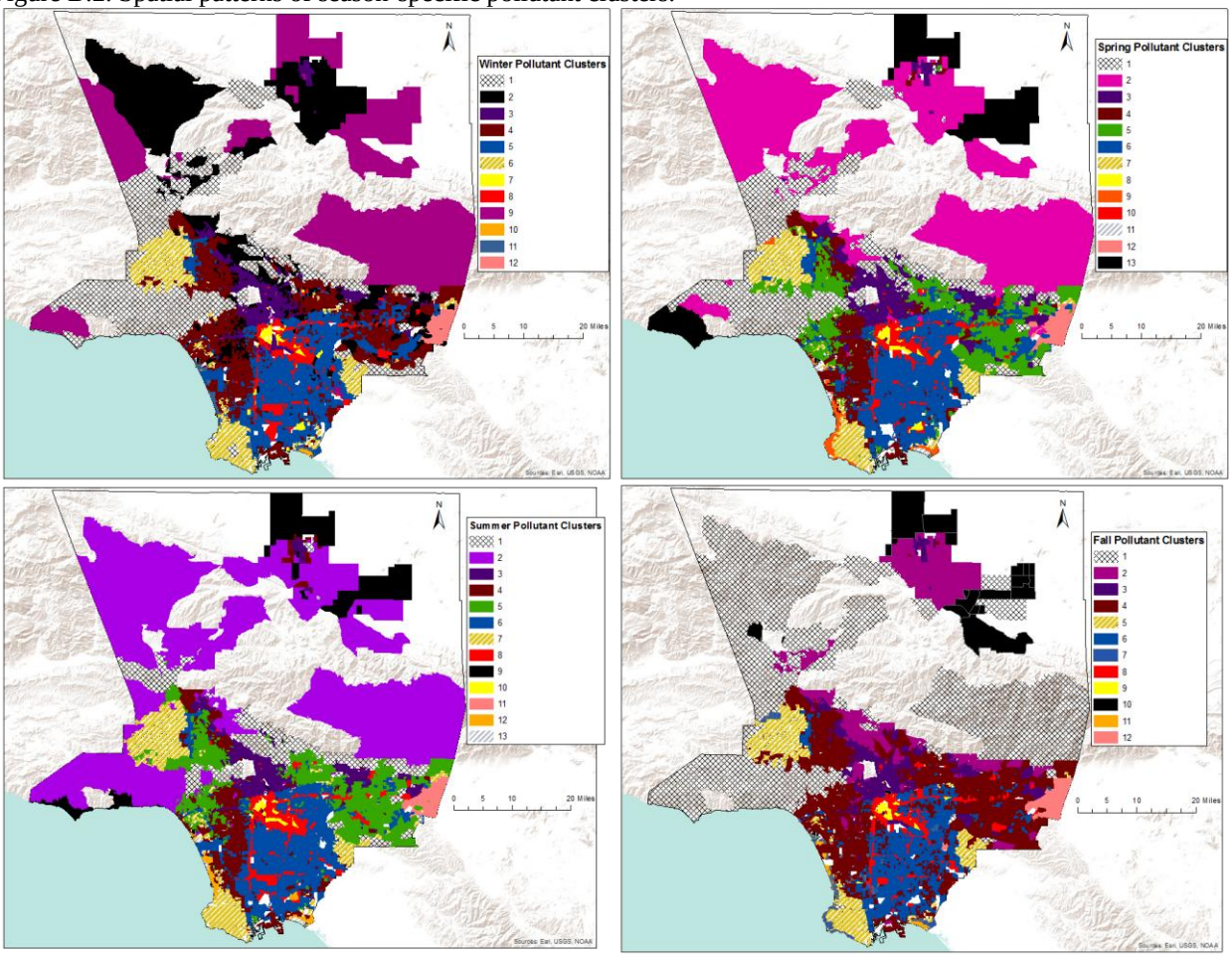
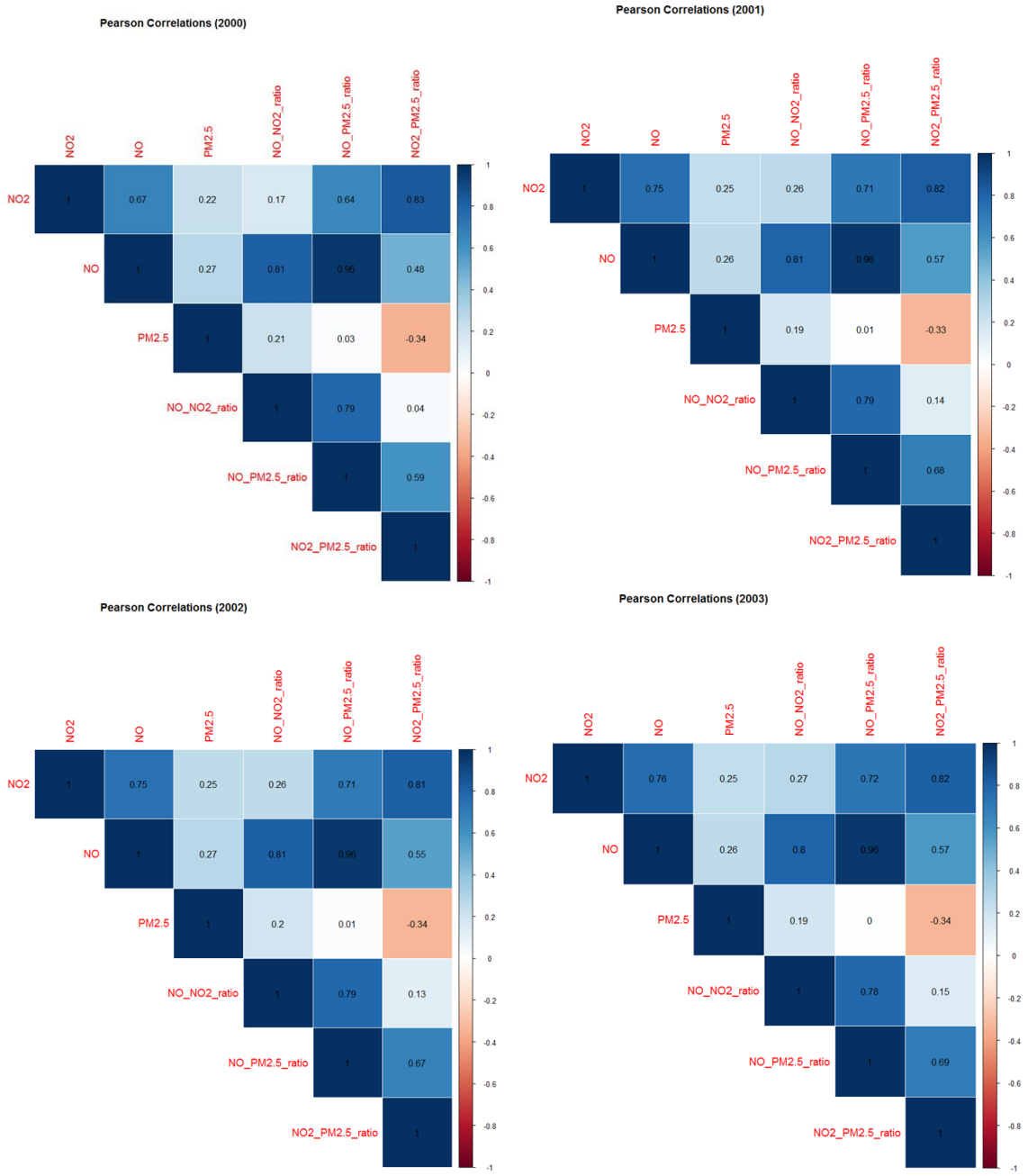
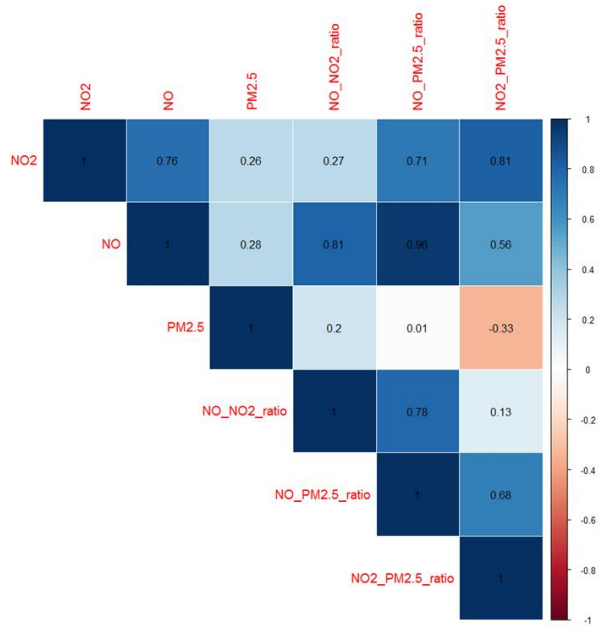


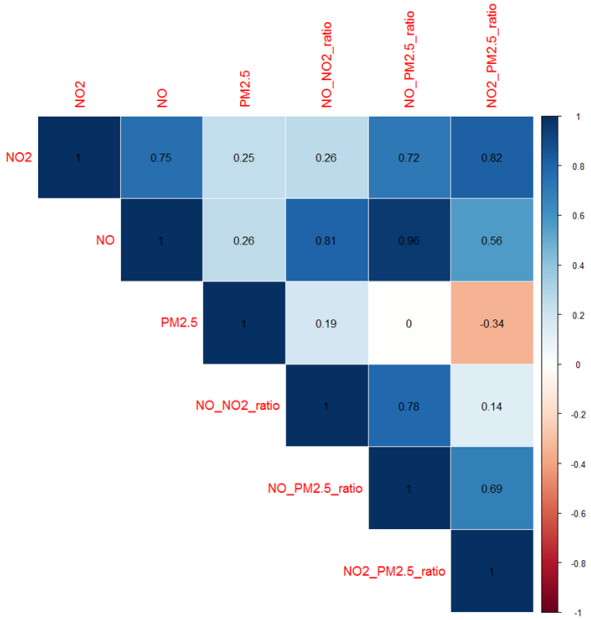
Figure B.3. Between pollutant correlations for each study year (2000-2006) using entire pregnancy average exposure.



Pearson Correlations (2004)



Pearson Correlations (2005)



Pearson Correlations (2006)

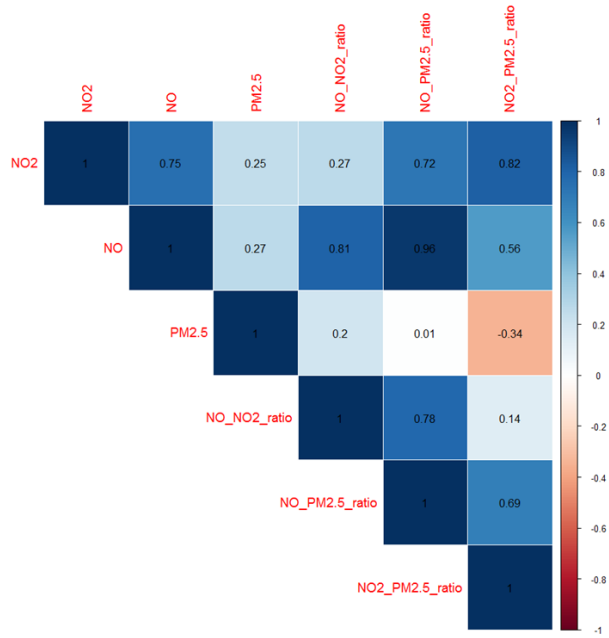


Figure B.4. Spatial patterns of year-specific pollutant clusters.

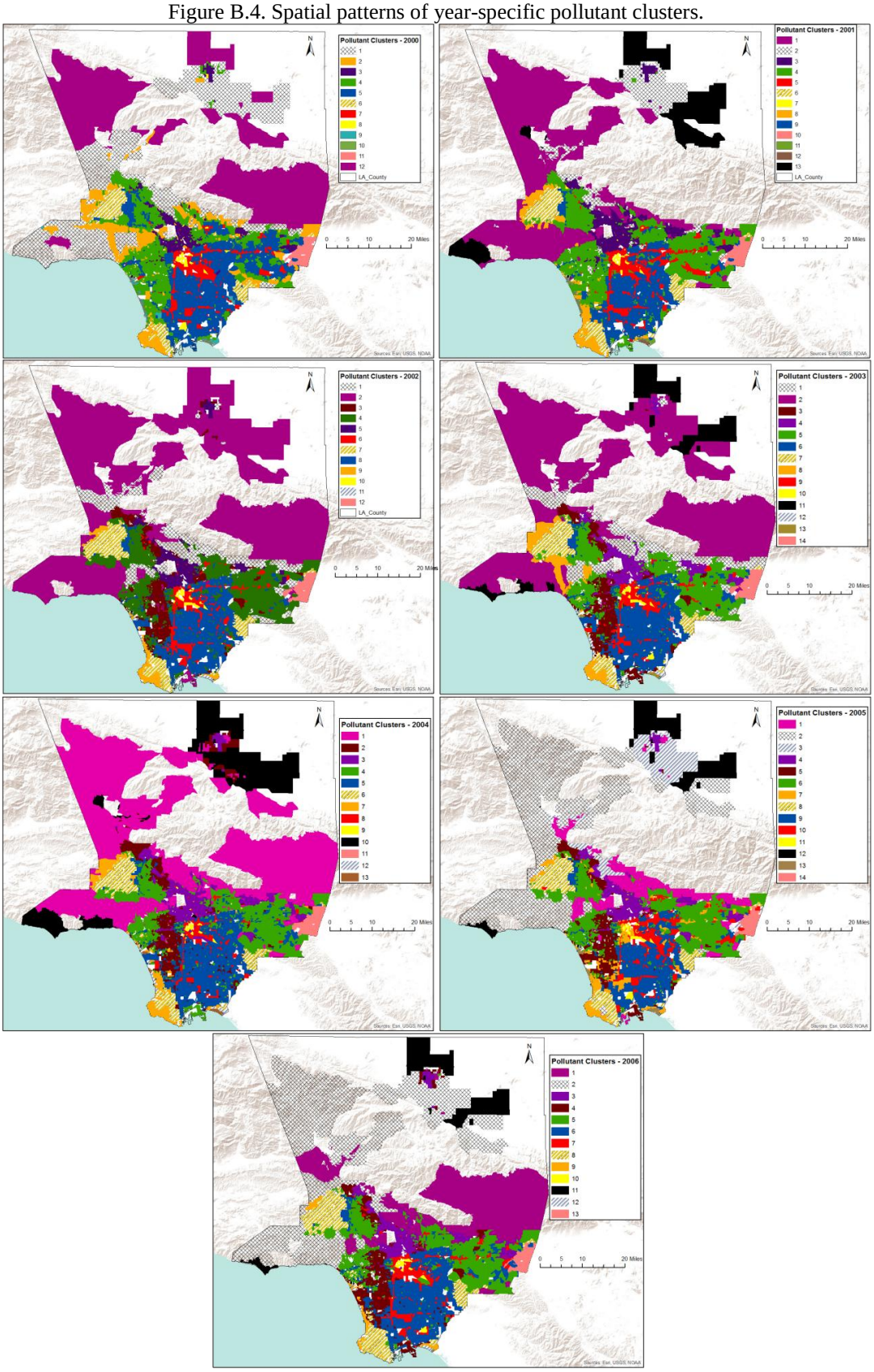


Table B.1. Odds Rations (95%CI) from Multivariate Logistic Regression Fixed Effects: Comparison between single pollutant versus multipollutant models

	Single Pollutant Model			Multipollutant Model		
Pollutants	**OR**	**Std. Error**	**p-value**	**OR**	**Std. Error**	**p-value**
$PM_{2.5}$ (10 $\mu g/m^3$)	1.05	0.0026	0.059	1.02	0.0029	0.59
NO_2 (10ppb)[a]	1.06	0.0015	0.0002	1.04	0.0019	0.03
NO (10 ppb)[a]	1.02	0.0006	0.002	1.01	0.0008	0.23

[a]A multiplicative interaction between NO_2 and NO was statistically significant (p-value=0.04).

Figure B.5. Census tract autocorrelation of TLBW prevalence using Local Moran's I test for spatial autocorrelation.

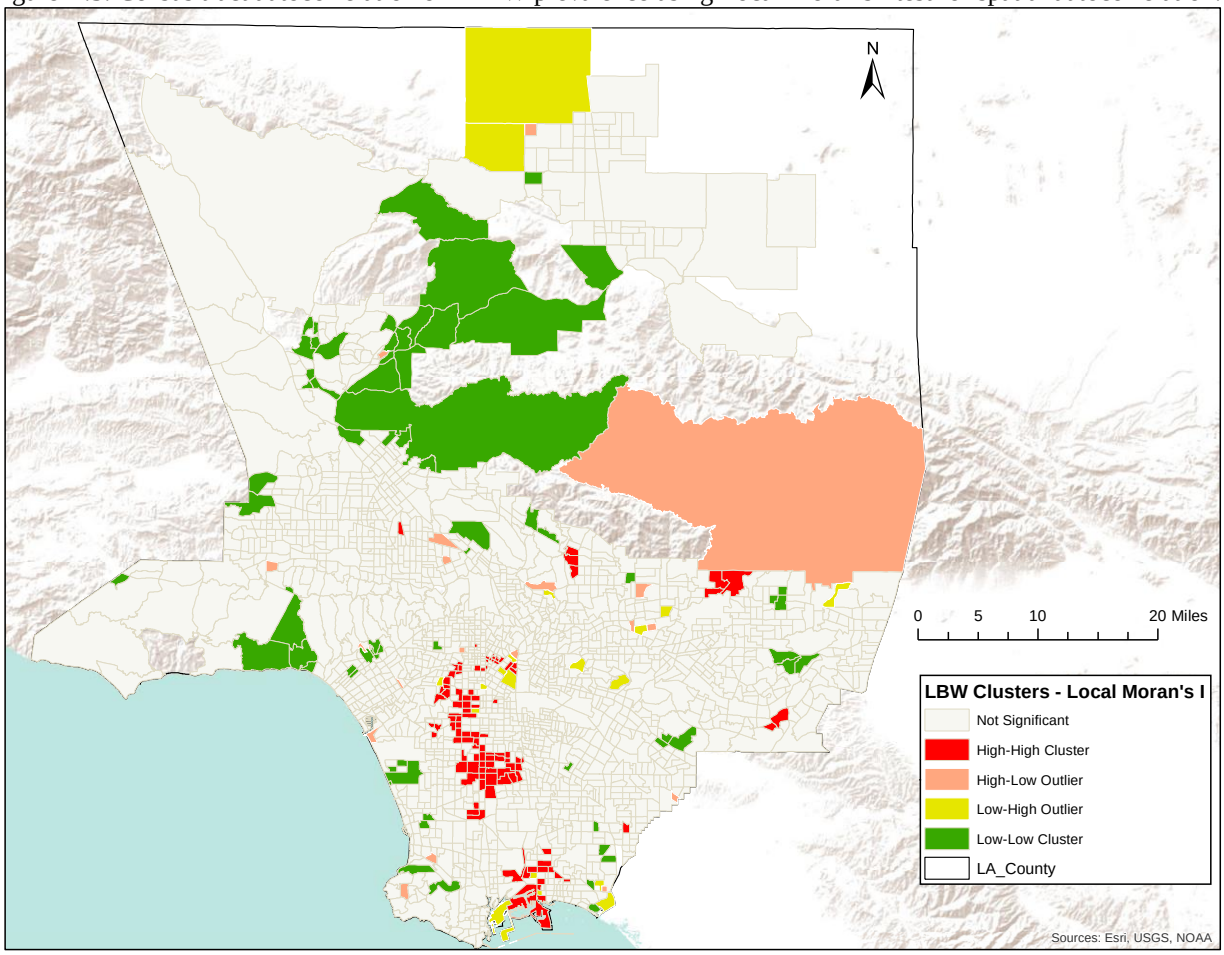
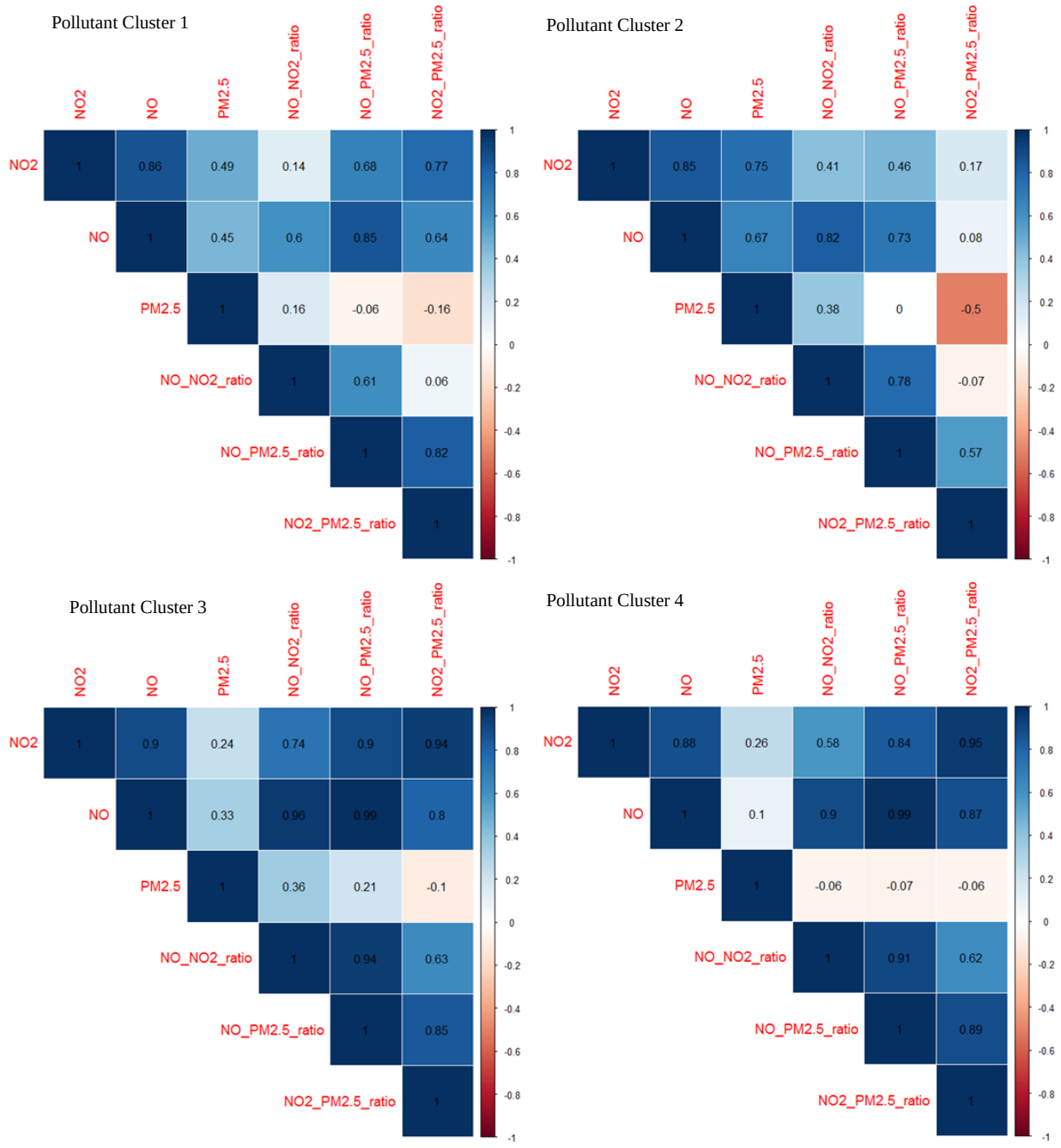
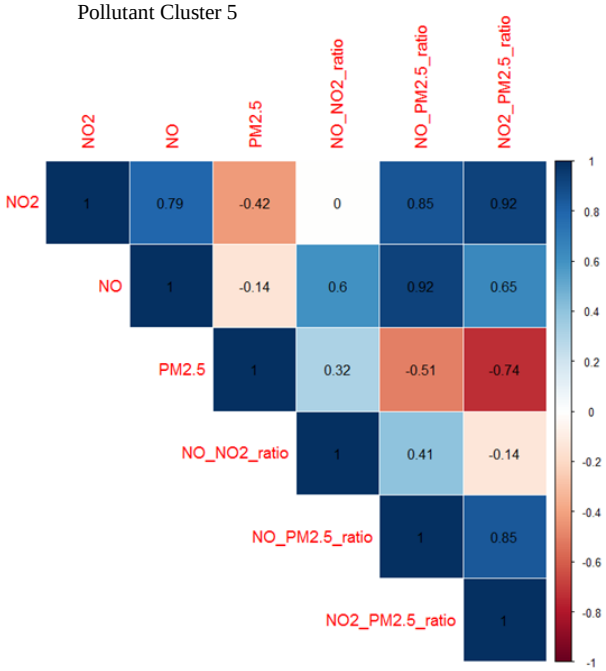


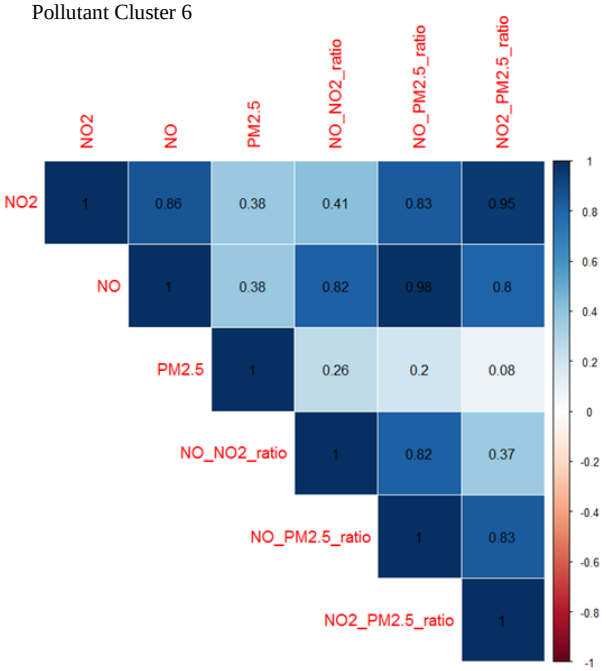
Figure B.6. Pearson Correlations Between Pollutants and Contextual Variables across all pollutant Clusters (P1-P13).



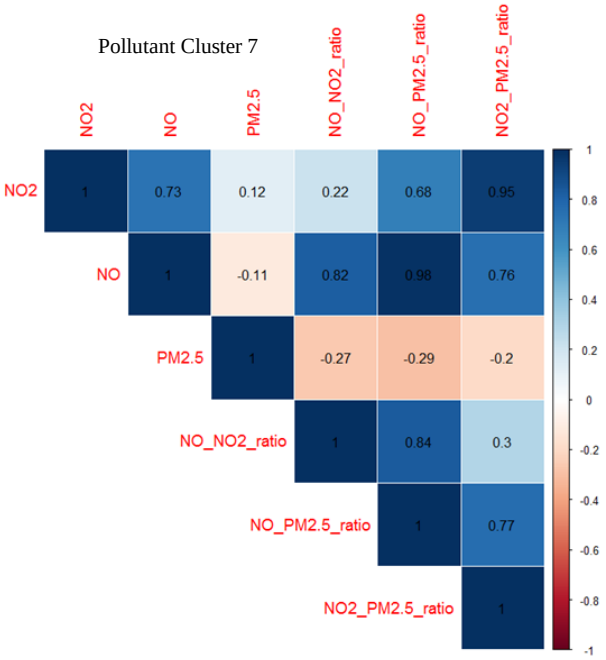
Pollutant Cluster 5



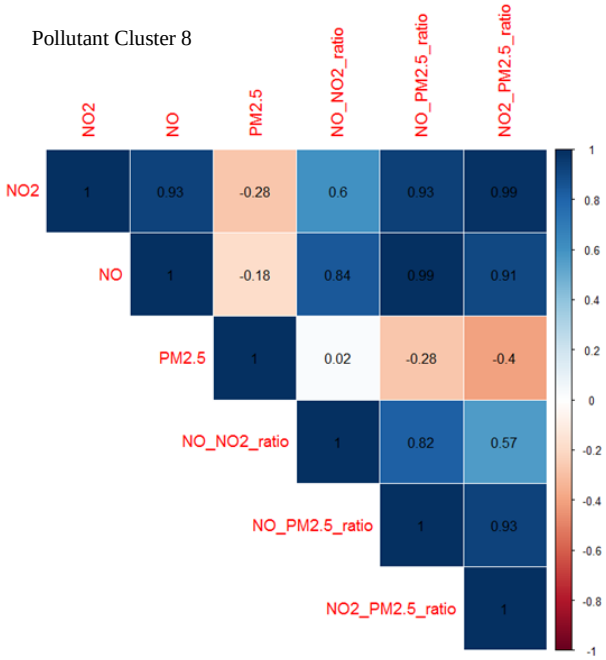
Pollutant Cluster 6



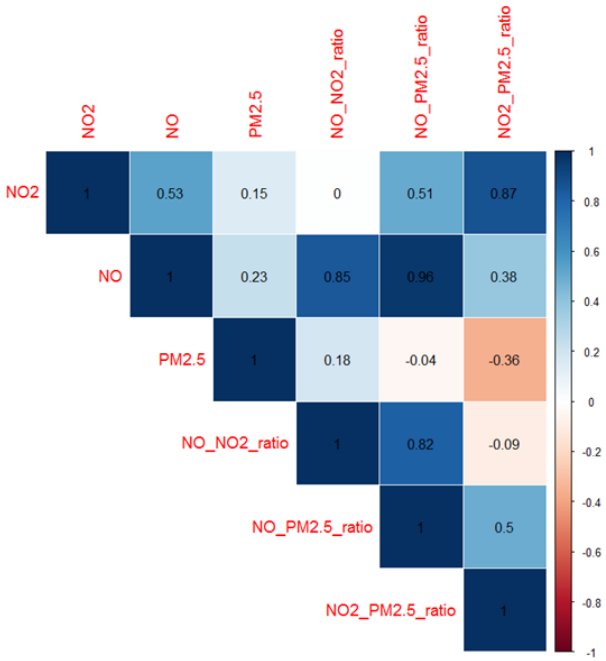
Pollutant Cluster 7



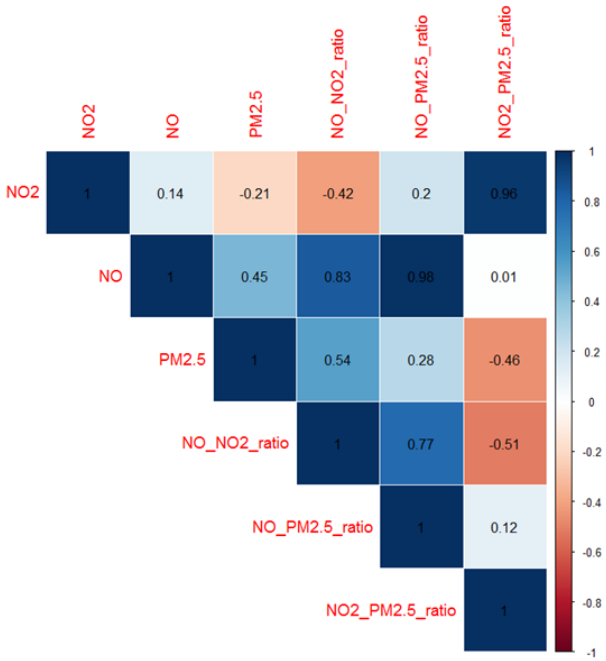
Pollutant Cluster 8



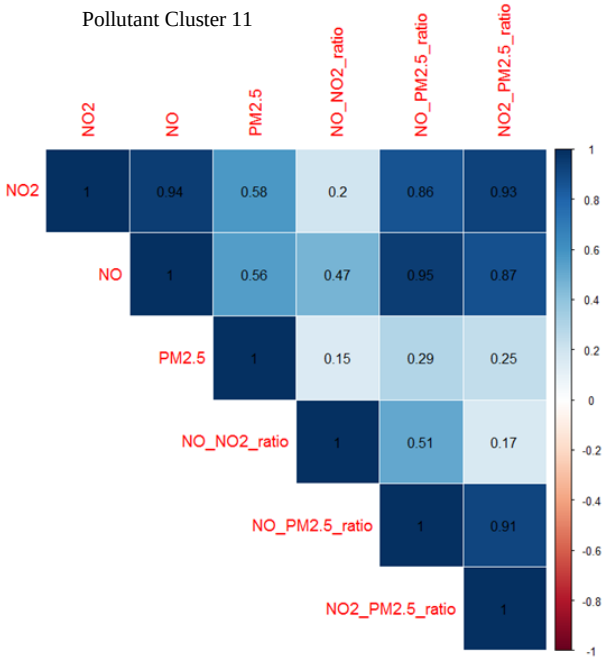
Pollutant Cluster 9



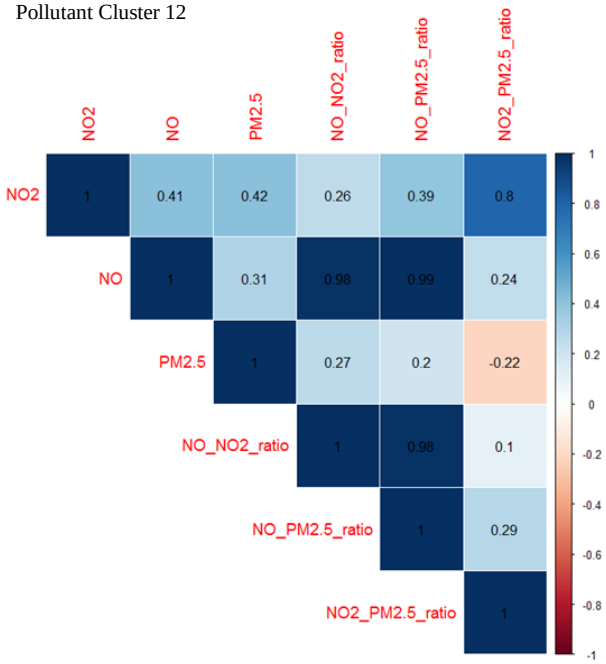
Pollutant Cluster 10



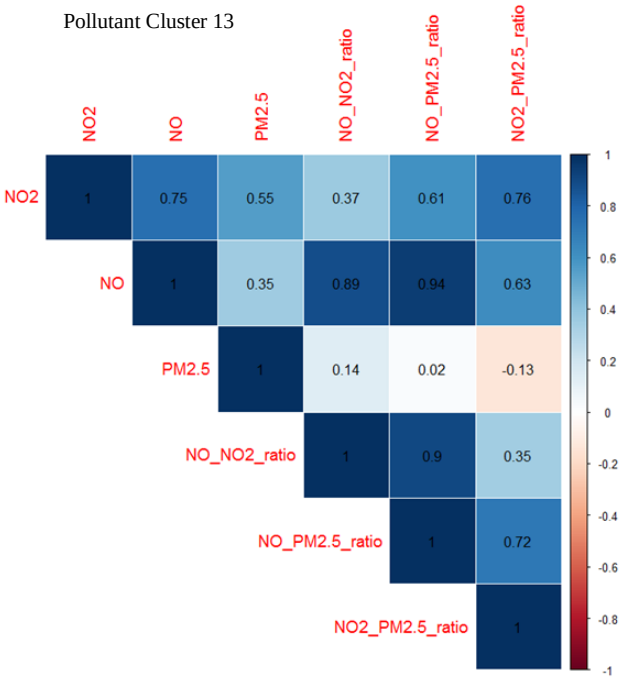
Pollutant Cluster 11

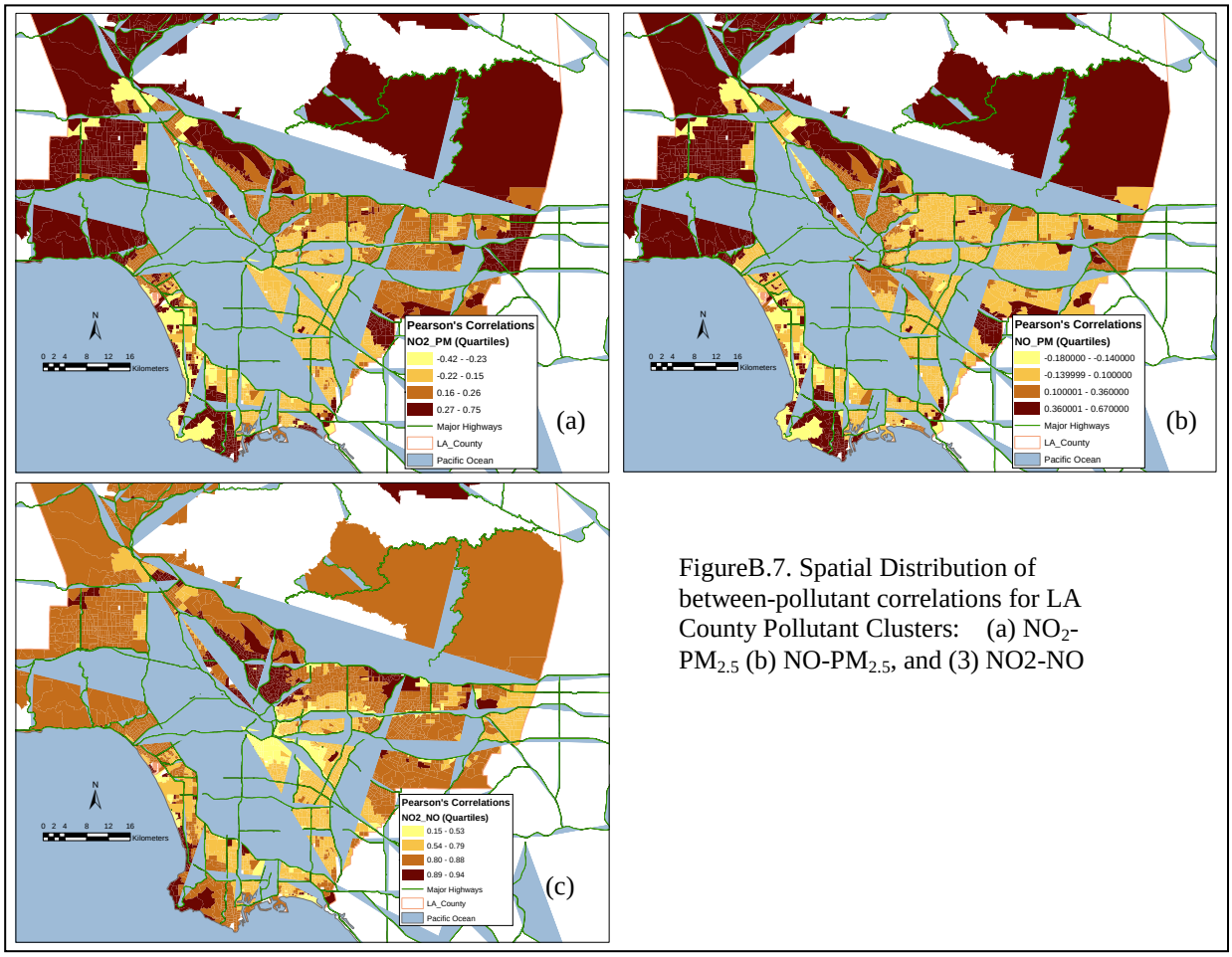


Pollutant Cluster 12



Pollutant Cluster 13





FigureB.7. Spatial Distribution of between-pollutant correlations for LA County Pollutant Clusters: (a) NO_2-$PM_{2.5}$ (b) NO-$PM_{2.5}$, and (3) NO2-NO

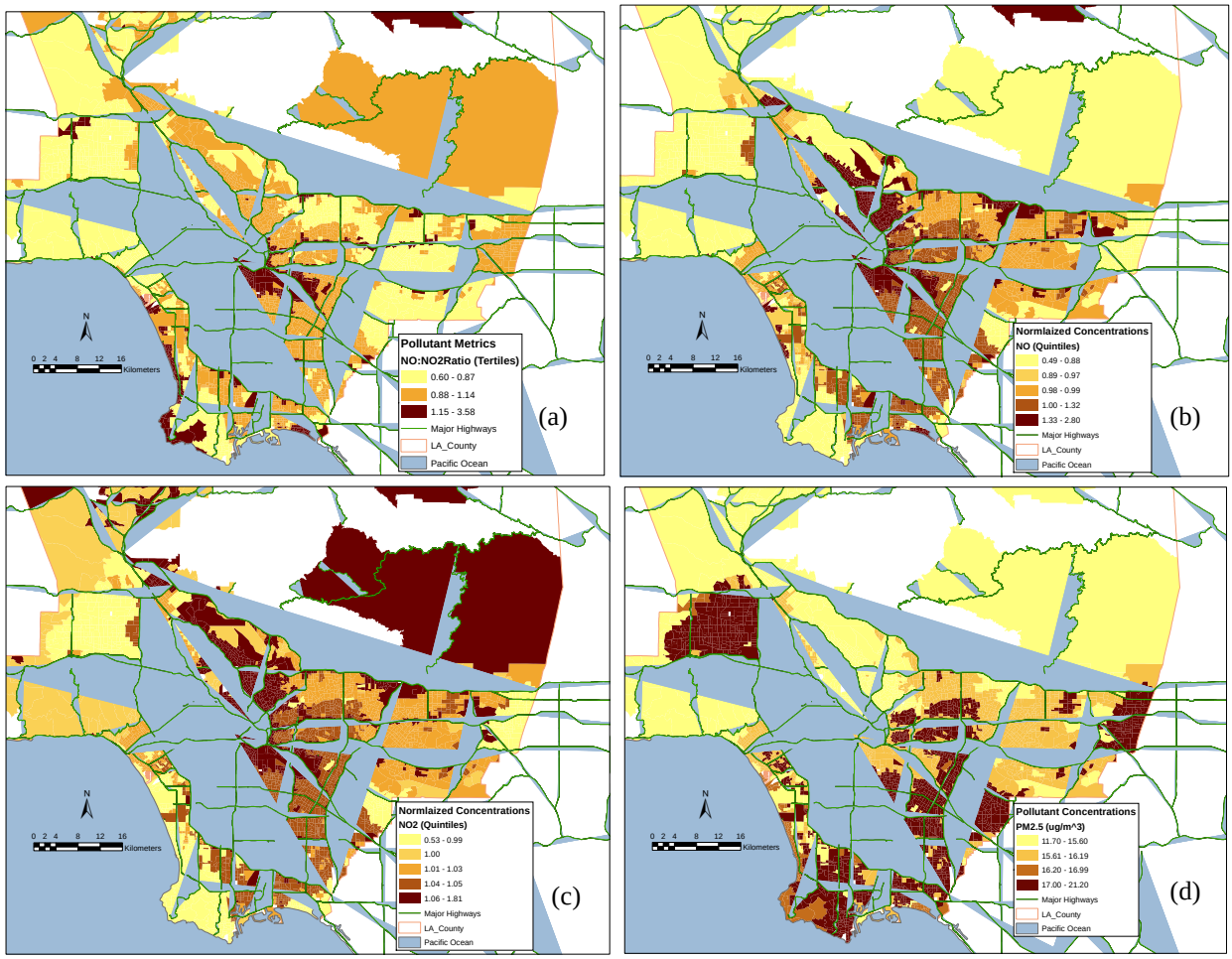


Figure B.8. Spatial Distribution of census block group averages for (a) NO/NO2 ratio, (b) Normalized NO concentrations, (c) Normalized NO concentrations, and (d) PM2.5 concentrations for LA County.

Appendix C - Supplemental Material for Chapter 4

Supplemental Materials

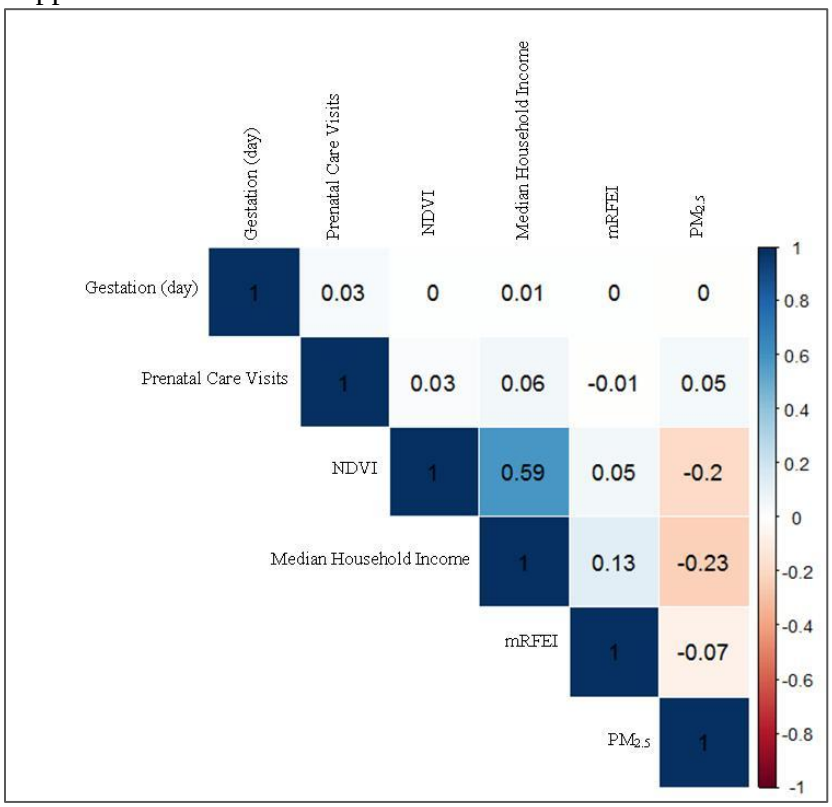


Figure C.1. Pearson correlations between continuous covariates.

Table C.2. Comparison of coefficients with and without $PM_{2.5}$ or mRFEI and coefficient estimate for multiplicative interaction term.

Type of Model	**β_{mRFEI} (95%CI)[a]**	**$\beta_{PM2.5}$ (95%CI)[b]**	**$\beta_{PM2.5*mRFEI}$ (95%CI)[c]**
Without $PM_{2.5}$	-0.4761 (-0.838, -0.118)		
Without mRFEI		0.021 (-0.004, 0.047)	
With PM2.5+ mRFEI	-0.4587 (-0.8219, -0.099)	0.019 (-0.006, 0.045)	
Interaction - mRFEI*$PM_{2.5}$	-0.441 (-0.813, -0.073)	0.012 (-0.028, 0.051)	0.073 (-0.215, 0.369)

[a] **Δ** β_{mRFEI} = -3.8% after adjusting for $PM_{2.5}$
[b] **Δ** $\beta_{PM2.5}$ = -10.5% after adjusting for mRFEI

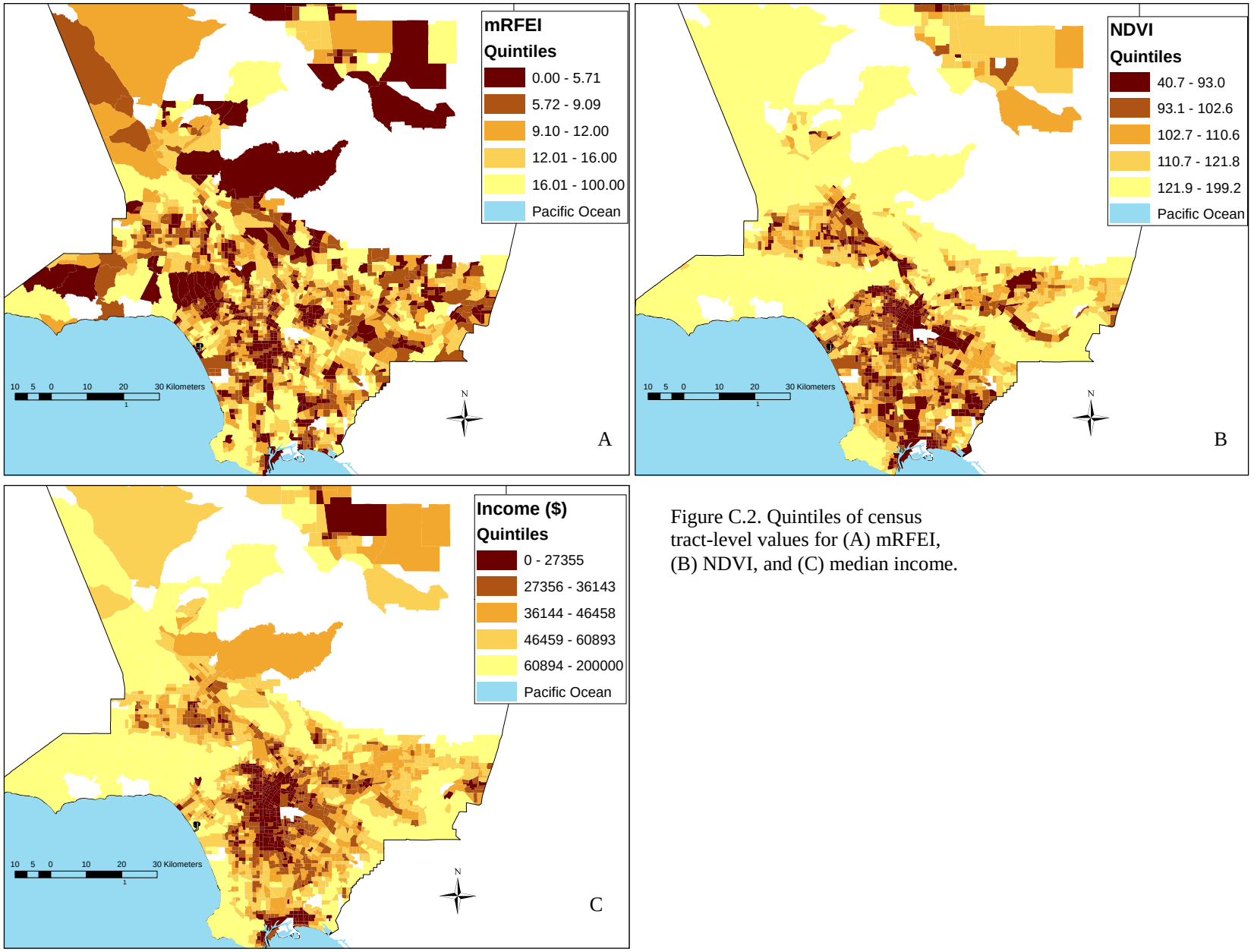


Figure C.2. Quintiles of census tract-level values for (A) mRFEI, (B) NDVI, and (C) median income.

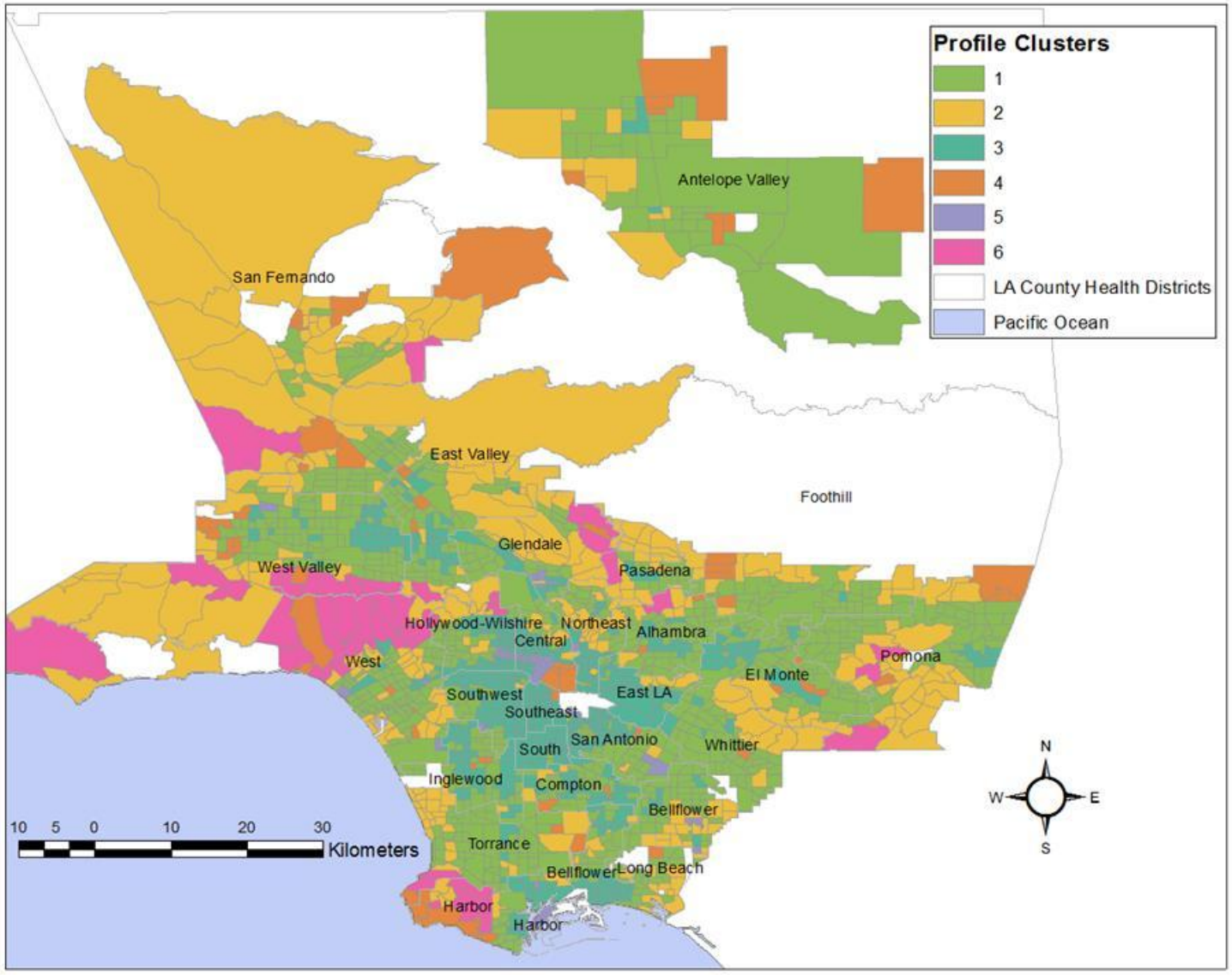


Figure C.3. Profile clusters from the Bayesian profile regression.

This Page Intentionally Left Black